OMB Staff Working Comments on EPA's Hexachloroethane (HCE) draft Toxicological Review (page numbers refer to the redline draft dated March 2010) **and Draft Charge to External Reviewers**

April 2 2010

General Science Comments:

- We appreciate the many clarifying changes EPA made in response to our earlier April 2009 comments and are pleased to see this assessment moving forward. In particular, for the cancer modeling we appreciate that EPA has clarified that no dose groups were excluded from the BMD multistage modeling.

- EPA is treating the 1985 16 week Gorzinski study as a subchronic study. The EPA definition of chronic exposure (see http://www.epa.gov/iris/help_gloss.htm#c) is: "Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans (more than approximately 90 days to 2 years in typically used laboratory animal species)." As the Gorzinski study is 112 days which falls into the definition of chronic as defined by EPA, it is still unclear why EPA is treating this as a subchronic study and is subsequently applying a full 10x default uncertainty factor for subchronic to chronic extrapolation. From the discussion on page 93, it seems that EPA has a new interpretation of what constitutes chronic exposure in a rodent study. It may be helpful for EPA to have a specific charge question that asks the expert reviewers to comment on how the study exposure duration should be treated, in light of the EPA definition.

Specific Science Comments:

- Page 21, Table 4.2, in footnote b, EPA discusses the severity of the atrophy and degeneration of the controls, but states that the severity of nephropathy was not reported for the HCE exposed rats. Has EPA tried to reach out to the study authors to get this information? It seems that it would be of critical importance, in particular since EPA is relying on this study for the RfD determination.

- Page 25, and elsewhere in section 5, states: "EPA considered 57 mg/kg-day the female LOAEL, based on dose-related increases in incidence and severity (minimal to marked) nephropathy." As none of the female rats showed 'marked' nephropathy, as per table 4-4, EPA may want to change the descriptor to "minimal to moderate". Only male rats showed marked nephropathy, but this was not statistically different from controls and no dose response relationship was seen. Similar comment for page 86.

- Page 26 states: "This study demonstrates specificity for HCE-induced renal effects in male rats. The males of both dose groups were administered 8 times less HCE than the corresponding females. However, the male rats demonstrated more severe nephropathy than female rats. Male, but not female rats, also exhibited renal hyperplasia and tumors." EPA may also want to mention here that the more severe nephropathy that was seen was also seen in the male control rats.

- Page 65, in discussing the weight of evidence for carcinogenic potential and application to all routes of exposure, EPA states: "An exception occurs when there is convincing toxicokinetic data that absorption does not occur by other routes." The cancer guidelines (page 2-52) state: "An exception occurs when there is convincing information, e.g., toxicokinetic data that absorption does not occur by another route." EPA may want to clarify that toxicokinetic data is only one example of the types of data that could provide convincing evidence. Is there any other scientific literature available regarding HCE that may be helpful to inform a determination regarding internal dose achieved after exposures other than those through the oral route?

- Page 84, section 4.7.3.3 has a very short discussion of the hypothesized mode of action for the rodent pheochromocytomas. It would be helpful to have discussion here, as is done in 4.7.3.1, regarding the relevance of these tumors for humans. We note that there is a broad array of literature (as well as some EPA/IRIS peer review panel reports) suggesting that these tumors may not be relevant to humans. See, for instance, Critical Reviews in Toxicology, September 2009, Vol. 39, No. 8: Pages 695-718.

- Page 91, from Table 5-2, in the footnotes EPA states: "Gamma, Quantal-linear, and Weibull models had identical AIC, goodness of fit p-values, as well as BMD_{10} and $BMDL_{10}$ values." It seems highly unusual that all these values were identical for multiple models and also identical for BMD values. Perhaps you mean similar rather than identical. The text on page 87 seems to imply that when multiple models had adequate fit, EPA chose the lowest BMDL. It may be helpful to clarify what was done. It may also be useful to have a charge question on EPA's approach to choosing the best fitting model and picking the appropriate POD.

