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Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose

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LIST OF ABBREVIATIONS AND ACRONYMS

AUC	area under the curve
BMD	benchmark dose
BW	body weight
Cmax	maximum tissue concentration
DAF	dosimetric adjustment factor
HEC	human equivalent concentration
HED	human equivalent dose
HEE	human equivalent exposure
LOAEL	lowest-observed-adverse-effect-level
MOA	mode of action
NOAEL	no-observed-adverse-effect -level
NRC	National Research Council
PBTK	physiologically-based toxicokinetic
POD	point of departure
RDDR	regional deposited dose ratio
RfC	reference concentration
RfD	reference dose
RGDR	regional gas dose ratio
TD	toxicodynamic
TK	toxicokinetic
UF_A	uncertainty factor (animal to human extrapolation)
USEPA	U.S. Environmental Protection Agency

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PREFACE

This document is intended to be used in combination with other risk assessment tools, guidance, and guidelines. U.S. Environmental Protection Agency (EPA or the Agency) risk assessments may be conducted differently than envisioned in this document for many reasons including, for example, new information, new scientific understanding, or different science policy judgment. The practice of assessing interspecies differences from exposure to toxicants continues to develop, and specific components of this guidance may become outdated or may otherwise require modification in individual settings. It is EPA's intent to use, to the extent practicable and consistent with Agency statutes and regulations, the best available science in its risk assessments and regulatory actions, and this guidance is not intended to provide any substantive or procedural obstacle in achieving that goal. Therefore, this guidance has no binding effect on EPA or on any regulated entity. Where EPA does use this guidance in developing exposure and risk assessments, it will be because EPA has decided, in the context of that assessment, that the approaches from this guidance are suitable and appropriate. This judgment will be tested through peer review, and the risk assessment will be modified to use different approaches, if appropriate.

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EXECUTIVE SUMMARY

This document is a product of efforts by the Agency to develop and promote biologically based and harmonized approaches for all toxicological endpoints used in human health risk assessments. EPA risk assessors routinely use body weight (BW) as the basis for scaling toxicity data from animal models for human health risk assessments. However, the Agency has used $BW^{1/1}$ for non-cancer endpoints and, at various times $BW^{2/3}$ or $BW^{3/4}$ for cancer endpoints to normalize dose across species. This document promotes the use of $BW^{3/4}$ as a default method to convert data between species for both categories of endpoints. A hierarchy of methods for interspecies scaling is presented along with the rationale for selection of the scaling factor and guidance on how to conduct the conversion.

EPA endorses a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically-based toxicokinetic modeling. Other approaches may include using chemical-specific information, without a complete physiologically-based toxicokinetic model. In lieu of data to support either of these types of approaches, body weight scaling to the ¾ power (i.e., $BW^{3/4}$) is endorsed as a general default procedure to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purposes of deriving an oral Reference Dose (RfD). Use of $BW^{3/4}$ scaling in combination with a reduced default interspecies uncertainty factor, UF_A, is recommended as the Agency default approach to replace the previous default approach for this purpose which involved $BW^{1/1}$ scaling with a full uncertainty factor (i.e., a UF_A value of 10). Use of $BW^{3/4}$ in derivation of RfD values is consistent with its 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.

While recognizing that, as supported by the available information for a given substance, priority be given to more data-reliant approaches to interspecies extrapolation, the scope of this document is limited to discussion of the generic default procedure that is viewed as an informed, species-specific, dosimetric adjustment factor (DAF) addressing predominately toxicokinetic and some toxicodynamic aspects of the interspecies uncertainty factor, UF_A. The DAF is multiplied by the animal exposure (in mg/kg-day) to achieve the human equivalent exposure (in mg/kg-day). A detailed derivation of the DAF described in this document results in the following:

$$DAF = (BW_a / BW_h)^{1/4},$$

where the subscripts "a" indicates animal, "h" indicates human, and the ¼ exponent results from the application of $BW^{3/4}$ scaling to exposure in units of mg/kg-day (rather than mg/day) such that

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$$BW^{3/4} / BW^{1/1} = BW^{-1/4}$$

.

This procedure results in derivation of a human equivalent exposure, specifically a human equivalent dose (HED), that is an estimate of the animal exposure of interest translated to a biologically-motivated common scale for use in derivation of the RfD in a manner parallel to the human equivalent concentration (HEC) in derivation of a Reference Concentration (RfC). A reduced interspecies UF_A (with a default value of 3) is then applied to the HED as part of the RfD calculation. The quantitative significance of this procedure with regard to the magnitude of a RfD will depend on the body weight of the species (as well as the value assigned to the UF_A) and may be more or less than the current procedure of dividing by the default composite UF_A of 10. The Appendix A (Table A1) contains example calculations of numeric impact on RfDs for different body weight of the animals.

$BW^{3/4}$ scaling for derivation of the HED is recommended as the default approach for RfDs for remote, as well as portal-of-entry effects. It is noted that this scaling is not inclusive of lethal or frank effects for which maximum concentration (C_{max}) may be the most appropriate dose metric and that such effects are not among those effects recommended for use in deriving RfDs (USEPA, 2002). This default approach generally applies to different durations of exposure. The basis for the overarching assumption is outlined in Sections 3 and 4. The limitations inherent in the application of this approach are related to acute durations of exposure, early life stages, and clearly frank effects such as lethality. The limitations are detailed in Section 5.

The reader is encouraged to read the document carefully in order to fully understand how to apply the procedure appropriately. Additionally, although non-oral RfDs can be estimated (e.g., a dermal RfD), this document focuses only on oral RfDs and for this document the acronym will refer only to RfDs for oral exposure. The overarching assumption in this default approach is that measurable characteristics of anatomy and physiology scale as a function of $BW^{3/4.}$

It is recognized that this procedure, as all default procedures, may not always predict oral exposures associated with precise toxicologically-equivalent doses for specific chemicals. It should be emphasized that other biological information not discussed in this document may inform interspecies adjustments. As a general default procedure, however, it may be anticipated to provide a reasonable description of average behavior of many chemicals much of the time. As with the HEC, appropriate chemical-specific data and information would supersede or modify this default procedure for the HED, with the optimal approach being use of a physiologically-based toxicokinetic (PBTK) or other biologically-based model. Thus the recommended *hierarchy of approaches is as follows:*

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- ***Preferred approach:*** *PBTK modeling*
- ***Intermediate approaches:*** *use of chemical-specific data*
- ***Default approach:*** *use of* $BW^{3/4}$ *scaling and reduction of uncertainty factor default value from 10 to 3*

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1 INTRODUCTION

In using animal data in carcinogen risk assessment, the U.S. Environmental Protection Agency (EPA or the Agency) has been scaling oral exposures from animals to humans on the basis of equivalence of $mg/kg^{3/4}$-d (milligrams of the agent normalized by the 3/4 power of body weight per day) since the early 1990s (USEPA, 1992a). As part of more recent Agency efforts to harmonize human health risk assessment for cancer with that for other toxicological endpoints, this document explores the use of allometric scaling using the 3/4 power of body weight ($BW^{3/4}$) as the default approach for oral exposures associated with noncancer endpoints. Allometric scaling is scaling of physiological rates or quantities to relative growth and size (mass or volume) of one animal species relative to another animal species. The specific purpose of this document and the associated technical report (Rhomberg and Lewandowski, 2004, 2006) is to assess such a broadened application of allometric scaling using the $BW^{3/4}$ as the Agency default approach in light of current scientific knowledge. Aspects of such application across toxicological endpoints, such as different exposure conditions, toxicokinetics, and different life-stages, have also been considered to the extent allowed by the current information.

This document is a product of efforts by the Agency to develop and promote biologically-based and harmonized approaches for all toxicological endpoints used in human health risk assessment. Specifically, this document describes approaches, inclusive of the use of $BW^{3/4}$ scaling, to estimate oral exposures in terms of human equivalents for all toxicological endpoints for the purpose of deriving an oral Reference Dose (RfD)[1]. In doing so, this work is intended to follow and be concordant with the mode of action (MOA) as the guiding paradigm for toxicological evaluations, both cancer and noncancer (USEPA, 1994; 2002; 2005). That the dose at the target site, the internal dose, "is the ultimate determinant of risk" (NRC, 1994), is a fundamental generalization of this paradigm. Use of $BW^{3/4}$ combined with consideration of a reduced interspecies uncertainty factor is recommended here as the default approach in deriving RfDs from animal data in replacement of the previous Agency default approach which involved $BW^{1/1}$ scaling with a full uncertainty factor. The procedure would by default (in lieu of other information) apply to any and all laboratory species, although in practice, the rat is a predominant species, with mice, rabbits, and dogs also represented.

This document is intended to be consulted for future EPA risk assessments. The decision to apply this approach retroactively is left to the discretion of the Agency's programs.

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[1] Although non-oral RfDs can be estimated (e.g., a dermal RfD), this document focuses only on oral RfDs and, for this document, the acronym will refer only to RfDs for oral exposure.

