<u>Charge to Reviewers for the Revised Sections of the Boron Toxicological Review and IRIS Summaries.</u>

The U. S. EPA is conducting a peer review of the scientific basis supporting the health hazard and dose response assessment for Boron that will appear on the Agency's online data base, the Integrated Risk Information System (IRIS). Peer Review is meant to ensure that science is used credibly and appropriately in derivation of these dose-response assessments. The primary function of the peer reviewer should be to judge whether the choice, use and interpretation of the data employed in the derivation of the assessment is appropriate and scientifically sound. This review is not of the recommended agency risk assessment guidelines or methodologies as those have been reviewed by external scientific peers, the public and the EPA Science Advisory Boards.

The IRIS Toxicological Review for Boron and IRIS Summary Sheets have previously gone through two internal and external reviews. However, certain sections of the Toxicological Review have been revised since these peer reviews took place. Revisions to the last external review draft were made based on some external reviewer comments and comments from the public when the external review draft was posted on the National Center for Environmental Assessment web site.

While all external peer review and public comments strongly supported using a data-derived approach for addressing uncertainty factors, a few methodological issues remained. Therefore, the previous method for using data to derive an uncertainty factor has been revised with this new draft. This revised method has been through the agency's internal review process, and has been submitted for one more formal external peer review.

Due to the amount of review that this document has already received we are requesting review comments **only** on the revised method of using toxicokinetic data to replace uncertainty factors. However, you will probably need to familiarize yourself with other parts of the document that pertain to the data used in the assessment. The following sections have been revised. The questions for reviewers apply to those sections only.

Toxicological Review: 5.1.3 Derivation of the RfD

RfD Summary Sheet: I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

Questions for Reviewers

1.   The Agency as yet has no guidance for using toxicokinetic or toxicodynamic data for modification of uncertainty factors for Reference Doses. Therefore the use of

toxicokinetic data for establishing the boron RfD could set some precedents that will need scrutiny.   Please carefully evaluate the many different and sometimes complex arguments in Section 5.1.3 as to their organization, clarity, and scientific merit. Do they hang together?

2.   Is the approach we're taking for an uneven split of the kinetic and dynamic components of the interspecies uncertainty factor reasonable? Is the default split for the interspecies uncertainty factor of 4.0 for kinetics and 2.5 for dynamics the correct one?

3.   For the interspecies extrapolation, a simple kinetic model is presented for linking the specific kinetic extrapolation variable (boron clearance) to external exposure. Is this model reasonable? Are there any implicit assumptions that need to be stated? Are the various surrogacy assumptions reasonable? Are the clearance data adequate for the purpose. Do you agree that the data are adequate for reduction of the interspecies kinetic uncertainty subfactor (UF_{AK}) to 1.0?

4.   For the intra-human toxicokinetic variability assessment, do you agree that GFR variability is an adequate surrogate for variability in boron clearance and provides a less uncertain estimate than using the boron clearance data of Pahl et al. (2001)? Do you agree with the general approach for determining intra-human variability (ratio of mean GFR to 0.1 percentile)? If not, is there a more viable alternative? Is the assumption of a lognormal distribution adequately supported? Is the magnitude of the residual uncertainty in UF_{HK} appropriate?

5.   Are there any other critical issues on which we have not explicitly asked for comment?