

MASS TRANSPORT ANALYSIS: Inhalation RfC Methods Framework for Interspecies Dosimetric Adjustment

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In 1994, the U.S. Environmental Protection Agency introduced dosimetry modeling into the methods used to derive an inhalation reference concentration (RfC). The type of dosimetric adjustment factor (DAF) applied had to span the range of physicochemical characteristics of the gases listed on the Clean Air Act Amendments in 1991 as hazardous air pollutants (HAPs) and accommodate differences in available data with respect to their toxicokinetic properties. A framework was proposed that allowed for a hierarchy of dosimetry model structures, from optimal to rudimentary, and a category scheme that provided for limiting model structures based on physicochemical and toxicokinetic properties. These limiting cases were developed from restricting consideration to specific properties relying on an understanding of the generalized system based on mass transport theory. Physicochemical characteristics included the solubility and reactivity (e.g., propensity to dissociate, oxidize, or serve as a metabolic substrate) of the gas and were used as major determinants of absorption. Dosimetric adjustments were developed to evaluate portal of entry (POE) effects as well as remote (systemic) effects relevant to the toxicokinetic properties of the gas of interest. The gas categorization scheme consisted of defining three gas categories: (1) gases that are highly soluble and/or reactive, absorbing primarily in the extrathoracic airways; (2) gases that are moderately soluble and/or reactive, absorbing throughout the airways, as well as accumulating in the bloodstream; and (3) gases that have a low water solubility and are lipid soluble such that they are primarily absorbed in the pulmonary region and likely to act systemically. This article presents the framework and the mass transport theory behind the RfC method. Comparison to compartmental approaches and considerations for future development are also discussed.

The U.S. Environmental Protection Agency (EPA) incorporated a dosimetric adjustment factor (DAF) term to account for interspecies extrapolation in the 1994 inhalation reference concentration (RfC) methods (U.S. EPA, 1994). The objectives of the DAF were to allow for extrapolation of inhaled dose across species for numerous hazardous air pollutants that span a range

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of physicochemical, pharmacokinetic, and toxicologic characteristics and for which data are likely to be limited. To meet that goal, an approach was taken that would provide for an integrated understanding of system and data needs using information generally available for all gases such as water solubility. A categorization scheme of gases was developed and embedded in a framework for choosing model structure as well as different default DAFs based on the fundamental knowledge that absorption rate was determined by water solubility and reactivity, with reactivity defined as the propensity to dissociate, oxidize, or metabolize.

The category scheme (Table 1) allowed special cases to be isolated from a generalized model structure of mass transport (Figure 1) based on an evaluation of its physicochemical and toxicological properties. As will be discussed in more detail later, the chemical mass transport across gas, liquid/tissue, and blood phases of the airways, as determined by these properties, was conceptualized in terms of the overall mass-transport coefficient (K_g) as a measure of the conductivity of a chemical across the three phases. Inversely, when expressed as its reciprocal ($1/K_g$), K_g is also a measure of the overall mass-transport resistance of the radial transport of the absorbing gas from the gas phase, through the liquid/tissue, and into blood. Similarly, the overall mass-transport resistance to the radial transport of the gas ($1/K_g$) may be viewed as the summation of the resistance through each phase (i.e., analogous to electrical resistance summations) as shown in Figure 2. Focusing on the gas and tissue liquid compartments, the form of the overall mass transport resistance would be expressed as the sum of the resistance through the gas, and liquid/tissue phases. The overall mass transport coefficient, considering only these two phases, is given by the following equation:

$$\frac{1}{K_g} = \frac{1}{k_g} + \frac{1}{H_{t/g}k_l} \quad (1)$$

TABLE 1. Gas category scheme specifies dosimetric adjustments

Category 1:	
Physicochemical characteristics:	Highly "reactive" and water soluble
Toxicokinetic properties:	Interact with the respiratory tract as the portal of entry
Default model:	Three respiratory-tract compartments Uptake defined by regional overall mass-transfer coefficient
Category 2:	
Physicochemical characteristics:	Water soluble, but some blood accumulation can occur
Toxicokinetic properties:	Both respiratory and remote effects
Default model:	Structure includes both respiratory-tract compartments and remote distribution Uptake defined by overall mass-transfer coefficient and flow-limited perfusion distribution
Category 3:	
Physicochemical characteristics:	Poorly water soluble
Toxicokinetic properties:	Remote effects
Default model:	Respiratory tract depicted as one compartment Uptake defined by partition coefficient and flow-limited perfusion

RfC Conceptual Model

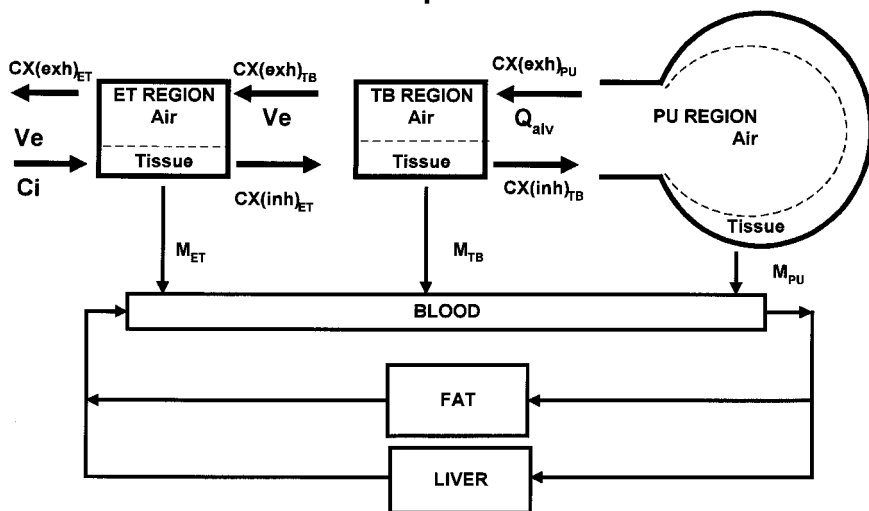


FIGURE 1. RfC conceptual model for dosimetry gas disposition in the three regions (ET, extrathoracic; TB, tracheobronchial; PU, pulmonary) of the respiratory tract. V_e , minute ventilation; C_i , inhaled concentration; Q_{alv} , alveolar ventilation; $C_{X(inh)ET}$, concentration exiting the ET region on inhalation; $C_{X(inh)TB}$, concentration exiting the TB region on inhalation; $C_{X(inh)PU}$, concentration exiting the PU region on inhalation; M_{ET} , net mass flux of inhaled gas from the ET region to the blood; M_{TB} , net mass flux of absorbed gas from the TB region to the blood; M_{PU} , net mass flux of absorbed gas from the PU region to the blood; $C_{X(exh)PU}$, concentration exiting the PU region on exhalation; $C_{X(exh)TB}$, concentration exiting the TB region on exhalation; and $C_{X(exh)ET}$, concentration exiting the ET region on exhalation.

where the first term, the gas-phase resistance, is the reciprocal of the gas-phase mass-transport coefficient (k_g), and the second term, the liquid-phase resistance, is given as the reciprocal of the product of the liquid/tissue to gas partition coefficient ($H_{v/g}$) where $H_{v/g}$ is the Henry's Law value of the gas, and the liquid/tissue phase mass transport coefficient (k_l) that incorporates the metabolism or depletion by other reactions (e.g., dissociation) of the gas being absorbed by the respiratory tract. It is important to note that Eq. (1) is not simply a conceptual notation but, in fact, has been shown to be the exact solution of Fick's Law describing mass transport between two phases (Marshall & Pigford, 1947).

