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A Lung Dosimetry Model of Vapor Uptake and Tissue Disposition
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A lung dosimetry model of vapor uptake and tissue disposition

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Abstract
Inhaled vapors may be absorbed at the alveolar-capillary membrane and enter arterial blood flow to be carried to other organs of the body. Thus, the biological effects of inhaled vapors depend on vapor uptake in the lung and distribution to the rest of the body. A mechanistic model of vapor uptake in the human lung and surrounding tissues was developed for soluble and reactive vapors during a single breath. Lung uptake and tissue disposition of inhaled formaldehyde, acrolein, and acetaldehyde were simulated for different solubilities and reactivities. Formaldehyde, a highly reactive and soluble vapor, was estimated to be taken up by the tissues in the upper tracheobronchial airways with shallow penetration into the lung. Vapors with moderate solubility such as acrolein and acetaldehyde were estimated to penetrate deeper into the lung, reaching the alveolar region where absorbed vapors had a much higher probability of passing through the thin alveolar-capillary membrane to reach the blood. For all vapors, tissue concentration reached its maximum at the end of inhalation at the air-tissue interface. The depth of peak concentration moved within the tissue layer due to vapor desorption during exhalation. The proposed vapor uptake model offers a mechanistic approach for calculations of lung vapor uptake, air:tissue flux, and tissue concentration profiles within the respiratory tract that can be correlated to local biological response in the lung. In addition, the uptake model provides the necessary input for pharmacokinetic models of inhaled chemicals in the body, thus reducing the need for estimating requisite parameters.

Keywords: Lung vapor uptake modeling, tissue dosimetry modeling, tissue uptake

Introduction
Calculations of vapor uptake by airways of the respiratory tract are paramount to study dose-dependent local effects and, in addition, systemic effects that may result from transport and disposition to other organs and tissues of the body. The lung dose of inhaled vapors provides the link between exposure concentration and biological response. Previous vapor dosimetry modeling efforts examined lung vapor uptake based on compartmental approaches (e.g. Haggard, 1924; Johanson, 1990; Kumagai & Matsunaga, 2000; Gloede et al., 2011; to name a few). Mechanistic models were also developed to study vapor uptake patterns and dose in the respiratory tract. Early mechanistic models examined vapor mixing, regional vapor concentration stratification and inhomogeneity in order to gain insight into airway function and structure. La Force and Lewis (1970) developed a mechanistic model to calculate the inhaled concentration of inert gases in the lung by numerically solving the diffusion equation. However, the simultaneous processes of convection and diffusion were not considered in the study. Consequently, Cumming et al. (1971), Scherer et al. (1972), Chang and Farhi (1973), and Paiva (1972, 1973) solved the convective-diffusion equation in the Weibel (1973) symmetric lung geometry to find air-phase vapor concentration throughout the pulmonary air space. The primary objective of these studies was to evaluate concentration stratification and its contribution to the slope of the alveolar plateau. Other investigators studied the effect of airway geometry based on the washout of inhaled inert gases, such as N₂, H₂, and SF₆, to examine lung structural changes (e.g. Baker et al., 1974; Paiva et al., 1972).
Inhalation Toxicology is useful for evaluating uptake of highly soluble and reactive vapors in the human respiratory tract. The model is a lung dosimetry model to predict uptake of inhaled vapors. Overton et al. (2001) also constructed a lung dosimetry model in rats to calculate ozone uptake in the lungs of guinea pigs, rabbits, and humans. The model was further extended by including tissue and blood compartments (Miller et al., 1985). Additionally, uptake of ozone in the lungs of children was investigated by using child-specific lung and breathing information (Overton & Graham, 1989). Overton et al. (1987) investigated the uptake of ozone in rats with symmetric lung geometries. The vapor uptake model in rats was extended to asymmetric lung geometries (Overton & Graham, 1995) for more detailed dose assessment. Bush et al. (1996, 2001) computed the uptake of ozone and chlorine in human lungs. Their predictions matched in vivo uptake measurements for ozone inhalation for different lung distal penetrations. Based on the same transport model developed earlier for ozone vapor uptake predictions, Overton et al. (2001) also constructed a lung dosimetry model to predict uptake of inhaled formaldehyde in the human respiratory tract. The model is useful for evaluating uptake of highly soluble and reactive vapors (Overton, 2001).

The aforementioned models were applicable only to vapors with first-order reaction rates in the tissue. While capable of predicting airway uptake and wall fluxes, these studies did not calculate tissue concentrations, which are needed to relate model predictions to effects observed in vivo, to study tissue damage and health risk impact. Thus, the models could not predict the systemic dose, from inhaled vapors, that was available to other organs of the body. For health risk assessment due to vapor exposure, tissue susceptibility in these studies was correlated to vapor flux to airway walls. However, the relationship between wall fluxes and tissue concentrations are not known and may not necessarily correlate proportionally. Additional studies are required to investigate the subsequent tissue concentration profiles while including metabolism and reaction of the vapor in the tissue by various pathways.

