Chapter VIII: Modeling Deposition of Inhaled Particles

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II. INTRODUCTION

The mathematical modeling of the deposition and distribution of inhaled aerosols within human lungs is an invaluable tool in predicting both the health risks associated with inhaled environmental aerosols and the therapeutic dose delivered by inhaled pharmacological drugs. However, mathematical modeling of aerosol deposition requires knowledge of the intricate geometry of the respiratory network and the resulting complex motion of air and particles within the airways. In this chapter, an overview of the basic engineering theory and respiratory morphology required for deposition modeling are covered. Furthermore, current deposition modeling approaches are reviewed, and many factors affecting deposition are discussed. Experimental methods for measuring lung deposition are presented, albeit briefly, and the comparison between experimental results and modeling predictions are examined for a selection of modeling efforts.

III. FLUID DYNAMICS IN AIRWAYS

The deposition patterns associated with inhaled particulate matter are intrinsically linked to the airflow patterns within the respiratory system. Therefore, any effort to realistically model particle deposition requires an understanding of the fundamental fluid dynamics theory behind the motion of air in the extrathoracic and lung airways.

A. FUNDAMENTAL EQUATIONS

Fluid motion is governed by the conservation of mass (continuity) equation and conservation of momentum (Navier-Stokes) equation. The flow of air in the respiratory airways is usually assumed to be incompressible.[1] For incompressible flow, the continuity equation is given by

$$\nabla \cdot \boldsymbol{V} = 0 \tag{1}$$

And the Navier-Stokes equation is

$$\left[\frac{\partial V}{\partial t} + (V \cdot \nabla)V\right] = \rho f - \nabla p + \mu \nabla^2 V \tag{2}$$

where $\nabla\cdot$and ∇^2 are the gradient and Laplacian operators, respectively (defined below), ρ is the fluid density, μ is the absolute fluid viscosity, and p is the hydrodynamic pressure. The parameter f is any externally applied volumetric force, such as gravity.

In studying fluid flow in airways, it is convenient to use the cylindrical coordinate representation of the motion equations. Noting that the gradient operator ∇ in cylindrical coordinates is

$$\frac{\partial}{\partial r} + \frac{1}{r}\frac{\partial}{\partial \theta}_{\theta} + \frac{\partial}{\partial \mathrm{z}} \tag{3}$$

The continuity equation in cylindrical coordinates becomes

$$\frac{1}{r}\frac{\partial}{\partial r}(rV_r) + \frac{1}{r}\frac{\partial}{\partial \theta}V_\theta + \frac{\partial}{\partial \mathrm{z}}V_z = 0 \tag{3}$$

where V_r, V_θ, and V_z are the components of the fluid velocity in the radial (r), circumferential (θ), and axial (z) directions, respectively (Figure 1). The corresponding equations for momentum in the r, θ, and z directions become

$$\frac{\partial V_r}{\partial t} + (\boldsymbol{V} \cdot \nabla)V_r - \frac{1}{r}V_\theta^2 = -\frac{1}{\rho}\frac{\partial p}{\partial r} + f_r + \frac{\mu}{\rho}\left(\nabla^2 V_r - \frac{V_r}{r^2} - \frac{2}{r^2}\frac{\partial V_\theta}{\partial \theta}\right) \tag{4}$$

$$\frac{\partial V_\theta}{\partial t} + (\boldsymbol{V} \cdot \nabla)V_\theta + \frac{\mathrm{V_r V_\theta}}{r} = -\frac{1}{\rho \mathrm{r}}\frac{\partial p}{\partial \theta} + f_\theta + \frac{\mu}{\rho}\left(\nabla^2 V_\theta - \frac{V_\theta}{r^2} + \frac{2}{r^2}\frac{\partial V_\mathrm{r}}{\partial \theta}\right) \tag{5}$$

$$\frac{\partial V_z}{\partial t} + (\boldsymbol{V} \cdot \nabla)V_z = -\frac{1}{\rho}\frac{\partial p}{\partial z} + f_z + \frac{\mu}{\rho}\nabla^2 V_z \tag{6}$$

where

$$\boldsymbol{V} \cdot \nabla = V_r \frac{\partial}{\partial r} + \frac{1}{r} V_\theta \frac{\partial}{\partial \theta} + V_z \frac{\partial}{\partial z} \tag{7}$$

and the Laplacian operator in cylindrical coordinates is defined as

$$\nabla^2 = \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial}{\partial r} \right) + \frac{1}{r^2} \frac{\partial^2}{\partial \theta^2} + \frac{\partial^2}{\partial z^2} \tag{8}$$

If the flow is steady, then the time derivatives in eqs. 4-6 can be ignored.

B. BOUNDARY CONDITIONS

The above system of four nonlinear partial differential equations can only be solved analytically when a number of assumptions are made for very simple flow geometries. Therefore, in most cases, numerical methods are required to determine a solution for the velocity and pressure fields. Numerical solution of the equations of motion requires knowledge about the velocity or pressure at some or all boundaries of the flow geometry. The nature of the flow characteristics and geometry determine which boundary conditions need defining.

As flow has been studied in a vast variety of geometric lung models, it is difficult to recommend boundary conditions that are appropriate in every circumstance. In almost all cases, however, it is assumed that the no-slip condition (V at the wall = 0) exists along the walls of any airway. The definition of any inlet and outlet boundary conditions is not as straightforward. For instance, the flow velocity at the inlet may be designated steady (time-invariant) or unsteady, and may be uniform over the diameter of the inlet or vary with radial direction. In addition, in different cases, the velocity, the velocity gradient, the pressure, or the pressure gradient may be defined. In airway flow modeling, the velocity profile at the exit of an airway is often assumed

parabolic, and the conducting airway is assumed sufficiently long enough for the flow to be fully developed.[2]

In some simplified cases, only the inlet conditions may need to be specified. For example, if one assumes that the pressure in the fluid varies only in the axial direction, then the mathematical character of the equations change and only the inlet velocity profile is needed to obtain a solution.[3] In this case the outlet velocity profile is determined as part of the model solution.

