



Memorandum

Date: February 10, 2012

From: Agency for Toxic Substances and Disease Registry / Centers for Disease Control and Prevention

Subject: Comments on EPA's Toxicological Review of Trimethylbenzenes

To: Environmental Protection Agency

We appreciate the opportunity to review EPA's Toxicological Review of trimethylbenzenes. ATSDR does not have a Toxicological Profile developed for trimethylbenzenes, and CDC does not have a particular subject matter expert in this area. We do offer the following comments from our Division of Toxicology and Environmental Medicine:

1) Pg. 19. *Chemical and Physical Information*. The document points out that the trimethylbenzenes are usually a mixture of three substances but only describes 2 of them (1,2,4 and 1,3,5). The justification (see page 21, *Programmatic Interest*) does not describe why 1,2,3 has been left out of the assessment or why the mixture as a whole is not addressed. The mixture would be of more interest to ATSDR scientists working at superfund sites since single compounds seem to be rarely found.

Also missing from the discussion, but of interest to ATSDR, is why the RfD and RfC for 1,2,3 could not be adapted from study data on 1,2,4 as were the RfD and RfC for 1,3,5. The section on Chemical and Physical Information states that all three isomers have similar chemical and physical properties.

- 2) Pg. 22 *Executive summary*. Consider writing out the full acronym for PODAD the first time it is used in the document.
- 3) Pg. 23 *Inhalation Reference Concentration*. We suggest EPA explicitly state which PBPK model was used for this analysis. For example, was it the Hissink model?
- 4) One concern we have is related to the selection of "confidence levels" for the Korsak and Rydzynski paper when used to derive RfD and RfCs for trimethylbenzenes. A

confidence level of “medium” has been assigned to the Korsak and Rydzynski manuscript when the study findings were used to derive an RfC for 1,2,4. Korsak and Rydzynski is an inhalation study on 1,2,4 that is used to derive an inhalation RfC for 1,2,4; therefore, we find the confidence level of “medium” to be appropriate in this case. However, Korsak and Rydzynski is also used to derive an oral RfD and an RfC of a different compound: 1,3,5. Our assumption would be that the “confidence level” assigned to this study of 1,2,4 when used to derive the RfD and RfC for 1,3,5 would be lower than the “medium” confidence level assigned previously when deriving an RfC for the exact compound (1,2,4) from the inhalation study. We have some concern that the review assigns the same “confidence level” to this study for all derivations.

- 5) Pg 25. *Effect other than cancer observed following oral exposure.* We find the wording of the first two sentences in this section to be somewhat confusing. Wouldn't a series of oral doses be considered a short-term study?
- 6) Pg 25. *Oral RfD for 1,2,4 TMB.* Please clarify the duration (number of days) used in the model for the oral RfD for 1,2,4.
- 7) Pg 26. *Oral RfD for 1,2,4 TMB.* The first pass effects are critical in the derivation of the RfD. The 4-fold higher blood concentrations for inhalation seem reasonable but we would like to see their specific derivation. Can you please site reference(s) and provide justification for using these concentrations?