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Biologically-based modeling insights in inhaled vapor absorption and dosimetry

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ABSTRACT

The lung is a route of entry and also a target site for inhaled vapors, therefore, knowledge of the total absorbed dose and/or the dose absorbed in each airway during inhalation exposure is essential. Vapor absorption characteristics result primarily from the fact that vapors demonstrate equilibrium/saturation behavior in fluids. Thus, during inhalation exposures blood and airway tissue vapor concentrations increase to a steady state value and increase no further no matter how long the exposure. High tissue concentrations can be obtained with highly soluble vapors, thus solubility, as measured by blood:air partition coefficient, is a fundamentally important physical/chemical characteristic of vapors. While it is classically thought that vapor absorption occurs only in the alveoli it is now understood that this is not the case. Soluble vapors can be efficiently absorbed in the airways themselves and do not necessarily penetrate to the alveolar level. Such vapors are more likely to injure the proximal than distal airways because that is the site of the greatest delivered dose. There are substantial species differences in airway vapor absorption between laboratory animals and humans making interpretation of laboratory animal inhalation toxicity data difficult. Airway absorption is dependent on vapor solubility and is enhanced by local metabolism and/or direct reaction within airway tissues. Modern simulation models that incorporate terms for solubility, metabolism, and reaction rate accurately predict vapor absorption patterns in both animals and humans and have become essential tools for understanding the pharmacology and toxicology of airborne vapors.

Contents

1. Introduction

The respiratory tract can serve as both a route of entry and also a target for toxic or pharmacologic agents. Understanding the processes involved in absorption of inhaled vapors is essential from both perspectives. For those vapors which exert effects in distant organs, such as inhalational anesthetics, a generalized understanding of absorption behavior is likely adequate. Many inspired vapors, however, have been shown to be toxic to selective airways. These include (depending on the agent) the nose all the way down the tracheobronchial tree to the terminal bronchioles and alveoli. A detailed understanding of absorption behavior is necessary to understand the inhalation toxicology of such agents. Moreover, since human health hazard assessment is often based on inhalation toxicity studies in rodents, it is necessary to understand how absorption behaviors differ between rodents and humans. This review will describe the development of biologically-based models of vapor absorption, indicate their strengths and weaknesses, and highlight the fundamental insights into absorption behavior that these models provide.

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The importance of pharmacokinetic modeling lies in the premise that "the dose determines the poison." That the response is proportional to the dose is a tenet of pharmacology and toxicology that is recognized by all experts in the field. Perhaps not as well recognized is the fact that, relative to airborne materials, an exposure concentration is not a dose. In order for an airborne vapor to injure an airway (or distant tissue) it must actually be delivered to that airway (or tissue). Inhalation dosimetry is the field which endeavors to describe the complex relationships between the inspired concentration and the total absorbed dose and/or the dose delivered to critical targets within the respiratory tract itself. Inhalation dosimetric models have been developed to describe total respiratory tract absorption of vapors and also to describe regional absorption patterns within individual airways. The application of these models is contextual. A detailed model of regional airway absorption of vapors is likely not necessary for vapors which exert their effects in distant organs. This would not be the case, however, for vapors which exert effects within the airways themselves.

The importance of inhalation dosimetry is highlighted by the fact that a number of vapors have been shown to produce nasal injury in rodents but are associated with small bronchiolar injury in humans. This latter issue is highly problematic in the context of modern quantitative inhalation risk assessment. For example, hydrogen fluoride vapor produces severe nasal injury in nose breathing- and severe tracheal injury in mouth breathing-rats, yet is associated with small airway injury in humans (NRC, 2009). Similarly, severe bronchiolar injury is seen in microwave popcorn manufacturing workers exposed to diacetyl (Kreiss et al., 2002), yet inhalation exposure to diacetyl only produces nasal and large airway injury in rats (Hubbs et al., 2008). This discrepancy lead to doubt as to whether or not diacetyl was the causative agent in the bronchiolar disease seen in humans. Dosimetry modeling, however, indicated that vapor absorption patterns of diacetyl differed greatly between rats and humans, thus cementing the cause and effect relationship between diacetyl exposure and bronchiolar injury in workers (Gloede et al., 2011). Importantly, these modeling efforts provide evidence that diacetyl demonstrates a generalized dosimetry pattern that exists for many, rather than a few select vapors.

The literature and approaches used for mathematical descriptions of inhaled vapor disposition are vast. The aim of this review is not to describe, in detail, the mathematical equations that are used, but to highlight the conceptualization of these models and the biological insights afforded by the relationships that have been developed. Most pharmacology texts provide information regarding the use of inhalational anesthetics and include basic information on absorption processes (Evers et al., 2006; White & Trevor, 2007). The simplified approaches described in such texts highlight the importance of vapor solubility in determining the time to achieve anesthesia, how changes in pulmonary ventilation or perfusion alter the time to anesthesia and how quickly gases are exhaled after cessation of exposure. Perhaps the most lucid explanations of these fundamental processes were published nearly 70 years ago (Henderson & Haggard, 1943); this model is described below in detail. While this straightforward approach is predictive for anesthetic gases it is, in actuality, a grossly oversimplified model. It is only predictive for gases/vapors within a small range of physical chemical properties. More modern models have been developed which describe absorption of a wider range of vapors. This review will rely on an historical approach in which the modeling assumptions and their implications are described in the order in which they were first described. As the field advanced models become progressively more and more complex. As will become apparent, the models are all based on the same fundamental concepts; therefore, understanding of the earliest, most simple modeling approaches, is essential for understanding the current state-of-the-art models.

This review will provide information on the key physical chemical properties of gases and vapors relative to their inhalation dosimetry. This will be followed by a description of the classic ventilation–perfusion models of vapor uptake which are still used to describe anesthetic gas delivery. More modern physiologically-based and/or engineering-based approaches for upper airway (i.e., nasal) and lower airway (i.e., tracheobronchial) vapor absorption will then be described. Throughout this review a physiologically-based mechanistic approach will be taken to highlight and reinforce the fundamental processes that are involved in vapor dosimetry. When relevant, specific examples will be given to provide insights into the practical importance of inhalation dosimetry in real world settings.

2. The essential process

Vapor absorption requires the diffusion of airborne vapor in the airspace to the air:tissue interface, solubilization in the tissue phase at the interface and ultimately, diffusion into the tissue away from the interface. This basic conceptualization can be applied to the airways in their entirety, to an individual airway, or even to a tiny portion of the nose; irrespective of the dimensions of the area of interest, the fundamental processes are the same. While this conceptualization may seem intuitively obvious, the recognition and quantitative description of the processes involved in vapor absorption resulted only from several decades of research.

Shown in Fig. 1 is a schematic of the processes that are important in vapor disposition in the respiratory tract airways (Medinsky & Bond, 2001). Vapor absorption occurs by diffusion. In essence, absorption occurs when there is a downhill concentration gradient between air and tissue, in the absence of a concentration gradient no net absorption will occur. More specifically, in the moving air phase vapor molecules can diffuse to the air:tissue interface and then can dissolve in the outermost tissue layer, which in the airways is the mucus. Once in the mucous lining layer vapor may diffuse away from the interface, potentially to the depth of the underlying capillaries. The rate at which this diffusion occurs depends on the steepness of any concentration gradients in the air or tissue phases. In the tissue, the concentration gradient is influenced by the rate removal of vapor from the tissue itself (e.g., by metabolism or direct chemical reaction) and also on the local blood flow rate. This entire process is fully reversible. Thus, vapors are absorbed (e.g., net transfer is from the air to tissue) when the effective concentration in air exceeds that in tissue, and are desorbed (e.g., net transfer is from the tissue to air) when the effective concentration in tissue exceeds that in air.

Vapor absorption in the alveoli is fundamentally identical to that in the airways. The differences lie in the fact that alveolar air:blood barrier is extraordinarily narrow and the superficial lining layer is surfactant, not mucus. As in the airways the processes of 1) movement to the interface, 2) dissolution in tissue, and 3) diffusion to the capillary blood must all take place in the alveoli as well for vapor absorption to occur. Irrespective of location in the airways or alveoli, mathematic models of vapor absorption must allow for each of these processes to occur and must allow for the interdependence of air and tissue factors in the absorption process. The extent and speed of these processes are dependent on the physical chemical properties of the vapor molecule; thus, vapor absorption models must include physical chemical constants as well.

3. Important physical/chemical properties

Gases and vapors exist as individual molecules dispersed in air (or more precisely a gas phase). They differ in that vapors, unlike gases, may exist in the liquid state at common temperatures and pressures. The fundamental quantitative physical/chemical behaviors of both gases and vapors are the same at low partial pressures (i.e., that do not approach the vapor pressure). Thus, in the context of this review the terms will be used interchangeably.

