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19. ABSTRACT (Continue on reverse if necessary and identify by block number) We have been studying how to use compartmental models to reliably extrapolate toxicologic experiment results from one animal species to another with the ultimate goal of useful extrapolation to man. We have taken as the fundamental core of our analysis the physical necessary equations describing mass balance. These equations are the classical Fickian equations of the form $VdC/dt = Q(a-v)$. These equations are not a complete set since they are insufficient to provide estimation of venous arterial or tissue concentrations with time. Therefore, the mass balance equations must be augmented with additional phenomenological relations to permit the desired calculations. Many investigators use the venous exit condition. While it is clear how to extrapolate the mass balance equations from one sized animal to another or from one species to another, it is not clear how to extrapolate the venous exit condition. In this research we have evaluated the venous exit condition by comparing it with approximate analyses of perfusion and substance diffusion in the tissue.			
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Animal-to-Human Extrapolation Using Compartmental Models

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MEDINA, R. L. AND R. A. ALBANESE. *Animal-to-human extrapolation using compartmental models*. NEUROSCI BIOBEHAV REV 15(1) 57-61, 1991.—We have been studying how to use compartmental models to reliably extrapolate toxicological experimental results from one animal species to another with the ultimate goal of useful extrapolation to man. We have taken, as the fundamental core of our analysis, the physically necessary equations describing mass balance. These equations are the classical Fickian equations of the form $VdC/dt = Q(a - v)$. These equations are not a complete set since they are insufficient to provide estimation of venous, arterial, or tissue concentrations with time. Therefore, the mass balance equations must be augmented with additional phenomenological relations to permit the desired calculations. Many investigators use the venous exit condition. While it is clear how to extrapolate the mass balance equations from one sized animal to another or from one species to another, it is not clear how to extrapolate the venous exit condition. In this research we have evaluated the venous exit condition by comparing it with approximate analyses of perfusion and substance diffusion in the tissue.

Fickian equation Extrapolation	Venous exit condition Partial differential equation	Compartmental modeling	Diffusion model	Mass balance
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THIS report describes research the authors have pursued concerning compartmental modeling in toxicology with particular regard to the problem of animal-to-man scale up. Several benefits would accrue if medical scientists could reliably extrapolate biological effects findings from one sized animal to another, or from one species to another. For example, imagine that, in mice, a chemical administered for 3 months at a daily dose D results in an increment in cancer C, where $C = f(D)$, when the presence or absence of cancer is determined by autopsy performed when the mice reached 2 years of age. Given the data based equation, $C = f(D)$, for mice, what relation between cancer and exposure might exist for man? The question concerning man would usually go beyond a regimented daily dose D given only for a standard 3-month period, and concern for cancer would extend for the entire human life span.

This article addresses the introduced class of problems. The approach applied to this problem is compartmental modeling. We believe the prospects for this endeavor can be favorable as is already indicated in the pharmacokinetics literature. In this article, we will address the general methodology of extrapolation using compartmental modeling, and will not be treating a specific application.

TWO PLAUSIBLE APPROACHES TO COMPARTMENTAL MODELING

For purposes of discussion we will use the block diagram shown in Fig. 1. Figure 1 represents a simplified version of Ramsey and Andersen's PB-PK model, which described the pharmacokinetics of styrene in rats and humans during and after inhalation exposure (9).

In the setting of this block model, the following mass balance equations are applicable:

$$V_L dC_L/dt = Q_L(v - a)$$

$$\begin{aligned} V_n dC_n/dt &= Q_n(a - v_n) \\ V_{ad} dC_{ad}/dt &= Q_{ad}(a - v_{ad}) \\ V_{abs} dC_{abs}/dt &= Q_{abs}(a - v_{abs}) + k_{abs}(X_s - C_{abs}) \\ V_{exc} dC_{exc}/dt &= Q_{exc}(a - v_{exc}) - \lambda C_{exc} \\ Qv &= Q_n v_n + Q_{ad} v_{ad} + Q_{abs} v_{abs} + Q_{exc} v_{exc} \end{aligned}$$

(EQUATION 1)

The five symbols, V_j , represent compartment volumes and the five symbols, Q_j , are compartment flows. The symbols C_j refer to substance concentration in each organ. The following subscript convention is used: L designates the lung, n designates nonadipose tissue, ad designates adipose tissue, abs designates the absorbing organ (for example, the intestine or integument), and exc designates the excretory organ (for example, the kidney). The symbol a refers to the arterial concentration of substance, v refers to the combined venous concentration and the symbols v_j refer to concentrations of material in the venous outflow of the individual organs (excluding the lung). The symbol X_s corresponds to an external substance concentration impinging on the absorbing surface.

