



June 10, 2014

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Dear Mr. Carpenter:

I am writing on behalf of the Hydrocarbon Solvents Panel of the American Chemistry Council (ACC). The Panel represents the major US producers of hydrocarbon solvents, including trimethylbenzenes¹. The Panel is hereby providing comments in response to the Federal Register notice announcing meetings of the Chemical Assessment Advisory Committee Augmented for the Review of the Draft Trimethylbenzenes Assessment (CAAC-TMB Panel) (79 Fed. Reg. 16324, March 25, 2014). The EPA's draft Integrated Risk Information System (IRIS) Toxicological Review of Trimethylbenzenes dated August 2013 (Draft Assessment) is to be assessed at the CAAC-TMB Panel peer review meeting to be held June 17-19, 2014.

The Panel appreciates the opportunity to comment on EPA's Draft Assessment of Trimethylbenzenes (TMBs). The Panel strives to ensure appropriate product stewardship; and, as part of its mission, the Panel addresses important science, regulatory and public policy issues related to the hydrocarbon solvents industry, such as EPA's Draft IRIS Assessment.

I. Introduction

As stated in the Draft Assessment, trimethylbenzenes are aromatic hydrocarbons with the chemical formula C₉H₁₂, of which three separate isomers exist. Apart from the structural similarity, trimethylbenzene isomers are similar in terms of physical/chemical, toxicity and

¹ Members of the ACC Hydrocarbon Solvents Panel are Chevron Phillips, CITGO, ExxonMobil Chemical Company, and Sasol North America.



metabolic profiles. This similarity has been utilized by the EPA in considering data from one or more isomers as representative of other trimethylbenzene isomers and in read-across justification for applying reference values calculated from a study of one isomer to others. As EPA indicates, trimethylbenzenes are primarily produced as a complex C₉ aromatic fraction (containing other structurally similar aromatic hydrocarbons with nine carbons such as ethyltoluenes and propylbenzenes) by catalytic reforming and are used either as blending agents in gasoline or as solvents. Vehicle emissions are the major anthropogenic source of trimethylbenzene exposure.

These comments cover three major topics, each addressed in an attachment:

- Attachment I: Justification for considering the “pain sensitivity” neurotoxicity endpoint as evidence of acute CNS effects with no persistent effects with continuous exposure
- Attachment II: Justification for the inclusion of complex C₉ aromatic fraction in the draft IRIS assessment for trimethylbenzenes
- Attachment III: Justification for employing the Adenuga et al. (2014) study as the basis for the derivation of a reference dose (RfD)

Within each attachment, the Panel addresses specific EPA charge questions.

II. The Draft IRIS Assessment Contains Major Deficiencies

The EPA Draft Assessment of TMBs contains key deficiencies that range from a lack of a scientifically sound rationale for inclusion/exclusion of studies to the failure to utilize the best available science, as well as a failure to use a ‘weight-of-evidence’ approach that considers all relevant information and its quality in the Draft Assessment. Briefly, the major deficiencies highlighted in our comments include:

- Flawed assessment of “pain sensitivity” as the critical endpoint for derivation of the reference concentration (RfC),
- Exclusion of the TSCA Section 4(a) guideline studies where complex C₉ aromatic fractions were tested, and
- Unwarranted use of additional uncertainty factors.



A. *Flawed assessment of “pain sensitivity” as the critical endpoint for derivation of the reference concentration (RfC)*

The Panel agrees with the EPA that both acute and long-term effects of trimethylbenzenes are important and that any derived reference value should be protective of both effects. The selection of the “pain sensitivity” endpoint in the Korsak and Rydzynski (1996) study is an appropriate selection for the derivation of an RfC, as it is both amenable to benchmark dose (BMD) analysis and also covers the transient and systemic effects of trimethylbenzene exposure. However, the Panel disagrees with the EPA’s assertion that the “pain sensitivity” endpoint is indicative of a persistent effect following subchronic exposure to trimethylbenzenes. As detailed in Attachment I, the EPA wrongly conflates two completely different models of evaluating neurotoxicity (“pain sensitivity” and “conditioned analgesia”) to give the impression of persistency. As is shown in the Korsak and Rydzynski (1996) study, effects on pain sensitivity were only significant with exposure when the animals were tested using the hot plate method immediately after the last exposure. When the animals were tested 2-weeks after exposure, no exposure-related effects were noted with 123- or 124-trimethylbenzene. This is consistent with all other studies on individual trimethylbenzene isomers or complex C9 aromatic fraction. On the other hand, the studies where footshock is applied before or during exposure to the hot plate stimuli should be considered models of “conditioned analgesia” with no relevance to pain sensitivity measured without the application of footshock. Overall, weight-of-evidence considerations of the “pain sensitivity” and other neurotoxicity and neuropathology endpoints support the fact that trimethylbenzenes cause only an acute central nervous system (CNS) response with no evidence for persistence with prolonged exposure.

