Draft External Peer Review Charge Questions for the IRIS Toxicological Review of Perfluorodecanoic Acid [PFDA, CASRN 335-76-2] and Related Salts

April 2023

Introduction

The U.S. Environmental Protection Agency (EPA) is seeking a scientific peer review of the draft *IRIS Toxicological Review of Perfluorodecanoic Acid (PFDA) 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 perfluorodecanoic acid (PFDA). The draft Toxicological Review of PFDA 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 PFDA or salts of PFDA. The systematic review protocol for PFDA and appendices for dose-response modeling, mechanistic evaluations and pharmacokinetic information and other supporting materials are provided as *Supplemental Information* (see Appendices A to I) to the draft Toxicological Review.

REVIEW MATERIALS PROVIDED

- Draft PFDA Toxicological Assessment
- Supplemental Material (PFDA Appendices)

Charge Questions on the Draft Toxicological Review of PFDA

In response to the numbered charge questions below organized by topic area (italicized headers), the advice provided as part of this peer review would be most useful when prioritized to indicate its relative importance as follows:

- Tier 1: *Necessary Revisions* – Use this category for any revisions you believe are necessary to adequately support and substantiate the analyses or scientific basis for the assessment conclusions, or to improve the clarity of the presentation in the PFDA Toxicological Review.
- Tier 2: *Suggestions* – Use this category for any revisions you encourage EPA to implement to strengthen the analyses or scientific basis for the assessment conclusions, or to improve the clarity of the presentation in the PFDA Toxicological Review.
- Tier 3: *Future Considerations* – Use this category for any advice you have for scientific exploration that might inform future work. While these recommendations are generally outside the immediate scope or needs of the PFDA Toxicological Review, they could inform future reviews or research efforts.

Literature Search Methods and Documentation

1. The Toxicological Review for PFDA describes and applies a systematic review protocol for identifying and screening pertinent studies. The protocol is described in brief detail in Section 1.2.1 (*Literature Searching and Screening*) and in full detail in Appendix A (*Systematic Review Protocol for the PFAS IRIS Assessments*). Please comment on whether the literature search strategy and screening criteria for PFDA are appropriate and clearly described. EPA synthesized the literature published through April 2022 in the external review draft while monitoring newly identified studies[1]. Please identify additional peer-reviewed studies of PFDA that EPA should consider incorporating prior to finalizing the assessment.

Noncancer Hazard Identification

2. 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, including whether the presentation and analysis of study results are clear, appropriate, and effective to allow for scientifically supported syntheses of the findings across sets of studies. Please comment on whether the study confidence conclusions for the PFDA studies are scientifically justified, giving appropriate consideration to important methodological features of the assessed outcomes[2]. Please specify any study confidence conclusions that are not justified and explain any alternative study evaluation decisions. For each, please also comment on whether the weight-of-evidence decisions for hazard identification have been clearly described and scientifically justified. Note that the data from studies considered informative to the assessment are synthesized in the relevant health effect-specific sections and available in HAWC.

    a. For liver effects, the Toxicological Review concludes that the available ***evidence indicates*** PFDA exposure is likely to cause liver effects in humans given sufficient exposure conditions, on the basis of a series of short-term studies in rats and mice demonstrating consistent and coherent effects with a clear biological gradient. The liver findings for PFDA were similar to those for other structurally-related long-chain PFAS and determined to be adverse and relevant to humans.

        i. Additional considerations influenced the liver effects hazard identification decisions. Appendix A (*Systematic Review Protocol for the PFAS IRIS*

[1] Newly identified studies (i.e., studies identified by EPA or the public that meet the PECO criteria or otherwise inform key assessment conclusions, but which were not addressed in the external review draft, for example due to publication after April 2022) will be characterized by EPA and presented to the peer review panel in a document that will be made public and included as an Appendix to the assessment prior to finalization. The 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 based on the panel's interpretation of the expected impacts, provide tiered recommendations to EPA regarding which studies, if any, to incorporate into the assessment before finalizing, as well as the panel's interpretation of the impact of those studies to be incorporated.

