Department of Defense
Comments on the Interagency Science Discussion (Step 6)
Draft IRIS Toxicological Review of Hexavalent Chromium [Cr(VI)]
June 2024

*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.

Section	Pages	Comment	Suggested Action, Revision and References (if necessary)	*Category
XV XXI	Executive Summary ES.4 Table ES-5 and elsewhere throughout the assessment report.	Critique applies to all sections considering linear slope factor and low-dose risk assessments, uncertainty, and extrapolation. The recent literature has persistently criticized the use of traditional approaches for cancer dose-response assessment (cancer slope factor or CSF) and its inherent limitations, which includes the erroneous assumption of linearity in low-dose extrapolation (relevant to environmental exposure assessments) neglecting uncertainties in model selection/choice and inter-species differences, the lack of incorporating human variability, a lack of determining the contributions provided by uncertainty, and the lack of distinguishing between the concept of individual and population cancer risk; this latter issue is very important, and the combined impacts of all these identified limitations may potentially lead to inaccurate and misleading cancer dose-response assessment from oral exposure to hexavalent chromium, or indeed any environmental toxicant of concern. To	USEPA is asked to review and revise use of linear cancer slope factor. USEPA are urged to consider the **probabilistic framework** developed by WHO/IPCS that includes considering variability in susceptibility across the population wherein the risk estimates at the individual and population levels are not the same. Please see: 1. Chiu, W.A., Slob, W., 2015. A unified probabilistic framework for dose-response assessment of human health effects. Environ. Health. Perspect 123 (12), 1241–1254. Https://doi.org/10.1289/ehp.1409385. 2. WHO/IPCS. (2018). Guidance document on evaluating and expressing uncertainty in hazard characterization (2nd ed). WHO. Https://apps.who.int/iris/handle/10665/259858. USEPA is again urged to consider using **a Bayesian Model Averaging (BMA) for dose-response relationship** assessments for hexavalent chromium, particularly where is the concern of heightened uncertainty and blunted confidence at low-dose environmental exposures. There is broad utility and acceptance of BMA and similar approaches across many disciplines, and it is unclear why US EPA is not aligning to itself to an increasingly accepted and improved system of dose-response modeling: 1. Bailer, A.J., Noble, R.B., Wheeler, M.W., 2005. Model uncertainty and risk estimation for experimental studies of quantal responses. Risk. Anal. Int. J. 25 (2), 291–299. 2. Bazrafshan, O., Ehteram, M., Latif, S.D., Huang, Y.F., Teo, F.Y., Ahmed, A.N., El-Shafie, A., 2022. Predicting crop yields using a new robust Bayesian averaging model based on multiple hybrid ANFIS and MLP models. Ain. Shams. Eng. J. 13 (5), 101724.	

		the cancer risk assessment concern, risk estimates for both population and individual risk are of concern. The traditional CSF does not distinguish between POPULATION OR INDIVIDUAL RISK in response to lifetime exposure to that toxicant, and essentially assumes that everyone has the same individual risk, which is therefore equal to the population risk. This limitation was identified by the NRC (2009): National Research Council, 2009. Science and Decisions: Advancing Risk Assessment. https://doi.org/10.17226/12209. In addition, there is another concern regarding uncertainty in low-dose cancer risk assessment. Unlike non-cancer dose-response modeling assessments, uncertainty derivation aligned to animal-to-human extrapolation and inter-species variability is often omitted in cancer dose-response assessment – please see: U.S. EPA, 2002. A Review of the Reference Dose and Reference Concentration Processes. U.S, Washington, DC. EPA Retrieved from https://www.epa.gov/sites/default/files/2014-12/documents/rfd-final.pdf. The U.S. EPA Guidelines for Carcinogen Risk Assessment (2005) does not require quantifying uncertainties beyond	3. Massoud, E., Lee, H., Gibson, P., Loikith, P., Waliser, D., 2020. Bayesian model averaging of climate model projections constrained by precipitation observations over the contiguous United States. J. Hydrometeorol. 21 (10), 2401–2418. 4. Shao, K., Gift, J.S., 2014. Model uncertainty and Bayesian model averaged benchmark dose estimation for continuous data. Risk. Anal. 34 (1), 101–120. Bayesian BMD Analysis (probabilistic approaches) addresses this issue by utilizing the uncertainty and variability distributions that were previously utilized for non-cancer effects only (Chiu, W.A., Axelrad, D.A., Dalaijamts, C., et al., 2018. Beyond the RfD: Broad Application of a Probabilistic Approach to Improve Chemical Dose-Response Assessments for Noncancer Effects. Environ. Health. Perspect 126 (6), 067009. https://doi.org/10.1289/EHP3368. However, Bayesian BMD also allows for uncertainty distributions to be better understood by analyzing the relative contribution of each uncertainty to the composite or overall	