The gas-phase mass-transport coefficient (k_g) is defined as the proportionality constant relating the flux, N (mass transported per surface area per second), and the concentration difference between the central gas stream and that at the interface of the liquid/tissue phase such that:

$$N = k_g \Delta C \quad (2)$$

This equation is similar to that used in defining the permeability constant. In contrast to a permeability constant, the gas-phase mass-transport coefficient (k_g) is known to be a function of flow geometry and flow rate (Bird et

Mass Transport Resistance Analysis

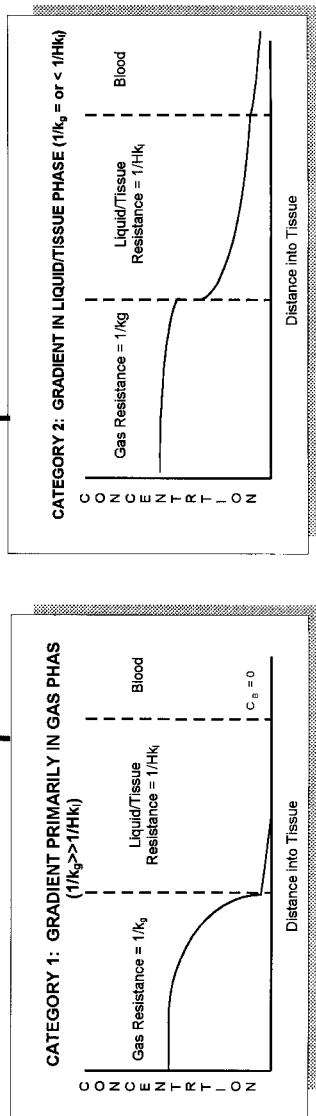
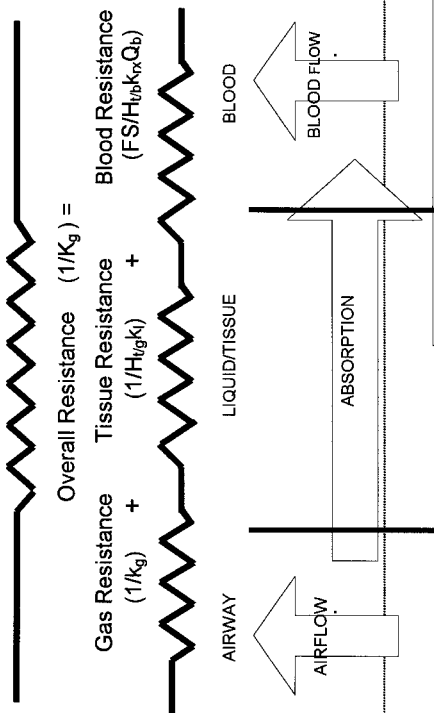


FIGURE 2. Mass transport resistance analysis and schematics of concentration gradient across phases. K_g , mass-transport coefficient; k_g , gas-phase mass-transport coefficient; H_{lg} , gas:tissue partition coefficient; k_l , liquid:tissue mass transport coefficient; F , flux fraction; S , surface area available to the bloodstream; H_{lg} , liquid:tissue to gas partition coefficient; k_r , reaction rate; Q_b , regional blood flow; and C_B , blood concentration. An assumption of zero blood concentration can be invoked for Category 1. A Category 2 model structure must address systemic disposition and toxicity including delivery via the blood to the respiratory tract.

al., 1960; Lou, 1993). Both flow rate and airway geometry affect k_g by altering the thickness of the gas stream in which a concentration gradient exists between the central gas stream and the gas immediately adjacent to the absorbing surface liquid.

Similarly, a mass-transport coefficient (k_l) for the liquid/tissue phase is used to evaluate the penetration of the gas into and through the liquid/tissue lining the respiratory tract. The amount of gas transported into the liquid/tissue phase depends on the solubility of the gas, its diffusivity in the liquid/tissue phase, the thickness of the liquid/tissue layer, the reaction rate of the gas in the liquid/tissue phase, and the gas concentration. With the exception of the solubility term that is explicitly included in the tissue/liquid-phase resistance term, as shown in Eq. (2), the liquid/tissue-phase mass-transport coefficient (k_l) combines diffusivity and reaction rate to develop a quantitative analysis of mass transport in the liquid/tissue phase.

By comparing the gas-phase, liquid/tissue-phase, and blood-phase resistances, the phase limiting or controlling mass transport can be determined, from which the categorization of gases was developed. For example, Category 1 was designated as those gases that were so reactive and soluble, as quantified by the gas-phase and liquid/tissue-phase resistances, that toxicity would be restricted to the portal of entry so that absorption to the blood was not necessary to accurately describe their uptake (Figure 2). The formulation of this default was based on mass transport analyses that had been successfully used to describe uptake of sulfur dioxide and other reactive, water-soluble vapors (Aharonson et al., 1974). In contrast, Category 3 gases were designated as those that are determined principally by transport in the systemic circulation because of their low water solubility and reaction while also having sufficient lipid solubility to be absorbed into the blood. Consequently, toxicity is generally remote to the portal of entry except for circumstances in which an effect on the respiratory system is a result of the systemic blood concentration (e.g., delivery via the blood to the respiratory endothelium). To incorporate the blood phase into the analysis of the phases limiting or controlling transport, blood-phase resistance is incorporated into the overall mass transport coefficient definition as shown by inclusion of the third term here:

$$\frac{1}{K_g} = \frac{1}{k_g} + \frac{1}{H_{t/g}k_l} + \frac{FS_p}{H_{b/g}Q_b} \quad (3)$$

where F is the flux fraction (to account for the fraction reacted in the previous transport phase), S_p the available surface area, $H_{b/g}$ the blood to gas partition coefficient, and Q_b the regional blood flow.

The 1994 methods also provided for a framework for model choice based on the degree of detail used to define the dose metric as shown in Table 2 (U.S. EPA, 1994; Jarabek, 1995). This framework is consistent with the intent of the proposed 1996 guidelines for cancer risk assess-

TABLE 2. Hierarchy of dosimetry model structures for exposure-dose-response and interspecies extrapolation**“Optimal” 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 metrics described at level of detail commensurate with 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 metrics at generic level of detail

Note. From U.S. EPA (1994).

ment that emphasized consideration of the mode of action—defined as a chemical’s influence on molecular, cellular and physiological functions in producing tumors (*Federal Register*, 1996). This concept has been extended to encompass all toxicity and is now being used as a basis for the use of dosimetry modeling and the use of key events or biomarkers in risk assessment (Bogdanffy & Jarabek, 1995; Jarabek, 1999). Bogdanffy et al. (1999) used mode of action to develop a rationale for a cellular dose metric for vinyl acetate-induced lesions in the upper respiratory tract.

Thus, the RfC method, or any method used to extrapolate dose across species, must be sufficiently robust to describe the exposure-dose relationship for more than one type of laboratory animal and must also predict human dose to allow the dosimetric adjustment to be made. It is therefore essential that a dosimetric model be descriptive of the anatomy, physiology, and metabolism of the species of interest without introducing extraneous parameters that add to the overall level of uncertainty particularly when experimental data are used to “fit” the model. Additionally, the results should not be extrapolated to conditions or gases with differing physicochemical parameters without recognizing that the extrapolation may not be appropriate. Every effort should be made to obtain a solution appropriate to the physicochemical properties of the specific gas. The opportunity for model verification is essential to the modeling framework. This article illustrates how the mass-transport approach of the RfC methods provides a framework for choosing model structure to accommodate tissue and blood compartment considerations and, eventually, tissue dose metrics based on mode of action insights.

MODEL FRAMEWORK DEVELOPMENT

Physiologically based pharmacokinetic (PBPK) models to date are the most utilized models within the toxicology literature and have been particularly informative for evaluating the systemic distribution of a toxicant.

These models have also been used to describe gas absorption (as opposed to particles) in the respiratory tract. Generally, these PBPK gas absorption models have focused on the limiting case of gases with high lipid solubility (e.g., volatile organic compounds like styrene) such that their uptake is determined by perfusion. Within the 1994 RfC framework, these gases are defined as Category 3. These models focus on the systemic distribution of the toxicant so that the respiratory tract is typically characterized as a compartment in which gas transfer between alveolar gas and venous blood is determined by an equilibrium relationship. Hence, the respiratory tract is conceived as merely a conduit to pulmonary absorption and systemic delivery of dose. Therefore, the dynamics of the modeling is inherent in the blood flow, not in the diffusional mass transport across the blood-gas barrier.