These equations are all a direct reflection of the principle of conservation of matter (3). Except for the $k_{abs}(X_s - C_{abs})$ and λC_{exc} terms, which are not necessarily applicable, these equations must be true in any compartmental system because they are based on physical principles. In these equations the V_j , Q_j , k_{abs} and λ terms are considered known, but the C_j , a, v and v_j terms are not. Thus, there are eleven unknown variables and only six equations. Therefore, the question arises of how to complete these equations, or close the set, so the C_j , v and v_j values can be cal-

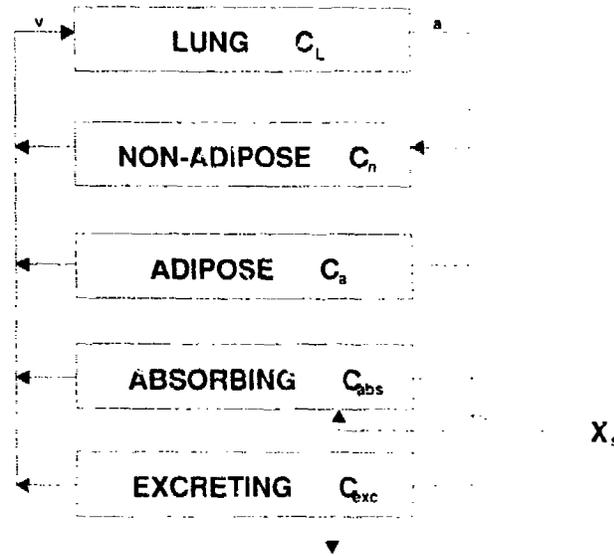


FIG. 1. A five compartment block diagram of a physiological pharmacokinetic model studied in this paper.

culated given V_j , Q_j , k_{abs} , and λ .

One way to complete the mass balance equation set is through use of the *venous exit condition* (8). This condition asserts that blood flowing out of an organ always has a substance concentration proportional to the concentration of the substance in the organ. The following venous exit condition equations can be written to complete the mass balance set.

$$\begin{aligned} a &= \alpha_L C_L \\ v_n &= \alpha_n C_n \\ v_{ad} &= \alpha_{ad} C_{ad} \\ v_{abs} &= \alpha_{abs} C_{abs} \\ v_{exc} &= \alpha_{exc} C_{exc} \end{aligned} \quad (\text{EQUATION 2})$$

The coefficients α_j may be thought of as simply constants of proportionality or may be thought of, more specifically, as inversely proportional to the partition coefficients (9). The venous exit condition is a simple algebraic expression which may or may not hold true in any given case. This condition is an attempt to approximate a complex perfusion-diffusion system actually governed by partial differential equations (8).

It is possible to complete or close the mass balance equations in a second way. Recognizing that transport into an organ compartment occurs through a diffusion process, approximate diffusion equations may be written (6,7). We have used the following diffusion approximation closure equations:

$$\begin{aligned} V_L dC_L/dt &= -k_L [C_L - (a + v)/2] \\ V_n dC_n/dt &= -k_n [C_n - (a + v_n)/2] \end{aligned}$$

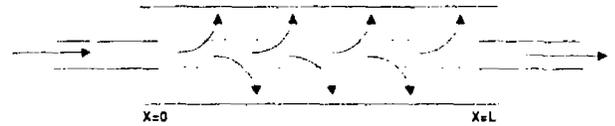


FIG. 2. The proposed perfusion-diffusion model showing substance diffusion into a tissue segment supplied by a central blood vessel.

$$\begin{aligned} V_{ad} dC_{ad}/dt &= -k_{ad} [C_{ad} - (a + v_{ad})/2] \\ V_{abs} dC_{abs}/dt &= -k_{abs} [C_{abs} - (a + v_{abs})/2] + k_{abs} (C_s - C_{abs}) \\ V_{exc} dC_{exc}/dt &= -k_{exc} [C_{exc} - (a + v_{exc})/2] - \lambda C_{exc} \end{aligned} \quad (\text{EQUATION 3})$$

Thus, we now have two complete compartmental models corresponding to Fig. 1. A part of each model is physically exact, being based on conservation of matter. However, each model also contains mathematical expressions that do not exactly reflect physical laws, but are approximations. Specifically, the approximations in the models use algebraic or ordinary differential equations when the perfusion-diffusion phenomena in tissue is actually governed by partial differential equations (8). Two questions immediately arise. First, which of the two-compartmental models will best describe substance pharmacokinetics in a living animal? Second, which of these two models is most accurate when used to extrapolate from a smaller to a larger animal?

