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The application of dosimetry models to identify key processes and parameters for default dose-response assessment approaches

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Abstract

Mathematical dosimetry models should improve the accuracy of various extrapolations required in dose-response assessment because they include explicit descriptions of the major mechanistic determinants of the exposure-dose-response continuum. The availability of these anatomic and physiologic parameters for different mammalian species (including humans) and the physicochemical parameters for individual chemicals is an important consideration in the formulation of model structures and the application of simplifying assumptions to develop default models. A framework is presented that includes iterative development of model structures as more data become available. Development of the default dosimetry adjustments for interspecies extrapolation used in the inhalation reference concentration (RfC) methods of the U.S. Environmental Protection Agency (EPA) is discussed as an example of iterative model development, a process intended to ensure that model structures are commensurate with available data. The framework also aids evaluation of different model structures and can be applied to identify key parameters. Examples are provided to illustrate how insight on the key mechanistic determinants of exposure-dose-response can guide interpretation of data in the absence of comprehensive model structures, identify gaps in the database for a given chemical, or direct data gathering for chemicals that are yet to enter production.

Keywords: Physiologically based pharmacokinetic modeling; Dosimetry; Risk assessment; Interspecies scaling; Uncertainty

1. Introduction

Mathematical dosimetry models[1] that incorporate mechanistic determinants of disposition (deposition, absorption, distribution, metabolism, and elimination) of chemicals have been useful in describing relationships between exposure concentration and target tissue dose, particularly as ap-

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[1] Although the discussion at this symposium focused on physiologically based pharmacokinetic (PBPK) modeling, dosimetry modeling is used in this paper as a more comprehensive term. Mathematical modeling is defined as the use of the physical laws of mass, heat, and momentum conservation to quantify the dynamics of a system of interest. Dosimetry modeling is defined as the application of mathematical modeling to characterize the determinants of exposure-dose-response.

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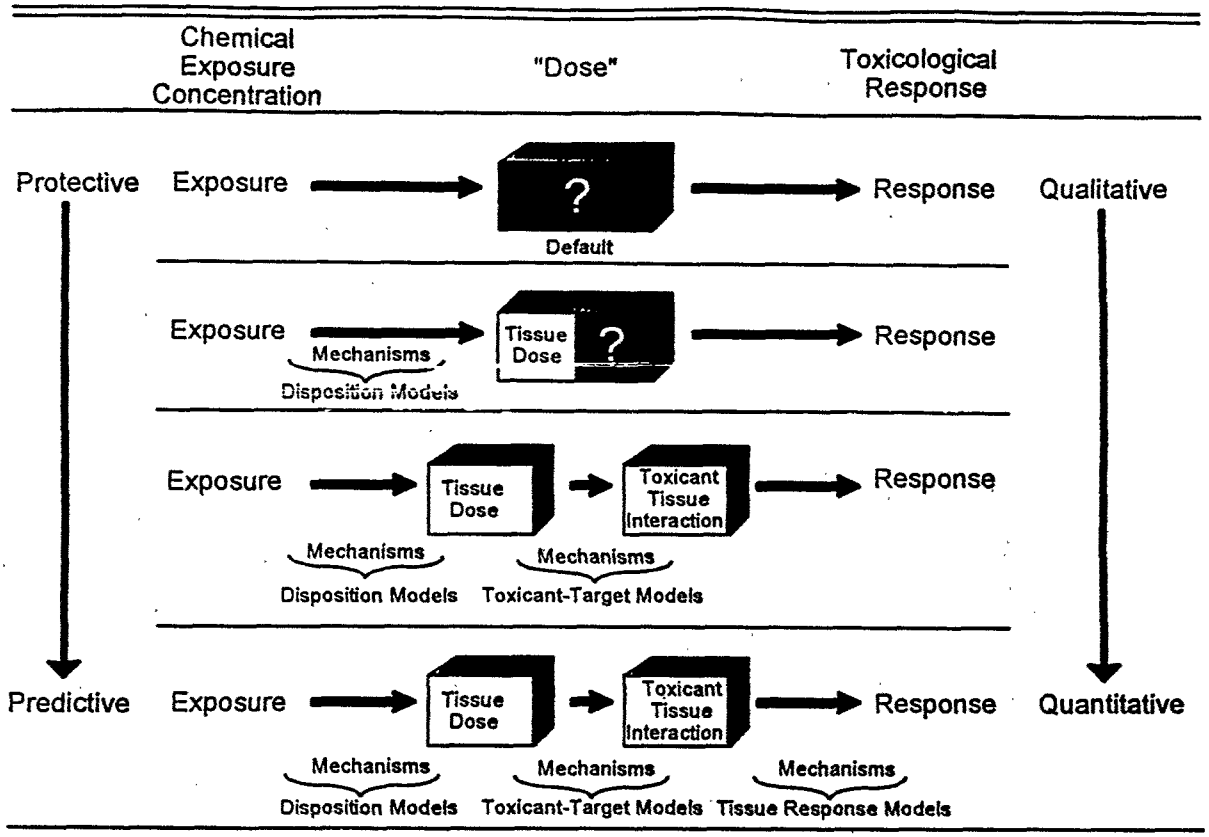


Fig. 1. Schematic characterization of comprehensive exposure-dose-response continuum and the evolution of protective to predictive dose-response estimates. (Adapted [1].)

plied to describing these relationships for the dose-response component of risk assessment. Because the tissue dose of the putative toxic moiety is not always proportional to the applied dose of a compound, emphasis has been placed on the need to distinguish clearly between exposure concentration and dose to critical target tissues. Consequently, the term 'exposure-dose-response assessment' has been recommended as more accurate and comprehensive [1]. This expression refers not only to the determination of the quantitative relationship between exposure concentrations and target tissue dose but also to the relationship between tissue dose and the observed or expected responses in laboratory animals and humans. The process of determining the exposure-dose-response continuum is achieved by linking the mechanisms or critical biological factors that regulate the occurrence of a particular process and the nature of the interrelationships among these factors.

