OMB Staff Working Comments on EPA's Hexavalent Chromium draft Toxicological Review (page numbers refer to the draft dated April 2010) **and Draft Charge to External Reviewers**

May 10, 2010

General Science Comments:

- We applaud EPA for providing a document that is concise, transparent, and easy to follow. In particular, the presentation of the epidemiology studies was particularly informative and useful. For instance, where there were doubts or concerns about exposures in a particular Provence of China, EPA very clearly presented the impact of keeping this population in the overall analysis and the impact of removing it from consideration. This type of consideration and treatment of uncertain information was extremely informative. If peer reviewers should determine that human data may be more informative than animal data for the cancer quantification, this information should prove helpful. EPA may want to include a charge question regarding the determination not to exclude the more uncertain information, just in case reviewers suggest that EPA use this dataset.

- We are pleased to see that EPA has collaborated with other Federal (ATSDR) and State Agencies (Cal EPA and NJDEP) in producing this document. Consistent with the OMB Guidance on Peer Review (and likely conforming EPA guidance), while EPA typically has employees from State agencies on their peer review panels, to prevent any real or perceived conflicts of interest or concerns regarding independence, EPA should ensure that employees from collaborating agencies do not serve as expert reviewers.

- Page X, mentions that the intent of Section 6 is to characterize overall confidence by addressing the quality of data and related uncertainties and to convey limitations to aid and guide risk assessors. It was not clear to us that Section 6 addressed confidence, uncertainties and limitations. EPA may want to consider adding this information to Section 6, as is typical for most IRIS assessments.

- In discussing the results of the non-neoplastic lesions in the NTP 2007 and 2008 studies, Section 4 does present, in tables, the severity of these lesions. In almost all cases, the severity was minimal to mild and occasionally moderate at the highest doses. As EPA relies on these endpoints for the RfD determination, it would be useful in Sections 4, 5, and 6 to include discussion regarding the severity of the lesions at the point of departure (in most cases the BMDL). This should be an important part of the discussion of the RfD determination and subsequent description of the RfD endpoint. Similarly, discussion of whether or not these lesions are considered to be adverse effects, adaptive changes (as NTP refers to diffuse epithelial hyperplasia) biologically significant changes, biomarkers of another endpoint (eg malignant neoplastic tumors), and/or perhaps precursors to adverse effects would also be helpful. EPA may want to

consider a specific charge question on both these aspects as the reviewers consider the RfD determination.

- EPA has determined that the mutagenic effects of hexavalent chromium are due to its reduction within the cell to trivalent chromium (see section 4.4.2). As the current IRIS summary file for trivalent chromium does not have a significant discussion of its mutagenic effects (except for a sentence which cites Nakamura 1978 which finds that trivalent chromium mutagenicity was low compared to compounds of hexavalent chromium), and classifies the compound as a group D carcinogen, is EPA now revising its views regarding the carcinogenicity of trivalent chromium? If so, does EPA plan to update its IRIS file for trivalent chromium? EPA may want to consider updating the trivalent chromium file first as this may then inform the hexavalent chromium update (rather than doing hexavalent chromium first since EPA is stating that its mutagenicity is due to the trivalent form). Discussion of any plans for updating the trivalent chromium file could be informative to this assessment.

- In discussing mutagenicity, in Section 4.6.2, as EPA is quantifying cancers in B6C3F1 mice, EPA may want to provide some discussion of the *in vivo* genotoxicity results in this strain. It seems a bit inconsistent that the studies presented in Table 4-23 were negative or equivocal (as depicted by +) in this strain, yet EPA is hypothesizing a mutagenic mode of action. More discussion of these data, and perhaps a charge question to expert reviewers, may be helpful.

