

# Draft External Peer Review Charge Questions for the Draft IRIS Toxicological Review of Perfluorononanoic Acid [PFNA, CASRN 375-95-1] and Related Salts

June 2024

## INTRODUCTION

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

## REVIEW MATERIALS PROVIDED

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

## CHARGE QUESTIONS

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.
- **Tier 2: *Suggested Revisions*** – 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 PFNA 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 PFNA Toxicological Review, they could inform future reviews or research efforts.

### Literature Search Methods and Documentation

1. The Toxicological Review for PFNA 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:
  - a. Comment on whether the literature search strategy and screening criteria for PFNA

are appropriate and clearly described.

- b. Identify additional peer-reviewed studies of PFNA that EPA should consider incorporating prior to finalizing the assessment.
  - i. EPA fully synthesized the literature published through April 2022 in the external review draft and has been monitoring newly identified studies (i.e., studies identified by EPA or the public that meet the PECO (population, exposure, comparator, and outcome) criteria or otherwise inform key assessment conclusions but that were not addressed in the external review draft—for example, due to publication after April 2022. EPA characterizes these studies in a tabular format in Appendix B.2 (studies identified in the most recent 2023 literature search update or public comments on perfluorodecanoic acid [PFDA] and perfluorohexanesulfonic acid [PFHxS]) and in a second table provided to peer reviewers (studies identified from the PFHxS peer review or PFNA public comment). In both tables, the characterization focuses 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. Studies that were classified as having a possible material impact on the conclusions (e.g., epidemiological studies of hepatic effects and breastfeeding duration; absorption, distribution, metabolism, and excretion/pharmacokinetic [ADME/PK] studies that informed clearance values or otherwise were helpful in the interpretation of the available ADME/PK data) were incorporated into the evidence synthesis. Please review EPA’s characterizations and provide tiered recommendations regarding which additional studies, if any, would have a material impact on the draft’s conclusions and should be incorporated into the assessment before finalizing, as well as your interpretation of the impact of those studies to be incorporated.

## Noncancer Hazard Identification

2. For each health effect considered in the assessment and outlined below (a-h), please comment on the following:
  - Are the available data 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.
  - Are the study confidence conclusions for the PFNA studies scientifically justified, providing appropriate consideration of important methodological features of the assessed outcomes.<sup>1</sup> Please identify any study confidence conclusions that are not justified and explain any alternative study evaluation decisions.
  - Are the weight-of-evidence decisions for hazard identification clearly described and scientifically justified.

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<sup>1</sup>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](#). 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 online resource.

- Are there any studies not considered in the assessment that would be expected to have a material impact on the identified hazards or weight-of-evidence decisions. Please detail the rationale for any recommended inclusions.

Note that the data from studies considered informative to the assessment are synthesized in the relevant health effect-specific sections and are available in the Health Assessment Workspace Collaborative (HAWC).

