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PHARMACOKINETIC MODELS FOR UPTAKE OF VAPORS A REVIEW

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INTRODUCTION

The uptake of a toxicant volatile vapor by inhalation leads to incredibly complex transport processes influenced by unsteady convection through a non-dichotomously branching network of conducting tubes known as the *pulmonary airways*. The properties of the chemical, its solubility in and the diffusion through the mucous linings of those conduits play a crucial role in the subsequent uptake by the pulmonary capillary bed and distribution of the chemical throughout the systemic circulation and through the organs which it perfuses.

The first step in the formulation of a realistic model is the development of a working hypothesis for the presumed mechanisms of uptake of toxicants by the lungs in the forms of: (a) vapors, (b) aerosols, and (c) particulate matter. At the same time, based on basic principles of biophysics and physiology, one may identify the primary and eventually the secondary and tertiary parameters and variables that need to be taken into account in such a model. The process may be accomplished in successive phases of increasing complexity, gaining valuable experience upon the completion of each phase of the overall program.

The transport of gases and vapors within the pulmonary airways is a highly complex and dynamic process. Substantial differences in airway breathing patterns between humans and quadrupeds used in toxicological research severely limit our ability to extrapolate the effects observed in animals to humans (Lippmann 1984). The penetration of vapors into the lungs depends critically upon the flow characteristics within the conducting airways; i.e. the length, diameter and branching angles of the airways and the pattern of breathing. Only the larger airways are accessible to direct measurements in either humans or animals.

In the course of normal respiration, a tidal volume of about 600 ml. is inhaled during the approximate 2 sec inspiratory phase. The total lung capacity is about 3000 ml at normal deflation. The conducting airways proximal to the alveolated airways are termed the *dead space*. Their volume of about 200 ml is the first to be traversed by the inspired gases and vapors. At its peak flow rate, the flow may exhibit characteristics of turbulence in the trachea and upper airways at high Reynolds numbers $R_e > 1500$ to 2000. The flow Reynolds number (ratio of inertial to viscous forces) based on airway diameter decreases markedly with distance along the pulmonary airway tree, reaching values of $R_e < 2$ in the terminal bronchioles where the flow remains laminar (Bouhuys 1964). It has been estimated by Davis (1972) that $R_e \cong 2.10^{-4}$ at the openings of the alveoli, indicating a predominance there of viscous forces with negligible inertia.

Altshuler et al. (1959) have studied the intrapulmonary mixing of gases by developing a technique allowing separate detection of the amount of aerosol recovered in tidal and residual air. They postulated that all mechanical mixing occurs in the deadspace airways. However, on the basis of that same work, Taulbee et al. (1978) concluded that such mixing occurs primarily in the alveolar region. We would tend to support the latter view on the basis of observed flow field patterns, comparative volumes and residence times of the fluid in that region.

Pedley et al. (1977) conducted measurements for expiratory flow through six generations of branching conduits. Their results indicate that a virtually flat velocity profile across the tube cross-section is achieved within one diameter downstream from the flow divider (carinal edge). Pedley proposed that the induced secondary motions at the branch junctions affect the velocity profiles in a manner similar to turbulence. According to West et al. (1959) and Dekker (1961), who experimented with casts of the trachea and the first few bronchi, expiratory flow is less susceptible to the onset of turbulence than is inspiratory flow. Measured values of the transition or critical Reynolds number are of the order of $R_{e\,crit} \cong 1500$ in the trachea.

Scherer et al. (1982) attribute an important longitudinal convective transport mechanism to differences between inspiratory and expiratory bronchial velocity profiles and this interesting phenomenon will be discussed further. As mentioned above, the branching patterns of the airways differ substantially between humans and test animals such as rodents. The larger size of the human airways results in larger Reynolds numbers R_e for similar flow velocities and leads to more turbulence. Turbulence is rare or absent in animal airways. Furthermore, human pulmonary branching patterns are relatively symmetrical and dichotomous in contrast to the highly asymmetric or monopodal branching of quadrupeds. In human airways, at each bifurcation the carinal ridge (flow divider) is situated near the centerline of the parent airway where the flow velocity is maximal. In animals, however, the bulk of the flow continues into the larger (major) daughter branch with very little change in flow direction. The lesser flow directed into the smaller (minor) daughter branch emanates from more slowly moving streams nearer the wall of the parent airway. In general, much less mixing would develop for such flow patterns in animals as compared to humans.

Significant differences between human and animal pulmonary flow patterns have also been observed during expiration (Schlesinger et al. 1983). For the more symmetrical branching patterns of humans, gas jets impinge on the opposite sides of the parent airway directly downstream from the two daughter airways. This contrasts with the animal branching patterns for which the parent and major daughter branches are more closely aligned, so that a small jet issuing from the minor daughter airway during expiration is not likely to persist across the full diameter of the parent tube.

In summary, one would expect less mixing to occur in the conducting airways in rodents than in humans for identical Reynolds numbers as a result of the profoundly different anatomical characteristics of the pulmonary branching patterns in the two species.