As illustrated in Fig. 1, it is ultimately desirable to have a comprehensive biologically based dose-response model that incorporates the mechanistic determinants of chemical disposition, toxicant-target interactions, and tissue responses integrated into an overall model of pathogenesis. Dose-response assessment estimates based on characterization of the exposure-dose-response continuum at the rudimentary ('black-box') level necessarily incorporate large uncertainty factors to ensure that the estimates are protective in the presence of substantial data gaps. With each progressive level, incorporation and integration of mechanistic determinants allow elucidation of the exposure-dose-response continuum and, depending on the knowledge of model parameters and fidelity to the

biological system, a more accurate characterization of the pathogenesic process. Due to the increase in accuracy of the characterization with each progressive level, dose-response estimates also progress from more conservative (protective) to factually based (predictive).

Unfortunately, data to construct such comprehensive models do not exist for the majority of chemicals that EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) are evaluating. Without dosimetry, default methods for dose-response assessment are limited to the rudimentary ('black-box') default level of characterization depicted in Fig. 1. Even in the absence of data to construct more comprehensive models, analysis of comprehensive dosimetry models according to chemical categories may aid the construction of an interpretative framework that provides for development of default models. The framework provides that the default models are commensurate to the available data and part of an iterative process that is amenable to revision as relevant new data are obtained. Analysis of dosimetry models within such a framework also can identify key processes and parameters that may be useful to interpretation of the available data and provide insight on research that could reduce the uncertainty of required extrapolations for risk assessment.

This paper presents the construction of such an interpretative framework derived from dosimetry models for interspecies extrapolation of inhalation exposures. Because major determinants of particle and gas disposition are addressed by the dosimetry models, the accuracy of the extrapolation should be improved. Depending on the amount of mechanistic information, the determinants can be described by either a sophisticated model or by a default structure. Although the framework is adapted from EPA's methods for derivation of RfCs [2], the principles apply to other exposure routes (e.g., oral or dermal) and to all toxic endpoints (noncancer and cancer)[2].

[2] The identification of a threshold currently distinguishes approaches for noncancer toxicity assessment from those for carcinogenic endpoints (neoplasia), which dose-response assessment procedures typically approach as resulting from nonthreshold processes. However, the identification of a threshold is a function of the available data and the current understanding of the pathogenesis process, which may be revised as more information on mechanistic determinants is developed and evaluated.

2. Mechanistic determinants of disposition

The various species used in inhalation toxicology studies that serve as the basis for dose-response assessment do not receive identical doses in a comparable respiratory tract region, r (extrathoracic, ET; tracheobronchial, TB; pulmonary, PU; thoracic, TH; or the entire tract) when exposed to the same aerosol or gas [3]. Such interspecies differences are important because the adverse toxic effect is likely more related to the quantitative pattern of deposition within the respiratory tract than to the exposure concentration; this pattern determines not only the initial respiratory tract tissue dose but also the specific pathways by which the inhaled material is cleared and redistributed [4].

Disposition encompasses the processes of deposition, absorption, distribution, metabolism, and elimination. Differences in ventilation rates and in the upper respiratory tract (URT) structure and in size and branching pattern of the lower respiratory tract between species result in significantly different patterns of particle deposition and gas transport due to the effect of these geometric variations on air flow patterns. Disposition varies across species and with the respiratory tract region. For example, interspecies variations in cell morphology, numbers, types, distributions, and functional capabilities contribute to variations in clearance of initially deposited doses. Physicochemical characteristics of the inhaled particle or gas also influence the disposition and interact with the anatomic and physiologic parameters such as ventilation rate, cardiac output (perfusion), metabolic pathways, tissue volumes, and excretion pathways. The relative contributions of these processes and interactions with the physicochemical characteristics are affected by the exposure concentration and duration.

Particles are deposited in the respiratory tract by mechanisms of impaction, sedimentation, interception, diffusion, and electrostatic precipitation. For a given aerosol, the 2 most important parameters determining deposition are mean aerodynamic diameter and the distribution of the particles about the mean. Subsequent clearance of a deposited dose is dependent on the initial site of

deposition, physicochemical properties of the particles (e.g., solubility), and on time since deposition. Clearance routes include dissolution into respiratory tract tissues, absorption into the blood, the gastrointestinal tract via the nasopharynx or mucociliary escalator, and absorption into the lymphatic channels.

Initial deposition occurs for gases as well as particles because contact with the respiratory tract surface precedes absorption. The major processes affecting gas transport involve convection, diffusion, absorption, dissolution, and chemical reactions. The bulk movement of an inhaled gas in the respiratory tract is induced by a pressure gradient and is termed convection. Convection can be broken down into components of advection (horizontal movement of a mass of air relative to the airway wall) and eddy dispersion (air mixing by turbulence so that individual fluid elements transport the gas and generate flux). Molecular diffusion is superimposed at all times on convection due to local concentration gradients. Absorption removes gases from the lumen and affects concentration gradients. Chemical reactions in the respiratory tract can increase absorption by acting as a sink to drive the concentration gradient. Systemic metabolism can also drive the concentration gradient for insoluble gases that are removed from the respiratory tract tissue by perfusion. Thus, the rate of transfer from the environment to the tissue, the capacity of the body to retain the material and elimination of the parent and metabolites by chemical reaction, metabolism, exhalation, and excretion influence the disposition of gases.

Integration of these various physicochemical characteristics with the species-specific anatomic and physiologic parameters is necessary for estimating the respiratory tract surface deposition and absorbed dose in order to assess respiratory and extrarespiratory toxicity, respectively [5].

