

**Summary Report of the
Peer Review Teleconference on
*Harmonization in Interspecies Extrapolation:
Use of $BW^{3/4}$ as Default Method in Derivation of the Oral RfD***

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NOTICE

This report was prepared by Versar, Inc., an EPA contractor (Contract No. 68-C02-061, Task Order No. 124), as a summary of the discussion of the Peer Review Teleconference on the draft Harmonization in Interspecies Extrapolation: Use of $BW^{3/4}$ as Default Method in Derivation of the Oral RfD (June 14, 2006). This report captures the main points and highlights of the teleconference. It is not a complete record of all detailed discussion, nor does it embellish, interpret, or enlarge upon matters that were incomplete or unclear.

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EXECUTIVE SUMMARY

A peer review teleconference on the draft U.S. Environmental Protection Agency (EPA), Risk Assessment Forum Technical Workgroup document "*Harmonization in Interspecies Extrapolation: Use of BW^{3/4} as Default Method in Derivation of the Oral RfD*" was held on June 14, 2006. This one-day teleconference was organized and hosted by Versar, Inc. for EPA's Risk Assessment Forum. Seven experts were convened by Versar with expertise in areas such as interspecies extrapolation and uncertainty factors, allometric scaling, cancer dose-response analysis, and general risk assessment approaches. The reviewers provided comments and suggestions for improvements to the document in the form of general recommendations, responses to six charge questions, and other specific changes to the document's text, tables, and figures. The reviewers felt that these revisions will improve the clarity, accuracy, and applicability of the document to the target audience.

The reviewers commended the authors for the development of this clearly and carefully framed document supporting the use of BW^{3/4} scaling for interspecies extrapolation in derivation of oral RfDs. This document is a welcome addition to guidance for developing regulatory values for non-cancer effects. The document is well written and organized. It makes a scientifically sound case for the use of BW^{3/4} scaling as a generic default for cross-species equivalence of oral exposures. In the reviewers' opinions, the recommendation to proceed to use of BW^{3/4} scaling of chemical toxicity to humans as the default approach is scientifically sound, superior to the currently used approach, and consistent with interspecies scaling approaches used for deriving inhalation toxicity and carcinogenicity reference values. However, the document needs to maintain a focus on the appropriateness of BW^{3/4} scaling as a replacement for the current BW scaling plus uncertainty factor default, rather than justifying its use de novo. There also needs to be an early discussion of the applicability of the default relative to the preferred approaches of employing PBTK modeling or use of available chemical specific data. The BW^{3/4} scaling formulas should be presented when the concept is first presented.

The conclusion that BW^{3/4} should be used for acute or portal of entry exposures needs to be put in the executive summary rather than in an appendix or buried in the discussion. The portal of entry discussion is very confusing, and needs to be clarified. Further, the assumptions and limitations, which are discussed at many different points in the document, need to be summarized near the front of the document. The document also needs to characterize the species for which default scaling applies and species that may not fit. Only rat and mouse are explicitly mentioned. Other species of common use in toxicity studies should also be discussed (monkeys, dogs, rabbits, etc.) The discussion of the limitations of the default scaling for the case of metabolite toxicity is inadequate.

The reviewers agreed with the document's conclusion that human equivalent doses (HEDs) for toxicity observed in adult animals should be based on BW^{3/4} scaling using the adult animal and human body weights and that this approach is likely to be protective for early life exposures. However, the discussion in the document (particularly Table 2) may give the impression that the Agency also supports the use of BW^{3/4} scaling for intraspecies extrapolation in humans which the

reviewers do not endorse as a default approach. Therefore, the text needs to clearly state that the question of a default intraspecies scaling approach is outside the scope of this document and should emphasize that addressing human variability is a separate consideration in the process of deriving a RfD. Also, Table 2 should be deleted or at the least heavily caveated to ensure that there is no confusion on this point. Also, the document needs to include a discussion of the issues associated with the cross-species extrapolation of endpoints in young animals as opposed to adults.

The document presents sufficient justification for use of $BW^{3/4}$ scaling for acute endpoints, except in the case of lethal effects (e.g., LD_{50} s). The basis for $BW^{3/4}$ scaling from a consideration of clearance holds for short-term exposures as well as for long exposures. Some acute frank effects may depend on C_{Max} , which depends on the rate of absorption and the volume of distribution, as well as clearance, so that $BW^{3/4}$ scaling would not apply. There needs to be a clarification of the types of guidelines that are being considered as it is unlikely that an RfD would be based on frank or lethal effects.

There also needs to be a more complete discussion of the considerations for determining whether to use chemical-specific data versus using the default. An evaluation of the chemical-specific evidence consistent with the IPCS CSAF approach should be used for this purpose. A detailed decision tree that considers the nature of the risk assessment (lifestage, portal of entry vs. systemic, acute vs. chronic, etc.), chemical properties (mode of action, parent chemical vs. metabolite toxicity, species-dependent half-life/clearance differences, etc.) is needed. The use of clearance concepts provides a connection between the default and the CSAF approach and provides insight on the considerations that are necessary for determining whether the default should be applied. The default scaling and CSAF approaches should be brought together eventually, but even in this document the basic concepts underlying the CSAF approach can be used to direct decision making regarding the use of the default.

The discussions in the document need to be more succinct in order to make more of an impact on the reader. The discussion should be focused on the simple idea that the proposed default is practicable and is more scientifically justifiable than the present default, and therefore represents a step forward. The document should acknowledge that a chemical may have multiple target tissues included in the discussion.

Finally, the document would be improved by a list of acronyms and a glossary.

1.0 INTRODUCTION

1.1 Purpose

A peer review teleconference of the draft U.S. Environmental Protection Agency (EPA), Risk Assessment Forum (RAF) Technical Workgroup document *Harmonization in Interspecies Extrapolation: Use of $BW^{3/4}$ as Default Method in Derivation of the Oral RfD* was held on June 14, 2006. This one-day teleconference was organized and hosted by Versar, Inc. for EPA/RAF.

The document reviewed endorses body weight scaling to the $3/4$ power, i.e., $BW^{3/4}$, 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 RfD. The supporting document by Rhomberg and Lewandowski provides a critical review and analysis of the scientific literature on this subject. Use of $BW^{3/4}$ in derivation of RfD values is parallel with current Agency use in derivation of oral cancer slope factors. Thus, this default scaling procedure is a point of harmonization between the two main Agency oral dose-response procedures. This generalized default procedure is viewed as an informed, species-specific, dosimetric adjustment factor (DAF) that addresses predominately toxicokinetic and some toxicodynamic aspects of the interspecies uncertainty factor, UF_A . Use of this procedure would result in derivation of a human equivalent exposure, specifically a human equivalent dose, HED, that is to be used in derivation of the oral RfD in a manner parallel to the human equivalent concentration, HEC, in derivation of an inhalation RfC.

1.2 Participants

The seven reviewers selected by Versar, Inc. to perform the peer review are experts in areas such as interspecies extrapolation and uncertainty factors, allometric scaling, cancer dose-response analysis, and general risk assessment approaches. The reviewers included individuals from academia, consulting, industry, and the government. The experts certified that they had no conflicts of interest relative to this document prior to being selected by Versar for the peer review. The list of reviewers is presented in Appendix A. A list of observers is listed in Appendix B.

1.3 Agenda

The agenda for the peer review teleconference is presented in Appendix D. The call began with a welcome, introductions, and outline of the goals of the peer review. Background on the document's purpose, intended audience, and scope was provided by EPA. The reviewers were charged with providing technical feedback, recommendations, and input to the document, based on six charge questions (Appendix C) developed by EPA to help guide and focus the discussion. The reviewers made recommendations throughout the teleconference as they responded to each charge question.

1.4 Organization of Summary Report

This report presents information on the presentations and discussions from the teleconference:

- Section 2 of this report summarizes the opening presentations and discussion on the purpose and procedures for the conduct of the peer review workshop. Section 3 contains summaries of the reviewers' general comments, responses to charge questions, and summary points from the teleconference.
- The appendices to this report are as follows:

Appendix A - List of Peer Reviewers

Appendix B - List of Observers

Appendix C - Charge Questions

Appendix D - Agenda for the Teleconference

Appendix E - PowerPoint Presentations

Appendix F - Written Comments from the Reviewers

2.0 SUMMARY OF PRESENTATIONS AND BACKGROUND ON THE DOCUMENT

This section presents summaries of the opening presentations and introductions given by David Bottimore, Versar, Inc., William Wood, EPA Risk Assessment Forum, Peer Review Chair Harvey Clewell, CIIT Centers for Health Research, and Resha M. Putzrath, EPA Risk Assessment Forum. Slides supporting the presentations can be found in Appendix E.

2.1 Goals of Teleconference and Introductions

Mr. David Bottimore, of Versar, Inc., provided welcoming remarks and outlined the objectives and procedures for the teleconference. He stated that the goal of the peer review was to provide feedback on the scientific content and utility of the document, but noted that they would not be seeking consensus. A diversity of opinions would be welcome reflecting the different disciplines and perspectives of the experts. Mr. Bottimore reviewed the materials that the participants should have received, which included pre-meeting comments from the expert reviewers, the charge questions, and the agenda for the teleconference. He then initiated introductions by each of the reviewers.

Dr. William Wood introduced the Risk Assessment Forum as a standing committee of the Agency that issues risk assessment guidance. Dr. Wood noted that the Forum most recently issued revised cancer risk assessment guidelines. The present document is the result of the EPA's desire for harmonizing the Agency's approaches for deriving toxicity reference values for cancer and non-cancer risk assessment. Dr. Wood said that after the Forum revises the document, taking into account the results of the peer review and the public comments, the revised document will be sent to the Science Policy Council for its approval. At that point, it

will become EPA policy. Once it is completed, a Federal Register notice will announce the document's availability.

The chair, Mr. Harvey Clewell, briefly reviewed the ground rules for the teleconference. He stated that he wanted a different reviewer to begin the discussion of each of the six charge questions and made his choices based on the areas of expertise, which was often reflected in the pre-meeting comments. Accordingly, he also expressed the desire to modify a few of the charge questions, moving some of the sub-bullets under other charge questions for improved continuity of discussion. Finally, Mr. Clewell also stated that reviewer's members had the option to submit revised written comments after the teleconference.

Dr. Resha Putzrath of the Risk Assessment Forum provided background for the document and stated that this document is part of a series of documents that are attempting to harmonize cancer and non-cancer risk assessment. Dr. Putzrath stated that this topic has come up in a number of forums and is incorporated in the 2005 cancer guidelines. Dr. Putzrath stated that typically before using a default, the risk assessor should consider all of the data on the particular chemical before going to a surrogate or to a default value. It is in situations where there is little or no information on a chemical that the default would be used. Other documents in this series include the 1992 Federal Register for cancer endpoints, the 2002 on RfD, the 2005 cancer guidelines, and this document. Dr. Putzrath stated that a default value is needed for oral, non-cancer endpoints and the decision was made to use the $BW^{3/4}$.

3.0 PEER REVIEW COMMENTS ON THE DOCUMENT

This section presents a summary of the reviewers' comments and suggestions for improving the document. The summary is organized according to the discussion during the teleconference – starting with general overview comments followed by specific responses to the six charge questions. The reviewers prepared pre-meeting comments (Appendix F), which were the starting points for discussion during the teleconference. The following general comments and specific responses to charge questions were developed by the reviewers.

3.1 General Comments

Mr. Clewell requested general comments from the reviewers on the document, requesting that they focus on overarching issues. The reviewers commended the authors for the development of this clearly and carefully framed document supporting the use of $BW^{3/4}$ scaling for interspecies extrapolation in derivation of the oral RfD. This document is a welcome addition to guidance for developing regulatory values for non-cancer effects. The document is well written and organized. It makes a scientifically sound case for the use of $BW^{3/4}$ scaling as a generic default for cross-species equivalence of oral exposures. The document needs to maintain a focus on the appropriateness of $BW^{3/4}$ scaling as a replacement for the current BW scaling plus uncertainty factor default, rather than justifying its use de novo.

