

Compilation of Slides and Discussion Points the TMB Panel Discussed on June 19, 2014 in Developing Responses to the Charge Questions.

General Charge Question 1

- Discussion about role of / need for Preamble
- Address scope of IRIS program?
- Sect.2 on steps clear, but what happens at each one less so:
 - - "problem formulation" step?
 - - how are public comments addressed in ongoing process?
 - - more explicit on stopping rule
- Sections 3-7 and existing guidance:
 - - Preamble is not itself guidance but explains guidance
 - - citations/links to operative guidance
 - - flag places where guidance is changing (eg, cancer classification?)
 - - objections to certain guidance-like statements

General Charge Question 2

- good progress on restructuring document, with supporting information in tables/appendices; good use of hyperlinks
- important to organize around evidence on each endpoint
- consistency of table format and information -- carried across IRIS assessments?
- short text overviews to set context and issues for each endpoint
- locus in report structure for evidence integration (cf Preamble Sect.5)
- brief PK/metabolism summary in intro
- dose-specific response reporting
- sections in each HazID on consistencies/inconsistencies/issues in applying/MoA

General Charge Question 3

- good progress on restructuring document, with supporting information in tables/appendices; good use of hyperlinks
- will be an ongoing challenge to bring the right details into the text to support analyses and to avoid burying important considerations in appendices
- process of systematic review good but needs more work:
 - rules for inclusion and especially quality evaluation, strength/weakness characterization, relevance scoring
 - tabulating studies with enough (but not too much) info and arraying them for cross-study consistency evaluation
 - document basis for choice of or focus on particular studies
 - integration of evidence across studies and study types
- need to go ahead with assessments even as develop, improve, test new approaches -- therefore, try to articulate *target principles* that specific practices aim to achieve and do good faith attempt to live up to them even as processes/rules change

General Charge Question 4

- Appendix F clearly addressed public comment questions individually

- Responses tended to reiterate EPA positions rather than make changes
- Several specific comments on the validity of comments, responses on particular issues

Executive Summary

Question A1

- No text was presented to discuss the recommendations on the Executive Summary
- Panel members agreed that the Executive Summary does summarize the major conclusions pertaining to hazard identification and the dose-response analysis
- Some members thought the summary should be truncated and contained too much detail.

Literature Review

Question B1

- No text was presented to discuss the recommendations on the Literature Review
- The search strategy is clearly articulated. The databases are clearly defined, as are the search terms (Table LS-1).
- A flow chart is provided (Figure LS-1) to tabulate the studies that were included and excluded. However there is limited information on exclusion criteria
- A description of the selection process should separate the reasons and number of articles “considered” but not included for human and animal studies. It is difficult to assess the goodness of the exclusion criteria without knowing the reasons for exclusion for human studies,
- This is common practice in epidemiologic reviews and meta-analyses. for example.

Hazard Identification.

Synthesis of Evidence

Charge Question C1

- An introductory paragraph describing the section layout, including the summary tables for each endpoint, would improve readability
- Synthesis of evidence is otherwise well laid out, but details such as statistical claims should be reconsidered
- The neurotoxicity endpoints are weaker than is desirable, and the uncertainty that this brings should be more fully addressed
- Including more perspectives on toxicity of related solvents could strengthen the interpretation of the individual endpoints
- Limitations in human relevance of respiratory depression as a toxic effect should be addressed more completely

Summary and Evaluation

Charge Question C1 *

- Include potential TK differences as they relate to toxicological observations – note effects associated with different durations of exposure or latent effects may be related to TK [Difference of opinion of whether there is sufficient data to do this] Some panel members felt 1,3,5-TMB is somewhat different than 1,2,3- & 1,2,4-TMB in terms of TK and toxicological evidence
- Clearly identify which isomers have empirical data and which are based on extrapolation

- Improve discussion of uncertainties (e.g. sensitivity of endpoints assessed, effects observed with other similar compounds but not assessed for TMBs.
- Clearly convey relative importance of the different health effects
- Discuss the potential for cumulative neurotoxicity
- Acknowledge lack of mechanistic data/evidence – add potential MOAs from structurally similar compounds (currently potential MOAs are discussed in effect specific subsections, except but not in Section 1.2.1)

*Assumed question applied to contents of Section 1.2.1 of the document only and NOT the individual effect MOA & summary subsections (e.g., 1.1.1.1. MOA Analysis – Neurological Effects; 1.1.1.2. Summary of Neurological Effects; etc.)

