Executive Office of the President: Office of Information and Regulatory Affairs
Comments on the Interagency Science Discussion (Step 6)
Draft IRIS Toxicological Review of Perfluorodecanoic Acid (PFDA) and Related Salts
April 2024

Date: 05/21/2024

Thank you for the opportunity to review the draft IRIS Toxicology Review of PFDA. We have some constructive comments and suggestions that we hope will bolster an already well-written evaluation.

General Comments:

- **On page 3-2, first paragraph under 3.1.1 (Absorption), lines 5-9**

As written, this paragraph is very convoluted and difficult to follow. Please determine if is likely there are typos, or part of a sentence was mistakenly deleted.

- **On page 3-2, Lines 25-26**

It states that there is no explanation for why there is higher blood AUC following ingestion when compared to IV exposure. Is it possible that following IV, there is a greater amount of PFDA that doesn't bind to the plasma proteins (due to short-term saturation), and instead is "free" and rapidly uptakes to a long-term storage tissue (i.e. liver) to a greater extent than oral exposure (where uptake to plasma is slower, and a greater proportion can become bound to plasma proteins)?

- **On pages 3-31 to 3-32, Data-derived extrapolation factor**

For rats, internal dose for animal-to-human extrapolation was the measured or estimated serum concentration. For mice, it's an adjusted ratio of clearances.

Can EPA provide more support, or past precedent, in using a clearance ratio as an extrapolation factor for interspecies extrapolation? Did EPA compare what the POD_HEDs for rats would have been, had this same clearance ratio approach been taken? A comparison of the two methods (clearance ratio and steady-state plasma concentration) for just one of the PODs for rats would give an indication of the potential variability or bias in this approach when applying to mice.

- **In Section 5.2.4, Subchronic RfD uncertainty factor (Page 5-33 Table 5-15 and p 5-35 lines 23-32)**

Is the subchronic RfD supposed to only be applied when humans are exposed for short durations? If this is true, it is not clear why a subchronic-to-chronic uncertainty factor (UFs) of 10 is applied, to consider that effects may worsen with increasing duration. Was the concern that the effects observed in rodents (at 28 days) may have worsened if exposure continued to a longer (but still less-than-lifetime) duration? For example, would a better subchronic RfD study in animals have been 90 days or 180 days, rather than 28 days? Or was the concern that effects in

humans may worsen with increasing duration (which may be counter-intuitive for a subchronic RfD)?