Review of experimental studies

Esch et al. (1988) reported the results of lung airway branching patterns on gas penetration into human and canine lungs. Aerosol was inhaled from one bag and exhaled into another through a solenoid-controlled valve. Volume changes in the two bags were measured with a bell spirometer. The volumes of breath held were controlled. Aerosol concentrations in the

two bags were monitored photometrically. The studies were conducted on both excised lungs and *in vivo*. For the excised lungs, the minimal volume, defined as the air volume at zero transpulmonary pressure, was determined by measurement of the water displacement as the lung was totally immersed in a water tank. For all pulmonary function tests, the lung was suspended in an acrylic artificial thorax and was then slowly inflated to -30 cm H_2O by creating a vacuum in the artificial thorax. In this way, any collapsed airways were opened and leaks were detected. Subsequently, the lung was inflated in increments of -3 cm H_2O and held at each point until the pressure reached -24 cm H_2O, which was assumed to be its *in vitro* lung capacity. No further difference in lung volume occurred for pressure changes beyond -25 cm H_2O. The lung was then deflated in increments of 3 cm H_2O to produce a static compliance curve of pressure vs. volume and a determination of *in vitro* vital capacity.

It was then possible to ventilate each right lung within a range of breathing rates of 12 - 90 bpm with a tidal volume of about 250 ml using a calibrated 1.5 liter syringe. A single-breath nitrogen washout test (Fig. 2) was performed on each lung to test the variability of composition of the inspired air. The percentage of nitrogen versus volume exhaled was recorded in real time.

A group of tests was then conducted using controlled breath-holding manoeuvers of 0 - 40 sec at 5-sec intervals and then up to 90 sec at 10-sec intervals (Fig. 3). Aerosol recovery (RC) after breath-holding (B_2) was calculated from

$$\mathrm{RC} = \frac{B_2 - 32\,B_1 / V_1}{(A_i - 32)\,B_1 / V_1}$$

where RC is the fraction of aerosol recovered, B_1 and B_2 are the measured volumes of bags 1 and 2 respectively, V_1 is the volume of aerosol remaining in bag 1 after inhalation and A_i is the volume of aerosol inhaled, corrected for the 32 ml deadspace in the apparatus.

Convective gas transport experiments were more recently reported by Fang et al. (1992) on a cast of the human tracheobronchial airways which included all branches to less than 1 mm in diameter. Latex particles of 0.5 μm serve as excellent tracers to label the convective transport as they diffuse only negligibly and have a short relaxation time. The time of arrival of tracer particles transported to peripheral segments of the cast during high-frequency ventilation was measured by an optical particle counter at various oscillatory tidal volumes and frequencies. High-frequency ventilation is known to be capable of delivering gases to the alveolar region with tidal volumes much less than the pulmonary deadspace.

Such oscillatory flows in a branching network of pulmonary airways can be characterized by:

a) the oscillatory Reynolds number R_e representing the ratio of inertial to viscous forces:

$$\mathrm{R_e} = \frac{4 f V_T}{\pi D \nu}$$

b) the Womersley number α reflecting the ratio of oscillatory forces to viscous forces

$$\alpha \equiv \left(\frac{D}{2}\right)\sqrt{\frac{2 f \pi}{\nu}}$$

c) the Strouhal number α^2/R_e as a combination of a) and b), reflecting the ratio of oscillatory to inertial forces. The Strouhal number is often used in the evaluation of vortex shedding from an oscillating aerofoil surface.

In the above, f is the frequency of oscillation, V_T the tidal volume, D the diameter of the airway, and ν the kinematic gas or vapor viscosity.

Such results can be used to establish criteria for effective gas convective transport in the pulmonary airways. It has been demonstrated both theoretically and experimentally by Grotberg and co-workers (1984, 1986) that flow resistance is greater during exhalation (convergent flow) than during inhalation (divergent flow). Schroter and Sudlow (1969) have measured significantly different flow velocity profiles during inspiration and expiration in a physical branched airway model. From direct measurements in a human (or animal) airway cast during high-frequency ventilation, one can determine the time-dependent particle concentrations at the exits of the peripheral airways. These can be used to evaluate quantitatively the carrier gas convective transport from the trachea down to the peripheral airways as well as the influence of tidal volume, breathing frequency and the kinematic viscosity of the carrier gas on this convective transport.

Fang et al. (1992) suggest, on the basis of such measurements performed on a cast of the human airways, that convective gas transport becomes essentially independent of Reynolds number and Strouhal number in the regions in which unsteadiness dominates, that is, above a critical value of the Womersley number α_{crit} lying in the range $27 < \alpha_{crit} < 46$.

For the human (but not the rat), this corresponds to the upper few generations distal to the trachea. In that region and for that flow regime, there may exist an effective symmetry between inspiratory and expiratory velocity profiles in the trachea.

As the flow direction at a branch changes abruptly in time during the transition from inhalation to exhalation, and vice versa, significant secondary flows develop which induce flow instability and enhance gas mixing. This is the case particularly during flow reversal. The structure of the oscillatory flow field at the level of the terminal airways ($R_e < 1$) can be considered to be jet-like during inhalation and to act as a sink during exhalation. A bi-directional flow is established, comprised of an axial core stream and an annular return as depicted in Fig. 1. There is likely little gas exchange between the two streams, except at the terminal airway openings. The spatial division between the core and the annulus is likely to vary with time throughout the dynamic breathing cycle.