- a. For developmental effects, the Toxicological Review concludes that the available **evidence demonstrates** that PFNA exposure causes developmental effects in humans given sufficient exposure conditions, based primarily on growth impairments observed in epidemiological studies. It was determined that there was *robust* evidence of decreased birth weight in studies of exposed humans, with support from generally coherent epidemiological findings for other fetal and postnatal growth restriction endpoints (e.g., birth length, postnatal weight and height). In further support, cross-stream coherence is provided by *moderate* animal evidence for PFNA-induced developmental effects in gestationally exposed rodent offspring that included reduced postnatal survival and body weights, and delays in attaining developmental milestones.
  - i. The evidence synthesis and integration for potential PFNA-induced developmental effects included a meta-analysis (see Appendix C.1) conducted by EPA (Wright et al., 2023) that considered the findings of birth weight deficit to be statistically robust across all sampling periods and study confidence levels, indicating there are demonstrated birth weight deficits as PFNA exposure levels increase. Although the epidemiological data were ultimately judged as *robust*, there is residual uncertainty regarding some potential for confounding by other per- and polyfluoroalkyl substances (PFAS) and sample timing; however, these factors were not interpreted by EPA to substantially reduce confidence in the evidence base. Please comment on whether the determination that the epidemiological evidence is *robust* is scientifically justified.
- b. For liver effects, the Toxicological Review concludes that the available **evidence indicates** PFNA exposure is likely to cause liver effects in humans given sufficient exposure conditions, based on consistent and coherent evidence from human, animal, and mechanistic studies. There is *moderate* evidence in human studies that PFNA is associated with liver injury based on increased ALT, AST GGT, and bilirubin. In animals, there was *robust* evidence from a series of short-term studies in rats and mice demonstrating consistent and coherent effects on liver weight, clinical pathology, and histopathology that included hepatocellular necrosis, cholestasis, and triglyceride accumulation. The liver findings for PFNA were similar to those for other structurally related long-chain PFAS and were determined to be adverse.
  - i. The judgment that there is *moderate* evidence in human studies was based primarily on cross-sectional studies in general population adults. For nearly all epidemiological studies of PFNA exposure, there is potential that exposure to other highly correlated PFAS could contribute to the observed effects. The evidence synthesis for potential PFNA-induced hepatic effects included evaluation of the adequacy of studies with exposure and outcome measured concurrently as well as the likelihood of confounding across PFAS. It was concluded that these sources of uncertainty were unlikely to

explain the observed effects. Please comment on whether these conclusions are scientifically justified.

- ii. Additional considerations influenced the liver effects hazard identification decisions. Appendix A (*Systematic Review Protocol for the PFAS IRIS Assessments*) outlines the human relevance of hepatic effects in animals that involve peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ) receptors as a key science issue. For PFNA, there is evidence of both PPAR $\alpha$ -dependent and -independent (e.g., CAR/PXR) pathways contributing to hepatotoxic effects, consistent with the judgment drawn for several other PFAS. The Toxicological Review evaluates the evidence relevant to the potential involvement of PPAR $\alpha$  and non-PPAR $\alpha$  pathways with respect to the reported liver effects. The Toxicological Review ultimately concludes that evidence from in vivo and in vitro studies supports a potential role for multiple pathways operant in the induction of hepatic effects from PFNA exposure and that the effects are potentially relevant to humans. Detailed information is provided in the Mechanistic and Supplemental Information of Section 3.2.4, Hepatic Effects. Please comment on the basis for the judgment of human relevance of the liver effects and whether it is scientifically justified.
- iii. In judging that the animal evidence for hepatic effects is *robust*, the Toxicological Review concludes that the hepatic effects in animals were adverse (vs. adaptive), based in part on consideration of criteria from Hall et al. (2012). The liver enlargement from short-term testing in rats and mice was accompanied by histopathological lesions, including adverse lesions such as necrosis. However, the lack of longer-duration exposures was a substantial source of uncertainty. Therefore, although the linkage between liver hypertrophy and histological evidence of necrotic changes was found to support adversity, the short-term data were further evaluated based on additional criteria set forth in Hall et al. (2012) that considers dose-dependent and biologically significant changes in at least two clinical pathology parameters (see Hall et al., 2012) as confirmatory indicators of hepatocellular damage. The PFNA database was found to meet at least two of the additional criteria set forth by Hall et al. (2012), including large increases in ALT and AST in mice (effects in rats were mild); large increases in bile acids and bilirubin in male rats considered by the National Toxicology Program (NTP) to be indicators of intrahepatic cholestasis; in addition to reductions in blood proteins, increasing triglyceride accumulations and disrupted lipid homeostasis. Please comment on the basis for determination under the criteria set forth in Hall et al. (2012) and others (e.g., U.S. EPA, 2002; EMEA, 2008; Thoolen et al., 2010; Boone et al., 2005) that the hepatotoxic effects observed in rodents are considered adverse.
- c. For male reproductive effects, the Toxicological Review concludes that the available **evidence indicates** PFNA exposure is likely to cause male reproductive effects in humans given sufficient exposure conditions. This conclusion is based primarily on a *high* confidence 28-day oral toxicity study in adult rats that reported a consistent and

coherent pattern of adverse male reproductive effects, with additional support from *medium* confidence, short-term studies in adult rats and prepubertal mice observing effects at similar doses.