Accurate assessment of vapor uptake, and tissue disposition, in the lung must include vapor transport by diffusion in the tissue as well as vapor metabolism and reaction within the tissue. Since the transport of inhaled vapors into the lung tissues depends on the concentration of the vapor in the tissue, vapor transport equations in the air and tissue phases are coupled and must be solved simultaneously. Models of coupled air-tissue transport in the lung have already been developed for non-reactive vapors (Tsu et al., 1988; George et al., 1993).

In this study, an air-tissue vapor transport model during a single breathing cycle is described that can simulate a wide range of vapor solubilities and tissue reactivities. Vapor transport in the airway lumen was considered as a conductive and diffusive process. Vapors that were taken up by the surrounding airway tissues would be metabolized and react with the tissue by first-order and saturable reaction within the tissue. Since the transport of inhaled vapors into the lung tissues depends on the concentration of the vapor in the tissue, vapor transport equations in the air and tissue phases are coupled and must be solved simultaneously. Models of coupled air-tissue transport in the lung have already been developed for non-reactive vapors (Tsu et al., 1988; George et al., 1993).

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**Materials and methods**

To determine uptake of inhaled vapors in the airways, airflow distribution and vapor concentration must be determined airway-by-airway through solving the momentum balance (Navier-Stokes) and mass balance (convective-diffusion) equations for the inhaled air and vapor, respectively. However, intra- and inter-subject variability in airway shape, the large number of airways, and multi-scale dimensions of the airways pose a challenge to solving the complete sets of transport equations. To formulate a predictive model of regional and local uptake of inhaled materials, each lung airway is assumed to be cylindrically shaped with a uniform tissue thickness within the airway. However, tissue thickness decreases distally in the lung with airway generation number. Since the airflow Reynolds number in the lung drops below unity just after a few airway generations, the airflow velocity profile is assumed to be uniform with average parabolic velocity. In addition, because of steady and slow decrease, airway concentration is assumed to vary only with lung distal penetration. Consequently, the convective-diffusion transport equation of the inhaled vapor in an airway can be described by the following equation:

\[
\frac{\partial C_a}{\partial t} + U \frac{\partial C_a}{\partial z} = D_a \frac{\partial^2 C_a}{\partial z^2} - \frac{2}{R} I_R
\]  

Where, \(C_a\) is the vapor concentration in the air phase, \(t\) is the elapsed time, \(U\) is the average air velocity in the airway, \(z\) is the axial direction, \(D_a\) is the vapor diffusion coefficient in air, \(R\) is the airway radius, and \(I_R\) is the radial flux of vapor at the air-tissue interface (Miller et al., 1985). Since vapor transport occurs only
in the axial (z) direction, the flux (sink) term in equation (1) replaces wall boundary conditions. Equation (1) must be solved for each airway in the lung with appropriate initial conditions and inlet and outlet boundary conditions to find vapor concentrations at various locations within the lung. Unlike particles that are removed from the air stream once they come into contact with airway walls, vapor losses depend on their interaction with tissue constituents. Thus, air and tissue phase transport processes are coupled and, in principle, must be solved simultaneously. However, the two-way dependency can be reduced to a one-way, vapor-to-tissue coupling to allow the solution of the uncoupled equation (1) for vapor concentration in the air, if the radial diffusion flux of the vapor is equal to the vapor concentration at the air-tissue interface times a constant coefficient, referred to as the overall mass transfer coefficient \((K_o)\). Asgharian et al. (2011) derived analytical expressions for the overall mass transfer coefficients during inhalation, pause, and exhalation time intervals during the breathing cycle. By substituting for the overall mass transfer coefficient in the flux, \(I_R\) equation (1) became:

\[
\frac{\partial \overline{C}}{\partial t} + U \frac{\partial \overline{C}}{\partial z} = D \frac{\partial^2 \overline{C}}{\partial z^2} - \frac{2K_o}{R} \overline{C}
\]

Where,

\[
\overline{C} = C_a + \frac{K_t}{K_1}
\]

In which, \(K_t\) is the tissue-phase mass transfer coefficient and coefficient \(K_1\) arose due to unsteady transport of vapor across the air-tissue interface. Expressions for \(K_t\) and \(K_1\) are given by Asgharian et al. (2011) as a function of vapor physico-chemical properties and airway dimensions. The overall mass transfer coefficient \(K_o\) during each breathing time was given by:

\[
\frac{1}{K_o} = \frac{1}{K_1} + \frac{1}{K_t}
\]

In which, \(K_t\) is the air-phase mass transfer coefficient (Bush et al., 2001). Vapor flux across the air-tissue interface was given by the product of the mass transfer coefficient and vapor concentration at the air-tissue interface (Asgharian et al., 2011). By network analogy, the overall mass transfer coefficient can be represented by an overall resistance of two resistances in parallel: air-phase resistance \((K_0)\) and tissue resistance \((K)\). The relative values of air and tissue resistances signify the contribution of each phase to vapor uptake.

