EPA's Response to Selected Interagency Comments on the Final Interagency Science Discussion Draft of the IRIS Toxicological Review of Benzo[a]pyrene

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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 Benzo[a]pyrene were provided by the Department of Defense (DOD), National Aeronautics and Space Administration (NASA), Agency for Toxic Substances and Disease Registry (ATSDR), National Toxicology Program (NTP), Office of Management and Budget (OMB), and the Small Business Administration (SBA). ATSDR and NTP provided favorable comments which did not require response or clarification. OMB did not have major comments or issues to raise regarding this assessment. DOD, NASA, and SBA provided several comments for clarification. 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: Benzo[a]pyrene (BaP) as an index chemical- NASA questioned EPA's decision to consider benzo[a]pyrene BaP as an "index chemical" for polycylic aromatic hydrocarbons (PAHs). NASA commented that BaP, with its conservative approach, results in a potentially over restrictive approach to address the large number of PAHs in the environment without a defensible justification. NASA requested that EPA reconsider this approach and target BaP as one chemical. NASA also requested that EPA clarify that relative potency factors were developed for evaluating cancer (not noncancer endpoints).

> **EPA Response:** This assessment is the IRIS toxicological review of BaP as one chemical. Regarding using BaP as an index chemical for assessing the carcinogenicity of PAHs, justification of suitable index chemicals is more pertinent in PAH assessment support documents. Text was added to the Preface of the BaP assessment to clarify that the relative potency factors for PAHs (U.S. EPA, 1993) were developed for evaluating cancer.

Topic #2: Absence of PECO statements- DOD noted that BaP did not use PECO statements in the literature search and suggested adding a disclaimer about procedures described in preamble which were not utilized in the BaP assessment.

> **EPA Response**: Parts of the BaP assessment development process which differ from procedures in the preamble were noted in the preface of the document (see pages xv-xvi). Text in this section notes that the implementation of systematic review by the IRIS program is a process of continuous improvement. The IRIS program conducted literature searches for benzo[a]pyrene using tools and documentation standards available at the time. Protocol development (including the use of PECO statements) began with assessments starting draft development in 2015, after this assessment was well into peer review.

Topic #3: Clarifications concerning Wu et al. (2003)- DOD requested clarification of the fetal survival/birth index data reported by Wu et al. (2003), especially pertaining to the response level at the lowest dose tested. DOD also inquired whether EPA obtained the data and if so, why dose response modeling was not performed.

> **EPA Response**: Different interpretations of the Wu et al. (2003) birth index results were feasible, depending upon whether the response at the lowest exposure was compared to its concurrent control group or to an estimated response from pooled controls. All analyses of the data relied on assumptions regarding the likely number of dams in each exposure group, because this information had not been provided in the publication. Ultimately, further clarification from the study authors has confirmed that the pregnancies that Wu et al. (2003) relied upon were the same pregnancies studied (and more robustly reported) by Archibong et al. (2002). Therefore, the birth index data reported by Wu et al. (2003) do not constitute an independent replication of the Archibong et al. (2002) study. This clarification has been added to Appendix D, and all references to these birth index results were removed from the Toxicological Review.

Topic #4: Benchmark Dose Model Selection- DOD commented that Table E-18 (which provides modeling results for the endpoint of ovulation rate) states: "Polynomial 2° had the lowest AIC. However, the BMDL at 1% was excessively low. No model was selected." DOD requested clarification regarding when the lowest AIC should be rejected, i.e., how is a value determined to be "excessively low"?

EPA Response: EPA follows the BMD Technical Guidance (U.S. EPA, 2012), which in addition to evaluating AICs and goodness-of-fit tests also recommends statistical judgment in identifying adequate model fits. While nearly all of the models considered demonstrated adequate goodness-of-fit to the observed data and yielded AICs in a narrow range, most of the fits showed extensive model uncertainty in extrapolating to a 1% relative change from control in the observed data, as indicated by a large range in BMDs (a 16-fold range) and BMDLs as much as 30-fold lower than their respective BMDs. While the data set could support BMDs in the range of observation, the statistical judgment reached was that it did not support extrapolation to a BMD01. Therefore, no model was selected. These issues have been clarified in the assessment in Section 2.2.2 and Appendix E.1.2.

References

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U.S. EPA (U.S. Environmental Protection Agency). (1993). Provisional guidance for quantitative risk assessment of polycyclic aromatic hydrocarbons. (PB94116571, EPA600R93089). Cincinnati, OH: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=49732

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