There needs to be an early discussion when the use of the default is applicable. One of the reviewers believed that this was a significant weakness in the document, which could be

improved by introducing the topic in the Executive Summary or Introduction sections of the document. The $BW^{3/4}$ scaling formulas should be presented when the concept is first presented. This discussion should also use material from the Rhomberg and Lewandowski support document and the general comments from Dr. Gaylor (Appendix F).

The conclusion that $BW^{3/4}$ should be used for acute or portal of entry exposures needs to be put in the executive summary rather than in an appendix or buried in the discussion. Also, even though the document is well written, there seems to be at times too much justification presented.

The document would be improved by a list of acronyms and a glossary.

3.2 Response to Charge Questions

3.2.1 Charge Question 1

Please comment on the recommendation of applying body weight scaling to the $3/4$ 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 Reference Dose values.

In the reviewers' opinions the recommendation to proceed to use of $BW^{3/4}$ scaling of chemical toxicity to humans as the default approach is scientifically sound, superior to the currently used approach, and consistent with interspecies scaling for deriving inhalation toxicity and carcinogenicity reference values.

- *Is the rationale underlying this approach scientifically supported and adequately explained in the report?*

The draft document's "guiding paradigm" is "that a common internal dose is the ultimate determinant of risk." This is a highly reasonable default position. The reviewers agree, in general, with the rationale presented in the document, which focuses on the strong empirical support for less than body weight scaling. However, the document should also present the emergence over the last ten years of more scientific rationale for $BW^{3/4}$ (West, Brown and Enquist publications cited by Dr. Hayton). Moreover, the document, should discuss the allometric scaling of clearance as support for the use of $BW^{3/4}$ scaling. The comments of Dr. Hayton in this area should be considered (Appendix F). Users of the default approach need to be aware of why it would fail (e.g., differences in metabolism), and clearance concepts would help in this respect. The document should discuss these issues in greater detail.

The actual computational approach for $BW^{3/4}$ scaling needs to be better explained. The formulas should be presented early in the document, perhaps even in the Executive Summary. Rhomberg and Lewandowski provide a clear explanation of the approach in Appendix A (p. A-2) of their paper. It is also important to better explain when the use of the default is appropriate and when it is not.

- *Do you believe that alternative methods of interspecies default scaling procedures have been adequately presented and discussed in the text?*

The document describes the current use, by USEPA for non-cancer effects, of BW with an exponent of unity; i.e., of application of mg/kg dosage associated with toxicity in animals directly to humans, along with an uncertainty factor. The proposed $BW^{3/4}$ approach for scaling is superior. The reviewers also support the preference of $BW^{3/4}$ scaling to $BW^{2/3}$ (body surface area) scaling.

The document should discuss the fact that the concentration in the diet can also serve as the basis of equivalence. The document should also point out that the scaling of dietary intake corresponds roughly to $BW^{3/4}$. This point can serve as a rationale for using $BW^{3/4}$ for oral portal of entry effects. However, it is important to note that dosing is not always in food.

- *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?*

Discussed in the context of charge question 5.

- *Is the discussion of the extent to which $BW^{3/4}$ scaling accounts for toxicokinetics and toxicodynamics clear?*

Discussed in the context of charge question 3.

- *Do you know of critical data in the literature not cited here that would impact the recommendations?*

Krishnan and Andersen (1991, Interspecies scaling in pharmacokinetics. In: New trends in pharmacokinetics, Rescigno A and Thakur AK, eds. Plenum press, NY, pp203-226) indicate that the dose scaling for stable metabolites is likely to follow BW. The present document is in variance with this publication.

- *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?*

The assumptions and limitations, which are discussed at many different points in the document, need to be summarized near the front of the document as do the conclusions in the document regarding the applicability of $BW^{3/4}$ scaling for portal of entry and acute exposures.

The document needs to characterize the species for which the default scaling applies and species that may not fit. Only rat and mouse are explicitly mentioned. Other species of common use in toxicity studies should also be discussed (monkeys, dogs, rabbits, etc.) The discussion of the limitations of the default scaling for the case of metabolite toxicity is inadequate. The portal of entry discussion is very confusing and needs to be clarified. The reviewers did not see a clear way forward in what was presented. Some sort of a decision tree that would show when to use

or not to use the default would be very helpful, as was discussed in more detail under charge question 5.

3.2.2 Charge Question 2

Although BW scaling analyses have dealt almost exclusively with adult organisms, the document includes some discussion with respect to early lifestages 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?*

On this question, it was apparent that the reviewers had very different interpretations of what the section was presenting. The reviewers did agree with the document's conclusion that human equivalent doses (HEDs) for toxicity observed in adult animals should be based on $BW^{3/4}$ scaling using the adult animal and human body weights and that this approach is likely to be protective for early life exposures. However, the discussion in the document (particularly Table 2), may give the impression that the Agency also supports the use of $BW^{3/4}$ scaling for intraspecies extrapolation in the human which the reviewers do not endorse as a default approach. Therefore, the text needs to clearly state that the question of a default intraspecies scaling approach is outside the scope of this document. The document should emphasize that addressing human variability is a separate consideration in the process of deriving a RfD. Also, Table 2 should be deleted or at the least heavily caveated to ensure that there is no confusion on this point. A number of the reviewers did suggest that Table 2 should simply be deleted.

- *Should early life or other lifestages be addressed in this document, or should a default be assumed to encompass all lifestages?*

The document currently only addresses the question of whether the use of adult animal-to-adult human $BW^{3/4}$ scaling of toxicity observed in adult animals is protective for early life exposure in the human; it does not address the case of a risk assessment based on a developmental endpoint, where the toxicity is observed during early life in the animal. In the latter case, the $BW^{3/4}$ extrapolation would presumably be performed either using the body weights of the pups and the human infant (for direct pup dosing studies), or using the maternal body weights (for maternal dosing studies). The reviewers support the use of $BW^{3/4}$ scaling as a default for these early life endpoints as well, but believe that there is much greater uncertainty in these cases. It is not possible to adequately define the limitations of this approach because of a lack of studies. At present, the justification for using $BW^{3/4}$ scaling of early life effects is essentially pragmatic; it is more conservative than the current default and makes the early life endpoint approach consistent with the adult endpoint approach. Therefore, the document needs to include a discussion of the issues associated with the cross-species extrapolation of endpoints in young animals as opposed to adults. This discussion needs to differentiate the issues of concern for direct pup dosing and maternal dosing.

- *Do you know of critical data in the literature not cited here that would impact the recommendation?*

The Agency will need to review the literature on comparisons of early life kinetics across species, including differences in maturation of clearance processes and lactational transfer.

- *Have the uncertainties and data limitations associated with the extrapolation across lifestages and other sensitive subgroups been sufficiently addressed?*

No. Currently, the document does not provide a rationale for $BW^{3/4}$ scaling when the critical effect occurs during the period of development. In fact, the evidence for the use of $BW^{3/4}$ scaling comes from data on adult animals, and its applicability to early life endpoints is more uncertain. (The Reviewers considered early life in the human as perinatal to approximately two years of age.) The document should discuss these uncertainties, including potential differences in maturation (ontogeny) of clearance processes (metabolic, renal, etc.), and placental/lactational transfer (similar to portal of entry effect discussion) across species. The document needs to identify the key data gaps in this regard to encourage the research that could address them. It is clear that further studies are needed. The document should present a rationale for the use of scaling $BW^{3/4}$ to early life. In addition, the reviewers strongly suggested that $BW^{3/4}$ should not be used for scaling health endpoints across ages in the human. However, the panel agreed that scaling $BW^{3/4}$ between animals and humans is an acceptable practice.

3.2.3 Charge Question 3^a

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?*

No. The rationale for using 3 for the residual default uncertainty factor (UF) is not adequate, and probably cannot be made adequate. The basis appears to be science policy for consistency with the RfC dosimetry approach. If so, this should be so stated. It should also be pointed out that the residual factor is different from the factor of 2.5 recommended by IPCS and that there is a different rationale for the derivation of the residual factor (10 divided by the PK factor in the case of IPCS vs. the square root of 10 each for PK and PD in the RfC guidelines). Most importantly, it should be made clear that there is no empirical evidence to support the use of 3 for the residual UF. The discussion of PD scaling is philosophical not evidential. It is a policy decision. Further, the discussion on page 15 is confusing and at times contradictory. The text need to only address it once not multiple times.

The discussion in the last paragraph on page 32 should be moved to the beginning of the document and the Executive Summary to show the impact of the default change.

- *Is the division of and the accounting for toxicokinetics and toxicodynamics clearly presented?*

^a For clarity, it is noted that the values of uncertainty factors discussed in the charge questions and by the Reviewers are the “defaults” or “maximum” values that would be used. As is common practice at EPA, these values may be lower, including as low as 1, based on chemical-specific information.

The reviewers agreed that it was not clearly presented. The reviewers noted that there are conflicting statements throughout the document on this issue. There should be one discussion that clearly states the basis for the decision to use 3 for the residual UF. The reviewers seemed to agree that the decision to use 3 was based on a policy decision and not on the analysis of empirical data.

- *Do you know of critical data in the literature not cited here that would impact the recommendation?*

In the case of the RfD for boron, a CSAF was used for animal-to-human PK, and 3 was used for animal-to-human PD, whereas in this document the same factor of 3 appears to include uncertainty in PK.

3.2.4 Charge Question 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?

There appears to be sufficient justification for use of $BW^{3/4}$ scaling for acute endpoints, except in the case of lethal effects (e.g., LD_{50} s). The basis for $BW^{3/4}$ scaling from a consideration of clearance holds for short-term exposures as well as for long exposures. Some acute frank effects may depend on C_{Max} which depends on the rate of absorption and the volume of distribution as well as clearance so that $BW^{3/4}$ scaling would not apply in these situations. There needs to be a clarification of the types of guidelines that are being considered as it is unlikely that an RfD would be based on frank or lethal effects. The definition “acute” needs to be clearly defined to avoid any confusion of its usage in the document. This discussion should also be incorporated into the Executive Summary.

3.2.5 Charge Question 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?

The reviewers agreed that the authors need to expand Table 3 in the document using the discussion on pages 17 and 18 of the document as well as Figure 3 in Rhomberg and Lewandowski. It was suggested that Table 3 and Figure 3 be combined and introduced earlier in the document.

There needs to be a more complete discussion of the considerations for determining whether to use chemical-specific data versus using the default. An evaluation of the chemical-specific evidence consistent with the IPCS CSAF approach should be used for this purpose. A detailed

decision tree that considers the nature of the risk assessment (lifestage, portal of entry vs. systemic, acute vs. chronic, etc.), chemical properties (mode of action, parent chemical vs. metabolite toxicity, species-dependent half-life/clearance differences, etc.) is needed. The use of clearance concepts provides a connection between the default and the CSAF approach and provides insight on the considerations that are necessary for determining whether the default should be applied. The default scaling and CSAF approaches should be brought together eventually, but even in this document the basic concepts underlying the CSAF approach can be used to direct decision making regarding the use of the default. The issue of bioavailability should also be discussed.

One of the reviewers, commenting on whether to use the default in a particular instance, noted that it is often possible to delay completing the risk assessment until more data are available.

The discussion of portal of entry effects needs a great deal of work. It should be revamped to include allometric considerations of dietary/drinking water exposure (see comments of Dr. Gaylor on charge question 6 in Appendix F) and reduce the discussion of the relationship to the RfC methodology.

3.2.6 Charge Question 6

Please provide any additional comments pertinent to the recommendation of body weight scaling to the $3/4$ power for derivation of RfDs that would help improve the overall quality of document.