Diffusion towards or away from the air:tissue interface is an essential step in vapor absorption. It, therefore, can be appreciated

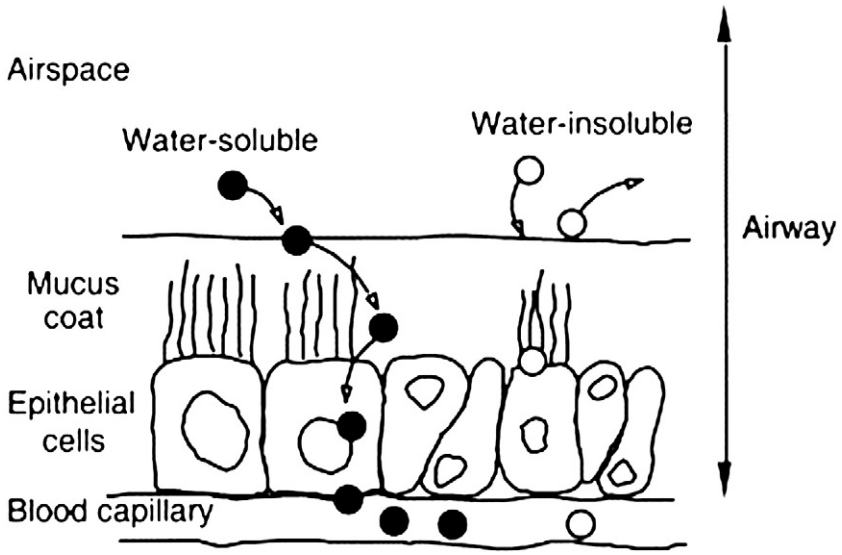

Fig. 1. Schematic of the essential steps of airway vapor absorption from Medinsky and Bond (2001). Vapor in the airspace can enter the mucus lining layer if sufficiently soluble. Once in the lining layer vapor molecules have the potential to diffuse through the tissue to the capillary blood where they are removed.

that molecular weight is a potentially important physical/chemical property relative to this process. Because molecular diffusion is inversely related to molecular weight, smaller vapor molecules diffuse more readily than larger vapor molecules. Molecular diffusivity in air is orders of magnitude quicker than in fluid, e.g., tissue. As explained below, this important fact has profound impact on vapor absorption behavior during the breathing cycle.

Vapors exhibit solubility/saturation behaviors in fluids. When present in low concentrations in an air and fluid phase which are in contact with each other, vapor partitions between phases in accordance with Henry's Law which states that the partial pressure of vapor over a fluid is directly proportional to the concentration of vapor in the fluid. It should be noted that Henry's Law describes equilibrium behavior and the achievement of equilibrium requires a finite amount of time (and may not occur in the time course of a single breath, see below). The Henry's Law equilibrium constant between air and fluid phases can be expressed in a variety of ways, but perhaps the most useful from an inhalation dosimetric perspective is as a partition coefficient. The partition coefficient is the ratio of the concentration of vapor in the fluid phase to that in the air phase at equilibrium.

Partition coefficients can be determined for water, blood or tissues. Modern modeling efforts often rely on the blood:air, tissue:air or the tissue:tissue (e.g., fat:blood) partition coefficients. Vapors may distribute into both the water and lipid components of blood or tissue; thus the blood:air partition coefficient is dependent on both the hydrophilicity and lipophilicity of the vapor. Algorithms have been developed to estimate the blood:air partition coefficient based on the water:air and oil:air or octanol:air partition coefficients (Meulenberg et al., 2003; Poulin & Krishnan, 1995). In the absence of any other information, the blood:air partition coefficient for hydrophilic substances can be crudely estimated as the ratio of the aqueous solubility divided by the vapor pressure of that substance (Henderson & Haggard, 1943). However, estimation of blood:air partition coefficients on the basis of water solubility alone is dangerous. For example, acetone is miscible with water and its blood:air partition coefficient is ~260 (Morris et al., 1986) and is reflective of its high water solubility. In contrast, naphthalene is only slightly soluble in water yet its blood:air partition coefficient is 725 and is reflective of its high lipid solubility (Morris & Buckpitt, 2009).

Henry's Law provides a useful approximation for the fluid:air equilibrium for inert vapors, but does not strictly apply to reactive vapors. If a vapor is reactive with water or tissue components, then the molecule is chemically transformed in the fluid phase. Only the parent molecule can equilibrate in accordance with Henry's Law and the presence of reaction products (even if they are volatile) does not alter that equilibrium value. Reactive vapor behavior can be modeled by assuming a Henry's Law equilibrium across the air liquid interface but allowing the vapor molecule to be removed from the interface by reaction (see below). For reactive vapors, a much greater amount of vapor will be transferred to the fluid phase than would be predicted by solubility (Henry's Law) alone. Indeed, if the vapor is highly reactive then the fluid phase may act as an infinite sink and there may be essentially complete transfer to the fluid phase.

4. Early modeling approaches: ventilation–perfusion

The fundamental concepts of inhalation dosimetry of inspired vapors have long been appreciated. For example the importance of vapor solubility in controlling overall absorption, and even regional absorption within the airways, was perhaps first discussed nearly 90 years ago (Haggard, 1924). During inhalation exposure the absorption of vapors can be separated temporally into three phases. At the onset of exposure there is no vapor within the body and vapor absorption at its maximum efficiency. This is the “initial” period. This is a quasi-steady state period because vapor absorption efficiencies remain constant during this initial period. This period may last from several minutes to hours depending on the vapor. As vapor is absorbed in the body, the ever-increasing body burden retards absorption. The phase during which body levels are slowly climbing is the “transitional” phase. This phase does not occur instantly upon the onset of exposure because it takes some time for body levels to build up sufficiently to retard the uptake process. The transitional phase itself may last from minutes to hours, depending on the vapor. Finally, during prolonged exposure body levels build up to reach a steady state value. During this “steady state” phase the amount of vapor that is absorbed exactly equals the amount of vapor that is eliminated from the body. The phase is maintained as long as the exposure continues and could last a lifetime if there were continuous exposure. Kinetically, differing factors are important during the different phases of absorption. For example during the initial phase, absorption is determined solely by events occurring in the lungs. In contrast, during the final steady state phase, whole body elimination kinetics are essential.

Henderson and Haggard (1943) provided a lucid description of the physiological factors involved in vapor absorption (Fig. 2). Their approach can be used to conceptualize events in all three phases of

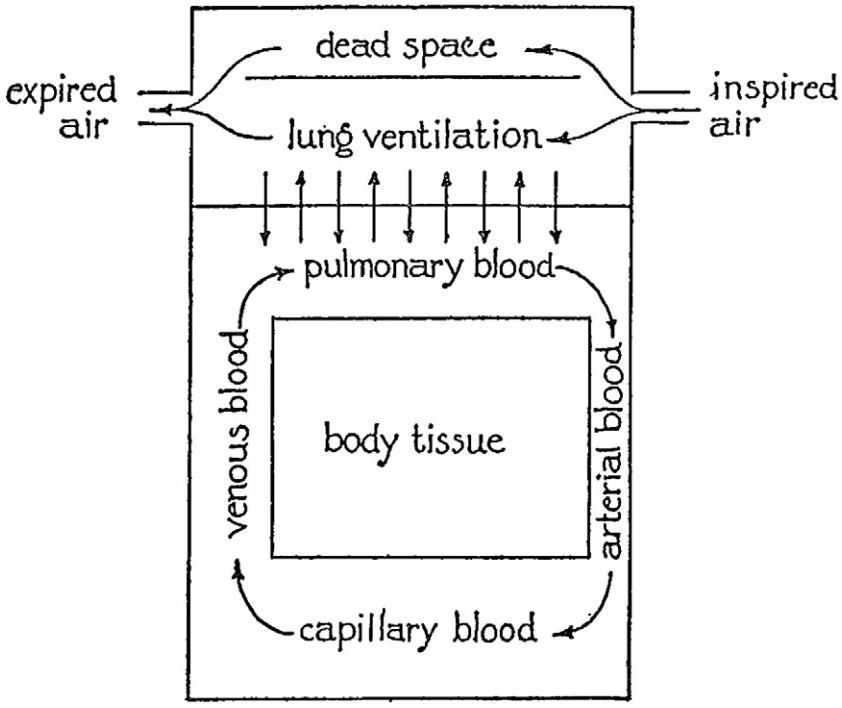

Fig. 2. Schematic diagram of the ventilation perfusion model of Henderson and Haggard (1943). Inspired air equilibrates with pulmonary blood in the lungs. It is assumed that ventilation is continuous and of constant velocity rather than cyclic. Absorbed vapor is transported to the body tissues in arterial blood and can return (recirculate) to the lungs via the venous blood.

absorption, initial, transitional and steady state. Absorption characteristics at the onset of exposure during the initial phase will be discussed first, and are depicted in the top portion of Fig. 2. This early model of pulmonary vapor absorption was based on the assumption that the airways were inert (i.e., dead space) and that inspired vapors instantaneously equilibrate with the blood in the alveoli. In this approach the tissue phases are ignored and the air is assumed to act as though it was in direct contact with the blood. Respiration is not assumed to be cyclic, but is assumed to be continuous. Recognizing that the airways (e.g., dead space) are ventilated in normal breathing, this model splits the inspired air into "dead space" and "lung ventilation" paths. Thus, if the dead space is equal to 30% of the tidal volume then a maximum of 70% absorption of inspired vapor can occur because only 70% of the inspired air reaches the "lung" (e.g., alveoli) where absorption can occur.

For a simple conceptualization of the air and fluid phase interactions during the initial phase vapor uptake, consider the situation in which a vapor is introduced into a closed vessel containing air and water. The vapor will diffuse from the air into the water phase, a process which diminishes the concentration remaining in the air. Eventually a Henry's Law equilibrium will establish between the air and water phases with the ratio of the concentrations in each phase given by the partition coefficient. It is important to recognize that the concentration in the fluid phase does not equal the product partition coefficient times the *initial* concentration of vapor in the air, but equals the product of the *final* airborne vapor concentration times the partition coefficient. This is because the airborne concentration diminishes as vapor is absorbed into the water. The situation is no different in the lungs in which the air phase and fluid phase (e.g., blood) are moving. The partition coefficient-based equilibrium is not established with the initial (e.g., inspired) air concentration and the blood entering the lungs (e.g., arterial blood) but with the final (e.g., exhaled) air concentration and the blood exiting the lungs (e.g., venous blood). This concept forms the basis of the often used venous equilibration assumption, viz., a xenobiotic in a tissue is in equilibrium with the venous blood draining that tissue.