- d. For immune effects, the Toxicological Review concludes that the available **evidence suggests**, but is not sufficient to infer, that PFNA exposure has the potential to cause immunosuppression in humans. This conclusion is primarily based on epidemiological studies (see Table 3-22) providing evidence of reduced antibody response with PFNA exposure, and possible evidence for effects on asthma and asthma-related outcomes, but with concerns regarding imprecision and potential residual confounding by other PFAS. The human evidence was considered *slight* and the animal evidence *indeterminate*.
  - i. The evidence for immune effects for PFNA differs from that of other long-chain PFAS (e.g., PFDA and PFHxS), which found stronger evidence of immunosuppression. Please comment specifically on whether the weight-of-evidence decisions for immunosuppression have been clearly described and are scientifically justified.
- e. For thyroid effects, the Toxicological Review concludes that the available **evidence suggests**, but is not sufficient to infer, that PFNA exposure may have the potential to cause effects on the thyroid in humans. This was a complex evidence base to interpret, and the judgment was based primarily on *moderate* animal evidence from a *high* confidence 28-day study in adult rats that showed large, dose-dependent reductions in serum free and total T4 in females and in serum free T4 in males. Although this study provided evidence of effects on T4 homeostasis, there were uncertainties surrounding the reliability of methods used for measuring free T4 in both sexes. There were also body weight losses in males at higher doses that challenged interpretation of the T4 reductions, as well as additional responses in males that were difficult to decipher (i.e., decrease in thyroid-stimulating hormone [TSH], including at doses absent substantial body weight loss). The epidemiological database was *slight* and did not demonstrate coherence with the animal evidence, with the strongest evidence showing positive associations with T4 in children/adolescents, although effect sizes were small. However, there was considerable uncertainty in the human evidence because of inconsistent directions of association and concerns related to study sensitivity.
- f. For cardiometabolic effects, the Toxicological Review concludes that the available **evidence suggests**, but is not sufficient to infer, that PFNA exposure may have the potential to cause cardiometabolic effects in humans. This conclusion was based on studies in humans that showed generally increased serum lipids and some potentially supportive but mixed results for other increased risk factors for cardiovascular disease. However, the evidence has unexplained inconsistencies within and across studies and concerns for imprecision, which add 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 PFNA exposure may have the potential to cause neurobehavioral effects in humans, based on associations between PFNA and outcomes related to attention and behavior in epidemiological studies. However, there is considerable uncertainty in this association, including imprecision in

all the estimates from the three studies evaluating attention-deficit/hyperactivity disorder (ADHD) diagnosis, the most specific outcome, and some unexplained inconsistency. There was no relevant evidence in experimental animals to inform this outcome.

- h. For female reproductive, urinary, adrenal, and other noncancer effects (i.e., hematological, respiratory, digestive, dermal, and musculoskeletal), the Toxicological Review concludes there is *inadequate evidence* to determine whether PFNA exposure has the potential to cause these effects in humans based on the sparsity and/or uncertainties of available evidence.