The limitations of scaling to the $3/4$ power for derivation of RfDs should be clearly presented and integrated along with those of existing methods, to ensure a more transparent presentation of the valid domain of application of the proposed dose scaling approach. It would be helpful to develop a decision tree regarding the appropriate application of the $BW^{3/4}$ default, based on what is known about the mode of action of the substance, its relative half-lives in various species, and other relevant factors. This decision tree and the related discussion should make heavy use of the IPCS CSAF concepts and decision trees:

“Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability. Guidance Document for Use of Data in Dose/Concentration – Response Assessment” World Health Organization, Geneva, 2005. ISBN #92 4 154678 6.

Indeed, since the new definition of a default is the approach that should be used only when no chemical-specific data or approach is available, the CSAF concept should be introduced early in the document and referred to throughout to inform the discussion of the nature of the evidence for when the default $BW^{3/4}$ scaling should or should not be applied.

The discussions in the document need to be more succinct in order to make more of an impact on the reader. The discussion should be focused on the simple idea that the proposed default practicable, is more scientifically justifiable than the present default, and, therefore, represents a step forward.

There should be an acknowledgment that a chemical may have multiple target tissues included in the discussion. A likely place to include this concept is in Section IV, in the context of the discussion on measure of delivered dose.

In the document the rationale for the $BW^{3/4}$ approach to scaling toxic dose is described as “empirical” in that it generally seems to work for a number of chemicals. The work of West and colleagues has moved beyond empiricism and it is now possible to indicate that there is a mechanistic, theoretical basis for the $BW^{3/4}$ approach that goes beyond an empirical basis. It would strengthen the document to highlight this important development, referencing the West and Brown (2005) paper listed below:

West, G. B., and Brown, J. H. (2005). *The Origin of Allometric Scaling Laws in Biology from Genomes to Ecosystems: Towards a Quantitative Unifying Theory of Biological Structure and Organization*. *J Exp Biol* 208, 1575-92.

Appendix A
List of Peer Reviewers

List of Peer Reviewers

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Appendix B
List of Observers

List of Observers

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Appendix C
Charge Questions

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 ³/₄ 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 ³/₄ 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 ³/₄ 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 $3/4$ power for derivation of RfDs that would help improve the overall quality of document.

Appendix D
Agenda for the Teleconference

External Peer Review of
Harmonization in Interspecies Extrapolation:
Use of BW3/4 as Default Method in Derivation of the Oral RfD

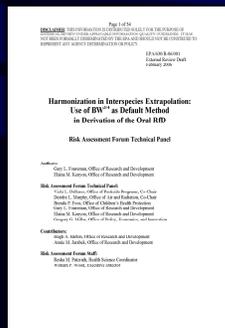
Agenda

WEDNESDAY, June 14, 2006

- 9:00AM **Welcome, Goals of Conference Call, and Reviewer Introductions**
David Bottimore, Versar, Inc.
- 9:20AM **Welcome**
William P. Wood, Ph.D., Executive Director, U.S. EPA Risk Assessment Forum
- 9:25AM **Chair's Introduction and Review of Charge**
Harvey J. Clewell, Chair
- 9:35AM **Background on *Harmonization in Interspecies Extrapolation:***
Use of BW3/4 as Default Method in Derivation of the Oral RfD
Resha M. Putzrath, Ph.D., DABT, Health Science Coordinator, Risk Assessment
Forum
- 9:45AM **Reviewer Roundtable of Overview Comments**
Harvey J. Clewell, Chair
- 10:15AM **Observer Comment Period**
- 10:45AM **Reviewer Discussion and Responses to Charge Questions**
- 12:00PM Lunch
- 1:00PM **Reviewer Discussion and Responses to Charge Questions (continued)**
- 4:00PM **Summary of Comments**
- 5:00PM Adjourn

Appendix E
PowerPoint Presentation

Expert Peer Review of the "Harmonization in Interspecies Extrapolation: Use of BW^{3/4} as Default Method in Derivation of the Oral RfD"



June 14, 2006

David Bottimore
Versar INC.

Overview of Peer Review Conference Call

- **Goal** - Provide feedback on the scientific content and utility of the draft document by responding to the six charge questions
- **Peer Reviewers** - 7 experts from different disciplines/areas of expertise, including interspecies extrapolation and uncertainty factors, allometric scaling, cancer dose-response analysis, and general risk assessment approaches, etc.

Peer Review Process

- Individual comments: everyone participates
- Chair will facilitate to clarify, expand, and summarize major points
- Consensus is not necessary and will not be actively sought
- Document suggestions and recommendations
- Peer review report - summary and individual comments

Ground Rules

- Keep to the logistics of time, subject, and scope (scientific issues)
- Identify yourself when speaking
- Peer review among the 7 reviewers is the primary activity - not a dialogue with EPA and observers
- Chair's prerogative – timing, breaks, etc.

Overview of Agenda

9:00AM	Welcome, Goals of Conference Call, and Reviewer Introductions David Bottimore, Versar, Inc.
9:20AM	Welcome William P. Wood, Ph.D., Executive Director, U.S. EPA Risk Assessment Forum
9:25AM	Chair's Introduction and Review of Charge Harvey J. Clewell, Chair
9:35AM	Background on <i>Harmonization in Interspecies Extrapolation: Use of BW3/4 as Default Method in Derivation of the Oral RfD</i> Resha M. Putzrath, Ph.D., DABT, Health Science Coordinator, Risk Assessment Forum
9:45AM	Reviewer Roundtable of Overview Comments Harvey J. Clewell, Chair
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10:45AM	Reviewer Discussion and Responses to Charge Questions
12:00PM	Lunch
1:00PM	Reviewer Discussion and Responses to Charge Questions (continued)
4:00PM	Summary of Comments
5:00PM	Adjourn

Introduction of Reviewers

Harvey Clewell (Chair)
CIIT Centers for Health Research

Sandra J.S. Baird, Ph.D.
Massachusetts Department of
Environmental Protection

Kannan Krishnan, Ph.D.
Universite de Montreal

David W. Gaylor, Ph.D.
Gaylor and Associates

Bette Meek
Health Canada

William L. Hayton, Ph.D.
Ohio State University

Andrew Renwick, Ph.D.
University of Southampton

Appendix F
Written Comments from the Reviewers

Preliminary Comment Summary Report

***External Peer Review of Harmonization in Interspecies Extrapolation: Use of
BW3/4 as Default Method in Derivation of the Oral Rfd***

Submitted to:

Risk Assessment Forum
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20004

Submitted by:

Versar, Inc.
6850 Versar Center
Springfield, VA 22151

Contract No. 68-C02-061
Task Order 124

Reviewers:

Sandra J.S. Baird, Ph.D.
Harvey J. Clewell, III (Chair)
David W. Gaylor, Ph.D.
William L. Hayton, Ph.D.
Kannan Krishnan, Ph.D.
Mary E. (Bette) Meek
Andrew G. Renwick, Ph.D.

May 31, 2006

PEER REVIEWERS

Sandra J.S. Baird, Ph.D.
Menzie-Cura & Associates, Inc.
Winchester, MA

Harvey J. Clewell, III (Chair)
CIIT Centers for Health Research
Research Triangle Park, NC

David W. Gaylor, Ph.D.
Gaylor and Associates
Eureka Springs, AR

William L. Hayton, Ph.D.
The Ohio State University
Columbus, Ohio

Kannan Krishnan, Ph.D.
Universite de Montreal
Montreal, Canada

Mary E. (Bette) Meek
Health Canada
Ottawa, Ontario, Canada

Andrew G. Renwick, Ph.D.
Emeritus Professor, School of Medicine
University of Southampton
Southampton, United Kingdom

CHARGE TO THE PEER REVIEWERS

1. Please comment on the recommendation of applying body weight scaling to the $3/4$ 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 $3/4$ power for derivation of RfDs that would help improve the overall quality of document.

GENERAL COMMENTS

Sandra J.S. Baird

I commend the authors for the development of this clearly and carefully framed document supporting the use of $BW^{3/4}$ scaling for interspecies extrapolation in derivation of the oral RfD. This document is a welcome addition to guidance for developing regulatory values for non-cancer effects.

This document provides a substantial description of the rationale supporting the use of $BW^{3/4}$ scaling for interspecies extrapolation as well as clear instruction on how to implement $BW^{3/4}$ scaling for a particular dose. However, additional guidance documents should be developed by EPA to support this document including the following:

- Guidance on how the $BW^{3/4}$ scaling will be implemented within the IRIS program (e.g., incorporated in new chemical reviews only, incorporated in existing toxicity files with limited additional review, etc.);
- Guidance on when data are sufficient to conduct interspecies extrapolation using an intermediate approach or a physiologically-based toxicokinetic approach; and
- Guidance on developing an appropriate UF_A for non-default approaches.

Harvey J. Clewell, III

The document is very well written and nicely organized. It makes a very strong case for the use of $BW^{3/4}$ scaling as a generic default for cross-species equivalence of oral exposures. I am very impressed by the transparency, clarity, and objectivity of the analysis.

While I have essentially no negative comments concerning the justification of $BW^{3/4}$ as a default, I believe that the document needs to provide a better context for its use. I am referring in particular to the Hierarchy of Approaches described in Table 3 and in the associated text in the Conclusions (Section V). The concept of the hierarchy of approaches should be presented in the introduction of the document and maintained as a basic premise throughout the document. The discussion of the hierarchy of approaches needs to be moved to the previous section on "Considerations" and greatly expanded to provide a better description of the nature of the chemical-specific evidence that would suggest that the use of the default may not be appropriate. This discussion should emphasize such considerations as looking for evidence of species differences in elimination half-life or clearance that depart from the allometric expectation of $BW^{3/4}$ scaling, either for the compound of concern or for structurally similar compounds. Moreover, the discussion of the intermediate level of the hierarchy should refer to the methodology described by the IPCS for the development of Chemical-Specific Adjustment Factors (CSAFs) for animal-to-human kinetics.

David W. Gaylor

The document is informative for readers that are very familiar with interspecies dose scaling issues. However, the document does not clearly present the method for interspecies dose scaling based on $BW^{3/4}$. The general formula is not explicitly presented until finally occurring as a column heading in Table D of Appendix B. The formula for the Human Equivalent Dose (HED) and the derivation and general formula for the Dosimetric Adjustment Factor (DAF) need to be presented in Section III or earlier. Many statements in the text are not clear because the formula for interspecies dose scaling from mg/kg in animals to $mg/(kg)^{3/4}$ for humans is not presented early in the document. The derivation of DAF is not clear. The following straightforward description is recommended:

It is hypothesized that an equal biological effect is obtained in an animal and human when the dose (mg) is expressed relative to body weight to the $3/4$ power ($BW^{3/4}$), i.e., when

$$mg_h / BW_h^{3/4} = mg_a / BW_a^{3/4}$$

where the subscripts h and a refer to human and animal, respectively.

Since $BW^{3/4} = BW / BW^{1/4}$, the above equation can be expressed as

$$mg_h / (BW_h / BW_h^{1/4}) = mg_a / (BW_a / BW_a^{1/4})$$

giving

$$(mg_h / kg_h) = (mg_a / kg_a) \times (BW_a / BW_h)^{1/4}.$$

That is, the human equivalent dose (HED) expressed as $(mg/kg)_h$ is calculated by multiplying the animal dose expressed as $(mg/kg)_a$ times the dose adjustment factor, $DAF = (BW_a / BW_h)^{1/4}$. It is strongly recommended that this straightforward derivation should be presented early in the text and the result given in the Executive Summary.

The near equivalence across species of dose expressed as food concentration (ppm) or $mg/BW^{3/4}/d$ should be discussed in the Document.

The dose scaling factor from a 25 gram mouse and 250 gram rat to a 70 kg human is presented often. It is never explicitly mentioned in the body of the report that the actual body weights of the test species are used in calculating the DAF and HED for an experiment. A naïve reader may conclude that there is a single DAF for all strains of mice, another for rats, and one for dogs. Actually, for mice a single conservatively low $DAF = 0.14$ based on a relatively small 25 gram mouse would provide a single simple default value for most mouse studies. Similarly, for rats a $DAF = 0.24$ based on a relatively small 250 gram rat provides a simple minimum conservative dose scaling factor for almost all rat studies.

