OMB Staff Working Comments on EPA's Draft Charge Entitled: NCEA Proposed Draft SAB Peer Review Charge for EPA's Response to "Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment (2006)" Published by the National Research Council of the National Academies [dated May 2010]

May 17, 2010

Recognizing the complexity and importance of this document, we thank EPA for providing us with this further opportunity to comment on the charge revisions.

Specific Charge Questions:

Section 2:

- Q2 asks about the epidemiology and animal bioassay study criteria/ considerations. We note that there are differences in the two criteria (epi and animal) in that the epidemiology criteria includes only studies that show "adverse effects" and yet the animal bioassays include studies which show "responses outside the range of normal variability." It may additionally be helpful if EPA defines, and then takes comment on their definition of an adverse effect for the purposes of this document.

- In Q3 EPA may want to take comment on how they included and considered negative studies as well as studies with non-linear low-dose responses (eg the Eskenzi study) in their evaluation.

Section 4:

- In Q1 EPA refers to the endpoints identified as co-critical effects. It would likely be helpful to the reviewers for EPA to explain what is meant by "critical effects". The IRIS glossary defines a critical effect as: "The first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases". Specifically, whether or not the RfD endpoint is an adverse effect or a precursor effect is likely to be an important issue for risk managers. Thus it would be helpful for EPA to specifically characterize each co-critical endpoint (as either adverse or a precursor, or perhaps something else) and ask for comment on the characterizations.

- In Q5, EPA takes comment on the approach of averaging TCDD blood concentrations over the entire dosing period. Page 4-13, line 8, mentions that EPA started by using the initial peak TCDD blood concentration. It may be helpful for EPA to take comment on the use of peak blood concentration. Additionally page 4-14 discusses critical choices made during EPA's model fitting approach, including the exclusion of supralinear fits and saturated models. EPA may also want to ask the expert reviewers to comment on these specific choices.

Section 5:

- Section 5.2.3.4.1.2, EPA spends some time interpreting the cancer guidelines and applying new terminology to define threshold/non-threshold responses as well as nonlinear models and defines them in an individual and population sense. In particular, it may also be helpful for EPA to seek confirmation of interpretations of the "zero slope at zero" model for the population and the impacts that receptor kinetics may have on the ultimate population response. This is a critical point that EPA makes and seems to underlie the EPA response to the NAS, as EPA argues against the NAS conclusion favoring a nonlinear model that would include a threshold response.

- In Q4 and Q5, it might be helpful to ask the reviewers to comment on EPAs choice of using a $BMDL_{01}$ (1% excess risk) as the POD for the development of candidate oral slope factors. Similarly, as NAS

recommended that EPA consider nonlinear models, EPA may want to specifically ask a charge question about their choice of relying on the linear model rather than the nonlinear models. Reviewers could also be asked to comment on EPA's conclusion that linear low dose extrapolation should be preferred.

- In Q10, EPA states that they considered nonlinear approaches and asks the expert reviewers to comment on other approaches that could be developed. It may also be helpful if EPA asks the expert reviewers to provide scientific comments on the two illustrative approaches EPA has provided. It may also be helpful to ask the reviewers to comment on EPA's conclusions regarding the limitations and utility of these approaches.

- EPA may want to consider a charge question that takes comment on EPA's determination to not conduct a meta-analysis.