Proposed mechanisms of action

Godleski and Grotberg (1988) formulated a theoretical basis for the establishment of a steady axial stream in a three-dimensional tapered tube. The magnitude of the stream is greatly increased in three-dimensions relative to its two-dimensional counterpart; in fact, by an estimated factor of five. Briant et al. (1992) have succinctly summarized the combined effects of the bi-directional convection described above during oscillatory flow in the pulmonary airways. As portrayed in Fig. 2, the flow profiles are flatter during expiration (Fig. 2b) and more tongue-like during inspiration (Fig. 2a).

The two factors tending to flatten the velocity profile during exhalation are suggested to be: a) the inertial effects which tend to carry the faster-moving flow from each daughter

airway over to the opposite far side of the parent airway, and b) the lubrication layer effect which tends to flatten the profile from a parabolic shape.

The two effects combine to create a net velocity profile as shown in Fig. 2c. The resultant profile strikingly resembles the bi-directional flow at a bifurcation (Fig. 1) and suggests that the origin of this core/annular bi-directional flow resides in the difference in velocity profile shapes in the inspiratory (divergent) and expiratory (convergent) flows.

The position of inflection of the velocity profile corresponding to the boundary between the core and the return annulus may be governed by the kinematic viscosity of the gas for a given wall geometry (Grotberg 1984). On the other hand, Paloski et al. (1987) have proposed that the relative size of the core is dictated by the gas composition in the airway; the higher the viscosity, the narrower the core. One would intuitively expect the flow velocity to increase as the core narrows, and the opposite to occur in the annulus. For a low viscosity gas, one would anticipate the formation of a wide core with correspondingly lower flow velocities in both core and annulus.

Experimentally, it may not be straightforward to distinguish between labeled particles originating in the axial core (bag 1) from those transferred into the annulus which feeds back into bag 2 without actually clearing such particles from the entrance to the over 1000 terminal airways of the pulmonary cast model.

The airflow distribution in cast models of the human and animal airways can be readily measured (Cohen et al. 1993) using hot-wire anemometry. The primary parameters which determine flow velocities are: airway cross-sectional areas, branching angles and total pathlengths. The lower lobe alveoli open before those in the upper lobes due to the existence of a gravity-dependent thoracic pressure gradient impressed on the pulmonary circulation and acting externally on the alveolar sacs. The Womersley number remains consistently below unity for generations 4 and onward of the pulmonary airway tree.

Mass transport

A solubility coefficient may be defined as

$$\alpha = c/p' \qquad (1)$$

where p' is the equilibrium partial pressure and c the concentration of a gaseous species physically dissolved in a liquid phase. Generally, $\alpha = \alpha(T)$ only, where T is the temperature. Should a chemical reaction occur, the concentration of reacted species can be far greater than that of the originally dissolved species. However, in the mucous lining of the airway walls, buffering action may suppress other solutes, causing the total concentration to exceed that in pure water (Ultman 1986).

The mass transport is given by

$$dM/dt = - \mathcal{D} S \, dc/dy \qquad (2)$$

where y denotes the direction of diffusion $\mathcal{D}$, the diffusion coefficient, and S the surface area perpendicular to y.

The concentration c may be eliminated in favor of partial pressure p' using relation (1).

A concentration boundary layer forms adjacent to the airway wall where the flow is retarded by friction (Fig. 1). Mitchell et al. (1966) have formulated an expression for total uptake rate at the mucous blanket/air interface in terms of local shear rate γ as

$$dM/dt = 0.807\ \alpha\ S\ (\ \gamma\ \mathcal{D}\ /L\ )^{1/3} \qquad (3)$$

where L is the length of the exposed surface S. The thickness of the concentration boundary layer varies as $L^{1/3}$. A two-dimensional formulation of the velocity field is the minimal requirement for evaluation of shear rate $\gamma = \mu\ du/dy$, where u is the axial velocity and y the transverse coordinate.

In general, the mass transport normal to a diffusion barrier may be expressed as:

$$dM/dt = \alpha\ k_m\ S\ (\ p'_1 - p'_2\ ) \qquad (4)$$

where k_m is the individual mass transport coefficient of species m. Illustrative values of the mass transfer coefficients α and k_m in a conducting airway model have been compiled by Ultman (1986) in his Table 5.

Lung anatomy and its influence on fluid mixing

Review articles by Pedley et al. (1977) and by Ultman (1986) describe in some detail the complex flow patterns which develop in the lung during inspiration and expiration. They have been summarized briefly by Collins (1994) and will therefore be alluded to only summarily in this report.

The upper airways will not be considered here. Advanced computational work is well underway at the Chemical Industry Institute of Toxicology (CIIT) in Research Triangle Park, NC. for numerical solution of the fully three-dimensional unsteady flow patterns prevailing in the rat's upper airways. This region extends from the nares and lips down to the larynx. Rather, attention will be focused here on the: a) conducting airways, a branching network of mucus-lined conduits extending through some 23 generations from the trachea down to and including the terminal bronchioles (diameter = 0.07 cm) and b) the respiratory zone consisting of the alveolated bronchioles and alveolar sacs. Taken together, a) and b) are termed the lower respiratory tract, constituted by the complete tracheobronchial tree (see Table 6). The combination of the upper and conducting airways are referred to as the anatomical dead space (volume = 0.16 liter). Gas exchange takes place primarily in the respiratory zone (volume = 3 liters).