The best way to answer these two questions is through the use of extensive data obtained from different sized animals, for example, rats and humans. Since the large data sets needed were not available to us we have pursued an alternative analysis of the competing compartmental models. We have compared the venous exit and diffusion approximation models to a simple perfusion-diffusion system governed by partial differential equations for which analytic mathematical solutions exist. This test perfusion-diffusion system exhibits, qualitatively at least, much of the actual substance movement behavior of tissue. We have determined how well the compartmental models approximate this exact perfusion-diffusion system, and we have studied how well the compartmental models follow a scale-up of the exact system.

AN EXACT PERFUSION-DIFFUSION SYSTEM

We propose to examine and develop an exact solution of the Sangren and Sheppard model of tissue clearance (4,10). We consider a Krogh cylinder (4, 10, 11) of length L as diagrammed in Fig. 2. The tissue segment is supplied by a central blood vessel with volume γ and the concentration of the substance in the blood $B(x,t)$, varies as a function of linear position and time. Let $C(x,t)$ be the concentration in the tissue itself. Assuming simple diffusion across the vessel wall and no axial or radial diffusion in the tissue, the following equations apply:

$$\begin{aligned} \gamma \partial B(x,t)/\partial t &= k[C(x,t) - B(x,t)] - \gamma \mu \partial B(x,t)/\partial x \\ V \partial C(x,t)/\partial t &= -k[C(x,t) - B(x,t)] \end{aligned} \quad (\text{EQUATION 4})$$

In these equations, $B = B(x,t)$ is the concentration of substance

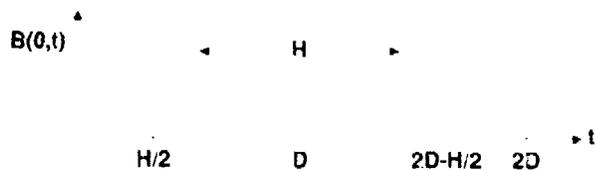


FIG. 3. The substance temporal profile in the blood entering the Krogh cylinder.

in the blood, $C = C(x,t)$ is the concentration of substance in the tissue, γ is the volume of blood in the tissue, μ is the velocity of blood flow in the tissue, V is the tissue volume, and k is the permeability constant for the vessel wall.

We have taken $B(0,t)$ to be the trapezoidal function of time t shown in Fig. 3. This function has the following Fourier series representation (1):

$$B(0,t) = (1/2) - 4/[\pi^2(1-2p)] \sum_{j=1,3,\dots}^{\infty} (1/j^2) \cos(j\pi p) \cos(\omega_j t)$$

where $\omega_j = j\pi/D$ and $p = H/2D$. Using this Fourier series representation, equation 4 can be readily solved to find

$$B(x,t) = (1/2) - 4/[\pi^2(1-2p)] \sum_{j=1,3,\dots}^{\infty} (1/j^2) \exp(-\psi_j x/\mu) \cos(j\pi p) \cos\{\omega_j(t - \theta_j)\}$$

and

$$C(x,t) = (1/2) - 4(k/V)/[\pi^2(1-2p)] \sum_{j=1,3,\dots}^{\infty} (1/j^2) \exp(-\psi_j x/\mu) \cos(j\pi p) \{[\omega_j/(\omega_j^2 + (k/V)^2)] \sin[\omega_j(t - \theta_j)] + [(\mu/V)/(\omega_j^2 + (k/V)^2)] \cos[\omega_j(t - \theta_j)]\}$$

where

$$\Psi_j = \omega_j^2 (k/\gamma)/(\omega_j^2 + (k/V)^2)$$

$$\theta_j = (x/\mu) \{ \omega_j^2 + (k^2/V) \} / \{ (\mu/V) + (1/\gamma) \} / (\omega_j^2 + (k/V)^2)$$

