



**Comments of the Hydrocarbon Solvents Panel of the American Chemistry Council in
Response to the EPA's Draft IRIS Toxicological Review of Trimethylbenzenes
Public Teleconference – May 22, 2014**

Public statement on behalf of the American Chemistry Council's Hydrocarbon Solvents Panel, that represents the interests of the hydrocarbon solvent producers, to the Scientific Advisory Board Chemical Assessment Advisory Committee (CAAC) for the review of the Draft IRIS Trimethylbenzene (TMB) Assessment.

The members of the Hydrocarbon Solvents Panel of the American Chemistry Council are ChevronPhillips, Citgo, ExxonMobil, and Sasol. The two presenters are Dr. David Adenuga and Dr. Richard McKee, both of ExxonMobil Biomedical Sciences.

Background

Trimethylbenzenes are primarily manufactured as part of a refining process known as catalytic reforming that produces aromatic rich streams for use in gasoline blending. The hydrocarbon solvents industry uses these aromatic rich streams to manufacture hydrocarbon solvents, in particular one type of solvent which contains primarily C9 aromatic constituents, principally trimethylbenzenes and ethyltoluenes. Because of the manufacturing processes and end uses, potential exposure is primarily to mixtures of these substances rather than to the individual isomers. This is acknowledged in the EPA draft assessment of trimethylbenzenes where it is noted that trimethylbenzenes are largely produced as a mixture of all three individual isomers (1,2,3-, 1,2,4-, and 1,3,5-trimethylbenzene) "*during petroleum refining and production of aromatic hydrocarbons with nine carbons (i.e. C9 aromatic fraction)*" and that emissions from gasoline vehicles are "*expected to be the major anthropogenic source of TMBs*"¹. In view of this, there are two critical concerns the Hydrocarbon Solvents Panel would like to highlight pertaining to the EPA's draft assessment of TMB (points A and B).

A. The current literature database should be expanded to include studies on trimethylbenzene mixtures

With respect to the first, it is important to understand that potential exposure to trimethylbenzenes is most commonly to mixtures rather than to individual isomers. Recognizing

¹ EPA draft assessment on the toxicological review of TMBs (August 2013). Executive Summary. Page xxxiv



this, the EPA concluded, in a 1985 TSCA Section 4(a) rule (50 FR 20662, 1985), that the various C9 aromatic isomers would likely have similar toxicological properties and that the hazards could best be assessed through studies of commercial substances (C9 aromatic mixtures) rather than via tests of the isomers individually. Because the isomers have similar toxicological properties, industry used commercial mixtures of these isomers in a series of toxicology tests which provided data with which the repeated dose, developmental, reproductive, neurologic and genotoxic properties of these complex aromatic substances could be characterized. The studies were done in response to TSCA Section 4(a) test rules (50 FR 20662, 1985 and 58 FR 59667, 1993) and in accordance with EPA guidelines. The data were provided by the study sponsor (American Petroleum Institute [API]) to the EPA, and the results were published in the peer-reviewed literature (Schreiner et al., 1989; Douglas et al., 1993; McKee et al., 1990; Clark et al., 1989).

More recently a series of studies were published in which toxicology data for the individual trimethylbenzenes and ethyltoluene were summarized and/or published (Janik-Spiechowicz & Wyszynska, 1998; Swiercz et al, 2000; Swiercz et al, 1996; USEPA, 2009). These data provide evidence that the toxicological properties of these individual isomers are equivalent and similar to the data from the complex commercial substances. In fact, the current EPA draft assessment of TMB provides a robust weight of evidence showing that TMB isomers are both metabolically and toxicologically equivalent and it is on this basis that the reference concentration (RfC) calculated from data on 1,2,4-trimethylbenzene was considered to be adequately protective of adverse effects from exposure to other TMB isomers via both the oral and inhalation routes of exposure.

We agree with this assessment. However, we note further that if all isomers are equivalent, that studies of mixtures of isomers are also equally relevant, more so in relation to relevant exposure conditions. This brings us to two important points: (1) the data on the mixed isomer substances should also be considered in the overall IRIS evaluation as it provides a much richer data base than the individual isomer studies and addresses uncertainties related to data insufficiencies; and (2) the data on ethyltoluene isomers indicate that the toxicological properties of these substances are sufficiently similar to the TMB isomer data to allow the overall assessment to be generalized to include all C9 aromatics.