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2 BACKGROUND

Human risk assessments are often based on toxicity data from laboratory animal species, thereby necessitating several extrapolations for estimating the exposure conditions for which a similar toxicity is projected. A critical step is relating the exposure-dose-response relationships for laboratory animals to those pertaining to humans, that is, the need to adjust the exposure used in an animal study to a human equivalent exposure (HEE). The most scientifically sound approach by which this may be accomplished is through the use of chemical- and species-specific toxicokinetic and toxicodynamic information to estimate the internal dose at the target tissue(s). Note that this approach is based on and concordant with the mode-of-action paradigm mentioned above. In most cases, however, there are insufficient toxicokinetic and/or toxicodynamic data available to compare internal dose between different species. In these cases, science-based intermediate and default approaches are needed to derive the estimate of human equivalent dose or concentration.

The methods used by the Agency to extrapolate from animal experimental exposures or doses to human equivalent estimates have evolved since the assessments of the early 1980s. There have been differences in that evolution for oral versus inhalation exposures, as well as for cancer versus non-cancer assessment approaches. The Agency's cancer risk guidelines have and continue to endorse the application of scaling procedures, either on body surface area using ($BW^{2/3}$) or on body weight (BW), for purposes of default interspecies extrapolation in calculation of an HEE. This document recognizes and uses the term HEE in referring collectively to human exposures[2] via any route. When exposures are via the oral route, the more specific term Human Equivalent Dose (HED) may be applied; when via the inhalation route, the term Human Equivalent Concentration (HEC) may be applied.

In EPA cancer assessments for the oral route prior to 1992, extrapolation from laboratory animal exposures to a human cancer risk estimate were typically adjusted based on surface area scaling (derived using $BW^{2/3}$ as in Anderson et al., 1983; USEPA, 1980; 1986; 1992a). In cancer assessments for the inhalation route prior to development of the Agency's inhalation dosimetry methodology (USEPA, 1989; 1994), interspecies extrapolation from the animal exposure concentration differed depending on judgment regarding the chemical's absorption following

[2] The term "exposure", as used here, is roughly analogous here to the terms "administered" or "potential dose" as used in the *Guidelines for Exposure Assessment* (USEPA, 1992b).

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inhalation. For chemicals judged to be completely absorbed upon inhalation, surface area scaling ($BW^{2/3}$) was employed in the extrapolation, e.g., dichloromethane (USEPA, 1985).[3]

The interspecies extrapolation practice for cancer assessments was recommended in 1992[4] when the EPA, in collaboration with the Food and Drug Administration and the Consumer Product Safety Commission, proposed the use of a cross-species scaling factor for administered dose based on equivalence of body weight to the ¾ power per day ($BW^{3/4}$/day) (USEPA, 1992a). While acknowledging that empirical data on comparative carcinogen potency was compatible with scaling either by body weight or surface area ($BW^{2/3}$/day), the document proposed use of $BW^{3/4}$ because of its underlying basis in established allometric interspecies variation in anatomy and physiology, much of which is explored and documented further in this policy paper and accompanying appendices. Similarly, the Agency's 2005 cancer risk guidelines (USEPA, 2005) endorse the application of $BW^{3/4}$ for purposes of interspecies extrapolation when chemical-specific data are absent.

The EPA (1992a) action provided a source of standardization for predictive cancer risk assessment via the oral route. However, the procedures employed for derivation of the RfD, the Agency's traditional dose-response method for noncancer effects from a toxic agent via the oral route were, and remained, quantitatively different. In the derivation of an RfD, the dose administered orally is expressed in mg/kg-day and is considered directly proportional across species on a body weight basis, (i.e., $BW^{1/1}$ versus $BW^{3/4}$). An uncertainty factor, UF_A, is subsequently applied to the laboratory animal exposure for consideration for interspecies extrapolation.

Since 1989, extrapolation from laboratory animal inhalation exposure concentrations to HECs has been performed as per *Interim Methods for Development of Inhalation Reference Doses* (USEPA, 1989) and *Methods for Derivation of Inhalation Concentrations and Application of Inhalation Dosimetry* (USEPA, 1994). The methods described in these documents give preference to the use of toxicokinetic modeling for extrapolation, but also recognize the use of intermediate and default options for exposure concentration adjustment approaches, based on consideration of physicochemical characteristics of a given agent as key determinants of interaction with the respiratory tract and ultimate disposition of the agent in the body. In these procedures, which may be considered as inhalation dosimetry, particles and gases are treated separately, and the type of toxicity observed, respiratory tract (i.e., portal of entry) or toxicity remote to the portal-of-entry tissues, determines the adjustment procedure applied. Since its

[3] Subsequent toxicokinetic analysis with dichloromethane (USEPA, 1987; 1989) informed the *Methods for Derivation of Inhalation Concentrations and Application of Inhalation Dosimetry* (USEPA, 1994) development, leading to different default adjustments for remote acting gases.

[4] The Agency has since reaffirmed the method in carcinogen risk assessment (see USEPA, 2005).

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inception, derivation of the HEC for this extrapolation has been utilized in cancer and noncancer inhalation assessment procedures. With regard to the latter, the Reference Concentration, RfC (initially termed an "inhalation Reference Dose" or RFD_i), originated with the publication of these documents (USEPA, 1989; 1994). Concordant with the RfD process, *these methodologies* include recognition of an uncertainty factor for uncertainties associated with interspecies extrapolation, UF_A, with the default value of this UF automatically reduced (i.e., by half, logarithmically) in recognition of the dosimetric adjustment employed to estimate the HEC.

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3 TOXICOLOGICALLY EQUIVALENT DOSES IN THE RFC AND RFD

3.1 ESTIMATING TOXICOLOGICALLY EQUIVALENT DOSES EXTRAPOLATION AND DOSIMETRY IN THE RFC

As previously discussed, dose-response assessment for human health, by the Agency as well as the risk assessment community, often uses toxicological effect information from laboratory animals, requiring extrapolation to humans. The goal of one of the extrapolation procedures is to determine toxicologically equivalent doses for animals and humans, ideally by "matching" with respect to the internal dose, or in other words, determining the externally applied exposure for humans that would result in the same internal dose. In derivation of the RfC,[5] this extrapolation is accomplished through application of a suite of procedures that range from application of a sophisticated physiologically-based toxicokinetic (PBTK) model of site-specific dosimetry to default procedures.

These default procedures are described fully in the Agency's 1994 document and are represented here schematically in Figure 3-1a[6]. Dosimetric adjustment factors (DAFs) are used to extrapolate laboratory animal exposure concentrations to human equivalent exposure concentrations. The DAFs differ with chemical categories and include the Regional Gas Dose Ratio (RGDR) for gases and the Regional Deposited Dose Ratio (RDDR) for particles. When the default approaches are employed, the interspecies uncertainty factor is reduced. While the remaining uncertainty may include elements of toxicokinetics as well as toxicodynamics, the dosimetric adjustment, for simplicity is generally described as addressing cross-species differences in chemical disposition or toxicokinetics. A more in-depth discussion of the aspects of inter- and intra-species extrapolation considered to be accounted for with the default dosimetric adjustments is presented elsewhere (USEPA, 1994; Jarabek, 1995a; 1995b; Bogdanffy and Jarabek, 1995).

Figure 3-1a shows the experimental animal exposure of an agent, in ppm or mg/m^3, extrapolated to an HEC, via application of DAFs. In this case, the animal exposure extrapolated is a point of departure (e.g., NOAEL, LOAEL, or BMDL) derived from analysis of the findings from an animal study. DAFs are based on the determinants of disposition considered most

[5] The same suite of procedures is applied in determining the HEC when deriving the inhalation cancer risk estimate (USEPA, 2005).

[6] It is noted that this description of the default approach is, for the purposes here, a simplification of the recommended process that is based on the selection of the measure of dose which best expresses the internal dose at the target. Consideration of duration adjustment, e.g., from discontinuous to continuous exposures, is not described here (See USEPA, 1994, for the full recommended methodology).

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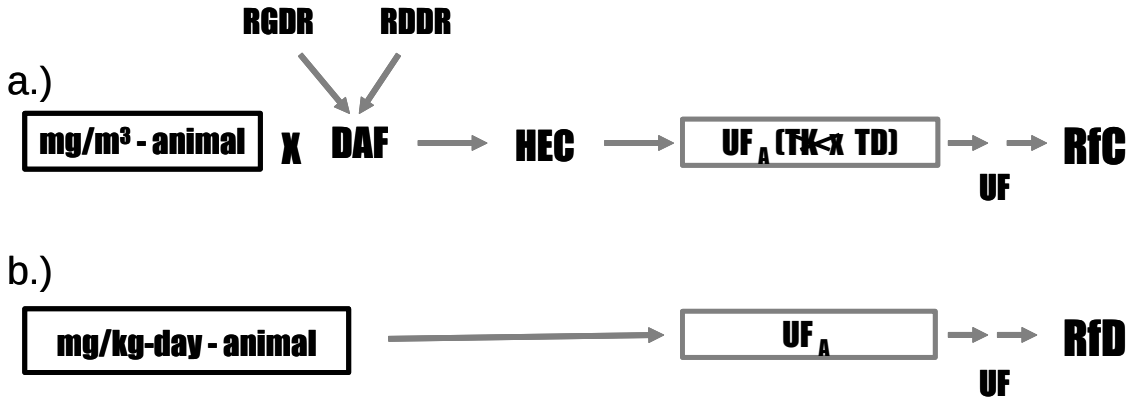

Figure 3-1. Schematic of procedures in the RfC (a.) and previous RfD (b.) processes. An HEC is derived in the case of the RfC, but an HED has not been derived for the RfD. UF_A denotes the animal-to-human uncertainty factor, with UF representing other factors applied for various extrapolations (as per *USEPA, 1994*). In the RfC pathway, TK denotes toxicokinetic and TD toxicodynamic components of the UF_A.

influential to differences between animals and humans. For example, with inhaled agents that affect the upper airways, DAFs are constructed from the surface areas of various regions of the airways and the minute inhalation volume of the species involved. For inhaled agents that involve transport by blood to affect systemic tissues, DAFs are constructed from partition coefficients of the agent (e.g., blood:gas and blood:tissue). The DAFs listed above are actually ratios constructed of animal and human values for these default determinants of disposition. As application of this ratio is projected to result in the human exposure that would bring about the same internal dose as the laboratory animal exposure to which it is applied, the DAF may also be considered as a factor used to "normalize" an animal external exposure to the corresponding human external exposure under the guiding paradigm that a common internal dose is the ultimate determinant of risk (see Appendix D).