According to Ultman (1986), the total path length along the alveolated airways is only 0.6 cm, compared to 40 cm between the nose and the terminal conducting airways.

Because the volume of the respiratory zone exceeds that of the deadspace by a factor of almost 20, relatively little axial mixing of inspired and expired gases occurs in the deadspace. The added volumes associated with freshly inspired air and vapors is accommodated largely by an expansion of the alveoli, the deadspace walls being more rigid.

Having said this, it is clearly of the utmost importance to be able to determine the concentration of volatile vapors inhaled in the upper respiratory tract which finally appear at the entrance to the respiratory zone. Before reaching that zone, toxic vapors may be absorbed in the mucous layer of the conducting airways and will be expelled by both mucociliary action as well as by evaporation during expiration. The solubility of such vapors in the hydrophilic

and lipophilic tissues of the upper tract and conducting airways is of paramount importance in this respect.

Once such vapors are taken up by the mucus lining the conducting airways, they will diffuse into the wall tissue and possibly into the capillary bed perfusing that tissue. The ensuing processes of diffusion and metabolism provide a sink which subtracts from the initial uptake.

The nature of the flow dynamics (creeping flow, laminar or turbulent viscous flows, etc.) is determined by the value of the Reynolds number $R_e = UL/\nu$, where U is the freestream velocity, L a characteristic length which, in this case, is taken as the airway diameter, and ν is the kinematic viscosity of the gas/vapor ($= \mu/\rho$: the molecular viscosity / fluid density). The critical Reynolds number for transition from laminar to turbulent flow is on the order of $R_{e\ crit} = 2000$.

Let us consider a typical bifurcation as depicted in Fig. 11. The angles of branching of the daughter vessels (not necessarily dichotomous) relative to the parent conduit and the sharpness of the carina (junction between the daughter conduits) will determine the splitting of the flow from the parent conduit during inspiration. These angles have been measured by Horsfield and Cumming (1969). The mean branch angle was found to vary from 64° for the larger airways (diameter > 0.4 cm) to over 100° for the smaller airways (diameter < 0.1 cm). They also showed that the parent airway transforms from a circular to an elliptic cross-section before dividing . Olson (1971) shows that the aerodynamic effects of a local ellipticity disappear within about two tube diameters proximal to the junction.

The general anatomy of the respiratory zone is illustrated in Figs. 12 and 13. Weibel (1968) estimated the presence of about 300 million alveoli in the human lung, each with a volume of 10.5×10^{-6} cm^3, giving a total of some 3 liters of volume available for gas exchange.

When the cross-sectional area of a rigid tube changes as at the branching junction, the streamlines converge during inspiration and diverge during expiration as in Fig. 14.
Viscous dissipation occurs at the branch junction along with a drop in total (stagnation) pressure. If the expansion is sufficiently rapid, the flow may detach from the airway wall, with the formation of re-circulating eddies.

As the flow turns in passing through a branch junction, the fluid (and particularly dense particles caught up in it) will be subjected to a centrifugal force tending to push it towards the outside wall.

As this happens, a secondary swirling flow is created which will carry fluid from the inside wall to the outer wall as depicted in Figs. 15, 16 and 17. The transverse flow patterns so created are complex (Fig. 18) and may be responsible for much of the mixing which occurs in the conducting airways. These streamline patterns may be visualized by injecting smoke into a glass replica of a branch junction. The velocity fields may be measured by hot-wire anemometry.

As the flow divides from parent to daughter airways, viscous and concentration boundary layers are formed (Fig. 19). These are important to consider for the uptake of toxicants on the mucus lining the conducting airways (Fig. 20).

In the smaller airways, where the flow is laminar, Taylor dispersion promotes enhanced radial diffusive mixing in adjacent annular rings as a result of local concentration gradients, in addition to axial mixing along the length of the airway. This tends to produce a bi-directional flow: the components with the higher alveolar concentration are transported outward along the

walls of the airway, while the components with the higher mouth concentration appear to move toward the alveoli along the center core of the airway.

The process is cyclic and highly dynamic. Following an inspiration, the "tongue" of the O_2 pulse from the mouth extends down the airway, diffusing out to the wall, while at the same time, CO_2 diffuses in toward the center of the airway. The latter CO_2-rich air is then carried out toward the mouth during expiration, while O_2 diffuses into the tongue of the pulse as CO_2 diffuses outward. The process is repeated at each new cycle, and is cumulative so that total mixing is augmented, particularly at higher frequencies, even for small tidal volumes less than the dead space.

It has been proposed by Lehr (1980) that the different regions of the lung do not inflate uniformly, but may at any time be up to 180° out of phase with one another. Indeed, stroboscopic photography of excised dog lungs indicates a "Pendelluft" movement with significantly different time constants (resistance´compliance) for different individual airway units, engendering retrograde flows. Very similar predictions came out of the computations of Collins et al. (1979) for blood flow in the lung as a direct consequence of significant measured differences in the anatomical structures and wall compliances of the pulmonary vasculature. They successfully mathematically modeled the flow profiles within the five pulmonary interconnected lobes of the pulmonary circulation.