[2] The Toxicological Review provides an overview of individual study evaluations within each evidence synthesis section, and the results of those outcome-specific evaluations are made available in the Health Assessment Workplace Collaborative linked here HAWC. Note that a "HAWC FAQ for assessment readers" document, linked here (scroll to the bottom of the page, and the document is available for download under "attachments"), is intended to help the reviewer navigate this on-line resource.

Assessments) outlines the human relevance of hepatic effects in animals that involve PPARα receptors as a key science issue. To the extent supported by the PFDA 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 liver effects. The Toxicological Review ultimately concludes evidence from *in vivo* and *in vitro* studies support a potential role for multiple pathways operant in the induction of hepatic effects from PFDA exposure, although how those pathways interact within a MOA cannot be specifically determined.

b. For immune effects, the Toxicological Review concludes that the available ***evidence indicates*** PFDA exposure is likely to cause immunosuppression in humans given sufficient exposure conditions, primarily on the basis of consistent evidence of reduced antibody responses from two epidemiological studies in children and one study in adults. Although some evidence for coherent immunomodulatory responses consistent with immunosuppression were identified in short-term animal studies, the animal evidence overall is uncertain. The Toxicological Review concludes the immune effects are considered relevant to humans as the judgment is based on studies in humans.

    i. For nearly all epidemiology studies of PFDA, there is potential that exposure to other highly correlated PFAS could contribute to the observed effects. The evidence synthesis for potential PFDA-induced immune effects included evaluation of the potential for confounding across PFAS as well as other sources of confounding and, based on the available data, determined that residual confounding could explain part of the observed effect, but concern was minimal, and it was unlikely to fully explain the associations seen in the literature.

c. For developmental effects, the Toxicological Review concludes that the available ***evidence indicates*** PFDA exposure is likely to cause developmental effects in humans given sufficient exposure conditions, based primarily on consistent findings of dose-dependent decreases in fetal weight in mice gestationally exposed to PFDA supported by some coherent evidence of decreased birth weight from studies of exposed humans in which PFDA was measured during pregnancy, although uncertainties in the available epidemiological evidence reduced the impact of these latter findings. The Toxicological Review concludes the developmental effects in mice are considered relevant to humans given similar findings of fetal growth restriction in mice and humans.

    i. As described in question 3.c and footnote to 3.c, the evidence synthesis for potential PFDA-induced developmental effects considered potential confounding factors and concluded that confounding across PFAS or from other potential sources of bias (e.g., pregnancy hemodynamics in studies where PFDA was measured during or after pregnancy) introduce significant uncertainty. These sources of uncertainty ultimately reduce the strength of the available human evidence to *slight* for an evidence base that might otherwise be interpreted as *moderate*.

d. For male reproductive effects, the Toxicological Review concludes that the available ***evidence indicates*** PFDA exposure is likely to cause male reproductive effects in

humans given sufficient exposure conditions, based on coherent evidence in adult male rats exposed to PFDA for 28 days. Although no direct information on the human relevance of the animal evidence is available, the findings in animals are presumed to be relevant based on the conserved role of androgen-dependent pathways in male productive functions across species.

e. For female reproductive effects, the Toxicological Review concludes that the available ***evidence indicates*** PFDA exposure is likely to cause female reproductive effects in humans given sufficient exposure conditions, based primarily on coherent evidence from a 28-day study in adult female rats. Although human studies are available examining associations between PFDA and female reproductive toxicity (e.g., fecundity), the results were mostly null, possibly due to their low sensitivity for observing effects. The Toxicological Review concludes the female reproductive effects are considered relevant to humans given that mechanisms of female reproduction are similar between rats and humans.

f. For cardiometabolic effects, the Toxicological Review concludes that the available ***evidence suggests*** but is not sufficient to infer that PFDA exposure may have the potential to cause cardiometabolic effects in humans given sufficient exposure conditions, based on associations between PFDA and serum lipids, adiposity, cardiovascular disease, and atherosclerosis in a few epidemiological studies. However, the evidence is largely inconsistent across studies, which adds considerable uncertainty. Evidence in experimental animals was *indeterminate*.