C. IDEALIZED VELOCITY PROFILES

The velocity profiles present in real lung airways are determined by a great many factors including ventilatory conditions, lung morphology, and the airway generation(s) being considered. Experimental studies[4-6] have shown that these profiles may be skewed, and in general geometrically complex. However, by assuming idealized velocity profiles in individual airway generations, fundamental equations of fluid motion can reduced and the development of simplified expressions for deposition via different mechanisms can be obtained. Idealized velocity profile types include laminar fully-developed (parabolic), laminar undeveloped (plug), and turbulent. The type of velocity profile selected determines the appropriate expressions for particle deposition (for example, via sedimentation, diffusion or inertial impaction) in a given airway. Examples of such expressions were presented in detail in Chapter VI: *Mechanisms of Particle Deposition.*

Martonen[7] presented recommendations for velocity profiles in different generations of lung airways, based on previously published experimental measurements.[8] At the entrance to the trachea, it was assumed that the velocity profile was determined by the action of the laryngeal jet. In the upper tracheobronchial (TB) airways, the flow was considered turbulent, while in the lower TB airways the flow was assumed laminar undeveloped. In the pulmonary region, both

laminar undeveloped and developed profiles were considered to serve as limiting cases, since the actual velocity profiles in this region are likely to lie in the transitional region between plug and parabolic flow. These flow conditions have been used in several particle deposition model studies.[2] A more recent modeling study[9] provided further evidence that the flow in the TB airways is not fully developed. Specifically, it was determined that an undeveloped flow model more accurately predicted total deposition of ultrafine particles than did a fully developed flow model.

D. COMPUTATIONAL FLUID DYNAMICS

The field of study concerning the numerical solution of the equations of motion for fluids is known as *computational fluid dynamics,* or CFD. CFD is an invaluable tool in the study of fluid and particle motion under circumstances that are difficult to simulate with a physical experiment or a simplified theoretical model. CFD involves segmenting a flow area (e.g. a system of airways and bifurcations) into many discrete elements or volumes, collectively called a *mesh*. In each element, the partial differential equations that describe the fluid motion are converted into algebraic equations by relating the fluid properties of the elements to the properties in adjacent elements. There exist several schemes for performing this *discretization*, including finite difference, finite element, and finite volume methodologies. In the finite difference method, the differential equations are approximated by Taylor series expansions. The theories behind finite element and finite volume discretizations are beyond the scope of this chapter.

Many commercial packages are available for performing CFD, including the finite-volume based programs CFX-F3D and FLUENT (both now provided by Ansys, Inc.). FIDAP, a finite-element based package that has been used to study respiratory system airflow in studies by

Martonen et al.[10-15] and Kimbell et al.,[16] is now mostly unavailable. CFX-F3D has been used by Yu et al.[18] and Martonen et al.[19]

IV. AEROSOL DEPOSITION MODELS

A. CLASSES OF MODELS

The modeling of aerosol deposition in the lungs has been approached from several different conceptual directions. However, the vast majority of aerosol deposition models can be categorized as empirical, deterministic, or stochastic in nature. Empirical models are based on fitting numerical relationships to experimental data. In deterministic modeling, both the physical nature of the lung and the fluid and particle dynamics associated with respiration are quantified by simplified expressions and the resulting particle motion is calculated. In stochastic modeling, the geometry of the airways is varied randomly to account for inter- and intra-subject variation.

Empirical and deterministic models were the first efforts designed to simulate and predict aerosol deposition in airways, and stochastic models were later developed to intrinsically incorporate biological variability into such simulations. However, as computer resources became more powerful, computational fluid particle dynamics (CFPD) models of particle motion and deposition (based on CFD analyses) began to be developed. While CFPD models do not comprise a distinct class by themselves (i.e. they may be either deterministic or stochastic in nature), they are also discussed below.

1. Empirical Models

In empirical deposition models, regional or total aerosol deposition is described by equations derived by fitting algebraic relationships to experimental data. Stalhofen et al.[20] developed a semi-empirical model for total and regional deposition, deriving equations for

aerosol deposition in the extrathoracic (nasal, oral and laryngeal), “fast-cleared” thoracic (ciliated airways), and “slow cleared” thoracic (peripheral) regions as a function of respiratory parameters and aerodynamic diameter. The model, which was based on previous empirical models,[21] considered data from a wide variety of deposition experiments; theoretical relationships were used for particle sizes for which no data were available. The empirical ICRP respiratory tract dosimetry model[22] was developed by the International Commission on Radiological Protection. This model can be used to estimate regional deposition in the lungs as a function of particle characteristics and ventilatory conditions via a number of algebraic equations based on the work of Rudolf et al.[21,23-25] Other empirical deposition models have been developed for the head,[26,27], tracheobronchial,[26,27,28] and alveolar[29] regions, and for the entire lung.[30]

Empirical models have been combined with pharmacokinetic models,[31] and modeling predictions derived from empirical relationships have been used to validate and confirm results from mechanistic deposition models.[9,32]

2. Deterministic Models

Deterministic models are developed using an engineering approach to the simulation of air and particle motion. In deterministic models, simplifying assumptions about airway geometries and airflow conditions are made in order to derive expressions for particle trajectories from particle momentum equations. Such models vary in complexity; deterministic modeling efforts may range from simple analytical expressions that can be solved algebraically to systems of non-linear ordinary or partial differential equations. In addition, deterministic models may describe particle deposition in a single airway, a bifurcation, or a complete branching network of respiratory airways.

