Draft Charge to External Reviewers for the
IRIS Toxicological Review of Chloroprene
September, 2009

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of chloroprene 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). Currently an IRIS assessment of chloroprene does not exist on the database.

The draft health assessment includes a chronic reference concentration (RfC) and a carcinogenicity assessment. Below are a set of charge questions that address scientific issues in the assessment of chloroprene. 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 hazards?

2. Please identify any additional studies that should be considered in the assessment of the noncancer and cancer health effects of chloroprene.

Chemical-Specific Charge Questions:

(A) Oral reference dose (RfD) for chloroprene

1. An RfD was not derived for chloroprene. Has the scientific justification for not deriving an RfD been clearly described in the document? Please identify and provide the rationale for any studies that should be selected as the principal study.

(B) Inhalation reference concentration (RfC) for chloroprene

1. A chronic RfC for chloroprene has been derived from an inhalation toxicity study (NTP, 1998) investigating non-cancer effects in multiple organ systems. 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 studies that should be selected as the principal study.

2. An increase in the incidence of degenerative nasal lesions in male rats, characterized by olfactory epithelial atrophy and/or necrosis with increasing severity, was selected as the critical effect. Please comment on the scientific justification for combining the incidence of atrophy and necrosis and for selecting this endpoint as the critical effect. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. Benchmark dose (BMD) modeling was used to define the point of departure (POD) for the derivation of the RfC. The POD was based on increased incidence of degenerative nasal lesions in male rats at a benchmark response (BMR) of 10% extra risk. Has the BMD approach been appropriately conducted? Is the BMR selected for use in deriving the POD (i.e., 10% extra risk of degenerative nasal lesions of less than moderate severity) 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 RfC. If changes to the selected UFs are proposed, please identify and provide a rationale(s).

(C) Carcinogenicity of chloroprene

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that chloroprene is *likely to be carcinogenic to humans* by all routes of exposure. Please comment on the cancer weight of evidence characterization. Is the cancer weight of evidence characterization scientifically justified?

2. A two-year inhalation cancer bioassay in B6C3F1 mice (NTP, 1998) was selected as the basis for derivation of an inhalation unit risk (IUR). Please comment on whether the selection of this study for quantification is scientifically justified. Please identify and provide the rationale for any other studies that should be selected as the basis for quantification.

3. A mutagenic mode of carcinogenic action is proposed for chloroprene. Please comment on whether the weight of evidence supports this conclusion. Please comment on whether this determination is scientifically justified. Please comment on data available for chloroprene that may support an alternative mode(s) of action.

4. Data on hemangiomas/hemangiosarcomas (in all organs) and tumors of the lung (bronchiolar/alveolar adenomas and carcinomas), forestomach, Harderian gland (adenomas and carcinomas), kidney (adenomas), skin and mesentery, mammary gland and liver in $B6C3F_1$ mice were used to estimate the inhalation unit risk. Please comment on the scientific justification and transparency of this analysis. Has the modeling approach been appropriately conducted? Please identify and provide the rationale for any alternative approaches for the determination of the inhalation unit risk and discuss whether such approaches are preferred to EPA's approach.

5. Lung tumors have been alternatively treated as systemic or portal-of-entry effects in the modeling of cancer endpoints. Please comment on the scientific justification for this modeling approach. Please comment on whether the rationale for this decision has been transparently and objectively described. Please comment on data available for chloroprene that may support an alternative method for modeling the observed lung tumors in mice.

6. An oral slope factor (OSF) for cancer was not derived for chloroprene. Is the determination that the available data for chloroprene do not support derivation of an OSF scientifically justified?