A list of acronyms would be extremely helpful. A glossary should also be considered.

William L. Hayton

The relationship between dose associated with toxicity and species body weight has long been known to scale not to body weight (BW) directly, but to body weight raised to a fractional power.

When the dose associated with toxicity is plotted versus BW on log-log coordinates, a linear relationship is generally obtained and the slope of the line tends toward the value of $\frac{3}{4}$. For many chemicals this has been demonstrated and it is generally accepted as an expected relationship, albeit until recently the relationship was considered to be empirical; i.e., without a compelling theoretical basis. This has changed in recent years with the elaboration of an underlying theory for the $BW^{3/4}$ scaling relationship by West, Brown, and Enquist.

It therefore is appropriate to consider this $BW^{3/4}$ scaling relationship in the context of extrapolation of the chemical dosage associated with toxicity in humans from measured dosage associated with toxicity in laboratory animals. The subject document undertakes this task by review of pertinent background, discussion of the approaches that have been used by EPA and are currently used for inhalation toxicity and carcinogenicity, and description of how $BW^{3/4}$ scaling should be used to estimate the human equivalent dosage from the dosage associated with toxicity in animals.

In this reviewer's opinion, the recommendation to proceed to use of $BW^{3/4}$ scaling of chemical toxicity to humans as the default approach is scientifically sound, superior to the currently used approach, and consistent with interspecies scaling of inhalation toxicity and carcinogenicity. The approach described in the subject document is recommended for chronic, oral exposure to chemicals. The authors have attempted to enumerate assumptions and limitations of the method. The document is clearly written and appears to be accurate and unbiased.

Kannan Krishnan

This document presents a default dose scaling approach, applicable for chronic oral exposures. The proposed default approach, which is in line with the existing knowledge base, is recommended for application in the absence of chemical specific data or PBPK models. The scaling approach is clearly presented and situated with some of the other more commonly used tools/approaches. However, one default dose scaling approach is unlikely to be applicable for all situations and chemicals. Appropriately, the authors indicate that they do not recommend this approach for application to: acute exposure scenarios, chemicals producing reactive metabolites, infants and children, chemicals with modes of action unrelated to AUC, inhalation or dermal route, and saturable kinetics. However, these limitations have not been integrated along with those of existing methods, to ensure a more transparent presentation of the valid domain of application of the proposed dose scaling approach.

Mary E. (Bette) Meek

None

Andrew Renwick

The proposal is logical and represents a pragmatic way forward, given the physiological differences between different test species (e.g. mice vs dogs) to which the same 10-fold uncertainty factor is usually applied. The case is well supported for extrapolation from adult animals to adult humans.

The discussion and rationale for consideration of age-related differences is spurious. The conclusion that $BW^{3/4}$ is better than $BW^{1/1}$ for interspecies scaling of adults will be equally applicable to interspecies scaling of other age groups if there are similar underlying age-related physiological differences (this point is lost within the rather convoluted and irrelevant text written – see below).

There is too much use of the RfC methodology to support various aspects of the proposal. Such comparisons with and reliance on an established method are not necessary and tend to add confusion rather than clarity.

There is no acknowledgement of the work by WHO-IPCS on chemical specific adjustment factors (CSAFs), which also considered the subdivision of the interspecies default factor into different aspects. The guidance developed from that activity would be useful for deciding when the proposed default based on $BW^{3/4}$ might not be suitable, and also when sufficient data might be available to move away from a default inter-species toxicokinetic default factor.

The text on portal of entry effects (appendix C) is very weak and poorly rationalized (see below).

RESPONSE TO CHARGE QUESTIONS

Charge Question 1: Please comment on the recommendation of applying body weight scaling to the $\frac{3}{4}$ 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?

Sandra J.S. Baird

- *Is the rationale underlying this approach scientifically supported and adequately explained in the report?* YES
- *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?* NO, see comments below.
 - *Is the discussion of the extent to which $BW^{3/4}$ scaling accounts for toxicokinetics and toxicodynamics clear?* YES
- *Do you know of critical data in the literature not cited here that would impact the recommendations?* NO
- *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?* YES

The report provides a thoughtful and clear discussion of the scientific data, assumptions and uncertainties associated with the selection of a default approach for scaling exposures from animals to humans. While the report supports the use of the chemical-specific interspecies scaling, the guidance provided in the report for when and how to implement a scaling approach other than the default is limited to general issues to consider. It would be useful to include specific guidance on when it is acceptable to use an interspecies extrapolation approach (other

than default), however it is understandable that guidance is limited given the difficulties in knowing *a priori* the types of information that will be available for any specific chemical.

The section on alternative approaches in this report would benefit from the addition of a discussion of the need to weigh the uncertainty associated with using a default approach based on knowledge of other chemicals with the uncertainty associated with using a chemical-specific approach in the absence of “perfect” information.

Harvey J. Clewell, III

1. Please comment on the recommendation of applying body weight scaling to the $3/4$ 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 Reference Dose values.

I agree with it.

- *Is the rationale underlying this approach scientifically supported and adequately explained in the report?*

Yes. The description of the rationale is very clear, and is well supported scientifically.

- *Do you believe that alternative methods of interspecies default scaling procedures have been adequately presented and discussed in the text?*

Yes.

- *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?*

No. This discussion needs to be expanded to describe the nature of the experimental evidence that could suggest the need for departure from the default, e.g., evidence of species differences in elimination half-life or clearance that depart from the allometric expectation of $BW^{3/4}$ scaling, either for the compound of concern or for structurally similar compounds. Other examples of potentially useful evidence include changes in the ratio of C_{max} or AUC to dose.

The discussion of the intermediate level of the hierarchy should refer to the methodology described by the IPCS for the development of Chemical-Specific Adjustment Factors (CSAFs) for animal-to-human kinetics -- in particular the use of the ratio of clearances as a basis for the AF_{AK} .

- *Is the discussion of the extent to which $BW^{3/4}$ scaling accounts for toxicokinetics and toxicodynamics clear?*

As much as can be expected, yes.

- *Do you know of critical data in the literature not cited here that would impact the recommendations?*

No.

- *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?*

Yes.

David W. Gaylor

- The rationale underlying this approach is scientifically supported and adequately explained.
- As pointed out in the Section on General Impressions above, there needs to be a discussion showing the similarity of interspecies dose scaling based on concentration (ppm) of an agent in the diet and dose based on $BW^{3/4}$.
 - o It would be difficult to provide more detailed guidance for the intermediate level in Table 3.
 - o The section on toxicokinetics and toxicodynamics on page 15 is very brief and could benefit from more discussion.
- No additional critical data comes to mind.
- Assumptions, limitations, effects at the portal of entry, and physiological time scaling are presented. As pointed out in the Section on General Impressions above, the derivation of the formula for dose scaling based on $BW^{3/4}$ in Appendix B is not clear. Only examples of dose scaling based on $BW^{3/4}$ are presented in the text. Without providing the formula for dose scaling based on $BW^{3/4}$ in the text, it is not clear how to implement the procedure.

William L. Hayton

Application of $BW^{3/4}$ as a general default procedure to extrapolate dose from laboratory animals to man for chronic orally administered agents.

Scientific Rationale. The draft document's "guiding paradigm" is "that a common internal dose is the ultimate determinant of risk" (page 9, lines 1-2). This is a highly reasonable default position, informed by the long history of using laboratory animals to gain insights about the toxicity of chemicals. Because animals and human beings show marked congruence in their genome, physiology and biochemistry, it is scientifically reasonable that insights obtained from animal studies will be applicable to humans. Dose – toxicity relationships, metabolite profiles, bioavailability properties, pharmacokinetic behaviors, and so forth observed in animal studies are generally relevant to predictions for humans. Decades of toxicology and drug development research have validated the utility of animal studies in characterization of chemical toxicity, and informed the uncertainty involved in extrapolation of animal results to humans. Occasionally marked divergences have been observed, which sometimes have been unpredictable and difficult to explain. Nevertheless, the guiding paradigm is generally true and a reasonable starting point in the absence of contrary information.

Acceptance of the guiding paradigm leads to the central problem in dose extrapolation among species, namely to arrive at a species-specific dosage that provides the same exposure of the toxicologically sensitive (target) tissue(s) to chemical. The plasma concentration is often used as a surrogate measure of exposure because of the relative ease of sample collection and determination of chemical concentration. For chronic orally administered agents, distribution of agent between target tissue and plasma would generally be at or near steady state and plasma concentration should be a generally reliable surrogate for target tissue concentration; i.e., not the same as the active tissue concentration but proportional to it.

The linkage of steady-state plasma concentration (C_{ss}) to chronically administered dose generally follows the relationship $C_{ss} = \text{Dose Rate} \div \text{Clearance}$, where Dose Rate is the amount of agent administered per unit time that reaches the systemic circulation and Clearance (CL) is the proportionality constant that relates the rate of agent elimination to its plasma concentration. This relationship is based on the concept of a steady-state, where *rate in* (Dose Rate) equals *rate out* ($CL \times C_{ss}$). Since the C_{ss} (surrogate index of exposure) is dependent on CL, the interspecies relationship between CL and BW is a key to determination of species-specific dosage that provides the same exposure of target tissue to chemical. In other words, if the interspecies variation in CL is known, then the dosage in humans that provided a particular exposure in animals could be calculated:

$$\text{HED} = \text{Animal Dose Rate} \times (\text{CL}_{\text{human}} / \text{CL}_{\text{animal}})$$

Clearance values of most chemicals (including drugs) vary among mammalian species according to the BW^{3/4} relationship. Therefore a scientifically sound basis underlies the recommended use of BW^{3/4} to extrapolate toxicologically equivalent doses of chronic orally administered agents from laboratory animals to humans.

Alternative Scaling Procedures? Alternatives are mentioned in the document. The document describes the current use, by USEPA for noncancer effects, of BW with an exponent of unity; i.e., of application of mg/kg dosage associated with toxicity in animals directly to humans, along with an uncertainty factor (p. 6). The proposed BW^{3/4} approach for scaling is superior. The document also indicates that when data are available to support a physiologically based toxicokinetic (PBTK) model, site-specific dosimetry is possible and preferred (p. 7). However, as the document notes, a PBTK-based approach is not possible for most chemicals due to lack of supporting data.

Other scaling procedures could focus on the exposure of target tissues (directly or via plasma concentration) to the toxicologically relevant metabolite(s) if appropriate data were available, and for extremely long half-life chemicals, the cumulative dose received rather than the dose rate would form a better basis for scaling. In some instances, it may be the duration of exposure that is critical, for which species life span may be an appropriate scaling variable. As default scaling procedures, however, these approaches are inferior to the BW^{3/4}-based approach. No alternative to the BW^{3/4}-based approach is available that is generally applicable while being so parsimonious in its data requirements that it is also feasible for general use.

Critical Data Not Cited?

Pertinent references not cited in the draft document are under the **Specific Recommendations** section.

Assumptions and Limitations? The Executive Summary (para. 3) acknowledges that the BW^{3/4}-based approach may not always predict toxicologically equivalent doses across species. On pages 7 & 12 portal-of-entry as the site of toxicity is mentioned and on p. 17 it is discussed as a case where the BW^{3/4}-based approach is inappropriate. On page 12, there is acknowledgment that the BW^{3/4}-based approach applies most appropriately to agents that act directly (not via a metabolite) and to agents cleared by first-order processes. On page 15, the issue of whether toxicodynamics scales among species according to the BW^{3/4} relationship is raised. Assumptions and limitations are more fully enumerated on pp. 17-18 and included as footnotes to Table 3.

While assumptions and limitations are presented in the document, it would be beneficial to succinctly state them (list them) near the front of the document; i.e., a statement to the effect that the BW^{3/4}-based approach is not (less?) applicable when

- ❖ the toxic species is not the parent chemical
- ❖ the chemical is cleared by metabolism via pathways that are different among species
- ❖ the site of toxicity is the portal of entry
- ❖ etc.

