Office of Management and Budget (OMB) and Office of Science and Technology Policy (OSTP) Comments on the Interagency Science Consultation Draft IRIS Assessment of Perfluorohexanoic Acid (PFHxA) and Related Compounds Ammonium and Sodium Perfluorohexanoate (PFHxA-NH_4 and PFHxA-Na) dated August 2021

Date: 9/24/2021

Dear EPA IRIS:

Thank you for the opportunity to provide comments on the draft Toxicological Review of PFHxA. We have comments on sections throughout the text.

Major Comments

1. We are concerned with EPA's use of the word "causes" in some evidence integration sections. None of the endpoints examined by EPA was rated as strong epidemiological evidence; without such evidence it is impossible to claim a causal relationship in humans based only on animal evidence. In one case EPA claims a causal relationship in humans based only on moderate evidence. We see this as an over interpretation of the available data. Claiming causal relationships on inadequate data may result in an overly conservative appreciation of the degree of hazard.

In other evidence integration sections EPA uses the phrase "could cause" or "might cause." These phrases provide the appropriate signaling that there is the possibility of causation. **We recommend that this language be used throughout, rather than definitely claiming causation in the face of inadequate data.**

Edit to charge question 3, page 2

For each, please also comment on whether the weight of evidence decisions for hazard identification, including EPA's conclusions regarding causality in humans, are scientifically justified and clearly described.

2. Inaccurate description of offspring postnatal body weight in both the Iwai and Hoberman, 2014, and the Loveless et al, 2009 study.

Page 73, lines 7-8: "After weaning, body weight deficits persisted in females but not males, however body weight gain during this period was unaffected (Iwai and Hoberman, 2014).

> This statement is incorrect. In Iwai and Hoberman, there were no statistically significant body weight changes at the end of weaning (PND 20) and there were no statistically significant differences in terminal body weights.

Page 73, lines 14-15, "Offspring body weight decrements persisted through PND 21 in 14 the 100 and 500 mg/kg-d dose groups but no treatment-related effects on body weight gains occurred between PND 21–41 (Loveless et al., 2009)."

> The study by Loveless et al did not show statistically significant changes in offspring body weight at the end of weaning or postweaning (PND 20).

Therefore, there is coherence between the studies and in both species (rats and mice) that the effects of PFHxA on body weight were restricted to the early postnatal period (likely when the pups depended exclusively on maternal milk for their energy consumption).

Please correct the statement on lines 7-8, 14-15, and elsewhere throughout the text where EPA states that there was a persistent effect on offspring body weight post weaning. Without statistical significance between control and treatment groups at the postnatal time point, the "decrements" EPA refer to are meaningless. Catch up growth as a result of prenatal or early postnatal growth restriction is a phenomenon seen in both humans and other mammals and explains the results observed in both the Loveless and Iwai/Hoberman studies. It does not mean that the statistically significant effects on body weight at earlier timepoints are not toxicologically significant – indeed, those deficits in growth indicate a growth restrictive effect during the prenatal time period or during lactation, altered maternal behavior, or on pup behavior or ability to nurse. We note that reduced birth weight has been associated with human exposure to other PFAS (e.g. PFOA) in the epidemiological literature.

EPA's assessment would be more authoritative by directing the reader to potential preweaning effects that may indicate an issue with lactation, nursing, or milk quality, rather than claiming a continued deficit in body weight which is clearly not significant and likely represents catch up growth subsequent to preweaning energy restriction.

Edit to charge question 6: Page 4:

For PFHxA the study chosen for use in deriving the RfD is the Loveless et al. (2009) one-generation reproductive toxicity study based on decreased offspring body weight during the pre-weaning time period in rats exposed continuously….

Other Comments:

Page 13, line 4:

are ~~members of the group~~ per- and polyfluoroalkyl substances (PFAS).

Page 13, line 7:

they are ~~manmade~~ anthropogenic compounds that have been used widely

Page 16, "Confidence in the Oral Reference Dose (RfD)"

Please include the number of dams per treatment group so the reader can more readily assess the power/confidence of the study. Dams (litters) are the relevant statistical unit for this endpoint, so please use that metric, not number of pups.

