**DRAFT EXTERNAL PEER REVIEW CHARGE**
**February, 2008**

# Charge to External Reviewers for the IRIS Toxicological Review of 2-Hexanone

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of 2-hexanone 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). There is currently no assessment on the IRIS database for the health effects associated with 2-hexanone exposure.

The draft health assessment documents include a chronic Reference Dose (RfD) and a chronic Reference Concentration (RfC). Below are a set of charge questions that address scientific issues in the assessment of 2-hexanone. Please provide detailed explanations for responses to the charge questions.

## (A) General Charge Questions:

1. Is the Toxicological Review logical, clear and concise? Has EPA accurately, clearly and objectively represented and 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 2-hexanone.

3. Please discuss research that you think would be likely to increase confidence in the database for future assessments of 2-hexanone.

4. Please comment on the identification and characterization of sources of uncertainty in sections 5 and 6 of the assessment document. Please comment on whether the key sources of uncertainty have been adequately discussed. Have the choices and assumptions made in the discussion of uncertainty been transparently and objectively described? Has the impact of the uncertainty on the assessment been transparently and objectively described?

## Chemical-Specific Charge Questions:

## (B) Oral reference dose (RfD) for 2-hexanone

1. A chronic RfD for 2-hexanone has been derived from a 13-month drinking water study (O'Donoghue et al., 1978) in male rats. Please comment on whether the

selection of this study as the principal study has been scientifically justified. Has this study been transparently and objectively described in the document? Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. Myofibrillar atrophy of the quadriceps muscle was selected as the critical effect. Please comment on whether the rationale for the selection of myofibrillar atrophy as the critical effect has been scientifically justified. Has this selection been transparently and objectively described in the document? Please provide detailed explanation. Please comment on the selection of myofibrillar atrophy of the quadriceps muscle as the critical effect rather than other endpoints identified in O'Donoghue et al. (1978). Please comment on the selection of myofibrillar atrophy of the quadriceps muscle as compared to the peripheral nerve axonal swelling. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. Please comment on the selection of the uncertainty factors applied to the point of departure (POD) for the derivation of the RfDs. For instance, are they scientifically justified? Are they transparently and objectively described in the document?

4. Please comment specifically on the database uncertainty factor of 3 applied in the RfD derivation. Please comment on body of information regarding reproductive, developmental toxicity, and immunotoxicity on 2-hexanone as well as the relevance of toxicity data on n-hexane in the determination of the database uncertainty factor. Please comment on whether the selection of the database uncertainty factor for the RfD has been scientifically justified. Has this selection been transparently and objectively described in the document?

5. Please provide any other comments on the derivation of the RfD.

**(C) Inhalation reference concentration (RfC) for 2-hexanone**

1. A chronic RfC for 2-hexanone has been derived from a 10-month inhalation study (Johnson et al., 1977) in rats and monkeys. Please comment on whether the selection of this study as the principal study has been scientifically justified. Has this study been transparently and objectively described in the document? Please comment on the use of a 10-month monkey study (Johnson et al., 1977) as opposed to a 72-week rat study (Krasavage and O'Donoghue, 1977). Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. Motor conduction velocity of the sciatic-tibial nerve in monkeys was selected as the critical toxicological effect. Please comment on whether the selection of this critical effect has been scientifically justified. Has this selection been transparently and objectively described in the document? Please provide detailed explanation. Please comment on the use of motor conduction velocity of the sciatic-tibial nerve instead of motor conduction velocity of the ulnar nerve. Please comment on the use of monkey

data instead of rat data. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. Estimates of the standard deviation of the responses in each dose group are needed to calculate benchmark doses (BMDs) and their corresponding lower confidence limits (BMDLs). This information was not provided in Johnson et al. (1977), the principal study. Therefore, an indirect method for estimating this missing information on response variability was devised. Please comment on the procedure used to determine the standard deviation. Please comment on the use of digitization as a method to abstract data from Johnson et al. (1977) for the derivation of the inhalation reference concentration.

4. Please comment on the selection of the uncertainty factors applied to the POD for the derivation of the RfCs. Are they scientifically justified? Are they transparently and objectively described in the document?

5. Please comment specifically on the database uncertainty factor of 3 applied in the RfC derivation. Please comment on body of information regarding reproductive, developmental toxicity (including developmental neurotoxicity), and immunotoxicity on 2-hexanone, as well as the comparability and relevance of toxicity data on n-hexane and 2,5-hexanedione in the determination of the database uncertainty factor. Please comment on whether the selection of the database uncertainty factor for the RfC has been scientifically justified. Has the selection of the database uncertainty factor been transparently and objectively described in the document?

6. Please provide any other comments on the derivation of the RfC.

**(D) Carcinogenicity of 2-hexanone**

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 2-hexanone. Please comment on the scientific justification for the cancer weight of the evidence characterization.