3. Generalized model default approach

The methods used by EPA to derive an RfC are very similar to the methods used by ATSDR to derive a minimum risk level. There is one major exception. The RfC methods incorporate a dosimetric adjustment factor for respiratory tract region, r (DAF_r). The DAF_r is used in the RfC methods to adjust for species differences in dosimetry. The DAF_r is a multiplicative factor that represents the laboratory animal to human ratio of a particular dose. It is applied to laboratory animal exposure effect levels to calculate the human equivalent concentration (HEC). The HEC is expected to be associated with the same delivered dose to the observed target tissue as in the experimental species. Because many inhalation toxicity studies of laboratory animals use discontinuous exposure regimens (e.g., 6–8 h/day, 5 days/week), the default DAF_r is usually applied to duration-adjusted exposure levels. The default convention for calculation of the duration-adjusted levels is to perform a linear prorated adjustment (i.e., adjustment by number of hours per day and number of days per 7 days of exposure). The rationale is that the resultant human exposure concentration should be the concentration multiplied by time ($C \times T$) product of the experimental animal exposure level. The validity of this assumption is questionable because the influence of dose rate vs. concentration on toxicity is dependent on the mechanisms of toxicity. One advantage of the use of dosimetry models is that the models obviate the need for this default duration adjustment.

The DAF_r calculated depends on (1) the physicochemical characteristics of the inhaled toxicant (particle or gas) and (2) the location of observed toxicity (i.e., either one of 3 respiratory tract regions or at remote sites). The DAF_r is used in conjunction with default normalizing factors for the physiological parameters of interest. Because insoluble particles deposit and clear along the surface of the respiratory tract, dose per unit surface area is a commonly used normalizing factor for respiratory effects due to particulate deposition. Body weight is often used to normalize the dose delivered to remote target tissues. In some cases, it may be appropriate to normalize by regional volumes or target organ weights. For gases, mass flux (mass per surface area-time) is considered a reasonably accurate predictor of the peak localized concentration driving the absorption gradient for respiratory tract effects.

This section briefly describes the derivation of the DAF_r for interspecies extrapolation of particles and gases. Default DAF_rs are based on model structures that have been reduced to forms requiring a minimal number of parameters (i.e., commensurate with the amount of data typically available on a chemical) from more comprehensive descriptions by utilizing the dominant determinants of disposition and simplifying assumptions. Thus, the third consideration for applying a DAF_r is the type of model available (optimal or default).

An understanding of the basis for the model structures allows development of a framework for the evaluation of whether an alternative model structure may be considered optimal relative to the default. An alternative model structure might be considered more appropriate than the default for extrapolation when default assumptions or parameters are replaced by more detailed, biologically motivated descriptions or actual data, respectively. For example, a model could be preferable if it incorporates more chemical or species-specific information or if it accounts for more mechanistic determinants. These considerations are summarized in Table 1. The sensitivity of the model to these differences in structure may be gauged by its relative importance in describing the response function for a given chemical. A model that incorporates many parameters may not be any better at describing ('fitting') limited response data than would a simpler model. In these instances, the principle of parsimony might dictate the use of the simpler model. Woodruff et al. [6] recently have used Monte Carlo analyses to assess the impact that structure and parameterization of PBPK models have on model output predictions and variability.

Table 1
Hierarchy of model structures for dosimetry and interspecies extrapolation

Optimal[a] model structure
Structure describes all significant mechanistic determinants of chemical disposition, toxicant-target interaction, and tissue response
Uses chemical-specific and species-specific parameters
Dose metric described at level of detail commensurate to toxicity data
Default model structure
Limited or default description of mechanistic determinants of chemical disposition, toxicant-target interaction, and tissue response
Uses categorical or default values for chemical and species parameters
Dose metric at generic level of detail

[a]Optimal is defined as preferable or more appropriate relative to the default.

As more comprehensive model descriptions are developed, accuracy and predictive capabilities are increased as shown in Fig. 1. The general default model structure places the RfC methods in the second tier of this progression because the mechanistic determinants of inhaled gas and particle disposition are addressed to some extent. Accordingly, the uncertainty factor (UF) applied for interspecies extrapolation has been reduced by one-half for the RfC methods from a factor of 10 to a 3 (i.e., $10^{0.5}$ on a log scale). The increase in accuracy provided by more comprehensive (optimal) descriptions is anticipated to result in additional reduction of applied UFs.

3.1. Dosimetric adjustment for particle exposures

A theoretical model of particle deposition requires detailed information on all of the influential parameters (e.g., respiratory rates, exact airflow patterns, complete measurement of the branching structure of the respiratory tract, pulmonary region mechanics) across the various species used in toxicity studies. In the RfC methods, an empirical model (i.e., a system of equations fit to experimental data) was developed instead as the default due to the limited availability of these types of data [2].

The model used in the 1994 EPA methods is a significant revision of previously published models used to calculate the DAF_r in the 1990 methods [7]. Rather than linear interpolation between the means of deposition data measured at discrete particle diameters, equations were fit using the raw data of Raabe et al. [8]. The logistic function has mathematical properties that are consistent with the shape of the deposition efficiency function [9]. Deposition efficiency was calculated as a function of an impaction parameter $d_{ae}^2 Q$ for ET deposition, where d_{ae} is aerodynamic particle di-

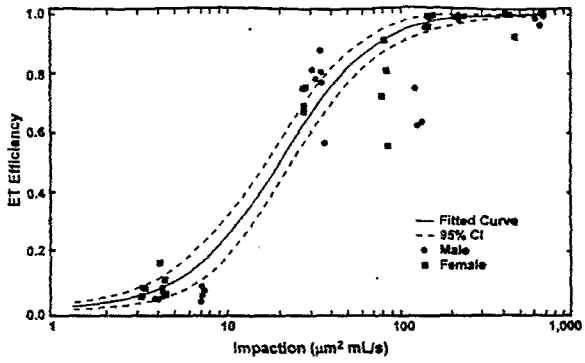


Fig. 2. ET deposition efficiency modeled as a logistic function of impaction parameter d_{ae}^2Q, where d_{ae} is the aerodynamic particle diameter (in μ) and Q is the ventilatory flow rate (in ml per s). The empirical model is described in detail elsewhere [2]. (Data shown for rats [8].)