The asymmetry of the airway architecture and material properties can induce gas exchange in regions whose anatomical dead space V_D is less than the global dead space. In such regions with tidal volumes $V_T < V_D$, adequate alveolar ventilation could obtain without resorting to diffusive transport.

Steady-state exchange is proportional to tidal volume V_T minus dead space volume V_D and no steady state gas exchange occurs for $V_T \leq V_D$. According to Mitzner (1986), this conclusion is based on the assumption that gases traverse the dead space with a blunt flow profile (velocity constant over the airway cross-section) during the breathing cycle. Under such conditions, a small tidal volume V_T could not traverse a large dead space volume V_D. However, the velocity profile is not blunt or flat, but rather tongue-shaped, as discussed earlier. Thus, in this context, some appreciable alveolar ventilations and gas exchange can occur for $V_T < V_D$, a result which could not be modeled readily using a simple one- or two-compartment idealization of a steady-state pulmonary airflow.

In fact, it would appear that this bi-directional axial dispersion, or spreading of the gas front into a tongue along the tube (airway) axis during both inspiration and expiration, contributes significantly to the gas mixing process. A corresponding model then should include branching networks of idealized airway tube segments, with varying airway path lengths and corresponding transit times.

Accordingly, an improved global model is proposed for vapor uptake reflecting this inherent asymmetry over the the two halves of the breathing cycle, as flow streamlines cannot be precisely retraced between inspiration and expiration. The true anatomical dimensions, branching characteristics and physical properties of the distensible airways may be used to characterize the underlying mechanisms responsible for the overall axial dispersion of the flow profiles. From these, realistic gas mixing rates can be computed for a variety of unsteady pulmonary flow regimes.

MATERIALS AND METHODS

Formulation of a proposed computational model for human pulmonary dynamics

A complete branching model of the respiratory system is proposed on the basis of detailed anatomical measurements (Fredberg et al. 1978). A quasi one-dimensional formulation for the coupled fluid/wall interaction can be resolved numerically using a modified two-step Lax-Wendroff finite-difference technique. This model can subsequently be used to estimate the regional deposition of fine aerosol particles in the human lung.

Preliminary theoretical models of particle deposition coupled with experimental studies appear to corroborate the overall importance of particle size (Hext et al. 1993). Particle-laden air, inhaled through the nose, finds its way through to the ends of the trachea, where the branching of the airways begins; extending eventually down through the bronchi and bronchioles to the alveolar ducts and sacs. In the Landahl (1950) model of the respiratory tract, eleven primary regions have been identified, along with their average anatomical dimensions and corresponding air velocities. It will remain to associate with these the corresponding mechanical properties of wall elasticity or compliance for use in the mathematical model to be formulated.

As the particles entrained in the airflow do not have the same density as the surrounding air, their trajectories will not follow the aerodynamic streamlines. Particularly at bifurcations and flow dividers, where the curved streamlines predispose to the development of secondary flows, the centrifugal forces on such particles will push them laterally out toward the walls where they may deposit by impact and be captured.

As the airways continue their branching with successive generations, the cross-sectional area of the respiratory network increases dramatically. Air velocities decrease from 150 cm/sec at the trachea to about 2 cm/sec at the terminal bronchioles. It is especially in this region of slowly moving flow that one would expect an increased influence on particle deposition due to the action of sedimentation and Brownian diffusion.

To a lesser extent, electrical charges associated with particles dispersed into the air by grinding or combustion may cause particle aggregation and a concomitant alteration in the effective particle size distribution, with their consequences on particle deposition patterns.

Thermal forces are likely even less important. Although the temperature in the respiratory tract may rise slightly during inhalation, these minimal temperature differences are thought to have only a minor effect upon particle deposition due to Brownian motion (Morrow 1960).

Mathematical formulation

The first task is to determine the flow patterns of air in the respiratory network. The fluid equations of mass continuity and momentum must be solved in conjunction with a realistic “law of the wall” which relates local cross-section of the airways to instantaneous transmural pressures as a function of local wall properties (modulus of elasticity). Special provisions can be made for airway collapse under sporadic conditions of negative transmural pressure.

The governing equations are solved numerically in a manner similar to that used by Collins et al. (1979), for the pulmonary circulation. The true physiological variations in pressure and flow rate as recorded during respiration will serve as boundary conditions to the model. Once the flow field has been computed in this manner, one may calculate the transport of particles of different

sizes and densities which are entrained in this known flow. This proposed decomposition of the problem tacitly implies:

a) the basic "clean air" flow will not be substantially altered by the intake of dispersed particles, and

b) a lack of interaction between particles of differing sizes as they deposit onto the walls of the respiratory tract. This allows the deposition distributions to be summed for given particle size distributions.

The alternative to this more simplified approach would be a fully coupled two-phase treatment of the particle-air equations, including particle-particle interactions in a non stationary two-dimensional flow with rotational symmetry. The zones of possible momentary turbulence and flow re-circulation can be evaluated in terms of corresponding losses in stagnation pressure due to viscous dissipation for given bifurcation angles and parent-daughter area ratios. Nondichotomous branching may impose additional difficulties, leading to the necessity of discretizing groups of similar airway generations into equivalent simplified networks.