Charge question C2

- No text was presented to discuss the recommendations on the hazard identification for the carcinogenicity of the TMB isomers.
- Panel members agreed that EPA could not conduct a quantitative cancer assessment for any isomer due to the lack of appropriate studies. Furthermore, based on the lack of genotoxicity of all three isomers, and the similarity in structure to toluene and xylenes, which do not appear to be carcinogenic in experimental animals.

Toxicokinetics and pharmacokinetic Modeling

Charge Question D1

- An independent QA/QC of the PBPK model confirmed the simulations reported in EPA's report (Appendix B). No fundamental flaws or issues were found. A separate QA/QC report is provided.
- The poor fits of the model to PK of TMB in rats at high exposure levels (>100 ppm) might could be improved (see suggestion about addition of a first-order metabolic pathway consistent with Jarberg et al., OR EPA could use the suggested approach of conducting BMD modeling of the Korsak and Rydzynski (1999) data using air concentration to derive the POD (see comment to E3). The PBPK model could then be used to convert the POD (air concentration) to weekly Cavg blood concentration in the rat.
- When the EPA modifies an existing PBPK model to support an IRIS assessment, the EPA should have undertaken an independent peer-review of their revised PBPK model and the extent of this peer-review should match the extent of modifications made to the existing PBPK model. The EPA should provide to the CAAC the model code and associated m files so that members can easily reproduce figure and calculations of dose metrics used in the risk assessments. Explore the use and effort of inclusion of first-order and sustainable metabolism on predictions by the model of Hissink et al. (2007)
- Consider and assess the influence of alternative/human model input parameters (e.g., work load, cardiac output, ventilation, liver blood flow, and human Vmax)
- Explore the utility and relative merits of the model of Hissink et al. and the human model of Jarnberg et al. (1998)
- Recalibrated rat model consistently overpredicts rat blood levels with better prediction at lower dose but overprediction by 3 fold or more still occurs within the range for dose-response modeling. Therefore, the rat model needs to be adjusted to improve accuracy of predictions.

Charge Question D2

- Given that the critical effects upon which the RfC is being determined are neurological and, therefore, are extrapulmonary effects due to inhalation of the TMBs, the selection of venous blood concentration as the internal dose metric is reasonable
 - steady state weekly average venous blood concentration claimed but the half life of the isomers indicates a longer exposure time needed
 - Clarification needed on how the average weekly venous concentration used in the BMD model was determined
 - the experimental data for both rats and humans show that steady state is not achieved within a weekly exposure period
- Using the PBPK model-estimated internal dose metrics as the dose inputs for BMD modeling required the Agency to drop the high dose exposures from all modeling efforts because the venous blood dose metrics consistently over predicted experimental results for high exposures
 - PBPK model does not decompose minute ventilation into its two parts – tidal volume and breathing frequency
 - Shifts upward in the respiratory tract the absorption of gases or deposition of particles
 - High dose does not need to be dropped if an exponential rising model is fit – e.g., the R^2 is 0.98 for pain sensitivity versus the concentration of 1,2,4-TMB using all dose group means and then PBPK model used to back calculate the venous blood level
 - External air can be used as the dose metric and then back calculate venous blood levels – shows it does not matter

Inhalation RfC for 1,2,4-Trimethylbenzene

Charge Question E1

- Panel generally agreed with the choice of this study for the derivation of the RfC but recommends modifications to the text to clarify the presentation:
- State specific reasons for the choice of this study in the text and perhaps reasons for exclusion of other pertinent studies
- Alter the text to differentiate terminology related to exposure vs outcomes
- Alter the text to include separate sections on acute vs. permanent/irreversible effects and cumulative effects
- Consider biological rather than just statistical significance

Charge Question E2

- The panel agreed that increased latency to the pawlick response in a hot plate test is a valid adverse effect on the nervous system and is appropriate for the use in deriving the RfC

Charge Question E3

- There was general concern that EPA dropped the high dose group from the Korsak and Rydinski (1999) study before dose-response (BMD) modeling. However, it was shown

that conducting BMD modeling on the same dataset using air concentration as the dose metric yields an air concentration that yields the same internal dose metric as using BMD modeling on internal dose as the dose metric and using only the low and mid dose group. As a result, the panel is OK with the overall results for the POD generated by EPA. The panel also considered Appendix C-2 to be not appropriate. The panel recommends deleting and if EPA is inclined, they could replace it with the analysis using air concentration as the dose metric.