ameter and Q is the flow rate estimated as the species-specific minute volume ($\dot{V}_E$)/30. The geometric standard deviation of the particle diameter distribution is also an input parameter. A plot of deposition efficiency vs. this impaction parameter is shown for the rat in Fig. 2. Deposition efficiency for the TB and PU regions was estimated as a function of d_{ae}. Measurement techniques for deposition are such that only generalized regions can be defined, so that localized deposition (e.g., respiratory vs. olfactory epithelium) is not estimated. Nonetheless, these deposition data were chosen because they were available for 5 laboratory animal species under the same exposure conditions (unanesthetized, nose-only) and because of the experimental design and reporting detail. An empirical model of regional fractional deposition data also had been used previously to calculate deposition in humans [9] and these equations were updated and extended [2]. The calculated efficiencies are adjusted for inhalability [10] to produce predicted deposition fractions for various regions of the respiratory tract. The regional deposition fractions may then be normalized for regional surface area and the species ventilation rate. The same is done for humans and the species to human ratio is used to calculate the DAF_r.

Fig. 3 shows a plot of the DAF_r vs. particle diameter for the TH region, and illustrates the impact that the use of DAF_r for particles can have on the resultant HEC. Because the DAF_r is a multiplicative factor, a DAF_r above the value of 1.0 indicates that the human receives a relatively smaller deposited dose than the particular laboratory animal species. Values of the DAF below 1.0 indicate that the human receives a relatively larger dose than the laboratory animal species, and the DAF_r would adjust the resultant HEC lower than the laboratory animal exposure level. The line drawn as a constant across all particle diameters at 1.0 represents essentially no adjustment for differences in interspecies dosimetry and thus has no deflections reflecting the contribution of different deposition mechanisms based on interaction with particle size and distribution. An identical exposure concentration with a mass median aerodynamic diameter of 2.0 μm and a geometric standard deviation of the size distribution (σ_g) of 1.73 to the 4 species shown would result in different HEC estimates (0.59, 0.88, 0.30, and 0.54 times the exposure concentration for rats, mice, hamsters, and guinea pig, respectively). The dosimetry adjustment can change the apparent (now based on HEC vs. exposure levels) sensitivity between species, e.g., the hamster would have the lowest HEC. This emphasizes the necessity of dosimetri-

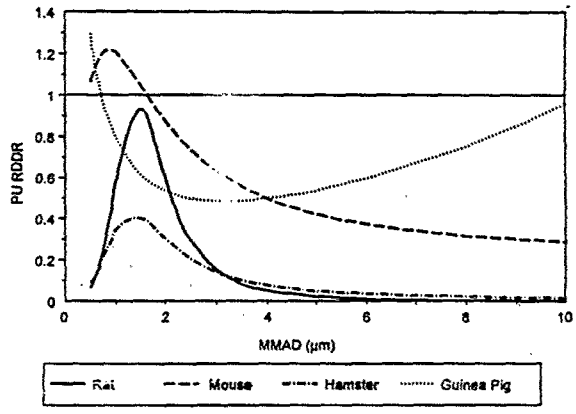


Fig. 3. Dosimetric adjustment factor (DAF_r) vs. particle diameter for PU region. DAF_{PU} is the Pulmonary regional deposited dose ratio of the laboratory animal species to humans. Ratio values are shown for rat, mouse, hamster, and guinea pig vs. humans. MMAD, mass median aerodynamic diameter; σ_g, geometric standard deviation of the particle distribution.)

cally adjusting the observed toxicity data to HEC values before identifying the 'most sensitive' species and choosing the critical study [5].

The default empirical deposition model equations used to calculate regional deposition fractions for the DAF_r are appropriate for nonhygroscopic, approximately spherical particles. Application of these equations to aerosols of different characteristics results in greater uncertainty. Further, dose may be accurately described by deposition alone because the particles exert their primary action on the surface contacted [11], but, if the dose-response estimate is for chronic exposures, a more appropriate model may be one that takes into account clearance of the deposited dose and thereby calculates the retained dose. According to the framework for evaluation of model structures, the physicochemical properties or mechanisms of action of the inhaled toxicant often can be used to gauge the importance of accounting for a given factor controlling dose. For example, the model of Yu and Yoon [12] was used as an optimal model to calculate the DAF_r for the RfC for diesel engine emissions [13] because the toxicity is related to particle overload, and the model incorporates clearance components to calculate retained dose.

3.2. Dosimetric adjustment for gas exposures

Numerous model structures have been used to describe gas uptake in the respiratory tract. The type of model often reflects the physicochemical characteristics of the gases to which they are applied. For example, the model of Miller et al. [14], describing the respiratory tract uptake of ozone (a highly reactive and moderately water-soluble gas), is a detailed, distributed parameter model of the convective-diffusion-chemical reactions; whereas respiratory uptake for styrene (a nonreactive and water-insoluble gas) can be described adequately by a single ventilation-perfusion model compartment [15]. Ozone concentrations in the respiratory tract tissues are governed by concentration variables that depend on spatial position, as well as on time, and are formulated by solving partial differential equations that require the specification of boundary and initial value conditions [16]. Examples of the data required by such a model include (1) anatomic dimensions of the airspaces and tissue thicknesses, (2) dispersion rates in the airspace, (3) reactivity in the liquid lining (mucus or surfactant) covering the cells of the lower respiratory tract, and (4) lateral mass transport resistance from the airspace to the blood. Models such as that for styrene that employ well-mixed compartments and are governed by concentration variables that depend on time alone are known as 'lumped parameter models' [16]. The formulation of these models requires the solution of ordinary differential equations and their accompanying initial conditions.

