Instructions to Peer Reviewers of IRIS Summaries and Supporting Documentation

The U.S. EPA is conducting a peer review of the scientific basis supporting the health hazard and dose response assessments for the subject chemical that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). Materials to be reviewed include the summary information that will appear on IRIS (the inhalation reference concentration [RfC], oral reference dose [RfD], and cancer assessment) and the supporting document, the Toxicological Review, which will also be made available to the public.

Peer review is meant to ensure that science is used credibly and appropriately in derivation of these dose-response assessments. You have been chosen as an expert on the chemical under consideration, on a scientific discipline related to at least one of the assessments, or in the field of risk assessment. At least three peer reviewers per chemical are being chosen to review the scientific basis of these draft dose-response assessments before they are forwarded on to the EPA's Consensus Process for final approval and adoption by the EPA. These hazard and dose-response assessments will then appear on IRIS and become available as Agency consensus health effect information.

The primary function of the peer reviewer should be to judge whether the choice, use, and interpretation of data employed in the derivation of the assessments is appropriate and scientifically sound. This review is not of the recommended Agency risk assessment guidelines or methodologies used to derive cancer or RfD/C assessments as these have been reviewed by external scientific peers, the public, and EPA Science Advisory Boards. The reviewer's comments on the application of these guidelines/methodologies within the individual assessments is, however, welcomed and encouraged. For example, the reviewer may ascertain whether or not there is data sufficient to support use of other than default assumptions for areas such as sensitive sub-populations or linear cancer extrapolation. The reviewer may also have opinions on other areas of uncertainty such as sub-chronic to chronic duration (when only a subchronic study is available) or an incomplete data base but should focus on the specific area of uncertainty rather than on the magnitude of the overall estimate.

A listing of Agency Guidelines and Methodologies that were used in the development of these hazard and dose-response assessments included the following: The Risk Assessment Guidelines (1986), the (new) Proposed Guidelines for Carcinogen Risk Assessment (1996), Guidelines for Developmental Toxicity Risk Assessment, Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity, Guidelines for Neurotoxicity Risk Assessment, Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry, Recommendations for and Documentation of Biological Values for Use in Risk Assessment and Use of the Benchmark Dose Approach in Health Risk Assessment. Copies of these documents (and/or their relevant sections) will be made to the reviewer upon request.

Below are two groups of questions regarding this review. The first is a set of general questions that are meant to guide you through your review. It is not imperative that you specifically answer each question of this group. The second group of questions, however, are specific for the chemical assessments and deal with areas of scientific controversy or uncertainty in which the Agency may have

to make a scientific judgment. Your input to this set of questions is considered vital to the review process.

QUESTIONS FOR IRIS PEER REVIEWERS - GENERAL

1. Are you aware of any other data/studies that are relevant (i.e., useful for the hazard identification or dose-response assessment) for the assessment of the adverse health effects, both cancer and non-cancer, of this chemical?

2. For the RfD and RfC, has the most appropriate critical effect been chosen (i.e., that adverse effect appearing first in a dose-response continuum)? For the cancer assessment, are the tumors observed biologically significant? relevant to human health? Points relevant to this determination include whether or not the choice follows from the dose-response assessment, whether the effect is considered adverse, and if the effect (including tumors observed in the cancer assessment) and the species in which it is observed is a valid model for humans.

3. For the RfD and RfC, have the appropriate studies been chosen as "principal"? The principal study should present the critical effect in the clearest dose-response relationship. If not, what other study (or studies) should be chosen and why?

4. Studies included in the RfD and RfC under the heading "Supporting/Additional studies" are meant to lend scientific justification for the designation of critical effect by including any relevant pathogenesis in humans, any applicable mechanistic information, any evidence corroborative of the critical effect, or to establish the comprehensiveness of the data base with respect to various endpoints (such as reproductive/developmental toxicity studies). Should other studies be included under the "Supporting/Additional" category? Should some studies be removed?

5. Are there other data which should be considered in developing the uncertainty factors or the modifying factor? Do you consider that the data support use of different values than those proposed?

6. Do the Confidence statements and weight-of-evidence statements present a clear rationale and accurately reflect the utility of the principal study, the relevancy of the critical effect to humans, and the comprehensiveness of the data base? Do these statements make sufficiently apparent all the underlying assumptions and limitations of these assessments? If not, what needs to be added?

QUESTIONS FOR IRIS PEER REVIEWERS - CHEMICAL SPECIFIC

1. Do you agree that the minimal hepatocellular swelling (Quast et al., 1983) is not an adverse response but the minimal hepatocellular fatty change in the midzonal region (Quast et al., 1983; Quast et al., 1986) is an adverse response?

2. Do you agree that the cardiac changes (Dawson et al., 1993) are properly characterized as variations in cardiac morphology and should not be considered adverse effects?

3. Is the weight of evidence for cancer from both oral and inhalation exposure assigned at the appropriate level?

4. Do you agree that an inhalation unit risk should not be derived from the data on kidney adenocarcinomas in male Swiss mice (Maltoni et al., 1985)?