EPA's Response to Select Interagency Comments on the Interagency Science Discussion Draft of the IRIS Toxicological Review of Trimethylbenzenes

September 2016

Purpose: The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (Step 3 and 6b) where other federal agencies and the Executive Office of the President can comment on draft assessments. Comments on the Interagency Science Discussion (Step 6b) draft of the IRIS Toxicological Review of Trimethylbenzenes were provided by the Office of Management and Budget (OMB), the Department of Defense (DOD), and the Small Business Administration (SBA). The following are EPA's responses to select interagency comments. All interagency comments were taken into consideration in revising the draft assessment prior to final posting (Step 7).

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

Select Interagency Science Discussion Comments and Responses:

Topic #1: The Preamble to IRIS Toxicological Reviews. – *OMB, DOD, and SBA all provided extensive comments on the Preamble including, but not limited to, the lack of references throughout the Preamble, information relating to the IRIS process, the derivation of toxicity values, and systematic review and evaluation of studies and study quality.*

> **EPA Response:** The Preamble to IRIS Toxicological Reviews has been extensively edited to incorporate, where appropriate, the recommendations provided by the peer reviewers, public commenters, interagency reviewers, and EPA reviewers.

Topic #2: Development and application of reference values for developmental and maternal endpoints. – *DOD requested that additional information be included in the assessment relating to the derivation of developmental reference values and guidance on the intended use of the developmental organ-specific reference values.*

> **EPA Response:** Additional information was included in the assessment regarding the use of the developmental reference values; clarifying text on the use of developmental reference values, including selection of averaging times, was added to Section 2.1.4 (page 2-21), Table 2-7 (page 2-22), Table 2-8 (page 2-27), and the Executive Summary (Tables ES-1 and ES-2, pages xxv and xxvii, respectively).

Topic #3: Consideration of biological versus statistical significance. – *DOD expressed concern that EPA was possibly not following its guidance regarding selecting BMRs for dose-response models,*

given possibly conflicting statements in the assessment regarding the use of biological vs. statistical significance.

EPA Response: The statements highlighted by DOD (Section 2.1.2 [page 2-8, line 15] and Appendix A [page A-14]) are not in conflict. Appendix A (page A-14, lines 30-31) is correct in that it is EPA's practice to consider biological significance *to the extent possible*. Further down in this paragraph (A-14, lines 36-37), EPA states that when biological significance is uncertain or understood less clearly, statistical significance testing has been used to augment this evaluation. While this text is referring to synthesis of evidence in Hazard Identification, it is analogous to the selection of BMRs for dose-response modeling. Consistent with EPA's Benchmark Dose Technical Guidance Document (U.S. EPA, 2012), the benchmark dose (BMD) and the 95% lower confidence limit on the BMD (BMDL) are estimated using a benchmark response (BMR) to represent a minimal, biologically significant level of change. In the absence of information regarding the level of change that is considered biologically significant, a BMR of 1 standard deviation (SD) from the control mean for continuous data or a BMR of 10% extra risk for dichotomous data is used to estimate the BMD (BMDL), and also to facilitate a consistent basis of comparison across endpoints, studies, and assessments.