In the RfC process, the default application of DAFs is considered to produce HECs associated with toxicokinetically equivalent doses to the human tissue. Application of the default DAFs is not generally described as accounting for the toxicodynamic portion of response, as is indicated in Figure 3-1a, although as noted above, that is a simplification. Other chemical-specific information may inform consideration of toxicodynamic differences. As a simplification, Figure 3-1a shows the elimination of the toxicokinetic (TK) component from the UF_A in consideration of the use of an HEC and implies the residual is within the toxicodynamic (TD) component, although depending on the chemical assessment, this may or may not be the case.

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3.2 EXTRAPOLATION IN THE RFD DERIVATION PROCESS

Currently, no document or dosimetry procedures comparable to the the RfC methodology exist for the RfD. As with the RfC, derivation of this reference value is frequently reliant on experimental animal data. In general, the UF_A had been applied along with other UFs to the animal experimental dose to give the RfD value. Figure 3-1b reflects this simplified process showing application of the UF_A with no "HED" formally calculated. Appendix A illustrates the numerical consequences of this practice (e.g., use of $BW^{1/1}$ versus $BW^{3/4}$).

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4 $BW^{3/4}$ SCALING FOR DERIVING TOXICOLOGICALLY EQUIVALENT DOSES IN THE RFD

The following subsections discuss various considerations in interspecies extrapolation, with focus on the use of $BW^{3/4}$ scaling (long used for Agency cancer risk assessment) of oral exposures as a default approach in extrapolation for the derivation of RfDs to replace the use of $BW^{1/1}$, which has been the Agency default for that purpose.

4.1 SCALING IN CROSS-SPECIES EXTRAPOLATION

Use of a fractional power of body weight, most often $BW^{3/4}$, as a means to derive toxicologically-equivalent doses across species is an accepted risk assessment practice (e.g., USEPA, 1992a; 2005). The basis for this acceptance is along several lines. Literature exists on general allometric relationships between $BW^{3/4}$ and physiological and biochemical processes, mostly related to kinetics (Kleiber, 1932; 1961). Empirical information on the kinetics and toxicology of pharmacologic agents has been examined in relation to BW (e.g., Dedrick et al., 1970; Dedrick, 1973). Much of the information related to these arguments are described and explained in the report by Rhomberg and Lewandowski (2004, 2006) and in EPA's Federal Register notice (USEPA, 1992a). Some of the more compelling information on BW scaling in relation to basic life processes and to the effects and kinetics of pharmaceuticals and toxic agents is reviewed below.

4.2 INTERSPECIES $BW^{3/4}$ SCALING AND LIFE PROCESSES

Kleiber's (1947) synthesis of data on energy utilization in mammals resulted in his observation that the allometric relationship of $BW^{3/4}$ is an accurate reflection of "metabolic body size" in mammals. Subsequent to his work, a large number of characteristics and functions of mammalian biological systems were examined for their relationship with BW. Table 4-1 shows some examples. Volumes and capacities tend to retain their proportionality across species, i.e., $BW^{1/1}$. A number of physiological processes, in addition to those listed here, are proportional to $BW^{3/4}$ (see, for example, West et al., 1997).

From these relationships, it can be deduced that, in mice and humans, weight increases in direct proportion with characteristics such as blood volumes and organ weights. Other processes (e.g., those involving flow and energy production, and food and water consumption) increase in absolute values but in proportion only to the three-quarters power of the body weight. It may also be seen that in processes involving rates and time, a decrease in the absolute value may actually occur. Thus, although the body mass and absolute heart mass are both about 2300-fold greater in humans than in mice (scaling to $BW^{1/1}$), cardiac output in humans is only about

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Table 4-1. Cross-species body weight scaling for various metabolic and physiological functions.

Function	Units	Species Scaling
Energy utilization	kcal/day	$BW^{3/4}$
Glomerular filtration	L/min	$BW^{3/4}$
Glucose turnover	mg/min	$BW^{3/4}$
Heart rate	min^{-1}	$BW^{-1/4}$
Respiratory rate	min^{-1}	$BW^{-0.26}$
Blood volume	L	$BW^{1/1}$
Vital capacity	mL	$BW^{1/1}$
Food consumption	g/day	$BW^{3/4}$
Water consumption	L/day	$BW^{3/4}$

300-fold greater than in mice (scaling to $BW^{3/4}$), whereas the heart rate in humans is about 7-fold less than in mice (scaling to $BW^{-1/4}$). The latter relationship, where certain processes between species are related one to another in an inverse manner (i.e., are decreased rather than increased), follows from $BW^{3/4}$ allometry when processes varying by a three-quarters power are normalized against an aspect that varies directly, i.e, $BW^{1/1}$, such that

$$BW^{3/4} / BW^{1/1} = BW^{-1/4}$$

This inverse relationship between the absolute rates of processes (e.g., glomerular filtration, minute ventilatory volume, and cardiac output) and BW is supported by the concept of physiological time across species (e.g., USEPA, 1992a). Thus, processes that are related by $BW^{1/4}$, such as physiological time, are actually corollaries of $BW^{3/4}$ scaling that have been: (1) predicted mathematically and (2) substantiated by empirical observations. This concordance between hypothesis and observations imparts considerable credence to the overall relational theory of $BW^{3/4}$ scaling.

4.3 INTERSPECIES $BW^{3/4}$ SCALING AND TOXICITY PROCESSES

The $BW^{3/4}$ allometric scaling relationship of Kleiber (1932; 1961) was derived from general kinetic processes of living systems. The relevancy of these general processes to the more refined relationship of kinetics of pharmaceuticals and other xenobiotics, such as toxicants, has also been examined. In general, the information available in this area supports the three-

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quarters power relationship (including the quarter power relationship) for toxicologic and toxicokinetic behavior of a number of compounds over a reasonable number and range of species.

Travis and White (1988) undertook an analysis of the maximum tolerated dose from the dose-response relationship of 27 direct-acting agents (i.e., where the agent causing toxicity is the administered or parent chemical) administered orally (once per day, 5 days a week) in mice, rats, dogs, monkeys, hamsters, and humans. They then used regression techniques to determine the optimal power of body weight to achieve the best fitting relationship. They reported $BW^{0.73}$ (95% confidence bounds $BW^{0.69\text{-}0.77}$) as the geometric mean of the cross-species predictions. This study is a reanalysis of data sets from two other studies (Freireich et al., 1966; Schein et al., 1970) and provides support to the relationship of $BW^{3/4}$ in making interspecies extrapolations for direct-acting toxicologic agents. The analysis also rejected the relationships of $BW^{1/1}$ (the exponent associated with direct proportionality) and $BW^{2/3}$ (the exponent associated with body surface area scaling), although a subsequent report offered an analysis suggesting that $BW^{2/3}$ still may fall within the confidence bounds (Watanabe et al., 1992).

The analyses by Boxenbaum (1982) and Dedrick (1973) of elimination rate constants for 8 drugs in 4 different species found this parameter to be proportional to $BW^{0.22}$, which is reasonably close to the expected value for $BW^{1/4}$ scaling related to time processes of $BW^{3/4}$.

Kirman et al. (2003) employed PBTK models as tools to assess the performance of allometric scaling. These authors used PBTK models for 12 volatile and lipophilic compounds to estimate the kinetic disposition of these various agents in yielding a measure of internal dose (area under the curve or AUC) in mouse, rats, and humans. Model estimates were obtained under conditions of continuous and gavage dosing over a range of experimental exposures considered low (0.0001-1 mg/kg-day) and high (10-10,000 mg/kg-day). The estimates from the models were then compared to predictions calculated from allometric scaling of the administered dose based solely on $BW^{3/4}$. The results indicated that $BW^{3/4}$ generally performed better at relatively low administered doses (where metabolism is not saturated and clearance rates were pseudo-first order) than at high administered doses. The results also indicated that the scaling factors were applicable in oral administration not only to parent chemical but also for the formation of stable metabolites and amount metabolized by first-order pathways (see *Metabolism and Clearance* below).

