NCEA Proposed Draft Charge to External Reviewers for the IRIS Toxicological Review of Trimethylbenzenes

June 2012

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). There is currently no entry on the IRIS database for any isomer of trimethylbenzene.

IRIS is a human health assessment program that evaluates qualitative and quantitative health information on effects that may result from exposure to specific chemical substances found in the environment. Through the IRIS Program, EPA provides quality science-based human health assessments to support the Agency's regulatory activities. Combined with specific exposure information, government and private entities use IRIS to help characterize public health risks of chemical substances in site-specific situations in support of risk management decisions.

The external review draft Toxicological Review of Trimethylbenzenes is based on a comprehensive review of the available scientific literature on the human and animal health effects of 1,2,3-TMB, 1,2,4-TMB, and 1,3,5-TMB, and was developed according to guidelines and technical reports published by EPA (see Preamble). This draft IRIS assessment provides an overview of the data regarding the toxicokinetics of TMB isomers in humans and animals and characterizes the potential hazard posed by TMB exposure for noncancer and cancer health effects. The draft assessment also includes a qualitative characterization of the human cancer potential for all isomers. In addition, a chronic oral reference dose (RfD) and a chronic inhalation reference concentration (RfC) is derived for all three isomers.

Charge Questions

In April 2011, the National Research Council (NRC) released its "Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde." In addition to offering comments specifically about EPA's draft formaldehyde assessment, the NRC included comments and recommendations to improve IRIS documents generally. 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. Is the Toxicological Review logical, clear and concise? Has EPA clearly presented and synthesized the scientific evidence for noncancer and cancer effects of 1,2,4-TMB, 1,2,3-TMB, and 1,3,5-TMB.

2. 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 1,2,4-TMB, 1,2,3-TMB, and 1,3,5-TMB.

Chemical-Specific Charge Questions

(A) Hazard Identification

Synthesis of Evidence

1. A synthesis of the evidence for trimethylbenzene toxicity is provided in Section 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 justified.

Summary and Evaluation

1. Does EPA's hazard assessment of non-cancer human health effects of trimethylbenzenes clearly and objectively represent and synthesize the available scientific evidence to support its conclusions that trimethylbenzenes pose a potential human health hazard for non-cancer toxicity 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 and objectively represent and synthesize the available scientific evidence to support its conclusions that under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment*, there is inadequate information to assess the carcinogenic potential of trimethylbenzenes?

(B) Toxicokinetics and Pharmacokinetic (PBPK) Modeling

Data characterizing the toxicokinetics of 1,2,4-TMB, 1,2,3-TMB, and 1,3,5-TMB following inhalation and oral exposures in humans and experimental animals supports the development of 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 to calculate internal dose metrics following exposure to 1,2,4-TMB alone. Additionally, the model was further modified by the addition of an oral route of exposure for use in route-to-route extrapolations 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 was the steady-state weekly average venous blood concentration (mg/L) of 1,2,4-TMB for rats exposed to 1,2,4-TMB 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?

(C) 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. 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 and clearly described.

    a) Has the modeling been appropriately conducted and clearly described, based on EPA's draft *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000)? Has the choice of the benchmark response (BMR) for use in deriving the POD (i.e., a BMR of a change equal to 1 SD of the estimated control mean 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.

(D) 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. Benchmark dose (BMD) modeling was used in conjunction with default dosimetric adjustments 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 and clearly described.

    a) Has the modeling been appropriately conducted and clearly described, based on EPA's draft *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000)? Has the choice of the benchmark response (BMR) for use in deriving the POD (i.e., a BMR of a change equal to 1 SD of the estimated 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.

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

Two short-term neurotoxicity studies (Wiaderna et al., 2002; Gralewicz and Wiaderna, 2001) and one developmental toxicity study (Saillenfait et al., 2005)following inhalation exposure to 1,3,5-TMB were identified in the literature and were considered as potential principal studies for the derivation of the RfC of 1,3,5-TMB. However, an RfC was not derived for 1,3,5-TMB based on these data for reasons described in the Toxicological Review. The available toxicokinetic and toxicological databases for 1,2,4-TMB and 1,3,5-TMB indicate several similarities between the two isomers. Thus, EPA concluded that given the similarities, including similarities in chemical properties, toxicokinetics, and potential 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 chemical-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 EPA's approach to developing the RfC for 1,3,5-TMB. Has the rationale for using the RfC for 1,2,4-TMB as the RfC for 1,3,5-TMB been appropriately and clearly presented?

Please comment on whether this approach is scientifically supported and clearly described in the document.

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

A route to route extrapolation from inhalation to oral exposure using the modified Hissink et al. (2007) PBPK model has been 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 chemical-specific information, an assumption was made that 100% of the ingested 1,2,4-TMB was 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 justified 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 a chronic 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.

(G) 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 between the 1,2,4-TMB and 1,2,3-TMB isomers, EPA concluded that there was sufficient similarity 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 justified 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 EPA's approach to developing the RfD for 1,2,3-TMB. Has the rationale for using the RfD for 1,2,4-TMB as the RfD for 1,2,3-TMB been appropriately and clearly presented? Please comment on whether this approach is scientifically supported and clearly described in the document.

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

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

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 justified 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 EPA's approach to developing the RfD for 1,3,5-TMB. Has the rationale for using the RfD for 1,2,4-TMB as the RfD for 1,3,5-TMB been appropriately and clearly presented? Please comment on whether this approach is scientifically supported and clearly described in the document.

(I) Carcinogenicity of 1,2,4-TMB and 1,3,5-TMB

1. Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), the draft Toxicological Review of Trimethylbenzenes concludes that there is "inadequate information to assess the carcinogenic potential" of 1,2,4-TMB, 1,2,3-TMB, and 1,3,5-TMB. Please comment on whether this characterization of the human cancer potential for 1,2,4-TMB, 1,2,3-TMB, and 1,3,5-TMB is scientifically supported and clearly described.

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