OMB Staff Working Comments on EPA's Toxicological Review of Chloroprene and draft IRIS Summary (dated July 2010)

August 30, 2010

General Science Comments:

- OMB staff focused this review on EPA's response to the external peer review. Where EPA agrees with the comments, we suggest that appropriate conforming changes be made in the main text of the toxicological review and the IRIS summary.

- While we note that the peer review report is already final, it would be helpful if the peer review report provided short summaries of the background of the expert reviewers. It may also be helpful if the peer review reports were to include information discussing any monetary funding (perhaps through a grant, cooperative agreement, sole-source agreement, or competitive contract) that the expert reviewer may have received from EPA's ORD. This would be consistent with generally-accepted disclosure practices for peer reviewers, particularly for reviews with significant public policy implications.

- In general, we find that Appendix A seems to lump together, in paragraph style, all the comments responding to a particular question and then lumps together the response. Clarity would be much improved, and it would be easier to follow EPA's responses, if a response was provided after each specific comment relating to the particular question.

- Page A4, we note that although suggested for inclusion by expert reviewers, EPA has not incorporated results from other epidemiology reviews. While we agree EPA should be providing an independent review, it is not clear to us why EPA is declining to present the findings of other independent reviews.

- Because EPA has been responsive to peer review comments regarding changes needed to the RfC methodology, EPA is now relying on a completely new critical effect, splenic hematopoietic proliferation in female mice, for the RfC. Since the external review in January, has EPA had this new choice of endpoint peer reviewed for its appropriateness? In reading the peer review report, it does not appear that this endpoint was mentioned, discussed or considered as a point of departure. As this is a large scientific change, EPA may want to consider a quick external review of this new choice. (We note that the previous IRIS process included a step where EPA went back to the external reviewers using a quick letter review approach to ensure that the expert reviewers were comfortable with the way their comments were addressed. Such an approach may be appropriate here). EPA could also take comment on its decision to use a 5% BMR for this endpoint, as the rationale for this choice is unclear in the toxicological review. Perhaps expert reviewers can help inform what BMR response levels would represent a biologically significant change before EPA finalizes the assessment based upon this endpoint.

- Throughout the peer review report, Dr. Hattis makes comments relating to the partial saturation of metabolic activation of chloroprene. It is not clear where in Appendix A EPA has addressed these re-occurring concerns.

- In response to an expert reviewer who questions the appropriateness of stating that choloroprene is likely to be carcinogenic by all routes of exposure (in particular through dermal exposures), it is not clear why EPA states that convincing toxicokinetic data is needed. Couldn't EPA also take an alternate science based approach, as suggested by the expert reviewer, which would consider the fact that chloroprene is non-reactive and relatively insoluble in water? It would be helpful if EPA provided a science based response to this expert commenter. We note that EPA cites the NLM hazardous substance database, but when we look closely, there is only one statement about dermal absorption and it is a study from 1968. We suggest EPA review this study to ensure its robustness and cite it directly and provide some details if it indeed provides scientific support for dermal absorption.

- Page A-23, it is unclear why conducting a meta-analysis would be beyond the scope of the choloroprene tox review. Wouldn't this help to inform cancer effects and aren't meta-analyses conducted for other IRIS chemicals?

- In section 4.7.1.1.1, shouldn't this include a discussion of specificity? It is unclear why this has been deleted. Isn't specificity still part of the Hill Criteria for causality?

- Page A-41, it appears as if EPA is adopting the Dourson 1992 recommendation. It would be helpful if EPA clarified all the criteria that are evaluated to determine when a partial or full database uncertainty factor is warranted and when it is not.

- Dr. Ruder commented that the statements of conclusions in Section 6 are less clear than those presented elsewhere. As we also found Section 6 to be not as transparent in presentation as previous IRIS assessments, it is unclear why EPA chose not to address the external reviewers comment. A clearer separation of the non-cancer and cancer discussions would be helpful.