It should be clear to users of the BW^{3/4}-based approach that one should have more information than the toxicity-associated dosage in an animal [$\text{mg kg}^{-1} \text{ day}^{-1}$] and the BW of the animal.

An issue that seems to be absent from the document is consideration of the number of species to use and their body weight range for extrapolation to humans. While there are 4000+ mammalian species, the species most commonly used in toxicity testing of chemicals are rat, dog, rabbit, mouse, and monkey. These species have well established background pathology and other species are generally not used for toxicology testing. The document does not appear to specify that the test animals should be mammals and it would seem that should be stated. Would toxicity data from reptiles or fish be acceptable for extrapolation of the HED? Ideally, to extrapolate (rarely is the test animal body weight greater than 70 kg) HED, one would have toxicity – dosage data from more than one animal species, and their body weights should span a range. For example, rat-rabbit-dog with BW's of 0.2, 2, and 20 kg would span a suitable range of BW. Extrapolation from a single species would be risky, even perilous.

Another issue is the extrapolated “distance”. More accurate extrapolation would be expected when the largest BW was 20 kg compared with 2 kg.

Kannan Krishnan, Ph.D.

- *Is the rationale underlying this approach scientifically supported and adequately explained in the report?*

Yes; fairly well. Still, the presentation of the applicability and limitations of the proposed

approach along with that of other approaches needs to be improved. Even though the $\frac{3}{4}$ scaling is appropriate for systemically acting agents, the discussions regarding the applicability to portal of entry effects are incomplete and should be the focus of a separate document. The applicability of the $\frac{3}{4}$ scaling to chemicals producing stable metabolites needs to be justified appropriately.

- *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?*

To some extent yes.

- *Is the discussion of the extent to which BW^{3/4} scaling accounts for toxicokinetics and toxicodynamics clear?*

Yes, but in some places, claim is made that $\frac{3}{4}$ scaling also accounts for certain toxicodynamic differences – meaning that there is no need for the use of UF_{toxicodynamics}. However, in other places, it is mentioned that $\frac{3}{4}$ scaling only accounts for toxicokinetic differences such that the application of UF_{toxicodynamics} of 3 is necessary to account for residual uncertainty relating to interspecies extrapolation. This aspect needs to be rectified.

- *Do you know of critical data in the literature not cited here that would impact the recommendations?*

Krishnan and Andersen (1991, Interspecies scaling in pharmacokinetics. In: New trends in pharmacokinetics, Rescigno A and Thakur AK, eds. Plenum press, NY, pp203-226) indicate that the dose scaling for stable metabolite is likely to follow BW¹. The present document is in variance with this publication.

- *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?*

Yes. The portal of entry issue is a bit confusing and out of place, in my opinion. The proposed default approach is conceptually applicable only to systemic toxicants (regardless of the portal of entry). If the effect is induced at the portal of entry, then it is unclear as to why this default approach should even be considered – even there is an acknowledged need to determine appropriate dose scaling methods for such situations.

Mary E. (Bette) Meek

- *Is the rationale underlying this approach scientifically supported and adequately explained in the report?*

The supporting information is well explained and presented. The rationale as it relates particularly to harmonization of cancer and non-cancer approaches and in broad terms, consistency with the approach to development of reference concentrations for inhalation, is also well articulated. Recommendations for additional clarification and development of the document in the areas mentioned below should be balanced against the need to expedite progress in acquiring greater consistency in harmonization in approaches while incorporating the maximum possible information to increase the reliability of dose-response extrapolations.

While it is noted in passing at the outset that the work is intended to be concordant with MOA as the guiding paradigm for toxicological evaluations, the importance of consideration of mode of action in thoughtful application of body surface area scaling has not, perhaps, been sufficiently emphasized in the draft document. This may be due, in part, to the restriction of content principally to current default assumptions in dose-response analysis without much reference to preceding steps of data consideration, for specific chemicals. However, development of a decision tree that takes into account several factors including chemical specific information on mode of action could in my view, result in more meaningful application of body weight scaling (see below).

The important take away message is that as we progress from blanket defaults of 10 fold to incorporate increasingly more refined categorical or species specific defaults, mode of action considerations are critical.

- *Do you believe that alternative methods of interspecies default scaling procedures have been adequately presented and discussed in the text?*

Options here would appear to be limited. However, in relation to potential “portal of entry” effects following ingestion, while potential options have been discussed (Appendix C), and “development of a dosimetric adjustment factor involving aspects relating dose to a surface area at or within the portal is considered appropriate (Summary of Assumptions and Limitations)”, the specific nature of additional work has not been delineated. While lack of a species-specific

dosimetric adjustment factor (DAF) for portal of entry considerations for ingestion should not preclude immediate steps to increase consistency for approaches between cancer and non-cancer effects, presumably additional work is warranted as a priority to ensure consistency in development of reference concentrations/doses for the inhalation/oral routes. Should there not then be strong recommendation for additional interpretive analysis of existing data and/or possibly generation of other specific empirical information on anatomical differences, relative surface areas, rates of uptake, etc., to consider appropriate defaults for various categories of substances for the oral route?

° 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?

The document is explicit that body weight scaling is “best guess” to be replaced by chemical specific data when available”. Seems though, that meaningful application of body weight scaling can also be “informed” by chemical specific data, among other factors (see reference to decision tree, below).

While in Table 3, there is information on the types of chemical-specific data taken into consideration in deviating from default, there is limited to no guidance included in the current document as to considerations in determining adequacy of such data. Guidance on adequacy of kinetic and dynamic data as a basis for replacement of default in dose-response analysis is included in the IPCS document “Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability. Guidance Document for Use of Data in Dose/Concentration – Response Assessment” World Health Organization, Geneva, 2005. ISBN #92 4 154678 6. Aspects considered therein include determination of the active chemical species, choice of the appropriate kinetic metric and nature of available data including relevance of the population and route examined, dose/concentration and numbers of subjects/samples. While not strictly the objective of this document, it may be helpful to include reference to the kinds of information which are taken into consideration. It might also be helpful to make distinction between compound-related versus chemical-specific adjustments in the continuum of increasingly data-informed approaches.

° Is the discussion of the extent to which BW^{3/4} scaling accounts for toxicokinetics and toxicodynamics clear?

This is an area where I found the discussion quite unclear. Discussion in the section entitled “Toxicokinetics and Toxicodynamics in Toxicological Equivalence” indicates only that BW^{3/4} addresses **some but not all** of dynamic aspects of toxicity. While there is some reference to toxicodynamic aspects such as cellular repair and regeneration, signaling cascades and proliferative responses also scaling as a fractional power of body weight, I couldn’t discern meaningful attempt to systematically consider extent that body weight scaling addresses toxicodynamic aspects. There is also confusing text about the dosimetric adjustment for Reference Concentrations seemingly indicating that it addresses only toxicokinetics in one part of the text but including reference to some aspects of toxicodynamics in another.

Also, what is the basis for the remaining factor of 3?. Are the toxicokinetic and toxicodynamic aspects addressed by body weight scaling sufficiently similar to the dosimetric adjustment for the Reference Concentration, such that the remaining interspecies UF should be 3 in both cases? Are there analyses to support this?

• *Do you know of critical data in the literature not cited here that would impact the recommendations?*

No.

• *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?*

I believe that there has been considerable attempt to robustly address a considerable proportion of the assumptions and limitations in the application of scaling of BW^{3/4}. However, there are a few notable exceptions that could be addressed in a decision making framework which considers chemical specific and other factors in the application of body weight scaling (see below). For example, in Section IV, there is limited reference to considerations of body weight scaling when toxicity is a consequence of exposure to reactive metabolites at or removed from the site of formation. Also, there is no indication of appropriate consideration when half-lives vary across species.

Andrew Renwick, Ph.D.

• *Is the rationale underlying this approach scientifically supported and adequately explained in the report?*

The overall rationale underlying this approach is supported and adequately explained in the report and the papers cited therein.

• *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?*

This is not well described. Moving away from a very simplistic default (BW^{1/1}) to a more logical default (BW^{3/4}) does not mean that the default is any more generally applicable – especially since the residual default has been reduced to 10^{0.5} such that for rats the new total default (BW^{3/4} x 10^{0.5}) will approximate to the old default of 10 for BW^{1/1}. There is therefore insufficient reference to the intermediate level in Table 3, which was the basis for the WHO-IPCS discussions on CSAFs. Guidance has recently been published by WHO (see end of this report).

- *Is the discussion of the extent to which BW^{3/4} scaling accounts for toxicokinetics and toxicodynamics clear?*

There is no clear indication as to how much of the species differences in toxicodynamics would be taken into account by the use of BW^{3/4}. It is suggested that this should be considered on a case-by-case basis, but there is no guidance on what considerations would suggest the extent to which the different body weight scaling takes dynamic into account. It is true that some dynamic processes will scale to BW^{3/4} but it is not clear when this may or may not apply. The CSAF approach proposed by the WHO is that when using a 10-fold interspecies factor based on BW^{1/1} a subfactor of 10^{0.6} covers kinetics and that 10^{0.4} is retained for dynamic differences. This allows either kinetic or dynamic data to be replaced by a CSAF. Replacement of the interspecies toxicokinetic default with chemical-specific data would leave 10^{0.4} for interspecies dynamic differences. Comparison of this approach with the new default method of EPA means that major generalized sources of interspecies kinetic differences are covered by BW^{3/4} (which for rats approximates to 10^{0.6}) leaving a residual of 10^{0.5} to cover any remaining kinetic uncertainties plus the uncertainties associated with dynamics. Incorporation of mechanistic data on species differences in dynamics would represent an intermediate level (Table 3) and it would have been helpful if the WHO approach had at least been referenced.

- *Do you know of critical data in the literature not cited here that would impact the recommendations?*

All major references are included for the physiological/metabolic considerations – but the development of the WHO approach and its final publication should be cited.

- *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?*

The main problems relate to the issue of separation of kinetics and dynamics (see above), age-related scaling (see below) and portal of entry effects (see below).

Charge Question 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?

Sandra J.S. Baird

The rationale underlying this recommendation is adequate for this document. As the authors are well aware, this is an area of uncertainty in need of additional research. It is important to have this discussion in this document even though the default $BW^{3/4}$ scaling based on adult body weights serves as a pragmatic default approach given the current state of knowledge. I recommend that the Agency continue to support research to better understand early life toxicity, including toxicokinetics and toxicodynamics, and exposure for use in both noncancer and cancer risk assessments.

The second paragraph on the section discussing early life-stages (pg 13) mentions a potential case of scaling from early life studies in animals to early life exposure in humans and states that in some cases this may be desirable. Does the agency intend for $BW^{3/4}$ scaling to be used to scale from young animal to young child? When would this be desirable compared to the default? This is another area where it would be useful to develop additional guidance. Editorially, this discussion is not connected to the remainder of the section discussing scaling *across* life-stages although it is used as a lead in.

Finally, the argument made for the justification of the DAF approach for portal-of-entry effects (Appendix C, pg. 32) that use of the $BW^{3/4}$ approach combined with the default UF_A of 3 results in derivation a lower human exposure level compared to the current approach for rats and mice, is applicable to supporting use of adult human body weights for estimating early life scaling. This is touched upon in the 1st paragraph on page 15, but not stated as strongly as in the portal-of-entry section.

Harvey J. Clewell, III

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?*

Yes.

- *Should early life or other lifestages be addressed in this document, or should a default be assumed to encompass all lifestages?*

The interspecies default scaling should continue to be treated as an adult animal to adult human adjustment, and special consideration of different lifestages should be considered in the context of intrahuman variability.

- *Do you know of critical data in the literature not cited here that would impact the recommendation?*

No.

- *Have the uncertainties and data limitations associated with the extrapolation across life stages and other sensitive subgroups been sufficiently addressed?*

For the purposes of this document, yes.

