| Department of Defense Comments on the<br>NCEA Proposed Draft SAB Peer Review Charge Questions for Dioxin | | | | | |
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| Comments submitted by: Robert Boyd | | | Organization: Department of Defense | Date Submitted: 13 April 2010 | |
| *Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment. | | | | | |
| **Comment No.** | **Section** | **Page & Paragraph or Global** | **Comment** | **Suggested Action, Revision and References (if necessary)** | **Category*** |
| 1 | | Global | NCEA's response document discusses modeling both animal data and epidemiological data, even though only the epidemiological data are used for quantitative analyses of toxicity values. As the current charge questions take 6 pages, and will take a considerable amount of time by the review panel, we suggest that the questions involving analyses that are not used directly to develop either cancer potency factors or reference values be eliminated. | If EPA believes that the animal data is important for an understanding of the human health assessment it would be helpful if the those charge questions reflected this significance, otherwise we recommend that EPA consider eliminating the questions relative to animal data to better focus the efforts of the panel | S |
| 2 | | Section 3; 1.c. | With regard to EPA's modification of the published PBPK model, the question is not clear as to whether EPA wants comments on the changes made or whether it is appropriate to modify a published, peer-reviewed model without having the modifications peer reviewed. This question is especially relevant as (1) EPA states that their modifications made little difference in the quantitative results (although they do not present the results of the unmodified model) and (2) the model was developed by EPA laboratory scientists and modelers, i.e., this part of EPA is substituting their judgment for that of EPA scientists who developed the data and the model. | As both questions are relevant, we suggest modifying the question to read: "c. Whether the modifications implemented by EPA to the published Emond et al. model are appropriate for the analysis and whether such modifications should be externally peer reviewed prior to their use in a regulatory analysis such as this." | S |
| 3 | | Section 5. 1 | As presented, the SAB panel members are likely to infer that only one descriptor may be used per chemical. EPA's 2005 cancer guidelines, however, clearly state (and give examples) that several descriptors may be applied to one chemical. In this case, we suggest that the reviewers be given the option (as one of the examples in EPA's cancer guidelines) of different descriptors for different intensities of exposure. | Recommend adding the following sentences after the last sentence: "EPA's cancer guidelines also allow different descriptors for different exposure levels. Do the data and weight of the evidence suggest that very high, acute exposures should be "known human carcinogen" and low, chronic exposures should be "likely to be carcinogenic to humans"? | S/M |

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| 4 | | Section 5.7.b. | EPA did not develop one OSF, but presents several risk-specific slope factors. As this is a procedure that has not been done before, it is important to ask the reviewers if they are relevant for the use and consistent with current guidance and policy. Moreover, as other questions ask whether this procedure follows EPA's cancer guidelines, we suggest that this issue be addressed, as this procedure is not consistent with the guidelines. | Add the following to the end of 7.b: "EPA's 2005 Cancer Guidelines" state that, if the dose-response curve is nonlinear a low doses (even if it is nonlinear with no threshold), the extrapolation below the point of departure should use the reference dose procedure. Does this derivation of dose-dependent OSFs follow the cancer guidelines? Also, is the use of these multiple, risk-specific OSFs, clear,?" | S/M |
| 5 | | Section 5.10 | The NAS panel recommended a threshold dose-response model to characterize dioxin's carcinogenicity. The questions listed in #10 do not directly address this issue. | Recommend adding a question in #10 that asks whether EPA gave appropriate consideration to nonlinear approaches per the NAS recommendation. | S/M |
| 6 | | Section 5. 10 | NCEA's response document models nonlinear extrapolations for the animal models but uses epidemiological data to derive its OSFs. EPA's cancer guidelines indicate that the same point of departure should be used for both the linear and nonlinear extrapolations to low doses. Therefore, the correct comparison should be for those two, and this should be reflected in the charge questions. | Add the clause in bold to the third sentence: "Are there other nonlinear approaches**, including the one specified by EPA's 2005 Cancer Guidelines,** that could be readily developed based on existing data for the assessment of TCDD carcinogenicity?"<br>Also add the following at the end: "EPA's 2005 Cancer Guidelines specify that, when there are sufficient data to indicate that at low doses the dose-response curve is nonlinear, an RfD approach should be used from the point of departure. As NCEA has determined a point of departure for its OSFs, should one or more of these be used for an RfD approach for estimating low-dose cancer risks?" | S/M |