The solution of equation (2) follows from the solution of nanoparticle deposition (Asgharian & Price, 2007), replacing nanoparticle flux losses with \((2K_o/R) \times \overline{C}\) for inhalation and exhalation. Further details can be found in Asgharian and Price (2007). Vapor losses in an airway during pause are governed by the diffusion equation

\[
\frac{\partial C_a}{\partial t} = D \frac{\partial^2 C_a}{\partial z^2} - \frac{2K_o}{R} C_a
\]

Assuming a linear variation of concentration along airway length and no exchange of vapor between parent or daughter branches during pause (i.e. zero concentration at the ends of the airway), equation (5) may be solved to give:

\[
C_a(z,t) = \frac{2(C_p - C_a)z^2}{L} + \frac{2}{\pi} \sum_{n=0}^{\infty} \frac{[C_p - (-1)^n C_a] \gamma_n}{n} \sin \left( \frac{n\pi z}{L} \right)
\]

Where,

\[
\gamma_n = \frac{2k_o r_n^2 + n^2 \pi^2 D_s}{R L^2}
\]

In which, \(C_p\) and \(C_a\) correspond to vapor concentrations at the proximal and distal ends of the airway at the beginning of the pause, and \(L\) is the airway length. Uptake fraction is the fraction of inhaled vapor that is cleared from the air, in an airway or region of the lung, during a complete breathing cycle. Vapor uptake fraction (UP) in an airway during inhalation, pause, or exhalation time interval is found from:

\[
UP = \frac{2\pi R}{C_p V_t} \int_0^L k_o C_a \, dz \, dt
\]

Where, \(C_p\) is the inhaled (exposure) concentration of vapor, \(V_t\) is the inhaled volume of air during one breath, or tidal volume, and \(T\) is inhalation, pause, or exhalation time interval.

Vapor concentration in the lung tissues of an airway during any given breathing interval can be found by solving the reaction-diffusion equation (Schroeter et al., 2006):

\[
\frac{-\partial C_i}{\partial t} + D \frac{\partial^2 C_i}{\partial r^2} = K_i C_i + \frac{(V_{max}/V_t) C_i}{K_m + C_i}
\]

Where, \(C_i\) is the vapor concentration in the tissue, \(D_i\) is the vapor diffusion coefficient in the tissue layer, \(K_i\) is a first-order rate constant, \(V_t\) is the lung tissue volume, \(r\) is the tissue depth, and \(V_{max}\) and \(K_m\) are Michaelis–Menten rate constants. According to equation (9), the transport of vapor through the tissue occurs by radial diffusion and is cleared by first-order and saturable pathways. When warranted, expression (9) may be extended to vapors of multiple saturable pathways (e.g. high-capacity, low-affinity and low-capacity, high-affinity pathways) and can also include additional first-order clearance terms.
Once air-phase concentration is determined during each time interval of the breathing cycle, the parabolic partial differential equation (9) is subsequently solved using an implicit finite-difference method (Asgharian et al., 2011) to find vapor concentration and elimination in the tissue walls of each airway. Tissue initial and boundary conditions must also be specified to allow the solution of equation (9). During inhalation, initial vapor concentration in the tissue is zero when modeling a single breath exposure. In addition, vapor concentration in the air \( C_a \) is constant (Yu, 1978). Vapor concentration at the air-tissue interface \( C_{at} \) is given by (Asgharian et al., 2011):

\[
C_{at} = \frac{k_g}{k_g + k_t} C_a - \frac{k_s}{k_g + k_t} \quad (10)
\]

Tissue concentration at the other end of the tissue layer (tissue-blood interface) is assumed to be zero to simulate complete clearance from the tissue due to blood perfusion. During pause and exhalation, initial tissue concentration is already determined from the solution of equation (9) at the end of the previous breathing time interval. Tissue concentration at the air-tissue interface is also found from equation (10). However, vapor concentration in the air, and thus at the air-tissue interface (equation 10), varies over time during pause and exhalation. It should be noted that vapor concentration at the other end of the tissue layer, where vapor is transported to the blood flow, is assumed to be zero at the interface to allow for the highest transfer of vapor to the blood and other organs of the body and does not imply a concentration of zero entering the blood. This scenario corresponds to the most conservative (highest) estimate of whole body burden and is particularly useful in risk analysis from exposure to inhaled compounds. However, this assumption could affect regional dosimetry estimates, especially for vapors that penetrate to the deep lung since uptake in the pulmonary region depends on the amount of vapor absorbed in the upper airways.

