Agency for Toxic Substances and Disease Registry - OIA
Comments on the Interagency Science Discussion (Step 6)
Draft IRIS Toxicological Review of Hexavalent Chromium [Cr(VI)]
June 2024

Date: 06/27/2024

All the changes made in response to the external peer review and public comments by EPA in the external review draft IRIS Toxicological Review of Hexavalent Chromium [Cr (VI)] dated June 2024 are satisfactory. Below are comments provided by ATSDR to EPA to assist them in improving or clarifying some of the responses provided in the Supplemental Information document of the Hexavalent Chromium Toxicological Review (ToxReview).

Supplemental Information, Appendix G:

G.1.1. External Peer Reviewer Comments on Systematic Review and Documentation

Page G-5, line 35+: EPA responds to a comment that is not part of the comment appearing on page G-3 lines 31-33 and page G-4 lines 1& 2. The EPA response on recently published human studies is not part of the summary or comment for charge questions 1 & 2; is truncation occurring with the comments? The EPA responses get to be confusing to a Reviewer because EPA is including the SAB information in the response even though this appendix appears to only be including the public external peer review comments. If the G appendix is a response to SAB and public external peer review then suggest the title of the appendix indicate this and the SAB comments get incorporated into the appendix. The lack of the SAB comment in the appendix confuses the Reviewer when suddenly a SAB comment is being addressed that has not been previously stated.

Page G-9: The text in Table G-2 for Behrens et al. 2023 indicates "it was not incorporated into the assessment" is confusing considering further down in the notes column it says "Discussion of this article has been added to the cancer dose-response section (Section 4.4.5.7)." Continuity is needed between these statements since it is the Reviewer's understanding that the assessment is the entire ToxReview which includes the cancer dose-response section.

Page G-9, Table G-2, notes column for Leese et al. (2023) row: How the following statements relate to the prior portion of the note is unclear: " For example, Santonen et al. (2022) and Viegas et al. (2022) are tagged mechanistic. Others are tagged as review articles, or as excluded not pertinent (if they are proof-of concept papers, discussions on future research directions, etc.)." Perhaps adding that Santonen et al. (2022) and Viegas et al. (2022) are HBM4EU studies would clarify this note.

Page G-10, line 12: Is another instance of replying to a SAB comment and the Reviewer does not have the comment. Text reads "The MOA frameworks listed in Appendix A of the SAB Report".

Page G- 11, lines 13-14: It will be helpful to describe the criteria for the analysis of genotoxic biomarkers,. Some of the genotoxic endpoints following Cr (VI) exposure are defined in- NEHA December 2023 Journal of Environmental Health

G.1.2. Public Comments on Systematic Review and Documentation

Page G-13 and throughout: It is unclear why the full text of each Submitters' comment is not included in Appendix G, specifically, the first comment under G.1.2 (page G-13) appears to be a summary statement for multiple Submitters due to use of "several comments" and "one commenter" in the comment itself. Perhaps EPA could add text at the beginning of Appendix G explaining they do not include original Submitter text but summarize SAB and external peer review comments. Then go on to explain why summation is done for these comments.

G.2.2. External Peer Reviewer Comments on Noncancer Gastrointestinal Effects

On page G-22, line 19: In response to a comment about modeling rat GI data, particularly Thompson et al. 2012c, EPA states: "These results are now tabulated alongside other GI endpoints", however the Reviewer looked at Table 4-4 of the ToxReview and did not find the addition of Thompson et al. 2012c in the table. It is unclear where the results were tabulated other than in the response to the comment.

Page G-22, line 27-28: " A lower BMR and hence animal POD would have been used as a starting point for HED and RfD calculation with a more adverse endpoint." Suggest addition of example of what a "more adverse endpoint" would be as have rarely seen a BMR lower than 10% applied in modeling a noncancer endpoint. Would it have to be a frank effect (e.g., significantly decreased longevity/death) to qualify for a lower BMR? At what level would pathological changes elicit a lower BMR?

Page G-22, line 32 to page G-23, lines 1-3: If using the 1% value and 3 for intraspecies uncertainty which produces PODs 80% higher than that with an intraspecies UF of 10; how is that more protective of those individuals that are more sensitive than what can be estimated by modeling? If UF10 POD is 1 then what is stated is that a 1% with 3 intraspecies would be 1.8; was this statement supposed to say "lower than"? Or maybe there is an incorrect name being used in the statement? Perhaps this response could be clarified as the follow-on sentences, lines 3-5 then discuss the HED which is not the POD of the previous sentence making interpretation challenging.