The essential assumption in the model of Henderson and Haggard (1943) is that airborne vapor instantaneously equilibrates with the blood in the alveoli. Given the huge alveolar surface area and the fact that the lungs evolved to allow rapid transfer of oxygen and carbon dioxide this assumption is well supported. The mean harmonic thickness of the air:blood barrier in the alveoli is ~1 μm (Cloutier, 2007). From a chemical diffusivity perspective, equilibrium is anticipated to occur very rapidly across an air blood barrier of this thickness (Kety, 1951). At onset of exposure, the concentration of vapor in blood entering the lungs is zero and there is a huge concentration gradient between air and blood. The efficiency of absorption in this situation will be critically dependent on the flow rates of air (ventilation rate) and blood (perfusion rate). Henderson and Haggard (1943) recognized this relationship as proposed perhaps the first "ventilation–perfusion model." In essence this model predicts that the vapor absorption efficiency at the onset of exposure during the initial-quasi-steady state period, will depend solely on the ventilation rate, inhalation rate and the vapor solubility as defined by the blood:air partition coefficient.

Although perhaps not intuitively obvious, a highly practical approach to conceptualize the ventilation perfusion relationships is to consider the concept of "equivalent volumes" (Goldstein et al., 1974). If, for example, a vapor has a partition coefficient of 10, then the vapor can be conceptualized of as being 10-times more soluble in blood than air, and, consequently, 1 ml of blood will "hold" 10 times the vapor as 1 ml of air. Therefore, multiplying the volume of blood by the partition coefficient (10, in this case) will provide blood volume as an equivalent volume of air, e.g., 10 ml of blood is equivalent to 1 ml of air. Partitioning of vapor between air and blood can then be estimated on the basis of equivalent volumes. For the example in which the blood:air partition coefficient is 10, if 1 ml of air and 1 ml of blood are placed together, the total equivalent volume is 11 ml (1 ml of air and 10 ml of blood). At Henry's Law equilibrium the fraction of vapor in either blood or air is given by the blood or air equivalent volume divided by the total equivalent volume of the system: 1/11 (9.1%) will remain in the air and 10/11 (90.9%) will remain in the blood. If instantaneous equilibrium occurred and the system consisted flowing phases with 1 ml/min of air and 1 ml/min of blood, the partitioning would be the same, i.e., that the air and fluid phases are moving is not relevant as long as

instantaneous equilibrium occurs. The advance made by Henderson and Haggard (1943) was to use this simplistic approach to describe uptake behavior in the lungs during the initial absorption phase.

At the onset of exposure, the ventilation perfusion model of Henderson and Haggard (1943) estimates the absorption of vapors based on Henry's Law blood:air partition coefficient (PB), alveolar ventilation rate (V), cardiac output (Q), and the inspired concentration (Cin). Essential assumptions were: the lung receives the entire cardiac output, ventilation is continuous rather than cyclic, the airways are inert (e.g., no vapor absorption/desorption occurs), and instantaneous equilibration occurs in the alveoli. (Alveolar ventilation rate is used because the dead space is ignored, see Fig. 1). Mathematically:

The fraction of inspired air

$$\text{Entering the blood} = PB^{*}Q/(PB^{*}Q + V) \quad (1)$$

which can easily be seen is a ratio based on equivalent volumes as described above. The fraction of vapor remaining in the air is given by

$$\text{Fraction exhaled} = V/(PB^{*}Q + V). \quad (2)$$

These simple equations would predict a smooth curve in a plot of absorption efficiency (fraction absorbed) versus the partition coefficient. In fact, the predicted relationship (see Fig. 5) is a hyperbolic increase in absorption efficiency as blood:air partition coefficient increases. As described above the maximal absorption efficiency is 70% because it is assumed that the dead space is 30% of the tidal volume. In actuality the relationship is considerably more complex for vapors with partition coefficients greater than 10 (see below). Modern anesthetic gases have blood:air partition coefficients less than 2 (Evers et al., 2006). This sample modeling approach is quite predictive for these vapors.

The mass absorption rate during the initial phase of exposure can easily be estimated by manipulation of Eq. (1):

$$\text{Inhalation rate} = Cin^{*}V \quad (3)$$

$$\text{Fraction absorbed} = PB^{*}Q/(PB^{*}Q + V) \quad (4)$$

$$\text{Absorption rate} = Cin^{*}V^{*}[PB^{*}Q/(PB^{*}Q + V)]. \quad (5)$$

For low solubility vapors this equation predicts interesting relationships relative to the effect of changes in ventilation or perfusion on absorption rate. For very low partition coefficient gases ($PB<0.1$) the absorption rate into the blood is not strongly influenced by the ventilation rate. For example, at a cardiac output of 6 L/min and inspired concentration of 1 mg/L, Eq. (4) predicts absorption rates of 0.54 and 0.6 mg/min at ventilation rates of 6 and 12 L/min, respectively. Conceptually this is due to the fact that blood is removing all the vapor it can (due to its low solubility), therefore increasing the ventilation rate is of minimal importance. In contrast, increasing the blood flow rate will dramatically increase the absorption rate. Eq. (4) predicts absorption rates of 0.54 and 1.0 mg/min at cardiac outputs of 6 and 12 L/min, respectively. Conceptually, if blood is removing all the vapor it can, then doubling blood flow should essentially double its capacity to remove vapor. This model predicts the converse behavior for highly soluble vapors ($PB>10$), with a dependence on ventilation but not perfusion rates in absorption rate. However, uptake for soluble vapors is considerably more complex (see below) so these quantitative comparisons should be made with caution. Current anesthetic gases have blood:air partition coefficients of 0.4–1.8 (Evers et al., 2006) and demonstrate mixed behavior with absorption rate being dependent on both ventilation and perfusion. This simple modeling approach described behavior at the onset of exposure during the initial quasi-steady state phase. The initial phase can exist for several minutes to several hours depending on the vapor solubility. The initial phase ends when significant amounts of vapor accumulate in the body and recirculate to the lung in the blood. This serves to diminish the air:blood concentration gradient in the alveoli and retard uptake.

The initial quasi steady state phase of absorption is followed by the transitional phase of absorption. As the exposure progresses absorbed vapor is delivered to the tissues. As the vapor accumulates in tissues, the vapor concentration in venous blood draining the tissues increases as well. Eventually vapor is "recirculated," meaning that quantitatively significant amounts of vapor are present in the blood entering the lungs. This results in diminished uptake efficiency because vapor accumulates in lung tissues and exerts "backpressure" which retards uptake. (Recall that absorption is dependent on the magnitude of the concentration gradient between air and tissue, see above.) This is the transitional phase of absorption, i.e., when continually increasing recirculation occurs which diminishes the uptake efficiency of airborne vapor. During this phase respiratory tract absorption efficiencies depend on the rate at which vapor accumulates in the whole body; therefore, whole body disposition factors become important. Absorption efficiency continuously diminishes during the transitional phase until the final steady state occurs. In essence, at the final steady state the entire body is in Henry's Law equilibrium with the inspired air. If there is no elimination of vapor from the body (e.g., by metabolism or renal excretion) then there is no net absorption during the final steady state. If elimination pathways exist, then the rate of absorption exactly equals the rate of elimination. Importantly, body levels of vapor remain constant during the final steady state whether or not there is hepatic or renal elimination. Blood levels reach a maximum level and remain at that level throughout the duration of exposure, even if the exposure is of lifetime duration.

For those vapors which are not eliminated via the liver or kidney, the final steady state levels of vapor in the body will be determined by the airborne vapor concentration and the effective partition coefficient; in essence the entire body achieves Henry's Law equilibrium with the inspired air. This is a dynamic equilibrium, while there may be an exchange of vapor molecules between the air and blood there is no net absorption, e.g., absorption efficiency drops to zero. Body levels in the final steady state are given by the product of the airborne concentration and the effective partition coefficients; therefore, at identical exposure concentrations steady state body levels will differ dramatically for vapors with differing solubility. For example, the blood:air partition coefficients for desflurane and ethanol, 0.45 and 1800, respectively (Evers et al., 2006; Morris et al., 1986), differ by three orders of magnitude. Therefore, even at constant exposure concentrations the steady state tissue levels of these vapors will differ by three orders of magnitude as well. It can be readily appreciated that without knowledge of the partition coefficient, the ambient exposure concentration to a particular vapor is a relatively meaningless number with respect to the ultimate tissue concentration that is achieved.