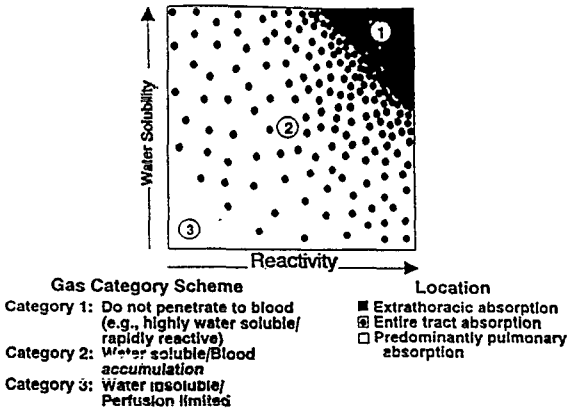


Fig. 4. Gas categorization scheme based on water solubility and reactivity as major determinants of gas uptake. Reactivity is defined to include both the propensity for dissociation as well as the ability to serve as a substrate for metabolism in the respiratory tract. Definitive characteristics of each category and the anticipated location (region) for respiratory tract uptake are shown.

The chemical-specific or class-specific nature of these models has been dictated by the physicochemical characteristics of the subject gases, and the mechanisms of tissue response. No single model structure will be applicable to the broad range of gases that the EPA RfC methods must address. A gas categorization scheme (Fig. 4) was constructed based on the physicochemical characteristics of water solubility and reactivity as major determinants of gas uptake. Reactivity includes both the propensity for dissociation and the ability to react either spontaneously or via enzymatic reaction in the respiratory tract. The scheme does not apply to stable gases that exert their effects by

reversible 'physical' interactions of gas molecules with biomolecules (e.g., 'displacement' of oxygen by carbon dioxide). The dominant determinants are used to construct default dosimetry model structures that are reduced further by simplifying assumptions to forms requiring a minimal number of parameters commensurate with the data typically available in order to derive a DAF_r for each gas category.

Gases in Category 1 are defined as highly water soluble or irreversibly reactive in the surface-liquid/tissue of the respiratory tract. Optimally, they are distinguished by the property that they do not develop significant back pressure (i.e., reversal in the concentration gradient at the gas-liquid interface) from the surface-liquid/tissue phase during exhalation. Category 1 gases are also distinguished by the property that the gas does not significantly accumulate in the blood, which would reduce the concentration driving force and hence reduce the absorption rate. Examples of Category 1 gases are hydrogen fluoride, chlorine, formaldehyde, and the volatile organic acids and esters. At the other end of the scheme are the gases in Category 3. These gases are relatively water insoluble and unreactive in the ET and TB surface liquid and tissues so that these tissues receive relatively small doses. The uptake of Category 3 gases is predominantly in the PU region. Styrene is an example of a Category 3 gas. The gases in the intervening Category 2 have characteristics that are less pronounced than those of the gases at either end. These gases are moderately water soluble and react rapidly but reversibly or react irreversibly at a moderate to slow rate. Examples of Category 2 gases include ozone, sulfur dioxide, xylene, propanol, and isoamyl alcohol.

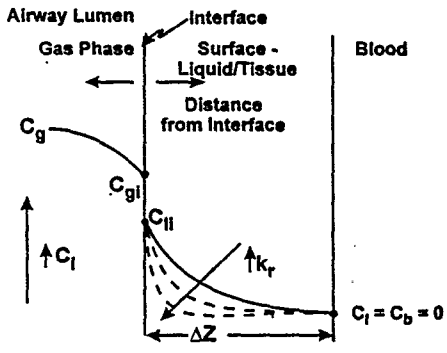
Note that the boundaries between categories are not clear and may be difficult to establish in practice for a specific chemical. Some compounds may appear to be defined by either Category 1 or 2 because water solubility and reactivity are a continuum. For example, although sulfur dioxide is reversibly reactive, as is a Category 2 gas, it is also highly water soluble like a Category 1 gas. Ozone is highly reactive but only moderately water soluble. The scheme is intended as a conceptual construct to aid choice of default models. The appropriateness of a default model structure for a given gas depends on the degree to which available data allow delineation between categories.

Gases with the greatest potential for respiratory tract effects are those in Category 1 or 2. The objective of the default modeling approach for these 2 categories is to describe the effective dose to 3 regions of the respiratory tract by addressing the absorption or 'scrubbing' of a relatively water-soluble or reactive gas from the inspired airstream as it travels from the ET to PU region. That is, the dose to the distal regions (TB and PU) is affected by the dose to region immediately proximal. The requirement to address proximal to distal scrubbing of these types of gases from the inhaled airstream is supported by a similar pattern of toxicity observed with increasing concentrations in many inhalation studies [17]. At low concentrations, the observed effects are largely isolated to the ET region. At higher concentrations, more severe effects occur in the ET region, and toxicity is also observed to progress to the distal regions. The severity of toxicity progresses distally with increased exposure concentrations. Even though respiratory tract uptake is not described in detail to the level of local airflow distribution (e.g., respiratory vs. olfactory epithelium), and reactions in the surface liquid vs. tissue layers are lumped into one phase compartment, the default model structures do adequately describe the scrubbing of the gas from the inhaled airstream.

The default structure used to model gases in Categories 1 and 2 is based on the concept of an overall mass transport coefficient, K_g, which uses a concentration gradient similar to Fick's law of diffusion to describe transport through several different surface phases such as air and liquid. Two-phase, mass transport resistance models using K_g have been used to describe absorption in the respiratory tract [18]. To simplify uptake by the respiratory tract as a 2-phase resistance model, it must be assumed that the blood concentration is constant. For the types of gases in Category 1, the blood concentration is actually assumed to be zero. The overall mass transport resistance is defined by the reciprocal of the mass

transport coefficient, $1/K_g$, composed of the resistance to lateral movement of the absorbing gas through the air and surface-liquid/tissue phases (Fig. 5).