G.2.3. External Peer Reviewer Comments on Noncancer Respiratory (Lower Respiratory Tract) Effects

Page G-25, lines 32-36-the comment is based on the ToxReview submitted to peer review which has since been updated. The updated ToxReview table numbering does not align with the response (i.e., Table 3-7 is now summary results for Lindberg and Hendenstierna in the updated ToxReview). It is suggested that EPA, in the response, indicate the table numbers have changed and to refer to evidence profile table for respiratory effects which is now Table 3-9.

Page G-26, lines 19-21: EPA indicated an illustration of fast and slow cellular uptake was added to Section 3.1.1. The Reviewer could not locate a figure in Section 3.1.1 depicting fast and slow uptake in red blood cells. It would be beneficial to the Submitter and Reviewers if EPA would identify the figure number that was added to the ToxReview for fast and slow cellular uptake.

G.2.4. External Peer Reviewer Comments on Noncancer Respiratory (Nasal Cavity) Effects

Page G-29, lines 6-9: The statement, "However, dose-response data from chromate production facilities [specifically, Gibb et al. (2000a)] may provide a better estimate of Cr(VI)-specific nasal toxicity" which partly addresses the Submitter's comment on justification, but the statement does not appear in the updated ToxReview Section 4.2.4.1 (page 4-40 to 4-41). Recommend adding it to address the Submitter's comment fully in the ToxReview.

G.2.5. External Peer Reviewer Comments on Noncancer Hepatic Effects

Page G-32, lines 11-21: In response to “No effects on serum markers of liver damage were reported following inhalation exposures.” Severity of Cr (VI) exposure based on routes of exposure (oral/inhalation) is now clear (page 436; line 18-21).

Page G-32, lines 22-32: Conclusion and uncertainties regarding animal hepatic histopathology and inflammation are now clearly explained. Furthermore, the text is revised to differentiate the sensitivity between male and female following Cr (VI) exposure in section 3.2.4.4., pages 3-202 through 3-203.

G.2.6. External Peer Reviewer Comments on Noncancer Developmental Hepatic Effects

Page G-34, lines 19-21: The Reviewer requested better explanation of two studies (Remy et al. 2017, Elizaguirre-Garcia et al. 2000) with geographically based exposure measures. EPA’s reply, “Ecologic studies can provide valuable information on unique exposure scenarios. While there is a potential for ecologic fallacy in these studies, they are not automatically excluded”, did not address the comment. Neither did the ToxReview, Section 3.2.9.1 (page 3-308) get revised to reflect the comment.

Page G-35, Table G-4: Please check table is in the text of the ToxReview.

G.2.7. External Peer Reviewer Comments on Noncancer Hematologic Effects

Regarding page G-36, lines 3-5: In the draft hexavalent chromium ToxReview EPA had not developed an organ specific (os)RfD for hematological effects. The updated ToxReview does develop an osRfD of 1 $x10^{-2}$ mg/kg/day on page 4-17. The following notes differences in ATSDR and EPA derivations leading to differences in the health guidance value.

In 2012 ATSDR derived a 5 x 10^{-3} mg/kg/day intermediate-duration oral MRL from the anemia endpoint that occurred in rats (NTP 2008). The BMDL-2 standard deviations for multiple hematological endpoints (hemoglobin, MCV, and MCH), that established a clinically relevant anemia finding, were averaged to 0.52 mg/kg/day and divided by a total UF of 100 (10 for animal to human extrapolation and 10 for human variability). At the time the final Toxicological Profile for Chromium was completed, there were no useful PBPK models.

Unlike ATSDR, EPA used a benchmark response of 1 standard deviation and only for the hemoglobin endpoint from the same study (NTP 2008). The hemoglobin data went through BMD analysis. The BMDL was converted to an internal dose using a rodent PK gastric model (Schlosser and Sasso 2014; Sasso and Schlosser 2015) and a bodyweight correction factor, termed "scaling". A human PBPK model with Monte Carlo analysis that accounted for interindividual variability then estimated the daily mg/kg dose which was 0.126 mg/kg/day. A 3 was used for the intraspecies UF and another 3 for the interspecies UF resulting in a total UF of 10. The final osRfD value for hematological effects is 0.01 ($1x10^{-2}$) mg/kg/day.

