NCEA Proposed Draft Charge to the Science Advisory Board for the IRIS Toxicological Review of Trimethylbenzenes

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Introduction

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the draft Toxicological Review of Trimethylbenzenes (1,2,3-trimethylbenzene [1,2,3-TMB], 1,2,4- trimethylbenzene [1,2,4-TMB], and 1,3,5-trimethylbenzene [1,3,5-TMB]) that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by the EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD). This is a new assessment; there is currently no entry on the IRIS database for any isomer of trimethylbenzene.

IRIS is a human health assessment program that evaluates scientific information on effects that may result from exposure to specific chemical substances in the environment. Through IRIS, EPA provides high quality science-based human health assessments to support the Agency's regulatory activities and decisions to protect public health. IRIS assessments contain information for chemical substances that can be used to support the first two steps (hazard identification and dose-response assessment) of the human health risk assessment process. When supported by available data, IRIS provides health effects information and toxicity values for chronic health effects (including cancer and effects other than cancer). Government and others combine IRIS toxicity values with exposure information to characterize public health risks of chemical substances; this information is then used to support risk management decisions designed to protect public health.

The external review draft Toxicological Review of Trimethylbenzenes is based on a comprehensive review of the available scientific literature on the noncancer and cancer health effects in humans and experimental animals exposed to 1,2,3-TMB, 1,2,4-TMB, or 1,3,5-TMB. This draft IRIS assessment includes:

- a *Preamble* to describe the methods used to develop IRIS assessments;
- an *Executive Summary* to concisely summarize the major conclusions of the assessment;
- a *Literature Search Strategy and Study Selection* section to describe the process for identifying and evaluating the evidence for consideration in developing the assessment;
- a *Hazard Identification* section to systematically synthesize and integrate the available evidence of organ/system-specific hazards; and
- a *Dose-Response Analysis* section to describe the selection of studies for consideration in calculating toxicity values and to provide details of the analysis and methodology in deriving and selecting toxicity values.

Additionally, appendices for chemical and physical properties, toxicokinetic information, summaries of toxicity studies, and other supporting materials are provided as *Supplemental Information* (See Appendix A to C) to the draft Toxicological Review. The draft assessment was developed according to guidelines and technical reports published by EPA (see Preamble) and contains a qualitative characterization of the hazards for TMBs, including a cancer descriptor of a chemical's human carcinogenic potential, and noncancer toxicity values, including a chronic oral reference dose (RfD) and a chronic inhalation reference concentration (RfC) for all three trimethylbenzene isomers. A quantitative cancer assessment for trimethylbenzenes was not

[1] The charge for TMBs was updated to include general charge question #4 requesting comment from the external peer review panel on the adequacy of EPA's assessment revisions and response to the public comments.

conducted due to inadequate data.

Charge Questions

In April 2011, the National Research Council (NRC) released its *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde* (NRC 2011). In addition to offering comments specifically about EPA's draft formaldehyde assessment, the NRC included comments and recommendations for improving the development of IRIS assessments. The IRIS Program's implementation of the NRC recommendations is following a phased approach. Phase 1 of implementation has focused on a subset of the short-term recommendations, such as editing and streamlining documents, increasing transparency and clarity, and using more tables, figures, and appendices to present information and data in assessments. Phase 1 also focused on assessments that had been near the end of the development process and close to final posting. The IRIS Program is now in Phase 2 of implementation which addresses all of the short-term NRC recommendations. The Program is implementing all of these recommendations but recognizes that achieving full and robust implementation of certain recommendations will be an evolving process with input and feedback from the public, stakeholders, and external peer review committees. This phased approach is consistent with the NRC's *Roadmap for Revision* as described in Chapter 7 of the formaldehyde review report. The NRC stated that "the committee recognizes that the changes suggested would involve a multi-year process and extensive effort by the staff at the National Center for Environmental Assessment and input and review by the EPA Science Advisory Board and others."

Below is a set of charge questions that address scientific issues in the draft IRIS Toxicological Review of Trimethylbenzenes. The charge questions also seek feedback on whether the document is clear and concise, a central concern expressed in the NRC report. Please provide detailed explanations for responses to the charge questions. EPA will also consider the Science Advisory Board review panel's comments on other major scientific issues specific to the hazard identification and dose-response assessment of trimethylbenzenes. Please consider the accuracy, objectivity, and transparency of EPA's analyses and conclusions in your review.

