EPA's Response to Major Interagency Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of Trimethylbenzenes

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Purpose: The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (i.e., Steps 3 and 6b) where White House offices and other federal agencies can comment on draft assessments. The following are EPA's responses to selected major interagency review comments received during the Interagency Science Consultation step (Step 3) for the draft IRIS *Toxicological Review of Trimethylbenzenes*.

The Interagency Science Consultation draft Toxicological Review of Trimethylbenzenes (January 2012) represents a significant advancement in implementing the 2011 recommendations from the National Research Council on the development of IRIS assessments[1]. Comments on the draft trimethylbenzenes (TMBs) assessment were received from the National Institute for Occupational Safety and Health (NIOSH), the National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP), the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry (CDC/ATSDR), Department of Defense (DOD), and Council on Environmental Quality (CEQ). In addition to the January 2012 draft, an abbreviated version of the Toxicological Review containing only information on 1,2,3-trimethylbenzene (1,2,3-TMB) was sent to interagency reviewers in May 2012 in response to their request (Topic # 7) that 1,2,3-TMB be added to the document. All interagency comments provided were taken into consideration in revising the draft assessment prior to posting for public comment and external peer review. The complete set of interagency comments is available on the IRIS website (http://www.epa.gov/ncea/iris).

For a complete description of the IRIS process, including Interagency Science Consultation, visit the IRIS website at http://www.epa.gov/ncea/iris.

Interagency Science Consultation Comments – Selected Major Comments and Responses:

Topic #1: Consistency of elements of the Preamble with EPA Guidance – *As for the recently released external peer review draft Toxicological Review of Ammonia (May 2012), the Toxicological Review of Trimethylbenzenes includes a new preamble that describes the application of existing EPA guidance and the methods and criteria used in developing IRIS assessments. The new preamble includes information on identifying and selecting pertinent studies, evaluating the quality of individual studies, weighing the overall evidence of each effect, selecting studies for derivation of toxicity values, and deriving toxicity values. DOD offered a series of comments asserting that elements of the draft*

[1] National Research Council, 2011. Review of Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.

preamble were inconsistent with EPA risk assessment guidelines, including: 1) none of the cited EPA guidelines suggests use of a "standard value" for a point of departure for extrapolation, much less 10% response for animal data and 1% for epidemiologic data (depending on the observed response rates) as stated in the preamble; 2) that EPA's Cancer Guidelines differentiate low-dose extrapolation procedures for modes of action (MOAs) that are linear at low dose, MOAs that are nonlinear at low doses, and chemicals for which the MOA cannot be determined, but do not provide for a linear extrapolation where "the dose response curve is expected to have a linear component below the point of departure" as stated in the preamble; 3) that the following language from Section 7.4 of the draft preamble is not included in the cited guidelines: "Agents or their metabolites for which human exposures or body burdens are near doses associated with key events leading to an effect."; and 4) that, contrary to the text of the preamble, the statement that "the agent does not demonstrate mutagenic or other activity consistent with linearity at lower doses" is not part of the criteria in EPA's Cancer Guidelines for using a nonlinear extrapolation. Rather, DOD commented, the guidelines state that chemicals with a mutagenic MOA, not just mutagenic activity, are expected to have a linear extrapolation.

EPA Response: In reference to point #1, for dichotomous data, EPA guidance recommends specific response levels for use across IRIS assessments to derive the point of departure (POD) for extrapolation. For example, EPA's draft 2000 *Benchmark Dose Technical Guidance Document* states "the actual 'benchmark dose' used as a POD may correspond to response levels below (or sometimes above) 10%, although for convenience standard levels of 1%, 5%, or 10% have typically been used" (p. 19). Further, this guidance document states that "[a]n excess risk of 10% has generally been the default BMR for quantal data" (p. 19) and that "epidemiology studies often have greater sensitivities and a BMR of 1% has typically been used for quantal human data" (p. 20). Similarly, EPA's 2005 *Guidelines for Carcinogen Risk Assessment* ("Cancer Guidelines") state that "[c]onventional cancer bioassays, with approximately 50 animals per group, generally can support modeling down to an increased incidence of 1–10%; epidemiologic studies, with larger sample sizes, below 1%" (p. 3-17).

