

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

August 2013

Purpose: The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (Step 3 and 6b) where the Executive Office of the President and other federal agencies can comment on draft assessments. Comments on the Final Interagency Science Discussion draft of the IRIS Toxicological Review of Biphenyl and IRIS Summary for biphenyl (Step 6b) were jointly provided by the Office of Management and Budget (OMB) and the Office of Science and Technology Policy (OSTP). These comments were largely clarifying comments and were not related to how EPA responded to the recommendations from the public and external peer reviewers. Comments were also received by the Council on Environmental Quality (CEQ). CEQ stated that EPA successfully incorporated input from the external peer reviewers and the public, and improved the clarity and transparency of the draft assessment consistent with the advice provided by the National Research Council in 2011. No other comments were received. The following are EPA's responses to selected interagency comments. All interagency comments were taken into consideration in revising the draft assessment prior to posting on the IRIS database.

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

Selected Interagency Science Discussion Comments and Responses:

Topic #1: Human Equivalent Dose (HED) derivation – *OMB/OSTP pointed out that the equation used to estimate the dose of biphenyl to humans that would be equivalent to the dose administered to experimental animals (i.e., the human equivalent dose or HED) for the oral reference dose (RfD) appeared to differ from that used for the oral cancer slope factor, and asked that EPA confirm that the correct calculations were used. OMB/OSTP noted that the HED that served as the basis for the oral RfD was derived using EPA 2011 guidance, whereas the HED that served as the basis for the oral cancer slope factor was derived using a scaling factor as per EPA 1992 guidance.*

EPA Response: The calculations used to derive the HED for the RfD and oral cancer slope factor were confirmed to be mathematically equivalent and correct as presented.

Guidance provided in [U.S. EPA \(1992\)](#) and endorsed in EPA's 2005 *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005](#)) directs the calculation of the HED for deriving a cancer slope factor. EPA's *Recommended Use of Body Weight^{3/4} as the Default Method in Derivation of the Oral Reference Dose* ([U.S. EPA, 2011](#)) specifically outlines the method to be used to estimate the HED when deriving an oral RfD. The methods for interspecies extrapolation of dose in [U.S. EPA \(1992\)](#) and [U.S. EPA \(2011\)](#) are both based on scaling of body weight to the ^{3/4} power. As noted in [U.S. EPA \(2011\)](#), the HED equations in [U.S. EPA \(1992\)](#) and [U.S. EPA \(2011\)](#) are essentially the same:

Use of BW^{3/4} in derivation of RfD values is consistent with its current Agency use in derivation of oral cancer slope factors. Thus, this default scaling procedure is a point of harmonization between the two main Agency oral dose-response procedures.

EPA agrees that minimizing differences in the presentation of the HED equations used in deriving the RfD and oral cancer slope factor is important in increasing the transparency of the Toxicological Review. Therefore, the HED equation for the oral slope factor in Section 5.4.3.1 of the Toxicological Review was revised to match the corresponding equation for the RfD in Section 5.1.2.

Topic #2: Mouse liver tumor data – *OMB/OSTP observed that EPA did not provide a sufficient response to one external peer reviewer's comment regarding the choice of the tumor dataset for derivation of the oral cancer slope factor for biphenyl. Specifically, this peer reviewer stated that the Toxicological Review did not discuss the discrepancy in liver tumor response between male and female mice in the study selected for slope factor derivation and did not adequately defend the choice of female mouse liver tumor incidence as the basis for the slope factor in light of the decrease in liver tumor response in male mice in the same biphenyl study. OMB/OSTP observed that the external peer reviewers agreed with EPA's selection of the female mouse liver tumor endpoint and the derivation of a cancer slope factor, but commented that EPA should acknowledge in the Toxicological Review the decrease in male mouse liver tumor incidence with dose as an uncertainty associated with this endpoint. OMB/OSTP also recommended that the lack of gender concordance be discussed as part of the justification for the cancer descriptor of "suggestive evidence of carcinogenic potential."*

EPA Response: EPA agrees that the difference in liver tumor response in male and female mice in the [Umeda et al. \(2005\)](#) bioassay is relevant to the characterization of biphenyl carcinogenicity. This difference in response was addressed in Sections

4.2.1.1.1, 4.2.1.2.2, 4.7.1, 5.4.1, and 5.4.2 of the Interagency Science Discussion draft of the Toxicological Review.

