Department of Defense Comments on EPA IRIS Toxicological Review of Hexavalent Chromium

Comments submitted by: OASD(EI&E), ESOH Directorate, CMRM Program	Organization: Department of Defense	Date Submitted: 3/24/2022

*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment.

Comment No.	Section	Pages	Comment	Suggested Action, Revision and References (if necessary)	*Category
1	1.2.5 Dose Response Analysis	1-20	The qualitative difference between "evidence indicates" and "evidence demonstrates" is not clear in the document. It would be helpful if this was clearly defined.	Please clearly define the difference between "evidence indicates" and "evidence demonstrates". There is a suggested difference in the document.	S
2	3.2.3 Cancer	3-66	Metanalysis is a useful tool to summarize cancer effect estimates based on weighted averages, even when individual effect sizes are not themselves significant. Nonetheless, it should be noted that the very large uncertainty due to exposure (or lack of accurate exposure measures) remains unaccounted for in such analysis. So the end result is a measure of effect size without incorporation or acknowledgement of the very large uncertainty due to exposure.	Please elaborate more on the assumptions behind metanalysis for CrVI exposure and cancer, especially those involving disparate qualitative and quantitative CrVI exposures. Large uncertainty exists in the definition and assignment of exposure groups in observational studies and the compression of effect sizes into a singular number without acknowledgment of the large uncertainty on the exposure side of the equation is misleading.	S
3	3.2.3.4 Mode-of-action integration of	3-131	While global gene expression data can support MOA, it should be noted that this falls somewhat under the category of descriptive	Please note on page 1-131 or in Appendix C on microarrays that microarray analysis provides descriptive evidence of toxicology while	S

	evidence for carcinogenesis		toxicology and without follow-up phenotypic anchoring as well as follow-up work is still somewhat speculative. In addition, when a few genes in a pathway are "up" it does not necessarily indicate that the pathway is "turned-on" or "activated". The best descriptor might be that such Kegg pathways are found to be statistically significant and provide supporting evidence.	enrichment analysis of pathways due to up or downregulated genes is primarily a statistical rather than a biological judgement, unless phenotypic anchoring is carried out.	
4	4.1.6.6. Uncertainty in dose-response modeling	4-21	"If dropping the two highest doses..." It's unclear what this statement is trying to get across. If dropping the two highest doses is acceptable when performing benchmark dose modeling, the question stands as to why this approach wasn't used in the derivation of the RfD. If such an approach is not acceptable, then it is unclear why this is even mentioned. Ultimately it doesn't appear to make much difference in the RfD value, with the BMD-derived value still being within one order of magnitude of the LOAEL-derived RfD, but some explanation is warranted regarding why the more information-rich BMD method was not used. Additionally, dropping the two highest doses from this study leaves only two doses remaining in addition to the control. It's questionable whether such a small amount of data would be amenable to benchmark dose modeling in the first place. If this is indeed the case, such an explanation would be useful here and in Appendix D.	Please elaborate on this particular sentence. More reasoning as to why this particular path with regards to benchmark dose modeling was not pursued would be useful in understanding the Agency's approach to RfD derivation.	S

