OMB Staff Comments on EPA IRIS draft TCE Toxicological Review and Draft Charge
(drafts dated June 2009)

Thank you for the opportunity to review this draft Toxicological Review and associated charge to the peer reviewers. OMB's comments focus predominantly on the charge to the peer reviewers as it relates specifically to the chapters that provide the derivation of the RfD, the RfC, the cancer risk values, and the major conclusions (chapters 5 and 6).

The Peer Review and Associated Charge

On the planned review itself, we suggest that EPA clarify where this document will be sent for external peer review. Given that the National Academies of Science (NAS) review in 2006 identified key scientific issues for EPA's consideration, we recommend that the EPA request that the NAS re-constitute the previous TCE committee, or a similar committee with many of these same members to conduct the peer review of this response. This group is very familiar with the TCE literature, as well as EPA's most recent previous efforts, and will be able to provide a robust evaluation of EPA's hard work to address the technical scientific issues that were identified in 2006. Due to the nature of the issues, the history of interagency technical discussions on TCE, the substantive comments from interagency scientific experts on the current draft, and the large interest in TCE across stakeholders and other government agencies, an effort to have the most independent review possible will help to ensure confidence in EPA's final product for this contaminant. We would welcome the opportunity to work with EPA and other interested agencies to formulate a very specific and robust charge for the NAS that will ensure a timely scientific review is conducted. We are particularly interested a charge that is more specific about the need for an evaluation of how EPA has integrated all the scientific evidence and when, why, and how defaults were used. Below we provide some suggestions for improving the charge.

- The current version of the charge does not include a clear question about whether or not external reviewers agree with EPAs finding that TCE is "carcinogenic in humans by all routes of exposure". This is a very important question, particularly since the previous National Academies review, which considered all the available epidemiology data as well as experimental and mechanistic studies, supported a conclusion that TCE "can be considered a potential human carcinogen." We recommend that EPA include a charge question that specifically asks for comment on EPA's characterization of TCE as carcinogenic, as well as a question that asks peer reviewers to comment on the scientific justification that TCE is carcinogenic by all routes of exposure. EPA should also clarify what they mean by "all routes of exposure".
- We also recommend that the charge question on the metadata analysis be tailored to how the analysis is used – that is, is the analysis sufficient to support the individual conclusions that are being drawn based on it (e.g., its role in the causality conclusion and as an input to the pbpk modeling).

- The charge questions should specifically ask about EPA's choice to rely on human data for the inhalation unit risk value and the oral unit risk estimate and the charge should explicitly ask for comment on the appropriateness of these choices, based on a consideration of the available scientific evidence.
- A charge questions should be added regarding the extent the Review's conclusion (Chapter 6) convey the amount of uncertainty in the evidence (as discussed in chapters 3, 4, and 5), and the implications for the resulting unit risk estimates.
- In the current charge, EPA has framed the non-cancer questions such that they ask for comment on changes that should be considered that would make a "significant impact" on the quantitative conclusions. We note that what constitutes a 'significant impact' may be different to different reviewer groups. The preferred approach under OMB's Bulletin on Peer Review would be to focus the reviewers on the scientific validity and correctness of EPA's approach, rather than asking if changes would lead to 'significant impact'.
- For the non-cancer evaluation, the charge should explicitly ask, about the methodological approaches used to characterize the point of departure (POD) as well as the specific uncertainty factors applied to each POD that drives the final values.
- For the non cancer evaluation, EPA cites a draft of a Benchmark Dose guidance that is not publicly available. EPA should cite the previous draft document, which is available to the public, and should be transparent regarding the draft nature of this document. Thus instead of relying on this document for default approaches (e.g. dropping high dose group values to improve model fitting to the lower dose groups), EPA should specifically talk about whether the available data, and a review of such data, support the dropping of particular dose group. Such questions should be asked in the charge to the external reviewers as statistical and scientific questions regarding EPA's methodological approach.