3.2.1. Category 1 gases. A fractional penetration model [18–20] is used to determine the fraction of the inhaled concentration absorbed in each region. The uptake in the ET region and the output to the TB (fractional penetration, fp_{ET}) is dependent on K_g, so that uptake in the ET region is defined as $1 - fp_{ET}$. A ventilation-perfusion model is used to estimate the uptake in the PU region by substituting the concentration of the air exiting the TB region for the inhaled concentration. The overall schematic for the model for Category 1 gases is shown in Fig. 6. The rate of mass absorbed at the gas-surface interface of the airway in a region (r) is simply the product of the absorbed fraction, $(1 - fp_r)$, and the total mass inhaled during a single breath, $\dot{V}_E C_i$, where C_i is the inhaled concentration. The $\dot{V}_E$ is used as the default volumetric flow rate because it approximates the flow rate at which the animal was breathing during the experimental exposure. The



$$\frac{1}{K_g} = \left[\frac{1}{k_g} = f(\dot{V}_E, D_{geometry})\right] + \left[\frac{1}{k_l} = f(k_r, D, \Delta Z, H_{l/g})\right]$$

Fig. 5. Schematic of 2-phase mass transport resistance model used to describe respiratory tract uptake. This can be depicted as a resistance in a series where $1/K_g$ is the reciprocal of the overall mass transport coefficient, $1/k_g$ is the gas-phase resistance, and $1/k_l$ is the surface-liquid/tissue phase resistance. Parameter symbols and definitions are provided in the Appendix. Factors that influence flux are shown and described in the text. The definitive characteristic for Category 1 gases, that the concentration in the blood (C_b) is zero, is illustrated.

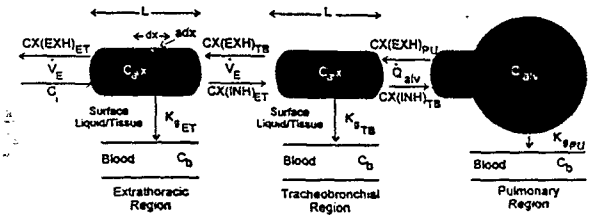


Fig. 6. Schematic of model to estimate default DAF_r for gases in Category 1; parameter symbols and definitions are provided in the Appendix.

alveolar ventilation rate is used to calculate the absorption rate for the PU region.

The DAF_r for each region is calculated based on equations describing the relationship between K_g and $1 - fp_r$ for each region, the ventilation rate, and regional surface area. The assumption that absorption is distributed equally within a region allows the description on a regional basis. Although this is a drastically reduced number of parameters in comparison to distributed parameter model descriptions, the default model does require regional K_g values for different animal species and gases. Values of K_g obtained in a single animal species may be scaled within a species for a different gas in the same category by decomposing K_g to the individual gas-phase and surface-liquid/tissue phase transport resistances [18]. The default equations can be further reduced by applying additional simplifying assumptions regarding the likely values of K_g. The derivation of the equations and DAF_r for each region, and the hierarchy of simplifying assumptions for each, are provided in detail elsewhere [2].

3.2.2. Category 2 gases. Because they are not as reactive or soluble in the respiratory tract tissue as Category 1 gases, gases in Category 2 have the potential for significant accumulation in the blood and thus have a higher potential for both respiratory and remote toxicity. Accumulation of Category 2 gases in the blood will reduce the concentration driving force during inspiration and thereby reduces the absorption rate or dose upon inhalation. Category 2 gases also have the potential for significant desorption during exhalation. Back pressure (i.e., reversal of the concentration gradient at the air-liquid interface) may occur during exhalation when the exhaled air concentra-

tion is less than the concentration of the surface liquid established during inhalation. Thus, uptake for these gases cannot be described by the 2-phase resistance model structure alone, and a hybrid structure between that for Category 1 and that for Category 3 was developed. The model structure is shown in Fig. 7. The PBPK component is necessary to evaluate the steady-state blood concentration, which is required to calculate both the absorbed flux on inhalation and the desorped flux during exhalation. The derivation of the analytic solution to the model structure and the reduction to forms with a minimal number of parameters are described in detail elsewhere [2].

3.2.3. Category 3 gases. Gases in Category 3 are relatively water insoluble and unreactive in the ET and TB surface liquid and tissue and thus result in relatively small doses to these regions. The uptake of Category 3 gases is predominantly in the PU region and is perfusion limited. The toxicity of these gases is generally at sites remote from the respiratory tract, and a lumped compartmental structure can be used to describe respiratory tract uptake and distribution to various systemic tissues. Thus, the default model for Category 3 gases is similar in structure to the PBPK model used by Ramsey and Andersen [15] to describe styrene distribution. The optimal model structure for Category 3 gases is obviously a comprehensive PBPK model of the type described for specific chemicals. The default model structure and the derivation of the DAF_r are described elsewhere [2,21].

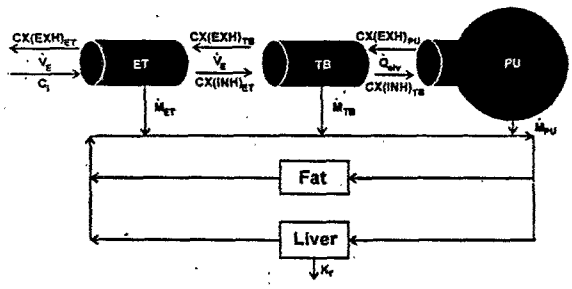


Fig. 7. Schematic of model to estimate default DAF_r for gases in Category 2; parameter symbols and definitions are provided in the Appendix.