g. For neurodevelopmental effects, the Toxicological Review concludes that the available ***evidence suggests*** but is not sufficient to infer that PFDA exposure may have the potential to cause neurobehavioral effects in humans given sufficient exposure conditions, based on associations between PFDA and outcomes related to attention and behavior in epidemiological studies. However, the evidence is largely inconsistent across studies, which adds considerable uncertainty. No evidence was found in experimental animals to inform this outcome (*indeterminate)*.

h. For endocrine, urinary, and other noncancer effects (i.e., hematological, respiratory, digestive, dermal, musculoskeletal, and nervous systems), the Toxicological Review concludes there is ***inadequate evidence*** to determine whether PFDA exposure has the potential to cause these effects in humans on the basis of the sparsity of available evidence.

Noncancer Toxicity Value Data Selection and Modeling

3. For PFDA, no RfC was derived for inhalation exposures. An RfD is derived based on studies by Budtz-Jorgensen and Grandjean (2018) and Grandjean et al. (2012) showing decreased serum antibody concentrations for both tetanus and diphtheria in children (male and female) at age seven years and PFDA measured at age five years and developmental effects (i.e., reduced birth weight in humans) from the Wikstrom (2020) study. Given the close proximity of the developmental and immune PODs and resulting osRfDs and because these effects are observed during the developmental period, they are selected as co-critical effects supporting the RfD. Are the selection of the studies for the immune (Budtz-Jorgensen and Grandjean, 2018) and

developmental (Wikstrom, 2020) effects for use in deriving the RfD values for PFDA scientifically justified? Are the modeling approaches appropriate?

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 lifetime 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 lifetime RfD, including considerations regarding adversity (or appropriateness in representing an adverse change) and the scientific support for their selection[3]. Please also see charge questions 2b and 2c.

d. EPA used benchmark dose modeling (BMD) (U.S. EPA, 2012) to identify points-of-departure (PODs) for PFDA. Are the BMD modeling approaches, selection and justification of benchmark response levels, and selection of the BMD models used to identify each POD for toxicity value derivation scientifically justified and clearly described?

e. For liver, male reproductive and female reproductive effects, quantitative information was limited to studies in animals exposed to PFDA for 28 days and little to no information was available to evaluate the effects of chronic exposure on these health hazards. Therefore, the derivation of lifetime organ-specific (os) RfD values was not attempted for liver, male reproductive and female reproductive effects. However, these endpoints were considered for the derivation of subchronic osRfDs. Does the provided scientific rationale support this decision? Please explain.

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

4. In addition, for PFDA, an RfD for less-than-lifetime ("subchronic") exposures is derived. No subchronic RfC was derived. The same studies and outcomes were chosen for use in deriving the lifetime and subchronic RfDs. Are the selection of these studies and these effects for the derivation of the subchronic RfD for PFDA scientifically justified?

---

[3] For the decreased antibody responses, Selgrade (Tox Sci 2007;100:328–332) suggests that these specific immunotoxic effects may be broadly indicative of developmental immunosuppression impacting these children's ability to protect against a range of immune hazards.

For developmental effects (i.e., fetal growth restriction), the human evidence was determined to be *slight*, primarily due to potential confounding by hemodynamic changes among studies showing birth weight deficits. For the study (i.e., Wikström, 2020) used to derive the developmental RfD, there is no presumed impact of pregnancy hemodynamics given the early sampling (96% from trimester 1). However, unlike the Wikström (2020) study, some uncertainty remains across many of the available human developmental studies given the predominance of associations that were detected were for studies with later pregnancy sampling.

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 subchronic RfD, including considerations regarding adversity (or appropriateness in representing an adverse change) and the scientific support for their selection.

d. Please comment on the other subchronic osRfDs (i.e., for liver, male reproductive, and female reproductive effects).

