EPA's Response to Selected Major Interagency Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of Biphenyl

September 30, 2011

Purpose:

The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (Step 3 and 6) where White House offices and other federal agencies can comment on draft assessments. The following are EPA's responses to selected major interagency review comments received during the Interagency Science Consultation step (Step 3) for the draft IRIS Toxicological Review of Biphenyl (dated July 2011). All interagency comments provided were taken into consideration in revising the draft assessment prior to posting for public comment and external peer review. The complete set of all interagency comments is attached as an appendix to this document.

For a complete description of the IRIS process, including Interagency Science Consultation, visit the IRIS website at www.epa.gov/iris.

July 2011 Interagency Science Consultation Draft IRIS Assessment—Selected Major Comments and Responses:

Topic #1: Cancer Weight of Evidence for Biphenyl - *ATSDR commented that the peer reviewed literature provides very limited evidence of biphenyl carcinogenicity, as indicated by lack of genotoxicity, bladder tumors in male rats only following high doses and calculi formation, liver tumors in high dose female mice only (a species known for liver cancer susceptibility), and lack of promoting activity.*

> **EPA Response:** As per EPA's *Guidelines for Carcinogen Risk Assessment ("Cancer Guidelines")* (U.S. EPA, 2005a), the cancer descriptor of "suggestive evidence of carcinogenic potential," is appropriate when "a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion. This descriptor covers a spectrum of evidence associated with varying levels of concern for carcinogenicity, ranging from a positive cancer result in the only study on an agent to a single positive cancer result in an extensive database that includes negative studies in other species."

The carcinogenic database for biphenyl includes evidence from chronic 2-year cancer bioassays showing an increase in the incidence of liver tumors (hepatocellular adenomas and carcinomas) in female BDF_1 mice (Umeda et al., 2005) and urinary bladder tumors (transitional cell papillomas and carcinomas) in male F344 rats (Umeda et al., 2002). The induction of urinary bladder tumors in F344 male rats by dietary biphenyl exposure is a high-dose phenomenon closely related to the formation of urinary bladder calculi. Therefore, EPA concluded that at environmentally relevant exposure levels the database provides "suggestive evidence of carcinogenic potential" based on the findings of liver tumors. The limitations identified by ATSDR are addressed below.

- Genotoxicity is a consideration in evaluating the mode of carcinogenic action for a chemical, but not in the determination of carcinogenic potential. As discussed in Section 4.5.2 (Genotoxicity) of the draft Toxicological Review of Biphenyl, the overall weight of evidence for biphenyl genotoxicity from short-term tests is negative or equivocal (also see Table B-2 in the Toxicological Review). Biphenyl did not induce mutations in a variety of bacterial test systems (in the absence or presence of exogenous metabolic activation), but in vitro assays of genotoxicity in mammalian test systems yielded a mix of negative and positive results, with positive results mostly in the presence of metabolic activation.

- With regard to the observation of bladder tumors in male mice at high doses, EPA agrees that induction of bladder tumors in male rats was related to calculus formation, and that this is a high-dose phenomenon. No risk of bladder tumors is expected at environmental exposures. This was taken into consideration when assigning the cancer descriptor of "suggestive."

- The finding of liver tumors in one sex of mice (females) was also taken into consideration in assigning the cancer descriptor of "suggestive." It is not uncommon to find an increased incidence of tumors in only one sex in a study; the absence of an increased incidence of liver tumors in male mice in the Umeda et al. (2005) bioassay does not negate the positive finding in female mice. EPA also recognized that some strains of mice have a high spontaneous incidence of liver tumors that can complicate interpretation of treatment-related tumors. In the case of BDF_1 mice used in the Umeda et al. (2005) bioassay, the spontaneous incidence of liver tumors in concurrent control mice was about 6%. Compared to other strains of mouse, this background liver tumor incidence is not considered particularly high. EPA also obtained historical control data from the study

investigator (Dr. Umeda). The incidence of liver tumors (combined incidence of hepatocellular adenoma and/or carcinoma) in historical control female mice was 7.1% (similar to the incidence in the concurrent control), with a range of 2-14%. The liver tumor incidences in all three groups of female mice treated with biphenyl exceeded both the concurrent control and the historical control range. Therefore, susceptibility to liver tumors in female mice did not appear to be an issue in the biphenyl bioassay in the mouse.

- In response to ATSDR's comment that biphenyl did not promote kidney cancer in rats that received an initiator, it is important to note that not all carcinogens are cancer promoters.