Page 17, line 6:

are ~~members of the group~~ per- and polyfluoroalkyl substances (PFAS).

Page 18, Table 1-1, Row 11.

Comma usage is inconsistent across the row. No preference in format other than consistency

Page 20, section 1.1.4

It may be helpful for EPA to extend further the potential for elevated infant daily exposure via contaminated drinking water. There is a substantial proportion of parents who use tap water to reconstitute powdered formula. Infant intake of formula per kg body weight is high; thus most contaminants or additives found in powdered infant formula (or drinking water used to reconstitute the powder) tend to result in greater exposures in infant than to any other human subpopulation.

Page 26, line 24: The syntheses focus on describing aspects of the evidence that best inform ~~causal interpretations~~ likely associations…

Section 3.1

It may be worth comparing the trends seen with PFHxA (lower internal exposure, faster excretion in female rats and mice than male rats and mice) with other PFAS – I believe that the PFHxA data are consistent with PFAS that have PK data available for analysis. If true, this lends confidence to the PK analysis (and also may help with identifying general trends within PFAS).

Page 34:

"Distribution in Humans," lines 8-16. Wouldn't the Perez 2013 study also be limited in that there is substantial accumulation of PFAS in blood, via binding serum proteins? Therefore, their analysis would not be representative of accumulation/body burden as a whole. This could be helpful to disclose as another shortcoming of the published study.

Page 35, line 28

"Chinese women and their newborn children" – the matched samples were between mother and child, from what I can tell. It would be helpful to clarify that point.

Page 36, lines 14-22

Could part of the difference in elimination kinetics seen for PFAAs be based in OAT-1 binding affinity, or differences in the affinity of PFAAs for other transporters? We see this discussion covered around page 40 of the text, perhaps a cross reference to that section would be helpful.

Page 43, Line 1-2:

…specifically the 3 with the most rapid elimination, reducing the 2 extent to which the conclusion can be assumed to ~~represent~~ **extrapolated to** the study population as a whole

The aim of the referenced study for the above statement was to determine concentrations of PFCAs and FTOH metabolites in blood from ski wax technicians.

Page 66, line 10

"causes" is a pretty strong word given the limited epidemiological evidence. We recommend replacing the word "causes" with something like "may be associated with" to avoid confusion that EPA is proposing a causal pathway in the traditional epidemiological sense.

Table 3-10:
Please include the number of dams per treatment group. This is an extremely important parameter of DART studies and something DART experts look for to inform the study quality rating.

Page 75, "Eye Opening"

Attainment of developmental milestones is correlated with body weight gain during the postnatal period. The significant decreases in pups body weight in the higher dose group may have influenced when the pups exhibited eye opening. This consideration should be mentioned in the text.

Page 76, "evidence integration"

EPA should discuss in the text that none of the effects in the preweaning period persisted postweaning (outside of perinatal mortality) in the Iwai and Hoberman 2014 study. How does this influence EPA's interpretation of the effects, given that this sort of phenomenon can indicate transient effects rather than persistent effects?

Page 77 line 30

Similar to the previous section, "causes" is too strong a word to be used with relatively limited data and no studies in human populations. We recommend changing this word to avoid confusion that the IRIS program is proposing epidemiological causality based on insufficient data.

Page 89 line 20

We reiterate our concern with the use of "causes" – this time in the presence of only moderate confidence in the animal studies. How can this result in a finding of causal relationships?

Page 110, "Sperm Parameters"

It could be helpful for EPA to explicitly state that the male rat spermatogenetic cycle is 6 weeks, which is why the short duration of the 28 day NTP study can provide only limited evidence of effects on sperm parameters. EPA mentions this in evidence integration, but it could be useful to mention it in the specific section on sperm parameters as well.

We agree with EPA that the 10 week exposure prior to mating that was done in the Loveless study should counter any potential effects (likely spurious) observed in the 28 day NTP study since the Loveless study covered an entire spermatogenetic cycle and tested reproductive function (mating indices, etc) and did not observe any significant effect on male reproductive performance.

Page 138

"likely to cause" – we reiterate our concern that this is an overinterpretation of the available data. We recommend that EPA continue to use the phrase "might cause" or "could cause," as they do in other sections.