The final steady state phase does not occur instantly upon onset of exposure. The time required for the achievement of the final steady state is dependent on the vapor solubility with relatively short times (minutes) being required for low partition coefficient vapors and long times (hours, days) being required for high partition coefficient vapors. The simplest explanation for this phenomenon is that only a finite amount of vapor is delivered to the lungs in each breath, and since a large amount must be absorbed to achieve whole body saturation of a highly soluble vapor, a long time is required. Whole body models are necessary to describe vapor absorption behaviors and blood/tissue concentrations during the transitional phase and final steady state phases of absorption. Henderson and Haggard (1943) proposed a very simple model in which vapor circulated around the body by the bloodstream (Fig. 2). Vapor in arterial blood was assumed to equilibrate with body tissues such that the concentration in venous blood draining each tissue was equal to that in the tissue. It was also assumed that the vapor was neither metabolized

in the liver nor eliminated in the urine. (Subsequent modeling efforts do not rely on this assumption.) Vapor laden venous blood returns to the lungs. This simple model is remarkably predictive of the absorption behavior of many vapors and, more importantly, provides key kinetic insights into absorption behavior.

In summary the ventilation–perfusion approach of Henderson and Haggard (1943) described how ventilation rate, perfusion rate and vapor solubility interact to determine vapor absorption efficiency in the lungs. The model provides the conceptual basis for understanding the three phases of vapor absorption: the initial phase, which depends solely on events within the respiratory tract, and the transitional and final steady state phases in which recirculation of vapors in the bloodstream significantly impacts pulmonary absorption rates. Importantly this model provides the conceptual basis for why blood vapor concentrations slowly increase to a steady state level that remains constant throughout the duration of exposure. The Henderson and Haggard (1943) model, despite its advantages, is too simplistic to adequately describe the actual whole-body disposition of vapor which is essential during the transitional and final-steady state phases of absorption. More detailed physiologically based modeling is required to achieve this goal.

5. The advent of physiologically-based pharmacokinetic modeling

The simple ventilation–perfusion modeling described above best describes absorption of low partition coefficient vapors and is limited to vapors which are eliminated by neither hepatic metabolism nor renal excretion. This is obviously a limited subset of vapors. While this simple model predicts generalized behavior, particularly for vapor absorption at the onset of exposure, it is clear that more complex approaches are needed for vapors which are metabolized and/or excreted as well as for modeling behavior during prolonged exposures. Much work in the 1960s and 1970s focused on solvent vapor uptake, distribution and elimination, in particular Astrand (1975) and Fiserova-Bergerova (1983) made significant contributions to the literature in this area. Theoretic and mathematical advances were also made by Kety (1951) and Riggs (1970). With the advent of improved computer algorithms and hardware for solution of simultaneous linear and non-linear differential equations it became possible to develop physiologically-constrained mathematic models of vapor disposition. The seminal study in the development of these "physiologically-based pharmacokinetic" (PBPK) models is likely that of Ramsey and Anderson (1984). These authors developed an inhalation pharmacokinetic model for styrene vapor. The structure of this model is given in Fig. 3. This basic structure is still used today for PBPK models.

In PBPK models the whole body disposition of vapors is modeled as a series of mass-balance-derived differential equations for various compartments within the body. These compartments can reflect single organs (e.g., the liver) or lumped tissues with common kinetic characteristics (e.g., richly perfused tissues). The mathematical equations for these models are not the focus of this review. Briefly, however, each tissue or compartment was modeled on the basis of mass balance in which the mass entering the compartment is given by the product of the arterial blood concentration and the blood flow rate to that compartment. Each tissue/compartment was assumed to exhibit venous equilibration behavior in which the vapor in blood leaving the tissue was in equilibrium with the vapor concentration in that tissue. The mass of vapor leaving a compartment is, therefore, equal to the venous concentration times the venous blood flow rate. Vapor metabolism was described by inclusion of Michealis–Menten kinetics for the relevant compartments. Through this approach mass balance equations are developed for each tissue/compartment. These equations are solved simultaneously to provide a description of the whole body disposition of vapor. Modern desktop computers can solve these models in seconds to minutes.

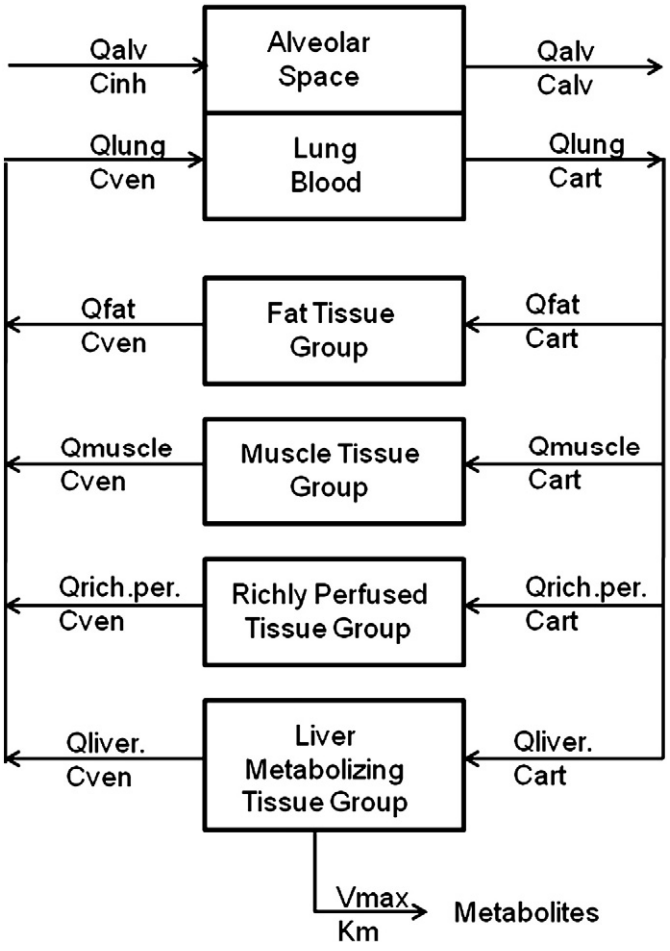

Fig. 3. Schematic diagram of the styrene PBPK model of Ramsey and Anderson (1984). The inhaled vapor is assumed to equilibrate between the alveolar space and blood within the lung. The body is models as consisting of four tissue groups: fat, muscle, richly perfused and liver. Flow rates are represented by Q, with the subscripts representing the lung and/or tissue group. Concentrations are represented by C, with the inhaled and exhaled (alveolar) concentration given by Cinh and Calv. Arterial concentration is given by Cart and the concentration in venous blood exiting the tissue groups given by Cven for each group. Styrene metabolism is allowed in only the liver and is modeled by Michaelis–Menten kinetics with a V_{max} and K_m.
From Fig. 1,Ramsey and Anderson (1984).

It is important to recognize that these PBPK models are simply an extension of the ventilation–perfusion approach devised by Henderson and Haggard (1943). The respiratory tract was handled identically to the Henderson and Haggard approach in that ventilation was assumed to be continuous, the airways were assumed to be inert, and Henry's Law equilibrium was assumed to be instantly achieved in the alveoli such that the exhaled air and blood leaving the lungs were assumed to be in equilibrium with each other. Henderson and Haggard considered the body to be a single compartment (see Fig. 2), whereas Ramsey and Anderson (see Fig. 3) separated the body into several compartments. The PBPK modeling represents significant improvement, particularly in two contexts. These models explicitly described a fat tissue group which allowed for the sequestration of lipid soluble vapors in this site. Additionally, the PBPK model allows for metabolism. In early models metabolism was confined to the liver, but it can easily be included in any tissue compartment, including the lung (Andersen et al., 1987; Sarangapani et al., 2002).

The PBPK model of Ramsey and Anderson (1984) successfully described the whole body kinetic behavior of styrene, even during the transitional phase when recirculation of vapor to the lung diminishes

lung uptake efficiency. The modeling approach clearly described the rate of increase in blood styrene levels during a multi-hour exposure as well as the rate of decline in blood levels after the exposure ceased. This model successfully described this behavior in both the human and the rat. Since the physiological values (i.e., pulmonary ventilation rates, cardiac output, organ specific perfusion rates) and the metabolic values (V_{max}, K_m) differ between species this modeling approach represented a spectacular advance relative to understanding species differences in inhaled vapor disposition. PBPK approaches have become the standard manner for understanding whole body vapor disposition kinetics for toxicological risk assessment; numerous reviews are available on their use (Clewell & Clewell, 2008; Clewell et al., 2005; Thompson & Beard, 2012).

Important insights into vapor disposition are provided by PBPK approaches. For metabolized vapors a true equilibrium never exists between the inspired air and the body. In a true equilibrium the body would become saturated in accordance with Henry's Law and net uptake would cease (see above). For metabolized vapors, vapor is continuously absorbed in the lungs as long as the exposure progresses with the absorption rate exactly replacing the amount metabolized in the liver (or in other tissues). This is not an equilibrium, but a steady state. In the steady state, liver metabolism rates determine lung vapor absorption rates. This simple relationship was elegantly demonstrated in a companion paper to the styrene PBPK model (Andersen et al., 1984) in which it was shown that inhibiting and inducing liver styrene metabolism diminished and increased, respectively, lung absorption rates of styrene. Species differences in xenobiotic metabolism are common and often of large magnitude. Because PBPK models explicitly incorporate metabolic terms as well species specific terms for pulmonary ventilation, they are well suited for the species extrapolations for predicting human health risks from laboratory animal inhalation toxicity studies. Moreover, because PBPK models incorporate Michealis–Menten kinetics, they can describe vapor disposition at the high, perhaps metabolically saturating, exposure concentrations used in animal toxicity testing, all the way down to low sub-saturating conditions. Describing such "non-linear" behavior is quite important for quantitative risk assessment because the kinetics and disposition patterns of vapor at the high concentrations used in animal toxicity studies will likely differ from those at low, environmentally-relevant levels.