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5 CONSIDERATIONS ON USING $BW^{3/4}$ SCALING AS A DEFAULT FOR ESTIMATING TOXICOLOGICALLY EQUIVALENT DOSES

This section discusses a variety of aspects pertinent to using $BW^{3/4}$ as a default for estimating toxicologically equivalent doses for the purposes of deriving an RfD. This discussion is intended to be informative to this application (e.g., with regard to assumptions or limitations).

5.1 METABOLISM AND CLEARANCE

Observations of a fractional power relationship between body weights with regard to processes across species has been hypothesized to be related fundamentally to differences in exchange surfaces and distribution networks, which constrain internal concentrations and flux associated with general metabolic processes of endogenous substances and reactants for all living systems (West et al., 1997; Enquist et al.,1998).

The applicability of this general body weight scaling relationship to more specific metabolic processes, such as xenobiotic metabolizing systems involved in the clearance or activation of exogenous substances (where disproportional relationships among species often exist) would depend on the similarity in the kinetic behavior of the exogenous substance to endogenous reactants. The degree of similarity would reflect whether the parent or a stable or reactive metabolite is the relevant dose to the target tissue (O'Flaherty, 1989; USEPA, 1992a; Beck and Clewell, 2001) and on the specific kinetics of the clearance process, as to whether it is a first-order or capacity-limited process (O'Flaherty, 1989). Both of these factors prominently influence the dose to the target tissue over time, i.e., the AUC (see below).

Accordingly, $BW^{¾}$ scaling would apply most appropriately to those exogenous substances for which the unmetabolized parent or a stable metabolite is the relevant toxic species and clearance is according to first-order processes (USEPA, 1992a). Conversely, the applicability of $BW^{3/4}$ scaling is less well supported when toxicity is a consequence of exposure to a very reactive parent compound or metabolite that is not removed from the site of formation by biological processes (e.g., subsequent metabolism) but chemically reacts with cellular constituents (Travis, 1990; Beck and Clewell, 2001).

5.2 MEASURE OF DELIVERED DOSE: CHOICE OF THE APPROPRIATE DOSE METRIC

As discussed above, the species BW scaling interrelationships among volumes ($BW^{1/1}$), physiological processes ($BW^{3/4}$), and rates ($BW^{-1/4}$) have been shown to result in a normalization of dose across species (USEPA, 1992a) with respect to time. This normalization, based on the concept of physiological time implicit in $BW^{-1/4}$ scaling, is in terms of exposure to a

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concentration over some duration of time (e.g., AUC that is adjusted for species). Thus, the measure of dose that is being scaled for kinetic equivalency between species in this process is the AUC (O'Flaherty, 1989).

It is recognized that toxicants may not exert their effects through a single mode or mechanism of action and that, in some cases, measures of delivered dose other than AUC may be more appropriate. However, for agents causing cumulative irreversible damage, a common definition of toxicity, an expression of integrated exposure such as AUC may be considered appropriate (recognizing the caution raised in the previous section regarding toxicity at the portal of entry).

5.3 EARLY LIFESTAGES

Investigations with BW scaling have dealt almost exclusively with interspecies scaling across adult organisms, consistent with much of the experimental toxicity information that is generated through exposure of adult organisms. The default application of $BW^{3/4}$ scaling prior to this document has been for cancer assessment based upon adult animals (USEPA, 2005). This document extends that application to derivation of the RfD by scaling the administered exposure for the mature laboratory animal to that for the adult human. As the toxicant typically is administered to an adult animal, this practice would generally be employed even when the target is a fetus or developing pup, such as in developmental or multigenerational reproductive studies.

Exposure and internal dosimetry of pregnant, nursing, and growing animals may vary compared to adult animals, so use of the administered dose for toxicity studies involving these periods is associated with relatively greater uncertainty, absent lifestage-specific information. In some situations, the Agency may have data on effects resulting from exposure of young animals and be interested in derivation of an exposure value particular to infants or children as described in *A Framework for Assessing Health Risk of Environmental Exposures to Children* (USEPA, 2006). In those instances, extrapolation from the young animal to a young human exposure may be desirable (Barton, 2005). When doing such an extrapolation, however, key developmental processes need to be matched in a species-dependent manner, because the temporal pattern of development (of physiological systems, organs, etc.) differs across species (Finlay and Darlington, 1995; Clancy et al., 2001; USEPA, 2002; 2006). Because of these differences in temporal patterns of development, such matching is usually done on an endpoint-specific basis for both toxicokinetics and toxicodynamics, which may also differ (USEPA, 2002; 2006). The Agency's *Review of the Reference Dose and Reference Concentration Processes* (USEPA, 2002) also discusses such considerations, with particular focus on the Agency's toxicity testing protocols. Further analysis of this important aspect of interspecies extrapolation of early

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lifestages is not presented here, as it is anticipated to generally depend upon analyses with lifestage-specific information rather than application of default approaches.

Given that the default application of $BW^{3/4}$ scaling would be to scale the administered exposure for the mature laboratory animal to that for the adult human, potential limitations were considered for this default application in deriving RfDs, which, by definition, apply to the human population inclusive of children. The following discussion focuses primarily on recent analyses of pharmacokinetic differences across ages of humans. An attempt to systematically evaluate quantitative scaling differences in toxicodynamic processes across lifestages (Hattis, 2004) observed that data for such an analysis are limited. Analyses of pharmacokinetic data on 45 therapeutic drugs for different age groups of children indicate that a number of toxicokinetic parameters, including activity of various xenobiotic metabolizing enzymes, generally reflect adult values by 6 months of age, with the largest differences from the adult values occurring in the first 2 months (Ginsberg et al., 2002; 2004). Using largely the same database, Hattis et al. (2004) analyzed clearance rates on a $BW^{1/1}$ basis for a number of drugs representing a wide-ranging spectrum of clearance mechanisms in adults, children, and infants. These data showed that, from the age range of 2 months to 12 years, clearance rates were higher in children than in adults, whereas values for very young infants (1-8 weeks, full-term neonates, and premature neonates) were deficient relative to adults, ratios for premature infants being about 1/2 those for adults (Hattis et al., 2004; 2003a). Analysis of these clearance rate data on a $BW^{3/4}$ basis resulted in ratios that approximated 1 (children equal to adults) down to 6 months of age (Hattis et al., 2004). This analysis indicates that the occurrences of higher clearance rates in children (down to about 6 months) relative to adults are consistent with the use of $BW^{3/4}$ allometry across ages, while not being consistent with such allometry for young infants.

PBTK models are a method to integrate changes in physiological and biochemical factors (including development of metabolizing enzymes) to assess their impact on dosimetry by making predictions across ages and genders (Kedderis, 1997; Rodriguez et al., 2007). Clewell et al. (2004) used a PBTK lifestage model that integrated various age- and gender- specific differences from birth to 75 years old and reported results by age categories including one for “birth to 6 months”. The authors predicted measures of internal dose (e.g., parent, circulating metabolite, or reactive metabolite) for 6 different chemicals, and reported that values for each were within a factor of 2 across the age groups evaluated, with the larger transient variations predicted particularly during the neonatal period. Their results indicated that the most important age-related PK factor appeared to be the potential for decreased clearance of a toxic chemical in the perinatal period, although this same factor could also result in reduced production of a reactive metabolite.

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Application of $BW^{3/4}$ scaling to derive a human equivalent dose from another species by scaling to the body weights of children rather than adults would yield a higher equivalent dose. Scaling to children's body weights might not be appropriate for RfD or short-term guidance value intended to apply to a population that includes young infants and children due to the comparatively slower clearance during this period and the limited toxicokinetic data available to assess the appropriateness of body weight scaling in early life. Similar analyses on potential sensitivity of toxicodynamic processes during developmental periods are not currently available.[7]

5.4 TOXICOKINETICS AND TOXICODYNAMICS IN TOXICOLOGICAL EQUIVALENCE

Species differences in dose-response functions may be elicited both: (1) as a consequence of distribution of agent affecting the target-tissue dose between species and (2) from intrinsic differences in the tissue response between species. Achieving "toxicological equivalence" across species requires that aspects of both toxicokinetics and toxicodynamics be considered. Therefore using $BW^{3/4}$ to achieve "toxicological equivalence" for interspecies differences implies that scaling is inclusive of both aspects.

From the preceding discussion on allometry, it is apparent that many physiological processes relating to kinetics conform to a $BW^{3/4}$ relationship. This is not to say, however, that $BW^{3/4}$ scaling encompasses all kinetic processes related to toxicity. Neither does this statement intend to indicate that $BW^{3/4}$ scaling does not address any dynamic aspects of toxicity. It has been established that there are processes considered to be toxicodynamic in nature, e.g., cellular repair and regeneration, signaling cascades, and proliferative responses that also scale as a fractional power of BW (see Rhomberg and Lewandowski, 2004, 2006; USEPA, 1992a, for additional examples).

It is necessary to acknowledge the overlap in kinetic and dynamic factors addressed by $BW^{3/4}$ scaling. That $BW^{3/4}$ scaling applies only to metabolic types of kinetic processes between species is a misconception. Many potential modulating factors that may be considered as dynamic, such as the intrinsic sensitivity of the target site, may be highly species dependent. The

[7] While the focus of this document is on interspecies extrapolation (not intraspecies extrapolation), it is noted that inclusion in the RfD derivation of the UF for intraspecies variation in susceptibility due to the possibility that a given data base may not be representative of the exposure-response relationship for some susceptible subgroups within the overall population further addresses this toxicodynamics data gap (USEPA, 2002). As with the UF_A, this UF is also considered to comprise both toxicokinetic and toxicodynamic components (Renwick and Lazurus, 1998). Additionally, the RfD methodology includes a database UF intended to account for the potential for deriving an inadequate RfD as a result of an incomplete characterization of the chemical's toxicity, including toxicity to early life developmental processes, and any associated toxicodynamic changes (Dourson et al., 1992; USEPA, 2002).