In contrast, gases that are water-soluble and/or reactive within the airway tissue, that is, Category 1 and some Category 2 gases, distribute regionally within the airways themselves. Distributed parameter models have been used to describe the uptake of these gases and also have been successful in regulatory applications (Miller et al., 1985; Overton et al., 1987; Overton & Miller, 1988). Sulfur dioxide and formaldehyde are examples of reactive and soluble gases that are unlikely to reach the lung periphery except in extreme circumstances (e.g., high concentrations). Ozone, which is less soluble than both formaldehyde and sulfur dioxide, is nonetheless sufficiently reactive with the surface liquid and tissue to be distributed throughout the airways, such that the gas stream concentration decreases with distance into the airway, thereby determining local tissue exposures. All three of these gases establish a quasi-steady-state concentration gradient on inspiration and expiration in both the airways and the tissue lining the airways. Under these circumstances, the respiratory tract itself may be the site of the critical effect, unless a metabolite is sufficiently stable to distribute systemically. The need for dosimetry measures within the respiratory tract itself requires differentiation of the various respiratory tract regions rather than a focus only on the blood-gas exchange region.

The establishment of quasi-steady-state concentration gradients for these water-soluble and/or reactive gases also contrasts sharply to the equilibrium conditions that are assumed to prevail between alveolar gas and venous blood in the case of lipid-soluble gases. Because of the dynamic process of uptake within the respiratory tract, the equilibrium assumption is inappropriate. The transport of these gases is not determined primarily by the distribution of blood flow but rather by the transport of the gas along the concentration gradient from within the gas stream extending laterally to the liquid/tissue compartment. Understanding the distinction between the equilibrium assumption in which transport is dependent on regional blood flow and dynamic models in which transport occurs across a concentration gradient near the transport barrier is essential to formulating dosimetric models (Lutz et al., 1980; Gerlowski & Jain, 1983; Kohn, 1997). A transport barrier is essentially the boundary of another phase. The distinction between a

system in which an equilibrium can be assumed across the transport boundary and that in which a gradient exists is illustrated by contrasting the flow-limited or perfusion models from the membrane-limited transport models.

Flow-limited or perfusion-limited models represent a limiting case of the general mass balance equation in which the permeability of the transport barrier (or membrane) is far greater than the flow or perfusion to the transport barrier (Lutz et al., 1980; Gerlowski & Jain, 1983). Hence, the flow volume or perfusion rate ultimately limits the transport of toxicant to systemic compartments. This model is relevant to lipid-soluble gases that are absorbed in the alveolar region of the lung. For such gases, the alveolar ventilation rate determines the alveolar gas-phase concentration. The equilibrium partition coefficient of the gas is then used to establish the blood concentration in equilibrium with the alveolar gas concentration. Ultimately, however, transport to systemic compartments is determined by the blood flow and, although the systemic concentrations may change as a function of time until steady state, the fundamental transport is established by the equilibrium condition and the distribution of blood flow.

The alternate limiting case of the general mass balance equation is the membrane-limited transport model. In this case, equilibrium is not established; instead, there exists a concentration gradient between the tissue and blood. The gradient is established because of the transport limitation imposed at the membrane or the transport barrier itself. Using the perfusion analogy, perfusion rate does not limit intracellular or tissue concentrations in this case, but rather the membrane or transport barrier itself limits the rate at which the toxicant permeates the barrier to enter the systemic circulation or to act on the tissue itself.

Typically, these membrane-limited transport models are understood and applied to chemical uptake in organs absent airflow. In modeling chemical uptake to such organs, diffusion within the blood is typically ignored because the concentration gradient is of minor significance compared to the gradient in the tissue. By contrast, for airflow in the respiratory tract, diffusion in the gas stream itself may result in the establishment of a significant concentration gradient that, in addition to the airway lining, also affects the rate of uptake. This case therefore requires models capable of describing the dynamic transport process both in the gas phase and within the tissue.

It also should be noted that there are circumstances under which the gas-phase concentration gradient completely controls the rate of uptake. Highly water-soluble gases that are readily absorbed by the airway lining and gases that react nearly completely within the airway lining are examples of gas-phase-limited transport cases and, within the RfC framework, comprise Category 1. For these gases, the tissue is almost a relatively infinite sink for the gas. Consequently, the rate of absorption is limited by the rate at which the gas can cross the gas-phase concentration gradient, or gas-phase transport barrier, to the tissue. Despite the fact that airflow limits

the availability of toxicant to the tissue in these cases, this is not the “flow-limited or perfusion-limited” case as described in the PBPK literature (Pang & Rowland, 1977; Kohn, 1997). In this gas flow-limited case, equilibrium cannot be assumed between the gas-phase concentration and the transport barrier of the airway surface because the gas-phase concentration gradient represents a barrier to transport requiring the mass to diffuse across this barrier.

In summary, the RfC methodology was developed to estimate absorbed dose based on the physicochemical properties of a gas so as to utilize the limiting cases described earlier. In the case of a poorly water-soluble and unreactive gas that is lipid soluble, the equilibrium established between alveolar gas and blood can be used to estimate systemic dose as in the classic “perfusion-limited” case. However, for gases whose rate of uptake is “membrane limited,” the concentration gradient within the gas phase and/or tissue also must be considered part of the barrier. Depending upon the physicochemical properties of the gas, there are cases in which the absorption of an inhaled gas may be controlled entirely by gas-phase transport alone such that the liquid-phase transport resistance may be ignored. Similarly, when the liquid phase controls transport, the gas-phase transport resistance can be ignored. When both phases contribute to the overall transport resistance, both phases must be considered to quantitatively evaluate the absorption rate.

To simplify the transport modeling and derivation of default dosimetric adjustment factors (DAFs), the RfC methodology categorized the gases by evaluating the phases limiting transport. Gases for which the alveolar ventilation rate and equilibrium of the blood-gas barrier apply are assigned to Category 3. Gases whose rate of uptake is primarily limited by tissue/liquid barriers but for which the blood phase also plays a role are assigned to Category 2. Gases whose uptake is primarily limited by the gas stream concentration gradient, although the tissue compartment may play a role, are assigned to Category 1. Differentiation of these categories can be made on the basis of the resistance comparison of Eq. (3). Thus, while the category scheme has been illustrated through qualitative differences in solubility and reactivity, the categorization can be developed quantitatively using Eq. (3). The separation of the physicochemical and anatomic or physiological parameters is an important aspect of the RfC approach in that it allows cross-species extrapolation. Consequently, since anatomic considerations are included in Eq. (3), the categorization of a gas may be species dependent.

TERMINOLOGY

While the genesis of the RfC dosimetric methods for gases is the same as that for the PBPK models that toxicologists are most familiar with, the terminology used in these RfC models differs from that of the PBPK models.

Unfortunately, the introduction of engineering terms into the RfC methodology has led to difficulties in understanding and utilizing the RfC dosimetric methods within the toxicological community. These engineering terms were introduced to model the transport across a concentration gradient and, since many mass transport coefficients have been derived analytically for various types of reactions, the introduction provides a means to simplify transport modeling when it cannot be assumed that equilibrium between two phases determines the transport rate.

To clarify the RfC dosimetric approach, the commonalities and differences in terminology between this method and the flow- or perfusion-limited PBPK modeling approach are discussed in this section. The Category 2 model was considered the universal structure, but physiochemical attributes of the gases in the other two categories allowed simplifying assumptions to reduce model structures and, therefore, the number of parameters. To acquaint readers with the models, the RfC method to derive a DAF for a Category 1 gas that is analogous to a membrane-limited transport process is contrasted to the flow- or perfusion-limited scenario of the PBPK approach. The approaches are contrasted by illustrating the assumptions and model formulation of the perfusion-limited model as opposed to the membrane-limited transport process.

Flow- or Perfusion-Limited Transfer

The basis of the gas dosimetric models used to evaluate flow- or perfusion-limited transfer is to establish a mass balance across a control volume. This concept is no different than evaluating toxicant transfer through systemic organs. Therefore, to simplify the discussion of the primary differences in terminology between the RfC and PBPK methods, the following example examines transfer from blood plasma to intracellular fluid as a surrogate for transfer in the lung airways (see Figure 3).

