DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Agency for Toxic Substances
and Disease Registry

Memorandum

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.