Martonen[7,33] has developed deterministic models of particle deposition in humans lungs. These models were formulated by modeling the airways of the lung as either straight or curved smooth-walled tubes, and assuming a fixed (laminar or turbulent) velocity profile in each airway generation. Other deterministic models of particle deposition in the respiratory system have been developed by Gradón and Orlicki,[34] Yu et al.,[35,36] Egan and Nixon,[37] Anjilvel and Asgharian,[38] Asgharian et al.,[39] Phalen et al.,[40,41] and Choi and Kim.[42]

In deterministic models, the simulated particle deposition patterns are determined solely by the input parameters to the model. Therefore, for any set of model input parameters, the same deposition pattern is found. This is not necessarily true of the next class of models, stochastic models.

3. Stochastic Models

Models of particle deposition are categorized as stochastic if the morphological description of the lung is considered to vary in a random manner, within prescribed limits. The concept of stochastic deposition modeling, first introduced by Koblinger and Hofmann,[43] has been used by Hofmann and co-workers to simulate aerosol particle deposition in both human[43-46] and rat[47-49] lungs. Radon progeny,[50] cigarette smoke,[51] and diesel exhaust[52] deposition have been specifically addressed.

In stochastic deposition modeling, the morphometric parameters describing the geometry of the lung are not given constant values, but are described instead by statistical (e.g. lognormal) distributions, which are in turn based on experimental measurements. These morphometric parameters may include airway diameters, lengths and branching angles. Other, less obvious, parameters (such as ratios of parent airway cross-sectional area to the sum of daughter airway cross-sectional areas) may also be stochastically defined. Then, as each modeled particle enters

the lungs, its pathway is determined by a random selection of values for each of the required morphometric parameters within their corresponding lognormal distribution. For example, the properties of the daughter airways are randomly assigned for each bifurcation.[53] The average resulting deposition in each airway is then calculated from the behavior of the entire ensemble of particles.

4. Computational Fluid-Particle Dynamics (CFPD)

Computational fluid-particle dynamics (CFPD) refers to the study of the motion of particles as determined by computational fluid dynamics (CFD) simulations. In CFPD studies of particle deposition, CFD solutions of fluid velocities are coupled with the solution of particle trajectory equations developed from Newton's Second Law.[54] Particles are deposited when their trajectory intersects with an airway wall.

CFPD methods have been used to examine the effects of complex flow patterns on particle motion and deposition in the respiratory system. An example of such flow patterns in a model airway are shown in Figure 2. Martonen and Guan[55,56] performed linked fluid dynamics and particle motion studies that examined the effects of tumors on the deposition of particles in an idealized 2D airway bifurcation. In recent years, as desktop computing capabilities have increased, many 3D simulation studies have been performed. These studies can be categorized into three groups: 1) studies in idealized bifurcations 2) studies in physiologically-realistic (data-driven) bifurcating lung airways and 3) studies in models of extrathoracic airways.

a. CFPD Studies in Idealized Bifurcations

In these types of studies, CFPD is used to examine airflow and particle deposition in smooth-walled, tubular airway systems having regular (usually symmetric) branching angles.

An example of a CFPD simulation in a multiply bifurcating idealized airway (performed in FLUENT) is shown in Figure 3. Zhang et al.,[57-60] Comer et al.,[54,61] Longest et al.[62,63] and Martonen and coworkers[19,64] have all performed CFPD studies aimed at predicting particle deposition in idealized bifurcating airways or networks. Zhang et al.[65] have also considered idealized representations of tumors within the airways.

b. CFPD Studies in Physiologically Realistic Bifurcating Airways

As available computing resources have grown, it has become easier to generate three-dimensional morphological models of the lung airways from medical images. As this capability has grown, more and more CFD studies are being performed to study the airflow and particle deposition in bifurcating networks developed from images of real human lungs. Studies have also been performed in the trachea and upper airways[66] and in more complicated networks involving several airway generations,[67-69] and in models representative of asthmatic lungs.[70]

c. CFPD Studies in the Extrathoracic Airways

Much of the recent work being done in CFPD is in simulations of particle deposition in the extrathoracic airways. The extrathoracic airways, such as the mouth, throat, and larynx, have very irregular geometries, and thus generalizing flow and deposition patterns in these areas is more difficult than in lung airways). Morphological models of these airways are discussed later in this chapter. CFPD studies have performed for the oral cavity, [71-73] nose,[74-78] and pharynx (throat).[79]

B. MERITS AND LIMITATIONS OF DEPOSITION MODELS

Each deposition model class has both scientific strengths and drawbacks. In selecting a suitable deposition model one must consider many factors, including the scientific foundations of

the models, the desired level of biological realism, and the available data and computing resources.

1. Scientific Foundations

The scientific foundations of the different classes of models must be considered when selecting a model for the interpretation of experimental data or the prediction of particle deposition pattern. Empirical models may be valid for the physical system for which they were derived, but application to other systems may result in spurious conclusions. In addition, deterministic models are only as valid as the assumptions made in their derivation. One must be aware of these assumptions and use the models accordingly. Stochastic models are derived from observations of morphological variability; however, such formulations can be generated only if an appropriate amount of experimental data is available. One must be mindful of the limitations of stochastic models derived from limited experimental data. CFPD modeling is based on well-established methods that have been in use for years in a wide variety of scientific fields, especially in mechanical and aerospace engineering. However, the scientific validity of any CFPD simulation is based on the appropriate application of these methods to the problem at hand. For example, the geometry of realistic respiratory system passages is more irregular than that in many industrial or engineering applications. Appropriate discretization of the complex geometry (for solution of the Navier-Stokes equations) may be very difficult, and an invalid mesh may result in specious computational results. However, more robust discretization (meshing) algorithms are continuously being developed and tested.