In recognition of the fact that selection of the response level used to derive a POD takes into consideration factors such as study design, sensitivity of the study, and nature or adversity of the effect, the text in Section 7.3 of the preamble was revised to better reflect those considerations. Although consistent values for response levels are generally used across IRIS assessments consistent with Agency guidance, EPA agreed that these response levels did not need to be characterized as "standard values" and revised the text of this section of the preamble accordingly.

In reference to point #2, the text highlighted by DOD from Section 7.4 of the draft preamble is a quote from the Cancer Guidelines (p. 3-21). Since the language in the preamble is an accurate reflection of EPA guidelines, no changes to this part of the preamble were made.

In reference to point #3, the text in Section 7.4 of the preamble is not an exact quote from EPA's Cancer Guidelines (p. 3-21), but closely follows the wording in the Cancer Guidelines (provided below):

> Linear extrapolation should be used when there are MOA data to indicate that the dose-response curve is expected to have a linear component below the POD. Agents that are generally considered to be linear in this region include:…
>
> - Agents for which human exposures or body burdens are high and near doses associated with key precursor events in the carcinogenic process…

The small changes to the text taken from the Cancer Guidelines were made only to more effectively and concisely capture the key points from the guidelines.

In reference to point #4, the text highlighted by DOD from Section 7.4 of the draft preamble is a quote from the Cancer Guidelines (p. 3-22). Since the language in the preamble is an accurate reflection of EPA guidelines, no changes to this part of the preamble were made.

Topic #2: Other suggested revisions to the Preamble – *Other comments were offered by Federal agencies and CEQ to improve the clarity and completeness of the draft preamble.*

EPA response: EPA appreciated the input provided during the Interagency Science Consultation step and incorporated a number of the suggested revisions to the Preamble.

Topic #3: Order in which PBPK modeling and BMD analysis was conducted for the derivation of the reference concentration (RfC) for 1,2,4-TMB – *In the Interagency Science Consultation Draft, EPA conducted benchmark dose (BMD) analysis with external exposure concentrations as the dose inputs in order to identify a point of departure (POD). EPA then converted the identified POD into a human equivalent concentration (HEC) using the available PBPK model (Hissink et al., 2007). DOD expressed concern regarding the order of BMD/PBPK analysis in the draft Toxicological Review, stating that apparent nonlinearities between internal dose metrics and external exposure concentrations may have some impact on the calculation of the RfC. DOD stated that the more scientifically-defensible manner in which to conduct the BMD/PBPK analysis would be the following: 1) use the available rat PBPK model (Hissink et al., 2007) to calculate internal rat blood metrics; 2) perform BMD modeling using the estimated rat blood metrics as the dose inputs in order to identify a POD; and 3) use the available human PPBK model (Hissink et al., 2007) to calculate HECs from the identified rat PODs.*

EPA Response: In response to interagency comments, and after evaluation of the relationship between the PBPK model-estimated internal blood dose metrics and the external exposure concentrations at the individual PODs identified from toxicity studies, EPA agrees that the

relationship between external concentrations and internal blood metrics is non-linear. EPA agrees that the most scientifically defensible methodology for conducting a BMD/PBPK analysis when non-linearity exists between internal doses and external concentrations is to convert external exposure concentrations into animal internal dose metrics and to use those metrics as the dose inputs for BMD modeling. Therefore, EPA has re-conducted the BMD/PBPK analysis for the derivation of the RfC for 1,2,4-TMB in the manner discussed above.