Many vapors have significant lipid solubility and partition into fat leading to complex kinetic behavior. Distribution into fat is a slow process because fat tissues are slowly perfused. During exposure vapor levels accumulate slowly in fat which forms a reservoir. After exposure, blood vapor concentrations decay slowly because vapor is slowly released from the fat reservoir into the blood. This behavior is widely appreciated relative to anesthetic gas disposition (Evers et al., 2006; White & Trevor, 2007). PBPK models provide a physiologically based description of this behavior.

PBPK models offer significant advantages over simple pulmonary ventilation perfusion models. By incorporating terms for vapor elimination, especially by metabolism, PBPK models provide a much more realistic estimation of whole body kinetics. Because the parameters in the model are physiologically constrained they offer a straightforward approach to describing species differences in vapor kinetics. As noted above, this latter aspect is highly beneficial for predictions of human risk from inhalation exposure to solvents based on animal toxicity data. A major limitation of the classical PBPK model is that the complexity of the respiratory tract is not fully incorporated into the model structure. Specifically, the early models assumed that respiration was continuous rather than cyclic and also assumed that the airways were inert, neither absorbing nor desorbing vapors. While the airways may be relatively "inert" with respect to insoluble vapors this certainly is not the case for soluble vapors. Consequently, classic PBPK models do not describe regional vapor absorption within the respiratory tract, nor do they precisely describe overall respiratory tract absorption of highly soluble vapors.

6. The real world

6.1. General model structure

Classic ventilation–perfusion and PBPK models assumed that the airways were inert tubes that merely allowed movement of inspired air to the alveoli. This approach allows for no interaction of vapor with the airway or alveolar tissues themselves. This is obviously a simplification as many vapors cause tissue injury within the airways, indicating they must be absorbed within the airways themselves. For example, it has long been recognized that inhaled vapors could be absorbed in and injure the nose (Cameron et al., 1946). As early as 1924 it was recognized that this process occurred and was dependent on vapor solubility. In his study on inhaled ethyl ether disposition, Haggard (1924) wrote, "the more soluble the irritant the greater the damage to the upper respiratory tract since it is there that a highly soluble irritant is largely removed from the air." Over the ensuing 60 years a large body of literature developed on airway, particularly nasal, vapor absorption (Dahl & Lewis, 1993; Morris et al., 2010). For some soluble reactive vapors (sulfur dioxide, hydrogen fluoride) greater than 95% absorption was shown to occur in the nose of laboratory animals as well as humans (Frank et al., 1969; Morris & Smith, 1982; Speizer & Frank, 1966). The implications of this phenomenon are straightforward. If 95% of inspired vapor deposits in the nose then the tissue concentrations in that site must be very high. Conversely, if only 5% penetrates to the lower airways than concentrations within the tracheobronchial tree must be low. As can be readily apparent, the assumption that the airways are inert, neither absorbing nor desorbing vapors is certainly untrue.

Comprehensive models of inhaled vapor absorption must consider the possibility of vapor absorption not only in the alveoli, but also within the airways themselves. This is particularly true for soluble vapors. Particularly for soluble vapors it is important that the model incorporates phenomena which occur due to the cyclic nature of breathing because vapors often absorb into airway tissues during inspiration but desorb out of airway tissues during exhalation. The fundamental structure of modern comprehensive models is shown in Fig. 4. Air and tissue phases are described for each airway (Fig. 4A) and then strung together in series to describe the entire respiratory tract (Fig. 4B). Computers solve for each compartment simultaneously. For each tissue compartment vapor, is allowed to diffuse across the airspace to the air:tissue interface, dissolve in the interface, and then diffuse through tissue to the underlying bloodstream. Metabolism is allowed to occur in the tissue as appropriate. Although not widely appreciated, respiratory tract tissues are rich in xenobiotic (drug) metabolizing enzymes such as cytochrome P450 mixed function oxidases. In fact, on a per cell basis, the level of some P450 isoforms is higher in the respiratory tract than the liver. This is particularly true in the nose of the rodent (Morris & Shusterman, 2010; Reed, 1993; Thornton-Manning & Dahl, 1997). Models that fail to incorporate this potential are not biologically reasonable.

In reality the relative diffusivity of vapor in air and tissue becomes biologically important. Molecular diffusivity in air is orders of magnitude faster than in tissue. This physical fact has many ramifications. During inspiration vapor molecules are quickly transferred to the tissue interface from which they diffuse away in the tissue only slowly. As air is inspired it is stripped of soluble vapor, a process which may be complete in the alveoli. During expiration, vapor free air passes retrograde over the airways. Since tissue diffusivity is low, a significant fraction of vapor molecules still reside at the air:tissue interface at the onset of expiration because there has not been sufficient time for complete diffusion into the tissue. These vapors will then desorb back into the moving exhaled airstream. Thus, because tissue phase diffusivity is much slower than air phase diffusivity, the airway tissues become a reservoir for vapor, absorbing vapor during inspiration and desorbing vapor during expiration. This is an important defense mechanism

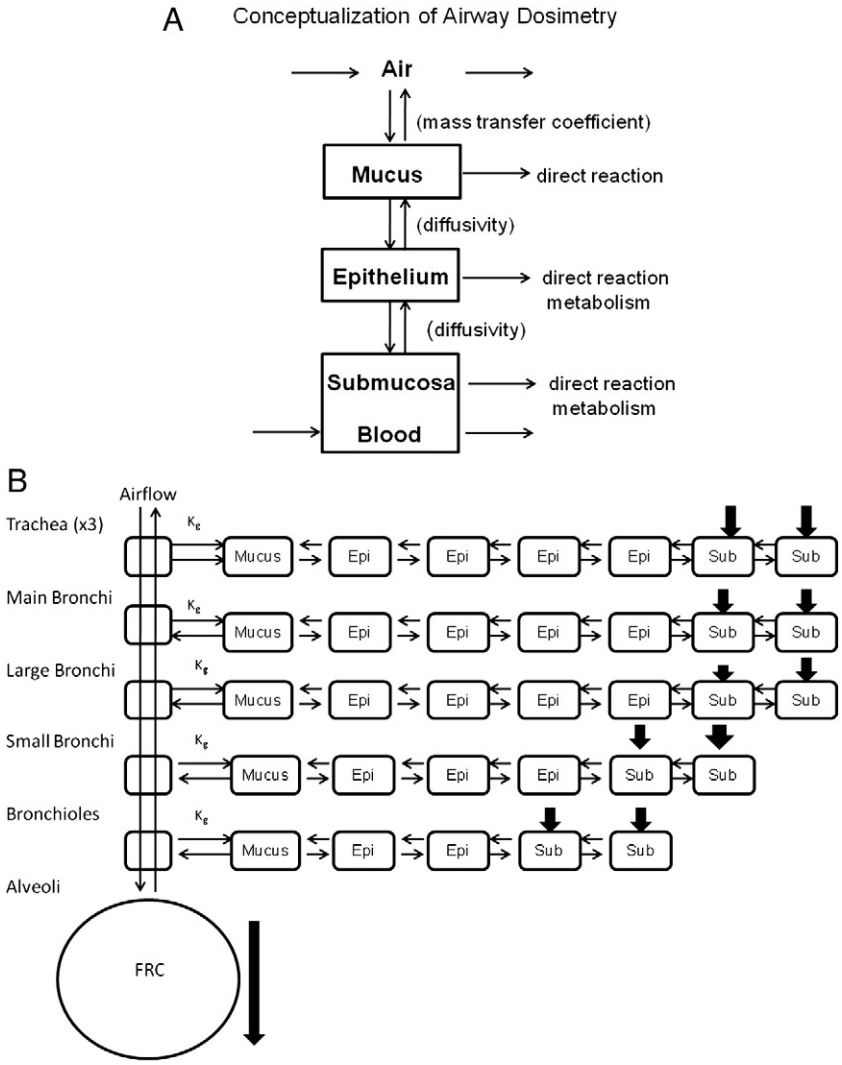

Fig. 4. A. Conceptual structure of airway compartmental model. Vapor in air passing over the airways is allowed to transfer into (and out of) the mucous lining layer as described by the mass transfer approached. Vapor in mucus can diffuse into tissues according to its diffusivity. Vapor can be removed from tissues by direct reactivity with tissue substrates and/or via metabolism. Vascular perfusion is allowed in the submucosal tissues only. From Gloede et al. (2011). **B**. Schematic representation of LRT model for the human. The thin vertical arrows represent the inspired and expired airstream. kg represents the overall mass transfer coefficient for vapor between the air and tissue phase (see text). The model consists of tissue stacks in each of multiple airways: trachea (three consecutive stacks, only one shown for sake of simplicity), mainstem bronchi, large bronchi, small bronchi, bronchioles and alveoli. The large bronchi, small bronchi, and bronchioles represent lumped airways (see text). Each box represents a 0.01 mm deep tissue compartment (Epi = epithelium, Sub = submucosal tissue), The thick arrows indicate compartments which are perfused. The gas exchange regions are modeled as a single compartment (FRC = functional residual capacity).

because sequestration of vapor in the airways serves to limit its penetration to the peripheral highly sensitive alveolar tissues. An important ramification of the absorption/desorption behavior is that it may contribute to species differences. The air and fluid phase diffusivities are determined by the laws of chemistry and are fixed. The duration of a breath in humans is ~5 s (12 breaths per minute), compared to 0.3 s in a rat (200 breaths per minute). Therefore, in a human there is considerably more time during a breathing cycle for vapor to diffuse away from the air:tissue interface than there is in the rat. This impacts the desorption behavior during expiration. Real-world models of vapor absorption must be sufficiently robust to incorporate such behavior.