Since tissue concentration at the start of inhalation is zero, vapor transfer always occurs from air to tissue, down the concentration gradient. During exhalation, however, the tissue concentration may be higher than that in the airway with the possibility of tissue off-gassing, or desorption of vapor, which may result in a decrease in tissue concentration, and increase in airway concentration, of vapor. The transient coefficient \( K_t \) in equation (10) accounts for unsteady and bi-directional transport of vapor across the air-tissue interface. While bi-directional transport of vapor across the tissue layer is often present for most chemicals, it has so far not been accounted for in the calculations of mass transfer coefficient.

A vapor uptake dosimetry model was developed based on equations (2) and (9) that allows for calculations of inhaled vapor in all airways of the lung and surrounding tissues during a complete breathing cycle that consists of inhalation, pause, and exhalation. The model solves equations (2) and (9) numerically and runs on a personal computer within a few minutes depending on the lung distal penetration of the selected vapor.

Results and discussion

The vapor uptake model described in the above section was used to predict uptake fractions of inhaled soluble, reactive vapors in the human lung. Uptake fraction was subsequently used to find the wall flux of vapors in each airway. The wall flux is the product of uptake fraction, exposure concentration, tidal volume, and breathing frequency divided by the surface area of the airway. In addition, vapor concentration in the lumen of an airway was used as an inlet boundary condition to calculate the concentration of the compound in the tissue of each airway. Unless otherwise specified, computations were performed at an exposure concentration of 1 mg/m³, a minute ventilation of 7.5 L/min, and a breathing cycle of 5 s with 2.5 s inhalation, 0.2 s pause, and 2.3 s exhalation (ICRP, 1994). Calculations were performed for a single breath. For multiple breaths, tissue concentration may remain nonzero at the end of exhalation and accumulate with repeated breathing. Information on the diffusion coefficients of compounds in the lung tissues is not available. A diffusion coefficient value of \( 10^{-6} \text{ cm}^2/\text{s} \), which is approximately an order of magnitude smaller than that in water, was used in the calculations to account for the increased viscosity observed in lung tissues (Bush et al., 1998; Pryor, 1992). The sensitivity of the tissue diffusion coefficient was analysed by increasing the value by an order of magnitude. This resulted in about a 10% decrease in lung tissue uptake. All predictions were made for the case of endotracheal breathing (no head). When comparing predictions with those of other studies or reported measurements, the data were corrected for head uptakes.

Model validation

Model predictions were first compared with available information in the literature. First, a comparison was made with another previous modeling effort for support of our predictions. Overton et al. (2001) solved equation (1) numerically to find vapor concentration in the airway lumen and wall mass flux of formaldehyde to airway walls via oral breathing using a Weibel (1963) lung geometry. Since formaldehyde is highly soluble, vapor is quickly absorbed by the walls on contact. Thus, wall uptakes are strongly influenced by the air-phase resistance, which is much larger than the tissue resistance (equation 4). Overton et al. (2001) assumed a constant tissue mass transfer coefficient of 4.7 cm/s, which was derived from computational fluid dynamics simulations of inhaled formaldehyde in the rat nose (Kimbell et al., 2001). However, if the mass transfer coefficient is defined in terms of the partition coefficient and tissue reactivity terms (Table 1), a significant variation of
mass transfer coefficient is observed with lung depth (Asgharian et al., 2011). In order to directly compare model predictions with those from Overton et al. (2001), the same mass transfer coefficient of 4.7 cm/s and the Weibel lung geometry were used in these calculations (Figure 1). Both models agreed, qualitatively, with similar vapor penetration depth and flux predictions. The shape of the flux predictions was also similar for the two models. The noticeable difference in flux predictions in the trachea is attributed to the difference in model assumption: Overton et al. (2001) assumed a rigid trachea while the current model assumes an expanding-contracting trachea, which reflects reality more closely (ICRP, 1994). When lung airways undergo a uniform rate of size change, by solving the mass conservation or continuity equation, the airflow rate per airway becomes proportional to the distal volume at any location within the airway. However, deposition calculations are calculated at a lung volume midpoint between rest and end of inhalation. For rigid airways, the flow rate is always proportional to airway cross-section area and does not vanish in the deep lung as expected. The difference in the tracheal mass flux between the two models amounted to about 25% but was otherwise small for other airways. As a result of predicting a higher tracheal mass flux, the lung distal penetration of formaldehyde was shorter by one airway generation in the current study as compared with that from Overton et al. (2001).

