

NCEA Proposed Draft Charge to External Reviewers for the IRIS Toxicological Review of 1,2,4-Trimethylbenzene (1,2,4-TMB) and 1,3,5-Trimethylbenzene (1,3,5-TMB)

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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 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 either 1,2,4-TMB or 1,3,5-TMB.

IRIS is a human health assessment program that evaluates qualitative and quantitative risk 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 1,2,4-TMB and 1,3,5-TMB is based on a comprehensive review of the available scientific literature on the human and animal health effects of 1,2,4-TMB and 1,3,5-TMB, and was developed according to general guidelines for risk assessment set forth by the National Research Council (1983) and guidelines and technical reports published by EPA (see Preface). This draft IRIS assessment provides an overview of the data regarding the toxicokinetics of 1,2,4-TMB and 1,3,5-TMB in humans and animals and characterizes the potential hazard posed by 1,2,4-TMB and 1,3,5-TMB exposure for noncancer and cancer health effects, including the derivations of a chronic oral reference dose (RfD) and a chronic inhalation reference concentration (RfC) for both isomers. Additionally, the draft IRIS assessment includes a qualitative characterization of the human cancer potential for both isomers.

Charge Questions

Below is a set of charge questions that address scientific issues in the draft IRIS Toxicological Review of 1,2,4-TMB and 1,3,5-TMB. Please provide detailed explanations for responses to the charge questions. EPA will also consider the Science Advisory Board reviewer panel comments on other major scientific issues specific to the hazard identification and dose-response assessment of 1,2,4-TMB and 1,3,5-TMB. Please consider the accuracy, objectivity, and transparency of EPA's analyses and conclusions in your review.

(A) 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 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 and 1,3,5-TMB.

(B) Toxicokinetics and Pharmacokinetic (PBPK) Modeling

Data characterizing the toxicokinetics of 1,2,4-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.

1. Does the selected PBPK model with EPA's modifications adequately describe the toxicokinetics of 1,2,4-TMB (Appendix A)? 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?

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

1. A 90-day inhalation toxicity study of 1,2,4-TMB in male rats was selected as the basis for the derivation of the RfC (Korsak and Rydzynski, 1996). 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 increased latency to pawlick response after hot-plate test) in male Wistar rats was concluded by EPA to be an adverse effect on the central nervous system and was selected as the critical effect for the derivation of the

RfC. Please comment on whether the selection of this critical effect and its characterization is scientifically supported and clearly described. If a different endpoint is recommended as the critical effect 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 estimate 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, 2000b)? Has the choice of the benchmark response (BMR) for use in deriving the POD (i.e. 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 and clearly described based on the recommendations described in *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002)? If changes to the selected UFs are proposed, please identify and provide scientific support for the proposed changes.

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

Two short-term neurotoxicity studies (Gralewicz and Wiaderna, 2001; Wiaderna et al., 2002) 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 chemical properties, toxicokinetics, and potential toxicity between the two isomers, there was sufficient similarity to support adopting the RfC for 1,2,4-TMB for both isomers.

1. Has the rationale for using the RfC for 1,2,4-TMB for both isomers been clearly presented? Please comment on whether the approach is scientifically supported. 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?

(D) 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. The available oral studies for 1,2,4-TMB were determined to be inadequate for derivation of an RfD. Please comment on whether the justification for the determination that the oral database is insufficient to support the derivation of an RfD for 1,2,4-TMB is clearly described in the document and whether there are available data to support the derivation of an RfD.
2. Has 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 and clearly described based on the recommendations described in *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002)? If changes to the selected UFs are proposed, please identify and provide scientific support for the proposed changes.

(E) 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. Has the rationale for using the RfD for 1,2,4-TMB for both isomers been appropriately and clearly presented? Please comment on whether the current is scientifically supported and clearly described in the document and whether there are available data to support the derivation of a 1,3,5-TMB-specific RfD.

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

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

2. The draft Toxicological Review of 1,2,4-TMB and 1,3,5-TMB did not derive a quantitative cancer risk estimate for 1,2,4-TMB and 1,3,5-TMB due to lack of available studies. Are there available data to support the derivation of a quantitative cancer risk estimate for 1,2,4-TMB and 1,3,5-TMB? If so, please identify these data.