To describe the real-world absorptive behavior of vapors it is necessary to include both the air phases and tissue phases of the individual airways and to consider the disposition of vapor within each phase. Vapor transfer between air and tissue is fully reversible with interdependent events occurring in both air and tissue phases. Events in the air phase can strongly influence the overall transfer rate to or from tissue. For example, the location and magnitude of air streamlines in the nose, or the degree of airflow turbulence at bifurcations, can be critical relative to local vapor transfer rates (Condorelli & George, 1999; Kimbell et al., 1993). Likewise, events in the tissue phase can strongly influence the transfer rate. For example, rapid reaction (and removal) in the tissue phase serves to make the air:tissue concentration gradient steeper and enhances uptake (Morris et al., 2010). Indeed, if reaction rates are sufficiently large the tissue concentration of vapor is essentially zero at all times and the tissue acts as an infinite sink. Conversely, buildup of vapor within the tissue serves to diminish the air tissue concentration gradient and decreases uptake. This buildup is often termed “backpressure.” When the backpressure in the tissue equals the partial pressure of vapor in the air, there is no concentration gradient between tissue and air and net uptake stops. This is conceptually identical to the total body equilibrium of early ventilation–perfusion models described above except that it is at the local tissue level rather than the whole body level.

The air and tissue phase dispositions of vapor molecules are interdependent and the interplay between these phases results in complex behaviors. Two limiting conditions exist, however. In one

case the overall absorption (e.g., transfer from the air to tissue phase) is controlled entirely by events occurring in the air phase. Uptake of vapors with this characteristic is best described by engineering-based convection–diffusion approaches, which are described briefly below. The other limiting condition occurs when events in the tissue phase control or at least dominate the overall transfer rate. In this circumstance the tissue phase contains the rate limiting step which, in essence, controls overall throughput. Uptake of these vapors is currently best described by localized PBPK modeling approaches as this approach is well-suited to describe tissue disposition. Whichever modeling approach is used, it is essential to recognize the fundamental limitation of modeling itself. Specifically, the models represent mathematic approximations. None is truly correct; all incorporate simplifying assumptions. Well-developed models can provide key insights and useful predictions of complex behavior, but they are only human-made conveniences.

6.2. Engineering-based approaches

Highly reactive vapors are instantly destroyed upon entry into the tissue. An example would be a weak acid which instantly ionizes. For such vapors tissue concentrations are essentially zero and the tissue acts as an infinite sink. In this circumstance tissue factors per se are not important, and the uptake patterns for the vapor are controlled solely on air phase factors. These vapors typically demonstrate a highly localized pattern of injury. An engineering-based, convection–diffusion approach can be used to model vapor uptake within in highly localized areas of the respiratory tract. These often rely on computational fluid dynamic (CFD) approaches to precisely define airflow characteristics. The elegant studies by Kimbell et al. (1993, 1997) relied on this approach to model highly localized deposition patterns of formaldehyde within the nose. Chronic exposure to formaldehyde results in tumors in only very specific locations within the nose of the rat (Morgan & Monticello, 1990) and the work of Kimbell indicated that these correlated with formaldehyde deposition hot spots (Kimbell et al., 1997). Extension of this approach to the human nose supported the development of a scientifically based quantitative risk extrapolation for this inhalation carcinogen.

The convection–diffusion approach is best suited for vapors that are highly reactive whose uptake is strongly, if not wholly, dependent on air phase factors. Formaldehyde represents such a vapor. Convection–diffusion based modeling of formaldehyde has been extended to include the entire (upper and lower) respiratory tract (Overton et al., 2001). Ozone is another highly reactive gas whose respiratory tract uptake has been modeled by convection–diffusion approaches. This was pioneered by Miller and colleagues whose work has brought great insight into the amount of ozone that is delivered to specific airways in the lungs of laboratory animals as well as the human adult and child (Miller et al., 1978, 1985; Overton & Graham, 1989; Overton et al., 1987).

Convection–diffusion models provide great insight into localized airway uptake of highly reactive vapors but are beyond the scope of the current review. The reader is referred to recent reviews (USEPA, 2009, 2011). This approach has been extended to describe nasal uptake of vapors which are less reactive and/or metabolized within tissues (Schroeter et al., 2006, 2008) but, currently, are not well suited to explicitly handle tissue phase (e.g., biologic) phenomena. In essence the current approach is to write convective-diffusion flux equations for loss of vapor from air and for flux away from the mucus lining layer in tissue. These can then be coupled and solved with standard computers. By making assumptions about tissue kinetics (e.g., V_{max}/K_m) the model can be made to fit uptake data, i.e., model parameters are manipulated until the model predictions conform to measured data. Thus, this approach does not represent a true "first-principles" description of uptake; however, direct measurement of enzyme kinetics in vitro and incorporation of these parameters in these models do allow a first-principles approach. Through either approach these models provide insights into highly localized vapor absorption behavior. Because they focus on air phase phenomenon, convection–diffusion approaches are not currently well suited to describe vapor uptake during the transitional or final steady state phases of exposure. At these times recirculation of vapor in the bloodstream is of quantitative importance and convection–diffusion equations are poorly suited to describe this behavior.

PBPK models are better suited to describe tissue phase phenomenon and can be used to construct first-principles models, i.e. the model parameters are pre-defined and no manipulation (data-fitting) is needed to describe uptake patterns. The PBPK models, however, do not precisely describe air phase convection–diffusion phenomenon. The convection–diffusion models however have been solved to provide average mass-transfer coefficients. These coefficients can be used to estimate the air phase contribution to the overall uptake processes by simple algebraic formulas. So doing results in hybrid computational fluid dynamic–physiologically based pharmacokinetic (CFD–PBPK) modeling. The first such models were proposed by Frederick and co-workers to describe vapor uptake in the nose; their work has provided the template for subsequent studies (Bush et al., 1998; Frederick et al., 1998, 2002). These authors based their modeling efforts on mass-transfer coefficients that were derived for the nose based on CFD models (Kimbell et al., 1993). Mass transfer coefficients have been estimated for the lower airways as well (Asgharian et al., 2011; Condorelli & George, 1999) and simplified estimates can be made based on airway geometry and air flow rates (Cussler, 1997; Sarangapani et al., 2002).

Air phase phenomena are often very important relative to absorption within specific airways, and, in particular, comparing airway absorption between rodents and humans. Because this is incorporated in models by an algebraic simplification, there may be a tendency to downplay the importance of air phase phenomena. This would be inappropriate. However, the model simulation results afforded by average mass transfer coefficients closely predict actual uptake behaviors (e.g. (Frederick et al., 1998, 2002)) suggesting that they provide reasonable estimate. It should be noted, however, that hybrid PBPK models rely on an average air phase mass transfer coefficient to provide approximations of airway uptake. Recent work suggests that using average coefficients may be subject to limitations because ventilation is cyclic and the actual uptake during the varying flow velocities of normal respiration may not be precisely predicted by values averaged over the entire respiratory cycle (Asgharian et al., 2011). This is an area in need of further study. Nonetheless incorporation of mass-transfer coefficients is an essential component of uptake models and serves to at least approximate the quantitative influence of air phase behaviors.

6.3. Biologically-based approaches — lower airways

Biologically-based approaches for airway vapor disposition rely on the same principles as those used in classic ventilation–perfusion models, but apply them to each airway. Specifically, in the simplest approach it assumed that the airborne vapor transfers into and out of with the mucus lining layer in each airway. Once in the lining layer, vapor may diffuse away from the surface towards the capillary bed where it might get removed by the circulation, tissue metabolism and/or direct reaction with tissue substrates (Fig. 4, above).

Johanson (1991) and Gerde and Dahl (1991) used the basic biologically-based approach described above to describe vapor disposition during cyclic breathing, and in so doing highlighted absorption/desorption behavior. Johanson (1991) described the lower airways as 18 successive generations of airway each 15 μm thick. He assumed equilibration of vapor between the air and tissue at the interface based on an estimate of vapor molecules that could diffuse to and collide with the airway wall (Davies, 1976), but allowed no blood flow or

metabolism within the airway tissues. His model was perhaps the first to describe airway absorption/desorption and predicted that soluble vapors would be absorbed in the airways and not penetrate to the alveoli during inspiration.

The airway model of Johanson (1991) was extended by Kumagai and Matsunaga (2000). Their model incorporated fewer airways than that of Johanson (1991), assumed equilibration of vapor with the mucus in the small airways and included airway perfusion terms, thus allowing for vapor to be removed from airway tissue by the bloodstream. This is important for longer-term exposures because whole body absorption and vapor recirculation will influence uptake parameters during the transitional and steady-state phases of prolonged exposure. Their model did not incorporate explicit airway geometry and relied on modulating values to obtain a fit with published uptake data. The model of Kumagai and Matsunaga (2000) successfully predicted the complex uptake behavior observed in humans during short-term (10 min) exposure to a variety of vapors.