General Charge Questions:

1. NRC (2011) indicated that the introductory section of IRIS assessments needed to be expanded to describe more fully the methods of the assessment. NRC stated that they were "not recommending the addition of long descriptions of EPA guidelines to the introduction, but rather clear, concise statements of criteria used to exclude, include, and advance studies for derivation of [toxicity values]." Please comment on whether the new Preamble provides a clear and concise description of the guidance and methods that EPA uses in developing IRIS assessments.
2. NRC (2011) provided comments on ways to improve the presentation of steps used to generate IRIS assessments and indicated key outcomes at each step, including systematic review of evidence, hazard identification, and dose-response assessment. Please comment on the new IRIS document structure and whether it will increase the ability for assessment to be more clear, concise and easy to follow.
3. NRC (2011) state that "all critical studies need to be thoroughly evaluated with standardized approaches that are clearly formulated" and that "strengthened, more integrative, and more transparent discussions of weight of evidence are needed." NRC also indicated that the changes suggested would involve a multiyear process. Please comment on EPA's success thus far in implementing these recommendations.

4. EPA solicited public comments on the draft IRIS assessment of trimethylbenzenes and has revised the assessment to respond to the scientific issues raised in the comments. A summary of the public comments and EPA's responses are provided in Appendix F of the Supplemental Information to the Toxicological Review of Trimethylbenzenes. Has EPA adequately addressed the scientific issues?

Chemical-Specific Charge Questions

A. Executive Summary

1. The major conclusions of the assessment pertaining to the hazard identification and dose-response analysis have been summarized in the Executive Summary. Please comment on the whether the conclusions have been clearly and sufficiently described for purposes of condensing the Toxicological Review information into a concise summary.

B. Literature Search Strategy/Study Selection

1. The process for identifying and selecting pertinent studies for consideration in developing the assessment is detailed in the Literature Search Strategy/Study Selection section. Please comment on the whether the literature search approach, screening, evaluation, and selection of studies for inclusion in the assessment are clearly described and supported. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of 1,2,3-TMB, 1,2,4-TMB, and 1,3,5-TMB.

C. Hazard Identification

Synthesis of Evidence

1. A synthesis of the evidence for trimethylbenzene toxicity is provided in Chapter 1, *Hazard Identification*. Please comment on whether the available data have been clearly and appropriately synthesized for each toxicological effect. Please comment on whether the weight of evidence for hazard identification has been clearly described and scientifically supported.

Summary and Evaluation

1. Does EPA's hazard assessment of noncancer human health effects of trimethylbenzenes clearly integrate the available scientific evidence (i.e., human, experimental animal, and mechanistic evidence) to support the conclusions that trimethylbenzenes pose potential hazards to the nervous system, respiratory system, the developing fetus, and the circulatory system (i.e., blood)?
2. Does EPA's hazard assessment of the carcinogenicity of trimethylbenzenes clearly integrate the available scientific evidence to support the conclusions that under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is "inadequate information to assess the carcinogenic potential" of trimethylbenzenes?

D. Toxicokinetics and Pharmacokinetic Modeling

Data characterizing the toxicokinetics of 1,2,3-TMB, 1,2,4-TMB, and 1,3,5-TMB following inhalation and oral exposures in humans and experimental animals supports the use of physiologically-based pharmacokinetic (PBPK) models for 1,2,4-TMB. For the purposes of this assessment, the Hissink et al. (2007) model, originally describing 1,2,4-TMB toxicokinetics following exposure to white spirit (a complex mixture of volatile organic compounds), was modified by EPA to calculate internal dose

metrics following exposure to 1,2,4-TMB alone for the derivation of an inhalation RfC for 1,2,4-TMB. Additionally, the model was further modified by the addition of an oral route of exposure for use in a route-to-route extrapolation for the derivation of an oral RfD for 1,2,4-TMB.

1. Please comment on whether the selected PBPK model (Hissink et al., 2007) with EPA's modifications adequately describe the toxicokinetics of 1,2,4-TMB (Appendix B). Was the PBPK modeling appropriately utilized and clearly described? Are the model assumptions and parameters scientifically supported and clearly described? Are the uncertainties in the model structure adequately characterized and discussed?

2. The internal dose metric selected for use in the derivation of the RfC and RfD for 1,2,4-TMB was the steady-state weekly average venous blood concentration (mg/L) of 1,2,4-TMB for rats exposed for 6 h/day, 5 days/week. Please comment on whether the selection of this dose metric is scientifically supported and clearly described. If a different dose metric is recommended for deriving the RfC, please identify this metric and provide scientific support for this choice. Are the uncertainties in the selected dose metric adequately characterized and discussed?