### Noncancer Toxicity Value Data Selection and Modeling

3. For PFNA, no reference concentration (RfC) was derived for inhalation exposures. A reference dose (RfD) was derived based on a meta-analysis (Wright, 2023, 10699259) examining reduced birth weight in humans from 10 studies with biomarkers collected early in pregnancy. Note that the selected RfD based on developmental effects is further supported by the lifetime oral hepatic organ-specific organ specific (os) RfD based on Kim et al. (2023).
  - a. Are the selected 10 epidemiological studies for developmental effects used in deriving the RfD values (both lifetime and subchronic) for PFNA scientifically justified and clearly described? If so, please provide an explanation. 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.
    - i. As part of the recommendations in “a” above, please comment on whether the effect selected is appropriate for use in deriving the lifetime RfD, including considerations regarding adversity (or appropriateness in representing an adverse change) and the scientific support for its selection. Please also see charge questions 2a and 2a(i).
    - ii. EPA used benchmark dose (BMD) modeling (U.S. EPA, 2012) to identify points of departure (PODs) for PFNA-induced developmental effects. In addition, different meta-analyses were performed to evaluate the relationship between PFNA and mean birth weight differences in humans (Wright, 2023, 10699259). Are the modeling and the meta-analysis for decreased birth weight based on 10 studies with biomarkers collected early in pregnancy appropriate for use in derivation of the RfD? Are the selection and justification of benchmark response levels, selection of the BMD models used to identify each POD for toxicity value derivation, and the POD selected for deriving the candidate value for developmental effects scientifically justified and clearly described?
  - b. For liver effects, an osRfD was derived based on the epidemiological study by Kim et al. (2023) examining biomarkers of liver functions in humans. Are the modeling approaches for the liver effects, selection of cutoff for abnormal, selection and justification of benchmark response levels, selection of the BMD models used to identify each POD for toxicity value derivation, and the POD selected for deriving the candidate value for hepatic effects scientifically justified and clearly described?

- c. For male reproductive effects, quantitative information was limited to studies in animals exposed to PFNA 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 osRfD values was not attempted for male reproductive effects. However, this endpoint was considered for the derivation of a subchronic osRfD (see Question 4). Please comment on whether the provided scientific rationale supports the decision to consider only these effects for the subchronic RfD? Are the selection and justification of benchmark response levels, selection of the BMD models used to identify each POD for toxicity value derivation, and the POD selected for deriving the candidate value for male reproductive effects scientifically justified and clearly described?
- d. For immune and thyroid effects, no reference values were derived given uncertainties in the databases that were judged to indicate *suggestive* evidence of effects (see questions 2d and 2e, respectively). However, while a dose-response assessment is typically not conducted for health effect judgments of “evidence suggests,” when the database includes at least one well-conducted study, quantitative analysis may still be useful for some purposes, such as providing a sense of the magnitude and uncertainty of estimates for health effects of concern, informing responses in potentially susceptible populations, or setting research priorities (U.S. EPA, 2005; U.S. EPA, 2020). For this assessment, immunosuppression in children and reduced serum T4 in adult female rats were advanced for dose-response modeling to facilitate comparisons with other PFNA PODs and to inform uncertainty factor (UF) selection given that effects have been observed for several other PFAS.
- i. For immune effects, the BMD modeling of the selected *medium* confidence epidemiological studies by Grandjean et al. (2012) using untransformed PFNA concentrations by Budtz-Jørgensen et al. (2018) was null and did not show effects of PFNA on antibody concentrations in children aged five and seven years in both the single-PFAS model and in the multi-PFAS model of PFNA controlling for PFOS and PFOA. Thus, BMDs and BMDLs (benchmark dose [lower confidence limits]) for the effects of PFNA on childhood antibody concentrations to diphtheria and tetanus are provided to compare to other PFNA PODs but are not advanced further for RfD derivations. Are the modeling approaches for immune endpoints appropriate and scientifically justified, and is the decision to not advance the modeling for derivation of reference values supported?
  - ii. For thyroid effects, with emphasis on results observed in females (results in males were uncertain), the 28-day study in adult rats indicates reductions in serum T4 that are suggestive of an effect but were found insufficient to infer a hazard. Despite the uncertainties, there is concern for effects given that the T4 reductions in rats from a *high* confidence study were large in magnitude, and there are concerns for downstream effects on neurodevelopment, which is generally a data gap for this chemical. These concerns were further informed by delays in eye opening observed in developmental toxicity studies in two strains of mice, which is a well-characterized effect of T4 insufficiency although thyroid effects were not evaluated in these studies. Given these results and observations