However, one unforeseen consequence of performing the BMD/PBPK analysis in this order was the necessity of dropping the high dose in all modeling datasets. During the validation and optimization of the animal PBPK model (Hissink et al., 2007) against available animal kinetic datasets, the model accurately reproduced venous blood concentrations of 1,2,4-TMB following repeated (6 h/day, 5d/week, 4 weeks) exposures to 123 or 492 mg/m^3 (see Section B.3.3.2, Appendix B, *PBPK Model Optimization and Validation*). However, the model consistently overpredicted venous blood concentrations following exposure to 1230 mg/m^3. EPA concluded that the optimized animal PBPK model produces acceptable simulations of venous blood 1,2,4-TMB concentrations for chronic exposures to 100 ppm (492 mg/m^3) in rats following inhalation exposure to 1,2,4-TMB (see Section B.3.3.2., Appendix B). Therefore, as the model-estimated internal blood dose metrics at the high exposure concentration are not representative of empirically observed blood concentrations, using the high-dose model estimates as dose inputs for BMD modeling was not appropriate. Consequences of dropping the high dose are a loss of information regarding dose-response characteristics at high doses and a reduction in the number of available dose-response models to run against the datasets (due to the number of model parameters > dose groups).

In the revised Toxicological Review, EPA has included a more thorough discussion of its modeling methodology, including detailed support and justification for conducting PBPK estimation of internal blood dose metrics first and BMD analysis using those internal metrics as dose inputs second. Additionally, EPA has provided a thorough discussion of the necessity of dropping the high dose in all modeling datasets due to poor PBPK model estimation of blood metrics at the high dose. In Appendix C, *Dose-Response Modeling for the Derivation of Reference Values for Effects Other than Cancer and Cancer Risk Estimates*, EPA has included alternative modeling results when the high doses were not dropped for comparison purposes only. These modeling results were not used in any reference value derivation.

Topic #4: Selection of the Principal Study and Critical Effect for derivation of the RfC for 1,2,4-TMB – *The inhalation database for 1,2,4-TMB contains three subchronic studies investigating the neurological, respiratory, hematological, and developmental toxicity of 1,2,4-TMB in Wistar rats (Korsak et al., 2000; Korsak et al., 1997; Korsak and Rydzyński, 1996). EPA selected Korsak and Rydzyński (1996) as the principal study and decreased pain sensitivity as the critical effect on which to base the derivation of the RfC for 1,2,4-TMB. Decreased pain sensitivity was selected as the critical*

effect based on the consistency of observation of this effect across multiple studies of acute, short-term, and subchronic durations (Gralewicz and Wiaderna, 2001; Gralewicz et al., 1997; Korsak and Rydzyński, 1996; Korsak et al., 1995) and the determination that this effect is adverse in accordance with EPA's Guidelines for Neurotoxicity Risk Assessment (1998). DOD noted that decreased pain sensitivity was observed to be reversible following termination of exposure, and raised concerns regarding the appropriateness of using a reversible outcome for derivation of the RfC. DOD commented that the uncertainties and limitations of the Korsak and Rydzyński (1996) were not appropriately discussed in the Toxicological Review.

EPA Response: Although the observation of decreased pain sensitivity in the Korsak and Rydzyński (1996) study was observed to be reversible, the ability of exposed animals to recover following termination of exposure does not discount this effect from consideration for derivation of an RfC. In particular, EPA's *Guidelines for Neurotoxicity Risk Assessment* (1998) state that neurotoxic effects that are slowly reversible are of high concern, while effects that are quickly reversible or "transient" relative to the toxicokinetics of the chemical are of "less" concern (although the guidelines do not state that rapidly reversible effects are of no concern).

