

**Charge to External Reviewers for the
Toxicological Review of 1,1,1-Trichloroethane and IRIS Summary
February 2007**

Introduction

The U.S. Environmental Protection Agency (EPA) is conducting a peer review of the scientific basis for the human health assessment of 1,1,1-trichloroethane that will appear on the Agency's online database, the Integrated Risk Information System (IRIS).

Feedback on the Toxicological Review of 1,1,1-Trichloroethane and IRIS Summary is currently being sought in three general areas: (1) general clarity and thoroughness of the documents, (2) issues concerning the derivation of reference values specific to 1,1,1-trichloroethane, and (3) characterization of the carcinogenic potential for 1,1,1-trichloroethane.

General Questions

1. Is the Toxicological Review logical, clear and concise? Has EPA objectively and transparently represented and synthesized the scientific evidence for noncancer and cancer hazard?
2. Are you aware of additional studies that should be considered in the assessment of the noncancer and cancer health effects of 1,1,1-trichloroethane?

Questions Related to the Derivation of Reference Values for 1,1,1-Trichloroethane

Oral Reference Dose (RfD) Values

1. The conclusion was reached that the available oral toxicity information was inadequate to support derivation of oral RfD values for acute and short-term exposure durations. Do you agree with this conclusion? Is the rationale for not developing an acute or short-term oral RfD transparent and objective? If you disagree, what study should be used to derive an oral RfD?
2. The 90-day dietary study by the National Toxicology Program (NTP, 2000) was selected as the basis for the subchronic and chronic oral RfDs. Is the selection of NTP (2000) as the principal study scientifically justified? Is the rationale for selecting this study transparent and objective? Are there any other studies that you believe would be justified scientifically as the bases for the subchronic and chronic RfDs?
3. A 10% decrease in mean terminal body weight of the mouse relative to the control mean served as the basis for the subchronic and chronic oral RfDs. Is the selection of decreased body weight gain as the critical effect scientifically justified? Has the rationale for selection of this critical effect been transparently and objectively described? Is a 10% decrease in mean terminal

body weight the most scientifically justified response to use given the findings of NTP (2000) of a statistically significant decrease in mean terminal body weight (compared to the control mean) at a dose lower than the BMDL₁₀? Would presenting a BMD analysis of the 1% and 5% responses be helpful to the reader? If you disagree with the choice of body weight as the critical effect is there a preferable alternative?

4. Are the uncertainty factors applied to the point of departure for the derivation of the subchronic and chronic RfD values scientifically justified and transparently and objectively described?

5. A database uncertainty factor of 3 was applied in deriving the subchronic and chronic RfDs principally because the available oral studies did not specifically examine the potential for subtle neurotoxicity following repeated exposures. Has the rationale and justification for this uncertainty factor been transparently and objectively described? Is the application of this uncertainty factor scientifically justified? Please consider the appropriateness of this UF in light of the full database for 1,1,1-trichloroethane and, in particular, whether consideration of uncertainties in the inhalation database with respect to neurotoxicity should be reflected in the database uncertainty factor for the oral reference values.

6. As an alternative to the subchronic and chronic oral RfDs derived using data from the NTP (2000) dietary study, consideration was given to use of physiologically-based pharmacokinetic (PBPK) modeling to extrapolate findings from a two-year inhalation bioassay (Quast et al. 1984, 1988) to the oral route (i.e., route extrapolation). Is the decision not to use route extrapolation to derive oral RfD values (as discussed in Section 5.1.1. of the Toxicological Review) transparently and objectively described?

Inhalation Reference Concentration (RfC) Values

1. The acute inhalation study by Mackay et al. (1987) involving the examination of neurobehavioral effects in humans was selected as the basis for the acute inhalation RfC. Is the selection of Mackay et al. (1987) as the principal study scientifically justified? Is the rationale for selecting this study transparent and objective? Are there any other studies that you believe would be justified scientifically as the basis for the acute RfC?