- The panel recommends that EPA provide better justification for 1 SD from the mean of the control group for the neurotox endpoint.
- EPA should provide better explanation of the issues associated with the homogeneity of variance across dose groups in the Korsak and Rydski (1999) and its implications for BMD modeling and how EPA addressed this in their BMD modeling.
- EPA should provide the functional form of the exponential 4 model.

Charge Question E4

- UF_A : the value of 3 is appropriate and justified
- UF_H : the value of 10 is appropriate and justified, although one panel member thought a value of 3 should be used
- UF_L : the values of 10 for BAL cell effects and 1 for all other effects are appropriate, but the justification should be strengthened in view of use of 1-SD for the BMDL
- UF_S : the value of 3 is appropriate, although opinions differed on the rationale (some agreeing with rationale in text on reversibility; others citing absence of accumulation per PK model, similarity in NOAELs from subchronic and shorter exposure studies). One panel member thought there was insufficient basis to reduce the UF_S from the default of 10.
- UF_D : the panel was divided, some considering the value of 3 and its justification (absence of DNT study) appropriate, while others thought it should be 10, citing [variously] the need for a larger UF to account for the missing DNT study, the absence of a multi-gen repro study, and the absence of toxicity data from more than one species.
- The panel was divided on the contribution of C9 aromatic data to the TMB database, some considered it relevant while others did not.

Inhalation RfC for 1,2,3-Trimethylbenzene

Charge Questions F1, F2, F3, and F4

- The points raised for 1,2,4-TMB are the same for 1,2,3-TMB.
- Charge Question F1, F2, F3, and F4 rely on the similarity of the isomers and the panel agreed that EPA appropriately uses the same data set for the RfC.
- The UFs are the same as for 1,2,4-TMB.
- The opinions and recommendations of the panel regarding each UF are the same.

Inhalation RfC for 1,3,5- Trimethylbenzene

Charge Question G.1

- Only one study (developmental toxicity by Saillenfait) was available to derive a RfC.

- The panel agreed that a neurotoxic endpoint is the most sensitive endpoint for derivation of the 1,2,4-TMB and 1,2,3-TMB isomers. Since the Saillenfait study did not measure this, the study should not be used.
- The panel would like to have EPA recalculate the RfC using the Saillenfait study for the organ/system specific reference concentrations of 1,3,5-TMB.

Charge Question G2

- Because of the limited 1,3,5-TMB toxicology data EPA can:
 - Derive a RfC for 1,3,5-TMB based on the 1,2,4-TMB data
 - A number of Panel members thought EPA should not derive a RfC until the appropriate database is available.

Oral RfD for 1,2,4-TMB

Charge Question H.1

- The oral database for 1,2,4-TMB is inadequate for RfD derivation and so EPA's approach of PBPK-based dose route extrapolation is appropriate

Charge Question H.2

- The adaptation of the Hissink et al. 2007 human inhalation model to the oral route of exposure, while simplistic regarding continuous dose infusion, is appropriate to the 1,2,4-TMB dose metric and overall is likely to be adequately predictive of human oral exposure.

Charge Question H.3

- The panel agrees that the UFs for the 1,2,4-TMB oral RfD should be the same as for the RfC.
- See E4 for opinions and recommendations for 1,2,4-TMB RfC UFs

Oral RfD for 1,2,3-TMB

Charge Question I.1

- As no oral studies of 1,2,3-TMB were located, review the Koch et al. study and describe its limitations and relevance to risk assessment of 1,2,3-TMB.

Charge Question I2:

- No oral exposure data or PBPK model are available for the 1,2,3-isomer so EPA recommends use of data for 1,2,4-isomer with the route-to-route extrapolation.
- Derivation of RfD is scientifically supported and clearly described.
- Uncertainty in extent of first-pass metabolism and oral bioavailability would reduce effective dose reaching target tissues. No change in UF_D or composite UF recommended.

Oral RfD for 1,3,5-TMB

Charge Question J1:

- The reason for rejection of the only isomer-specific & route-specific study (now in peer-reviewed literature) is not adequate.
- The Koch study should be carried through the process (develop POD or RfD as appropriate)

Charge Question J2:

- Derivation of RfD is scientifically supported and clearly described.