G.3.1. External Peer Reviewer Comments on Benchmark Dose Modeling

Page G-40, line 11+: EPA responded to a Tier 1 comment on toxicokinetic principles and low-dose nonlinearities for cancer and noncancer effects in the GI tract. For the assessment of potential low-dose nonlinearities in the GI tract, EPA added pharmacokinetic mechanisms, impact of nonlinearity from an alternate approach for the RfD and an alternate analysis of intestinal tumors using tissue doses under section 3.1.2.2, 4.1.6.7 (not in outline), and Section 4.3.5.1. Furthermore, fundamental concepts and equations governing diffusion and active transport is well explained under section 3.1.2.2. and clarifications regarding the need and justification for $BW^{3/4}$ scaling were also documented throughout the document in both cancer and noncancer sections.

Page G-40, lines 26-35: In this revised draft, analysis of small- intestine tumor data shifted the animal-to-human extrapolation to a lower dose range, resulting in a significant increase in the HED (as humans can reduce Cr (VI) more effectively). After this change, the most sensitive cancer endpoint is identified as the oral tumor response in rats, the OSF is 0.16 mg/kg- day, which is slightly lower than the estimate based on mouse small-intestine tumors presented in the draft assessment 0.3 mg/kg-day.

On page G-40, line 16: EPA indicates Section 4.1.6.7, but the Reviewer can find no such section or subsection in the ToxReview. There is a Section 4.1.5.7 that is titled "potential

low-dose nonlinearities in pharmacokinetics" and this may be the correct section number to indicate for this response. Additionally, the ToxReview page 4-28, line 5 indicates Section 4.1.6.6; yet again, the ToxReview outline and document has no such section.

Page G-41, lines 6-7: EPA indicates Section 4.1.6.7 which does not exist in the ToxReview document. It is likely that Section 4.1.5.7 is the section number wanted in this response. Suggest an update of the section number so that Submitters and Reviewers can find content easily.

G.3.2. Public Comments on Benchmark Dose Modeling

Page G-42, line 1: The wrong section is provided by EPA; Section 4.1.6.6 does not exist. The correct section with the title quoted is Section 4.1.5.6. Further suggest that EPA expand this response, and Appendix D1.1. 1 which is affiliated with this, to indicate (if it is true) that the BMD model results all passed visual fit inspection and residuals were within 2-fold so no models could be removed therefore there remains much uncertainty in BMD modeling results. ATSDR removes any model that is 10 times lower than the lowest non-zero dose from consideration for the practical purpose of still being able to use any adequately fitting remaining models that result from BMD analyses for derivation of an MRL. For the remaining models, ATSDR also visually inspects and determines whether residuals were within 2-fold and removes models that do not meet the criteria.

G.4.1. External Peer Reviewer Comments on Uncertainty Factors

Page G-44, lines 21-28: It is unclear where in the comment the Submitter suggested use of route-to-route extrapolation so the response about it is confusing. If the response on route-to-route extrapolation is kept then suggest the comment be amended to capture that there was a statement about it. Furthermore, it would be helpful to put a summary statement in the response as to the reasons (other than the protocol indicated it) that route-to-route extrapolation using PBPK should not be used. A summary statement based on reasoning in the Protocol would be more helpful to the Submitter and Reviewer then stating route-to-route extrapolation was not done in Sections 3.3.2, 4.1.1, and 4.3.1.

Page G-44, lines 31-34: Please indicate in the response the Section number with the rationale that it is not possible for a 10x higher incidence (page 4-38; Section 4.2.3) of nasal effects.

G.4.2. Public Comments on Uncertainty Factors

Page G-45, lines 5-17: Suggest that EPA expand this response, and Appendix D.1.1. 1 which is affiliated with this, to indicate (if it is true) that the BMD model results all passed visual fit inspection and residuals were within 2-fold so no models could be removed therefore there remains much uncertainty in BMD modeling results. ATSDR removes any model that is 10 times lower than the lowest non-zero dose from consideration for the practical purpose of still being able to use any adequately fitting remaining models that result from

BMD analyses for derivation of an MRL. For the remaining models, ATSDR also visually inspects and determines whether residuals were within 2-fold and removes models that do not meet the criteria.

Page G-45, line 14: Section 4.1.6.6 does not exist in the document. Please update the section number. Additionally suggest that the Charge Question responses for 3a and 4 be adapted similarly to provide EPA with more justification for keeping a model that is 150 times less than the lowest non-zero dose.