Instructions to Peer Reviewers for Reviewing 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.

A listing of Agency Guidelines and Methodologies that were used in the development of these hazard and dose-response assessments included the following: Guidelines for Carcinogen Risk Assessment (1986), Proposed Guidelines for Carcinogen Risk Assessment (1996), Guidelines for Developmental Toxicity Risk Assessment, Proposed Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity, Proposed 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.

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 EPA's Consensus Review 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 subpopulations or linear cancer extrapolation. The reviewer may also have opinions on other areas of uncertainty such as subchronic 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.

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 to quinoline 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 noncancer, 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. Have the noncancer and cancer assessments been based on the most appropriate studies? These studies should present the critical effect/cancer (tumors or appropriate precursor) in the clearest dose-response relationship. If not, what other study (or studies) should be chosen and why?

4. In the IRIS Summary document, 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. For the noncancer assessments, are there other data that should be considered in developing the uncertainty factors or the modifying factor? Do the data support the 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 studies chosen, the relevancy of the effects (cancer and noncancer) 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 - Specific for Quinoline

1. Regarding the RfD and RfC

   (a) Is the determination that "none of the oral exposure data were reported in a manner that would allow for a meaningful quantitative dose-response assessment" and that "no human or animal inhalation toxicity data were available for consideration of an RfC" appropriate?

   (b) Was adequate justification provided for the Agency's position?

3. Regarding the cancer assessment

   (a) Did the assessment make appropriate use of liver effects that may have been precursor to tumor formation in its qualitative and quantitative considerations?

   (b) Was the time-to-tumor approach and the use of the multistage Weibull model in the TOX_RISK version 3.5 software an appropriate approach, or should another approach/model have been considered?

   (c) Was enough detail presented to adequately inform the reader regarding (1) model results (e.g., model fit) and (2) how to duplicate the quantitative assessment (given access to TOX_RISK)?

RECOMMENDATIONS

Based on your reading and analysis of the information provided, please identify your overall recommendation for the IRIS materials you have reviewed as

- acceptable as is
- acceptable with minor revision (as indicated)
- acceptable with major revision (as outlined)
- not acceptable