2. Biological Realism

Particle deposition models vary greatly in their level of biological realism. For example, empirical models contain no information about particle motion or the physiology or anatomy of the respiratory system (i.e. the respiratory system is treated as a "black box"), yet they may be useful in interpreting data from experiments in which subjects breath well-characterized aerosols in a known manner. Many deterministic models take into account both respiratory system morphology and the motion of individual particles. They are therefore able to model deposition in different respiratory system regions (extrathoracic, tracheobronchial, or pulmonary), in individual lung airway generations, or within single airways.

Stochastic models may present a limited "anatomically realistic" model *per se* (that is, surface features not considered), however, they have the important advantage of being able to model the realistic biological variability that is present among each lung pathway in a single subject and between individual subjects.[80] Stochastic models by their construction provide estimations of intra- and inter-subject variability in deposition.[80]

CFPD models are capable of simulating deposition in realistic airway configurations, considering flow conditions that arise from airway surface features. Therefore, CFPD models can predict *local* deposition (i.e. at cells, bifurcations, carinal rings) caused by secondary flow currents, which cannot be predicted from simplified analytical models. CFPD can be used to predict deposition in complex anatomical geometries where the assumption of a smooth-walled cylinder should not be made, for example, in the larynx, mouth or nasal passages. A particular advantage of CFPD models is that they provide the potential for coupling imaging studies with deposition modeling. Irregular respiratory system morphologies can be extracted from CT or MRI images, and these morphologies can provide a basis for CFPD studies.

3. Hardware and Software Issues

Deposition models of different classes can require vastly different hardware and software resources. For example, empirical modeling requires no specialized computer programs, as the models are simple algebraic relationships. Deterministic models (those derived from particle motion and flow equations using various simplifying assumptions) vary greatly in computational efficiency, based on the nature of the assumptions made and the complexity of the airway geometry considered. However, CFPD modeling is typically computationally intensive, requiring high-performance hardware with adequate processing and memory resources. In general, CFPD also requires either expensive third-party software or a large amount of complicated, challenging, in-house programming. As an example, Zhang and Kleinstreuer[81] used the CFD package CFX 4.3 (AEA Technology, Inc.) to perform their studies of secondary flow patterns in an airway branching network. The software ran on a multiprocessor Silicon Graphics workstation, and a typical run time for a fluid flow and particle transport simulation for a single breathing cycle was approximately 72 hours. However, the use of CFPD models is becoming more frequent as the computing power of desktop personal computers and workstations rapidly increases.

4. Advantages of Modeling and Simulation

Up to this point we have focused on the merits and limitations of particular types of deposition models, we would also like to comment on the advantages and challenges of using models in the study of inhaled particle deposition. Modeling can be a powerful research tool, as it can be used to predict behaviors, phenomena, or physiological parameters that cannot be measured. In addition, modeling has the potential to help maximize both financial and animal resources, by aiding in the design of appropriate experiments for a given scientific hypothesis.

As noted by Martonen,[82] modeling studies should be integrated in a complementary manner with human inhalation exposure studies.

One of the main challenges in simulation is that its valid and rigorous use may require uniquely trained scientific personnel. For example, performing CFPD requires appropriately trained interdisciplinary scientists who are capable of understanding the computational, mathematical, and physiological nuances of modeling complex biological systems. Therefore, rigorous modeling studies may require collaboration among physicians, toxicologists, and engineers.

V. FACTORS INFLUENCING AEROSOL DEPOSITION PATTERNS

In the previous section, a brief overview of the different classes of lung deposition models was presented. Now we will discuss some of the morphological, ventilatory, and situational factors that affect deposition patterns in the human respiratory system. These are factors that may be considered in both deterministic and stochastic models of particle deposition and distribution.

A. AEROSOL PROPERTIES

As described in detail in Chapter VI of this handbook, the primary mechanisms by which particles deposit in the respiratory tract are inertial impaction, sedimentation, and diffusion. The influence of each of these mechanisms is dependent on various particle characteristics. Therefore, the vast majority of deposition models will include input parameters describing the size and density of the particles being studied. Some models only consider a single size of particles, while some may allow the user to describe a polydisperse aerosol having multiple sizes. Recently, the study of deposition of particles of nanometer or ultrafine scale (nanoparticles) has increased, both in inhalation toxicology[83,84] and aerosol medicine.[85,86] In addition to size, models also may consider the influence of particle shape (ex. spherical, tubular, fibroid) on deposition.

B. INHALABILTY

Inhalability is the ability of particles to be inhaled from the ambient environment into the mouth or nose. For small particles (those less than 5-10 microns in diameter) inhalability is essentially equal to 1. For larger particles, inhalability becomes a concern, and thus should be considered when modeling respiratory tract deposition. Particle aerodynamic diameter,

breathing conditions, and ambient conditions (such as windspeed) may all have an influence on the fraction of particles that can be inhaled. Typically, inhalability curves are empirical models that have been developed using experiments[87,88] Millage et al.[89] provide a review of several algebraic models of inhalability. In addition, CFPD has recently been used to examine particle inhalability,[90] including investigation of the effect of facial morphology.[91]

C. RESPIRATORY SYSTEM MORPHOLOGY

Any modeling of the deposition of aerosols in the human respiratory system requires a description of the morphology of the airway(s) being studied. Both the overall branching structure of the airway tree and dimensions (e.g. diameters and lengths) of individual airways must be considered. Both idealized morphology models and models based on specific experimental observations have been used in particle deposition modeling.

