American® Chemistry Council

August 10, 2007

Toxicology Excellence for Risk Assessment
Attn: Peer Consultation Program
2300 Montana Ave, Suite 409
Cincinnati, OH 45211

RE: Revised Ethylbenzene VCCEP Submission

Dear Sir or Madam:

The Ethylbenzene Panel (Panel) of the American Chemistry Council [1] hereby submits one electronic copy of the Panel's REVISED Evaluation of Ethylbenzene (CAS Number 100-41-4) under the Voluntary Children's Chemical Evaluation Program (VCCEP) Pilot Program. The document was revised to address comments of the TERA Peer Consultation Panel, to update citations, and to correct minor typographical errors. The revised documents are intended to "stand alone" without reference to the earlier submission. We understand that TERA will post this revised document on the TERA website with the other information from the Ethylbenzene Peer Consultation activity.

The RfC for noncancer effects is 0.3 ppm (based on ototoxicity). The RfD for noncancer effects is 0.5 mg/kg bwt/day (based on liver effects). The cancer reference value of 0.48 ppm was derived from the mouse chronic study and based on lung tumors. This value corresponds to a daily ingestion rate of 0.71 mg/kg bwt/day. The previously stated conclusions that even the most highly-exposed children and prospective parents are not at risk for noncancer or cancer effects of ethylbenzene were not altered after making these changes. Therefore, further evaluations of risks of ethylbenzene under VCCEP are unnecessary.

To facilitate the review of the revised document, the following substantive changes were made:

- Discussed cancer mode of action in the ILSI Framework (Section 8.3.3)
- Added a detailed discussion of the Leydig cell tumors in the rat bioassay (also using the ILSI Framework) (Section 8.3.3.4)
- Revised mouse PBPK model description and adjusted internal dose computations per the accepted manuscript (Section 8.3.4 and Appendix P)

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[1] The current members of the Ethylbenzene Panel are: Chevron Phillips Chemical Company, the Dow Chemical Company, INEOS Styrenics, NOVA Chemicals Inc., and TOTAL Petrochemicals USA, Inc.

- Revised the range of human lung dosimetry estimates to include scaling from new rat *in vitro* data (Saghir et al., 2007), resulting in a change in the cancer toxicity reference values to 0.48 ppm and 0.71 mg/kg bodyweight/day (Section 8.3.4.7 and Appendix P)
- Changed the subchronic-to-chronic uncertainty factor (UFS) from 1 to 3 in ototoxicity RfC/RfD derivation (Section 8.2.2.4). This change led to changes in the ototoxicity RfC and RfD (Sections 8.2.2.6 and 8.2.3.3, respectively) and a change in the recommended noncancer RfC to the value of 0.3 ppm (Sections 8.2.2.7 and 8.2.2.8).
- Revised the cancer and noncancer toxicity reference values (per the changes in internal dosimetry, dose-response assessment, choice of uncertainty factors, and extrapolation noted above) in the relevant summary sections (Sections 1.5, 8.4, and 9.1.2).
- Updated hazard index calculations per revised RfCs and RfDs developed for cancer and noncancer endpoints (Sections 1.6, 9.4, and 9.5).
- Appendices S and T have been removed, as the updates noted above rendered them unnecessary.

Additional revisions such as corrections of typographical errors and minor changes in wording occur throughout the document, but are not specifically identified in this cover letter.

Thank you for the efforts and the assistance of all the TERA staff throughout the Ethylbenzene VCCEP review process. If you have any questions, please call Dr. Elizabeth Moran, Manager of the Ethylbenzene Panel at 301 924 2006 or email Dr. Moran at Elizabeth_Moran@americanchemistry.com.

Yours truly,

Elizabeth J. Moran, Ph.D.
Manager, Ethylbenzene Panel

cc: Dan Briggs, TERA

Enclosures:
VCCEP Submission with appendices A-R