- In Section 5.1.2, it would be helpful for EPA to more clearly present when dose groups were dropped in the BMD modeling. EPA relies on a POD based on diffuse epithelial hyperplasia (as shown in Table 5-2). In the appendix it becomes clear that in order to make the model fit, EPA dropped the 2 highest dose groups. It would be helpful to explain, in Section 5, the justification for dropping dose groups. A robust statistical approach involves determining what data are relevant and sound before beginning a modeling exercise. Expert reviewers have commented on this issue in previous assessments (see Dr. Dale Hattis and Dr. Bruce Allen comments on 1,1,2,2 Tetrachloroethane available at: http://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=56732). As Dr. Hattis stated, in the context of BMD modeling, "In the light of Dr. Allen's pre-meeting comments I would recommend that EPA at least show earlier results with the highest doses and show the lack of fit that led the analyst to make the dose exclusions that were made. I agree that it is probably not correct to exclude the higher doses for all endpoints in summary fashion without analyzing the specific fits for different endpoints, if that is what was done in this case." A specific charge question about not using the two highest dose groups in the final model may be useful.

- In Section 5.1.2, it may be useful for EPA to describe how the best fitting model was determined, providing specific details on what standards for adequate fit were used. Looking at Appendix B, it is unclear if EPA chose values based on the highest x^2 p-value or based on the lowest AIC value.

- In Table 5.2, for endpoints where a BMD/BMDL was not determined, it may be helpful for EPA to provide the NOAEL/LOAEL values. In some recent assessments, EPA seems to not show a preference for the BMD approach over the NOAEL/LOAEL approach. If this is the case, showing the comparable values for all endpoints may be useful. Similarly, in cases where EPA dropped dose groups, it may be helpful to present the NOAEL/LOAEL value as a comparison.

- In Section 5.3.5, as the ADAF guidance recommends that information specific to the exposure scenarios of concern be used in case-specific evaluations, we recommend that EPA refer readers to the guidance for examples on how to apply the factors, rather than creating a full life time exposure value in this assessment. If the life-time exposure value is retained, EPA should remind risk managers to apply case specific exposure values that are appropriate to the particular risk management scenario under consideration.

Editorial Comments (with Scientific Impacts):

- Page 10, line 7/8, please add a citation for this sentence.

- In discussing studies, EPA often states "results of this study identified.." a NOAEL and/or LOAEL value. It would be useful to clarify if the values have been identified by study authors or EPA. This is particularly important in chapter 5 when EPA refers back to these studies as having identified such values. Understanding where the determination came from would be helpful.

- In section 4.3, it would be very useful to provide a table (perhaps one for 4.3.1 and one for 4.3.2) which presents a summary of the reproductive and developmental summary citing the dose levels at which effects were seen, the statistical significance, and any limitations and uncertainties associated with the study.

- Page 179, line 6/7, it may be helpful to clarify who has made the proposal that is discussed. If there is peer reviewed literature, EPA may want to cite it.

- Page 181, line 10, it is not clear what data and discussion have been provided to support the determination that the mutagenic mode of action is applicable to all tumor types. Section 4.6.3.5 discusses different routes of exposure, but not different tumor types.

- Page 188, EPA may want to clarify that the BMD Technical Guidance is a draft. Citation should also be 2000b.

Comments on the Draft Charge:

(Note: some suggestions for charge questions are provided in comments in the above sections. Many of those comments have not been reiterated here, but should be considered as equally important.)

- Since the development of Agency Information Quality (IQ) guidelines required by statute, many agencies have been using charge language that tracks with the standards of their own IQ guidelines. For example, such language often focuses on whether or not the information in question is accurate, clear, complete, transparently and objectively described, and scientifically justified. We believe it may be useful for EPA to follow a similar approach and incorporate some of the language from your IQ guidelines into the formulation of the charge questions. It may also be helpful for EPA to ask reviewers to comment on both the objectivity of the presentation and the objectivity of the substance regarding the critical decisions.

- Under the general questions, it is unclear why EPA is no longer asking reviewers to comment on future research needs that may decrease uncertainties. Similarly, it is unclear why EPA is no longer taking comment on the characterization and identification of uncertainties.

- In Q A2, as per comments above, EPA may want to describe whether or not this effect is considered adverse and ask the reviewers to comment on the determination.

- It may be helpful to have a specific charge question regarding EPA's review of epidemiology data and whether the human data should be considered for cancer and/or non cancer quantification.

- While EPA asks, in Q B2, if a mutagenic mode of action is supported, it may also be helpful for EPA to have a specific charge question requesting comment on EPA"s mode of action and key events discussion in Section 4.6.3. EPA may also want to specifically take comment on the determination that intracellular reduction to trivalent chromium is necessary for a mutagenic mode of action.