OMB Staff Comments on Acrylamide Final draft Tox Review and Final Draft IRIS Summary

General Comments:
OMB staff focused this review on EPA's responsiveness to the SAB peer review. Where EPA agrees with the comments, we suggest that appropriate conforming changes be made in the main text of the toxicological review and the IRIS summary.

Scientific comments on Appendix A:

- As compared to other Appendix A drafts that we have reviewed, this one was quite confusing. It would be helpful if EPA clearly identified the charge questions and then clearly arrayed the SAB comments by charge question. The typical EPA Appendix A lists the charge question, the reviewer comments and then the agency response. This format would be quite helpful here. It would also be helpful to tie the comment number to the charge question number. In addition it seems that EPA does not discuss some of the charge question responses at all (eg Q 15, 16, 17, 20, and 22). We suggest that the response to comments document clearly discuss the responses to all the questions. It would also be helpful if EPA makes clear in their responses when they have a made a change from the methodology that was reviewed.

- Throughout the SAB report, there is a discussion of data gaps and data needs. However in EPA's response section, the focus seems to be more on content than on the SAB recommendations for the future. It would be helpful if, in Appendix A, EPA simply presented the major SAB research recommendations. We found much of this information to be discussed on pages 18, 19, 22, 23, and 39 of the SAB report, although there are also many recommendations elsewhere. In some of the responses, EPA states that this information has been added to sections 5.1, 5.2, and 5.3 of the tox review. We could not find this presentation. It might be useful to have a section in 5.3 (and similarly in the cancer uncertainty section) that is clearly identified as research recommendations for the future.

- On page 23 of the SAB report, there is a recommendation from a panel member to derive an RfD based on the Burek study. We did not see where this comment was addressed in Appendix A. Has EPA provided this comparison in Chapter 5? This might be useful.

- Similarly on page A-3, in response to the SAB comment, EPA states that an alternate derivation of the RfC using Calleman et al was conducted and is presented in Appendix F. EPA mentions this on page 244 of the tox review; however, EPA does not present what the final value would be if the Calleman data were used. Considering the size of the document, it would be helpful if EPA presented in section 5.2.1 (page 244) what the actual numerical outcome of the analysis was, and then refers readers to Appendix F for the details.

- Page A-5, under comment 8, regarding use of the Kirman model, page 29 of the SAB report states: "The panel believed that the documentation is not adequate to determine whether the recalibrated Kirman model is appropriate for its intended use." We did not see where this important comment was addressed and responded to. In addition the panel was concerned about the ability of the model to "adequately simulate the kinetics of acrylamide and

glycidamide". We recommend that EPA include discussion of these comments as the panel discussed some approaches to presenting the model parameters, and also suggested that EPA review additional reports for data quality and suitability to see if they could be used in refining the model.

- Page A-5, comment 8, EPA mentions that instead of using the PBPK models, EPA has instead conducted a direct extrapolation of the rat dose response POD to a human equivalent administered dose based on equivalent AUC's in the blood. As this approach for deriving the RfD and RfC is new, and important to the final determinations, we would recommend that EPA have this new approach peer reviewed. We note that in the SAB report, page 32, there is some limited discussion of an AUC approach, but it seemed that reviewers were mixed in their conceptual support for it. Has EPA gone back to the SAB reviewers, or perhaps a subset of them, for any type of review? This would be very helpful and we would recommend such an approach. We also recommend that any peer review comments be docketed in the public record.

- Page A-6 in response #11 EPA states that "the default approach however, was grossly in error for the oral slop factor…". It is unclear exactly what EPA is referring to. Is EPA stating that the UF of 3 is wrong? Please clarify.

- Page A-6, comment #12, again this is a case where it would be helpful for EPA to reiterate the full question and have a response that clearly provides context. The question posed to the SAB asked about a table that could be used to conduct MOE analysis and the SAB response recommended such a use and states that the "Agency risk assessments would benefit from the inclusion of transparently-developed, peer-reviewed consensus hazard values" (see SAB page 13). The SAB comments (page 37) clearly support information presented in a manner which "could be used to conduct a variety of MOE analyses for specific endpoints of interest and/or for other than lifetime durations of exposure…" The SAB response also included suggestions for the inclusion not just of specific effects but also of specific risk levels (eg BMDs and BMDLs at 1%, 5%, 10%). These comments should be captured in appendix A and we encourage EPA to present the information as SAB has encouraged. EPA's response is that some of this information is presented in section 5.1 in a figure that is provided. However this presentation does not appear to be consistent with the level of detail and utility that SAB had in mind. We encourage EPA to follow the SAB recommendation to present a comprehensive table (not just a figure) such as the one EPA describes. We also encourage EPA to put this information/table in the IRIS Summary as well.

- Page A-7, question 13, the comment does not seem to mention SAB recommendation for further research nor the recommendation that "impacts on different cell types be determined and that biomonitoring data be utilized in any models developed". It would be useful for the comment and response to address these recommendations. It is also odd that the response section talks about what the panel said (eg "the panel agreed with the recommendation…"). Shouldn't this be in the comment section framed as a comment rather than a response?

- Page A-9, comment 17, it is unclear what charge question this comment and response is related to. As per previous comments, more clarity would be helpful.

- The SAB report, in response to charge Q 21 (page 49), discusses comments regarding details on tumor presentation and analysis. For instance, SAB recommends that EPA recheck some test results and further discuss clitoral gland findings. It is not clear whether or not EPA has followed these SAB recommendations. We suggest that Appendix A be clarified and include discussion of these SAB comments and how EPA has responded to them.

Comments on the Tox Review:

- Page 2, EPA has removed citations to acrylamide risk estimates derived by other organizations and EPA has removed references to the NLM/ TOXNET website. We recommend that EPA leave this information in the tox review, as it is provides useful comparative information for risk assessors and risk managers for many different scenarios. We also note that in other peer review reports, peer reviewers have commented on the usefulness of this information. We disagree with EPA's concern that EPA does not want to be responsible for providing such information, which in some cases could be outdated. We believe the NIH databases are well cited and it will be clear to readers when information is updated, as NIH provides an update status section and also in many of the documents provides clear dates regarding age of information and timing of updates.

- As per comments above, the analysis of the RfD and RfC, including derivation of the human equivalent concentration (HEC) using an area under the curve (AUC) approach, appears to be completely new since the peer review. As this approach was not presented to peer reviewers in the previous round as an alternative option, we would like to ensure that it is appropriately reviewed. No information has been provided by EPA. As per comments above, if this has not been reviewed, we encourage EPA to seek a quick peer review on this new methodology.

Comments on the IRIS Summary:

- Please see comment above regarding presenting a comprehensive table which could be used to conduct MOE analyses. As SAB recommended and endorsed such a table, it would be very helpful to have it in the IRIS summary as well as the tox review.

- In 2006, OMB staff had conversations with NCEA staff regarding presentation of the Age Specific Adjustment Factors (ADAF) information in the IRIS summaries. EPA stated that they were undertaking a project to redesign the IRIS summary to make it more useful for users. This assessment will present ADAF information, and should also address the SAB recommendation to provide information for MOE analyses; however, it is not clear to us that EPA has made any changes to the design of the IRIS summary. For this particular assessment, has EPA had any review of the presentation of the ADAF information in section II? We encourage EPA to expeditiously move forward with their project to redesign the IRIS summary. Focus groups and discussion with many of the IRIS users will be critical to ensuring that this information is presented in a most useable manner.

- The IRIS summary (and the tox review) should have a section which provides a link to, and information on, where readers can go to see the public docket (including interagency and public comments) related to the assessment.