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

Noncancer Toxicity Value Pharmacokinetic Extrapolation and Uncertainty Factors

5. Appendix A identifies the potential for pharmacokinetic (PK) differences across species and sexes as a key science issue and lays out a hierarchy for using relevant PK data in extrapolating doses between laboratory animals and humans. Section 3.1 evaluates and synthesizes the PK data in relevant species and sexes, and among human lifestages, up to the derivation of key PK parameters used in the subsequent analysis. However, the evaluation of existing PBPK models and a one-compartment PK model found that these options were not sufficiently reliable for use. Given the information available on potential interspecies differences in PFDA PK, EPA applied a data-derived extrapolation factor (DDEF) to POD values from toxicity studies in laboratory animals to estimate corresponding human equivalent doses (HEDs) in the derivation of the respective RfDs. Similarly, the estimated human clearance (CL) was used to convert internal dose POD (POD_{int}) values from epidemiological analyses to corresponding HEDs.

    a. Is applying the estimated DDEF values for PFDA scientifically justified for conversion of PODs from animal toxicity studies to HEDs? If not, please provide an explanation and detail on a more appropriate approach.

    b. Is application of the human CL to estimate HEDs from POD_{int} values scientifically justified? If not, please provide an explanation and detail on a more appropriate approach

    c. Have the uncertainties in the DDEFs and human CL been adequately evaluated and described?

    d. Do the methods used to derive toxicity values for PFDA appropriately account for uncertainties in evaluating the pharmacokinetic differences between the experimental animal data and humans?

6. 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 PFDA.

    a. Is uncertainty in the derivation of the toxicity values scientifically justified and clearly described? Please describe and provide comments, if needed.

b. For immune effects, a UF_S of 1 and 3 were considered to account for extrapolation from less than lifetime human data; ultimately a UF_S of 1 was selected. A UFs of 10 was not considered as the developmental period is recognized as a susceptible lifestage for these types of effects and therefore exposure during this time window can be considered more relevant than exposure in adulthood (U.S. EPA, 1991). Also important is the fact that, given PFDA's long half-life and the expectation that the children and their mothers have been exposed to elevated levels of PFDA for many years, the observed effects on immune response are considered to be the result of a cumulative, prolonged exposure. Uncertainties with regards to additional susceptible life stages (e.g., old age) are addressed as part of the UF_D. Does the provided scientific rationale support this decision? Please explain.

c. For liver effects, a value of 3 is applied to extrapolate between effects in laboratory animals and in humans during the derivation of the subchronic RfD. Although PPARα dependence might support a value of $UF_A = 1$ if that were the sole pathway leading to these effects, evidence for the involvement of non-PPARα pathways is available in the PFDA database. Thus, uncertainty remains regarding the potential differences in sensitivity across species due to the involvement of both PPARα-dependent and PPARα-independent mechanisms. 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 liver 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.

d. For liver, male reproductive, and female reproductive effects, a default value of 10 is applied for the UF_S when extrapolating from 28-day animal data to a subchronic exposure. Considering the potential for some health effects (prolonged diestrus, sperm measures and increased liver weight) to worsen with increasing duration and the large uncertainty associated with the lack of chemical-specific data to evaluate the effects of subchronic exposure on liver, male reproductive and female reproductive outcomes, the Toxicological Review concludes that application of a UFs of 10 is supported for the purposes of deriving the subchronic RfD from the 28-day toxicity data. Does the provided scientific rationale support this decision? Please explain.

e. Are the provided rationales for the remaining uncertainty factors (UF_L, UF_D, UF_H) scientifically justified and clearly described (to inform the UF_H, the assessment evaluates and considers the available evidence on potential susceptibility to PFDA within different populations or lifestages, including any potential impacts from early life exposure to PFDA on children's health or health later in life, although few studies on susceptibility were available)? If not, please explain.

Carcinogenicity Hazard Identification and Toxicity Value Derivation

7. The Toxicological Review concludes there is *inadequate information to assess carcinogenic potential* for PFDA and that this descriptor applies to oral and inhalation routes of human exposure. Please comment on whether the available human, animal and mechanistic studies,

and the analysis presented in the Toxicological Review are scientifically justified and clearly described.

8. Given the conclusion there was *inadequate information to assess carcinogenic potential* for PFDA, the Toxicological Review does not derive quantitative estimates for cancer effects for oral or inhalation exposures. Is this decision scientifically justified and clearly described?