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concept to be conveyed is that cross-species $BW^{3/4}$ scaling for toxicologically equivalent doses predominately addresses factors involved in estimating toxicokinetics, as well as some toxicodynamic factors. This concept is critical to how the interspecies uncertainty factor (UF_A) is applied in derivation of the RfD (see below).

5.5 ACUTE SCENARIOS

The focus of this default procedure is for the oral RfD and cancer assessments, both of which are concerned with lifetime repeated exposure scenarios at the time of writing this document. Application of this procedure to scenarios of shorter durations, such as acute exposures, is considered in this section (Hattis, 2003b).

As discussed above, $BW^{3/4}$ scaling is understood to address aspects of both TK and TD, the latter being inclusive of many repair types of processes. $BW^{3/4}$ scaling would not generally be relevant in the case of a single exposure eliciting sudden and severe toxicity resulting from immediate and intolerable damage to some critical biological pathway, and where repair processes (i.e., TD) would be overwhelmed. This case is in contrast to chronic exposures, where the organism or tissue has time available for repair processes to be elicited and functional, and where the level of damage is not severe (e.g., those routinely considered for an RfD).

Rhomberg and Wolff (1998) examined patterns in the correspondence of LD_{50} values from a single oral administration across several species. They found that direct scaling by body weight (i.e., $BW^{1/1}$), rather than scaling to $BW^{3/4}$, best fit the data. One limitation of this analysis is that most of the data were obtained in species of similar size (i.e., mouse, rat, guinea pig, and hamster) where the correlation was strongest. Rhomberg and Caprario (1999) extended the findings of Rhomberg and Wolff (1998) by examining information available on larger species via collating data from administration routes other than oral (i.e., intravenous, intraperitoneal, and intramuscular). LD_{50} values of over 3,000 agents were evaluated in pair-wise species comparisons across eight species (mouse, rat, hamster, guinea pig, rabbit, cat, dog, and monkey). Results were similar to the oral LD_{50} analysis, indicating that for lethal acute exposures, scaling to $BW^{1/1}$ provided a good extrapolation factor across species.

Thus, due to these toxicodynamic considerations, $BW^{3/4}$ would most likely not be applicable to scenarios under conditions of an acute exposure focused on the occurrence of immediate and severe or lethal effects. Application of $BW^{3/4}$ is considered a reasonable approach, however, for acute exposures in which the operative physiological processes are comparable to those for the chronic scenario.

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5.6 PORTAL-OF-ENTRY ISSUES FOR ORAL EXPOSURE

The utility and limitations of allometric scaling ($BW^{3/4}$) for oral route portal-of-entry effects has not been systematically evaluated. Portal-of-entry effects are caused by direct action of a chemical or its metabolites on tissues in the respiratory or gastrointestinal tract (or the skin, but that is not the focus here). Considerable conceptual similarity exists between inhalation and oral portal-of-entry exposure scenarios. In both cases, exposures would occur due to agents entrained in the incoming media (e.g., inspired air or ingested materials) to the surface respiratory or gastrointestinal epithelial tissues. This scenario differs fundamentally from delivery of a chemical from circulating blood to organs throughout the body and uptake into target tissue. The relevant dose metric for systemic effects is generally the mass per tissue (i.e., mg/kg), whereas with portal-of-entry effects the most relevant dose metric would be based on mass of agent per surface area (i.e., mg/cm^2).

For respiratory portal-of-entry effects considered in the RfC methodology (USEPA, 1994), species-specific surface areas for regions within the respiratory tract are used in calculating a DAF that is specific to that region. An approach for an interspecies DAF for oral portal-of-entry effects parallel to the inhalation portal-of-entry DAF process may be appropriate (see Appendix C). Such an approach would utilize species-specific surface areas for the affected area of the gastrointestinal tract of the laboratory animal and human and take into account other unique physiological differences. For example, rodents have a physiologically distinct forestomach region which humans lack, as well as a different average gastrointestinal pH. Implementing such an RfC -like approach for the gastrointestinal tract, however, entails further development.

A $BW^{3/4}$ relationship exists among species in studies where dose is administered in food, because interspecies food consumption follows a $BW^{3/4}$ relationship (see Table 4-1). Consequently, exposure among species to an agent, both overall and to the gastrointestinal tract, present at a constant concentration in food would also follow a $BW^{3/4}$ relationship. Therefore, it is reasonable to apply the $BW^{3/4}$ approach for gastrointestinally related, portal-of-entry effects.

5.7 SUMMARY OF LIMITATIONS IN $BW^{3/4}$ SCALING

From the preceding analysis, the following is summarized concerning the underlying limitations in the application of $BW^{3/4}$ scaling.

- Use of $BW^{3/4}$ scaling is most appropriate for toxicity where the measure of dose associated with the toxicity is the AUC for the parent chemical or stable active metabolite following oral exposure. Conversely, the applicability of $BW^{3/4}$ scaling is less well supported when toxicity is a consequence of exposure to a very reactive chemical that is

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not removed from the site of formation by biological processes (e.g., metabolism), but by chemical reaction with cellular constituents.

- Differing allometric patterns among various sized individuals of the same species (Rhomberg and Lewandowski, 2004, 2006) may pose an uncertainty to intraspecies scaling, while differences across species in patterns of development (Finlay and Darlington, 1995; Renwick and Lazarus, 1998; Clancy et al., 2001) can complicate interspecies extrapolation from immature animals to humans. With regard to variation in toxicokinetic proceses, recent analyses suggest that a $BW^{3/4}$ relationship is descriptive of some TK differences observed with pharmaceuticals among ages including early lifestages, down to about 6 months (Ginsberg et al., 2002; 2004; Hattis et al., 2004). Scaling to children's body weights might not be appropriate for an acute RfD or short-term guidance value intended to apply specifically to a population that includes young infants and children due to the comparatively slower clearance during this period and the limited toxicokinetic data available to assess the appropriateness of body weight scaling in early life.

- Cross-species $BW^{3/4}$ scaling for toxicologically equivalent doses predominately addresses factors involved in estimating toxicokinetics, as well as some toxicodynamic factors.

- Use of $BW^{3/4}$ scaling for orally administered acute exposures where effects such as lethality are manifest may be less accurate than for other exposures (Hattis et al., 2003b). It is considered more appropriate for non-lethal acute effects in which the functional status of physiological processes is comparable to the chronic scenario.

- For oral portal-of-entry effects, development of a DAF involving aspects relating dose to a surface area at or within the portal may be appropriate. Additionally, the $BW^{3/4}$ relationship exists for interspecies food consumption and diet-associated dosing.

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6 CONCLUSIONS

The recommended default procedure (in the absence of chemical-specific data or in lieu of information indicating an alternate approach) for extrapolating from laboratory animal oral exposure estimates to human equivalent estimates is body weight scaling to the 3/4 power ($BW^{3/4}$). The overarching assumption in this default approach is that measurable characteristics of anatomy and physiology scale as a function of BW ¾. The basis for the overarching assumption is outlined in Sections 3 and 4. The limitations inherent in the application of this approach are related to acute durations of exposure, early life stages, and clearly frank effects such as lethality.

The limitations of this approach are described in detail in Chapter 5 and summarized in section 5.7. The arithmetic involved in the application of this procedure to a given exposure scenario in representative animal species using mature body weights is demonstrated in Appendix B. Implementation of this scientifically-based, default dosimetric adjustment, which is already employed in the derivation of oral cancer slope factors, provides a parallel to the default dosimetric approach employed in derivation of the HEC for inhalation exposures.

Pending, or in lieu of, the development of specific information to employ an interspecies dosimetric adjustment based on dose to the specific site of toxicity within the gastrointestinal tract, the $BW^{3/4}$-based DAF is recommended as the default to derive a HED involving oral portal-of-entry toxicity (e.g., see Appendix C). This science-based policy decision provides consistency with methods used for scaling oral exposures for cancer assessment (USEPA, 2005).

6.1 DEFAULT PROCEDURE IN THE HIERARCHY OF APPROACHES

This default approach (as in the case of the HEC default approach) represents the base tier in the hierarchy of approaches (Table 6.1) to be considered in extrapolating from laboratory animal to human equivalent oral exposure scenarios for the purposes of developing a dose-response assessment pertinent to human risk assessment. A customization of the hierarchy presented in *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (USEPA, 1994; see also Appendix D), for the purposes of the oral route extrapolation, is shown in Table 6-1.

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Table 6-1. Hierarchical framework of approaches for interspecies extrapolation.

Optimal

If available, employ PBTK (or PBTK-TD) or other biologically based modeling.

