Office of Management and Budget (OMB) and Office of Science and Technology Policy (OSTP) Comments on the Interagency Science Consultation Draft IRIS Assessment of Toxicological Review of Hexavalent Chromium

Date: March 25, 2022

Dear EPA IRIS:

Thank you for the opportunity to provide comments on the draft Toxicological Review of Hexavalent Chromium. We appreciate the comprehensive evaluation of such a large dataset. We have comments on sections throughout the text.

Major Comments

1. Science transparency

    a. There is no public copy of the NTP, 1997 study "Reproductive Toxicity of Potassium Dichromate (Hexavalent) (CAS 7778-50-9) Administered in Diet to BALB/c Mice."

        i. EPA should include the study report in the docket for this assessment to make it accessible to the public.

        ii. EPA should indicate in the main text of the Cr(VI) assessment that the study was peer reviewed by experts external to the agency, and that this peer review meets the criteria for use within the IRIS assessment. Importantly, this peer review in combination with the EPA's own review of the study data negates the disclaimer on NTP's website in the context of the IRIS assessment, ("The following abstract presents results of a study conducted by a contract laboratory for the National Toxicology Program. The findings were not evaluated in accordance with the levels of evidence for reproductive or developmental criteria established by NTP in March 2009.").

    b. There is no public copy of the pathology review by Francke and Mog, 2021

        i. EPA should include the pathology report in the docket for this assessment to make it accessible to the public. Additionally, every citation in this assessment should be publicly available.

2. Caveats to use of continuous breeding studies for interpretation of developmental and reproductive toxicity endpoints

There are some major concerns that were identified in the last decade with the continuous breeding paradigm (e.g. NTP, 1997), which is one reason why NTP no longer conducts studies according to this design and these studies are no longer recommended by other regulatory institutions. One major consideration is the continual drain on maternal resources with constant breeding. Dams producing multiple litters may have lower weights at end of pregnancy, litters of smaller weight or a smaller number of pups after the first litter. This is considered due to the continued demand on maternal

resources of subsequent breeding. Page 3-270 of the IRIS assessment mentions that the 1997 NTP study was considered "high confidence" for dam weight at birth and for fetal and postnatal growth on page 3-294. Both of these endpoints could have been affected by the study paradigm.

We agree that effects from this study should not be discounted out of hand due to the continuous breeding design. However, we are interested additional description of how EPA incorporated these study design considerations in their DART analysis.

3. **"Evidence Suggests"** category seems to be overly broad.

    a. Hematology, immunology, and male reproductive toxicity fall into the "evidence suggests" category. All three endpoints were rated as having "slight" epidemiological evidence, despite a wide range of available studies and study quality. There was only one study in humans available for hematologic endpoints and it was rated as uninformative. For the immune endpoints there were several studies in humans that were all rated low confidence, and for the male reproductive endpoints there were a mix of both medium and low confidence epidemiological studies. Such a wide range of interpretation of epidemiological evidence (all ending in the "slight" category) continues to pose challenges to reviewers to follow the reasoning of the final evidence integration.

4. "**Table 3-10. Evidence profile table for effects in the GI tract other than cancer**" – additional table needed

    a. The evidence summary and interpretation of the findings in Table 3-10 describe human evidence that show that oral exposure to Cr(VI) likely causes GI tract toxicity in humans. However, the "inference and summary judgment" section of the table notes that "**the evidence is inadequate to determine whether Cr(VI) inhalation exposure might be capable of causing non cancer GI effects…**". EPA should include a separate table to describe the summary of evidence, including key findings and factors that decrease certainty for inhalation for this conclusion.

5. Page 4-15, lines 5-9 – Please provide clarity on decision points for final RfD derivation. This is broadly discussed in 4.1.4, but it is not clear if there is a hierarchy in the decision-making.

    a. In previous assessments and guidance, EPA put more emphasis on BMD analysis. If there was a possibility of an RfD being based on BMD, this superseded the use of NOAELs/LOAELs. The use of BMDS lessens the uncertainty in a value (i.e., lower UF because no LOAEL UF). However, in this assessment, the lower value was chosen even if a value based on BMDS was available (e.g., GI tract toxicity). Please clarify on EPA's process around this.

Minor Comments:

1. Lines 1-4, page xxv:

"The overall RfC was based on effects …. Ulceration of the nasal septum reported by medium confidence studies. Effects of CrVI on the nasal cavity have been well established…"

If the studies are medium confidence, how have these effects been "well established"? More context is needed here. Based on subsequent sections, it seems likely that EPA is basing the "well established" on mechanistic studies (e.g., page 95, "high concentrations at portal of entry tissues;" "may accumulate in susceptible areas such as airway bifurcation sites"). In this case, it could clarify EPA's reasoning to add "well established in mechanistic studies"

2. Figure 3-16 and Figure 3-18

Are these mechanistic drawings from EPA's integration of the data? Or were these taken from the literature? If it is EPA's mechanistic interpretation, then the peer reviewers should be asked if it accurately captures the evidence.

3. In Table 3-35, does IRIS mean for the "slight evidence from high, medium, and low confidence studies" to be the animal data?

4. Page 3-137, Line 35: "NTP considered the focal hyperplasia to be biologically significant preneoplastic lesions due to the pathological similarities…. (Francke and Mog, 2021).
    - This reviewer thinks the citation should be NTP, 2008, here if it is NTP's conclusion as opposed to the Francke and Mog independent review of the data.

5. Page 3-250, line 3, recommend the following text to clarify statement in context to data: "No effects on the ability to impregnate females (e.g. fertility parameters)"

6. Page 3-250, line 16: "pre- and post implantation mortality" should be replaced with "pre- and post implantation loss" – mortality is typically used in the context of the female rodent in these cases, while loss indicates the conceptus or fetus.

7. Page 3-252, lines 12-21 – please clarify if these studies included gestational exposure or just postnatal exposure.

8. Page 3-254, lines 9-25- please indicate whether there was a change in body weight along with organ absolute weights in the various studies reported in the paragraph.

9. Page 3-125, lines 5-7 – Is this statement regard pharmacokinetics consistent with Section 3.1 which suggests that reduction of Cr(VI) in tissues and red blood cells decreases uptake by other organ systems?

10. Section 4.3.2. - In sections addressing dose-response modeling using the BMD approach, it would be helpful to include some of the key graphs (BMD curves) in the body of the toxicological review so that the reader does not have to search and find the curves provided later in the appendix.

11. Page 4-52, Line 18-20- Did EPA calculate the point estimate of the ED10 and the corresponding upper and lower 95% statistical bounds for internal doses?