The ventilation perfusion models predicted a smooth relationship between uptake efficiency and partition coefficient (Fig. 5), however, this behavior is not seen. The closed circles in Fig. 5 represent the actual human lower respiratory tract absorption efficiency during 10 min exposure for a variety of vapors with partition coefficients ranging from 0.1 to 10,000. As can be seen a smooth relationship is not apparent, rather there exist maxima and minima at partition coefficients of ~10 and 500. This is due to airway absorption/desorption behavior. The concept of equivalent volumes is useful in understanding the potential quantitative significance of airway absorption/desorption. The surface area of the tracheobronchial tree is ~3000 cm^2 (Mercer et al., 1994). The total airway tissue volume (assuming an average tissue depth of 50 μm) is 15 cm^3 in comparison to a tidal volume of 500 ml. For a partition coefficient of 1, the equivalent volume of airway tissue is 15 ml (15∗1), compared to the tidal volume of 500 ml, thus insignificant amounts of vapor would be expected to absorb/desorb. However, if the partition coefficient is 30, the equivalent airway tissue volume is 450 ml (15∗30), a number that is quite significant with respect to the tidal volume of 500 ml and quantitatively significant levels of absorption/desorption would be anticipated. This is, indeed, the case. For vapors of partition coefficient less than 10 there is little deviation of measured uptake versus that predicted by V–P models. In essence, these vapors are of such little solubility that an insignificant fraction of vapor actually absorbs/desorbs from the airways during cyclic breathing. As partition coefficient increases airway absorption/desorption becomes important. Overall uptake is less than predicted from the V–P model because vapor desorbs from the airways during expiration and is exhaled, thus reducing the total absorption. Vapor absorption is less than that predicted by V–P until partition coefficients increase to 5000 or more. For higher partition coefficients absorption efficiency is actually greater than that predicted by V–P approaches. Recall that the V–P model predicts a maximum of 70% absorption because it is assumed that the airways are inert and the airway volume (dead space) is 30% of the tidal volume. Thus total absorption cannot exceed 70% because only 70% of the inspired air reaches the alveoli where absorption can occur. For highly soluble vapors (partition coefficient >5000), there is very high absorption in the airways and little desorption because the extreme partitioning serves to prevent desorption. In essence the airways are not dead space but serve to absorb vapor with little desorption due to the extraordinarily high partition coefficients. Therefore, vapor is scrubbed from the entire tidal volume, not just from the air that penetrates to the alveoli.

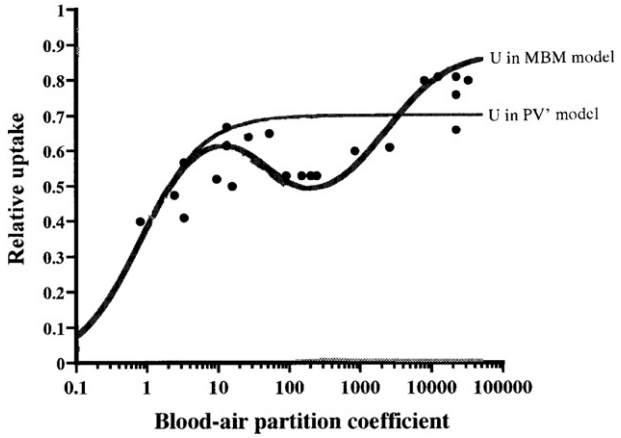

Fig. 5. Lower respiratory tract uptake of vapors of differing blood:air partition coefficients (Kumagai & Matsunaga, 2000). Closed circles represent experimental measurements. The thin line represents predictions of uptake by simple ventilation perfusion models (U in PV' model), the thick line represents predicted uptake by the cyclic ventilation model of Kumagai and Matsunaga (U in MBM model).

The modeling efforts of Johanson (1991) and Kumagai and Matsunaga (2000) served to greatly increase our understanding of the complexity of vapor absorption. These models, however, suffered from significant limitations. The model of Johanson (1991), did not precisely include air phase phenomena and did not allow for airway perfusion. The model of Kumagai and Matsunaga (2000) ignored the large airways and relied on model fitting to obtain the model parameters. Neither model included the potential for metabolism in airways to occur. In addition, neither model included the nasal airways. Advances in nasal vapor absorption modeling allowed development of model structures that overcame these limitations.

6.4. Biologically-based approaches — nose

Much effort was expended in the development of models for the upper respiratory tract (nasal) vapor absorption. Since it is possible to isolate the nose (via insertion of an endotracheal tube), exact measurements of nasal vapor absorption under defined air flow conditions have been made. The large database on nasal vapor absorption significantly aided the development of models for nasal uptake. Key aspects of the database defined the processes that needed to be included in modeling efforts. First, near total (>95%) nasal absorption occurs for vapors that are both water soluble and reactive (Morris & Smith, 1982; Morris et al., 2010). Therefore, any model that does not predict the potential for total absorption in the nose is deviant from actual measurements. Moderate to high nasal absorption efficiencies were observed for non-reactive but soluble vapors (~PB 200–1000) and low absorption efficiencies are observed for non-reactive low soluble vapors (PM<200) (Morris et al., 1993). (In this regard, it should be noted that "high" and "low" solubility for nasal absorption has a differing contextual meaning than for the lung where high absorption is seen for PB>10). Because the volume of nasal tissues is small, efficient absorption in this site leads to high tissue concentrations. Tissue concentrations in the mM range may well occur in the rodent during inhalation exposure (Morris & Hubbs, 2009). From this perspective it is easy to appreciate why the nose is such a common target for vapor-induced injury. The nasal absorption database indicates that local nasal metabolism occurs and serves to strongly enhance nasal absorption efficiencies. This is because metabolism removes vapor from tissue and in so doing makes the air:tissue concentration gradient steeper, thus increasing diffusion into the tissues. In summary, biologically reasonable models must include terms that allow for increased absorption efficiencies with increasing partition coefficients and also must include terms for local metabolism. It should be noted that while a robust experimental database exists, the experimental measurements have only been made at the onset of exposure. Thus nasal absorption is well defined during the initial quasi-steady state phase of exposure, but data are absent for absorption during the transitional and final steady-state phases of exposure.

Perhaps the first nasal model was that of Davies (1976). Based simply on air phase diffusion coefficients, the model predicted very efficient nasal absorption of vapors with low molecular weights. Aharonson et al. (1974) applied mass transfer approaches to describe nasal absorption of acetone vapor in the nose. A complexity of their approach was that the mass transfer coefficients were not known, and are strongly dependent on the air flow rate; thus a validated mathematic description was not obtained. Morris et al. (1986) proposed a very simplistic ventilation perfusion model for nasal vapor absorption. This model was identical in concept to the ventilation–perfusion approach of Henderson and Haggard (1943), except that the nasal perfusion rate was used. This simple approach successfully described the nasal absorption of soluble vapors assuming a nasal perfusion rate of ~0.2 ml/min for the rat, a physiologically reasonable number (Morris et al., 1986). Due to the thickness of the air:blood barrier in the nose, it is not physically possible for equilibration to occur between the air and bloodstream in the nose; thus although successful, the simple nasal ventilation–perfusion model was not physically reasonable.

The first successful PBPK model for nasal vapor absorption was proposed by Morris et al. (1993). This model relied on the conceptualization shown in Figs. 1 and 4A. Vapor was assumed to equilibrate with mucus in accordance with Henry's Law. Once in tissue vapor was allowed to diffuse down to the capillary bed and be removed by circulation. Metabolism was allowed to occur within nasal tissues. This model successfully described nasal vapor absorption of a wide range of metabolized and non-metabolized vapors. A major limitation of this model was the failure to include terms for air phase phenomena; it was purely a tissue-based model. Concurrent with the modeling efforts of Morris et al. (1993), Kimbell et al. (1993) used CFD approaches to fully define air phase behavior in the nose. In a major advance, that was highlighted above, Frederick and co-workers (Bush et al., 1998; Frederick et al., 1998), included mass transfer coefficients which were derived from Kimbell's CFD efforts (Kimbell et al., 1993), with the PBPK structures for tissue disposition. This approach was utilized to develop a first-principles model of nasal vapor absorption (Bush et al., 1998; Frederick et al., 1998). A significant feature of these models is that they have no undefined variables. Every variable is determined a priori, no fitting (e.g., artificial manipulation of variables to improve the model output) is required. These models closely described nasal absorption of multiple vapors of differing solubility and differing propensity for direct reaction and/or local metabolism. This approach has also been applied to the rat and human to describe nasal absorption of vinyl acetate (Hinderliter et al., 2005; Plowchalk et al., 1997) and also diacetyl, the toxic ingredient in butter flavoring vapors (Morris & Hubbs, 2009).

The reader is referred to the primary literature for a complete description of the hybrid CFD–PBPK models. Their success highlights several conceptually important issues. First, these were a priori models. If a key step was excluded in the model structure, the model predictions would fail; this has not been observed. Thus, the success of these models indicates that they incorporated all of the key events in the absorption process. These are the processes that have been highlighted numerous times in this review: movement in the air phase to the air:tissue interface, solubilization in the tissue at the interface, diffusion to the blood capillaries, and potential metabolism and/or direct reaction within the tissues. These models now provide validated tools to understand and predict nasal vapor absorption. In particular they allow for detailed comparisons among species. In general, vapors are absorbed more efficiently in the nose of the rat than human. This is due to a variety of factors including more effective air phase transfer to the air:tissue interface in the rat; a thinner air:blood barrier in the rat; and higher local metabolism rates in the rat. There are important implications of the enhanced nasal vapor absorption in the rodent compared to the human. Highly efficient absorption in the nose results in high nasal tissue concentrations during inhalation exposure. In fact, nasal concentrations in the millimolar range during inhalation exposure are certainly possible for soluble vapors (Gloede et al., 2011; Morris & Hubbs, 2009). Greater absorption in the rat compared to human nose indicates the rodent is more likely to develop nasal injury than the human because the delivered dose is higher. Conversely, the enhanced nasal absorption in the rodent results in less vapor penetrating to the lower airways in the rodent than in the human. Thus, the rat lower airways are at lesser risk than those of the human. Unlike the rodent, the human is capable of mouth breathing which totally bypasses the nasal absorption process. Thus, a challenge of modern inhalation toxicology is to use data obtained in nose-breathing rodents to predict risk to mouth-breathing humans.