David W. Gaylor

- It is not clear what the Document is recommending regarding dose scaling for children. Is the child BW to the $\frac{3}{4}$ power used? Is it only used in conjunction with BW to the $\frac{3}{4}$ power of juvenile animals?
- It is unlikely that a single default procedure would be generally applicable to all life stages.
- Not aware of additional literature.
- Uncertainties and limitations of extrapolation across life stages are adequately discussed, but the conclusions are not clear.

William L. Hayton

Rationale justification? The recommendation is justified as a default approach. Focusing on CL as the key toxicokinetic parameter that controls exposure of sites of toxicity to the chemical, it is generally the case that BW^{3/4} relationship for CL among species is also observed within species. Therefore, the smaller BW in children and infants is associated with a larger CL per kg BW, and the mg/kg HED for adults would generally overestimate the HED for children; i.e., there is generally a margin of safety built into the adult HED [mg/kg] when it is used for children. The discussion on pp. 13-15 captures this and cites appropriate literature.

An important issue is maturation of clearance; when are the clearing capacities of the kidneys, liver, etc. at adult levels? The document cites literature that suggests ages of 2 mo to 6 mo for attainment of adult clearance capacity (clearance per unit weight of clearing organ). Literature not cited indicates that full maturation of renal and liver clearance capacity may not occur until 1-2 years of age. In the case of glomerular filtration, Hayton (2000, citation below) found that the maturation of GFR appeared to proceed exponentially with a half life of 7.9 mo. and that

capacity increased by a factor of 3.1 due to maturation alone (separate from growth). Even so, the GFR in the new born on a mL/kg basis was equivalent to the adult value, so the adult HED for a chemical cleared by the kidney would provide a similar exposure in the very young. Whether the very young are more sensitive to the chemical is another issue, of the toxicodynamic type. In the case of metabolism, Alcorn and McNamara (Clinical Pharmacokinetics 12:959,2002) reviewed the literature on the maturation of activity of hepatic drug metabolism enzymes and reported differences in maturation rates of activity levels. CYP3A4 activity reached the adult value quickly; if the fetal form (CYP3A7) is included, there was adult activity at birth. Other CYPs were relatively slow to develop, with adult activity not occurring before several years of age. The overall tendency, however, is for CL per kg body weight to be elevated in the young compared with adults and as a default the use of the adult HED [mg/kg] in the young would generally provide a margin of safety.

Should adult RfD encompass all life stages? The very young, say below three or four months, may require special consideration. The adult RfD may be acceptable in some cases but not in others. If the agent is cleared by glomerular filtration, adult capacity is achieved soon (one week) after birth. If the agent is metabolized, the particular enzymes involved may have to be identified with consideration given to their temporal maturation profile. In the very old, there appears to be no consistent impairment of clearance capacity, particularly when disease-associated effects are removed. Cross-sectional studies show that renal function declines with increasing age, but longitudinal studies show that about two-thirds of those studied did not have decreased renal function. The age-associated decrease observed in cross-sectional study designs appears therefore due to relatively rapid decline in renal function with increasing age in about one-third of the population. The application of the uncertainty factor should provide a measure of safety for this group.

Critical Data Not Cited? Pertinent references not cited in the draft document are under the **Specific Recommendations** section.

Uncertainties sufficiently addressed? The uncertainty about maturation of clearance pathways and the uncertainty of relative intrinsic sensitivity of immature vs. mature humans to the agent are addressed. These uncertainties are in addition to the uncertainties associated with interspecies extrapolation. While there is a measure of safety that accrues from clearance capacity in the young being elevated compared with the adult, it would seem that special caution should be advised. Earlier it was suggested that assumptions and limitations be clearly specified early in the document. If this is done, it would seem appropriate to make special mention of application of the adult HED in the young.

Kannan Krishnan, Ph.D.

- *Is the rationale underlying this recommendation adequately justified?*

Adult to child dose scaling based on some fractional or full power to the BW (without adjustment for differences in metabolism and physiology) is unlikely to be scientifically defensible. Of course, the starting point is the dose for adult humans. But the derivation of toxicologically-equivalent dose for subpopulations (children or elderly) without accounting for appropriate metabolic or physiological differences is unlikely to be defensible. The document is consistent with this state of knowledge.

- *Should early life or other lifestages be addressed in this document, or should a default be assumed to encompass all lifestages?*

A default approach for all lifestages is probably not realistic.

- *Do you know of critical data in the literature not cited here that would impact the recommendation?*

The following references provide an evaluation of the magnitude of the adult-children dose scaling factor and the inadequacy of dose scaling based on allometry:

Price K, Haddad S and Krishnan K. (2003). Physiological modeling of age-specific changes in the pharmacokinetics of volatile organic chemicals. *Journal of Toxicology and Environmental Health* 66 (A): 417-433.

Nong A, McCarver D, Hines R and Krishnan K. 2006. Modeling interchild differences in pharmacokinetics on the basis of subject-specific data on physiology and hepatic CYP2E1 levels: A case study with toluene. *Toxicol Appl Pharmacol* Epubl Feb 6

- *Have the uncertainties and data limitations associated with the extrapolation across life stages and other sensitive subgroups been sufficiently addressed?*

Sufficiently so. But the above references are likely to add to the completeness of information provided in the document.

Mary E. (Bette) Meek

- *Is the rationale underlying this recommendation adequately justified?*

This seems reasonable based on the information presented, though I wondered if the uncertainty inherent in application to children could be additionally clarified, based on the review of the available data – i.e., generally considered additionally conservative for younger age groups with possible exception of young infants, where uncertainty is greater and available data inadequate to determine whether approach is more or less conservative than for adults?

- *Should early life or other lifestages be addressed in this document, or should a default be assumed to encompass all lifestages?*

To minimize complexity, suggest that default encompass all lifestages but that uncertainty in this assumption be clearly stated. This permits additional consideration of this uncertainty in application, taking into account chemical-specific information. Suggest to address in decision tree.

- *Do you know of critical data in the literature not cited here that would impact the recommendation?*

No.

- *Have the uncertainties and data limitations associated with the extrapolation across life stages and other sensitive subgroups been sufficiently addressed?*

See comment above.

Andrew Renwick, Ph.D.

- *Is the rationale underlying this recommendation adequately justified?*

No – the rationale is totally spurious, since it confuses the issues of interspecies scaling and human variability. It is very well established in clinical practice that critical dosages for infants and children, such as for anti-cancer drugs, are calculated on the basis of body surface area. This means that children get higher dosages than adults when expressed on a simple body weight basis ($BW^{1/1}$). The extensive text, on pages 13-15 and in appendix C, misses the key issue which is “If $BW^{3/4}$ scales logically for adult animals to adult human, does the same value scale from young animals in a developmental or multi-generation study to the corresponding human life-stages.” The answer to this question cannot be derived by looking at age-related changes in physiological processes in humans alone (as in the present text) but requires a consideration of age-related changes in animals and an analysis of whether these are similar to the changes in humans. The extensive text on scaling of drug data within humans are therefore not relevant to the use of a scaling of $BW^{3/4}$ for species differences at all ages. The fact that there is good scaling between young and adult humans using $BW^{3/4}$ is irrelevant because there is a 10-fold uncertainty factor to allow for human variability (which will include age) and the RfD is expressed on the basis of $BW^{1/1}$.

- *Should early life or other lifestages be addressed in this document, or should a default be assumed to encompass all lifestages?*

Given my comments above it would be better if the EPA simply accepted that there is an assumption that scaling by $BW^{3/4}$ is no worse and almost certainly better than scaling by $BW^{1/1}$.

- *Do you know of critical data in the literature not cited here that would impact the recommendation?*

There are some published data on toxicokinetics in juvenile animals, mostly on pesticides in rats, but these would need to be compared with similar data in humans. [I have performed exactly such studies with a selection of drugs for which there are good human neonatal data – but we have not yet published the results].

- *Have the uncertainties and data limitations associated with the extrapolation across life stages and other sensitive subgroups been sufficiently addressed?*

Overall the issue of sensitive subgroups is not relevant because these would be covered by the human variability factor (which has a long history of use and is based on $BW^{1/1}$) – so that the inclusion of analyses of subgroups would add to my criticism of irrelevant text.

Charge Question 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?

Sandra J.S. Baird, Ph.D.

The rationale is adequately explained and justified in the report.

The presentation of the division of and the accounting for toxicokinetics and toxicodynamics and their interaction is among the best that I have seen. However, the splitting of UF_A in half and assuming that the remaining factor of 3 is sufficient for accounting for the remaining uncertainty is a science policy decision and needs to be noted as such.

As in the cancer guidelines, application of $BW^{3/4}$ scaling for any specific chemical does not include a quantitative estimate of the uncertainty in the scaling power. While the analyses presented in the report find that $BW^{3/4}$ is a best estimate of the oral interspecies scaling power, the analyses by Watanabe et al. (1992) and Kirman et al. (2003) demonstrate that there is uncertainty in use of $BW^{3/4}$ to scale across species and the amount of uncertainty is dependent in part on chemical metabolism and nonlinear kinetics in the dose response function. Thus the remaining factor of 3 for UF_A accounts for, 1) imprecision in the BW scaling metric for describing the toxicokinetics of the specific chemical, 2) adjustment/scaling of toxicodynamics across species, and 3) for uncertainty in the toxicodynamics adjustment/scaling across species.

Harvey J. Clewell, III

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?*

Yes.

- *Is the division of and the accounting for toxicokinetics and toxicodynamics clearly presented?*

Yes.

- *Do you know of critical data in the literature not cited here that would impact the recommendation?*

No.

David W. Gaylor, Ph.D.

- It needs to be discussed in the text that dose scaling based on $BW^{3/4}$ reduces the human equivalent dose by a factor of about 7 from the mg/kg/d dose in mice and about a factor of 4 from the mg/kg/d dose in rats. An additional uncertainty factor of 3 results in an overall reduction of a factor of 21 below the typical mg/kg/d dose for mice and a factor of 12 for rats, compared to the usual uncertainty default factor of 10 for interspecies extrapolation. This is presented in the next to last paragraph of Appendix D. Clearly, this discussion needs to be moved to the text and it is important enough to be mentioned in the Executive Summary.
- Toxicokinetics and toxicodynamics are outside my area of expertise.

William L. Hayton, Ph.D.

Rationale justification? The rationale (p. 20) flows from the rationale for the current UF_A , which has a value of 10 that is partitioned equally between toxicodynamic and toxicokinetic uncertainties. To the extent that the $BW^{3/4}$ approach to HED extrapolation eliminates the toxicokinetic uncertainty, then it would be rational to reduce the UF_A to a value of three, to accommodate the toxicodynamic uncertainty. This reviewer is uncomfortable with the value of 10 for UF_A ; while a margin of safety is necessary, the value of 10 has the quality of extreme empiricism. Whether there was a strong scientific rationale for using 10 is not clear. That said, it would be appropriate to reduce the UF_A value if the $BW^{3/4}$ approach eliminated all the toxicokinetic uncertainty. However, it probably does not. Allometric scaling of drug clearance values among laboratory animal species to predict the human clearance is considered successful if the predicted value lies within 50-200% of the measured human value. Achievement of this degree of success generally requires use of a minimum of three and preferably four animal species. When only one or two animal species are used, the probability of failure is elevated considerably. It therefore seems that all toxicokinetic uncertainty is not removed by the $BW^{3/4}$ scaling approach and reducing the UF_A to 3 may not be justified. To the extent that the value of 10 was scientifically justifiable it would seem that reduction of UF_A to a higher value, say 5 or 6, rather than 3 would be more appropriate.

Differentiation of toxicokinetics and toxicodynamics? These two elements of toxicity are adequately identified and it is clear in the document that the $BW^{3/4}$ scaling approach is intended to scale the toxicokinetic element primarily.

Critical Data Not Cited? None that this reviewer is aware of.