1. Idealized Models

Many morphology models of the respiratory system have been derived from experimentally-obtained morphometric data. Early morphometric models were simplified to provide idealized representations of branching network of the human lung. The most widely used idealized model is the symmetric model of Weibel.[92,93] In his model, the lung is characterized as a symmetric and dichotomously branching tree of tubular airways. Idealized asymmetrical models of the airway tree have also been developed. These include Weibel's asymmetric "B" model[93] and the models of Horsfield[94] and Horsfield and Cumming.[95,96]

2. Data-Driven Models

Other more biologically realistic morphological models also have been derived from experimentally obtained morphometric data. Soong et al.[97] presented a stochastic model of the

human tracheobronchial tree, using Weibel's symmetric model as the underlying average model, and incorporating probability distributions of lengths and airways based on several experimental studies (e.g. Jesseph and Merendino[98] and Parker et al.[99]) Horsfield et al.[100] developed a theoretical model of the bronchial tree based on measurements from human casts. Kitaoka et al.[101] also presented a model of the three-dimensional branching structure of the lung based on morphometric studies. Their model was derived using an algorithm guided by several morphology- or physiology-based "rules", such as prescribed relationships between airway length and diameter and between airway diameter and flow rate.

3. Three Dimensional Morphological Models for Interpretation of Lung Images

Three-dimensional (3D) morphological models have been built for use in the interpretation of images in experimental deposition studies. These models consist of a branching network of line segments, oriented in three dimensional space via idealized or physiologically realistic branching and gravity angles. Martonen et al.[102,103] have developed models for image interpretation based on idealized branching networks. An example of such a model is shown in Figure 4. More recently, Montesantos et al.[104] have developed hybrid 3D models of branching networks for image analysis. These methods construct the first 5 airway generations of the branching network high resolution computed tomography data, potentially allowing the network to be personalized to a particular subject within a lung deposition study. The use of branching network models in gamma scintigraphy is discussed further in the section on experimental deposition measurements.

4. Three-Dimensional Morphological Models for CFPD

With the increase in use of CFPD as a research tool, there has been a drive to develop three-dimensional models of respiratory system morphologies for use in CFPD studies. These models, which may be developed directly from *in vivo* medical images or from the imaging of casts, provide a physiologically-realistic foundation for the studying the influence of local airway features on the motion and deposition of particles. Spencer et al.[105] have derived a morphological model of the lung airways using data-driven surface modeling techniques. In this model, anatomical data were used to define airway lengths, diameters, and orientation angles. The surfaces of the resulting airway network were then realized using advanced graphics rendering techniques. Specifically, non-uniform rational B-splines (NURBS) were used to model smooth airway connections and realistic lung surface features.

Models derived from imaging or cast data are especially useful in developing representations of the extrathoracic airways, as these passages are not easily modeled as idealized tubes. Figure 5 depicts a geometric model of the morphology of the human nasal passages derived from MRI images of an adult male. The irregular, tortuous shape of the nasal passages (as seen in the cross-sections) will result in a distinct particle deposition pattern that cannot be predicted using simplified geometries. Morphological models have been developed for the nose[106] and oral cavity.[107] Recently, Rosati et al.[108] have presented a combined extrathoracic-lung model for use in particle deposition studies. This model uses a nose and mouth constructed from imaging data from the U.S. National Library of Medicine Visible Human Project.[109] The extrathoracic model is combined with a 5-lobe lung airway model constructed using the morphological data of Yeh and Schum.[110] The combined system is depicted in Figure 6, which shows modeled deposition in a typical lobar path within the lung.

5. Surface Features

There is much evidence to suggest that surface features in the lungs should be considered when modeling particle deposition. Both the cartilaginous rings (which are a pronounced anatomical feature of the tracheobronchial airways), and the carinal ridges (which are situated at airway bifurcations) have been studied. Bronchoscopy images depicting these surface features are shown in Figure 7.

Cartilaginous rings affect airflow patterns in the large airways.[12,106] Using CFD modeling, Musante and Martonen[111] demonstrated that small eddies, produced between the rings, may increase localized particle deposition. They also predicted that flow instabilities produced by the rings could affect deposition in locations downstream from the rings themselves. In addition, errors in large airway deposition of up to 35% were possible if the rings were ignored.[112]

Martonen et al.[10] demonstrated via CFD modeling that localized deposition of particles at the carinal ridges could be explained by localized flow instabilities arising from the ridge geometry. They also predicted that the ridges could initiate flow effects that propagate to later generations, especially at high inspiratory flow rates. Using a numerical model, Balásházy and Hofmann[113] quantified deposition at carinal ridge sites for radon progeny of different sizes. They predicted that cells located at the ridge sites experienced deposition 20-115 times greater (depending on particle size) than the average airway dose.

D. VENTILATORY CONDITIONS

Ventilatory conditions have a distinct effect on aerosol deposition and distribution. Both the mode of respiration and breathing pattern must be considered when modeling particle deposition and clearance in the human lung.

1. Mode of Respiration

Humans have the ability to breathe either nasally or orally. In contrast, rodents such as mice and rats are obligate nasal breathers. Thus, extrapolation of particle deposition data from these animals to human beings is difficult.