E. Inhalation Reference Concentration (RfC) for 1,2,4-TMB

1. A 90-day inhalation toxicity study of 1,2,4-TMB in male rats (Korsak and Rydzyński, 1996) was selected as the basis for the derivation of the RfC. Please comment on whether the selection of this study is scientifically supported and clearly described. If a different study is recommended as the basis for the RfC, please identify this study and provide scientific support for this choice.

2. Decreased pain sensitivity (measured as an increased latency to pawlick response after a hotplate test) in male Wistar rats was concluded by EPA to be an adverse effect on the nervous system and was selected as the critical effect for the derivation of the RfC. Please comment on whether the selection and characterization of this critical effect is scientifically supported and clearly described. If a different endpoint(s) is recommended as the critical effect(s) for deriving the RfC, please identify this effect and provide scientific support for this choice.

3. In order to characterize the observed dose-response relationship comprehensively, benchmark dose (BMD) modeling was used in conjunction with dosimetric adjustments for calculating the human equivalent concentration (HEC) from a rat and human PBPK model (Hissink et al., 2007) to identify the point of departure (POD) for derivation of the RfC. Please comment on whether this approach is scientifically supported for the available data, and clearly described.

    a. Has the modeling been appropriately conducted and clearly described, based on EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012)?

    b. Has the choice of the benchmark response (BMR) for use in deriving the POD (i.e., a BMR equal to 1 standard deviation change in the control mean for the latency to pawlick response) been supported and clearly described?

4. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfC for 1,2,4-TMB. Are the UFs appropriate based on the recommendations described in Section 4.4.5 of *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002), and clearly described? If changes to the selected UFs are proposed, please identify and provide scientific support for the proposed changes.

F. Inhalation Reference Concentration (RfC) for 1,2,3-TMB

1. A 90-day inhalation toxicity study of 1,2,3-TMB in male rats (Korsak and Rydzyński, 1996) was selected as the basis for the derivation of the RfC. Please comment on whether the selection of

this study is scientifically supported and clearly described. If a different study is recommended as the basis for the RfC, please identify this study and provide scientific support for this choice.

2. Decreased pain sensitivity (measured as an increased latency to pawlick response after a hotplate test) in male Wistar rats was concluded by EPA to be an adverse effect on the nervous system and was selected as the critical effect for the derivation of the RfC. Please comment on whether the selection and characterization of this critical effect is scientifically supported and clearly described. If a different endpoint(s) is recommended as the critical effect(s) for deriving the RfC, please identify this effect and provide scientific support for this choice.

3. In order to characterize the observed dose-response relationship comprehensively, benchmark dose (BMD) modeling was used in conjunction with default dosimetric adjustments (U.S. EPA, 1994b) for calculating the human equivalent concentration (HEC) to identify the point of departure (POD) for derivation of the RfC. Please comment on whether this approach is scientifically supported for the available data, and clearly described.

    a. Has the modeling been appropriately conducted and clearly described, based on EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012)?

    b. Has the choice of the benchmark response (BMR) for use in deriving the POD (i.e., a BMR equal to a 1 standard deviation change in the control mean for the latency to pawlick response) been supported and clearly described?

4. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfC for 1,2,3-TMB. Are the UFs appropriate based on the recommendations described in Section 4.4.5 of *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002), and clearly described? If changes to the selected UFs are proposed, please identify and provide scientific support for the proposed changes.

G. Inhalation Reference Concentration (RfC) for 1,3,5-TMB

One developmental toxicity study (Saillenfait et al., 2005) following inhalation exposure to 1,3,5-TMB was identified in the literature and was considered as a potential principal study for the derivation of the RfC for 1,3,5-TMB. However, the candidate RfC derived for 1,3,5-TMB based on this study (and the critical effect of decreased maternal weight gain) was 20-fold higher than the RfC derived for 1,2,4-TMB (based on decreased pain sensitivity). Given the available toxicological database for 1,2,4-TMB and 1,3,5-TMB, there are several important similarities in the two isomers' neurotoxicity that support an RfC for 1,3,5-TMB that is not substantially different than the RfC derived for 1,2,4-TMB. Additionally, the available toxicokinetic database for the two chemicals indicates that internal dose metrics would be comparable. Thus, EPA concluded that deriving such disparate RfCs for these two isomers was not scientifically supported. Rather, EPA concluded that given the similarities in toxicokinetics and toxicity between the two isomers, there was sufficient evidence to support adopting the RfC for 1,2,4-TMB as the RfC for 1,3,5-TMB.