In a capillary, the mass balance approach essentially states that the decrease in blood concentration of a constituent as it flows through a known control volume ($C_{in} - C_{out}$) is equal to the rate at which it is transported into the adjacent tissue (flux), assuming metabolism in blood is negligible (see Figure 3). For this example, a mass balance across the control volume (i.e., the volume for which the mass balance equation is developed) can be expressed as follows:

$$V \frac{dC}{dt} = Q(C_{in} - C_{out}) = SA \cdot \text{Flux}_{(P-I)} \quad (4)$$

where V is the volume of plasma in the control volume (cm^3), dC/dt the rate of change of blood concentration ($\text{g}/\text{cm}^3\text{-s}$), Q the blood flow rate (cm^3/s), C_{in} the blood concentration entering the control volume (g/cm^3), C_{out} the blood concentration exiting the control volume (g/cm^3), SA the surface area of capillary in the control volume (cm^2), $\text{Flux}_{(P-I)}$ the toxicant

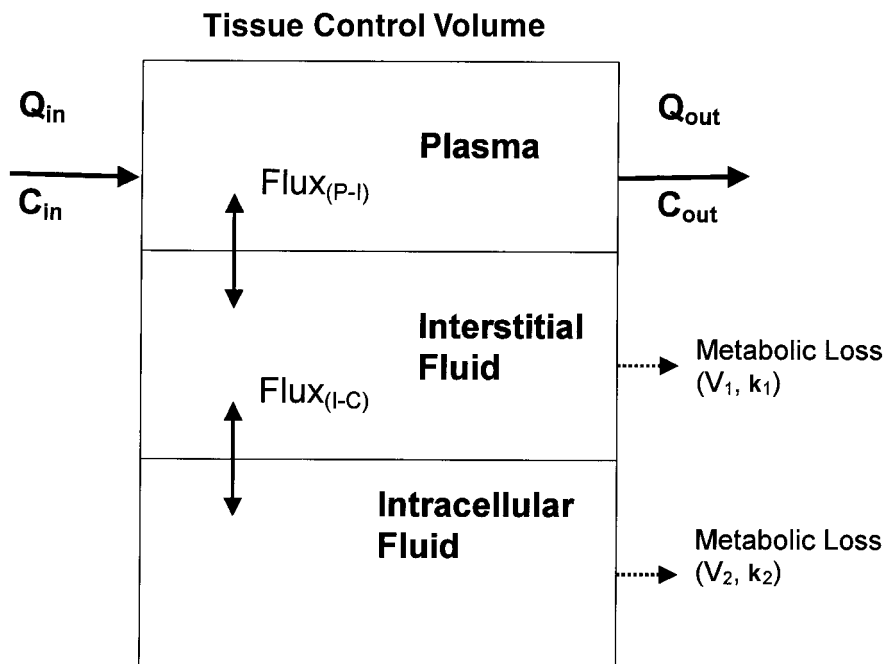


FIGURE 3. Control volume in systemic tissue compartment. Q_{in} , blood flow into compartment; C_{in} , concentration into the compartment; Q_{out} , blood flow out of the compartment; C_{out} , concentration out of the compartment; $Flux_{(P-I)}$, flux from plasma to interstitial fluid; $Flux_{(I-C)}$, flux from interstitial fluid to intracellular fluid; V_1 and k_1 , velocity and affinity terms for metabolism in interstitial fluid; V_2 and k_2 , velocity and affinity terms for metabolism in intracellular fluid.

flux from plasma to interstitial fluid ($g/cm^2 \cdot s$), and $Flux_{(I-C)}$ the toxicant flux from interstitial fluid to cellular fluid ($g/cm^2 \cdot s$).

It is assumed that the system is in a steady state, such that the rate of change in blood concentration (dC/dt) both entering and exiting the control volume is zero. Thus, the change in concentration in the plasma control volume is equal to the product of surface area (cm^2) and the flux (or efflux) from plasma to the interstitial space. Flux has units of mass/area-time and is defined, using Fick's Law, as the product of the permeability, P (in units of cm/s), of the tissue barrier and the concentration gradient between the two sides of the barrier. Thus, for the example discussed earlier, constituent flux is dependent upon cell or tissue permeability and the concentration gradient between the plasma and the interstitial space such that:

$$Flux_{(P-I)} = D \frac{dC}{dt} = P(C_p - C_i) \quad (5)$$

where C_p and C_i are the concentrations in the plasma and interstitial fluid, respectively. However, in the biological literature, cell or tissue perme-

ability is sometimes defined as the product of the permeability and surface area and has been designated PA with units of volume/time (Andersen & Sarangapani, this issue). For PA to be substituted into Eq. (5), the flux would need to be multiplied by surface area. Hence, the left side of the equation would become a mass-transfer rate in units of mass/time as opposed to units of flux in mass/area-time.

At steady state, the mass balance in the interstitial fluid portion of the control volume would require that the mass-transfer rate (dm/dt in units of mass/time) in and out of the fluid be balanced by the net rate of metabolism. Hence, in the interstitial fluid,

$$\left(\frac{dm}{dt}\right)_1 - \left(\frac{dm}{dt}\right)_2 = \frac{V_1 C_1}{k_1 + C_1} \quad (6)$$

where $(dm/dt)_1$ and $(dm/dt)_2$ are the mass-transfer rates entering and exiting the interstitial compartment, C_1 is the interstitial fluid concentration, and V_1 and K_1 are the Michaelis–Menten kinetic parameters for metabolism in the interstitial compartment.

Similarly, in the intracellular compartment at steady state,

$$\left(\frac{dm}{dt}\right)_2 = \frac{V_2 C_c}{k_2 + C_c} \quad (7)$$

where $(dm/dt)_2$ is the transfer rate entering the intracellular compartment, C_c is the intracellular concentration, and V_2 and K_2 are the Michaelis–Menten kinetic parameters for the intracellular compartment.

By substituting Eq. (5) through (7) into Eq. (4), the rate of change in the blood concentration may be defined in terms of the metabolic loss such that

$$Q(C_{in} - C_{out}) = \frac{V_1 C_1}{k_1 + C_1} + \frac{V_2 C_c}{k_2 + C_c} \quad (8)$$

This formulation has been used to develop a “clearance term” that is defined as the volume of blood per unit of time in which the toxicant (or drug) has been irreversibly removed (Pang & Rowland, 1977; Wilkinson & Shand, 1975). Clearance thereby references the initial concentration. To obtain this volume/time, Eq. (8) is simply divided by the inlet concentration, whereby:

$$Cl = Q \frac{(C_{in} - C_{out})}{C_{in}} = QE \quad (9)$$

As shown in Eq. (9), clearance can also be expressed in relation to an extraction ratio, E , a nondimensional parameter that expresses the frac-

tion of blood flow that is cleared of the drug or toxicant (Pang & Rowland, 1977; Wilkinson & Shand, 1975).

The concept of a volume of fluid that is completely cleared of toxicant mass is foreign to the engineering literature. Instead of evaluating the abstract notion of a volume of fluid from which toxicant mass has been cleared per unit of time, the engineering mass balance approach uses transport equations relating concentration distributions, mass fluxes, and mass transport rates to “track” the mass as it enters and exits compartments through the use of mass transport coefficients. Therefore, the RfC method maintains the concentration gradient analysis. In contrast, the compartment size (and volumes) must be carefully developed for the PBPK clearance-based approach to accurately evaluate toxicant gradients, flux and concentration across the transport barrier. As discussed later, for more complex scenarios than depicted in this example, PBPK model accuracy in simulating these gradients can be assured only by successive decreases in compartment dimensions, particularly as reaction rate increases.