Intermediate

Assess available information, considering what is known about species differences, and the toxicokinetic and toxicodynamics of the chemical. Use this information to derive an appropriate cross-species adjustment (e.g., a data-supported scaling function or a different UF or combination of the two).[1] Basic issues in this consideration include

1. indications that $BW^{3/4}$ scaling or an alternate approach would be preferred for interspecies extrapolation; and
2. the best quantitative judgment of the residual uncertainty in animal-to-human extrapolation that remains after BW scaling.

Examples of intermediate approaches include the use of chemical specific adjustment factors, as described in IPCS (2005), as well as the existing IRIS assessment for boron (USEPA, 2004).

Default

In lieu of useful information about the chemical being considered (see intermediate approach), the default is employed.

[1] Evaluate information available for laboratory animals compared to human with respect to:

- whether the active toxicant is the parent or a metabolite,
- appropriate dose metric (e.g., C_{max}, AUC, TACC [time-above-critical concentration], age-related concentration x time interval),
- critical TD event(s), and
- critical effect, including consideration of portal-of-entry issues.

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6.2 OPTIMAL AND INTERMEDIATE APPROACHES

An overriding aspect of the hierarchy in Table 6-1 is the incorporation of mechanistic data as feasible, ensuring that the methodology employed for a particular chemical assessment is commensurate with the available data. This is particularly important for extrapolations from developing animals to young humans due to the differences in developmental patterns across species. Whichever approach is employed, the individual chemical assessment is to include text clearly describing the consideration of all of the available and relevant information in the selection of approaches. When the default is employed, it is to be explicitly recognized that the default has its basis in our knowledge of other chemicals.

6.3 THE HED AND INTERSPECIES UNCERTAINTY FACTOR, UF_A

With the implementation of this approach, the RfD, like the RfC, will be derived from an HEE for the critical effect(s) by consistent application of UFs. The UFs are applied to account for various recognized uncertainties in the extrapolations from the experimental data conditions to an estimate appropriate to the assumed human scenario (USEPA, 2002; USEPA, 1994). For the extrapolation from experimental animals, *the RfC methodology* (USEPA, 1994) currently recommends that the default value for the animal to human uncertainty factor be 3 when the default dosimetric adjustments are employed. Further, *the RfC methodology* recommends that the use of more rigorous dosimetric adjustments may allow additional modification of the UF. Although *the RfC methodology* generally describes the default dosimetric adjustment as accounting for variability in disposition or toxicokinetics, it also states that the processes pertinent to the uncertainty factor include both toxicokinetics and toxicodynamics, indicating that the toxicokinetics versus toxicodynamics assignment reflects these considerations. Additional discussion on this point appears in Jarabek (1995a) and Bogdanffy and Jarabek (1995).

In considering the recommendation regarding the default value for UF_A when the default $BW^{3/4}$ scaling approach is used (i.e., in lieu of information indicative of an alternate approach), various options were considered, ranging from no change in the default of 10 to 1. The conclusion to reduce the UF from its current default value of 10 is a science policy decision based on the qualitative recognition that current scientific knowledge indicates that $BW^{3/4}$ scaling generally addresses the potential for species differences in both kinetic and dynamic processes, which the UF_A had been intended to address. Additionally, it is recognized that in the situation in which defaults are invoked, uncertainties remain. Thus, when $BW^{3/4}$ scaling is applied the recommendation is that the default value for the interspecies UF_A be set at 3.

In the recommended process, an HED would be derived using $BW^{3/4}$ as a DAF or kinetic equivalence factor that is to be applied in the derivation of an HED. As illustrated in Figure 6-1, UF_A denotes the interspecies or animal-to-human uncertainty factor and is divided into 2 separate

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components without designation of either TK or TD, but equal to one half, logarithmically, of the 10^1 value typically assigned to this UF. With the application of the default HED approach, one component is dropped. In the absence of additional data informing consideration of interspecies differences, a residual default interspecies uncertainty factor of 3 remains.

This recommended reduction of the default value from 10 to 3 is generally consistent with the approach for this uncertainty factor in *the RfC methodology* (as described in the preceding paragraph). As discussed in the previous sections, the scaling of chronic oral exposure via $BW^{3/4}$ addresses notable aspects of predominantly toxicokinetic and some toxicodynamic processes, yet leaving some residual uncertainty, which may flow from either area. As per *the RfC methodology*, it is recommended that, with the use of more rigorous dosimetric adjustments in deriving the HED (including the use of $BW^{3/4}$ scaling rather than the historical default), there is a modification of the default value for the UF_A. Implementation of the recommended default approach explicitly endorses a case-by-case evaluation with consideration of all available data in determining the modification of the uncertainty factor (with the default of 3 applied unless there are data indicative of an inappropriate scaling via $BW^{3/4}$). Similar to its application for the RfC, processes pertinent to the consideration of this UF are recognized to include both toxicokinetics and toxicodynamics, including relevance of the laboratory animal model and species sensitivity. Thus, while different concepts are emphasized in the default oral versus inhalation dosimetric adjustment approaches, there are some similarities in the residual uncertainty and consequently in the recommended default value for the UF_A.

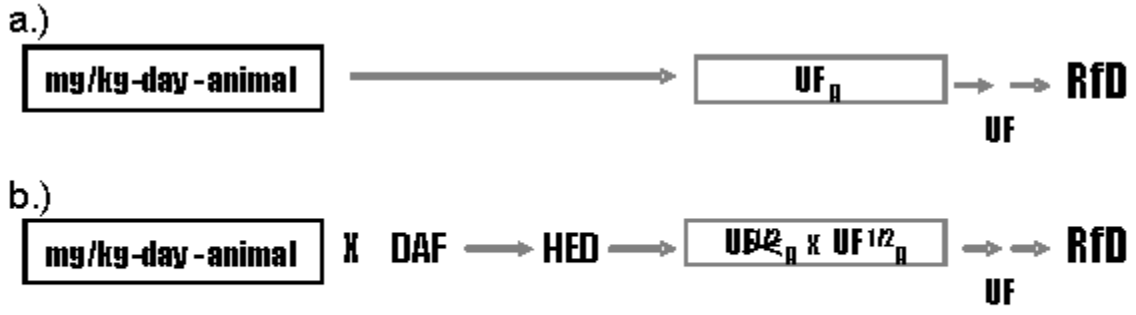

Figure 6-1. Procedures for (a.) the current RfD and (b.) recommended RfD processes. In the application of the recommended default approach, one component of UF_A is dropped. In the absence of additional data informing consideration of interspecies differences, a residual default interspecies uncertainty factor of 3 remains.

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6.4 SUMMARY

Instituting procedures by which the target tissue or some form of internal dose is considered, in this case indirectly through calculation of an HED, is conceptually compatible with the overarching paradigm that regards mode of action as central to understanding toxicity.

The default procedure described here involves first calculating an oral dosimetric adjustment factor or DAF that is then used to derive an HED that is subsequently used in derivation of the RfD. This procedure, of translating the animal exposure of interest to human equivalence using a biologically motivated approach, is parallel to derivation of the HEC in derivation of an RfC.

Adopting $BW^{3/4}$ scaling as a means to make dosimetric adjustments in calculating an HED, brings about harmonization of RfD procedures with that of the RfC *methods (USEPA 1989; 1994)* wherein the HEC is derived.

As with the RfC *methodology*, a hierarchy of models and procedures for interspecies extrapolation is established. $BW^{3/4}$ is acknowledged as the default approach for the oral route with more sophisticated models being considered, as being more data-informed approaches by which the internal dose may be estimated.

Pending, or in lieu of, the development of specific information to employ an interspecies dosimetric adjustment based on dose to the specific site of toxicity within the gastrointestinal tract, the $BW^{3/4}$-based DAF is recommended as the default to derive an HED involving oral portal-of-entry, as well as systemic, toxicity.

With the calculation of an HED using the DAF approach, a default value of 3 is recommended for the UF_A in the absence of additional, relevant information.

The quantitative significance of this procedure for translating an animal exposure into human equivalence, in terms of the magnitude of an RfD, will depend on the body weight of the species (as well as the value assigned to the UF_A) and may be more or less than the current procedure of dividing by the default composite UF_A of 10. In the case of mice and small rats, and with use of the default UF_A, the resulting RfD under the new approach will be lower than an RfD from the same data using the previous approach of a default UF_A of 10, whereas the opposite is the case for dogs (See Table A1).

Using $BW^{3/4}$ procedures in deriving an RfD harmonizes with its existing use as the default procedure in extrapolating from laboratory animal administered oral doses in oral quantitative cancer assessment as per the Cancer Guidelines (USEPA, 2005). Adoption of this procedure thus provides harmonization between the two main Agency dose-response assessment methodologies.

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APPENDIX A. $BW^{3/4}$ SCALING VERSUS $BW^{1/1}$ – A COMPARISON

Prior to this document, the use of an interspecies uncertainty factor (UF_A) applied directly to an animal experimental dose reported in mg/kg-day was the same as scaling $BW^{1/1}$ and factoring in uncertainty. When proceeding from a small to a larger animal, this procedure is not "conservative" in that it actually produces higher oral dose rates in comparison to $BW^{3/4}$-scaling procedures, as shown in Table A-1 comparing $BW^{1/1}$ and $BW^{3/4}$ scaling from animals to humans. This analysis also demonstrates the nonproportionality of the $BW^{3/4}$ scaling processes: The smaller the animal being scaled from, the smaller the scaled human dose, about 4-fold different from $BW^{1/1}$, when scaling from rats, and about 7-fold different from $BW^{1/1}$, when scaling from mice.