- Section 5.1.5, It is unclear why EPA has shortened the discussion of the previous RfD assessment compared to the current assessment. This discussion is particularly informative as EPA previously relied on the same study but had different uncertainty factors (1000 vs 3000 being applied today). Further elaboration of the differences could be very useful to reviewers.

- Page 111, in table 5-7, it implies that kidney and adrenal gland tumors in rats were determined to be relevant. However from the previous discussion, it does not appear that the pheochromocytomas were modeled (see Table 5-6). It may be helpful to clarify if these tumors were part of the dataset used to derive the final cancer oral slope values. If they were used, it may be helpful to have a specific charge question regarding their relevance to humans. At a minimum, it would be helpful to see the impact of these tumors on the final slope factor values.

- Page 118, as the RfD encompasses the maximum uncertainty, 3000, it is unclear why EPA is not simply calling the overall confidence in the RfD low, rather than low to medium. If the database confidence was truly near medium, then perhaps EPA would not have needed to apply the full 3000 value for the uncertainty. It may be helpful to have a charge question asking about these RfD/RfC confidence descriptors.

<u>Editorial Comments (with Scientific Impacts):</u>

- In section 4.5, EPA has replaced "negative" with "nonpositive" when referring to genotoxicity and other study results (including kidney neoplasia). The rationale for this

change is unclear as we typically refer to studies as being 'negative' or 'positive'. Does EPA mean to imply something different than 'negative' with the term 'nonpositive'? It may be useful to explain what is meant by this.

- Page 27 states: "The addition of GSH to the microsomal fractions also resulted in inhibition of HCE binding to DNA (data not included in report)." Please clarify where this information comes from as the data were not part of the report.

- Page 67 states: "Epidemiologic studies have reported associations between exposures to PERC and TCE and increased risks of several cancers including cancer of the lymphoid system, esophagus, cervix, bladder, kidney, and lung." Please provide citations for this statement. In this paragraph, it may also be helpful for EPA to specifically clarify that all the bioassay studies are referring to impacts in rodents.

- Page 81, in the discussion of metabolites, it may be helpful to clarify if the tumors were seen in humans or rodents.

- Sections 5.1.3 and 5.2.3, EPA may want to clarify that the uncertainty factors applied are default values.

- Page 114, EPA states: "These ratios did not exceed a value of 2.6, indicating that the estimated risk is not influenced by any unusual variability relative to other assessments." It is unclear what this means. What is the significance of "variability relative to other assessments?"

- Page 115, please provide a citation for the statement regarding human heterogenicity compared to animals.

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 in ensuring a rigorous peer review of this highly technical document.)

- 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 will 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.

- In the opening paragraph, it may be useful to discuss when the RfD and cancer assessment were last updated. Letting reviewers know that the RfC derivation is new may also be helpful.

- 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. One would think that this information would be particularly helpful as the uncertainty factors applied to the RfD and RfC are at the 3000 maximum; thus, ensuring that the uncertainties are accurately accounted for would seem to be important to EPA.

- In Q A5, EPA may want to take specific comment on the application of the subchronic to chronic uncertainty factor for the 112 day study. Additionally, it is unclear why EPA has removed the detailed question regarding the application of the database uncertainty factor.

- For the RfC derivation, it is interesting to note that previously, EPA did not have an RfC on IRIS. In this current assessment, EPA is relying on a fairly dated 1979 study (which existed when the previous assessment was conducted) and applying the maximum uncertainty factors (3000). In section B of the charge, EPA may want to consider an explicit charge question to reviewers asking them to comment on the robustness of the database for the quantification of an RfC.

- In Q C1, It is unclear why EPA has deleted the clause “by all routes of exposure” as EPA is making a finding (as per page 65) that HCE is likely to be carcinogenic by all routes of exposure. EPA may want to specifically ask the reviewers to comment on this.