Such an approach should constitute a substantial improvement over the analysis of Taulbee and Yu (1975), wherein the airway geometry was presumed to be bounded by rigid walls. Laminar flow was considered exclusively, and axial diffusion and particle deposition in the mouth and trachea were neglected. The effects of airway bifurcations on viscous dissipation and total pressure losses were not dealt with in that formulation.

Mixing Processes within the pulmonary airways

One is tempted at this point to draw a number of inferences from the foregoing discussion; namely that:

a) it would appear that the primary mechanism of fluid mixing of chemical vapor with inspired/expired air is through the *secondary flow process* which develops at each branching of the network of pulmonary airways depicted in Figs. 16-18 (as reproduced from silicone rubber casts),

b) secondary flow processes *do not occur* in either one- or two-dimensional geometries, but *only* in three-dimensional (3-D) tubes,

c) the branching tubes themselves do not lie in a single plane,

d) the density of computational grid mesh points in a 3-D discretization of the governing equations will rarefy as one loses computational grid lines in passing from a parent to a daughter tube, particularly over the entire 23+ generations of branching conduits.

The symmetrical lung model of Weibel as expressed in terms of the Horsfield branching orders n is probably the easier one to begin with. Weibel also proposed an asymmetric branching model. Both versions are set out in Tables 3 and 4.

The airways may be idealized into grouped generations for computational facility as portrayed in Fig. 22. Cross-sectional areas of the airway tubes vary as shown in Fig. 23 for the upper left lobe of the human lung, while the wall elastance (inversely proportional to the modulus of elasticity of the airway wall) varies with distance along the pulmonary airway tree as in Fig. 24.

The one-dimensional equations of motion are not appropriate for a pulmonary airway flow problem in which convective mixing is the primary concern due to the intrinsic 3-D nature of the secondary flows. However, for didactic purposes only, the following one-dimensional formulation is presented with the hope that it will be more readily understandable by a reader whose specialty lies in other fields.

A simple implicit time-marching Lax-Wendroff two-step staggered finite-difference scheme is used to illustrate the numerical algorithms developed to replace the partial differential equations governing the fluid motion. These algorithms have been chosen because of their inherent numerical stability resulting from the use of a staggered grid network.

The actual grid must be three-dimensional, but even in a two-dimensional grid mesh, one will lose mesh point density in passing from generation to the next (Fig. 25).

One begins by apportioning grid lines in the parent tube. If, for illustrative purposes, four such grid lines are placed across the width of the channel (in 2-D) or tube diameter (in 3-D), then two grid lines will continue into each of the daughter vessels. Of these two grid lines, only one will continue into the "grand-daughter" tube. There remain some 20 generations thereafter leading down to the alveolar levels. One problem is how to avoid this considerable and rapid rarefication of grid density without inserting so many grid lines into the larger proximal tubes as to waste valuable computational time and effort. Of course, additional grid lines and corresponding computational points can be inserted at each such branch by interpolation, in order to assure the uniformity of the overall grid density regionally, but one must be vigilant not to compromise the accuracy of the concentration distributions at the alveolar level in so doing.

This is illustrative of a series of technical problems which we are now addressing as, whatever the approximate or idealized formulation, the solution, which will depend most sensitively on the *airway geometry*, must finally be resolved numerically.

In the following pages, we set out in simplistic form the illustrative, but insufficient *quasi one-dimensional* formulation of the governing equations used to define the flow field in the pulmonary airways. These comprise the equations of continuity and momentum, but also a "law of the wall" relation to allow for a non rigid wall. In this simple case, we have adopted a linear relation between intraluminal cross-section A and the *transmural* pressure P. Friction factors F are estimated for wall friction during inspiration and expiration. A loss in head (stagnation) pressure must be estimated at the branching junction at each level or generation of bifurcation.

The Lax-Wendroff scheme for numerical computation of updated variables at each grid point in the x - t plane is summarized, and the corresponding boundary and intial conditions needed to formulate a "well-posed" problem are set out in the following pages. The report concludes with recommendations for future work.

Mathematical models

We will now examine several pragmatic options for the construction of a computational model responsive to the dynamics of an **acute short-duration exposure** by inhalation of a highly toxic volatile gas or gas vapors.

Such uptake is complicated by a number of physical and physiological factors, including but not limited to:

1. irregular and non uniformly distributed *airway geometry*, characterized by a distribution of different path lengths from trachea to alveoli,
2. *incomplete mixing of inspired and expired gases,* a large part of which do not penetrate into the lung beyond the first several generations as a result of their volatile nature and the
3. *lipid solubility* of the gas which is absorbed by the *mucous layer lining* the conducting airway walls and the *mucociliary clearance* via the esophagus into the stomach,

4. very *complex flow patterns at branch points* (bifurcations) characterized by *swirling secondary flows* engendered by centrifugal forces associated with the turning of the flow along curved streamlines as the gas proceeds from parent into daughter conduits throughout the 23-generation branching network,

5. *gas exchange processes at the alveolar level* with the pulmonary capillary bed as the alveolar volume varies in time and space with the breathing cycle, imposing cyclic fluctuations on the gradients of partial pressures which drive the inspired vapors into the bloodstream,

6. *insufficient knowledge of the underlying physical and physiological parameters*, such as regional permeability, solubility, lipophilic/hydrophilic tissue distributions, etc. Often blood concentration measurements are made from the organ of interest and may not be representative of true toxic concentrations of the parent compound in that organ, particularly under unsteady uptake conditions.