A common point of confusion in understanding and performing BW scaling is the expression of the experimental dose that will be scaled. In Table A-1 (below) showing examples of $BW^{3/4}$ scaling, note that what is being scaled is the absolute intake or exposure, in mg, not, for example, mg/kg. Therefore, it is the absolute exposure of 0.25 mg to the mouse that is scaled to the human by the $BW^{3/4}$ animal-to-human scaling factor of 385 to arrive at the absolute (and scaled) exposure of 96.25 mg for human. The mg/kg value is then derived by applying the human weight to this exposure, 96.25 mg/ 70 kg (human body weight), to arrive at the 1.4 mg/kg scaled human intake. Scaling of mg/kg (which is actually a rate process) rather than absolute mg, may be undertaken directly but with transformations of the $BW^{3/4}$ relationship that are used to scale rate processes, e.g., $BW^{-1/4}$. This procedure is addressed in Appendix B in derivation of the DAF. The reports of Clewell et al. (2002) and O'Flaherty (1989) both contain clear examples and helpful specifics in performing BW scaling.

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Table A-1. Comparison of $BW^{1/1}$ and $BW^{3/4}$ in estimating oral exposure in humans from a 10 mg/kg exposure to rats, mice, and a dog.

Scaling	Absolute Animal Intake or Administered Dose	Species	BW(h)/BW(a)	BW Scaling Factor	BW Scaled Human Intake or Oral Dose (mg/kg)
$BW^{3/4}$	0.25 mg/ 0.025 kg	mouse	70/ 0.025 = 2800	$2800^{3/4}$ = 385	(385 x 0.25 mg =96 mg) 96 mg /70 kg = 1.4 mg/kg
$BW^{3/4}$	2.5 mg / 0.25 kg	rat	70/ 0.25= 280	$280^{3/4}$ = 68	(68 x 2.5 mg = 170 mg) 170 mg/70 kg = 2.4 mg/kg
$BW^{3/4}$	120 mg / 12 kg	dog	70 / 12 = 5.8	$5.8^{3/4}$ = 3.7	(3.7 x 120 mg = 144 mg) 444 mg/70 kg = 6.4 mg/kg
$BW^{1/1}$	0.25 mg/ 0.025 kg	mouse	70/ 0.025= 2800	$2800^{1/1}$ = 2800	(2800 x 0.25 mg = 700 mg) 700 mg /70 kg = 10 mg/kg
$BW^{1/1}$	2.5 mg / 0.25 kg	rat	70/ 0.25 = 280	$280^{1/1}$ = 280	(280 x 2.5 mg = 700 mg) 700 mg /70 kg = 10 mg/kg
$BW^{1/1}$	120 mg / 12 kg	dog	70 / 12 = 5.8	$5.8^{1/1}$ = 5.8	(5.8 x 120 mg = 700 mg) 700 mg /70 kg = 10 mg/kg
none	700 mg / 70 kg	human	-	-	(700 x 1 mg = 700 mg) 700 mg /70 kg = 10 mg/kg

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APPENDIX B. THE INTERSPECIES $BW^{3/4}$ ORAL DOSIMETRIC ADJUSTMENT FACTOR (DAF) – $BW_A^{1/4}$ / $BW_H^{1/4}$

The application of a DAF in determining an HEE, or in the specific case of an oral exposure, an HED, would typically would be applied to the laboratory animal dose (in mg/kg) as:

Laboratory animal exposure (mg/kg) x DAF = HED (mg/kg)

where,

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

This equation demonstrates the mechanics of application of the DAF to attain an HEE or HED. The procedure would apply to any and all laboratory species, although in practice, rat and mouse are the predominant species, with dogs also at times represented. An analysis of DAFs, such as those derived and then applied to derive an HEC (see USEPA, 1989; 1994, 2002), reveals that they are composed of determinants that are intended to inform about the dose to the target tissue (the more accurate determinant of risk). A DAF is applied to adjust to the equivalent dose for animals and humans that is present at the target tissue (i.e., the internal dose). This analysis also reveals that the DAF is a ratio constructed of human and animal parameters that are predictive of processes that lead to the internal dose. Application of this ratio estimates the human exposure projected to elicit the same internal dose as the laboratory animal exposure. For adjustments based on $BW^{3/4}$ scaling, the DAF would be a factor that would:

- reflect the scaling of the absolute exposure amount of the animal to the corresponding absolute exposure amount of a human;
- reflect this human exposure on a mg/kg basis; and
- be constructed as a ratio of animal and human determinants of internal dose.

Table B-1 lists examples of scaling from various laboratory animals to humans based on a 10 mg/kg exposure in various species (see also Table A-1). The column showing the ratio of these scaled human-to-animal exposures reflects the scaling and normalization of this value to a mg/kg basis, corresponding to the requisites described above for a DAF. The column in Table B-1 labeled " $BW_h^{-1/4}$ / $BW_a^{-1/4}$ " lists the body weights to the negative one quarter power of the laboratory animals and a 70-kg human. The human to animal ratio of these scaled weights can be seen to correspond to the "Scaled Human to Animal Ratio".

Exposure expressed as a rate, such as mg/kg, rather than as an absolute amount is an example of this relationship. Table B-1 demonstrates when this exposure (actually an exposure-rate or dose-rate) relationship is expressed as a ratio of humans to laboratory animals(s). There is predictably parallel equivalence between this ratio and the $BW^{-1/4}$ scaling of human to animal

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ratio. This may be transformed into the corresponding positive (+) scaling relationship through inversion of the terms such that $(BW_h / BW_a)^{-1/4}$ is equivalent to $(BW_a / BW_h)^{1/4}$.

Table B-1. The animal:human $BW^{1/4}$ ratio as the Dosimetric Adjustment Factor (DAF) used in deriving an HED from an oral animal exposure.

	Species	$BW^{3/4}$ Scaled Human Equivalent Exposure (for a 70 kg human)	Scaled Human to Animal Dose Ratio	$BW_a^{1/4}/BW_h^{1/4}$= DAF
$BW^{3/4}$ Scaling of a 10 mg/kg-day Exposure in a …	Mouse (0.025 kg)	1.4 mg/kg-day*	1.4 / 10 = 0.14	0.40 / 2.89 = 0.14**
	Rat (0.25 kg)	2.4 mg/kg-day	2.4 / 10 = 0.24	0.71 / 2.89 = 0.24
	Dog (12 kg)	6.3 mg/kg-day	6.3 / 10 = 0.63	1.86 / 2.89 = 0.63

* mice/human = $0.025\ kg^{1/4} / 70\ kg^{1/4}$ x 10 mg/kg-day
** The complete arithmetic calculation is
mice/human = $0.025\ kg^{1/4} / 70\ kg^{1/4}$ = 0.398/2.89 = 0.137, which is rounded to 0.14.
Also (equivalently), human / mice = $70\ kg^{-1/4} / 0.025\ kg^{-1/4}$ = 0.345 / 2.51 = 0.137, also rounded to 0.14.

As pointed out in Section 4 of this document, rate-related processes scale across species in a manner related to both the direct ($BW^{1/1}$) and $BW^{3/4}$ aspects such that:

$$BW^{3/4} / BW^{1/1} = BW^{-1/4}$$

As $BW_h^{-1/4} / BW_a^{-1/4}$ can be readily calculated and applied to any combination of body weights, it is designated as the $BW^{3/4}$-based DAF, such that:

$$DAF = (BW_h^{-1/4} / BW_a^{-1/4})$$

and, the equivalent,

$$DAF = (BW_a^{1/4} / BW_h^{1/4}).$$

In summary then, the laboratory animal exposure (mg/kg) x DAF = HED (mg/kg).

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APPENDIX C. THE ORAL DAF AND PORTAL-OF-ENTRY CONSIDERATIONS

"Systemic" versus "portal-of-entry" considerations in toxicity from oral administration

Table 4-1 shows that interspecies allometric scaling via $BW^{3/4}$ is applicable over a wide range of functions and responses including kinetics and systemic toxicity (e.g., body weight loss). This has generally been demonstrated with information available from oral administration of pharmaceuticals.

Allometric scaling has not been extensively evaluated with toxicities such as those that occur at portal-of-entry tissues. "Portal of entry" is a descriptor used for those effects caused by direct action of an agent on barrier tissues at or proximal to the point of agent entry, i.e., the respiratory tract for an inhaled agent and the gastrointestinal tract for an ingested agent. Agents causing portal-of-entry effects are often highly water soluble and/or highly reactive, such that concentrations achieved in these barrier tissues may be much higher than in blood.

Portal-of-entry considerations – empirical relationships in feeding studies

A $BW^{3/4}$ relationship exists among species in studies where dose is administered in food, because interspecies food consumption follows a $BW^{3/4}$ relationship (see Table 4-1). Consequently, exposure among species to an agent, both overall and to the gastrointestinal tract, present at a constant concentration in food would also follow a $BW^{3/4}$ relationship. As with systemic effects, this empirical relationship implies that portal-of-entry effects could occur in increasingly larger species at decreasingly lower dose-rates in mg/kg-day. By extension, it is reasonable to apply the $BW^{3/4}$ approach for gastrointestinally related, portal-of-entry effects.