Kannan Krishnan, Ph.D.

- *Is the rationale underlying this reduction of the default value for this uncertainty factor adequately explained and justified in the report?*

The information presented in the report is contradictory to this effect. In some places, claim is made that $\frac{3}{4}$ scaling also accounts for certain toxicodynamic differences – meaning that there is no need for the use of $UF_{\text{toxicodynamics}}$. However, in other places, it is mentioned that $\frac{3}{4}$ scaling only accounts for toxicokinetic differences such that the application of $UF_{\text{toxicodynamics}}$ of 3 is necessary to account for residual uncertainty relating to interspecies extrapolation. This aspect needs to be rectified.

- *Is the division of and the accounting for toxicokinetics and toxicodynamics clearly presented?*

Yes

- *Do you know of critical data in the literature not cited here that would impact the recommendation?*

No

Mary E. (Bette) Meek

- *Is the rationale underlying this reduction of the default value for this uncertainty factor adequately explained and justified in the report?*

No. I cannot discern rationale for this factor additional to dosimetric adjustment for reference concentrations or following body weight scaling for oral. What data were analyzed as a basis for this factor? Where are the analyses referenced within the document?

- *Is the division of and the accounting for toxicokinetics and toxicodynamics clearly presented?*

No. See comments above (Question 1)

- *Do you know of critical data in the literature not cited here that would impact the recommendation?*

No.

Andrew Renwick, Ph.D.

- *Is the rationale underlying this reduction of the default value for this uncertainty factor adequately explained and justified in the report?*

This is a difficult issue and the logic is based on precedence for the RfC (this is the main justification for including some text on the RfC). Overall the recommendation is reasonable but difficult to justify scientifically (as is obvious from my comments above about the split into kinetics and dynamics).

- *Is the division of and the accounting for toxicokinetics and toxicodynamics clearly presented?*

See above.

- *Do you know of critical data in the literature not cited here that would impact the recommendation?*

There is a large literature on interspecies differences and scaling. The main references have been cited, since the default has to be largely based on general physiological/metabolic considerations. In consequence much of the literature cited is supportive rather than essential.

Charge Question 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?

Sandra J.S. Baird

This analysis presents sufficient information for the use of $BW^{3/4}$ scaling for other than chronic exposures, e.g., acute exposures. The chemicals in the analysis of Travis and White (1988) and others that provide empirical support of the selection of the $BW^{3/4}$ scaling power had relatively short exposure durations, ranging from 1 day to a week or so. These exposure durations are comparable to those of acute exposure.

While the empirical data suggest that LD_{50} s scale by BW^1 in general (Rhomberg and Wolff, 1998; Rhomberg and Caprario, 1999), short-term reference values are unlikely to be based on single exposures resulting in death. However, if the acute exposure value is based on a lethal or severe response, scaling by BW^1 should be considered.

Harvey J. Clewell, III

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?

It is adequate for the purposes of this document.

David W. Gaylor

Apparently, from the last sentence on page 16, the Document supports the use of $BW^{3/4}$ dose scaling for acute exposures in which physiological processes are comparable to those for chronic exposures. There is considerable literature on risk estimation as a function of the duration of exposure for cancer (e.g., Goddard, MJ, Murdoch, DJ, and Krewski, D. Temporal aspects of risk characterization. *Inhalation Toxicol.* 7: 1005-1018, 1995) and a series of reports by the National Research Council on Acute Exposure Guideline Levels including non-cancer and cancer effects. However, I do not believe this literature discusses body weight dose scaling.

William L. Hayton

In my opinion, the $BW^{3/4}$ scaling approach is applicable to other than chronic exposures. The steady state condition is not necessary for this approach to be scientifically valid. When CL is used as the theoretical basis for interspecies extrapolation of the HED, it is also the case that the area under the plasma concentration-time profile (AUC) has a similar relationship to dosage as does the steady-state C_{ss} : $AUC = Dose \div CL$ compared with $C_{ss} = Dose Rate \div Clearance$. As with the chronic exposure situation, if the interspecies variation in CL is known, then the acute dosage in humans that provided a particular exposure in animals could be calculated:
 $HED = Animal Dose \times (CL_{human} / CL_{animal})$

A similar argument applies to subacute exposure; the expected systemic exposure is determined by the CL and if it varies among species according to $BW^{3/4}$, then the toxic dosage will also vary among species according to $BW^{3/4}$. Caveats to use of the $BW^{3/4}$ scaling approach for chronic exposures would also apply.

Kannan Krishnan

No. The document appropriately presents arguments to suggest that $BW^{0.75}$ should not be used for dose scaling under other exposure durations (except repeated exposures).

Mary E. (Bette) Meek

Document pretty clearly outlines why $BW^{3/4}$ not most likely not applicable to acute exposure resulting in immediate and frank or lethal effects, though considered reasonable for acute exposures involving less severe definitions of acute effects in which operative physiological processes are comparable to those for the chronic scenario. However, decision tree would clarify what is recommended in relation to application of body weight scaling for these different types of effects (See reference to same, below).

Andrew Renwick

The report correctly flags the problems of acute, especially frank acute toxicity. However this is not really an issue if the new default is used for setting normal RfDs as these are usually derived from sub-chronic (with an extra uncertainty factor) or chronic data.

It needs to be made clear right at the very beginning of the document whether $BW^{3/4}$ would be used also for ARfD setting. If so then his discussion is relevant but needs more focus on the types of data that are actually used to derive ARfDs.

Charge Question 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?

Sandra J.S. Baird

In my opinion, the analysis of the literature is accurate, reliable, unbiased and reproducible. A strong supporting argument of $BW^{3/4}$ has been presented in the text. The report is clear, well organized and well written.

The report could be clearer on how the $BW^{3/4}$ scaling is to be implemented, i.e., should the HED be calculated for a specific chemical using the test animal (or default) body weights or should the HED be calculated using the default DAFs provided in Appendix B. The language in the Conclusions on page 18 for systemic effects is unclear; while the discussion on portal-of-entry considerations, suggests that the DAF itself is to be used as the default for deriving a HED.

Harvey J. Clewell, III

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.

Yes.

- *Has a strong supporting argument of $BW^{3/4}$ been presented in the text?*

Yes.

- *Is the report clear, well organized, and well written?*

Yes.

- *Do you believe any additional documentation is necessary to ensure clarity or transparency?*

No, except as noted above on the Hierarchy of Approaches.

David W. Gaylor

The Document is comprehensive and supports the use of $BW^{3/4}$ for dose scaling as a default procedure. The report would be clearer if the mathematical formula for interspecies dose scaling based on $BW^{3/4}$ were developed and presented early in the Document, rather than appearing only in Appendix B. Also, the similarity of dose scaling based on $BW^{3/4}$ and simply concentration in the diet (ppm) needs to be discussed.

William L. Hayton

Additional references to consider citing are listed under the **Specific Observations** section and suggestions are included in the foregoing review. Other than those concerns and the comment under Section 6 below, the document makes a strong argument for use of BW^{3/4} to extrapolate HED (and thereby RfD) from animal toxicology data. The report is clear, well organized and well written.

Kannan Krishnan

Supporting argument provided in the document is very limited. However the detail provided in the technical support document is somewhat sufficient.

Mary E. (Bette) Meek

In general, I found the report to be clear and well organized, with the possible exception of lack of clarity re recommendations in relation to application of body weight scaling in specific circumstances (need for decision tree) and lack of clarity about kinetic and dynamic aspects being addressed by body weight scaling vs. 3 fold remaining uncertainty factor.

I also believe that there is a strong supporting argument for use of body weight scaling as a species specific default, based not only on available data, but in the interest of increasing reliability of dose-response estimates by incorporating more species and increasingly chemical specific information, based on consideration of mode of action. This could be augmented by more fulsome consideration, however, of when and nature of body surface scaling to be applied (See reference to decision tree, below).

Andrew Renwick

There are a number of problems with following the logic as it presented in the text.

There is a lot of text about the RfC methodology which could be greatly simplified and removed in many places – because the RfD methodology must stand in its own right. The main reference to the RfC methodology is to explain how delivery into the general circulation and then target organ response are dealt with.

The portal of entry text is unfocussed and refers back too much to the RfC methodology. The text should concentrate on discussing the issues that would need to be addressed in such considerations, which are:

- concentration in food/drink,
- dilution within gastro-intestinal tract,
- the surface area available for exposure,
- the single direction of flow through the gut so that once a material has passed a site it has moved on,
- the episodic nature of ingestion, even when incorporated into the diet (such that there would be periods with no exposure (especially in the upper gastro-intestinal tract), the

transit time through that region of the gut (e.g. the difference between the forestomach and esophageal transit times in rats and humans respectively,

- poor absorption in the upper intestine may give greater delivered to the lower bowel and its metabolically active anaerobic bacterial flora and
- finally and most importantly the fact that the liver is part of the portal of entry and also the major route of elimination and could be exposed to higher concentrations after oral dosage in a species with higher hepatic extraction.

The text on age-related changes completely misses the point – which is inter-species scaling at different ages not intra-species (human) scaling for age.

Charge Question 6: Please provide any additional comments pertinent to the recommendation of body weight scaling to the $\frac{3}{4}$ power for derivation of RfDs that would help improve the overall quality of document.

Sandra J.S. Baird

I would like to see an acknowledgment that a chemical may have multiple target tissues included in the discussion. Section IV, Measure of delivered dose is a likely place to include this concept.

Harvey J. Clewell, III

None.

David W. Gaylor

This reviewer agrees that the use of $BW^{3/4}$ is generally appropriate as a default method for interspecies extrapolation in deriving an oral RfD. It should be pointed out that interspecies dose extrapolation based on concentration in feed (expressed as ppm) provides values quite similar to $BW^{3/4}$ scaling. Apparently, this simple fact is not well known even among scientists familiar with dose scaling techniques. Feed concentration of an agent for interspecies dose scaling certainly is easier to calculate and more familiar to toxicologists and provides a nearly equivalent default method. In fact, some of the physiological arguments supporting the use of $BW^{3/4}$ may be more readily accepted if it is realized that basically this is very similar to use of the dosimeter of mg agent per kg of feed (ppm) for interspecies dose extrapolation. That is, the same biological effect is predicted for mice, rats, and humans for nearly equal concentrations (ppm) in the diets of adults of these species. This can readily be illustrated by the following examples.

A 25 gram mouse consuming 4 grams of food per day containing 10 ppm of an agent is equivalent to $(10 \times 10^{-6} \times 4000 \text{ mg/d}) \div 0.025 \text{ kg} = 1.6 \text{ mg/kg/d}$. With dose scaling based on $BW^{3/4}$, $HED = 1.6 \times (0.025 / 70)^{1/4} = 0.22 \text{ mg/kg/d}$ for a 70 kg human, or $0.22 \times 70 = 15.4 \text{ mg/d}$. For a human consuming 1500 grams of food per day, this represents a concentration in food of $15.4 \text{ mg} / (1500 \times 1000 \text{ mg}) = 10.3 \text{ ppm}$, almost equal to the 10 ppm in the mouse diet. Thus, dose scaling based on $BW^{3/4}$ results in food concentrations (ppm) that are nearly equal. Conversely, equal concentrations (ppm) of an agent in the mouse diet and adult human diet result in nearly equal doses for mice and humans when expressed as mg per $BW^{3/4}$ per day.

Similarly, a 250 gram rat consuming 20 grams of food of food per day containing 10 ppm of an agent yields $(10 \times 10^{-6} \times 20,000 \text{ mg/d}) \div 0.25 \text{ kg} = 0.8 \text{ mg/kg/d}$. With dose scaling based on $BW^{3/4}$, $HED = 0.8 \times (0.25 / 70)^{1/4} = 0.20 \text{ mg/kg/d}$, giving $0.20 \times 70 = 14 \text{ mg per day}$. For a 70 kg human consuming 1500 grams of food per day, results in a food concentration of $14 \text{ mg} / (1500 \times 1000 \text{ mg}) = 9.3 \text{ ppm}$, approximating the 10 ppm in the rat diet. Conversely, equal concentrations (ppm) of an agent in a rat diet and adult human diet result in nearly equal doses for rats and humans when converted to mg per $BW^{3/4}$ per day.