Gas-Phase-Limited (Membrane-Limited) Transfer

Although useful for examining the terminology differences between the two methods, the flow or perfusion-limited model is not sufficient to describe the complexity of all potential gas transfer processes in the airways. As previously described, the perfusion-limited model in which there is no diffusional barrier at the transport boundary, assumes that equilibrium conditions apply. However, in the airways, this is likely to be the case only for lipid-soluble gases that are absorbed in the alveolar region (i.e., Category 3 gases). Category 1 and 2 gases may be absorbed throughout the airways and the rate of transfer may be limited by either their transport from the central gas stream to the airways surface and/or by the solubility and/or reactivity (metabolic or dissociation) within the surface liquid and/or tissue.

To develop the corollary of the perfusion-limited model for the airways and thereby introduce the terminology used in the RfC dosimetric methods, the airway control volume must consist of additional transport pathways. In particular, as shown in Figure 4, the control volume must account for both gas flow and blood flow into the control volume. In addition, as shown in Figure 4, the gas phase must be modeled as two compartments to appropriately account for the diffusional transport resistance across the concentration gradient in the gas phase. While these added dimensions increase the complexity of the mass balance equation from that of perfusion-limited transport described earlier, similar methods can be used to derive the mass-transport relationships for this dynamic system. For example, numerous investigators have developed the mass balance equations in differential form and solved the equations numerically (Miller et al., 1985; Hanna et al., 1989; Lou, 1993).

The concept of a resistance barrier in the gas phase is not well known in the biological literature, where there is a relatively limited need to

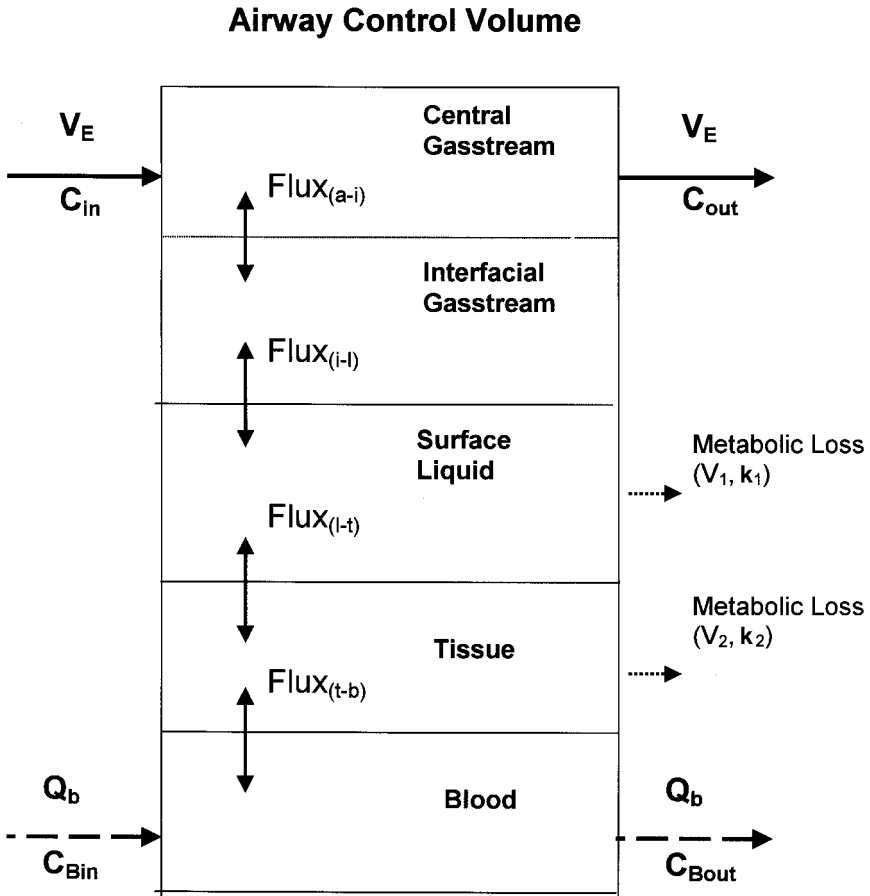


FIGURE 4. Airway control volume in respiratory tract. V_e , minute ventilation; C_{in} , inhaled concentration; C_{out} , exhaled concentration; Q_b , blood flow, C_{Bin} , blood concentration in to respiratory tract region; C_{Bout} , blood concentration out of respiratory tract region; $Flux_{(a-i)}$, flux from gas stream to interfacial gas stream; $Flux_{(i-l)}$, flux from interfacial gasstream to surface liquid; $Flux_{(l-t)}$, flux from surface liquid to tissue; $Flux_{(t-b)}$, flux from tissue to blood; (V_1 and k_1), velocity and affinity terms for metabolism in surface liquid; and (V_2 and k_2), velocity and affinity terms for metabolism in tissue.

understand airflow dynamics, although there are extensive publications in the biomedical engineering literature. The transport limitation induced by the gas phase at the boundary of a surface to which mass is transported is an important concept in environmental engineering, such as in transport to and from surface waters or impoundments, and in chemical engineering of the design of treatment systems and/or reactors, such as scrubbers.

Gas-phase transport resistance is also important in relation to heat transport. In certain cases, an analogy between the heat-transport and mass-transport equations may be made such that the solution for one can be used

to develop the solution for the other. The analogy is often relied upon to develop transport parameters, particularly for geometries in which it is easier to measure heat transport rather than mass transport (Bird et al., 1960). For example, an early investigation in heat transport in the airway bifurcation of dogs (Johnson & Linderoth, 1976) subsequently has been used to develop mass transport parameters using the analogy. Similarly, nasal cavity heat-transport studies also have been used to derive mass transport relations for the nasal cavity (Nuckols, 1981). Based on the heat- and mass-transport analogy, it has been demonstrated that the nasal cavity of laboratory animals is more efficient than humans in scrubbing and heating even when differences in volumetric flow rate and airway wall temperatures are considered (Hanna et al., 1989). The efficiency associated with the airways of laboratory animals is most likely associated with the role of the respiratory tract in thermoregulation for these animals, whereas in humans it is almost inconsequential.

The gas-phase resistance is represented by the region in which the temperature (or concentration) gradient exists (Figure 5). The resistance is sometimes identified as being synonymous with a boundary layer used in fluid mechanics to indicate where the boundary of a surface plays an important role. In the case of flow through a tube, the velocity at the wall is zero and rises very rapidly perpendicular to the tube wall. This region is the momentum boundary layer. Similarly, a heat-transport boundary layer and a mass-transport boundary layer exist in airways. These boundary layers represent not only the temperature or concentration gradient but also the resistance to transport across the barrier. The thinner the concentration boundary layer over which the concentration difference is established, the less resistance there is to transport. In Figure 5, the interfacial gas-stream compartment essentially represents the concentration boundary layer. Because the momentum boundary layer also affects the concentration boundary layer, the gas-phase resistance is dependent on the volumetric flow rate. Hence, the gas-phase mass-transport coefficient (k_g), which is a measure of this resistance, is a function of flow rate.

As noted earlier, measurement of the heat transport coefficient is generally easier than the gas-phase mass-transport coefficient (k_g) since the temperature of the conduit wall is more easily controlled than the concentration of the wall. However, techniques have been developed to directly measure k_g such as was used for the human nasal cavity (Hanna & Scherer, 1986; Lou, 1993). Alternatively, numerical calculation of the mass transport boundary layer such as those used in the computational fluid dynamics analysis of the nasal cavity (Cohen-Hubal et al., 1996), can establish the boundary condition from which to calculate the k_g . However, in either of these methods, care must be taken that the boundary layer is developed similar to that as would occur in the nasal cavity itself. In practice, this requires that the concentration boundary layer in the system for which