4. Identification of key processes and parameters for data interpretation and research: specific examples

Perhaps the most frequent application is to the evaluation of the database for a given chemical. By definition, a database for derivation of a exposure-dose-response estimate for noncancer toxicity should ensure that an adequate number of appropriate potential endpoints have been evaluated. Table 2 shows the minimum database for high and low confidence in the derivation of an RfC. Chronic inhalation bioassay data in 2 different mammalian species, developmental studies in 2 different mammalian species, and a 2-generation reproductive study may be required to establish high confidence. The rationale for these requirements is that, because the objective of the RfC is to serve as a lifetime estimate, all potential endpoints at various critical life stages must be evaluated. However, consideration of the physicochemical properties of a gas or pharmacokinetic data that indicate significant distribution is unlikely to sites remote from the respiratory tract should mitigate the requirements for reproductive and developmental data. For example, the critical effect of a highly reactive and water-soluble gas is likely to be at the portal-of-entry and would not result in significant remote accumulation until severe damage to the respiratory tract had already occurred.

When the inhalation database for a given chemical is not adequate, route-to-route extrapolation is sometimes considered. Principles providing guidance on route-to-route extrapolation reflect the interpretative framework based on consideration of key determinants of chemical disposition and the degree to which they are addressed by different model structures or default extrapolation equations (Fig. 8). Major considerations include whether a chemical is likely to exhibit first-pass effects or cause contact-site toxicity. Determination of whether contact-site toxicity is likely for a given gas certainly involves evaluation of its key physicochemical characteristics — reactivity and solubility. For example, route-to-route extrapolation is considered inappropriate for most metals, irritants, and sensitizers. If only remote toxicity is likely, then the chemical can be considered as a

Table 2
Minimum database for both high and low confidence in the inhalation RfC

	Mammalian database[a]	Confidence Comments
1. A. Two inhalation bioassays[b] in different species B. One 2-generation reproductive study C. Two developmental toxicity studies in different species	High	Minimum database for high confidence
2. 1A and 1B, as above	Medium to high	
3. Two of 3 studies, as above in 1A and 1B; 1 or 2 developmental toxicity studies	Medium to high	
4. Two of 3 studies, as above in 1A and 1B	Medium	
5. One of 3 studies, as above in 1A and 1B; 1 or 2 developmental toxicity studies	Medium to low	
6. One inhalation bioassay[c]	Low	Minimum database for estimation of an RfC

[a]Composed of studies published in refereed journals, reports that adhered to good laboratory practice and have undergone final QA/QC, or studies rated by the Office of Pesticide Programs as 'core-minimum'. It is understood that adequate toxicity data in humans can form the basis of an RfC and yield high confidence in the RfC without this database. Pharmacokinetic data that indicate insignificant distribution occurs remote from the respiratory tract may decrease requirements for reproductive and developmental data.
[b]Chronic data.
[c]Chronic data preferred but subchronic acceptable.

candidate for extrapolation. The ability to perform an accurate quantitative extrapolation is critically dependent on the amount and type of data available. Again, a comprehensive delivered-dose description would be preferred. In order of decreasing accuracy and increasing uncertainty, other extrapolations can be considered: use of measurements of bioavailability by internal markers, direct measures of absorption efficiency, and default absorption values. This hierarchy parallels the same considerations illustrated in Fig. 1.

Insight into the key determinants of disposition and toxicity for specific chemicals can be used to frame interpretation of available data on other chemicals that are in the same class. An example is provided by the evaluation of URT toxicity data for methyl methacrylate (MMA) in context with data on acrylic acid and various acrylate esters. Table 3 shows the no-observed-adverse-effect levels (NOAELs) and adverse-effect levels (AELs) from various inhalation toxicity studies performed with these chemicals. Mechanistic research and modeling efforts of a number of investigators had established that carboxylesterase

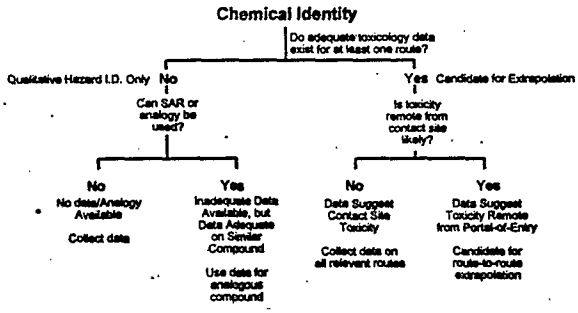


Fig. 8. Decision tree for route-to-route extrapolation [26]. SAR, structure-activity relationship.

Table 3
Assessment of NOAELs (N) and AELs (A) observed from 2-year bioassays for methyl methacrylate, acrylic acid, and other acrylates

Chemical	ppm											
	5	15	25	45	75	100	135	225	250	400	500	1000
MMA			?			?			A	A	A	A
MA		A		A			A					
EA	N		A		A			A[a]				
BA		A		A[b]			A[b]					
AA	A		A		A							

[a]Six-month exposure, 21-month follow up.
[b]Twenty-four-month exposure, 6-month follow up.

activity in the URT was responsible for the uptake and cytotoxicity in these tissues [22,23]. This information made the number of URT section levels at the higher concentrations and the lack of any URT histopathology data at the 2 lowest concentrations for MMA of concern, particularly because available kinetic data indicated that it had comparable rates of metabolism to these other acrylates. Certainly the 400-ppm exposure level would be considered an AEL, but the lack of an identified NOAEL would require application of an additional uncertainty factor. Agreeing with this rationale, the Methacrylate Producers Association obtained the original tissue blocks and resected the URT to obtain adequate histopathology. The subsequent evaluation established a NOAEL for MMA at 25 ppm [24]. These new data were obtained without the expense of additional exposures and obviated the requirement for application of an uncertainty factor for lowest-observed-adverse-effect levels (LOAEL) to NOAEL extrapolation.