Limited measurements of inhaled reactive vapors in human lungs are available. Model predictions were compared with the data by Egle (1970) who measured the exhaled concentration of inhaled acetaldehyde in eight subjects with varying breathing parameters to calculate uptake fractions. The experiments consisted of inhalation of 14 L acetaldehyde mixture over about 30 breathing cycles in contrast to our predictions, which were based on single-breath uptake calculations. The predicted uptake fractions and measurement-based reported values of Egle (1970) for inhalation of acetaldehyde via oral breathing are given in Figure 2. Information on vapor reaction rates with the lung tissues was not available. The value for the first-order clearance rate ($K_f$) was from the nasal region and zero reaction rate for saturable pathway was selected. Table 1 gives parameter values used in the simulations. Predicted uptake values were corrected by oral airway uptake measurements of Egle (1970). The agreement between model predictions and measurements were reasonable given the uncertainty regarding model parameters. Model predictions and reported measurements agreed closely at the breathing

Table 1. Compound properties in the air and tissue.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue-air partition coefficient ($P_{t:a}$)</td>
<td>Formaldehyde</td>
</tr>
<tr>
<td></td>
<td>Acetaldehyde</td>
</tr>
<tr>
<td></td>
<td>Acrolein</td>
</tr>
<tr>
<td>Diffusion coefficient in the air ($D_a$, cm²/s)</td>
<td>Formaldehyde</td>
</tr>
<tr>
<td></td>
<td>Acetaldehyde</td>
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<tr>
<td></td>
<td>Acrolein</td>
</tr>
<tr>
<td>Diffusion coefficient in the tissue ($D_t$, cm²/s)</td>
<td>Formaldehyde</td>
</tr>
<tr>
<td></td>
<td>Acetaldehyde</td>
</tr>
<tr>
<td></td>
<td>Acrolein</td>
</tr>
<tr>
<td>First-order rate constant ($K_p$, 1/s)</td>
<td>Formaldehyde</td>
</tr>
<tr>
<td></td>
<td>Acetaldehyde</td>
</tr>
<tr>
<td></td>
<td>Acrolein</td>
</tr>
<tr>
<td>Saturable pathway constant ($K_m$, mg/m³)</td>
<td>Formaldehyde</td>
</tr>
<tr>
<td></td>
<td>Acetaldehyde</td>
</tr>
<tr>
<td></td>
<td>Acrolein</td>
</tr>
<tr>
<td>Saturable pathway rate constant ($V_{max}/V_t$, mg/m³/s)</td>
<td>Formaldehyde</td>
</tr>
<tr>
<td></td>
<td>Acetaldehyde</td>
</tr>
<tr>
<td></td>
<td>Acrolein</td>
</tr>
</tbody>
</table>

*Oak Ridge national Laboratory’s Risk Assessment Information System (http://rais.ornl.gov/).
**Morris (1996).
†Conolly et al. (2000).
‡Teeguarden et al. (2008).
§Morris (1997).
δKimbell et al. (2001).
&Schroeter et al. (2008).
*Optimized to uptake data.

Figure 1. Comparison of predicted formaldehyde fluxes in the human lung with those by Overton et al. (2001). The same vapor and lung parameters, mass transfer coefficients, head losses, and lung geometry were used for model comparison.

Figure 2. Comparison of model predictions for acetaldehyde with measurements by Egle (1970).
rate of 2.5 breaths/min, with a slight overprediction for other breathing rates. Although the simulations showed that acetaldehyde was mostly removed from the tissue layer following a single breath, it is possible that acetaldehyde could accumulate in the tissue following multiple breaths, which would increase tissue resistance and decrease overall lung uptake.

Kumagai and Matsunaga (2000) used measured uptake fraction of inhaled vapors in the lung to calibrate a pharmacokinetic model for describing the disposition of vapors in the body. The uptake data were compiled from several studies and included vapors of different partition coefficients that had minimal metabolism in lung mucus and tissues. Uptake of inhaled vapors by the lung depends primarily on the liquid:air partition coefficient and diffusion coefficient through the lung tissues, provided that there are no reactions of the vapor in the tissue. The vapor taken up by the lung is quickly transported to capillary blood by diffusion. Since air:water (or mucus lining of the lung tissue) and air-blood partition coefficients are qualitatively similar in value, the uptake fraction versus partition coefficient relationship should be similar for the lung and blood. Figure 3 compares predicted lung uptake fractions versus vapor blood-air partition coefficients with the data collected by Kumagai and Matsunaga (2000) for uptake into the blood of several inhaled vapors. In addition, model predictions of this study were compared with predictions of a recent study by Gloede et al. (2011). Model predictions were conducted with a tissue diffusion coefficient of $10^{-6}$ cm$^2$/s and with no vapor uptake in the upper airways (head). There is a significant overlap between the reported measurements and predictions. The agreement is reasonable given the uncertainty regarding study parameters, inter-subject variability in lung geometry and ventilation, measurement techniques, and uptakes in the head airways. Model predictions were also in general agreement with the results of Gloede et al. (2011). Figure 3 also indicated that vapor uptake increased at low partition coefficient followed by a gradual rise to reach maximum uptake. The model was unable to capture the slight decrease in uptake for partition coefficients of $\sim 10$–100, which is likely a result of accumulated vapor in the tissue after multiple breaths. The shape of the uptake line was highly dependent on the tissue diffusion coefficient, or transport rate, through the tissue to reach the blood. In addition, the predicted vapor uptake was found from our parametric studies to be very sensitive to the thickness of the alveolar-capillary membrane.

