Draft Charge to External Reviewers for the
Toxicological Review of Hydrogen Cyanide and Cyanide Salts
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 hydrogen cyanide and cyanide salts that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD).

An oral reference dose (RfD) for cyanide was posted on the IRIS database in 1987 and an inhalation reference concentration (RfC) was posted in 1994. The draft reassessment includes an RfD, RfC, and a carcinogenicity assessment. Below is a set of charge questions that address scientific issues in this assessment. 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 hydrogen cyanide and cyanide salts.

Chemical-Specific Charge Questions:

(A) Oral reference dose (RfD) for Cyanide Salts

1. A 13-week drinking water study (NTP, 1993) was selected as the basis for the RfD. 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. Specifically, please comment on whether Jackson (1988) or Kamalu et al. (1993) (which found potentially lower points of departure) should be given greater consideration in the determination of the RfD.

2. Decreased absolute cauda epididymis weight in male rats 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 endpoints that should be considered in the selection of the critical effect.

3. Benchmark dose (BMD) modeling methods were applied to continuous data on absolute cauda epididymis weight to derive the point of departure (POD) for the RfD. Please provide comments with regard to whether BMD modeling is the best approach for determining the POD. Has the BMD modeling been appropriately conducted? Is the benchmark response (BMR) selected for use in deriving the POD (specifically, a decrease in the control mean of one standard deviation) 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 selection of the uncertainty factors applied to the POD for the derivation of the RfD. For instance, are they scientifically justified? If changes to the selected uncertainty factors are proposed, please identify and provide a rationale(s).

(B) Inhalation reference concentration (RfC) for hydrogen cyanide

1. The occupational inhalation study by El Ghawabi et al. (1975) was selected as the basis for the RfC. Please comment on whether the selection of this study as the principal study is scientifically justified. Specifically, are the study design, methods, and findings appropriate to support the derivation of an RfC? Also, please comment on whether the scientific justification and rationale for selecting the El Ghawabi et al. (1975) study as the principal study given the potential for possible co-exposure to other chemicals is adequately described. Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. Thyroid enlargement and altered iodide uptake were selected as the critical effects for the RfC. Please comment on whether the selection of these critical effects is scientifically justified. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. The chronic RfC has been derived utilizing the NOAEL/LOAEL approach to derive the POD for the RfC. Please provide comments at to whether this approach is the best approach for determining the POD. Has the approach been appropriately conducted? 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. Please comment on the rationale for the selection of the 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 hydrogen cyanide and cyanide salts

1. Under EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that data are *inadequate for an assessment of the human carcinogenic potential* of cyanide. Please comment on the cancer weight of evidence characterization. Is the cancer weight of evidence characterization scientifically justified?