Harmonization in Interspecies Extrapolation: Use of $BW^{3/4}$ as Default Method in Derivation of the oral RfD

CHARGE QUESTIONS - EXTERNAL PEER REVIEW

The current approaches to interspecies adjustments for dose are different for non-cancer and cancer dose-response assessments for ingested chemicals. This document is a draft Risk Assessment Forum Technical Workgroup paper. This document recommends body weight scaling to the ¾ power, $BW^{3/4}$, as a general default procedure to extrapolate human equivalent doses of orally administered agents from laboratory animals for the purposes of deriving an Reference Dose (RfD). Use of $BW^{3/4}$ in derivation of RfD values would be in parallel with current Agency use of $BW^{3/4}$ scaling in derivation of cancer oral slope factors. Thus, this paper would harmonize the two main Agency oral dose-response extrapolation procedures. The Peer Reviewers are being asked to review the scientific rationale for this recommendation. Final decisions on implementing the recommendation of body weight scaling to the ¾ power for derivation of RfDs will be made by the Agency's Science Policy Council. Comments from the external peer reviewers will help inform Agency with regard to the science.

CHARGE QUESTIONS

If you believe one of the questions is not applicable to your expertise, please state this as your answer.

1. Please comment on the recommendation of applying body weight scaling to the ¾ as a general default procedure to extrapolate toxicologically equivalent doses of chronic orally administered agents from laboratory animals to humans for the purposes of deriving an Reference Dose values.

- Is the rationale underlying this approach scientifically supported and adequately explained in the report?
- Do you believe that alternative methods of interspecies default scaling procedures have been adequately presented and discussed in the text?
    - Is there sufficient guidance on when the default may no longer be applicable *en toto,* i.e., the intermediate level in the hierarchy presented in Table 3?
    - Is the discussion of the extent to which $BW^{3/4}$ scaling accounts for toxicokinetics and toxicodynamics clear?
- Do you know of critical data in the literature not cited here that would impact the recommendations?
- Are the underlying assumptions and limitations in the application of $BW^{3/4}$ scaling clearly explained so the approach can be appropriately implemented? Are considerations, such as effects produced at the portal of entry and physiological time scaling of $BW^{1/4}$, adequately addressed?

2. Although BW scaling analyses have dealt almost exclusively with adult organisms, the document includes some discussion with respect to early life stages and recommends that, for deriving traditional chronic RfDs for the human population (including sensitive subgroups),

scaling be based on adult human body weight as a default approach.

- Is the rationale underlying this recommendation adequately justified?
- Should early life or other lifestages be addressed in this document, or should a default be assumed to encompass all lifestages?
- Do you know of critical data in the literature not cited here that would impact the recommendation?
- Have the uncertainties and data limitations associated with the extrapolation across life stages and other sensitive subgroups been sufficiently addressed?

3. The paper recommends reduction of the default interspecies uncertainty factor of 10 to 3 after application $BW^{3/4}$ scaling.

- Is the rationale underlying this reduction of the default value for this uncertainty factor adequately explained and justified in the report?
- Is the division of and the accounting for toxicokinetics and toxicodynamics clearly presented?
- Do you know of critical data in the literature not cited here that would impact the recommendation?

4. The Agency is working to implement reference values over varying durations of exposure. In your opinion, does this analysis present sufficient information for use of $BW^{3/4}$ scaling for other than chronic exposures, e.g., acute exposures?

5. Please comment on whether, in your opinion and to the best of your knowledge, the analysis of the literature is accurate, reliable, unbiased, and reproducible. Has a strong supporting argument of $BW^{3/4}$ been presented in the text? Is the report clear, well organized, and well-written? Do you believe any additional documentation is necessary to ensure clarity or transparency?

6. Please provide any additional comments pertinent to the recommendation of body weight scaling to the ¾ power for derivation of RfDs that would help improve the overall quality of document.