Kinetic studies in rats and humans indicate that metabolic clearance of TBM isomers from the blood and organs is rapid (on the order of hours in rats or up to 3 days in humans). Observations in toxicity studies (e.g., Gralewicz et al. (1997)) demonstrate treatment-related effects on pain sensitivity up to 50-51 days following termination of exposure, indicating that the presence of neurotoxicity is not related to the presence of TMB in the blood of exposed animals. Therefore, neurotoxic effects appear to be persistent following the rapid metabolic clearance of TMB. In accordance with EPA's *Guidelines for Neurotoxicity Risk Assessment* (1998), these effects would be of "high concern" and are therefore appropriate for derivation of RfC values.

Clarifying text has been added to the *Hazard Identification* and *Dose-Response Analysis* sections of the Toxicological Review specifically describing the reversibility of pain sensitivity in the Korsak and Rydzýnski (1996) study and why, in accordance with EPA's *Guidelines for Neurotoxicity Risk Assessment* (1998), EPA concluded that this effect was appropriate for selection as a potential critical effect for derivation of the RfC.

Topic #5: Selection and application of the uncertainty factors for the derivation of the RfC for 1,2,4-TMB and 1,3,5-TMB – *In deriving the RfCs for 1,2,4-TMB and 1,3,5-TMB, EPA applied a composite uncertainty factor (UF) of 1,000 to the HECs calculated with the available PBPK model (Hissink et al., 2007). This composite UF was comprised of the following individual UFs: a 3-fold UF_A to account for residual toxicodynamic differences between animals and humans, a 10-fold UF_H to account for human variability, a 10-fold UF_S to account for extrapolation from a subchronic study to a chronic reference value, and a 3-fold UF_D to account for deficiencies in the toxicity database. DOD provided extensive comments on EPA's selection and application of UFs, including: 1) that UFs should be applied*

to the internal dose metric calculated by the PBPK model (Hissink et al., 2007) before any intraspecies extrapolations; 2) the available PBPK model (Hissink et al., 2007) could be used to perform a sensitivity analysis in order to inform the selection of the UF_H; 3) the database uncertainty factor should be decreased to 1 as the lack of multigenerational reproductive/developmental toxicity study is unlikely to result in a lower POD; 4) the composite uncertainty of 10,000 applied to the 1,3,5-TMB short-term neurotoxicity effects should be reduced to 3,000; and 5) EPA should more thoroughly discuss and integrate the strengths and limitations of the toxicity database.

EPA Response: In the revised Toxicological Review, uncertainty factors are applied to the human equivalence concentration calculated using the available human PBPK model (Hissink et al., 2007). Uncertainty factors were applied in this manner based on the recommendation of EPA methods reports: *A Review of the Reference Dose and Reference Concentration Processes* (2002) and *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (1994). The available PBPK model (Hissink et al., 2007) was used to conduct a sensitivity analysis of the human internal dose metric near the POD to identify the model parameters that have an impact on model estimates. The results of this sensitivity analysis (included in Section B.3.3.4 (*Sensitivity Analysis of Human Model Predictions*)) indicate that the two fitted metabolic parameters, $V_{max}C$ and K_m both influence model predictions and are considered moderately sensitive (absolute value of the normalized sensitivity coefficient between 0.2 and 1.0). The sensitivity analysis did not provide sufficient information to reduce the current 10-fold UF_H.

The purpose of the database uncertainty factor, as defined by EPA's *A Review of the Reference Dose and Reference Concentration Processes* (2002) is "to account for the potential for deriving an underprotective RfD/RfC as a result of an incomplete characterization of the chemical's toxicity". In this regard, consideration of a study's duration and the potential for greater effects in chronic studies vs. subchronic studies should be accounted for in the subchronic to chronic uncertainty factor. EPA has removed any mention of the lack of a chronic study in the text justifying the selection of the database uncertainty factor. EPA's *A Review of the Reference Dose and Reference Concentration Processes* (2002) states that reproductive and developmental toxicity studies are often useful in determining the lowest NOAEL for a study and that application of an uncertainty factor is justified when either of these study types are missing. Although the Saillenfait et al. (2005) study did not observe overt developmental toxicity in the form of embryonic/fetal lethality or teratogenicity, it did observe statistically significant decreases in male and female fetal weight. Further, although no reproductive toxicity studies of 1,2,4-TMB are available, a study investigating the reproductive and multigenerational developmental effects of high flash naphtha (McKee et al., 1990) observed effects at doses in the F_3 generation that were lower than doses that elicited effects in the F_2 or F_1 generations. As high flash naphtha contains TMB isomers, this raises concerns that the multigenerational reproductive/developmental toxicity of 1,2,4-TMB may occur at lower doses than reported by Saillenfait et al. (2005).

