Comments from the National Institute for Occupational Safety and Health (NIOSH) on the Environmental Protection Agency (EPA) IRIS Toxicological Review of Perfluorohexanoic Acid (PFHxA) and Related Compounds Ammonium and Sodium Perfluorohexanoate (PFHxA-NH4 and PFHxA-Na)
EPA/635/R-20/326a Interagency Science Consultation Draft dated August 2021, (185 pages)
File name: PFHxA_IARdraft_23Aug2021_Clean.pdf

September 20, 2021

Overall comment and recommendation about treatment of epidemiological studies

Very little text addresses the decisions behind declaring epidemiological studies "uninformative," suggesting a general methodological bias in favor of animal studies despite other areas of uncertainty with those studies such as the uncertainty factors and interspecies scaling behind the human equivalent dose (HED). Bias can operate in either direction and multiple sources of bias are generally statistically independent. Important confounding would require other risk factors to be strongly associated with PFHxA exposure. These judgements should be transparent.

Specific comments

3.2.1. Hepatic Effects

Page 3-17 states: "*Two epidemiological studies report on the relationship between PFHxA exposure and liver enzymes. Of these, one (Jiang et al., 2014) was considered critically deficient in the confounding domain and was considered overall uninformative.*"

Comment: No discussion of putative confounders and likely impact is provided.

On the same page: *"The remaining study (Nian et al., 2019) was cross-sectional and was classified as medium confidence (Figure 3-1). Exposure levels for PFHxA, however, were low (detected in 70% of the study population, adult residents of Shenyang, China, median [interquartile range, IQR] = 0.2 [0.01–0.5]), which would reduce the study's ability to detect an association if present.*"

Comment: The problem is low power, not low exposure.

3.2.3. Renal Effects

Page 3-49 states: "*Two were considered uninformative due to critical deficiencies in multiple study evaluation domains (Seo et al., 2018; Zhang et al., 2019).*"

Comment: No discussion of the likely impact of deficiencies or the direction of bias (over- versus underestimation of effects) is provided.

In the same paragraph: "*The remaining study was a cross-sectional study of primarily government employees in China (Wang et al., 2019) and was classified as low confidence primarily due to significant concerns for reverse causality with this population and poor sensitivity because the exposure levels for PFHxA were low. They observed a significant decrease in estimated glomerular filtration rate (eGFR) with higher PFHxA exposure (β: −0.3 change in eGFR as mL/min/1.73 m_2 per 1 ln-unit PFHxA [95% CI: −0.6, −0.01]). No association was observed with chronic kidney disease.*"

Comment: Reverse causality could underestimate toxic effects if 1) kidney impairment terminates employment and exposure, or 2) prevalent kidney disease causes increased elimination and lower serum levels of PFAS. A false positive finding could result from prevalent kidney disease causing decreased elimination and higher serum levels of PFAS. What are the elimination kinetics for PFAS with prevalent kidney disease?

3.2.4. Hematopoietic Effects

Page 3-59 states: "*One human study (Jiang et al., 2014) evaluated blood counts in samples drawn from a population of 141 pregnant women living in Tianjin, China. The study was considered uninformative, however, due to lack of consideration of confounding in the analysis and inadequate reporting of population selection criteria.*"

Comment: No discussion of the likely impact of deficiencies is provided.

3.2.5. Endocrine Effects

Page 3-70 states: "*Two studies examined the association between PFHxA exposure and thyroid hormones in humans (Figure 3-17). One was considered uninformative due to critical deficiencies in confounding and statistical analysis (Seo et al., 2018). The other study was a cross-sectional study of the general population in China and was considered low confidence (Li et al., 2017) due to concerns around participant selection, outcome measures, consideration of confounding, and decreased sensitivity.*"

Comment: No discussion of the likely impact of deficiencies is provided.

In the same paragraph: "*Regarding the latter concern, the exposure levels and range in Li et al. (2017) were low (median [range]: 0.01 [<LOD−1.1]) and 47% of samples were below the LOD, which precluded a meaningful analysis of associations with health outcomes.*"

Comment: Exposures less than the limit of detection (LOD) are among the most precisely known exposure values. An environmental sample below the LOD is known to be very close to 0 (within the LOD of it), a much smaller range than the typical uncertainty of estimated concentrations at much higher levels (standard deviation or geometric standard deviation). There is a power problem only if there are not enough subjects exposed at concentrations much higher than the LOD.

3.2.8. Immune Effects

Page 3-92:
"Asthma

One medium confidence case-control study in Taiwan reported in three publications (Dong et al., 2013; Qin et al., 2017; Zhou et al., 2017) examined the potential association between PFHxA exposure and asthma, asthma symptoms, pulmonary function, and related immune markers (Figure 3-25). The only finding of note was a nonmonotonic positive association between incident asthma (i.e., diagnosis in the previous year) and PFHxA exposure (odds ratio [95% CI] for Q2: 1.2 7 [0.7, 2.1], Q3: 0.9 [0.5, 1.6], Q4: 1.6 [0.9, 2.9]) that was not statistically significant."

Comment: The data are probably not sufficient to rule out a linear response and could be statistically significant if estimated (on a continuous exposure metric).

Appendix A

Where is Table 3-1 in Appendix A (i.e., populations, exposures, comparators, and outcomes (PECO) criteria)? Present or cite the specific PECO criteria, including for epidemiological studies.