The model

Ideally, all of the above processes should be realistically accounted for in the computational model. Such a model then constitutes a valuable and efficient tool for :

a) evaluating numerically the relative importance of the above processes on the regional uptake of volatile toxicants as a function of time,

b) designing and experimental protocol for the controlled measurement of key parameters to a uniform and consistent degree of compatible accuracy, and

c) scaling of results between experimental species to predict human response reliably.

Suggested approach

The effort and underlying costs projected for the development of a useful computational model must not be underestimated. They fully merit serious reflection and careful consideration and must be balanced against the even more costly consequences of a hasty decision to launch a major computational effort off onto an inappropriate path.

Yet, the benefits of such a practical tool are self-evident in the increasingly important field of ***inhalation toxicology***. Other institutes and universities, in apparent recognition of the need for a new generation of PBPK models, have elected to face up to the considerable challenge of applying a full-scale commercially available 3-D time-dependent Lagrangian-Eulerian finite-volume computational code (FIDAP) to the determination of the intricate flow patterns of inspired and expired vapors in the geometrically complex rat's nose.

In my view, the method is equally applicable to the conducting respiratory tract, but I would suggest that less onerous alternatives should first be considered, even if not subsequently adopted. Below are listed the features which should be retained in a predictive flow dynamics/transport model, followed by a series of optional approaches to constructing such a model, proceeding from simpler to more complex. In contrast to the premises of the equilibrium-based 'well-stirred' compartmental PBPK models, all optional approaches listed below recognize the unsteady nature of the flow through the branching geometry of the respiratory tract.

Desirable features to be retained in computational model(s)

Features which should be preserved in a viable predictive model for the time-dependent transport of chemical toxicants (including particles) within the lower respiratory tract:

A. FLOW DYNAMICS:

a) fluid and concentration boundary layers along airway walls

b) secondary flows at branch junctions

c) axial streaming during inspiration and expiration

d) alveolar volume variations related to breathing cycle

e) time-dependent but cyclic fluid flows

f) distribution of path lengths from trachea to alveoli sacs.

B. TRANSPORT PHENOMENA:

g) across mucus lining airway walls: - transport of chemicals from air $\Rightarrow$ mucus $\Rightarrow$ tissue $\Rightarrow$ capillary beds, as a function of diffusion and solubility coefficients, layer thickness and capillary blood flows.

h) along airway lumen: - periodic convection and diffusion of chemical-laden air species longitudinally, toward mouth and toward alveoli during expiration/inspiration.

i) alveolar air $\Leftrightarrow$ capillary bed gas exchanges, taking account of gradients of partial pressure and concentration gradients of the various species contained in the inspired air, in addition to solubility and diffusion coefficients at the alveolar level. First order account of hydrostatic head in the pulmonary circulation (also related to postural changes).

j) mixing by secondary flows and turbulent bursts at branch points.

Modeling approaches

OPTION 1: Discretized equilibrium compartmental models

Multistage PBPK model of the respiratory tract, consisting of a series of interconnected "well-stirred" compartments.

Weaknesses:

1. flow equilibrium conditions not realized in practice during short-term acute exposures, invalidating basic assumptions underlying PBPK modeling,

2. no relation with the anatomy and the flow velocity profiles which produce concentration boundary layers along the walls of the respiratory tract and at branch points [see preceding section A(a)-(f)],

3. uncertainty and non uniqueness in determination of parameters to be discretized amongst the various stages of the PBPK model,

4. very little apparent saving in coding of computational algorithms relative to a continuum model.

OPTION 2: Non equilibrium continuum models -

a) time-dependent quasi one-dimensional formulation

Formulation of the governing fluid and species equations for flow and transport in terms of:

(i) axial distance x along the pulmonary axis, with dependent variable averaged across the local luminal cross-sections,

(ii) separate one-dimensional representation of the airway wall "layers" (mucus, tissue and blood),

(iii) one-dimensional representation of the alveolar-level gas exchange processes.

Weaknesses:

1. fails to capture the fluid dynamics detail necessary to evaluate the radial concentration and partial pressure gradients which serve as the driving forces for gas transport across the airway walls and the alveolated respiratory units [cf. section A(a)],

2. precludes proper evaluation of mixing by axial streaming and by secondary swirling flows at branch points.

OPTION 3: Non equilibrium continuum models -

b) time-dependent two-dimensional axisymmetric formulation

Formulation of the governing fluid and species equations for flow and transport in terms of:

(i) radial position r at a given axial station x along the respiratory tract,

(ii) use of radial gradients of concentration and partial pressure at the airway wall to evaluate mass transport through the tri-layer (mucus/tissue/blood) and at the alveolar level for gas exchange.

Weaknesses:

1. may still not characterize the 3-D secondary flows adequately at the branching junctions of the respiratory tract, but

2. accounts for axial streaming

3. considerably more complex computationally than option 2 in terms of both coding and CPU running time.