However, as developmental effects in the Saillenfait et al. (2005) study were observed at levels much higher than those eliciting toxicities in adult animals (Korsak studies), there is some doubt whether inclusion of a multigenerational study in the toxicity database would identify the lowest POD for 1,2,4-TMB. EPA's *Review of the Reference Dose and Reference Concentration Processes* (2002) also recommends that the database uncertainty factor take into consideration if there is concern from the available toxicology database that developing organisms may be particularly susceptible to effects in specific organ systems. TMB is able to cross the placenta (Cooper et al., 2001; Dowty et al., 1976); therefore, as neurotoxicity is observed in adult animals, there exists the concern that TMB may result in neurotoxicity in the developing organism. Effects in adult animals (motor activity and cognitive function) are reported by EPA's *Guidelines for Neurotoxicity Risk Assessment* (1998) as effects that can specifically impact the developing organism. EPA's *Guidelines for Neurotoxicity Risk Assessment* (1998) also indicate that neurotoxicants may have greater access to the nervous system in developing organisms due to the an incomplete blood-brain barrier and before metabolic detoxifying pathways are fully formed. Therefore, there is some concern that the inclusion of a developmental neurotoxicity study could potentially result in a lower POD identified from the TMB toxicity database, and therefore, a lower RfC would be derived. Section 2.1.3 (*RfC Derivation for 1,2,4-TMB*) has been revised to include a thorough discussion regarding the selection and justification of the database uncertainty factor for the derivation of the 1,2,4-TMB RfC.

Regarding the calculation of the 10,000-fold composite uncertainty factor for the effects observed in the short-term 1,3,5-TMB toxicity studies, EPA concluded that this composite uncertainty factor is appropriate. The database uncertainty factor for this database remains the same as the database uncertainty factor for 1,2,4-TMB. Given the observation of developmental effects and neurotoxicity in adult animals, there remains some concern due to the lack of a developmental neurotoxicity study. For this reason, the database uncertainty factor of 3 was retained in the document.

EPA agrees that the strengths and limitations of the TMB toxicity database should be discussed more thoroughly and integrated into the text describing and justifying the selection of the database uncertainty factor. The limitations and strengths of the database have been thoroughly discussed in more detail in the appropriate sections of the document, specifically addressing the issues discussed above (i.e., lack of a multigenerational reproductive/developmental toxicity study and the concern associated with the lack of a developmental neurotoxicity).

Topic #6: Selection of the benchmark response (BMR) for the derivation of the RfC for 1,2,4-TMB – *In deriving the RfC for 1,2,4-TMB in the Interagency Science Consultation draft assessment, EPA selected a BMR of 5% decrease from the control mean in fetal body weight to identify a POD, based on the determination that such a decrease in fetal body weight represents a minimal, biologically significant change. DOD commented that EPA provided limited support for this*

determination, and requested that EPA provide a clear rationale for the decision to use 5% decrease in body weight as the BMR.