Issue #2: Selection of Tumor Incidence as the Point of Departure (POD) - *ATSDR commented that the selection of an extra risk of 10% tumor incidence as a point of departure (POD) may be high for cancer effects. ATSDR suggested that an extra risk of 5% cancer incidence may be more acceptable.*

EPA Response: The tumor incidence at the point of departure (POD) does not reflect a level of acceptable risk; it is just a starting point for extrapolating to risks at lower exposures, through the use of a slope factor calculated from the POD on the dose-response curve to the origin. In identifying the POD, EPA followed guidance provided in EPA's Draft *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000) and EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005). As noted in the Benchmark Dose Technical Guidance, a 10% response is at or near the limit of sensitivity in most cancer bioassays and in some noncancer bioassays as well. This was the case for the biphenyl cancer bioassay in the BDF_1 mouse (Umeda et al., 2005) used to derive the cancer slope factor. An excess risk of 10% has been the BMR used most often for tumor data. The Toxicological Review was revised to clarify the use of a BMR of 10% extra risk to derive the biphenyl cancer slope factor.

Appendix
Comments on the Interagency Science Consultation Draft
IRIS Toxicological Review of Biphenyl

Agency for Toxic Substances and Disease Registry (ATSDR) Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of Biphenyl (dated July 2011)

Date: August 3, 2011

From: Agency for Toxic Substances and Disease Registry

Subject: Comments on EPA's Toxicological Review of Biphenyl

To: Environmental Protection Agency

We appreciate the opportunity to review EPA's Toxicological Review of Biphenyl. Overall, we found the draft IRIS Toxicological Review and fact sheet well-written and comprehensive in outlining the key studies.

General Comments:

1. Page 8: section 3.2 Distribution

The EPA document indicates that only 0.1% of the dose was detected in animal genital tract and less than 1% of the administered dose remained in tissues after 96 hrs of exposure. Since EPA's RfD was derived from the development study, can the author(s) of the documents add a discussion of the maternal blood (cord) levels and internal dose that cause fetal skeletal anomalies?

2. Page 10: section 3.3.1.2 Results from in vitro studies

The Benford et al. (1981) study revealed that levels of 2-hydroxylase metabolite in rats were 35 times higher than in humans. Large amounts of 2-hydroxbiphenyl was associated with urinary bladder tumor formation in rats. Subsequently, the differences in metabolites concentrations suggest that humans may be less likely to develop bladder cancer than the male rats. This should be added to the discussion in the cancer section.

3. Page 16: Possible Relationships between Metabolites and Toxic Effects.

The last sentence discusses gender differences in urine potassium concentrations, pH and calculi formation. In human urine, a 24 hr collection range is between 25-125 mEq/d depending on diet, while human ideal pH range is between 6-7 and can vary significantly. The question is how much resemblance is there between human and rat's urine by gender? Please clarify.

4. Carcinogenicity of Biphenyl

The reviewed literature provides very limited evidence of biphenyl carcinogenicity because:

a. Biphenyl is not genotoxic.
b. Renal tumor formation was found only in male rats and not in any other species. The tumor formation was observed in very high doses and followed calculi formation. Urinary bladder calculi induce continuous irritation and regeneration of urinary epithelium which may lead to cancer formation.
c. Even though male mice received a higher average dose than female mice, no cancer was detected in male mice.
d. Some mice strains, particularly females, such as C57BR/cdJ, are known for extreme liver cancer susceptibility.
e. Liver tumors occurred in very high doses.
f. Biphenyl did not promote kidney cancer in rats which received N-ethyl-N-hydroxyethylnitrosamine as initiator.

Due to the above, the weight of evidence for carcinogenicity determination is limited.

Page 45: Table 4-13 Summary of reproductive data in albino rats exposed to dietary biphenyl.

Please add to the table footnotes that 0.1% = 105 mg/kg and 0.5%= 525 mg/kg/day.

5. Page 88: section 4.7.3.2.2

"Evidence of peroxisome proliferation was restricted to the 16,000 ppm group of female mice …" One should take into account that female mice have some independent increased risk of developing liver cancer when attributing peroxisome proliferation to the chemical in question or to dose response.

6. Page 94: table 5-1. Please define the X-axis as dose (mg/kg/day).

7. Page 112:

Selection of an extra risk of 10% tumor incidence as a point of departure may be high for cancer effects. An extra risk of 5% cancer incidence may be more acceptable.