When sedentary, humans breathe through their nose, efficiently heating and humidifying the inhaled air. However, during exertion such as exercise, they switch over to oronasal breathing, or breathing through both mouth and nose. This switch is thought to occur when the breathing rate becomes so great that overcoming the relatively high pressure drop and resistance in the nasal passages is no longer an efficient means of respiration. In healthy adults, the switching point between nasal and oronasal breathing is thought to be approximately 35 L per minute.[114,115] In children, however, this switching point is more variable.[116] Gender does not seem to play a role in switching point determination.[114]

a. Effect of Oral or Nasal Breathing on Particle Delivery to Lungs

The route of breathing influences the quantity of inhaled contaminants or therapeutics delivered to human lungs. Particle penetration to the human lung is lower during nasal breathing (vs. oral breathing),[117] due to higher deposition efficiency in the nasal region, and there is thus more effective filtering of inhaled particles.[118,119] The higher deposition efficiency of nasal breathing is due to increased particulate matter removal by nasal hairs, impaction on pathway walls, and diffusion. Thus, it is less efficient to administer therapeutic aerosols to the human lung via the nose as opposed to the mouth.

b. Effect of Oral or Nasal Breathing on Total Particle Deposition within the Respiratory Tract

Due to efficient particle removal by the nose,[120-122] total respiratory tract deposition is higher for nasal breathing than for oral breathing in non-smokers.[51,123] As stated, the higher deposition efficiency in the nose versus the mouth is due to increased particle removal by nasal hairs, and inertial impaction. However, particulate matter removal in the nasal passages (and thus total deposition during nasal breathing) is highly dependent on particle size and inhalatory volume and flow, [119,121, 122,124] as well as nasal passage morphology and development. [120,125,126]

2. Breathing Pattern

Breathing pattern is an important factor in the respiratory deposition of therapeutic particles, as it may affect treatment efficiency.[127] Both spontaneous and regulated breathing patterns (Figure 8) have been used in human inhalation studies of particle deposition and clearance. The type of breathing pattern will affect the amount and pattern of particle deposition in the human lung. Studies comparing deposition data for spontaneous breathing patterns have been performed.[20,127,128-130]

Breathing pattern is typically described in terms of tidal volume (volume of air inhaled) and flow rate. In general, larger tidal volumes result in higher particle deposition in the human lung as particle-laden air penetrates deeper into the lung. Lower flow rates also result in higher particle deposition in the peripheral lung as velocities are slower and particles have more time to deposit by sedimentation or diffusion (see Chapter VI for discussion on deposition mechanisms).

a. Spontaneous Breathing

Spontaneous breathing is unprescribed, with subjects breathing at their own pace, with only approximate tidal volume or flow requirements. Figure 8A illustrates the relationship between tidal volume and time for a typical spontaneous breathing pattern. Chan and Lippman[27] and Brown et al.,[131] have used spontaneous breathing patterns in the study of deposition of inhaled particles. Other studies have shown that spontaneous breathing of human subjects resulted in large inter-subject variability in the fractional deposition of inhaled particles.[128,132,133] Furthermore, Bennett and Smaldone[129] determined that it was differences in spontaneous breathing pattern (and not peripheral air space size or morphology) that influenced inter-subject variation in peripheral deposition.

b. Regulated Breathing

Regulated or academic breathing occurs when human subjects are required to follow a specified breathing pattern that varies from their own natural breathing rate. In this pattern, illustrated in Figure 8B, a constant flow rate is maintained. Regulated breathing has been used to attempt to mitigate the inter-subject variability introduced by spontaneous breathing.[129] Studies by Heyder et al., [134] Stahlhofen et al.,[135] and Svartengren et al.[136] utilized regulated breathing in the determination of particle deposition in the human respiratory tract.

E. RESPIRATORY SYSTEM ENVIRONMENT

Temperature and relative humidity (RH) in the human respiratory system varies with mode of respiration and anatomical location. Table 1 provides temperature and humidity data[137-146] for different anatomical locations for both oral and nasal respiration. In general, a temperature of 37°C and a RH of 99.5% may be assumed for nasal respiration.[147] For oral

respiration, 37°C and 90% RH may be assumed for air entering the trachea, with RH increasing by 1% per airway generation until reaching 99.5% at the tenth generation.[147]

RH and temperature affect the growth of hygroscopic particles in the human lung. Hygroscopic growth occurs when the absorption of water from a humid environment causes changes in particle diameter and density. Since RH and temperature vary throughout the human lung, a particle's size and density may change while traveling through the respiratory system. Thus, a measured size distribution for hygroscopic particles is not likely to reflect actual particle sizes *in vivo*. A more extensive discussion of hygroscopicity and its effect on particle deposition in the human lungs may be found in Chapter VI.

Hygroscopic growth has been widely observed in many environmental and pharmaceutical aerosols[148-159] (Table 2). Therefore, it is often desirable to account for hygroscopic growth in particle deposition modeling. Deposition modeling studies[7,33] have accounted for hygroscopicity by incorporating the growth rate of aerosol particles as a function of residence time in the lung. Such experimental growth rate measurements for different aerosols have been presented.[160,161] The growth of aerosol particles has also been computationally predicted.[162-165]

F. CLEARANCE

Inhaled foreign material is continually cleared from the respiratory tract. From a simplified perspective, inhaled insoluble particles are cleared from the human lung in two phases, mucociliary (or fast phase) clearance and phagocytosis (or slow phase) clearance. In addition, free particles may translocate out of the alveolar region of the lung into the lymphatic system or the lung interstitium. Depending on their lipophilicity, hydrophilicity, and/or size, soluble particles may be dissolved prior to physical clearance. Other particles, such as asbestos

fibers and other biopersistent fibrous minerals, are often unable to be cleared from the lung; their retention may result in inflammation, tissue damage, and eventual disease. Oberdörster[166] provides a review of the clearance of both soluble and insoluble particles. Because the toxicity of a substance may be related to its time of residence in the respiratory system, clearance is an importance consideration in the risk assessment of inhaled particles. Thus we will present a brief overview of its mediation by drugs, inhaled contaminants, age and activity.

