Application of Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation (Draft)

Charge Questions for External Reviewers

In recent years, EPA and other international organizations have developed new approaches and guidance which are intended to improve the scientific support for risk assessment. In 2005, IPCS published its guidance on deriving Chemical Specific Adjustment Factors (CSAFs). This CSAF guidance describes approaches for use of kinetic and mechanistic data to refine interspecies and intraspecies extrapolation factors. The IPCS guidance is largely based on analyses by Renwick (1993) and Renwick and Lazarus (1998), which describe the use of toxicokinetic and toxicodynamic data as a means of replacing the traditional 10× for human sensitivity and experimental animal-to-human extrapolation.

The Risk Assessment Forum commissioned a technical panel within EPA to develop guidance similar in concept to the IPCS CSAF guidance. Guidance in this draft document differs from that of IPCS is several aspects, such as the values suggested for use as defaults when data are not available to develop factors derived from data. EPA's draft places an increased emphasis on determining concentrations of the active chemical species in the target tissue rather than in the central compartment (circulating blood), including target tissue metabolism as part of the toxicokinetic rather than the toxicodynamic component. In addition, compared to the IPCS document, the EPA has included more discussions of some issues such as mode of action in animals and its relevance to humans, the use and evaluation of *in vitro* data, and some specifics of computational methods.

Question 1: Purpose & Scope.

1a. Is the purpose of the draft document clearly communicated?

1b. The draft guidance does not address science policy issues, such as determining a critical effect or evaluating PBPK models which are described in other EPA documents. In addition, the draft guidance does not address issues related to developing points of departure from benchmark dose modeling or determining an appropriate percentile of regulation when using probabilistic approaches which were determined by the Panel to be beyond the scope of this effort. While some comments on terminology ("Extrapolation Factors", "Uncertainty Factors", and "Adjustment Factors") applied to these non-default (DDEF) values, a consistent recommendation for their nomenclature has not been identified. This draft chose not to use "uncertainty factors" because they are an improvement over gross uncertainty and not to use "adjustment" factors because of the negative connotations associated.

Please comment on the content and scope of the draft document and nomenclature applied to non-default values.

1c. The draft DDEF document is intended to complement, build upon, and be consistent current Agency guidance documents. For example, the draft document describes the relationship between DDEFs and other approaches such as the RfC methodology and the ¾ body weight scaling document.

Is the relationship of this draft document to other pertinent Agency risk assessment guidance and/or reference documents well described?

Question 2: Organization & Clarity

The draft document is organized in five major sections: introduction, technical concepts, toxicokinetics, toxicodynamics, and final steps. The draft document uses figures, tables, and equations as visual aids.

Please comment on the overall organization of the draft document with regard to readability and understanding. Do the figures, tables and equations enhance the presentation of materials?

Question 3: Technical Issues

3a. Is the document scientifically and technically sound?

3b. Both this document and the IPCS document advocate the use of clearance measures to quantify inter and intraspecies toxicokinetic differences. Clearance and AUC values are inversely related, in that for the same dose as clearance increases, AUC values decrease. This inverse toxicokinetic relationship forces a reversal of the usual arrangement of terms representing the sensitive species or individual in equations.

Please comment on the clarity of this presentation and equations.

Question 4: Case Studies

The Panel developed a series of case studies, primarily from assessments performed by IRIS and the Office of Pesticide Programs. These case studies are intended to show the application of the DDEFs and specific principles described in the draft guidance.

Are the example case studies logically organized and do they enhance the utility of the draft document?

Question 5: Additional Comments

Please provide feedback and comments on other issues you have identified in your review.