of thyroid effects for other PFAS, PODs were derived for total T4 in adult females for comparative purposes and to inform uncertainty. Is the approach taken for thyroid effects appropriate and scientifically justified, and is the decision to not advance the reductions in serum total T4 in female rats for derivation of a subchronic reference value supported?

- e. Given the lack of studies on inhalation exposure to PFNA, no RfC is derived. Please comment on this decision.
4. In addition, for PFNA, an RfD for less-than-lifetime (“subchronic”) exposures is derived. No subchronic RfC was derived. The same studies and outcome used in deriving the lifetime RfD for developmental effects were chosen for use in deriving the developmental subchronic RfD.
- a. Please comment on whether the selection of these studies and these effects for the derivation of the subchronic RfD for PFNA is scientifically justified.
  - 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 effect selected is appropriate for use in deriving the subchronic RfD, including considerations regarding adversity (or appropriateness in representing an adverse change) and the scientific support for its selection.
  - d. Please comment on the other subchronic osRfDs (i.e., for liver and male reproductive effects).
  - e. Given the lack of studies on inhalation exposure to PFNA, no subchronic RfC is derived. Please comment on this decision.

#### Noncancer Toxicity Value Pharmacokinetic Extrapolation and Uncertainty Factors

5. 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. Appendix E.1 provides a statistical analysis of PK parameters in male and female rats and mice while differences in clearance between male and female humans as a function of lifestage are evaluated in Section 3.1.4 (subsection Excretion in Humans). However, the evaluation of existing physiologically based pharmacokinetic (PBPK) models and a classic PK model described in Appendix E.4 found that these options were not sufficiently reliable for use.

For PODs derived from laboratory animal studies, given the information available on potential interspecies differences in PFNA PK and the results of comparing PK model predictions to bioassay data (E.4.1), EPA concluded that a hybrid approach for extrapolation of POD values in animals to estimate corresponding human equivalent doses (HEDs) was the best option in the derivation of the respective RfDs. Specifically, distinct approaches are proposed for estimation of internal doses in male and female rats from the NTP bioassay vs. estimation for mice examined in developmental studies:

- PFNA serum concentrations measured at the end of the NTP bioassay were algebraically



interpolated to estimate internal dose POD ( $POD_{int}$ ) values for the applied dose PODs identified from that study. The interpolation for male rats assumed a linear increase in serum concentration over the 28-day study, whereas that for female rats assumed the average concentration is close to the end-of-study value.

- For endpoints from mouse developmental studies (including results in nonpregnant females from those studies), the PK model was used to estimate the  $POD_{int}$  values. Specifically, the average serum concentration calculated from the time of mating until the day of observation for each endpoint was used to provide metrics consistent with the dosing regimen (gestation only) and endpoint evaluation at late gestation vs. multiple postnatal times.
- The estimated human clearance ( $CL_H$ ) was used to convert the  $POD_{int}$  values from these animal experiments to  $POD_{HED}$  values. Likewise, for  $POD_{int}$  values that are human serum concentrations identified from epidemiological analyses,  $CL_H$  was used to calculate the corresponding  $POD_{HED}$ .