- Uncertainty in extent of first-pass metabolism and oral bioavailability would reduce effective dose reaching target tissues. No change in UF_D or composite UF recommended.
- The EPA should make use of the Koch Industries study (now published in the peer-reviewed literature) for comparative purposes; appropriate language describing limitations should be used.

K. Carcinogenicity of the TMB isomers

- No text was presented to discuss the recommendations on quantitatively assessing the carcinogenicity of the TMB isomers.
- Panel members agreed that EPA could not conduct a quantitative cancer assessment for any isomer due to the lack of appropriate studies. Furthermore, based on the lack of genotoxicity of all three isomers, and the similarity in structure to toluene and xylenes, which do not appear to be carcinogenic in experimental animals.

Executive Summary and Letter to the Administrator

- The Panel acknowledges the improvement in the new format for IRIS assessments and commends the progress the agency has made in meeting the NAS recommendations. The Panel recognizes that the TMB assessment was developed “mid-stream” and looks forward to further enhancements and provides comments to assist the agency in further enhancing IRIS assessments.
- The Panel agrees that PBPK modeling is an appropriate approach to developing RfCs and RfDs and encourages the agency to continue to use the approach in appropriate circumstance and provides specific recommendations to improve the use of modeling.
- The Panel agreed that the PBPK approach is appropriate for 1,2,4-TMB and 1,2,3-TMB. provided specific recommendations in developing a RfC and RfD for 1,3,5-TMB to evaluate the additional data that are available for oral exposures and compare those approach EPA used to develop the RfC and RfD.
- The panel notes that there is a limited discussion of sensitive life stages and vulnerable populations and encourages the agency to add to this component of this and future assessments.

The TMB Panel identified an additional issues and one charge question during their discussions on the TMB assessment.

Panel Developed Charge Questions **Vulnerable Subgroups**

Has the TMB review document adequately addressed the potential for identifiable subgroups or life stages to be more vulnerable to the toxic effects of trimethylbenzene isomers due to toxicokinetic or toxicodynamic factors taking into account what is known about the mode of action for trimethylbenzenes and evidence regarding vulnerable groups that may be available for related chemicals.

US EPA Vulnerability Discussion

- Pages 1-54 to 1-55 – one paragraph

- Correctly identifies Phase I and Phase II immaturities as possible risk factors in early life
- Suggestions:
 - Better description of possible TK child/adult differences specific to TMBs
 - Add a description of possible life-stage specific TD vulnerabilities for the key toxic endpoints

TK Considerations

- Begin with statement about how MOA determines whether polymorphisms and early life stages may change response
- Parent compound or metabolite
- Which CYPs and Phase 2
- have different ontogeny
- Polymorphisms in certain cyps and conjugation enzymes that could affect metabolic clearance
- What is known about TMBs TK mechanism?
- What is known about related compounds
- Toluene – CYP2E1 involved
- Nong et al. 2006 – child/adult differences in toluene blood levels based upon 2E1 content of liver
- Pelekis et al. 2001 – adult/child PK diffs for volatile compounds

TD Considerations

- Begin with statement about what is known about early life vulnerability to neurotoxicants
- Focus on TMBs – any useful DNT data?
- Toluene – what DNT studies available?
 - Win-Shwe et al.2010,2012 - mice
 - Post-natal more sensitive than prenatal for toluene-induced changes in hippocampal gene changes
 - PND 8-12 toluene 5 ppm affects learning at Day 49

Considering the C9 as a mixture

Public commenters have suggested that using c9 mixtures and studies may be more appropriate to develop RfC and RfD rather than the isomers for trimethylbenzenes. The panel discussed this draft response.

- There is consensus that review of the C-9 studies should be brought into the body of the hazard assessment, including the Hungarian DNT C-9 study. There is also consensus that C-9 studies should not be used for dose response modeling but there is divided opinion on the extent to which these studies can be used to fill gaps in the TMB database. The committee will provide more input on this issue in written comments.

Developing a Subchronic RfC and RfD

- The agency should develop subchronic RfC and RfD for the TB isomers.
- Panel members noted that the approach the agency is using to develop the chronic RfC and RfD for TMB isomers also develops subchronic RfC and RfD for each isomer.
- Panel member also pointed out that the subchronic values can be helpful to risk assessors in appropriate situations