Uptake and Metabolism of Toxicants in the Respiratory Tract

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The sites of uptake and retention of inhalants within the respiratory tract influence which tissues are susceptible to damage (1,2). Inhaled materials are typically contained in complex mixtures; thus, knowledge of how physicochemical properties affect the dosimetry of individual components is required if individual contributions to toxic effects are to be evaluated. In addition, careful consideration must be given to how interspecies variations in biological parameters affect the dose of inhalants.

Inhalant concentration times exposure duration (c × t) is a commonly reported measure of dose, but it can lead to deceptive interspecies comparative-dose calculations. Because the ratio of ventilation rate to mass varies widely among animal species, the amount of material inhaled when normalized to body weight also varies widely for any c × t. For this reason, ventilation rate, body mass, and numerous other factors such as rates of metabolism, the nature of the metabolites produced, and the susceptibility of cells and subcellular structures to toxic effects are all important variables for comparing doses of inhalants among different species (Figure 1).

The Importance of Dosimetry in Explaining the Toxicity of Inhalants

The principal factors affecting the dosimetry of toxicants to the respiratory tract are the following: a) the route of exposure, b) the physicochemical properties of the inhalants, and c) the metabolic capacity of the respiratory tract cells.

The respiratory tract is exposed to toxicants by two routes: inhalation and systemic circulation. The dose received by specific tissues during exposure by inhalation depends on the physicochemical characteristics of the inhalant; the first cells exposed are epithelial cells. On the other hand, during exposure to toxicants circulating in the blood, the first cells exposed are the endothelial cells of the vasculature, with the greatest exposure occurring in the alveolar capillaries because they receive the entire cardiac output.

The primary factor controlling the site of initial deposition of inhalants is the size of the inhalant (Figure 2A). For inhalants classified as particles, there is little re-entrainment into the airstream once the airway surface has been contacted. When inhalant size decreases to molecular dimensions, the inhalants are classified as gases (or vapors for compounds also occurring in the liquid state at room temperature), and the phenomenon of desorption after initial deposition plays a key role in dosimetry. Molecules absorbed on the nasal or bronchial mucosa during inhalation and desorbed during exhalation do not contribute to the overall dose. For gases, the aqueous solubility (more precisely, high-

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**Figure 1.** Comparison of various expressions of inhalant dose in rats and people.
water and air partition coefficient) of the inhalants and their reactivity with components of the mucosa are the major factors determining the extent to which re-entrainment after initial deposition occurs (Figure 2B).

**Anatomy of the Respiratory Tract and Location of Xenobiotic Metabolism**

The topography of the rat nasal cavity is dominated by complex scroll-like structures (turbinates) through which air passes before entering the tubular nasopharynx (Figure 3). Air inhaled into the lungs descends through branching tubes of decreasing diameter until it reaches the gas exchange region containing the alveoli (Figure 4). This exchange region is characterized by the thin tissue barrier separating the endothelial cells of the vasculature from the epithelial cells exposed to air.

Cells with high xenobiotic metabolic activities in the respiratory tract include the cells of the nasal transitional and olfactory epithelia, and the Clara cells of the bronchiolar epithelium. The nasal respiratory epithelium, alveolar macrophages, alveolar type II epithelial cells, and alveolar endothelial cells also have substantial activities. Partially a result of the metabolic activation of toxicants, the cells of the olfactory tissue and the bronchiolar Clara cells are frequent targets for the toxic effects of inhaled or systemic toxicants (2). Enzyme activities in the respiratory tract include phase I enzymes responsible for initial metabolism of many lipophilic compounds, phase II enzymes responsible for conjugating products of phase I reactions to highly soluble biomolecules, and other xenobiotic-metabolizing enzymes (Table 1).

**Figure 2.** Effects of inhalant size (A) and reactivity (B) on deposition of inhalants. Reactivity as used here includes high affinity for the mucosa even when breaking or making chemical bonds is not involved.

**Figure 3.** (A) Major structures of the rat nasal cavity ventral view of the hard palate region and four transverse sections. Abbreviations: L, lumen; mx, maxilloturbinate; ND, nasolacrimal duct; nt, nasoturbinate; RI, root of incisor tooth; S, septum; V, vomeronasal organ; et, ethmoturbinates; OB, olfactory bulb of the brain. (B) Epithelia of the nasal cavity. Abbreviations: OE, olfactory epithelium; BG, Bowman’s gland; ON, olfactory nerve; SE, sensory cell; SuC, sustentacular cell; RE, respiratory epithelium; SE, squamous epithelium; TE, transitional epithelium; nt, nasoturbinate; mx, maxilloturbinate; et, ethmoturbinates; NP, nasopharynx; n, nares. Reprinted with permission of Dr. Jack Harkema.

**Figure 4.** (A) Diagrammatic illustration of the respiratory tract: N, naris; NC, nasal cavity; HP, hard palate; NP, nasopharynx; T, trachea; EB, extrapulmonary bronchus; IB, intrapulmonary bronchus; TB, terminal bronchiole; RB, respiratory bronchus; AD, alveolar duct. (B) Scanning electron photomicrograph of the exposed luminal surfaces of a terminal bronchiole, TB, respiratory bronchiole, RB, and alveolar duct, AD. Reprinted with permission from Dr. Jack Harkema.