Boundary Layer Concept

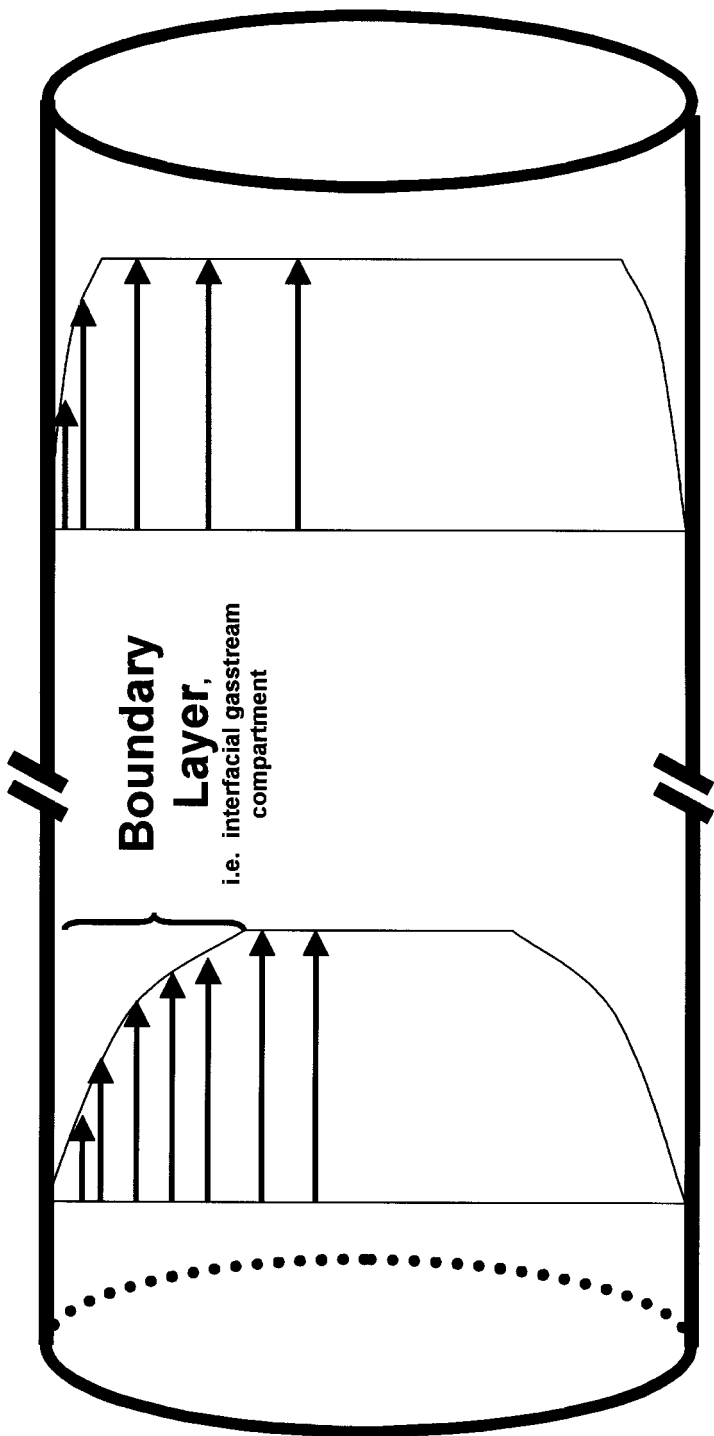


FIGURE 5. Boundary layer concept. The arrows indicate the magnitude of the local gas-stream concentration, temperature, or velocity. The thinner boundary layer, as indicated by the sparser and less parabolic arrows on the right, will have lower transport resistance.

the k_g is to be determined must be sufficiently developed to be similar to that in the airways. Otherwise, the measured k_g would be much greater than in the physiological system.

Defining the resistance in this gas-phase boundary layer, as well as the resistance to transport in the surface liquid and tissue, is the basis for parameterizing the RfC dosimetric model. The mass balances are developed as already described except that the details of the flux and metabolic losses are incorporated into the transport resistance term defined separately for each compartment and summed to characterize the overall transport resistance from the central gas stream to blood (Figure 2). The transport resistance for a specific gas is expressed using mass-transport coefficients for each compartment, or summed as an overall K_g , may be empirically derived or analytically developed from the solution of Fick's Law. Because of the complex airflow in the nasal cavity in particular, the gas-phase transport coefficients, k_g , generally have been determined empirically, although recent numerical methods using a finite element mesh developed from cross sections of the airway have been used (Cohen-Hubal et al., 1996).

To utilize the mass-transport coefficients, the flux equation does not differ much from that previously presented in Eq. (3), which is a simple form of Fick's Law. Fick's Law states that the flux within a region, or the mass transport rate, dm/dt is directly proportional to the concentration gradient in the tissue such that

$$\text{Flux} = \frac{1}{SA} \left(\frac{dm}{dt} \right) = -D \frac{dC}{dx} \quad (10)$$

where the flux into the surface liquid/tissue is in units of mass/time-cm², dm/dt is the mass transfer rate (mass/time), SA is the surface area, D is the diffusion coefficient, C is the concentration, and x is distance into the surface liquid/tissue. The flux is simply determined from the parameters that have been measured during inhalation studies based on the following relationship:

$$\text{Flux} = \frac{\dot{V}_E}{SA} (C_i - C_x) \quad (11)$$

where C_i and C_x are the inlet and outlet concentrations, and \dot{V}_E is the ventilation rate, or the volume flow rate during unidirectional flow. Species-specific minute volume is used in place of volumetric flow rate due to the averaging between inhalation and exhalation. Similar to that in Eq. (5), the gas-phase mass-transport coefficient k_g (in units of cm/s) can be substituted for the permeability coefficient such that

$$\text{Flux}_{(a-i)} = k_g (C_a - C_i) \quad (12)$$

where the concentration gradient ($C_a - C_i$) is the difference between the concentration in the central gas-stream compartment and the concentration in the gas interfacial compartment immediately adjacent to the airway wall.

Similar to the relationships defined in the perfusion-limited example, it is relatively easy to convey the RfC model for evaluating gas-phase transport resistance in terms of extraction and clearance parameters. Indeed, an expression of this relationship, at a single flow rate, was recently demonstrated by Andersen and Sarangapani (this issue). A generalized form of the relationship is developed later.

In formulating the RfC dosimetric method, the fractional penetration (f_p) is used to describe the fraction of the gas concentration exiting a control volume to that entering the control volume. The change in mass traversing the gas phase of the extrathoracic (ET) region is balanced by the mass absorbed at the gas-liquid interface of the airway. This balance is written as:

$$\dot{V}_E \frac{dC}{dx} = -K_g a (C_i - C_{b/g}) \quad (13)$$

where \dot{V}_E is the volumetric flow rate; dC/dx is the rate of change of the gas-stream concentration (gas phase) as a function of distance into the airway, x ; K_g is the overall mass-transport coefficient between the gas stream and the blood in the ET region; a is the local airway perimeter; C_i is the inspired gas concentration; and $C_{b/g}$ is the gas concentration that would be in equilibrium with the blood concentration. $C_{b/g}$ is equal to the ratio of the blood concentration, C_b , to the blood:gas (air) partition coefficient, $H_{b/g}$.

To evaluate the change in concentration over the length of a region, Eq. (13) is integrated, resulting in the following relationship:

$$\frac{(C_{out} - C_{b/g})}{(C_{in} - C_{b/g})} = e^{(-K_{gET} a L \dot{V}_E)} \quad (14)$$

where C_{out} is the gas concentration exiting the region during inhalation and L is the length of the airway such that the product of a and L is the surface area of the region, SA . Equation (14) indicates that C_{out} will equal the concentration entering the region, C_{in} , at an infinite volumetric flow rate.

In the case of Category 1 and, to some degree, Category 2 gases, C_{out} and C_{in} are much greater than $C_{b/g}$, so that Eq. (14) can be further reduced to

$$f_p = \frac{C_{out}}{C_{in}} = e^{(-K_g SA \dot{V}_E)} \quad (15)$$

where f_p is the penetration fraction through the region and is given as the ratio of the gas concentration exiting the region, C_{out} , to the gas concentration entering the region, C_{in} . The relationship shown in Eq. (15) suggests that the product of the overall mass-transport coefficient and the surface area may be obtained by plotting f_p as a function of volumetric flow rate. Indeed, many investigators have used this method to empirically model results (Aharonson et al., 1974; Kleinman, 1984; Morris & Blanchard, 1992).