Mean tissue substance concentration $\text{ave}[C(t)]$ can be calculated as:

$$\text{ave}[C(t)] = (1/L) \int_0^L C(x,t) dx$$

whence

$$\text{ave}[C(t)] = (1/2) - 4(k/V)/[\pi^2 L(1-2p)] \sum_{j=1,3,\dots}^{\infty} (1/j^2) \cos(j\pi p)$$

$$\{ [\xi_1(\xi_2 + \xi_3) + \xi_6(\xi_4 + \xi_5)] \sin(\omega_j t) + [\xi_1(-\xi_4 - \xi_5) + \xi_6(\xi_2 + \xi_3)] \cos(\omega_j t) \}$$

where

$$\xi_1 = \omega_j/(\omega_j^2 + (k/V)^2)$$

$$\xi_2 = [1/(\alpha_j^2 + (\omega_j \beta_j)^2)] [-\alpha_j \cos(\omega_j \beta_j L) + (\omega_j \beta_j) \sin(\omega_j \beta_j L)] \exp(-\alpha_j L)$$

$$\xi_3 = \alpha_j/(\alpha_j^2 + (\omega_j \beta_j)^2)$$

$$\xi_4 = [1/(\alpha_j^2 + (\omega_j \beta_j)^2)] [-\alpha_j \sin(\omega_j \beta_j L) - (\omega_j \beta_j) \cos(\omega_j \beta_j L)] \exp(-\alpha_j L)$$

$$\xi_5 = (\omega_j \beta_j)/(\alpha_j^2 + (\omega_j \beta_j)^2)$$

$$\xi_6 = (k/V)/(\omega_j^2 + (k/V)^2)$$

$$\alpha_j = \psi_j/\mu$$

$$\beta_j = (1/\mu) \{ \omega_j^2 + (k^2/V) \} / \{ (\mu/V) + (1/\gamma) \} / (\omega_j^2 + (k/V)^2)$$

In the exact perfusion-diffusion model, $\text{ave}[C(t)]$ is the value corresponding to the C_j terms in the compartmental approximations. Also $B(0,t)$ corresponds to substance concentration in in-flowing blood, while $B(L,t)$ corresponds to the concentration in tissue exiting blood.

COMPARING THE EXACT PERFUSION-DIFFUSION SYSTEM TO THE VENOUS EXIT AND APPROXIMATE DIFFUSION COMPARTMENTAL MODELS

For a specific compartment, the venous exit model is

$$VdC/dt + Q \alpha C = Q a$$

$$v = \alpha C$$

In this model, we take $a = B(0,t)$ and solve for C and v to be compared with $\text{ave}[C(t)]$ and $B(L,t)$ respectively from the exact perfusion-diffusion system.

Similarly, for a specific single compartment, the approximate diffusion model is

$$VdC/dt = Q(a - v)$$

$$VdC/dt = -k[C - (a + v)/2]$$

These equations are equivalent to

$$VdC/dt + [2kQ/(2Q + k)]C = [2kQ/(2Q + k)]a$$

$$v = [2k/(2Q + k)]C + [(2Q - k)/(2Q + k)]a$$

Again, we take $a = B(0,t)$ and solve for C and v to compare with $\text{ave}[C(t)]$ and $B(L,t)$ respectively from the exact perfusion-diffusion system.

We have contrasted the performance of the venous exit compartmental model and the approximate diffusion compartment model to the exact perfusion-diffusion system by treating rat and human liver. For the rat liver $V = 12 \text{ cm}^3$ and $Q = 35.2 \text{ cm}^3/\text{min}$

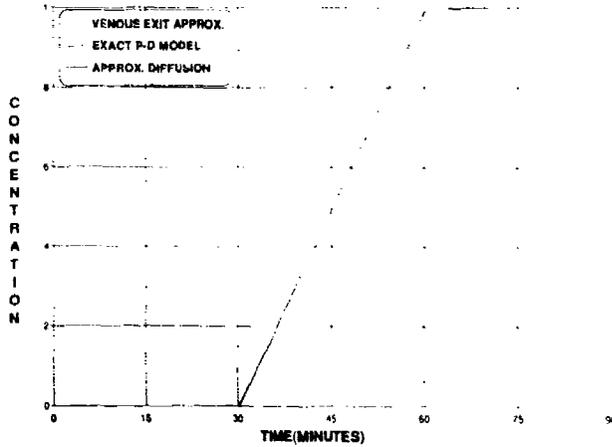


FIG. 4. Fitted data showing slow change in rat venous blood in: all three models.