1. Mucociliary Clearance

Mucociliary (or fast phase) clearance occurs in the tracheobronchial airways of the lung. Mucus is secreted by mucous glands in the bronchial walls and by goblet cells in the bronchial epithelium. This mucus is propelled by millions of cilia (collectively referred to as the mucociliary escalator) towards the pharynx, in the process transporting particles out of the conducting airways. At the pharynx, the mucus and particles are swallowed. The velocity of the mucus varies from at a rate of 1 mm/min in the smaller airways to 2 cm/min in the trachea.[167] Mucociliary clearance of deposited particles generally occurs within 24 hours after deposition in healthy individuals.[167-170] A comprehensive review of mucociliary clearance is presented by Yeates et al.[171]

a. Effect of Drugs and Inhaled Contaminants on Mucociliary Clearance

Numerous studies have shown that drugs can have a significant effect on mucociliary clearance. Beta-andrenergics, histamines and amiloride have all been shown to increase mucociliary clearance in the human lung.[166,172-176] In contrast, cholinergic antagonists, aspirin and anesthetics have all been shown to markedly decrease mucociliary clearance. [166,171,177,178]

Inhaled chemical contaminants such as sulfur dioxide, sulfuric acid, ozone and tobacco smoke effect mucociliary clearance. At low concentrations (<100 μg/m^3), sulfuric acid increases mucociliary clearance while at high levels, it seems to impair clearance by paralyzing the cilia.[179,180] Sulfur dioxide, ozone and acute cigarette smoke exposures all have been shown to increase clearance in humans, whereas chronic cigarette smoking decreases mucociliary clearance.[166,181-185]

b. Effect of Disease on Mucociliary Clearance

Mucociliary clearance is inhibited by numerous respiratory diseases. Acute respiratory infections such as pneumonia and influenza have been shown to impair clearance.[181,186,187] Chronic respiratory infections such as chronic bronchitis and bronchiectasis often result in an accumulation of mucus in the ciliary transport system, hindering mucociliary clearance.[188] While COPD patients generally have varied and erratic clearance rates,[170,171] asthma can result in reduced mucus transport rates and mucus plugging of the bronchi.[169,174,189,190] Patients with cystic fibrosis have been shown to have whole lung clearance impairment, as well as regional clearance impairment.[191] Small airway dysfunction or disease from chronic cigarette smoke also results in slowed mucociliary clearance.[183]

c. Effect of Age and Activity on Mucociliary Clearance

Mucociliary clearance has been shown to decrease with age, starting at the age of 20, with large differences between adults >54 years old and adults 21-37 years.[192-195] Ho et al.[196] showed that adults over the age of 40 have decreased ciliary beat frequency, thus leading to slowed mucociliary clearance.

Increased physical activity, particularly aerobic exercise, has been shown to increase mucociliary clearance in humans.[166,190,197,198] Normal activities that do not require significant exertion have no effect on mucociliary clearance, while sleep significantly slows mucociliary clearance.[166,190]

2. Macrophage Clearance or Phagocytosis

Macrophage (or slow phase) clearance occurs in the alveolar region of the lung. As alveoli do not have cilia, deposited particles are engulfed by large bodies called macrophages (phagocytosis). These alveolar macrophages then migrate to the cilia surface and are cleared by mucociliary clearance, or move into the lymphatic system or blood stream for removal. This type of clearance may take months or years.[166]

a. Effect of Particle Size/Fiber Length and Shape on Macrophage Clearance

Particle size affects macrophage clearance rates, with clearance efficiency decreasing for particles smaller than 1µm,[199] and optimal clearance occurring for particles between 1.5 and 3 µm.[166] Studies have shown that particle/fiber length affects alveolar clearance, with shorter fibers cleared more readily than longer fibers.[200-202] Particles such as asbestos and other non-soluble fibers are often unable to be removed by phagocytosis because the macrophage is unable to engulf the entire fiber. This may result in incomplete phagocytosis, damage to the macrophage, and the release of the macrophage's digestive enzymes. These digestive enzymes can cause extensive tissue damage. Thus, the persistence of these fibers in the lung can result in inflammation and disease.[203,204]

In addition, toxic non-fiber particles such as silica, that persist in the alveoli, provoke reactions that can lead to lung disease (i.e. silicosis). When a macrophage engulfs silica

particles, the macrophage may release enzymes that cause fibroblast proliferation. This release of enzymes results from the crystalline structure of silica, the crystalline structure having been linked to the particle's fibrogenic potential.[205]

b. Effect of Drugs and Inhaled Contaminants on Macrophage Clearance

Inhaled contaminants such as ozone, nitrogen dioxide and cigarette smoke affect alveolar macrophage activity. Ozone and nitrogen dioxide reduce phagocytosis as well as the bactericidal activity of macrophages, making it more difficult to fight bacterial lung infections.[206] Acute cigarette smoke exposures, as well as high level cigarette smoke exposures have been shown to inhibit macrophage action while low levels of cigarette smoke exposure have been shown to increase macrophage action. [207,208] Exposure to nongaseous aerosolized contaminants such as nickel, cadmium, lead, manganese, chromium, and vanadium have been shown to damage alveolar macrophages.[205,206] Such exposures may result in disease (i.e. cadmium inhalation causing emphysema), potentially leaving the alveolar region unable to defend itself against or remove other inhaled contaminants, as well as causing the macrophages to release enzymes that damage the neighboring lung tissue. As discussed previously, toxic particulate contaminants such as silica and asbestos can cause macrophage impairment and damage, resulting in particle persistence and disease. The next section discusses inhaled particle overload in the alveolar region of the lung and resulting particle translocation.

