THE ADMINISTRATOR OF THE ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

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Peter S. Thorne, Ph.D.
Chairman
Science Advisory Board

Cynthia M. Harris, Ph.D.
Chairwoman
Chemical Assessment Advisory Committee
Augmented for the Integrated Risk Information System
Trimethylbenzenes Assessment Review Panel
Science Advisory Board
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Dear Drs. Thorne and Harris:

Thank you for your September 29, 2015, letter providing the Science Advisory Board review panel's comments on the U.S. Environmental Protection Agency's draft "Toxicological Review of Trimethylbenzenes" developed through the Integrated Risk Information System Program and released for external peer review in August 2013.

We appreciate the panel's thorough review and constructive recommendations. We are pleased that the SAB panel commended the EPA for the progress made on addressing the National Research Council's recommendations for developing clearer and more consistent IRIS toxicological reviews.

We are also pleased that the SAB agreed with key decisions in the draft assessment, including the following:

- the use of the modified Hissink physiologically based pharmacokinetic model for developing reference concentrations and performing route-to-route extrapolations to derive reference doses;
- the use of the Korsak and Rydzyński (1996) study for developing the RfC;
- the conclusion that decreased pain sensitivity was an appropriate critical effect on which to base the derivation of the RfC;
- the determination that the TMB isomers are sufficiently similar to one another in their physiochemical, toxicokinetic and toxicological properties to adopt the reference value for the isomer with more data as the value for relatively data-poor isomers; and
- the conclusion that there is "inadequate information to assess the carcinogenic potential" of trimethylbenzene isomers.

In addition, your letter included several recommendations that will enhance the clarity of the EPA's assessment and strengthen the scientific basis for its conclusions. The EPA will carefully consider the SAB's report and make revisions to the assessment that address these recommendations. Some of the key SAB recommendations that we will address include:

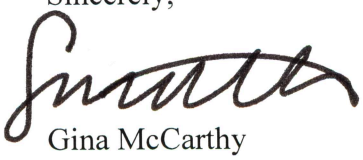
- increasing the transparency regarding the literature search by providing citations for all identified studies and the exclusion criteria by which studies were excluded from consideration;
- incorporation of relevant studies on the C-9 fraction or other related alkylbenzene compounds in the qualitative and mechanistic interpretations of TMB toxicity;
- performing benchmark dose modeling of toxicity endpoints identified in Korsak and Rydzyński (1996) using air TMB concentrations as the dose inputs and then using the Hissink PBPK model to derive a human equivalent concentration;
- deriving candidate RfD values for 1,3,5-trimethylbenzene using isomer-specific toxicity data observed in Adenuga et al. (2013);
- calculating candidate subchronic reference values for all isomers; and
- augmenting the discussion regarding susceptible populations and lifestages by incorporating mode of action and toxicity information for related alkylbenzene compounds.

The SAB panel also offered recommendations on the overall structure of the IRIS toxicological review, the clarity of the preamble, the transparency of integrative approaches and incorporation of other features of systematic review that will benefit both the trimethylbenzenes assessment and future IRIS assessments.

The EPA is working expeditiously to respond to these recommendations and to finalize the assessment.

I wish to reiterate my gratitude for your thoughtful review of the EPA's draft IRIS Toxicological Review of Trimethylbenzenes. Your contributions are invaluable to the EPA's ability to ensure that we use the best available science in finalizing this important health assessment.

Sincerely,



Gina McCarthy