Peer reviewers for the second draft of the Toxicological Profile for Ethylbenzene were:

John DeSesso, Ph.D.
Senior Fellow, Noblis
Falls Church, VA

James McDougal, Ph.D., Professor and Director of Toxicology Research
Boonshoft School of Medicine
Wright State University
Department of Pharmacology and Toxicology
Dayton, OH

Andrew Salmon, Ph.D.
Senior Toxicologist and Chief, Air Toxicology and Risk Assessment Unit
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
Oakland, CA

ATSDR would like to thank these scientists for their review of the document. When the reviewer's suggestions were followed, or when other revisions obviated the need to respond, no further response is provided herein. Revisions that may have obviated the need to respond included sections that were rewritten, moved, or deleted. Some of the editorial and format suggestions could not be followed without changing ATSDR established format. Additionally, several stylistic changes that were purely arbitrary were not incorporated. Other suggestions made by the reviewers that ATSDR decided not to follow are discussed below. In the discussion that follows, "PR" refers to the appropriate page of the assembled peer review document, "P" indicates a page number in the second draft of the profile, and "L" indicates the line number on that page.
**Review comments provided by Dr. John DeSesso**

PR8: Dr. DeSesso suggested that the uncertainty of age-dependent metabolism be mentioned with respect to infants and children.

Response: The implications of age-dependence of metabolism are discussed in Section 3.7.

All other comments provided by Dr. DeSesso were addressed as suggested.

**Review comments provided by Dr. James McDougal**

PR18, Section 2.3 (MRLs): Dr. McDougal indicated that the default value of 1 for the animal-to-human blood/gas partition coefficient ratio is a conservative assumption and thus an uncertainty factor of 3 for animal to human extrapolation is not needed.

Response: The uncertainty factor for extrapolating from animals to humans was decreased from 10 to 3 based on the dosimetric adjustment. The remaining factor of 3 accounts for uncertainty in pharmacodynamics.

PR19, P48, L25: Dr. McDougal noted that the study description of the Fustinoni et al. (1995) study does not appear to reflect the English language abstract of the Italian paper.

Response: Two publications by Fustinoni et al. (1995 and 1996) are included in the ethylbenzene database. It appears that Dr. McDougal referred to the 1996 paper (in Italian) instead of the 1996 paper (in English). The study summary as presented accurately reflects the Fustinoni et al. (1995) paper.

All other comments provided by Dr. McDougal were addressed as suggested.

**Review comments provided by Dr. Andrew Salmon**

PR25, P7, L7: Dr. Salmon suggested that ATSDR develop and list guidelines for exposures that would result in de minimis cancer risk.

Response: ATSDR does not conduct quantitative assessments of cancer risk.

PR28, regarding Ungvary and Tratai (1985) paper: Dr. Salmon stated that the conclusions for developmental effects should not be ignored due to concerns regarding study quality.
Response: In response to comments provided by Dr. DeSesso suggesting that all discussions of the Ungvary and Tratai (1985) study include qualifying statements that the data are unreliable due to poor study quality, additional statements stressing concerns of the quality of the Ungvary and Tratai (1985) study have been included. Findings of this study are highly uncertain.

PR29, P23, L28 through P24, L22; P35: Dr. Salmon suggested that at route-to-route extrapolation should be considered to develop oral MRLs.

Response: ATSDR is not aware of the existence of PBPK models that simulate ethylbenzene kinetics after oral exposure to animals or humans. All existing models simulate inhalation kinetics. In view of the extensive metabolism of ethylbenzene in the liver, application of inhalation models for predicting post-oral absorption kinetics of ethylbenzene would be highly uncertain. The need for a PBPK model that simulates ethylbenzene kinetics following oral exposure has been noted in Section 3.12.2 (Identification of Data Needs).

PR33; PR35, P41, L12; and PR38: Dr. Salmon stated that the lack of a dose-response analysis on the NTP carcinogenicity data is an omission and suggests that an analysis following the EPA (2005) guidelines be conducted.

Response: ATSDR does not conduct quantitative assessments of cancer risk.

PR34, regarding the LSE tables: Dr. Salmon suggested the use of shorter summary tables of experimental data, rather the comprehensive LSE tables.

Response: The LSE tables are standard features of every ATSDR toxicological profile. The Agency believes that a comprehensive table of reliable NOAELs and LOAELs is valuable to the reader rather a series of short summary tables because it gives a more thorough overview of available data.

PR35: Dr Salmon noted that the “cancer effect level” listed in the LSE tables does not provide information useful in protecting public health.

Response: The cancer effect levels presented in the LSE tables are similar to LOAELs for non-carcinogenic effects. They are not equivalent to cancer potency factors but rather indicate dose levels associated with increased incidences of tumors in a particular study.

PR39: Dr. Salmon notes that an analogy of genotoxic effect of ethylbenzene to benzene would be of interest.
Response: This analogy was not added to the profile because it would not provide valuable insight into the genotoxicity of ethylbenzene due to differences in the metabolism of the two compounds.

All other comments provided by Dr. Salmon were addressed as suggested.