**Vapor uptake simulations**

The vapor uptake model was used to find the uptake fractions of formaldehyde, acrolein, and acetaldehyde in all airway generations of the lung (Figure 4). Air and tissue phase parameters for these compounds are shown in Table 1. Acetaldehyde rate constants for first-order and saturable pathways of elimination were selected from Teeguarden et al. (2008), which were originally developed for nasal tissues but were extended to lung tissues in the current study. There were two reported pathways of clearance in the nasal tissues for acetaldehyde depending on the $K_m$ value. Since $K_m >> C_t$ for high $K_m$, $k_i = V_{max}/K_m$ for the first-order reaction rate in the lung tissues. In addition, $V_{max}$ was set to zero at low $K_m$ to optimize predictions to uptake data (Figure 2). All three vapors were efficiently absorbed in the lung except for the tail end of the inhaled vapor that entered the lung late in the breathing cycle and avoided uptake on exhalation. Formaldehyde is highly soluble and reactive in lung tissues and hence had a very high uptake in the trachea (airway generation 0). There was no formaldehyde remaining in the inhaled air past airway generation 8. Overall, about
97% of inhaled formaldehyde was absorbed into the tissue. Acrolein and acetaldehyde are moderately soluble in the tissue and therefore penetrated deeper into the lung. The uptake of these two vapors depended on their absorption, clearance, and diffusion in the lung tissue. Acrolein tended to be taken up by the lung at a higher rate than acetaldehyde and its peak uptake fraction occurred around airway generation 13. There was a small penetration of acrolein into the alveolar spaces with normal tidal breathing. Acetaldehyde had a higher tissue resistance (1/K\(_t\) in equation 4), or lower uptake, than acetaldehyde in early generations of the lung and therefore penetrated deepest into the lung to reach the end of the alveolar region. The uptake of acetaldehyde was smallest in the first few airway generations but rose steadily to reach its peak uptake in airway generation 19. Lung uptake fractions of acrolein and acetaldehyde were 84% and 80%, respectively.

Vapor flux to the walls (or the amount of vapor lost to the walls per unit time and surface area) is thought to reveal susceptible sites of injury within the lung, namely locations with the highest dose. Figure 5 compares wall fluxes for the three vapors. The highest wall flux for formaldehyde was in the trachea, which was over an order of magnitude higher than that for acrolein. Formaldehyde flux subsequently decreased distally in the lung until diminishing in airway generation 8, where there was no longer vapor present in the conducting air space. Acrolein and acetaldehyde fluxes to the walls were significantly lower than those for formaldehyde in the proximal airways. Wall fluxes for acrolein initially increased to reach its peak near generation 8 and subsequently declined to zero by airway generation 18. Acetaldehyde wall flux was highest in the trachea and gradually decreased with lung distal distance and vanished in airway generation 21.

Flux predictions were noticeably higher for formaldehyde in the proximal airways of the lung compared with the model predictions by Overton et al. (2001), mainly due to differences in the calculations of the tissue mass transfer coefficient. The tissue mass transfer coefficients in this study were calculated based on formaldehyde properties such as air:tissue partitioning and clearance from lung tissues by first-order and saturable kinetics (Conolly et al., 2000). The model used by Overton et al. (2001) simply used an average tissue mass transfer coefficient of 4.7 cm/s for all airways of the lung. These findings indicate that by accounting for the real physico-chemical properties of formaldehyde, we see higher absorption in the trachea and upper airways and less penetration into the mid-bronchial airways than was previously observed.

Vapor penetration and wall uptake vary with breathing maneuvers. Heavier breathing delivers a larger dose of vapor to the lung with deeper lung penetration and wall uptake. Wall fluxes of acrolein and acetaldehyde were calculated for rest (minute ventilation of 6.7 L/min) and heavy breathing (minute ventilation (V\(_{E}\)) of 53.3 L/min). The results are presented in Figure 6. The influence of (V\(_{E}\)) on wall flux was noticeable for both acrolein and acetaldehyde. The acrolein flux pattern was similar at both (V\(_{E}\)) in the first 8 generations of the lung. The flux increased rapidly for a higher (V\(_{E}\)), starting with airway generation 9, reaching its peak early in the alveolar region. The lung distal penetration of inhaled acrolein increased by 3 generations with increased (V\(_{E}\)). Acetaldehyde wall flux was highest at the trachea during rest breathing and declined gradually to zero around airway generation 21. There was a steady increase in acetaldehyde flux at heavy breathing, which remained uniform for most of the lung only to drop to zero in the last 3 generations the vapor passed through. Increased (V\(_{E}\)) (increased frequency and penetration of ventilation) led to increased lung distal penetration of acetaldehyde by 2 airway generations.

Figure 5. Comparison of predicted average lung wall flux of formaldehyde, acrolein, and acetaldehyde at different airway generations of the lung.