Although highly successful, the nasal hybrid CFD–PBPK models do suffer from limitations. Their handling of air phase factors is based on average mass transfer coefficients and represents a major simplification. These models use “lumped” compartments; tissue is modeled as large composite areas. Thus these models do not predict the highly localized hot-spots that CFD models show for formaldehyde, but rather predict the average absorption over large surface areas. Finally, these models, to date, have only examined the initial quasi-steady state period of exposure, but have not been extended to describe the transitional or final steady state phases.

6.5. Biologically-based approaches — the entire respiratory tract

The success of nasal dosimetry models indicates that they captured all essential behavior in the vapor absorption process. Recognizing the documented strengths of that modeling approach, Morris and co-workers developed a CFD–PBPK model for whole respiratory tract, by applying the modeling structures for nasal tissue to the individual airways of the lower respiratory tract (Gloede et al., 2011). The model was anatomically and physiologically defined; airway geometry and tissue depths as well as regional airway perfusion estimates were obtained from the literature. Air phase mass transfer constant estimates were utilized to account for air phase behavior. When applicable, tissue metabolism and direct reaction rates were included as well. This a priori model successfully described the lower respiratory tract absorption efficiencies of multiple vapors in the human lung (Fig. 6).

As for the nose, the closeness of the predictions to actual measurements provides confidence that the model structure includes all

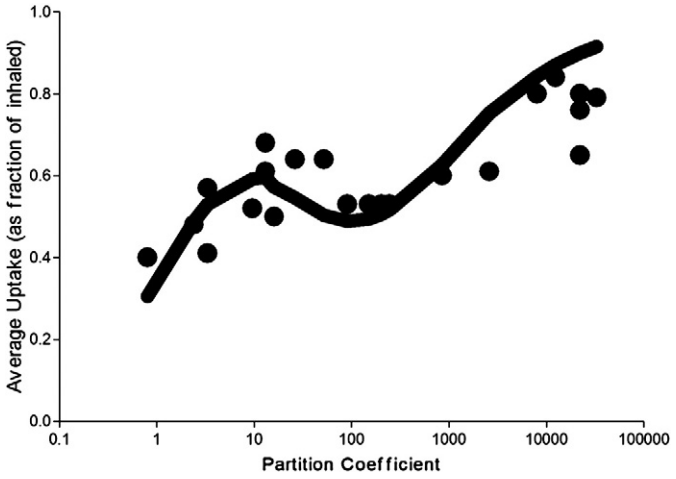

Fig. 6. Lower respiratory tract uptake of vapors of differing blood:air partition coefficients (Gloede et al., 2011). Closed circles represent experimental measurements. The line represents predicted uptake by the validated CFD–PBPK cyclic ventilation model of Gloede et al. (2011).

significant processes. By parameterizing the model with measurements for rat airway dimensions, perfusion, etc., this model structure also allows for examination of vapor absorption in the rat airways. The model also fit whole respiratory tract uptake of multiple vapors, again providing confidence that it provides a reasonable approximation.

These models provide an approach whereby vapor absorption in the rat versus human airways can be explicitly compared. The model estimates that the airways of the rat absorb inhaled vapors with greater efficiency than the human. Greater absorption in the proximal airways of the rat compared to human results in lesser amounts of vapor penetrating to the distal airways of the human than rat. Thus, the distal airways of the humans receive a greater delivered dose than those of the rat and likely are at greater risk. This difference is large; the model estimates as much as 20-fold more vapor penetrates to the terminal bronchioles of the lightly exercising, mouth breathing human than the sedentary rat. The model provides insights into the reasons for this behavior. One, but certainly not the only, aspect is the difference between nose and mouth breathing. Humans are capable of mouth breathing; the rat is not. Importantly, the lower airways themselves have greater absorptive capacity in the rat than human. The air phase mass transfer coefficients are higher in the rat, the thickness of the epithelium (i.e., the air blood barrier) is lower in the rat, and the relative airway perfusion rates are also higher in the rat (Gloede et al., 2011). Another important consideration is the differing breathing frequencies and airway absorption/desorption behavior. The duration of the average breath is 0.3 s in the rat compared to 5 s in the human. In the short breath duration of the rat little vapor can diffuse away from the air tissue interface into deeper regions of the tissue, thus much vapor is still present at the interface during expiration and is therefore desorbed. During the next inspiration, the desorbed vapor is simply replaced by the incoming air. Thus the absorption/desorption cycling is anticipated to be greater in the rat than human simply because of the short duration of each breath. Strictly speaking, vapor that absorbs/desorbs from the mucus lining layer is never absorbed into tissue; however this process limits the penetration of vapor to the distal airways. Without the development of biologically-based models these insights into species differences in vapor absorption would not have been possible. As noted above, diacetyl vapor produces nasal and large airway injury in the rat lung, but in the human is associated with small airway (bronchiolar) injury. The vapor dosimetry model provides the explanation for this discrepancy. In the rat little diacetyl penetrates to the small airways during inhalation exposure thus the lack of injury. In humans much larger fraction of inspired diacetyl reaches the small airways; thus the small airway injury is manifested.

Despite the success of CFD–PBPK modeling efforts limitations do exist. As noted above for the nose, the CFD–PPBK models rely on average mass transfer coefficients, and model large portions of airways as lumped compartments. Perhaps, surprisingly, a weakness of the whole respiratory tract CFD–PBPK model stems from simple anatomical and physiological factors. The models are based on simplified geometric models of lung airway branching pattern which may not be reflective of the true situation. Regional airway perfusion rates are an important input parameter in the models but are poorly defined. Finally, it can be noted that the precise value for vapor tissue diffusivity is not known. It is assumed to range from 15 to 33% of the diffusivity in water, but the precise value is not known.

Comprehensive models of airway vapor absorption to date have only focused on short-term exposures, i.e., the initial quasi-steady state phases of exposure. It is certainly possible to link the respiratory tract CFD–PBPK model to whole body PBPK model to describe uptake throughout prolonged exposure. This has not yet been performed with the cyclic ventilation models. One would anticipate that as whole body levels increase towards Henry's Law equilibrium that airway absorption and the degree of absorption/desorption cycling would decrease. However, this prediction remains to be proven. The linkage of the respiratory tract with whole body PBPK models has been done with models which assume continuous constant velocity flow (Sarangapani et al., 2002). These models successfully describe whole body absorption and blood levels both during and after multi-hour exposure. This suggests that simplified models are adequate for predicting whole lung absorption rates and blood vapor concentrations during long exposures because absorption/desorption issues become less important as exposure duration increases. In this context, the classic models of Henderson and Haggard (1943) may well be adequate. However due to extensive absorption/desorption cycling of soluble vapors during normal cyclic respiration, such simplified models must be used with caution to predict small airway dosimetry, particularly during short term exposure to soluble vapors.

7. Conclusions

A variety of modeling approaches are available to describe vapor absorption in the respiratory tract. Convection–diffusion models are well suited for predicting localized uptake patterns of soluble reactive vapors whose absorption is dependent primarily on factors occurring in the air space. These models accurately predict deposition "hot spots" within the nose or lower airways and these hot spots correlate with localize areas of injury that are produced by these vapors. The convection–diffusion approach is not sufficiently advanced to precisely incorporate tissue factors in their structure. Modern PBPK models are well suited to describe tissue phenomenon such as localized metabolism and whole body accumulation and recirculation of vapors. These models have typically been used for simulations of vapor absorption under simplified breathing patterns but recently have been extended to describe uptake during normal cyclic breathing. This latter approach may be necessary to describe the inhalation dosimetry of water soluble vapors that injury the airways. The biologically-based PBPK approaches have provided key insights into vapor uptake in differing species and greatly facilitate the animal to human extrapolations that are intrinsic in most human health hazard assessments. While these models are essential tools they do not precisely describe events occurring in the air space, and they have been used to predict absorption over large surface areas (e.g., entire airways), but are not well suited to understand localized hot spot phenomena. More comprehensive models of vapor absorption will require better linkage of the convection–diffusion with the PBPK approaches. Such models will be extraordinarily computationally intense, but may be necessary for full understanding of the inhalation dosimetry of some agents. Inherent in all modeling efforts is the concept that no model is truly correct. The current models are human-made conveniences for understanding inhalation dosimetry of airborne vapors. For some vapors only simple models may be needed, for other vapors future development of linked convection–diffusion–PBPK models may be needed. The state of the art is sufficiently well advanced that selection of the appropriate modeling approach is straightforward. Decades of research has shown that inhalation dosimetry patterns are often the critical factor determining the site of airway injury in animals and humans. Thus, assessment of the pharmacology or toxicology of inspired vapors is incomplete in the absence of definition and application of dosimetric factors in the analysis.

Conflict of interest

The author has been a consultant to ConAgra, Inc. on the inhalation toxicity of diacetyl and butter flavoring vapors.

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