Portal-of-entry considerations in the RfC Methods – theoretical application to oral exposures

In the case of the respiratory tract, RfC *Methods* (USEPA, 2002) provides a hierarchy for performing respiratory tract (portal-of-entry) dosimetry and derivation of an HEC with the default process proscribing use of species-specific physiological and anatomical measures such as ventilation volumes and rates and surface areas of various regions within the respiratory tract. The default HEC derivation is based on specifically where effects occur within these portal tissues. The paradigm is that dose to the target tissue will be related to risk of toxicity. Further, the Agency's *RfC methodology* specifies different dosimetric approaches for agents manifesting portal-of-entry versus systemic effects, giving considerable discussion as to why different approaches are advised. Use of these procedures derives a DAF would be used in calculating an HEE or HEC.

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Considerable physical and anatomic parallels exist between inhalation and oral portal-of-entry tissues. Both the respiratory tract and the gastrointestinal tract have a central lumen for the passage of the agent, a metabolically active epithelial cell layer covered by saliva/mucous that lines the lumen, and submucosal tissues containing blood vessels and other elements. The transport processes determining movement of agent from the lumen, such as convection, diffusion, and metabolic clearance, as well as those determining movement at the lumen-tissue interface, are also commonalities. Conceptual similarity exists between inhalation and oral portal-of-entry exposure scenarios. In both cases, exposures would occur due to agents entrained in the incoming media (e.g., inspired air or ingested materials) to the surface of epithelial tissues, either respiratory or gastrointestinal. This scenario differs fundamentally from systemic exposure scenarios, where delivery of an agent is from circulating blood to organs throughout the body and uptake into target tissue. In systemic toxicity the most appropriate measure of dose generally would be the mass of agent per tissue over the relevant period of time, e.g., body weight/day or mg/kg. Based on the portal-of-entry scenario, however, the most appropriate dose metric would likely be mass of agent per surface area, e.g., mg/cm^2.

A parallel approach to the RfC derivation process could thus be considered appropriate for an interspecies DAF for oral portal of entry. The basic relationship of measures specified in the default inhalation scenario is ventilatory rate divided by surface area of the respiratory tract. Using the ventilatory volume as a surrogate for mass of agent inhaled, this relationship would result in units of "mass per surface area", as discussed above. The parallel oral construction to the inhalation default construct of ventilatory volume (V_E) divided by respiratory tract surface area (SA_{RT}) could be ingestion rate (Q) divided by the surface area of a specified region of the gastrointestinal tract (SA_{GI}), such that:

$$V_E / SA_{RT} \parallel Q / SA_{GI}$$

In this case, the ingestion rate is the surrogate for mass of agent ingested. This relationship would similarly result in "mass per surface area".

Implementation of such an approach requires interpretive analysis of existing information, or possibly generation of other specific information. These analyses and data could, for example, address such concerns as interspecies anatomical differences (such as the lack of a human anatomical parallel to the rodent forestomach), surface areas of the gastrointestinal tract in laboratory animals and humans, rates and scenarios of ingestion, or diffusion rates. Integration of these data into appropriate models (for example, those estimating clearance or fractional penetration [as per Aharonson et al., 1974, or Hanna et al., 2001] or a valid –

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physiologically-based toxicokinetic [PBTK] model parameterized for both animal and humans) would also facilitate implementation.

In the case of the gastrointestinal tract, however, such specific considerations have yet to be developed for oral portal-of-entry effects. Nevertheless, because of the conceptual similarities in exposure between these portal-of-entry tissues, it is possible that some approaches could be applied for ingestion of toxicants.

Recommendations regarding DAF and oral "portal-of-entry" effects

For oral portal-of-entry effects occurring in laboratory animal studies in which the agent is administered via food, direct application of the $BW^{3/4}$ approach is recommended. This approach is generally consistent with existing Agency procedures for cancer assessment in calculation of oral slope factors, since they do not use portal-of-entry tumors for estimating systemic carcinogenic potency.

There exist conceptual similarities between the inhalation and oral portals of entry that could theoretically support development of a more sophisticated and refined oral portal-of-entry DAF. However, in the absence of an adequately developed theory and the further definition of information to develop and characterize such factor, this pragmatic and reasonable approach of applying the $BW^{¾}$ is recommended.

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APPENDIX D. HIERARCHY OF APPROACHES FOR INHALATION DOSIMETRY AND INTERSPECIES EXTRAPOLATION

(Adapted from Table 3-6 of USEPA, 1994)

Optimal Approach

- Is based on sufficient data to support a model structure that will describe all significant mechanistic determinants of chemical disposition, toxicant-target interaction, and tissue response.
- Uses chemical-specific and species-specific parameters.
- Describes the dose metric at level of detail commensurate to response data.

Immediate Approaches

Default Approach

- Is based on general (non-chemical specific) understanding of mechanistic determinants of chemical disposition, toxicant-target interaction, and tissue response.
- May use categorical or default values for chemical- and species-specific parameters.
- Describes the dose metric at a generic level commensurate to response data.

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GLOSSARY[8]

Allometry

The study of the usual variation in measurable characteristics of anatomy and physiology as a function of overall body size.

Allometric scaling

Scaling of physiological rates or quantities to relative growth and size (mass or volume) of one animal species relative to another animal species. The relationship is generally written as $A = a(B)^k$, where A is the physiological process, B is a measure of the size of the organism (e.g., body weight) and a and k are constants (e.g. a equals 1 and k equals the exponent 0.75 as used in this document)[9].

Benchmark Dose (BMD) or Concentration (BMC)

A dose or concentration that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background.

BMDL or BMCL:

A statistical lower confidence limit on the dose or concentration at the BMD or BMC, respectively.

Dosimetric adjustment factor (DAF)

Generally, a multiplicative factor used to adjust observed experimental data to human equivalent concentration or dose for an assumed ambient scenario, as used in this document refers specifically to a default adjustment factor for conversion of an animal oral dose to a human oral dose.

Human Equivalent Concentration (HEC) or Dose (HED)

The human concentration (for inhalation exposure) or dose (for other routes of exposure) of an agent that is believed to induce the same magnitude of toxic effect as the experimental animal species concentration or dose. This adjustment may incorporate toxicokinetic information

[8] Unless otherwise specified, all definitions are taken directly from official Agency guidance documents and may be referenced at http://www.epa.gov/iris/ or EPA (2005).

[9] See Dedrick (1973) and U.S. EPA (1992a).

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on the particular agent, if available, or use a default procedure, such as assuming that daily oral doses experienced for a lifetime are proportional to body weight raised to the 0.75 power.

Mode of Action (MOA)

A less-detailed description of the mechanism of action in which some but not all of the sequence of biological events leading to a toxic effect is known

Physiologically-based toxicokinetic model

A model that estimates the dose to a target tissue or organ by taking into account the rate of absorption into the body, distribution among target organs and tissues, metabolism, and excretion.

Point of departure

The dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMD), or a NOAEL or LOAEL for an observed incidence, or change in level of response.

Portal of entry

The tissue or organ of first contact between the biological system and the toxicant, including. oral tissues, stomach, nasal or pulmonary tissues, skin.

Reference Concentration (RfC)

An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3.

Reference dose (RfD)

An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure for a chronic duration (up to a lifetime) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used, generally used in EPA's noncancer health assessments.

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Regional deposited dose ratio (RDDR)

The ratio of the deposited dose in a respiratory tract region (r) for the laboratory animal species of interest (RDDA) to that of humans (RDDH). This ratio is used to adjust the observed particulate exposure effect level for interspecies dosimetric differences.

Regional gas dose ratio (RGDR)

The ratio of the deposited gas dose in a respiratory tract region (r) for the laboratory animal species of interest to that of humans. This ratio is used to adjust the observed gas exposure level for interspecies dosimetric differences.

Toxicodynamic

The determination and quantification of the sequence of events at the cellular and molecular levels leading to a toxic response to an environmental agent (sometimes referred to as pharmacodynamics).

Toxicokinetic

The determination and quantification of the time course of absorption, distribution, biotransformation, and excretion of chemicals (sometimes referred to as pharmacokinetics).

Uncertainty

Uncertainty occurs because of a lack of knowledge. It is not the same as variability. For example, a risk assessor may be very certain that different people drink different amounts of water but may be uncertain about how much variability there is in water intakes within the population. Uncertainty can often be reduced by collecting more and better data, whereas variability is an inherent property of the population being evaluated. Variability can be better characterized with more data but it cannot be reduced or eliminated. Efforts to clearly distinguish between variability and uncertainty are important for both risk assessment and risk characterization.

Uncertainty Factor (UF)

One of several, generally 3- to 10-fold factors, used in operationally deriving the inhalation reference concentration (RfC) or oral reference dose (RfD) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population (UF_H), (2) the uncertainty in extrapolating laboratory animal data to humans (UFA), (3) the uncertainty in extrapolating from data obtained in a study that is of less-than-lifetime

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exposure, (4) the uncertainty in using LOAEL data rather than NOAEL data, and (5) the inability of any single study to adequately address all possible adverse outcomes in humans. The RfC methods use 3 for the UF for interspecies extrapolation due to the incorporation of default dosimetric adjustments.

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