**Modeling Vapor Uptake**

The fundamentals of the classic ventilation and perfusion-controlled vapor uptake model are represented by Equation 1.
Table 1. Enzymes responsible for xenobiotic metabolism in the respiratory tract.

| Phase I (monooxygenases) | Phase II (transferases) | Others |
|-------------------------|------------------------|--------|
| Cytochromes P450         | Glutathione transferases | Carboxylesterases |
|                         | Alcohol dehydrogenase   | Aldehyde dehydrogenase |
|                         | Rhodanese               | Epoxide hydrolase |
|                         | Glutathione s-transferase | DT-diaphorase |

*From Dahl (3).*

\[
\text{Uptake} = \frac{Q \times PC_{w/a}}{Q \times PC_{w/a} + V} \times V \times [\text{vapor}]
\]

When the water and air partition coefficient \(PC_{w/a}\) of the vapor is large relative to the ventilation rate \(V\), then uptake is a function of \(V\) and the vapor concentration \([\text{vapor}]\) (Equation 2).

\[
\text{Uptake} = V \times [\text{vapor}]
\]

When the \(PC_{w/a}\) is small relative to \(V\), then the uptake rate is a function of the blood flow rate \(Q\) and \(PC_{w/a}\) (Equation 3).

\[
\text{Uptake} = Q \times PC_{w/a} \times [\text{vapor}]
\]

As \(PC_{w/a}\) increases, Equation 1 predicts that uptake will converge to 100% of the inhaled molecules; as \(PC_{w/a}\) decreases, uptake should become increasingly independent of the ventilation rate, depending increasingly on the blood flow rate. Experimental evidence, however, contradicts these predictions of the ventilation and perfusion model (Figure 5).

The ventilation and perfusion model fails to correctly predict uptake as a function of \(PC_{w/a}\) (or the blood and air partition coefficient) because of the inability of this simple model to take into account the cyclic nature of breathing. This inability would present no problem if the transport of vapor molecules into the blood deposited on the mucosal surface were fast relative to the breathing rate. However, both experimental evidence and theory indicate that this is not the case (5,6). Gerde and Dahl (6) developed a mathematical model for nasal uptake of stable vapors that included a term for diffusion. Nasal uptake data obtained during cyclic breathing in the dog and the results of the mathematical model agreed quite well (Figure 6), showing that diffusion of vapor molecules through the mucosa is a key parameter affecting uptake.

The diffusion and perfusion model works well for predicting the uptake of vapors having diffusivity on the order of \(10^{-9}\) m²/sec, as is the case for molecules with oil and water partition coefficients \(PC_{w/a} \approx 10^{5}\) diffusing through a homogeneous, aqueous barrier. However, the nasal and lung airway mucosa are not homogeneous (Figure 7), so that for compounds with \(PC_{w/a} > 10^{5}\), transport through the tissue barrier may be slowed to an important extent as the molecules are sequestered in the lipid components of the barrier (Figure 8) (7).

The Potential Effect of High Lipophilicity on the Disposition of Inhalants

The potential effects of a high \(PC_{w/a}\) on inhalant molecules are: a) slow transport through the tissue barrier separating the lumen from the vasculature, b) increased concentration of a compound in the tissue barrier (barrier thickness becomes an important consideration), and c) longer retention times and higher attained tissue concentrations that lead to clearance dominated by metabolism. Thus, it may be expected that highly lipophilic inhalants (which generally will be particles because substances having \(PC_{w/a} > 10^{5}\) have insubstantial vapor pressures) will be extensively metabolized in the respiratory tract with possible attendant activation. Moreover, the metabolism will be most important in the conducting airways because even very lipophilic compounds are likely to pass relatively quickly through the thin air and blood barrier of the alveoli.

Although water-soluble inhalants may not be extensively metabolized in the respiratory tract, a small fraction metabolized to toxicants may cause toxic effects. For example, the water-miscible solvent hexamethylphosphoramide is a potent nasal carcinogen, quite likely as a result of metabolic release of formaldehyde (8).

Fate of Pesticide in the Respiratory Tract

Inhaled pesticides as well as other inhalants may be metabolized by enzymes in the res-
Summary and Conclusions

The five main factors to consider when evaluating the fate of pesticides or any xenobiotics in the respiratory tract are as follows: a) Three important determinants of fate and toxicity for xenobiotics in the respiratory tract are the route of exposure, the physicochemical properties of the toxicants, and the metabolic capacity of the respiratory tract cells; b) Reactive or water-soluble (those having high PC_{50} values) inhaled gases are absorbed largely in the nasal cavity; c) The deposition sites of particulates are determined by aerodynamic size; d) Very lipophilic compounds are slowed in their passage from airways into blood and may be metabolized to effect clearance and toxicity; e) Cells of the olfactory tissue and the bronchial Clara cells have especially high metabolic capacities and often activate molecules to toxicants.