5	4.4.5.7 Uncertainty due to potential effect modulation	4-74	The uncertainty introduced here by this fact is somewhat downplayed in the text. It is well established that chromium is present in tobacco smoke. With next to no data regarding smoking habits of the smokers in the cohort, it can reasonably be expected that total chromium exposures among the smokers in the cohort is likely to be underestimated. Though this undoubtedly results in a more health-protective unit risk value, additional context surrounding the uncertain nature of the value would be useful.	Please consider revising this section, or whatever section in which it may be relevant, and adding text to account for the likely case that total exposure estimates to chromium are underestimated in the smoking portion of the cohort.	S
6	4.4.3 Inhalation Unit Risk Derivation	4-66	The life table analysis referenced in this section is not shown. While Appendix E shows the SAS code for life-table analysis, a table showing the calculations for each age internal is not available. The table would show the age intervals and age specific risks, as well as other factors used in calculation, with the overall summary R0 (unexposed risk) and Rx (exposed risk) for lung cancer.	Please consider adding an example excel table to Supplementary Appendix E showing the age intervals as well as other factors which contributed to the age interval calculation of risk, as well as the calculation of the overall summary risks for unexposed (R0) and exposed (Rx). This could then be referenced in section 4.4.3	S
7	4.4.5.1 Uncertainty in Exposure Assessment	4-71	While this assessment is based on exposure to CrVI in occupational settings, where the exposure to CrVI has been established by air monitoring and analysis, air samples are generally analyzed for total chromium, with a worst case assumption that all Cr is in the form of CrVI. So in most cases, unless there is an effort in sampling and analysis to assess CrVI, there will be an overestimation of risk in the	Suggest consideration or mention of the routine use of "total Cr" as a surrogate for CrVI in environmental and occupational analytical methods for Cr (i.e. ICP-MS) which differs from the reported CrVI for the human and animal studies selected for cancer and non-cancer numbers derived in this report.	S

			monitoring process. While this is not necessarily the purview of this assessment, it might be in the interests of "good science" to mention it as an additional bias that would increase the protective nature of the risk numbers. Analyzing for CrVI would require specialized sampling.		
8	4.4.5.6 and 4.4.5.7	4-74 and-4-75	Uncertainty also could include other exposures for this cohort, who were living at a time when smoking was ubiquitous in public places, including restaurants and bars, air pollution was probably worse than it is now. Passive smoking and industrial air pollution could might have resulted in a higher background of lung cancers which would reduce the effect size. It is also surprising to note the low incidence of arteriosclerotic associated deaths (barely significant overall and non-significant for whites in Gibb 2000 Lung Cancer Among Workers in Chromium Chemical Production) compared to lung cancers.	Consider additional discussion for the causes of death in the uncertainty section. Arteriosclerosis, for example, is somewhat low in the Gibb cohort (Table 1, Selected Causes of Death). Discuss further what might increase or decrease uncertainty. Risk factors for (non-asbestos) lung cancer include second-hand smoke, radon, diet, second-arsenic, and diesel exhaust, all of which were probably higher for this cohort compared to today's general population (or worker population).	S
9	Charge Question 1: Toxicological Review	All	This is a detailed, comprehensive document with weight of evidence determinations for hazard, in vitro modelling approaches, dose-response, PBPK modelling, and a number of derivations for oral and inhalation risk values. It would be helpful and beneficial to readers to have an overall map or flowchart of the process from systematic review to derivation of final numbers.	Please consider adding a flowchart in the form of boxes/arrows to show the progress of the risk assessment from systematic review to final derivation of numbers. The figure could even show page or section numbers for each box. This opening figure would give the reader a better initial picture of the detail that lies ahead, as well as showing how the various components of the toxicology and risk assessment tie together in a linear process.	S

10	Charge Question 1: Toxicology Review.	NA	The American Conference for Industrial Hygienists revised the TLV value for CrVI in 2006. The document contains a summary review of studies for CrVI (and other forms of Cr). Please consider it as a resource for the Toxicological Review, although the studies cited by ACGIH have already been included.	Please acknowledge and add the ACGIH TLV supporting paperwork for Cr as a reference to this document. While it is intended for occupational exposures, it includes and assessment of many of the studies used here by EPA. The ACGIH revised the 8-hour TWA TLV for CrVI to 0.0002 mg/m3 (2018).	S
11	Charge Question 5: Uncertainty	Various	The uncertainty factor approach used here is based on default values (or modifications therefore based on toxicokinetics). While this is considered standard, probabilistic or Bayesian approaches should be considered as a part of future assessments.	Consider an acknowledgement of the conservative approach used here in the light of the current availability of Bayesian approaches in both Benchmark Dose Modelling and Uncertainty Analysis.	S