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

1. A 90-day inhalation toxicity study of 1,2,3-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 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 of this critical effect and its characterization are 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 conducted using data for decreased pain sensitivity in male Wistar rats in conjunction with default dosimetric adjustments for calculating the human equivalent concentration (HEC) to estimate the point of departure (POD) for derivation of the RfC. 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 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 *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.

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 EPA's conclusion that the oral database for 1,2,3-TMB is inadequate for derivation of an RfD. If an oral study on 1,2,3-TMB is recommended as the basis for the RfD, please identify this study and provide scientific support for this choice.

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.