Figure 6. Wall fluxes of acrolein and acetaldehyde at rest (6.7 L/min) and heavy (55.3 L/min) breathing conditions.
Tissue disposition calculations
Concentrations of formaldehyde, acrolein, and acetaldehyde in the tissue layer surrounding each airway were calculated during the inhalation, pause, and exhalation aspects of the breathing cycle for an exposure concentration of 1 mg/m³. To assess vapor uptake in the tissue, each lung airway was supplemented with an epithelial layer, which was assumed to comprise the mucus/surfactant layer, epithelial tissue, and submucosal layer. Tissue thicknesses provided by ICRP (1994) were used for the tracheobronchial region, and by Miller et al. (1985) for the alveolar spaces. A gradual, linear decrease of tissue thickness from the trachea to the alveolar sacs was adopted using the reported thickness measurements by ICRP (1994). The uptake of the vapor by the tissue was sensitive to vapor properties and interaction with the tissue. Table 1 lists parameter values that were used to calculate tissue concentrations. Initial tissue concentration was zero at the start of inhalation. Initial tissue concentrations during pause and exhalation were the same as tissue concentrations at the end of the previous breathing interval.

Predicted concentrations of formaldehyde, acrolein, and acetaldehyde in the tracheal tissues of the lung are given in Figure 7A–7C for a 5 s breathing period. The results are shown only for the first 60-µm depth of the tissue because no significant penetration was predicted beyond this depth for any of the three compounds. The concentration of the three compounds in the tissue rose quickly during inhalation and reached their respective peak values at the end of inhalation (at 2.5 s). The highest concentration was observed at the air-tissue interface. Since air-phase concentration dropped during pause and exhalation to below tissue concentration levels, vapor desorption (or off-gassing) occurred by the transfer of the compounds from the tissue back into the air. Consequently, the depth of the peak concentration of the compounds moved to the inside of the tissue layer during exhalation. The depth and time of maximum concentration, within the tissue depended on the diffusivity and reactive properties of each compound. Tissue-phase concentration continued to decrease during exhalation by vapor release at both ends of the tissue with little penetration past the 60-µm depth. Concentration was essentially zero in the remainder of the tissue.

It is worth mentioning that there are thin walled capillary tubes in the submucosal layer of the trachea and bronchi that are approximately 40 µm deep (Parent, 1992). These vessels provide the initial means of transport of the absorbed compound in the tissue to the arteries. This is in contrast to our model configuration that for simplicity and practicality neglected such drainage and considers blood perfusion at the end of the tissue layer.

Absorption and retention of an inhaled vapor in the tissues of an airway depends on its solubility, diffusivity, and metabolism and reaction with the tissue. Figure 8A and 8B compares the concentrations of different vapors in the tracheal tissues after 2.5 s of inhalation (peak concentration in the tissue) and at end of one breathing cycle. Formaldehyde, with the highest solubility (partition coefficient), yielded the highest concentration in the tissue, which was about 1–2 orders of magnitude greater than that for the other two compounds. Formaldehyde was also the most reactive compared with the other two compounds and lost 97% of its inhaled mass to the tissue at the end of the breathing cycle (Figure 8B). High rate of loss of formaldehyde from the inhaled air resulted in the shallowest penetration of the vapor into the lung (Figure 4). Acrolein and acetaldehyde had similar solubility and diffusivity in the tissue (Table 1). Both compounds had similar tissue uptake after 2.5 s of inhalation and were cleared from the tissue similarly. The penetration depth in the tissue was about 80 µm for both compounds (Figure 8A and 8B). Formaldehyde concentration dropped to a third of its peak at the end of the breathing cycle and the depth of maximum concentration moved from the air-tissue interface to about 25 µm within the tissue. Due to a lack of a strong reaction within the tissue, and slow diffusional transport, acrolein and acetaldehyde concentrations decreased only about 20% at the end of

![Figure 7](image-url) Figure 7. Vapor disposition in the tracheal tissue during a complete breathing cycle, (A) formaldehyde, (B) acrolein, and (C) acetaldehyde. Solid lines indicate tissue concentration during inhalation and dashed lines denote tissue concentration during exhalation.
the breathing cycle from their peak concentrations at the end of inhalation (Figure 8B). Consequently, the relative order of lines switched in Figure 8A and 8B.

