Charge to Reviewers for the Methyl Ethyl Ketone (MEK)
Toxicological Review and IRIS Summary

The U.S. Environmental Protection Agency is conducting a peer review of the scientific basis supporting the health hazard and dose-response assessment for methyl ethyl ketone that will appear on the Agency's online data base, the Integrated Risk Information System (IRIS). Peer review is meant to ensure that science is used credibly and appropriately in derivation of these dose-response assessments. External peer reviewers have been provided with the following charge questions:

General Questions

a. Is the document logical, clear and concise? Are the arguments presented in an understandable manner?

b. Are you aware of any other data/studies that are relevant to the assessment of adverse effects, both cancer and noncancer, from exposure to MEK?

Reference Dose (RfD)

a. The RfD is based on data for 2-butanol, a metabolic precursor of MEK, from Cox et al. (1975). Is the use of 2-butanol as a surrogate for MEK adequately supported?

b. Reduced pup weight in the F1A generation, particularly at postnatal day 21, served as the critical effect. Do you consider this effect to be a biologically relevant response?

c. Do you agree with the application of a benchmark dose (BMD) approach to identify a point of departure using data from the Cox et al. (1975) study? Would use of a NOAEL/LOAEL approach be preferable?

d. Are the appropriate uncertainty factors applied? Is the explanation for each transparent?

Reference Concentration (RfC)

a. The RfC for MEK derived in 1993 (and currently on IRIS) is based on reduced fetal weight as reported in the mouse developmental toxicity study of Schwartz et al. (1991). The RfC proposed in this reassessment is based on a different developmental endpoint – increased incidence of misaligned sternebrae – from the same Schwetz et al. (1991) study. Do you consider an increased incidence of this skeletal variant to be a biologically relevant endpoint? Would an alternative endpoint (e.g., reduced fetal body weight in the mouse) be more appropriate?

b. Do you agree with the application of a benchmark dose (BMD) approach to identify a point of departure using data from Schwetz et al. (1991)? Would use of a NOAEL/LOAEL approach be preferable?

c. The State of California has developed a draft Reference Exposure Level (REL), which is comparable to EPA's RfC, of 3 mg/m^3 based on the Mitran et al. (1997) occupational study that reported various neurological effects in MEK-exposed workers. Because of certain critical limitations in this study, it was not selected as the basis for the RfC. Is this decision adequately supported? More generally, is the weight of evidence for the neurotoxic potential of MEK adequately described?

d. Has the matter of MEK's capacity to produce interactions with other toxicants (e.g., n-hexane) been sufficiently acknowledged and accommodated in the assessment?

e. Are the appropriate uncertainty factors applied? Is the explanation for each transparent? Considering the nature of the critical effect, is an additional factor needed to reduce the point of departure to one that poses minimal health risk?

Cancer Weight-of-Evidence Evaluation

The weight of evidence characterization is discussed in Section 4.6. Have appropriate criteria been applied from the 1999 EPA draft revised Guidelines for Carcinogen Risk Assessment (Review Draft, NCEA-F-0644, July 1999, Risk Assessment Forum)?

Cox et al. (1975)

The multigeneration reproductive and developmental toxicity study by Food and Drug Research Laboratories, Inc. (Cox et al., 1975) serves as the principal study for the RfD. EPA is seeking independent peer review of this laboratory report because the study findings were not published in the peer-reviewed literature and because the study was conducted prior to the introduction of Good Laboratory Practices.

a. Was the study design adequate?

b. Were the study findings adequately reported?

c. Were the author's conclusions supported by the results?

d. Are there any notable limitations or deficiencies in this study?

e. Is EPA's summary of the study in the Toxicological Review and analysis of the study findings appropriate?

f. Overall, was the study as designed, performed, and reported of sufficient quality to use as the basis for the RfD?