Draft Charge to External Reviewers for the
IRIS Toxicological Review of cis- and trans-1,2-Dichloroethylene (DCE)
August 2009

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of cis- and trans-1,2-dichloroethylene (DCE) that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by the EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD).

IRIS assessments for cis-1,2-DCE and trans-1,2-DCE were posted on the IRIS database in 1990 and 1988, respectively. For cis-1,2-DCE, neither an oral reference dose (RfD) nor an inhalation reference concentration (RfC) was derived. For trans-1,2-DCE, an RfD, but not an RfC, was derived. The previous assessments for cis- and trans-1,2-DCE characterized these isomers as "not classifiable as to human carcinogenicity."

The current draft health assessments include chronic RfDs for cis- and trans-1,2-DCE, an inhalation minimal data value for trans-1,2-DCE included in Appendix C, and qualitative carcinogenicity assessments for both isomers. Below is a set of charge questions that address scientific issues in the assessments of cis- and trans-1,2-DCE. Please provide detailed explanations for responses to the charge questions.

General Charge Questions:

1. Is the Toxicological Review logical, clear and concise? Has EPA clearly synthesized the scientific evidence for noncancer and cancer hazard?

2. Please identify any additional studies that should be considered in the assessment of the noncancer and cancer health effects of cis- and trans-1,2-DCE.

Chemical-Specific Charge Questions:

A) Oral reference dose (RfD) for cis-1,2-DCE

1. The McCauley et al. (1990, 1995) subchronic gavage study in rats was selected as the basis for the derivation of the RfD for cis-1,2-DCE. Please comment on whether the selection of this study as the principal study is scientifically justified. Please identify and provide the rationale for any other study that should be selected as the principal study.

2. Increased relative liver weight in male rats (McCauley et al., 1990, 1995) was selected as the critical effect for the RfD for cis-1,2-DCE. Please comment on whether the selection of this critical effect is scientifically justified. Please identify and provide the rationale for any other endpoint that should be considered in the selection of the critical effect.

3. Benchmark dose (BMD) modeling methods were applied to liver weight data to derive the

point of departure (POD) for the RfD. Has the BMD modeling been appropriately conducted? Is the benchmark response (BMR) selected for use in deriving the POD (i.e., a 10% change in relative liver weight) scientifically justified? Please identify and provide the rationale for any alternative approaches (including the selection of the BMR, model, etc.) for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.

4. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfD. If changes to the selected UFs are proposed, please identify and provide a rationale(s).

(B) Oral reference dose (RfD) for trans-1,2-DCE

1. The 90-day immunotoxicity study by Shopp et al. (1985) was selected as the basis for the RfD for trans-1,2-DCE. Please comment on whether the selection of this study as the principal study is scientifically justified. Please identify and provide the rationale for any other study that should be selected as the principal study.

2. Immune suppression, as indicated by the decrease of sheep red blood cell (sRBC)-specific IgM antibody-forming cells (AFCs) in the spleen in male mice, was selected as the critical effect for the RfD. Please comment on whether the selection of this critical effect is scientifically justified.
Please identify and provide the rationale for any other endpoint that should be considered in the selection of the critical effect.

3. BMD modeling was applied to data for suppression of AFCs in the spleen in male mice in the Shopp et al. (1985) study to derive the POD for the RfD. Has the BMD modeling been appropriately conducted? Is the BMR selected for use in deriving the POD (i.e., a change in response of 1 standard deviation from the control mean) scientifically justified? Please identify and provide the rationale for any alternative approaches (including the selection of the BMR, model, etc.) for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.

4. Please comment on the rationale for the selection of the UFs applied to the POD for the derivation of the RfD. If changes to the selected UFs are proposed, please identify and provide a rationale(s).

(C) Inhalation reference concentration (RfC) for cis-1,2-DCE

1. A chronic RfC was not derived due to the lack of available studies to characterize the health effects associated with cis-1,2-DCE administered via the inhalation route. Are there available data that might support development of an RfC for cis-1,2-DCE?

(D) Inhalation minimal data value for trans-1,2-DCE

Upon evaluation of the inhalation database for trans-1,2-DCE, EPA determined that it was not possible to derive an inhalation RfC as the proposed composite uncertainty factor (UF) of 10,000

would lead to a value with an unacceptable level of uncertainty (see *A Review of the Reference Dose and Reference Concentration Processes*, U.S. EPA, 2002 for a discussion of UFs). In lieu of deriving an RfC the available data were used to derive an inhalation value (i.e., a minimal data value) for limited risk assessment purposes as discussed in Appendix C.

1. The Freundt et al. (1977) study was selected as the basis for the derivation of the inhalation minimal data value. Please comment on whether selection of this study as the principal study is scientifically justified. Please identify and provide the rationale for any other study that should be selected as the principal study.

2. Fatty accumulation in liver lobules and Kupffer cells was selected as the critical effect for the inhalation minimal data value for trans-1,2-DCE. Please comment on whether the selection of this critical effect is scientifically justified. Please identify and provide the rationale for any other endpoint that should be considered in the selection of the critical effect.

3. A NOAEL/LOAEL approach was used to derive the POD (i.e., LOAEL of 200 ppm (792 mg/m^3) for fatty changes in the liver) for the inhalation minimal data value for trans-1,2-DCE. A BMD analysis was considered but was not conducted because of the nature of the data set (i.e., there was only one concentration used in this study). Is the NOAEL/LOAEL approach selected for use in deriving the POD scientifically justified? Please identify and provide the rationale for any alternative approaches for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.

4. A composite UF of 10,000 was applied to derive an inhalation minimal data value for trans-1,2-DCE. Please comment on the rationale for the selection of the UFs applied to the POD for the derivation of the inhalation minimal data value. If changes to the selected UFs are proposed, please identify and provide a rationale(s).

(E) Carcinogenicity of cis- and trans-1,2-dichloroethylene

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that there is *inadequate information to assess the carcinogenic potential* of cis- and trans-1,2-DCE. Please comment on the cancer weight of evidence characterization. Is the cancer weight of evidence characterization scientifically justified?