1. Please comment on EPA's conclusion to not base the RfC derivation for 1,3,5-TMB on isomer-specific data. Is the scientific justification for not deriving an RfC based on the available data for 1,3,5-TMB supported and has it been clearly described?

2. Please comment on whether EPA's approach to developing the RfC for 1,3,5-TMB is scientifically supported for the available data and clearly described.

H. Oral Reference Dose (RfD) for 1,2,4-TMB

The oral database for 1,2,4-TMB was considered inadequate for derivation of an RfD. However, available evidence demonstrates similar qualitative profiles of metabolism and patterns of parent compound distribution across exposure routes (i.e., oral and inhalation). Furthermore, there is no evidence that would suggest the toxicity profiles would differ to a substantial degree between oral and inhalation exposures. Therefore, route-to-route extrapolation, from inhalation to oral, using the modified Hissink et al. (2007) PBPK model was used to derive a chronic oral RfD for 1,2,4-TMB. In order to perform the route-to-route extrapolation, an oral component was added to the model, assuming a constant infusion rate into the liver. Specifically, in the absence of isomer-specific information, an assumption was made that 100% of the ingested 1,2,4-TMB would be absorbed by constant infusion of the oral dose into the liver compartment. The contribution of first-pass metabolism was also evaluated.

1. Please comment on whether EPA's conclusion that the oral database for 1,2,4-TMB is inadequate for derivation of an RfD is scientifically supported and clearly described. Please comment on whether oral data are available to support the derivation of an RfD for 1,2,4-TMB. If so, please identify these data.
2. A route-to-route extrapolation from inhalation to oral exposure using the modified Hissink et al. (2007) PBPK model has been used to derive an oral RfD for 1,2,4-TMB. Please comment on whether the PBPK modeling been appropriately utilized and clearly described. Are the model assumptions and parameters scientifically supported and clearly described? Are the uncertainties in the model structure adequately characterized and discussed? Please comment on whether this approach is scientifically supported and clearly described in the document.
3. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfD for 1,2,4-TMB. Are the UFs appropriate based on the recommendations described in Section 4.4.5 of *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002), and clearly described? If changes to the selected UFs are proposed, please identify and provide scientific support for the proposed changes.

I. Oral Reference Dose (RfD) for 1,2,3-TMB

The oral database for 1,2,3-TMB was considered to be inadequate for derivation of an RfD. Based on the similarities in chemical properties, toxicokinetics, and toxicity profiles between the 1,2,4-TMB and 1,2,3-TMB isomers, EPA concluded that there was sufficient evidence to support adopting the 1,2,4-TMB RfD as the RfD for 1,2,3-TMB.

1. Please comment on whether EPA's conclusion that the oral database for 1,2,3-TMB is inadequate for derivation of an RfD is scientifically supported and clearly described. Please comment on whether oral data are available to support the derivation of an RfD for 1,2,3-TMB. If so, please identify these data.
2. Please comment on whether EPA's approach to developing the RfD for 1,2,3-TMB is scientifically supported and clearly described.

J. Oral Reference Dose (RfD) for 1,3,5-TMB

The oral database for 1,3,5-TMB was considered to be inadequate for derivation of an RfD. EPA concluded that given the similarities in the chemical properties, toxicokinetics, and toxicity profiles between the two isomers, there was sufficient evidence to support adopting the RfD for 1,2,4-TMB as the RfD for 1,3,5-TMB.

1. Please comment on whether EPA's conclusion that the oral database for 1,3,5-TMB is inadequate for derivation of an RfD is scientifically supported and clearly described. Please comment on whether oral data are available to support the derivation of an RfD for 1,3,5-TMB. If so, please identify these data.
2. Please comment on whether EPA's approach to developing the RfD for 1,3,5-TMB is scientifically supported and clearly described.

K. Carcinogenicity of 1,2,4-TMB, 1,2,3-TMB, and 1,3,5-TMB

1. The draft Toxicological Review of Trimethylbenzenes did not conduct a quantitative cancer assessment for any isomer due to the lack of available studies. Please comment on whether data are available to support the derivation of a quantitative cancer risk estimate.