OMB Staff Working Comments on EPA's Methanol draft Tox Review (page numbers refer to the redline dated October 2009) **and Draft Charge to External Reviewers**

General Science Comments:

- IPCS/WHO (1997) states in their methanol assessment when evaluating human health risks: "Since formate occurs naturally in humans, it would seem reasonable to assume that normal background levels should not pose any risk to health and consequently that levels of human exposure that do not result in levels of blood formate above background levels could be considered to pose insignificant risk. In this respect, based on information from limited studies in humans, it might be concluded that occupational exposure to current exposure limits (around 260 mg/m3) or single oral exposure to approximately 20 mg/kg body weight would fall into this category." It appears, based on the IPCS findings, that EPA is proposing standards that would be below background levels? Has information on background levels of formate in the blood changed since 1997? It would be helpful to be more clear regarding how the background levels of formate were treated and considered.

- EPA has informed us that the NEDO 1987 study has been peer reviewed. To clarify this point, it would be helpful if the tox review mentioned, likely in a foot note the first time the study is referred to, that the study has been peer reviewed. Providing links to the peer review charge and peer review report which EPA plans to post on their website would also be helpful. It is our understanding that EPA has taken this approach in the past.

- EPA concludes that methanol is "likely to be carcinogenic to humans by all routes of exposure". While EPA discusses the inhalation and oral exposure pathways, the dermal exposure pathway is mentioned only a few times in passing. We presume that EPA's statement implies that methanol is also likely to be carcinogenic by the dermal exposure route. If so, it would be helpful to include more support for this finding.

Specific Science Comments:

- Suggest simply stating the document is "circulated for review by EPA scientists and interagency reviewers from other federal agencies."

- Page 1-27, EPA states that the relevant literature was reviewed through January 2009. Considering that 10 months have passed, EPA may want to consider conducting a quick review to see if there are any new studies which can be considered.

- Page 4-15 states: "Overall, there was no pattern of compound-related clinical signs of toxicity, and the available data did not provide any indication that the control group was not concurrent with the treated group (Cruzan, 2009)." Was there a reason to think that the control group was not concurrent with the treated group? We don't typically see statements like this.

- Page 4-17 states: "However, an infection of the ERF colony with *M. pulmonis* has not been confirmed (Caldwell et al., 2008) and, without confirmation, cannot be used to discount an existing dose-related trend (U.S. EPA, 2005)." Perhaps EPA is referring to 2005a, the Cancer Guidelines. If so, it is unclear where the Cancer Guidelines discuss this issue and make this strong statement. Please clarify.

- Page 4-112, we applaud EPA for providing information from other international bodies regarding toxicity of methanol, and other compounds such as formaldehyde, as relevant in the tox review. Page 4-112 provides the IARC formaldehyde classification. In addition to this information, shouldn't EPA also present the current EPA classification information? IRIS currently lists the compound as a B1, probable human carcinogen.

Comments on the Draft Charge:

- 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. We note that a previous version of the draft charge did have this language, but in the current draft, words which refer to transparency, accuracy and objectivity have been removed.

- The cancer guidelines state (at p2-20): "In analyzing results for uncommon tumors in a treated group that are not statistically significant in comparison with concurrent controls, the analyst may be informed by the experience of historical controls to conclude that the result is in fact unlikely to be due to chance. However, caution should be used in interpreting results." The NEDO data are compared to both concurrent and historical control data. It may be helpful to EPA to ask a charge question to reviewers regarding which approach is preferable for quantification in this particular case.

- In response to earlier interagency comments, EPA has added much helpful discussion regarding the design, quality and interpretation of the ERF and NEDO studies. It may be helpful to have a specific question asking the expert reviewers to comment on the confidence they have in the quantified risk values. EPA could then later use this information as part of the tox review and IRIS summary to communicate the certainty/confidence to the users of the IRIS values.

- EPA has a very specific set of questions regarding the PBPK modeling. We support the use of these types of questions. EPA may want to take comment on a few other aspects of the approach including specific questions on the appropriateness of the model chosen by EPA as well asking about the model calibration approach (using a

first-order rate rather than a saturable model). We appreciate EPAs addition of a charge question to address the concerns regarding background levels of methanol. It would be similarly helpful to have a question regarding background levels of formaldehyde and formate and how they were treated in the PBPK model.

- In the questions related to BMD modeling, it would be helpful to have a specific question taking comment on the final BMDL chosen by EPA (for both the RfD and RfC determinations). Page 5-11 of the tox review states that there was "a range of values from adequately fitting models" and EPA chose the value that "resulted in the lowest BMDL". It may be helpful to ask the peer reviewers to comment on the scientific justification of this choice in light of the model fit. EPA may also want to provide more detail in the tox review regarding how they determined adequate fit.

- Question D1 asks about the EPA cancer classification. We note that the NIH Hazardous Substances Database (HSDB), which is frequently updated, states: "There is no evidence from animal studies to suggest that methanol is a carcinogen" Considering this large difference in findings, it may be helpful if EPA provides a more detailed question for the expert reviewers which asks them to comment on the specific scientific aspects and decisions (eg the specific studies, species, tumor types etc) that led to the proposed EPA classification.

- In questions D3 and D6, it may be helpful to ask reviewers if they think there are any preferred alternative studies which could be relied upon for quantification of cancer effects.

- EPA has provided discussion in section 5.4.3.8 regarding the treatment of background levels and provides further analysis in Appendix E (section E-4). As this is such an important and critical issue, it may be helpful to have a specific charge question which asks the peer reviewers to comment on EPAs approach and the analysis that was conducted.