William L. Hayton

In the document the rationale for the BW^{3/4} approach to scaling toxic dose is described as “empirical” in that it generally seems to work for a number of chemicals. The work of West and colleagues has moved beyond empiricism and it is now possible to indicate that there is a mechanistic, theoretical basis for the BW^{3/4} approach that goes beyond an empirical basis. It would strengthen the document to highlight this important development, referencing the West and Brown (2005) paper cited below.

Kannan Krishnan

The limitations of scaling to the ³/₄ power for derivation of RfDs should be clearly presented and integrated along with those of existing methods, to ensure a more transparent presentation of the valid domain of application of the proposed dose scaling approach.

Mary E. (Bette) Meek

In my view, it would be helpful to additionally develop a decision tree regarding the appropriate application of body weight scaling, based on what is known about the mode of action of the substance and other factors. This would include but not be limited to knowledge of the relative half-lives in various species, whether effects are induced by parent compound and or stable metabolite by first order process, nature of the effect (acute frank or lethal, acute other, chronic) and whether effects are related to the parent compound or a reactive metabolite, etc.. It may be that this is envisaged but considered to be relevant at later stage?

Andrew Renwick

Overall I support the logic behind the approach suggested – it really is the scientific support that lacks focus. The bottom line questions should be

Is it practicable?

Is it better than we are doing at present?

The answer to both of these is “YES”. The excessive length of parts of the text simply gives critics something to aim at.

SPECIFIC OBSERVATIONS

Sandra J.S. Baird

Page	Paragraph	Comment
2		Inconsistent capitalization for names of sections and appendixes. Inconsistent formatting of in-text citations re: inclusion/exclusion of “;” between name and date.
5	footnote	Reference for EPA 1992, Guidelines for Exposure Assessments, is missing from reference list.
5	1	Reference for EPA 2002, RfC/RfD process document, is missing from reference list.
5	3	In the 4 th sentence “... estimate the internal dose at the target tissue.” Should “the” be “a” indicating the possibility of multiple target tissues? Or perhaps some other construct to include the idea of multiple target tissues.
6	1	1 st sentence – the word “as” following the BW ^{2/3} and the references in parenthesis are awkward.
6	Foot note 2	The “ <i>Methods</i> ” should be better identified. I think you mean the HEC methods 1994. I see that “ <i>Methods</i> ” is defined in the 4 th paragraph on that page. The footnote reference is in the 1 st paragraph.
6	Foot note 3	The references for USEPA 1999 and 2001 are not in the reference list. If these are referencing the draft Cancer guidelines, the list should also include the 2005 guidelines.
7	1	Last sentence seems awkward in describing “...the dosimetric adjustment employed to estimate the human equivalent concentration inherent in the derivation of the HEC.” Does the “HEC” take on a specific construct or is it just the abbreviation for human equivalent concentration?
8	1	The references in the sentence before figure 1 are incorrectly indicated. Jarabek 1995 needs an “a” or “b”, the “a” needs to be removed from “Bogdanffy and Jarabek, 1995a” The comma in the Bogdanffy and Jarabek cite needs to be removed.
8	Figure 1b	I recommend that “(TK x TD)” be added to the “UF _A ” box to parallel the expression in 1a. I recognize that TK and TD are not explicitly expressed for UF _A in the derivation of the RfD documentation. But the current version of the figure is not intuitive regarding the difference in application of the UF _A between the RfC and RfD.
8	1 st full	2 ^{cd} line, in “ ... Human Equivalent concentration, an HEC,” should “concentration” be capitalized?
9		Sentence ending at top of page. The reference to Appendix D appears to be incorrect since appendix D is the hierarchy of scaling approaches. I think that the reference to appendix D should be struck. No other appendix in the document specifically addresses or supports the statement “... under the guiding paradigm that a common internal dose is the ultimate determinate of risk (see Appendix D).” I think that this statement references the NRC 1994 as was done in the first paragraph of the background section on page 5.

Page	Paragraph	Comment
9	Last line	Kleiber 1947 is not listed in the reference section.
10	Table 1	The list of functions does not appear to have any specific order. I recommend that the functions in the tables be sorted so that the species scaling function is grouped, e.g., $BW^{1/1}$, $BW^{3/4}$, $BW^{-1/4}$. This ordering is consistent with the text description.
10	1 st full	First sentence, 2cd line, insert: "body" before "weight"
10	1 st full	last line before equation, "i.e." missing period after "e"
11	3	Dedrick ref needs "et al."
12	2	I get the point, but this paragraph is difficult to understand. Please rewrite.
12	3	Are there other situations where the $BW^{3/4}$ scaling may not be appropriate besides portal of entry effects? The discussion would be more complete if other situations were included, e.g. sequestered chemicals, nervous system of young children
15	1	Hattis et al. 2004 needs to specify a or b. The first of the Hattis et al 2004 references is incomplete in the reference section.
15	2	Since the term UF_A is used, I recommend that UF_H be added in parentheses and then used in the last sentence instead of "this UF"
15	4	Last line- "Rhomberg, 2004" should be "Rhomberg and Lewandoski 2004"
16	1	Last line "Hattis 2003b", should be "Hattis et al. 2003b"
16	2	The second sentence needs to be rewritten more clearly.
18	2	Second bullet "Hattis 2003b", should be "Hattis et al. 2003b". The second of the Hattis et al 2003 references is incomplete in the reference section.
26	2	Last sentence should refer to Appendix B, not D.
27	Table C	The column header on the 2cd column should include "(10 mg/kg)"
27 & 28	Tables C and D	The BW Scaled Human intake or oral dose (mg/kg) is 6.4 in table C and 6.3 in Table D. This is an issue of when rounding occurs during the derivation process.
27	Table C	Table C would be easier to navigate if it had demarcations (e.g., a bolder line) between the 3 groupings of BW scaling metrics.
29	Table D	It would improve transparency if Table D indicated that the contents of column "BW ^{3/4} Scaled Human exposure (10 mg/kg-day for a 70 kg human)" are taken from Table C.
31	1	Replace "vice"
32	1	2cd sentence, appendix D should be appendix B
32	3	2cd to last sentence- I think that the term "risk adverse" should be replaced. Perhaps, health protective or "conservative" as done earlier in the document.
33	1	First sentence – "se" replace with "use"; appendix D should be appendix B
34	Figure	"Immediate" should be replace with "Intermediate"

Harvey J. Clewell, III

None.

David W. Gaylor

Page 7, line 13 and also, Page 21, Fig. 2, line 6. The statement (e.g., by half, logarithmically) will not be clear to many readers. Replace with (e.g., to $\sqrt{UF_A}$, such that $UF_A = 10$ is reduced to $\sqrt{10} = 3.16$, generally rounded to 3).

2. Page 13, line 2 from bottom. Ratios of what?
3. Page 31. The symbol l in the equation is not clear.
4. Page 32. The last paragraph on this page is extremely important and should be presented in the text and the Executive Summary.

William L. Hayton

- p. 11, Further support for the $\frac{3}{4}$ value for the exponent of BW is available in (Hu, T. M., and Hayton, W. L. (2001). Allometric scaling of xenobiotic clearance: uncertainty versus universality. *AAPS PharmSci* 3, E292001, vol. 3, issue 4, paper no. 29. This e-journal – now listed as the AAPS Journal – is available at <http://www.aapspharmaceutica.com/>). They analyzed clearance values for 115 xenobiotics from published studies in which at least 3 species were used for the purpose of interspecies comparison of CL. The common BW exponent for this large data set was $\frac{3}{4}$, particularly for xenobiotics cleared by metabolism. For renally cleared xenobiotics, a relatively small subset, the common BW exponent was $\frac{2}{3}$.
- pp. 10&12, A recent paper (West, G. B., and Brown, J. H. (2005). The origin of allometric scaling laws in biology from genomes to ecosystems: towards a quantitative unifying theory of biological structure and organization. *J Exp Biol* 208, 1575-92.) is a powerful synthesis of the West, Enquist etc. group's work that provides a compelling theoretical basis for BW $\frac{3}{4}$ scaling in biology. Citation of this paper strengthens the scientific rationale for the BW $\frac{3}{4}$ approach to extrapolation of toxic dose from laboratory animals to humans.
- p. 14, Maturation and growth of renal function is characterized in a paper by Hayton (Hayton, W. L. (2001). Maturation and Growth of Renal Function: Dosing Renally Cleared Drugs in Children. The AAPS Journal 2000; 2(1), paper no. 3. This e-journal is available at <http://www.aapspharmaceutica.com/>).
- p. 14. Literature review of the time course of the development of clearance capacity would bolster this section. The references are Alcorn J. and McNamara PJ. Ontogeny of Hepatic and Renal Systemic Clearance Pathways in Infants Part I. Clinical

Pharmacokinetics 41:959-998, 2002. Part II, Clinical Pharmacokinetics 41:1077-1094, 2002

Kannan Krishnan

Table C is of limited use.

Table 2 is unnecessary and inappropriate without footnotes (indicating that this is not the recommended scaling approach).

Mary E. (Bette) Meek

None.

Andrew Renwick

Pages 7-9 – a lot of this is not strictly relevant and repetitive of material in the introduction. All that is needed is a description of the principle of taking delivery to the target organ by dosimetric correction or scaling and then conclude that this has removed much of the uncertainty inherent in the use of an uncertainty factor. For example the text on RGDR and RDDR etc is totally irrelevant to the setting of an oral RfD. This text runs the risk of confusing rather than informing.

Pages 11-12 – more attention should be given to toxicity caused by a reactive metabolite. The situation where a metabolite is formed which is then detoxified by non-metabolic processes needs to be discussed in the context of the need to move to a higher tier in Table 3 when the mechanism of toxicity is understood. The text on page 12 paragraph 3 does mention a stable metabolite cleared by a first-order process, but does not make it clear that the first-order process must reflect species differences in physiology/biochemistry for the $BW^{3/4}$ to remain appropriate (i.e. it would be correct for metabolism or renal extraction, but not for first-order decomposition).

Page 12 – the text discusses AUC but not the time frame (for chronic toxicity this would be AUC for a dose interval at steady-state).

Page 13 line 3 – delete the word “irreversible” as this becomes irrelevant in the context of a chronic toxicity study or daily human exposure.

Page 13-15 – this text completely misses the point and should be deleted and rewritten in relation to inter-species scaling at different ages not intra-species (human) scaling for age compared with an adult animal.

Page 15 last line before new heading – the text should use the WHO-IPCS CSAF document to support this concept.

Page 16 – citation of LD50 data in the context of an oral RfD seems overkill, as this would not even be used for an AcuteRfD.

Page 17 – Portal of entry – see my comments above.

Page 17 – Summary – the second bullet is incorrect. The citation is not optimal (a better reference would be Dorne et al, 2004 – which summarizes the large database of Dorne et al that has been published on human variability in recent years) BUT in reality this text totally misses the point as it is about intra-species differences and not inter-species scaling. This bullet needs rewriting after correction of the logic using available data (even if it is only generic data on the maturation of physiological and biological processes in animals and humans).

Page 28 line 4 of main paragraph – the delivered dose is a major determinant NOT the “true determinant” – as this implies that once you have allowed for this then species differences will be covered!

Pages 30-33 – as described above, most of this text misses the point that needs to be discussed.

Additional Useful References

Dorne, J.L.C.M., Walton, K. and Renwick, A.G. 2004. Human variability in xenobiotic metabolism and pathway-related uncertainty factors for chemical risk assessment: a review. *Food and Chemical Toxicology*, 43, 203-216.

WHO (2004). Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration-response assessment. Harmonization Project Document No. 2. World Health Organization, Geneva, 2005.