		the parameter uncertainties associated with BMD modeling, which implies that inter- and intra-species extrapolation are considered insignificant in cancer dose–response assessment. This is problematic.	uncertainty. Identifying the magnitude of uncertainties increases the transparency of a probabilistic CSF, enables the quantitative definition of uncertainties, and crucially aids better risk management decisions and higher confidence. USEPA is urged to consider probabilistic frameworks identified by WHO/IPCS (2018) and Chiu and Slob (2015) and Bayesian BMD analyses because they permit distinguishing between individual and population risk. Concerns focus on risk assessment confidence and knowing how protective traditional linear low-dose extrapolation is. Others have argued that traditional low-dose extrapolation is conservative, but **less protective** of **population risk** than the **probabilistic approach.** However, USEPA is urged to consider whether linear extrapolation is over-protective for hexavalent chromium – this is true in situations where the dose-response data are highly non-linear, giving linear extrapolations that overly protective by (potentially)orders of magnitude. USEPA is asked to consider use of Bayesian and Probabilistic Approaches for cancer dose-response assessment of hexavalent chromium. Supporting this suggested recommendation is the issue of appreciating the biggest sources of uncertainty in cancer risk assessment, which is of course, the inherent uncertainty in model choice. Thus, model choice provides the greatest uncertainty in cancer risk estimates. And similarly, of course, for non-cancer effects, in the absence of BMD modeling, the point of departure can be the biggest source of uncertainty. In addition, Chiu et al., (2018) found that, generally speaking, low dose-extrapolation of the shape of the dose–response curve remains the greatest source of uncertainty, which highlights the importance of probabilistic approaches to BMD modeling and parameter estimation. For datasets where the dose-response curve is	

			better characterized, human variability is the greatest uncertainty. Also, it should be emphasized that others have shown that model averaging approaches that incorporate model uncertainty yield more accurate prediction of low dose risks than the traditional approach of linear extrapolation from a POD. Please see the following: 1. Wheeler, M.W., Bailer, A.J., 2007. Properties of model-averaged BMDLs: a study of model averaging in dichotomous response risk estimation. Risk. Anal 27 (3), 659–670. https://doi.org/10.1111/j.1539-6924.2007.00920.x. 2. Wheeler, M.W., Bailer, A.J., 2013. An empirical comparison of low-dose extrapolation from points of departure (PoD) compared to extrapolations based upon methods that account for model uncertainty. Regul. Toxicol. Pharmacol 67 (1), 75–82. It was noted that in Section 4.1.2.1, Page 4-8 (404 of 549), footnote 67: "……. While Bayesian model averaging is an available feature of BMDS 3.2, only frequentist models were run in this assessment……." This was the only reference to Bayesian or Model Averaging approaches in the entire document, where in US EPA admit to restricting their low-dose modeling estimates to frequentist models only. This represents an issue of heightened concern, and blunted confidence in the derived protective risk estimates for Hexavalent Chromium. U.S. EPA are asked to re-consider and use probabilistic model averaging.	
XV XXI	Executive Summary ES.4 Table ES-5 and elsewhere throughout the assessment report.	We appreciate EPA's efforts to address the SAB comments on linearity and low-dose extrapolation, but concern remains on the technical approach. Particularly, considering the diverse opinions within the toxicology community on this issue it would be prudent to consult with the SAB and confirm the EPA's technical approach addresses the SAB's concerns.	Recommend consulting with the SAB and confirm the proposed approach addresses the SAB's concerns.	