EPA Response: In response to interagency comments, EPA has included further discussion of the biological justifications for selection of a BMR of 5% decrease from the control mean for fetal weight effects. EPA has concluded that this response level is a biologically significant response for fetuses in the Saillenfait et al. (2005) study for the following reasons: 1) decreased body weight gain in fetuses and/or pups is considered indicative of altered growth which is identified as one of the four major manifestations of developmental toxicity (U.S. EPA, 1991), a decrease in 10% body weight is generally recognized as a biologically significant response in adult animals associated with identifying a maximum tolerated dose; 3) fetuses and/or pups are generally recognized as a susceptible lifestage and are assumed to be more greatly affected by decreased body weight than adults; and 4) in humans, reduced birth weight is associated with (but not limited to) neonatal and postnatal mortality, coronary heart disease, arterial hypertension, chronic renal insufficiency, and diabetes mellitus (Barker, 2007; Reyes and Mañalich, 2005). Therefore, the selection of a BMR of 5% was considered a reasonable and biologically significant response level, and was used in the BMD modeling of fetal weight endpoints.

Topic #7: Exclusion of 1,2,3-TMB from the Toxicological Review – *The January 2012 Interagency Science Consultation draft assessment contained information on two of the three possible TMB isomers, 1,2,4-TMB and 1,3,5-TMB; derivation of human health reference values was limited to these two isomers. A third TMB isomer, 1,2,3-trimethylbenzene (hemimellitene), is present in some mixtures containing trimethylbenzenes. DOD, CDC/ATSDR, NIEHS/NTP, and CEQ commented that it was unclear why EPA decided not to include 1,2,3-TMB in the assessment, and suggested that inclusion of this isomer may be beneficial to users. These reviewers requested that a more thorough discussion of the rationale for not including 1,2,3-TMB should be included in the Toxicological Review.*

EPA Response: EPA agrees that the inclusion of the 1,2,3-TMB isomer in the assessment would likely be beneficial to users. Therefore, 1,2,3-TMB has been added to the document, including a full integration in the Toxicological Review of Hazard Identification information in Section 1, and RfC and RfD derivations included in Section 2.

Topic #8: Development of a PBPK model for 1,3,5-TMB – *In the Interagency Science Consultation draft assessment, EPA states that there is currently no PBPK model for 1,3,5-TMB that is parameterized for rats or humans. DOD commented that EPA should provide an explanation why a 1,3,5-TMB PBPK model was not adapted from the available 1,2,4-TMB model (Hissink et al., 2007). DOD indicated that development of a 1,3,5-TMB PBPK model would be relatively easy given the existence of the 1,2,4-TMB PBPK model, and development of a model would be consistent with previous EPA Toxicological Reviews that either developed models de novo or heavily modified existing models. Although development of a PBPK model for 1,3,5-TMB would represent a substantial level of effort,*

DOD felt it was an appropriate exercise if it resulted in a reduction of uncertainty in the draft assessment.

EPA Response: In the draft assessment, the RfC and RfD for 1,3,5-TMB are adopted from those derived from 1,2,4-TMB. This is due to a lack of suitable 1,3,5-TMB toxicity data on which to derive chronic reference values. Therefore, the utility of a PBPK model specifically addressing 1,3,5-TMB is questionable. However, in response to DOD's comments that development of a 1,3,5-TMB PBPK model should be relatively easy given the existing 1,2,4-TMB PBPK model and similar kinetics, EPA investigated model development for 1,3,5-TMB. The 1,2,4-TMB parameterized rat and human PBPK model was tested for its ability to predict 1,3,5-TMB venous blood concentrations reported in the literature. Validating the model against data from Swiercz et al. (2006), the model predicted the rat venous blood concentration following single or repeated exposure to 492 mg/m^3 1,3,5-TMB well; however, the model overpredicted the 123 mg/m^3 and 1,230 mg/m^3 exposure data for rats. In validating the model against data from Kostrewski et al. (1997), the model underestimated peak venous blood concentration following an 8 hr exposure to 150 mg/m^3 1,3,5-TMB in humans by about 30%; however, model prediction of 1,3,5-TMB clearance from the blood was very good. Therefore, EPA concluded that the 1,2,4-TMB PBPK model would need reparameterization in order to better characterize the observed kinetics of 1,3,5-TMB. This effort was not considered to be warranted at this time.

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