The fraction removed or extracted from the airway is given by $1 - f_p$ or

$$E = 1 - f_p = \frac{(C_{in} - C_{out})}{C_{in}} = 1 - e^{-K_g SA \dot{V}_e} \quad (16)$$

Hence, clearance from the gas stream is simply

$$Cl = \dot{V}_e E = \dot{V}_e (1 - e^{-K_g SA \dot{V}_e}) = \dot{V}_e (1 - f_p) \quad (17)$$

It should be noted that Eqs. (17) and (18) appear similar to the parallel tube model of perfusion-limited clearance as developed by Pang and Rowland (1977) as opposed to a single well-stirred compartment. The similarity is complete if the intrinsic clearance is assumed to be equal to the overall mass transport coefficient (K_g) multiplied by the surface area of the control volume. However, this general assumption is appropriate only if the exponential term can be approximated through a power series expansion such that

$$Cl = \dot{V}_e (1 - e^{-K_g (SA \cdot \dot{V}_e)}) = \dot{V}_e \left[1 - \left(1 + K_g \frac{SA}{\dot{V}_e} \right) \right] = K_g SA \quad (18)$$

For this to be the case, the exponent ($K_g \cdot SA \cdot \dot{V}_e$) must be small. The error of this approximation is less than 10% if the value for K_g (keeping SA and \dot{V}_e constant) is less than 0.2. The error becomes greater than 100% as K_g approaches values of 1.0 and greater.

Recall that clearance is defined as the equivalent volume/time of the gas stream that would have been completely cleared of the toxicant. It is therefore a volume/time cleared as opposed to the mass of the toxicant/time that is cleared. The preceding formulation maintaining the exponential term in Eq. (17) and (19) can be used to develop the relationship between the clearance and the flux. The final form of the relationship will depend on whether the power-series expansion is appropriate for the particular gas and animal species.

RfC DOSIMETRY APPROACH

The RfC methods rely on a categorization scheme to classify gases into groups based on their physicochemical and toxicological (e.g., loca-

tion of observed lesions) properties. This approach, which defines model structure, allows for the selection of a dosimetric model to analyze the uptake of each gas using the fewest number of parameters necessary to evaluate the dosimetric adjustment from animals to humans.

The penetration fraction model first developed by Aharonson et al. (1974) was used as the basis for the RfC dosimetric method. The model is essentially a control volume mass-balance approach, as described above, in which the variable used to describe earlier, is the penetration fraction (f_p). As noted, f_p is the ratio of the gas concentration exiting a region to the concentration entering the region and is related to the extraction ratio (E), as shown in Eq. (17). As shown in Eq. (17), the principal determinants of f_p , or the extraction ratio, are the surface area of the region, the ventilation rate through the region, and the overall mass transport coefficient (K_g).

The derivation of the overall mass transfer coefficient (MTC), k_g' , using Fick's Law of Diffusion [Eq. (10)] is shown as the proportionality constant relating the flux to the concentration gradient defined as the difference between the central gas stream and the blood concentration. The mass transport coefficient (K_g) is therefore related to flux as

$$\text{Flux} = D \frac{dC}{dx} = \frac{D}{\Delta x} \Delta C = K_g \Delta C \quad (19)$$

where, in this example, a simple system is envisioned with no reaction. Hence, under these circumstances, K_g is simply the diffusion coefficient divided by the distance over which the gradient occurs and is similar to the permeability relation. As defined earlier, the flux (i.e., the total chemical mass uptake per surface area per time) is the product of the overall mass-transport coefficient (K_g) and the concentration gradient across the transport phases of the airway control volume consisting of gas stream, respiratory-tract surface liquid and/or tissue layer, and blood. If there were a reaction, K_g would no longer be defined simply by D/dx as given in this example but rather would be derived to account for the reaction. Examples of analytic solutions for K_g that include reactions may be found in the engineering literature (Cussler, 1984; Bird et al., 1960; Marshall & Pigford, 1947). The development of K_g to account for toxicant transport through the various transport phases, and incorporating reactions without requiring extensive numerical calculations or compartments, is a major objective of the RfC dosimetry model.

The conceptualization of chemical mass transport across gas, liquid/tissue, and blood phases can be simplified by viewing the overall mass transport coefficient (K_g) as a measure of the conductivity of a chemical across the three phases, as shown in Figure 2 and discussed previously [Eq. (1)] for only the gas phase and surface liquid/tissue. Incorporating the blood, the general form of the overall mass-transport resistance, the reciprocal of the overall K_g , is expressed as the sum of the resistance through

the gas, liquid/tissue, and blood phases, respectively, and is given by Eq. (3) where k_g is the gas-phase mass-transport coefficient, k_l the liquid/tissue-phase mass transport coefficient, $H_{l/g}$ the liquid/tissue to gas partition coefficient, F the flux fraction (to account for the fraction reacted in the previous transport phase), S_p the available surface area to the bloodstream, $H_{b/g}$ the blood to gas partition coefficient, and Q_b the regional blood flow.

The significance of Eq. (3) is that there can be a determination of which phase is controlling or limiting absorption and, hence, the extent of modeling necessary to determine dosimetry. Thus, if the first term, $1/k_g$, is much greater than the other two terms, there is no need to establish parameters for the other terms. The dose can be determined on the basis of the gas phase (k_g) alone, thereby also reducing the number of compartments required to model the absorption of the gas. Similarly, to determine the need to incorporate blood flow, the third term, $FS_p/H_{b/g}Q_b$, would be compared to the other terms. It is through this analysis of the mass transport resistance that the RfC approach informs the necessary model structure to develop the DAF. An example of the resistance comparison is shown in Table 3.

In Table 3, resistance ratios are shown as calculated for ethanol, acetone, ethyl acetate, and xylene. Ethanol is designated as Category 1 because the transport resistance clearly is associated with the gas phase. Similarly, xylene is designated Category 3 because of the control of the blood indicated by its large resistance. Acetone and ethyl acetate are designated as Category 2 gases in which the gas does accumulate in the blood. With longer exposures, Category 2 gases such as acetone would effectively be modeled as a Category 3 gas. Thus, exposure time must be considered in assigning a gas into a category. Furthermore, because anatomic parameters are incorporated into the resistance terms, the categorization may also be species dependent.

MODEL STRUCTURES

Parallel with the development of the RfC method, several compartmental models, such as PBPK models (Morris et al., 1993; Bush et al., 1998), have been developed to model gas-transport processes while maintaining extensive detail in anatomy, physiology, and toxicology. Because any single model may not be applicable to the wide range of toxic gases

TABLE 3. Categorization using resistance ratio

Parameter	Overall resistance = gas resistance + tissue resistance + blood resistance			
	$(1/K_g)$	$(1/k_g)$	$(1/H_{g/l}k_l)$	$(FS/H_{l/g}k_{rx}Q_b)$
	Ethanol	Acetone	EtAc	Xylene
Resistance ratio (liquid:gas)	0.048	0.36	0.85	2.3
Resistance ratio (blood:gas)	0.1	0.9	2.8	7.6
Category	1	2	2	3

of concern, or may overparameterize the modeling, resulting in inclusion of unnecessary parameters that add to the uncertainty particularly when the model is fit (Kohn, 1997), the RfC approach was developed to simplify the dosimetry for those gases with limited information available such as the hazardous air pollutants (HAPs). The categorization was conceptualized and a DAF default methodology developed so as to rely on readily available physicochemical parameters of a gas, such as solubility and reactivity, while also providing adjustment for the distinct differences between the anatomy and physiology of the species of interest, such as rats and humans.

Beyond developing a method to estimate a default DAF, the RfC approach has also demonstrated its utility in informing model structure by determining which transport barriers need to be included. As discussed earlier, if the gas-phase mass transport resistance ($1/k_g$) is small, the dynamics of a mass concentration gradient in the gas phase need not be incorporated into the model. Therefore, the RfC approach may be used to simplify model structure.