Vapor flux from the air to tissue indicates the delivered dose to the tissue, which has often been assumed to cause site-specific lung injury (Figure 5). The wall flux must be compared with the tissue concentration (dose) to assess the validity of the assumption. Thus, vapor concentrations in the tissues of different airway generations were calculated at contact with the air after 2.5 s of inhalation, where tissue concentration was at its peak (Figure 9A). In addition, the same calculations were carried out for peak concentrations within the tissue at the end of a 5-s breathing cycle (Figure 9B). Comparison of Figure 5 and 9 showed that wall fluxes were proportional to tissue concentrations in the lung for reactive vapors such as formaldehyde. The flux patterns for formaldehyde and acetaldehyde were similar to the tissue concentration patterns at the end of the 2.5-s inhalation but different at the end of the 5-s inhalation. The flux and tissue concentration patterns were noticeably different for acrolein with the highest tissue doses being different for each plot. The differences between predicted flux and tissue concentration were most significant at the end of the breathing cycle. For reactive compounds, wall flux may be correlated to tissue damage for acute and chronic exposures. However, in general, tissue concentration within the lung (total lung burden) is the appropriate metric to assess susceptibility and health risk.

The absorbed vapor must travel through the tissue to reach the blood circulation to be accessible to other tissues of the body. For the same diffusivity and reactive rate constants in the tissue, the penetration of the vapor through the tissue depends primarily on vapor concentration and tissue thickness. Figure 10 gives predicted formaldehyde concentration in the tracheal tissue at the end of a 2.5-s inhalation for inhaled formaldehyde concentrations from 1 mg/m³ to 1000 mg/m³. While penetration depth increased by at least a factor of 2, the penetration remained shallow in the tissue and the vapor did not reach the arterial blood. This scenario may change with repeated breaths as vapor accumulates in the tissue with each breath. These observations are in agreement with the model predictions of Franks (2005) for penetration of formaldehyde vapor through nasal tissues. The same observation was made for acrolein and acetaldehyde, which had similar depths. Thus, for these reactive vapors, tissue thickness is the major barrier to the transport of the inhaled vapor to the blood circulation and extra-respiratory tissues. Based on results presented here for breathing of reactive vapors via the trachea (i.e. bypassing nasal and oral airways), to reach other organs of the body, these vapors must reach the alveolar airways (about 150 cm³ deep into the lung) where airway tissues are thin (terminal bronchioles and alveolar-capillary units).

As vapor penetrates deeper into the lung, the airway tissue thickness decreases and the probability of vapor transport to other organs of the body increases. To show the relative penetration, the normalized depth of peak concentration of inhaled formaldehyde, acrolein, and acetaldehyde in the tissue at the end of a 5-s breathing cycle is given in Figure 11 for different airway generations of the human lung. An inhalation concentration of 1 mg/m³ and a minute ventilation of 7.5 L/min were used in the calculations. The depth of peak concentration was normalized with respect to the tissue thickness, which decreased with increasing airway generation number or lung distal distance. It represents relative tissue penetration depth for each compound. The depth of peak concentration of inhaled vapor in the lung tissue increased with increasing lung distal distance, or higher airway generation number due to decreasing tissue thickness. However, for the stated conditions, none of the three vapors were able to completely penetrate the airway tissue walls to reach the arterial blood. Acetaldehyde had the deepest lung penetration and its normalized depth of maximum concentration in the tissue continued to increase to about 20% of the tissue depth.
Concluding remarks

A lung dosimetry model to simulate vapor uptake and tissue disposition of soluble, reactive vapors was developed for a single breath. Vapor transport and uptake in lung airways occurred by flow advection and vapor diffusion. Tissue absorption was governed by mass transfer coefficients that take into account air and tissue-phase diffusivity, air:tissue partitioning, and first-order and saturable clearance terms in lung tissues. Tissue parameters (diffusion coefficients and reaction rates) used in the lung model were based on reported values in the nasal passages, which were adopted for the lung in the absence of other information. The dosimetry model was used to find lung uptake and tissue concentrations for formaldehyde, acrolein, and acetaldehyde. An advancement of this approach over earlier mechanistic lung dosimetry models is the prediction of transient tissue disposition calculations over the entire breathing cycle and how tissue levels affect absorption from the airway lumen. In addition, it was shown that flux patterns do not necessarily correspond to tissue dose and concentration. Furthermore, model predictions elucidated the significance of tissue thickness as a barrier for the vapor to reach the blood. This dosimetry model has been implemented into the Multiple-Path Particle Dosimetry model (MPPD V2) to allow for user-friendly interfaces to simulate absorption of inhaled vapors.

The vapor uptake model presented in this study lacks the upper respiratory tract, which is responsible for further reduction of the vapor entering the lung. Future studies will be conducted to assess uptakes in the head airways for realistic assessment of the dose delivered to the lung tissue and other organs of the body. Since this...
study considered a single breathing cycle with zero initial concentration of the vapor in the tissue at the start of inhalation, predicted concentrations in the tissue may be under-predicted. The extension of the tissue uptake model to longer exposure periods will determine whether tissue concentration will reach steady-state. The steady-state vapor concentration in the tissue can be used to find the flux of the vapor to the arterial blood, which will provide an important input to a pharmacokinetic model for determining the distribution and burden in other organs and tissues of the body.

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References


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A Lung Dosimetry Model of Vapor Uptake and Tissue Disposition
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