OPTION 4: Non equilibrium continuum models -

c) time-dependent three-dimensional formulation

Formulation of the governing fluid and species equations for flow and transport in terms of:

(i) r, x and azimuthal branch angle Φ . The three-dimensional structure of the gas exchange region of the lungs has been described in full detail by Mercer et al. (1988),

(ii) in addition to features of option 3, permits a detailed evaluation of the pressure drop and swirling mixing at each branch junction, accounting for the non-circular cross-sections proximal and distal to those branch junctions.

Weaknesses:

1. Likely to lead to exorbitant levels of computational effort and CPU time, notwithstanding the availability of commercial codes potentially applicable to such 3-D time-dependent formulations (cf. FIDAP version 7.5 from Fluid Dynamics International utilized by CIIT for the rat's upper respiratory tract). A systematic search has been undertaken for a complete listing of all relevant computational codes.

For all options outlined above, attempts should be made to group generations of similar material properties and anatomical dimensions so as to reduce the number of generations to be computed from 23 to say 10 or 12 (cf. Fig. 22). However, extreme care must be exercised not to allow the rate of change of the combined cross-sectional areas with distance along the tracheobronchial tree to increase too rapidly. This could trigger an unrealistic detachment or separation of the flow from the conduit walls. For this reason, it may be advisable to re-configure those combined idealized generations into a *parallel* series with the same generation number, each having a lesser cross-sectional area.

The ultimate choice of one of the several options of progressively increasing complexity outlined above will depend upon the manpower, budgetary allocation and time-frame priorities to be accorded to this significant aspect of dynamic inhalation toxicology.

RESULTS

Implications for the extrapolation of toxicological animal test results to humans

From this very preliminary survey of modeling of pulmonary airflows, it becomes abundantly clear that:

1) current quasi-steady PBPK models for estimation of the uptake of chemical toxicants in small animals, typically rats, must correspond to the particular flow regime(s) prevailing in the animals,

2) the flow regimes applicable to human pulmonary uptake of given toxicants must exist in the animal tests as a necessary, if not sufficient, condition for evaluating quantitatively the same toxicant transport mechanisms of interest to human uptake.

Compliance with these essential requirements may, in some cases, require careful reconsideration of the basic design of particular animal testing programs.

DISCUSSION

Future work and conclusions

It would be very worthwhile to formulate a detailed respiratory model of the human lung based upon a branching network of distensible pulmonary airways. Species equations for each of the chemical constituents can then be incorporated and metabolic rate functions assigned locally. Model results may then be compared quantitatively with those of the previous compartmental models as a standard for evaluation of accuracy in assessing risk due to uptake of chemical toxicants via the respiratory tract.

Future work on meaningful approximate solutions not making direct use of the requisite computational production codes offers a real challenge. We may proceed along the following alternative paths:

a) performed detailed measurements ofthe flow velocity and concentration fields in hollow casts of the human and (scaled-up) rodent pulmonary airways. This technology is readily available and is feasible to implement in-house.

b) "borrow" a full computational solution for a 'standard' lung (human, rat, mouse) from another source which will have addressed the real computational problem. That flow field as established for a particular anatomy and breathing cycle can be used for computing the uptake of *all* chemicals by inhalation, including the volatile vapors of interest, provided that the concentrations introduced at the mouth and nose are sufficiently low as not to alter the flow fields from what they would have been in the absence of the chemical. This "passive transport" assumption would appear to be amply justified and reasonable for our purposes. Then, the uptake of a given chemical itself can be readily determined from Fick's law: $\partial c/\partial t +$

ugrad c = div (D gradc). If the diffusion coefficient can be deemed not to vary spatially, the above reduces to the now linear PDE (partial differential equation) $\partial c/\partial t + \mathbf{u}\text{grad } c = D \nabla^2 c$ which, in one dimension (which is not relevant here, but for didactic purposes only) can be expressed as

$$\frac{\partial c}{\partial t} + \mathbf{u} \frac{\partial c}{\partial x} = D \frac{\partial^2 c}{\partial x^2}$$

c) employ a quasi one-dimensional time-dependent formulation (which implies averaging velocities, concentrations, etc.) over the airway tube cross-sections with the addition of crude approximations for:

(i) wall friction through a "friction factor", and
(ii) mixing at the branches by a "mixing factor".

Again, one could attempt to determine some heuristic expressions for these fudge factors on the basis of someone else's numerical solution or, better yet, from experimental measurements. We are presently in contact with a number of colleagues for both aspects.

This potential project represents a challenge and an outstanding opportunity to envisage for the first time anywhere the elaboration of a complete computational model for inspiration/expiration in the lower respiratory tract.

When combined with the similarly comprehensive model of the upper respiratory tract now under development at the Chemical Industry Institute of Toxicology (CIIT), a tool will be available for the first time for widespread application in the increasingly significant field of *inhalation toxicology*.

Model development of this scale must be construed in terms of a sustained multi-year commitment. It should be possible to break the problem down into individual modules to be developed and tested in parallel before bringing all together to form an integrated and powerful computational tool.

Such a model will also prove instrumental in creating a quantitative framework for the efficient design of experimental protocols to establish the required material and chemical properties of the toxicants to be evaluated. The result will be a significant narrowing of the ranges of regimented tolerances in *risk analysis* for the EPA and DoD.

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