Another advantage of the RfC approach is that the transport resistances (e.g., k_g for the gas phase) used in the RfC approach are based on the actual concentration gradient, either from analytical solutions of Fick's Law or, in the gas phase, empirical as well as analytic determinations. This approach has advantages over the recent efforts to apply a PBPK approach for modeling absorption in the nasal cavity because of the limitations of compartmental models to effectively model concentration gradients (Morris et al., 1995; Bush et al., 1998). Within these models, the tissue compartment sizes have been held constant and the concentrations within those compartments assumed to be well mixed. The accuracy with which these models can predict the actual concentration gradient therefore is limited by the compartment sizes and reaction rates considered.

Differences between model structures and model results for the same chemical have been attributed, in part, to the modeling approach taken with respect to the concentration gradient (Kohn, 1997). Modelers must evaluate this relationship before relying on any single model and associated compartment dimensions and time steps. Compartmental models may produce results dependent on compartment size when metabolism is incorporated because of the inability of compartmental models to simulate the concentration gradient during simultaneous diffusion and reaction unless the compartment size is scaled to the reaction rate. This is illustrated below using a one-dimensional model of transport into the surface liquid/tissue.

In Figure 6, transport is considered to occur from the gas to mucus through several epithelial layers and into the blood. Using the dimensions of the compartments in the PBPK approach, the concentrations and fluxes were calculated assuming the well-mixed compartment of the PBPK models, as well as utilizing a finite difference solution of Fick's Law. As indicated, both the fluxes and the concentrations for the compartmental models are increas-

Comparison of Well-Mixed Compartment Concept to Diffusion Concept to Address Transport in Tissues

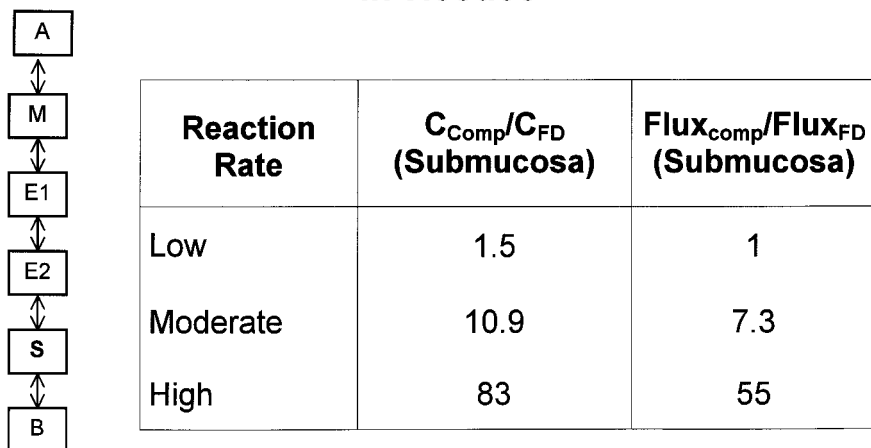


FIGURE 6. Comparison of compartmental analysis versus finite difference solution for transport through various tissue compartments lining the respiratory tract. Calculations are shown for submucosa (S) compartment (bold). M, mucus; E1, epithelial compartment 1; E2, epithelial compartment 2; E3, epithelial compartment 3; and B, blood. Subscript comp refers to the compartmental model solution, while FD refers to the finite difference solution.

ingly overestimated as the reaction rate increases. Not only do the results indicate higher doses to the tissue, but also they will mistakenly suggest lower doses beyond the region. Therefore, compartmental models using well-stirred compartments must consider the reactivity of the absorbing gas in determining the compartment size so as to adequately predict the concentration gradient.

For more complex analyses, PBPK model solution consistency can only be assured through correlating compartment dimensions with reaction rates such that the solution does not depend on compartment dimensions. Indeed, as reaction rates or metabolism increases, the compartment sizes will need to become so small that the methodology becomes equivalent to the finite difference numerical approach. By contrast, numerical solutions to the mass transport equations eliminate the concern for establishing the correct compartment sizes (and volumes).

Short of these numerical methods, the RfC approach provides an alternative. Through the use of the overall mass transport coefficient, the concentration gradient is retained within the analysis and thereby maintains a more realistic assessment of flux and concentration profile from which dose metrics such as average concentration, peak concentration, and mass of metabolite generated may be determined. Thus, although the default RfC approach used flux as the dose metric to flux, the approach can nonetheless

be extended to consider other dose metrics, as well as other specific tissue considerations defined by the mode of action of the toxicant.

FUTURE DIRECTIONS AND RESEARCH NEEDS FOR THE RfC METHODS

The DAF across species for Category 1 and Category 2 gases must be sufficiently robust to consider the numerous physicochemical properties of the gases for which RfCs must be derived, while also restricting the number of needed parameters since data are often sparse. For this purpose, detailed finite difference solutions that had been developed previously (Hanna et al., 1989) were set aside in favor of a conceptual model that relied on the flux across the gas-tissue interface as the dose metric. Because the flux is proportional to concentration, it may also be considered a surrogate for the concentration as the dose metric. The flux is quantified by parameterizing the gas-phase, liquid/tissue-phase, and blood-phase transport resistances that can be scaled for differing physicochemical properties of an inhaled gas. The conceptualized RfC dosimetric model based on specific gases for which extensive data exists thereby informs the general RfC model scaling of gases for which limited data exist.

The gas-phase mass-transport coefficient (k_g) can be scaled to any gas of interest simply through a scaling of the gas diffusivity. The transport coefficient, however, is highly dependent on the complexity of the airway morphometry and the airflow patterns induced by the morphometry. Thus, the overall mass-transport coefficient (K_g) is highly species specific. Furthermore, airway morphometry, particularly in the upper airways, can vary significantly dependent on ventilatory patterns, as well as ambient air temperature. For example, in humans, exercise results in nasal decongestion to reduce airflow resistance, while cold exposure may increase congestion to increase heat exchange (although nasal surface temperatures may decline).

For the RfC methods, gas-phase mass-transport coefficients are under development for humans and several animal species (Lou et al., 2001; Jarabek et al., 2001). The coefficients for the human nasal cavity are based on the airway morphometry obtained from computed tomography (CT) scans of several individuals and are therefore more likely representative of the true airway morphometry than those developed from cadaver-casted models (Lou, 1993). A comparison of the transport coefficients obtained in geometries from CT scans of living and cadavers demonstrated significant differences in transport (Lou, 1993).

The gas-phase transport coefficients in several animal species were obtained from analyses of uptake studies for specific gases during unicyclic flow studies. The transport coefficients developed from these specific gases have been verified by comparison of the predicted absorption to available absorption studies for other gases. In the analyses, the variability in nasal

morphometry and its influence on the transport coefficients could not be analyzed. Nonetheless, the analyses demonstrated significant influence of ventilation on the quantification of absorbed mass. These calculations are being compared to computational fluid dynamic calculations such as that by Kimbell and Subramaniam (this issue) to derive default k_g estimates at different flow rates (Jarabek et al., 2001).

For the tissue and blood phases, the mass-transport coefficients are formulated from solutions of Fick's Law. The tissue/blood transport coefficients require several physicochemical parameters, as well as physiologic/anatomic parameters for quantification. The species differences in the transport through the tissue phase and blood phase are determined mostly by species-specific metabolic activity in the tissue as well as airway dimensions and blood flow. Formulations for the mass transport coefficients rely on knowledge of the reaction type, that is, whether the reaction is first-order or saturated.

Because the RfC approach informs model structure, extension of the RfC framework into a suite of models for the respiratory tract, based on explicit consideration of the mode of action and corresponding different dose metrics, is underway as part of a U.S. EPA interagency project (Jarabek, 2000; Hanna & Jarabek, 2000). PBPK models such as those presented elsewhere in this issue are anticipated to be very informative in developing appropriate dose metrics for consideration. Development of robust data on physicochemical and toxicokinetic properties for specific gases or classes of gases will be necessary to develop appropriate DAFs outside the set of chemicals for which the robust models are developed. Furthermore, obtaining anatomical and physiological parameters for both sexes at various ages in both laboratory animal species and humans will further extend the understanding of the determinants of the DAF, their variability, and potential uncertainties when used to extrapolate across species.

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