Section 4.1.5		The previous RfD (1998) was 3x10-3 mg/kg-day and the new RfD is 0.9x10-4 mg/kg-day. This difference is approximately 1/2 log difference from the 1998 RfD. Within the document the EPA states that the RfD is "an estimate with uncertainty spanning perhaps a magnitude." Based on this assumption, the adoption of the newer RfD is not warranted - in section 4.1.5, after conducting alternative derivations using POD(HED) the organ specific (os) RfDs for GI hyperplasia and liver inflammation were noted to increase compared to the [GI effects] RfD - 11% for GI tract and 29% for liver. These increases were deemed to not be of sufficient difference and these osRfDs were rejected. Yet, the decrease in RfD from 1998 to current, one within the window of uncertainty, the osRfD differences is deemed sufficient. From these data, it appears that an opportunity to lower the RfD was taken even though the preponderance of the evidence suggests the RfD lies closer to the one developed in 1998.	The EPA should consider averaging the RfDs (= 2x10-3 mg/kg-day) and using this composite value rather than selecting the lowest RfD.	
ES.7 ORAL ABSORPTION UNCERTAINTIES AND ASSUMPTIONS APPLIED IN HAZARD 6 IDENTIFICATION AND MODE-OF-ACTION ANALYSES	xxv-xxvii	The authors do not present a credible mechanism of action (MOA) for how CrVI causes any non-cancer adverse effect. It seems logical to presume that CrVI has its non-cancer effects through its corrosive/oxidative activity when in contact with cells, macromolecules (proteins, fats, DNA, etc.) and that the lack of consistent effects within and across studies (i.e., variation) leading to a finding of low confidence in these studies is really	Strongly Recommend - USEPA describe, postulate, or hypothesize a MOA for CrVi that explains how low doses of CrVI (<1 mg.kg-day) are distributed throughout the body are not reduced to CrIII and cause some adverse effect.	S/M

		just the difference in how CrVI is reduced to CrIII in various tissues. In fact, it seems reasonable to assume that all non-cancer CrVI effects have a threshold and that threshold is dependent on the tissues ability to reduce CrVI to CrIII. With this putative MOA likely to dictate tissue-specific toxicity, how does the USEPA justify a low dose extrapolation of CrVI to the POD when statements like those found within ES.7 (pages xxiv to xxvii) suggest that only those oral doses exceeding 1 mg/kg-day are required for whole body CrIV exposure?		
Figure 3-	3-2	It is clear that high transport exists from the oral cavity to the gut and portal vein, but to other tissues is high transport driven by diffusion limitation or facilitated transport by sulfate and/or phosphate anion transporters?	Recommend explaining differences between high and low transport mechanisms.	S
Figures 3-11 and 3-12	3-26, 3-27	The tissue concentration from the lowest dose is not shown (however it was non-detect) and the authors indicate that PBPK analysis did support low-dose non-linearity. However, the assumption is made that the entire oral dose makes it to the intestines and will result in residual CrVI, supporting a linear approach. Given the human is more efficient at reducing CrVI, at what level or difference between the two approaches become insignificant?	Recommend further description of the PBPK analysis of the Kirman et al data.	S
G.3.2.Public Comments of	G-42	The paragraph refers to Section 4.1.6.6, which does not appear to	Please clarify	E

Benchmark Dose Modeling		exist. Likely this is meant to refer to Section 4.1.5.6		
D.1.1.1 Modeling issues related to diffuse epithelial hyperplasia in mice	D-9	It is stated and shown here that omitting the two highest doses when performing BMD modeling on the NTP (2008) data for diffuse epithelial hyperplasia results in an optimal model fit. Afterwards, it is not quite adequately explained why the RfD derived using this approach is ignored in favor of the LOAEL approach beyond simply that the LOAEL-derived RfD is “within the bounds of the alternatives.” It is well-known that reference doses are defined as an estimated value with an inherent uncertainty of around an order of magnitude, and indeed the reference dose from the LOAEL is only about 3 times lower than the reference dose calculated using the quantal-linear model. It appears then that the EPA is electing to go with the LOAEL approach as a conservative assumption. Is there some inherent issue with dropping the highest two doses int this case?	There should be a clearer explanation for using the LOAEL approach over the quantal-linear benchmark dose model (which excludes the highest two doses).	S