Charge to the Peer Reviewers: Toxicological Review and IRIS Summary for Mirex

1) Overall document quality

Please prepare a statement that addresses the overall quality of the document(s) and provide advice on approaches to improve the assessment from both technical and communication standpoint; and provide suggestions on the integration of data into an overall characterization of hazard. Questions to consider include:

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 (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) RfD derivation

a) Principal Study, Section 5.1.1: The RfD is based on a chronic rodent study in which rats were exposed to Mirex in the diet for 104 weeks (NTP 1990). The critical effect observed was toxic hepatitis. The principal study should present the critical effect in the clearest dose-response relationship. Is use of the NTP (1990) study as the principal study justified and is the rationale for this study adequately explained in the Toxicological Review?

b) Critical Effect, Section 5.1.1: The critical effect is identified as toxic hepatitis. Has the most appropriate critical effect for Mirex been chosen (i.e. that adverse effect appearing first in a dose-response continuum)? Has the critical effect been adequately described? Is this critical effect biologically significant? Finally, does the information presented from animal studies mirror what is known about the toxicity in humans and is this information adequately described?

c) Is the RfD determined for Mirex protective of adverse health effects in the general population and in sensitive sub-populations such as children and pregnant women?

d) Methods of Analysis, Section 5.1.2: Benchmark Dose Modeling (BMD) was applied to the chronic study for Mirex. Was the point of departure determined appropriately for this approach? Is the 10% response level appropriate and is the use of this response level supported adequately?

e) Uncertainty Factors, Section 5.1.3: Are the appropriate uncertainty factors used to develop the RfD? Are there other data which should be considered in developing the uncertainty factors? Is the explanation for the selection of each of the uncertainty factors transparent?

3) RfC derivation

a) No RfC has been developed in this assessment due to lack of adequate toxicity data for the inhalation route of exposure. Does the assessment appropriately addresses toxicity of mirex via the inhalation route of exposure?

b) Does the assessment appropriately addresses toxicity of Mirex via the inhalation route of exposure?

4) Cancer Weight-of-Evidence Characterization and Quantitative Assessment

The weight of evidence characterization and quantitative estimation (oral route) have been discussed in Chapters 4 and 5 of the Toxicological Review document and to a limited extent in the IRIS summary document.

a) Have the appropriate criteria from the U.S. EPA 1999 draft revised Guidelines for Carcinogenic Risk Assessment document been applied?

The available information on toxicity of mirex is discussed in the Toxicological Review and in the IRIS summary documents. The 1999 draft revised Guidelines for Carcinogen Risk Assessment state that a linear dose-response approach should be taken when the mode of action information is supportive of linearity or mode of action is not understood. In the absence of adequate data in support of mode of action for carcinogenesis at dosages higher than the non-cancer events this assessment presents a non-linear Dose-Response model for carcinogenic assessment.

b) Are the tumors observed biologically significant? Are the tumors observed 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.

c) Was the mode of action section presented clearly and logically? Are there any additional studies that would enhance the mode of action information presented in the Toxicologic Review? Based on the mode of action information in the Toxicological Review and IRIS summary as well as the 1999 draft revised Guidelines for Carcinogen Risk Assessment, is linear dose-response modeling for cancer assessment appropriate for Mirex?