Finally, the identification of key processes and mechanistic determinants can aid the development of models and provide for evaluation of chemicals not yet in major production. Phase-out of production and use of chlorofluorocarbons and other global warming and ozone-depleting chemicals, such as the halons, is under strict legislative deadlines. Because of the ubiquitous use and benefits of these chemicals, an expeditious search for safe replacements was necessary. A hydrochlorofluorocarbon, 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123) is a key replacement chemical candidate; it is a structural analog to the anesthetic gas halothane, and both chemicals are metabolized to potentially toxic intermediates via the same pathways. Based on considerable evidence that the hepatotoxicity seen in a 2-year inhalation bioassay was likely to be mechanistically similar to that induced by its structural analog halothane, a parallelogram approach for model development and interspecies extrapolation of the toxicity data on HCFC-123 as shown in Fig. 9 was proposed [25]. A PBPK model structure was developed using a volatile organic compound template hybridized with a classical one-compartment description of clearance of the

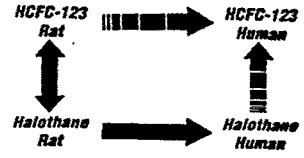


Fig. 9. Parallelogram for interspecies extrapolation of hepatotoxicity based on similarity of structure and mechanism of action between halothane and HCFC-123 [25].

oxidative metabolite. Use of the template provided physiologic parameters (e.g., compartment volumes, flows) so that experiments could be targeted at obtaining data on other key chemical-specific parameters for model development. For example, experimental data in rats were obtained with both HCFC-123 and halothane for partition coefficients and metabolic rates. Validation of the rat model for each compound was then performed by comparing model predictions against other experimental data not used in model development. Human PBPK models for the 2 compounds were then developed in a similar fashion. Data from human halothane exposures were used to validate the model and showed that model predictions agreed with experimental data. By structural and metabolic analogy, the human model is likely to adequately describe HCFC-123 kinetics as well. Because HCFC-123 is not yet in major production, this parallelogram approach enables extrapolation of the rat toxicity data for human dose-response estimation in the absence of human HCFC-123 exposure data. Because comprehensive PBPK model structures are considered the optimal approach for interspecies extrapolation, a decrease in the UF for interspecies extrapolation also has been proposed [25].

5. Conclusions: advantages of dosimetry modeling interpretative framework

Although comprehensive mathematical dosimetry models have been useful to the risk assessment process, the availability of key anatomic and physiologic parameters for different mammalian species (including humans) and of the physicochemical parameters for individual chemicals is an important consideration in the formulation of model structures and in the application of simpli-

fying assumptions to develop default approaches. Construction of a framework for evaluation of dosimetry models, based on the degree of incorporation of mechanistic determinants of exposure-dose-response, provides for iterative development of dosimetry models commensurate with available data. This framework permits integration of diverse data from independent experiments (e.g., general physiologic parameters for the animal species, metabolic data for the individual chemical) to predict complex kinetic behavior. Development of the description of mechanistic processes in an iterative fashion also provides for the capability to 'lump' or 'split' model structures in an attempt to explore the sensitivity of the exposure-dose-response relationship to different model structures. Such an approach provides for the use of template model structures for use across species and for reduction of data-testing requirements. The principles of model formulation also can be used to generate hypotheses, identify areas of needed research, and frame efficient experimental designs.

Appendix

Definition of parameter symbols

a	Airway perimeter
C_{alv}	Pulmonary region gas concentration
$C_a(x)$	Gas concentration as a function of x
C_b	Blood concentration
C_g	Gas phase concentration in airway lumen
C_{gi}	Gas-phase concentration at the interface of the gas phase with the surface-liquid/tissue phase
C_i	Inhaled concentration
C_l	Surface-liquid/tissue phase concentration
C_{li}	Surface-liquid/tissue concentration at the interface of the gas phase and the surface-liquid/tissue phase
$CX(EXH)_{ET}$	Concentration exiting from extrathoracic region upon exhalation
$CX(EXH)_{PU}$	Concentration exiting from pulmonary region upon exhalation
$CX(EXH)_{TB}$	Concentration exiting from tracheobronchial region upon exhalation
$CX(INH)_{ET}$	Concentration exiting from extrathoracic region upon inhalation
$CX(INH)_{TB}$	Concentration exiting from tracheobronchial region upon inhalation
dx	Differential of axial distance into airway
ET	Extrathoracic respiratory region
fp_{ET}	Fractional penetration through the extrathoracic region
$H_{t/g}$	Surface-liquid/tissue: gas (air) partition coefficient
k_g	Transport coefficient in the air phase
k_l	Transport coefficient in the surface liquid/tissue phase
k_r	Reaction rate constant in the blood
K_g	Overall mass transport coefficient
K_{gET}	Overall mass transport coefficient of the extrathoracic region
K_{gPU}	Overall mass transport coefficient of the pulmonary region
K_{gTB}	Overall mass transport coefficient of the tracheobronchial region
K_r	Elimination rate
$\dot{M}_d$	Desorbed mass
$\dot{M}_{ET}$	Mass flux from extrathoracic region to blood
$\dot{M}_{PU}$	Mass flux from pulmonary region to blood
$\dot{M}_{TD}$	Mass flux from tracheobronchial region to blood
PU	Pulmonary respiratory tract region
$\dot{Q}_{alv}$	Alveolar ventilation rate
SA_r	Surface area of unspecified respiratory region, r
t	Time
t_{EXH}	Time (duration) of exhalation
TB	Tracheobronchial respiratory tract region
$\dot{V}_E$	Minute ventilation
X	Distance into the airway
ΔZ	Surface-liquid/tissue phase thickness

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