Please comment on the following:

- a. Are the methods for calculating  $POD_{int}$  values for PFNA for endpoints in rats (adult animals) vs. mice (adult females and pups) 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 the use of maternal clearance (in women of reproductive age) to calculate HED values for gestational and early postnatal endpoints appropriate and scientifically justified? If not, please provide specific alternatives for extrapolation of these endpoints.
  - c. Are the selected values of  $CL_H$ , specifically the 95% lower CI of the geometric mean from Chiu et al. (2022), 0.090 mL/kg-day for males of all ages and females below 12.4 and above 40 years of age, and 0.124 mL/kg-day for women 12.4-40 years of age (Subsection: *Total clearance in humans*), appropriate and scientifically justified?
  - d. Is application of  $CL_H$  to estimate  $POD_{HED}$  values from  $POD_{int}$  values (from animal or epidemiological studies as summarized above) scientifically justified? If not, please provide an explanation and detail on a more appropriate approach.
  - e. Have the uncertainties in the  $POD_{int}$  estimates for animal studies and  $CL_H$  been adequately evaluated and clearly described?
6. EPA has evaluated and applied, where appropriate, uncertainty factors (UFs) to account for interhuman variability ( $UF_H$ ), interspecies differences ( $UF_A$ ), database limitations ( $UF_D$ ), duration ( $UF_S$ ), and LOAEL-to-NOAEL (lowest-observed-adverse-effect level to no-observed-adverse-effect level) extrapolation ( $UF_L$ ) for PFNA. For a–f below, please comment on whether the uncertainty in the derivation of the candidate and selected toxicity values is scientifically justified and clearly described.
- a. Please comment specifically on whether the methods used to derive toxicity values for PFNA appropriately account for uncertainties in pharmacokinetics, including accounting for differences between the experimental animal data and humans.
  - b. For developmental effects, a  $UF_A$  of 1 was used since the value was based on human

data. A  $UF_S$  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). Uncertainties regarding additional susceptible lifestages (e.g., other early-life developmental stages) are addressed as part of the  $UF_D$  of 3. Does the provided scientific rationale support this decision? If not, please explain.

- c. For liver effects and derivation of the lifetime osRfD using human studies, a  $UF_A$  of 1 was applied as the liver effects were reported in epidemiological studies and the value was based on human adult data. Does the provided scientific rationale support this decision? If not, please explain.
- d. For liver effects and derivation of the subchronic osRfD using animal studies, a value of 3 is applied to extrapolate between effects in laboratory animals and in humans during the derivation of the subchronic RfD. Although PPAR $\alpha$  dependence might support a value of  $UF_A = 1$  for hepatotoxicity if that were the sole pathway leading to these effects, evidence for the involvement of non-PPAR $\alpha$  pathways is available in the PFNA database. Thus, uncertainty remains regarding the potential differences in sensitivity across species because of the involvement of both PPAR $\alpha$ -dependent and PPAR $\alpha$ -independent mechanisms. As such, the Toxicological Review concludes the available data are not adequate to determine whether humans are likely to be equally or less sensitive compared to 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 and Derivation of Toxicity Values is clearly documented.
- e. For liver and male reproductive effects, a 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 (decreased reproductive organ weights and sperm measures, liver enlargement and concurrent effects) to worsen with increasing duration and the large uncertainty associated with the lack of existing or reliable chemical-specific data to evaluate the effects of subchronic exposure on liver and male reproductive outcomes, respectively, the Toxicological Review concludes that application of a  $UF_S$  of 10 is supported for the purpose of deriving the subchronic RfD from the 28-day toxicity data. Does the provided scientific rationale support this decision? If not, please explain.
- f. Are the provided rationales for the remaining UF values ( $UF_L$ ,  $UF_D$ ,  $UF_H$ ) scientifically justified and clearly described (to inform the  $UF_H$ , the assessment evaluates and considers the available evidence on potential susceptibility to PFNA within different populations or lifestages, including any potential impacts from early-life exposure to PFNA on lifelong health, 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 PFNA and that this descriptor applies to oral and inhalation routes of human exposure. Please comment on whether the available human, animal, and mechanistic studies, as well as 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 PFNA, the Toxicological Review does not derive quantitative estimates for cancer effects for oral or inhalation exposures. Is this decision scientifically justified and clearly described?