Office of Management and Budget (OMB) and Office of Science and Technology Policy (OSTP) Comments on the Interagency Science Discussion Draft IRIS assessment of Biphenyl (dated April 2013)

Date: May	23,	2013
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Dear EPA,

Below are the comments from the EOP on the IRIS Biphenyl Tox Review.

- 1) Were public comments received? Will these be available, and if so, where will they be posted?
- 2) The external peer reviewers' comments were summarized in Appendix A of the toxicological review. Will the original (non-summarized, non-paraphrased) comments be made publicly available? If so, where?
- 3) The human equivalent doses (HED) appears to be calculated using different methods for the oral RfD and the cancer slope factor. On page 84 of the tox review, the HED for the oral RfD is calculated using the EPA 2011 guidance document. However, on page 92 of the tox review (for BMD modeling of female mouse liver tumors), the HED was calculated using a scaling factor using the EPA 1992 guidance document. Can you please confirm that the correct calculations were used?
- 4) In the external peer reviewers comments (document Final Post-Meeting Comment Report), Dr. Frederick Miller states: "However, the Agency has not adequately defended their choice of using liver tumors in female mice to derive the oral slope factor; there is no discussion of the major discrepancy in the selected study between the diametrically opposite results seen in male mice versus female mice." (p. 9) On page 38, Dr. Miller states: "While there is not a different cancer endpoint that one could recommend, the Agency has not adequately defended their choice in that there is no discussion in Section 5.4.3 on the major discrepancy in the selected study between the results seen in male mice versus female mice. The discussion on pages 35 and 36 of this discrepancy is not brought forward in the consideration of the reasonableness of calculating an oral slope factor. There is a clear decrease in tumor incidence with increasing dose in the male mice and just the opposite situation in female mice. So the Agency just picked the female data."

EOP's comment is that this point (of the decrease in male mouse liver tumors) should be clearly stated as an uncertainty. Clearly the other external peer reviewers agreed with EPA's selection of the female mouse liver tumor endpoint and the derivation of a cancer slope factor, but there should be an acknowledgement in the tox review of the uncertainty of this endpoint. EPA should

be responsive to Dr. Miller's comments (EPA's response summarized in Table 5-11 on page 96 is not sufficient).

- 5) The BMDL for the oral RfD is derived using a BMR of 10% extra risk. Can you comment on why this is different from the recent methanol RfD that was derived using a BMR of 5%? Can you briefly describe the rationale for using different BMRs?
- 6) In the IRIS Summary for Biphenyl on page 9, the confidence in the Database is rated "high" in the table, but is rated "medium to high" in the text following the table.
- 7) In the IRIS Summary for Biphenyl (page 13-15), there is extensive discussion about the selection of "suggestive evidence of carcinogenic potential." Missing from this discussion is the gender difference for liver tumors in the mouse. This should be transparently conveyed that there was not gender concordance. (see Dr. Miller's comments).

Thank you for allowing EOP reviewers to comment on the IRIS Biphenyl Tox Review.