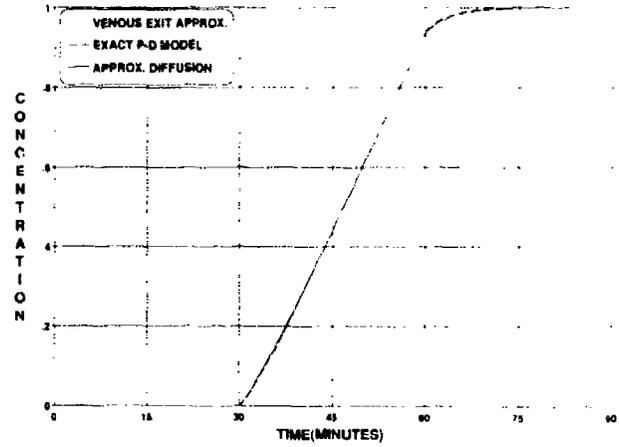


FIG. 6. Extrapolation results for man regarding the estimation of venous concentration.

min. For the human liver $V = 3320 \text{ cm}^3$ and $Q = 1800 \text{ cm}^3/\text{min}$ (9). We have used $V = 3.14 \times 10^{-5} \text{ cm}^3$ and $\gamma = 7.85 \times 10^{-8} \text{ cm}^3$ in the exact perfusion-diffusion model, assuming, for test purposes only, that both rat and human liver are made up of cylindrical regions 1-mm long, and $100 \mu\text{m}$ in radius with a central blood vessel having a $5 \mu\text{m}$ radius (2, 4, 5, 11). For the exact model, blood velocity was chosen to be 117 cm/min in the rat so the exact model would have a Q/V ratio of 35.2/12, and blood velocity was chosen to be 21.7 cm/min in the human to correspond to a Q/V ratio of 1800/3320.

Figures 4 through 7 show the results of our numerical experimentation. In these figures best fit α and k values were found so that the venous exit and approximate diffusion compartments best mimicked the rat exact model. Extrapolating the human liver situation, α was left unchanged while k was extrapolated using the relationship

$$\frac{(2k_{\text{rat}} Q_{\text{rat}})/(2Q_{\text{rat}} + k_{\text{rat}}) V_{\text{rat}}}{(2Q_{\text{man}} + k_{\text{man}}) V_{\text{man}}} = \frac{(2k_{\text{man}} Q_{\text{man}})}{(2Q_{\text{man}} + k_{\text{man}}) V_{\text{man}}}$$

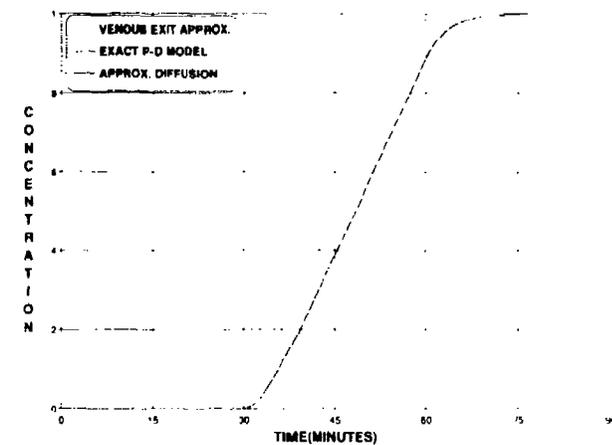


FIG. 5. Rat tissue concentration for all three models. Same parameters used which gave agreement in rat venous blood.

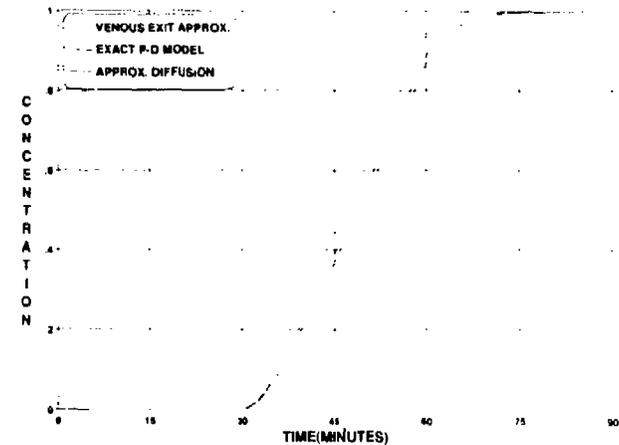


FIG. 7. Extrapolation results for man regarding the estimation of tissue concentration.

