Charge to External Peer Reviewers for the Toxicological Review of Toluene and IRIS Summary
December 2003

Note: The Toxicological Review of Toluene has previously undergone external peer review in August 2002. Revisions to the health assessment have been made and are summarized in Appendix A of the Toxicological Review. The revisions concerned issues of a significant nature, thereby necessitating an additional external peer review. The charge questions below reflect the changes made to the health assessment in response to the August 2002 external review.

1) **RfD Derivation**

a) *Principal Study, Section 5.1.1*: 1. The principal study is the subchronic gavage NTP (1990) study. Has the correct principal study been chosen? Is the explanation for the choice of principal study transparent?

b) *Critical Effect, Section 5.1.1*: The critical effect is identified as increased kidney weight. Is this the correct critical effect and is it adequately described?

c) *Methods of Analysis, Section 5.1.2*: Benchmark dose modeling has been used to derive the point of departure for determining the RfD. In the absence of information on the level of response to consider adverse, a change in the mean equal to one standard deviation from the control mean was used according to the U.S. EPA Benchmark Dose Guidance (U.S. EPA, 2000). Has the correct benchmark response (one standard deviation from the control mean) for the continuous data set for increased kidney weight been chosen? Have PBPK modeling issues (i.e., route-to-route extrapolation from inhalation data was not conducted) been adequately addressed?

d) *Uncertainty Factors, Section 5.1.3*: Have the appropriate uncertainty factors been applied? Is the explanation for each transparent? Is there sufficient justification to not include an uncertainty factor for data base insufficiencies?

2) **RfC Derivation**

a) *Principal Study, Section 5.2.1*: Several human occupational studies are available. The study used in the previous IRIS file (Foo et al., 1990) is not used in the reassessment; the study by Zavalic et al. (1998) is chosen as the principal study. Is this the correct choice for the principal study? Are adequate explanations given to explain why this study was chosen over the other available studies?

b) *Critical Effect, Section 5.2.1*: The critical effect is identified as impaired color vision. Is this the correct critical effect and is it adequately described? Is the biological basis for choosing this effect adequately explained?

c) *Methods of Analysis, Section 5.2.2*: Benchmark dose modeling has been used to derive the point of departure for determining the RfD. In the absence of information on the level of response to consider adverse, a change in the mean equal to one standard deviation from the

control mean was used according to the U.S. EPA Benchmark Dose Guidance (U.S. EPA, 2000). Has the correct benchmark response (one standard deviation from the control mean) for the continuous data set for the alcohol- and age-adjusted color confusion index (AACCI) been chosen? Have PBPK modeling issues (i.e., a chemical-specific duration adjustment was not conducted) been adequately addressed?

d) *Uncertainty Factors, Section 5.2.3*: Have the appropriate uncertainty factors been applied? Is the explanation for each transparent?

3) **Cancer Weight-of-Evidence Classification**

The weight of evidence and cancer characterization are discussed in Section 4.6. Have appropriate criteria been applied from the 1999 EPA Draft Revised Guidelines for Carcinogen Risk Assessment (Review Draft, NCEA-F-0644, July 1999. Risk Assessment Forum)? Is the statement that "data are inadequate for an assessment of the human carcinogenic potential" correct?