It is our belief that the expansion of the IRIS evaluation to fully consider the data on ethyltoluene and the commercial substances takes full advantage of the available data and results in a more broadly applicable IRIS assessment. More importantly, the inclusion or exclusion of this body of evidence is relevant to the decision on whether the use of an additional adjustment factor to account for database insufficiency is warranted or not.



B. Pain sensitivity is a sensitive indicator of an acute but not chronic neurologic effect to TMB exposure

The other issue that we would like to address concerns the critical endpoint identified in the draft assessment. We note that the IRIS office has identified pain sensitivity, specifically latency to paw lick, as the most sensitive indicator of neurological effects, and has used these data as the basis for the assessment.

However, we believe that the IRIS evaluation can be made more robust through a more complete consideration of the available information. More specifically, the IRIS office has identified a study by Korsak and Rydzynski (1996) as the source for the key information. The authors exposed rats to two TMB isomers at levels of 25, 100, or 250 ppm, 6 hours/day, 5 days/week for 3 months. They reported increased latency to response for two of the TMB isomers that were statistically significant and dose-related in rats tested immediately after termination of exposure. They also reported that when the rats were tested 2 weeks after termination of exposure, there were no differences, indicating that latency to response was a reversible response.

The study of the neurological effects of the complex aromatic material (Douglas et al., 1993), which is not included in the draft assessment, provides complementary information. In this study, rats were exposed 6 hours/day, 5 days/week for 90 days at exposure levels of 100, 500 or 1500 ppm. The potential for acute central nervous system (CNS) effects, including a hot plate stimulus test, was evaluated prior to exposure and repeated after 30, 60 or 90 days of exposure. In these studies the tests were performed 24 hours after the last exposure to avoid acute CNS effects. No differences in response were noted, indicating that latency to response is an acute, reversible effect that is not influenced by repeated exposure.

That trimethylbenzenes cause transient acute CNS effects in humans and rodents has been well known for many years. In fact several studies show no effects of prolonged exposure to inhaled trimethylbenzene in humans at concentrations below 30 ppm ($\sim 150 \text{ mg/m}^3$) (Jarnberg et al., 1996; Jarnberg et al., 1998; Jarnberg et al., 1997; Jones et al., 2006; Kostrewski and Wiaderna-Brycht, 1995; Kostrzewski et al., 1997), information which partly forms the basis for the current American Conference of Governmental Industrial Hygienists (ACGIH) 8-hour threshold limit value (TLV) of 25 ppm for all isomers of trimethylbenzene (ACGIH, 2013). However, with the exception of the studies incorporating the use of footshock, there have been no reports of chronic CNS effects with prolonged trimethylbenzene exposure, either in humans or in rodents. Similar to the Korsak and Rydzynski (1996) studies, no CNS effects are observed in trimethylbenzene-exposed rats beyond 24-hours post last exposure except when footshock is applied prior to the hotplate test. Even when significant changes in pain latency are observed in the footshock studies, no dose-response or temporal consistency is observed. **Therefore, in the absence of consistent evidence for a chronic CNS effect with repeated exposure to trimethylbenzenes, we recommend the Clark et al (1989) study as the most useful study for the determination**



of the RfC. This study provided the longest duration of exposure (12 months) in rats exposed to 450, 900 and 1800 mg/m³ of a C9 aromatic substance. The results of this study are consistent with existing subchronic toxicity data available for individual isomers of trimethylbenzene, ethyltoluenes and isomers of propylbenzene. In addition, a provisional RfC calculation based on results of the Clark et al. (1989) study was also similar to those calculated from subchronic neurotoxicity and reproductive/developmental toxicity studies of C9 aromatic substances (Douglas et al., 1989; Mckee et al., 1990).

Nevertheless, in the event that EPA continues to consider the acute neurotoxic effects of trimethylbenzene to be the endpoint of concern, the study by Korsak and Rydzynski (1996) can be used. However, since no cumulative damage was observed with repeated exposure, the inclusion of an adjustment factor to account for subchronic to chronic extrapolation does not appear warranted.

We urge the IRIS office to consider this additional information, and respectfully suggest that the availability of this information obviates the need for additional safety factors to adjust for acute to chronic exposure paradigms.

Overall, we commend the effort put in place by the EPA to provide a credible science-based assessment of trimethylbenzenes as a whole. We believe that the concerns highlighted provide an avenue to strengthen the assessment even further. We appreciate the opportunity to speak. We will provide more detailed written comments in anticipation of the peer review meetings on June 17-19, 2014.

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