In Fig. 4 we see that all three models can be made to agree as regards a slow change in rat venous blood. However, in Fig. 5 we see that the same parameters which gave agreement in rat venous blood do not work as well for rat tissue concentrations. In particular, the venous exit condition provides a poorer quality fit to rat tissue concentrations.

To correspond to man, the exact perfusion-diffusion system blood velocity was changed from 117 cm/min to 21.7 cm/min. The parameter α was left unchanged for the venous exit model and k was adjusted as described before. In Fig. 6 we see that the venous exit model and diffusion approximation model both extrapolate well to man as regards the estimation of venous concentrations. However, as seen in Fig. 7, the venous exit condition again does not perform well regarding tissue concentrations.

The patterns found in Figs. 4 through 7 are amplified when faster changes in blood levels are studied. In these settings again the diffusion approximation model excels the venous exit model.

CONCLUSION

Compartmental models have a core set of mathematical relations which are derived from the physical principle of conservation of matter. This core set of equations is not sufficient for modeling, but must be augmented by auxiliary conditions. The venous exit condition is commonly used, and a diffusion approximation also is possible. These approximations use algebraic equations or ordinary differential equations to describe perfusion-diffusion phenomena in tissue governed by partial differential equations. We compared a venous exit model and a diffusion approximation model to an exact perfusion-diffusion model of tissue governed by partial differential equations. We have found

that the diffusion approximation model performs better than the venous exit model in mimicking the perfusion-diffusion system, particularly as regards the prediction of tissue concentrations. We were surprised to observe that a model that fits blood concentration changes well may not fit tissue concentration events.

Only more experience with a variety of substances and real world animal-to-human extrapolation efforts will provide secure guidance concerning choice among competing compartmental models. This report suggests that comparison of competing compartmental models to perfusion-diffusion models governed by partial differential equations may be an additional important guide to compartmental model selection.

REFERENCES

1. Beyer, W. H., ed. CRC standard mathematical tables. 28th ed. Boca Raton, FL: CRC Press, Inc.; 1987:405-406.
2. Copenhaver, W. M.; Kelly, D. E.; Wood, R. L. Bailey's textbook of histology. 17th ed. Baltimore: The Williams & Wilkins Company; 1978.
3. Dedrick, R. L. Animal scale-up. *J. Pharmacokinet. Biopharm.* 1: 435-461; 1973.
4. Gosselin, R. P.; Gosselin, R. E. The kinetics of solute clearance by a single tissue capillary of limited permeability: Explicit solutions of two models and their bounds. *Bull. Math. Biol.* 49:329-349; 1987.
5. Hennessy, T. R. The interaction of diffusion and perfusion in homogeneous tissue. *Bull. Math. Biol.* 36:505-526; 1974.
6. Jacquez, J. A. Compartmental analysis in biology and medicine. 2nd ed. Ann Arbor: The University of Michigan Press; 1985:11-13.
7. Landahl, H. D. An approximation method for the solution of diffusion and related problems. *Bull. Math. Biophys.* 15:49-61; 1953.
8. Perl, W. An extension of the diffusion equation to include clearance by capillary blood flow. In: Whipple, H. E., et al., eds. Multi-compartment analysis of tracer experiments. New York: New York Academy of Sciences; 1972:92-105. (*Ann. NY Acad. Sci.*, vol. 108, art. 1.)
9. Ramsey, J. C.; Andersen, M. E. A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. *Toxicol. Appl. Pharmacol.* 73:159-175; 1984.
10. Sangren, W. C.; Sheppard, C. W. A mathematical derivation of the exchange of a labelled substance between a liquid flowing in a vessel and an external compartment. *Bull. Math. Biophys.* 15:387-394; 1953.
11. Thews, G.; Hutten, H. Gas exchange in tissue. In: Hoppe, W., et al., eds. Biophysics of respiratory gas transport. New York: Springer-Verlag; 1983.

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