B. *Exclusion of the TSCA Section 4(a) guideline studies where complex C9 aromatic fractions were tested*

In setting out criteria for the selection and/or exclusion of studies for the toxicological review of trimethylbenzenes, the EPA indicated that studies where complex C9 aromatic fractions were tested and/or were not in the English language would not be included in the review. However, a rationale for this decision was not included in the main document and application of these criteria was inconsistent. For example, Battig et al. (1956), cited as evidence for neurotoxic effects of trimethylbenzene exposure in humans, was not written in the English language. In addition, Hissink et al. (2007), on which the PBPK model employed in the Draft Assessment was based, was originally developed for a complex substance (white spirits).

As detailed in Attachment II, the complex C9 aromatic substances should be integrated into the main review document as they represent a critical set of data that can be used for weight-of-evidence evaluation of critical endpoints of concern while also addressing the EPA’s database insufficiency concerns. Contrary to the EPA’s comments, the composition of these complex C9



aromatic fractions are well characterized and consist of C9 aromatic constituents that are structurally, toxicologically and metabolically similar to trimethylbenzenes. While we agree with the EPA that exposure to individual trimethylbenzenes do occur, the manufacture and use conditions (as spelled out by the EPA) clearly indicate that exposures to trimethylbenzenes primarily occur in the context of a combined exposure to the complex C9 aromatic fraction rather than to individual isomers in isolation.

C. Unwarranted use of additional uncertainty factors

As described in Attachment I (response to Charge Question 4), the overwhelming evidence on the “pain sensitivity” endpoint clearly indicate that this is a transient acute response which does not become progressively more severe with prolonged exposure. Hence, the use of an additional subchronic to chronic uncertainty factor (U_F) of 3 is not justified and should be removed.

In addition, the EPA has included an U_F of 3 to account for database insufficiency (i.e. lack of standard reproductive/developmental toxicity studies). However, this “insufficiency” only occurs because the EPA has chosen to ignore studies where the complex C9 aromatic fractions have been tested. For example, and as explicitly detailed in Attachment II, a well-conducted 3-generation reproductive toxicity assay in mice, two developmental toxicity (mice and rats) assays and one developmental neurotoxicity (rats) assay are available for which the test substance was a complex C9 aromatic substance consisting predominantly of isomeric mixtures of trimethylbenzene and ethyltoluene. These should be incorporated into the main text of the assessment and an U_F for database insufficiency should be excluded.

III. The 90-Day Oral Toxicity Study of 135-Trimethylbenzene is the Most Appropriate Study for the Derivation of a Reference Dose (RfD)

In the Draft Assessment, the EPA considered a valid 90-day oral toxicity study of 135-trimethylbenzene, conducted according to EPA guideline 798.2650, as unsuitable for use in the development of the reference dose². EPA’s rationale for this decision was that the study did not identify any adverse effects because it evaluated “insensitive endpoints” and did not evaluate neurobehavioral and respiratory endpoints. As detailed in Attachment III, these reasons are not justified.

- First, the study was mandated by the EPA to be used in the development of Health Advisories (HAs) for drinking water contamination under the Safe Drinking Water Act (SDWA), and is therefore the most appropriate for the development of an oral RfD.

² The 90-day oral toxicity study was cited by EPA in the draft assessment as Koch Industries 1995b, but is now published as Adenuga et al. 2014 (see Attachment III).



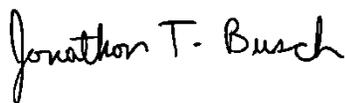
- Second, the argument that an endpoint is only “sensitive” when an adverse response is observed is flawed, as the goal of a toxicity test is to identify a threshold for a safe response.
- Third, the overall weight-of-evidence does not support the validity of the neurological and respiratory endpoints in this oral study. For example, the respiratory effects observed in the inhalation studies are “portal of entry” effects (irritation of the respiratory tract) that would be unreproducible in an oral study. Furthermore, acute neurological effects with oral exposure to trimethylbenzenes and other structurally similar aromatic hydrocarbons occur at exposure doses several fold higher than the highest dose in this study. In other words, the NOAEL in the oral toxicity study of 135-trimethylbenzene is conservative and protective of any potential neurological effects that may be of concern.

IV. Conclusion

EPA should substantially revise the Draft IRIS Assessment of TMBs to accurately incorporate the best available science. As set forth in these comments, the Draft Assessment does not accurately represent the health effects associated with exposure to TMB. The Draft Assessment should utilize a consistent and transparent data evaluation procedure for evaluating and weighing the full body of evidence in compliance with the Information Quality (IQ) Guidelines. The comments presented herein offer specific improvements that should be made to the Draft Assessment.

If you have any questions relating to these comments, please contact me.

Sincerely,



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