2. PBPK modeling was used to extrapolate from the LOAEL (950 mg/m³ exposure for one hour) to 4-, 8-, and 24-hour exposure durations. Is this duration extrapolation scientifically supported? Was duration extrapolation correctly performed? Please provide any other comments concerning EPA's conduct of this extrapolation. Is the PBPK approach transparently and objectively described?

3. The study results of Mackay et al. (1987) were used to derive the short-term RfC, with PBPK modeling used to extrapolate to steady state conditions. Is the Mackay et al. (1987) study the most appropriate as the basis for the short-term RfC? If so, is this extrapolation scientifically justified? Are the model assumptions, parameter values, and selection of dose metrics clearly presented and supported? Are there any other studies that you believe would be justified scientifically as the basis for the short-term RfC?

4. The Quast et al. (1984, 1988) 2-year inhalation bioassay and the McNutt et al. (1975) 14-week inhalation study were jointly used as the basis for the subchronic and chronic RfCs. Is the selection of these as co-principal studies (see Sections 5.2.3.1. and 5.2.4.1.) appropriate? Is the rationale for selecting these studies transparent and objective? Are there any other studies that you believe would be justified scientifically as the basis for the subchronic and chronic RfCs?
5. The minimal histopathological findings in the liver observed in the Quast et al. (1984, 1988) rat study were judged to reflect an adaptive physiological response and not an adverse effect. Is this judgment scientifically appropriate and objectively supported?
6. PBPK modeling was used to extrapolate the point of departure from Quast et al. (1984, 1988) to humans. Is the PBPK modeling for interspecies extrapolation scientifically justified and transparently and objectively described? Are the model assumptions, parameter values, and selection of dose metrics clearly presented and supported?
7. Are the uncertainty factors applied to the point of departure for the derivation of the acute, short-term, subchronic, and chronic RfC values scientifically justified and transparently and objectively described?
8. Database uncertainty factors were not applied in deriving the acute and short-term RfCs. A database uncertainty factor of 3 was used in deriving subchronic and chronic RfCs. Has the rationale and justification for the application of the database uncertainty factor been transparently and objectively described? Is the application of this uncertainty factor scientifically justified, particularly with respect to the existing literature (both human and animal) on 1,1,1-trichloroethane neurotoxicity?
9. Because the value of the subchronic and chronic RfC exceeded the values of the acute and short-term RfCs, the subchronic and chronic RfC was set at 5 mg/m^3 so as not to exceed the limiting reference value derived for short-term exposure. Is this decision scientifically justified and transparently and objectively described? Please comment on whether you believe there might be more appropriate explanations than those discussed in Sections 5.2.3.3 and 5.2.4.3 for why the acute and short-term inhalation RfC values were smaller than the subchronic and chronic RfC values.
10. Rosengren et al. (1985) reported increased glial fibrillary acidic protein (GFAP) – a marker for formation of astroglial fibrils in response to brain injury – in the sensorimotor cerebral cortex of 1,1,1-trichloroethane-exposed gerbils. The EPA did not consider these findings to be sufficiently reliable or of sufficient toxicological significance to use as the basis for the subchronic RfC. Is this decision scientifically justified, particularly in light of observed neurobehavioral effects associated with acute exposure to 1,1,1-trichloroethane? Is this decision transparently and objectively described? The Rosengren et al. study was used to inform the value of the database uncertainty factor used in deriving the subchronic and chronic RfDs and RfCs. Was consideration of this study appropriate in the context of the database uncertainty factor?

Questions Related to the Cancer Assessment for 1,1,1-Trichloroethane

1. Do the available data support the conclusion that the database for 1,1,1-trichloroethane provides inadequate information to assess carcinogenic potential based on the weight-of-evidence categories in the EPA 2005 *Guidelines for Carcinogen Risk Assessment*? Please describe the basis for your view.