DRAFT-DO NOT CITE OR QUOTE

Draft Charge to External Reviewers for the IRIS Toxicological Review of Chlordecone (Kepone)

January 24, 2008

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of chlordecone that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by the EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD). There is currently no assessment on the IRIS database for the health effects associated with chlordecone exposure.

The draft health assessment includes a chronic Reference Dose (RfD) and a carcinogenicity assessment. Below is a set of charge questions that address scientific issues in the assessment of chlordecone. Please provide detailed explanations for responses to the charge questions.

(A) General Charge Questions:

1. Is the Toxicological Review logical, clear and concise? Has EPA accurately, clearly and objectively represented and synthesized the scientific evidence for noncancer and cancer hazard?

2. Please identify any additional studies that should be considered in the assessment of the noncancer and cancer health effects of chlordecone.

3. Please discuss research that you think would be likely to reduce uncertainty in the future assessments of chlordecone.

4. Please comment on the identification and characterization of sources of uncertainty in sections 5 and 6 of the assessment document. Please comment on whether the key sources of uncertainty have been adequately discussed. Have the choices and assumptions made in the discussion of uncertainty been transparently and objectively described? Has the impact of the uncertainty on the assessment been transparently and objectively described?

Chemical-Specific Charge Questions:

(B) Oral reference dose (RfD) for Chlordecone

1. A chronic RfD for chlordecone has been derived from the 2-year dietary study (Larson et al., 1979a) in rats. Please comment on whether the selection of this study as the principal study has been scientifically justified. Has this study been transparently and objectively described in the document? Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. Kidney (glomerular) lesions, liver lesions, and reproductive effects are all sensitive

effects of chlordecone exposure. Glomerular lesions in the kidney was selected as the most appropriate critical effect. Please comment on whether the selection of glomerular lesions as the critical effect instead of reproductive endpoints (such as testicular lesions) has been scientifically justified. Is this choice transparently and objectively described in the document? Please provide detailed explanation. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. Some evidence exists to suggest that the mechanism of the critical effect selected for determination of the point of departure (POD) (i.e., glomerular lesions) may be mediated through an autoimmune mechanism. Please comment on whether the available immunotoxicity data support this proposed MOA. Is this proposed MOA scientifically justified and transparently described?

4. The chronic RfD has been derived utilizing benchmark dose (BMD) modeling to define the POD. All available models were fit to the data for the incidence of glomerulosclerosis in female rats. Please provide comments with regards to whether BMD modeling is the best approach for determining the POD. Has the BMD modeling been appropriately conducted and objectively and transparently described? Has the benchmark response selected for use in deriving the POD been scientifically justified? Is it transparently and objectively described? Please identify and provide rationale for any alternative approaches (including the selection of BMR, model, etc.) for the determination of the POD, and if such approaches are preferred to EPA's approach.

5. Please comment on the selection of the uncertainty factors applied to the POD for the derivation of the RfD. For instance, are they scientifically justified and transparently and objectively described in the document?

6. An uncertainty factor was considered necessary to account for deficiencies in the chlordecone toxicity database (e.g. absence of standard two-generation reproduction studies and immunotoxicity studies). Please comment on whether the rationale and justification for the application of the database uncertainty factor has been scientifically justified and transparently described in the document. Please comment on whether the available immunotoxicity data for chlordecone indicate that additional immunological studies could result in a different POD.

(C) Carcinogenicity of Chlordecone

1. Under the EPA's 2005 *Guidelines for carcinogen risk assessment* (http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=116283), there is *suggestive evidence of the human carcinogenic potential* of chlordecone. This characterization lies at the high end of the continuum for this weight of evidence descriptor. Please comment on the scientific justification for the cancer weight of the evidence

characterization. Has the scientific justification for the weight of evidence characterization been sufficiently, transparently, and objectively described? A quantitative cancer assessment has not been derived for chlordecone. Do the data support an estimation of a cancer slope factor for chlordecone? Please comment on the scientific justification for not deriving a quantitative cancer assessment considering the uncertainty in the data and the suggestive nature of the weight of evidence of carcinogenic potential.