EPA revised the Toxicological Review and IRIS Summary to increase the transparency of the discussion of this difference in liver tumor response and to strengthen the rationale for choosing female mouse liver tumor data as the basis for the derivation of the oral cancer slope factor. Specific revisions included the following:

- Discussion of the difference in liver tumor response between male and female mice in Section 4.7.1, Summary of Overall Weight of Evidence (for carcinogenicity), was expanded. Regarding the male mouse liver tumor response, Section 4.7.1 notes that the decreased incidences in male liver tumors in the [Umeda et al. \(2005\)](#) study were still within the range of historical controls, and that the decreased trends in male mouse liver tumors may have been associated with decreased body weight gain.
- Section 5.4.1, Choice of Study/Data—with Rationale and Justification, was revised to include an expanded rationale for choosing female mouse liver tumor data, and to more directly address the fact that the lack of an increased tumor response in male mice does not diminish the positive findings in female mice.
- In Section 5.4.5, Uncertainties in Cancer Risk Values, the discussion of female liver tumor data in Table 5-11 (Summary of uncertainties in the biphenyl cancer slope factor) was expanded to acknowledge the difference in liver tumor response between male and female mice.

Topic #3: Benchmark response (BMR) selection – *OMB/OSTP compared the BMRs used to derive the biphenyl RfD and methanol RfD, and observed that a BMR of 10% extra risk was used to derive the draft biphenyl RfD, whereas a BMR of 5% was used to derive the recent (May 2013) draft methanol RfD. OMB/OSTP requested that a brief rationale for using different BMRs be provided.*

EPA Response: As noted in the *Benchmark Dose Technical Guidance* ([U.S. EPA, 2012](#)), the selection of a BMR, which is one determinant in the derivation of the benchmark dose (BMD), involves making judgments about the statistical and biological characteristics of the dataset. The adverse outcomes used to derive the draft RfDs for biphenyl and methanol differed substantially in measurement type and biological significance. The RfD for methanol as presented in the May 2013 revised external review draft Toxicological Review of Methanol (Noncancer) was based on a decrease in

mean brain weight in rat pups following gestational exposure to methanol, compared with controls; pup brain weight is a continuous measure. A 5% relative decrease in mean pup brain weight was judged to be a minimally biologically significant degree of response, taking into account greater susceptibility during a critical window of development, as compared with, say, decreased adult body weight, which is typically assessed at a 10% decrease. In contrast, the RfD for biphenyl is based on increased incidence of papillary mineralization observed in the kidney of adult male rats exposed to biphenyl for 2 years. Incidence of kidney mineralization is a dichotomous (or quantal) measure, describing the extent that a population is affected, as opposed to a difference in a physical measurement such as weight. A 10% extra risk of kidney mineralization is judged to be a minimally biologically significant degree of response. The selection of BMRs for each of the datasets is consistent with EPA guidance ([U.S. EPA, 2012](#)).

References

- [U.S. EPA](#) (U.S. Environmental Protection Agency). (1992). A cross-species scaling factor for carcinogen risk assessment based on equivalence of mg/kg^{3/4}/day [EPA Report]. Washington, DC.
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- [U.S. EPA](#) (U.S. Environmental Protection Agency). (2011). Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose [EPA Report]. (EPA/100/R11/0001). Washington, DC. <http://www.epa.gov/raf/publications/interspecies-extrapolation.htm>.
- [U.S. EPA](#) (U.S. Environmental Protection Agency). (2012). Benchmark dose technical guidance. (EPA/100/R-12/001). Washington, DC: Risk Assessment Forum. http://www.epa.gov/raf/publications/pdfs/benchmark_dose_guidance.pdf.
- [Umeda, Y; Aiso, S; Yamazaki, K; Ohnishi, M; Arito, H; Nagano, K; Yamamoto, S; Matsushima, T.](#) (2005). Carcinogenicity of biphenyl in mice by two years feeding. J Vet Med Sci 67: 417-424.