

## **Charge to External Reviewers for the IRIS Toxicological Review for n-Hexane**

The U.S. EPA is conducting a peer review of the scientific basis supporting the human health risk assessment of n-hexane that will appear on the Agency's online database, the Integrated Risk Information System (IRIS).

The draft documents for the external peer review contain a description of the oral database, an inhalation reference concentration, and a qualitative cancer assessment. Please provide detailed responses to the charge questions below.

### **Charge questions:**

#### **1) Oral reference dose (RfD) for n-hexane**

No oral RfD has been derived. Has the rationale and justification for not deriving an RfD been transparently described in the documents? Are there additional studies that should be considered in this decision?

#### **2) Inhalation reference concentration (RfC) for n-hexane**

a) Has the rationale and justification for deriving an RfC been transparently described in the documents? Are there additional studies that should be considered in this decision?

b) The 1990 IRIS assessment for n-hexane used a human occupational exposure study by Sanagi et al. (1980) for the derivation of the RfC. The draft reassessment for n-hexane uses a subchronic rat study by Huang et al. (1989) for the derivation of the RfC. The workers evaluated in the Sanagi et al. (1980) study had co-exposure to acetone and n-hexane. Data were identified that indicate n-hexane metabolism and n-hexane-induced neurotoxicity are potentiated by co-exposure to acetone. Thus, this study was not selected for the derivation of the RfC in the current assessment.

The rationale supporting selection of the Huang et al. (1989) study versus the Sanagi et al. (1980) study as the principal study in the derivation of the RfC is presented in Sections 5.2.1 and 5.2.4 of the Toxicological Review. Is the Huang et al. (1989) study the most appropriate selection for the principal study (i.e., best study upon which to determine the point of departure)? Has the rationale for this choice been transparently and objectively described? Is the selection of Huang et al. (1989) as the principal study scientifically objective? Is the exclusion of Sanagi et al. (1980) as the principal study based on co-exposure to acetone justified? Should the Huang et al. (1989) study and the Sanagi et al. (1980) study be considered as co-principal studies in the derivation of the RfC?

c) Has the most appropriate critical effect (decreased motor nerve conduction velocity in male rats following 12 weeks n-hexane exposure) been selected? Has the rationale and justification for this effect been transparently described? Is the selection of the critical effect scientifically justified?

d) An RfC has been derived utilizing benchmark dose modeling to define the point of departure. Is benchmark dose modeling the best approach for determining the point of departure? Has the benchmark dose modeling been accurately and transparently described? In the absence of a biological rationale for choosing an appropriate effect level, a point of departure corresponding to a change in the mean equal to one control standard deviation from the control mean has been used. Is this the best approach for determining the effect level? Has the most appropriate model been utilized? Please comment on the model choice (and the values utilized for the model parameters) as well as the approach.

e) Are the uncertainty factors applied to the point of departure for the derivation of the RfC scientifically justified and transparently and objectively described in the Toxicological Review?

f) The database for n-hexane is lacking a developmental neurotoxicity study. Given the potential increased susceptibility of the developing fetus to n-hexane-induced toxicity and the increased neurotoxicity in humans and animals following n-hexane exposure, a  $UF_{DB}$  of 3 was applied. Has the rationale and justification for the  $UF_{DB}$  been transparently described? Is the application of this UF appropriate?

### **3) Carcinogenicity of n-hexane**

Under EPA's 1999 Draft Revised Guidelines for Carcinogen Risk Assessment ([www.epa.gov/ncea](http://www.epa.gov/ncea)), *data are inadequate for an assessment of the human carcinogenic potential of n-hexane*. Do the available data support this statement? Are there additional studies that should be considered in this decision?