3. Free Particle Uptake and Translocation to the Interstitium

Particles, particularly ultrafines, that are not rapidly cleared by macrophage action may persist in the alveoli or be taken up by epithelial cells and translocated from the alveolar region of the lung to the interstitial tissues and regional lymph nodes.[166,210-212] These particles may

remain in the interstitium or regional lymph nodes for years, building up over time,[213] or may be removed by interstitial macrophages and/or penetrate into the post-nodal lymph circulation.[212-214] It has been suggested that impaired clearance or a significant burden of particles in the lung (particle overload) increases translocation of particles to the interstitium.[209,210] Studies in animals have found that increasing particle number and dose rate, and decreasing particle size enhances translocation of particles to the interstitium.[215-217] Enhanced interstitium translocation, particularly when toxic dusts (i.e. silica) are involved, has been linked with tissue damage, tumors and fibrosis.[169,210,218]

4. Importance of Clearance in Particle Deposition Modeling

Several computational models of clearance mechanisms have been developed.[219-221] As clearance will affect both the residence time and local distribution of inhaled particles, the implementation of such models into particle deposition simulations would be desirable.

Hofmann et al.[222] developed a model of particle clearance in which different clearance rates (derived from experimental studies) were associated with different generations of tracheobronchial airways. Furthermore, Martonen and Hofmann[223] described a model of clearance as a function of spatial location within airway branching sites. Specifically, they incorporated distinct clearance rates for tubular airway segments, bifurcation zones, and carinal ridges.

As discussed in the previous sections, age, activity level, drugs, inhaled contaminants, and disease can affect the efficiency of particle clearance, in turn influencing the number and local concentrations of inhaled particles. Particle deposition models that consider these overlapping factors could be of great use in both inhalation toxicology and aerosol therapy.

Although we have discussed its influence as it relates to clearance, we will now provide a more complete discussion of the effects of disease on particle deposition and distribution.

G. DISEASE

Airway disease has a dual effect on particle deposition, both influencing breathing pattern and physically changing airway morphology. In this section, we will discuss common respiratory diseases and how they affect airflow and airway morphology, thus affecting the deposition and distribution of inhaled aerosols.

1. Chronic Obstructive Pulmonary Disease (COPD)

Chronic Obstructive Pulmonary Disease or COPD is a term that is generally applied to patients with emphysema and/or chronic bronchitis. Both of these diseases modify the structure of the human lung[169] resulting in either obstructed airways and/or degeneration of the alveolar structure.

Emphysema may affect the respiratory or terminal bronchioles or the peripheral alveoli. Cigarette smoke and air pollution are the likely causes of emphysema, resulting in the destruction of elastin in the alveolar wall. This elastin destruction leads to enlarged airspaces and loss of alveolar structure, often resulting in intrapulmonary bronchi collapse during expiration.[118,169] In addition, the loss of the alveolar structure results in the loss of capillary bed that transfers oxygen from the lungs to the blood.[169]

Chronic bronchitis is characterized by excessive mucus generation and alveolar wall thickening. The excessive mucus is a result of hypertrophied mucus glands, and causes the formation of mucus plugs that obstruct airways and may fully occlude small bronchi. Alveolar wall thickening results in reduced elasticity of alveolar walls, limiting regional ventilation.[118,169]

2. Asthma

Asthma is characterized by a reduction of the airway lumen due to constriction of the bronchial airways in response to a stimulus. This constriction may also in turn result in an increase in the mucus layer thickness. Chronic asthma can result in subepithelial fibrosis.[169] Asthma stimuli may include pollutants, allergens, or exercise. It has been noted that asthma has attained epidemic proportions on a global scale.[224]

3. Cystic Fibrosis

Cystic fibrosis (CF) is a genetic disease that causes the lung's epithelial cells to produce abnormally thick, excessive mucus. This slowly cleared mucus narrows airways and obstructs airflow making tissue vulnerable to inflammation and recurrent infection. This inflammation and infection causes progressive respiratory disease including bronchiectasis and chronic airway obstruction.[169,225] Impairment typically begins in the small airways and progresses proximally, with ventilation increasingly shifting from obstructed regions to healthy regions of the lung.[226]

4. Effect of Obstructive Disease on Particle Deposition and Distribution

Several studies have investigated the effect of obstructive disease on particle deposition and distribution in the human lung. Exploring the effect on particle deposition, Kim and Kang[227] found a marked increase in deposition of 1μm particles in patients with COPD and asthma compared to normal subjects. Anderson et al.[228,229] found that the deposition of fine and ultrafine particles was increased in patients with cystic fibrosis and obstructive disease. Brown et al.[131] found that COPD patients had a greater dose rate for ultrafine particles than healthy subjects. Also, the deposition of particles increased with severity of obstruction or decrease in lung function.[226,230-232] Reasons for increased deposition in patients with obstructive disease include

1) reduction of airway diameter by constriction or mucus build-up, thus increasing inertial impaction on airway walls, 2) increased residence time of particles in the alveolar region resulting from non-uniform ventilation distribution, 3) collapse of airways due to flow limitation, and 4) flow perturbations or induced turbulence at sites of obstruction.[226,227,229]

Investigating the effect of obstructive disease on particle distribution, Brown et al.[233] found that a significant number of coarse particles deposit in the poorly ventilated tracheobronchial airways of CF patients, while these particles follow regional ventilation in healthy subjects. Other studies indicate that the deposition pattern of particles in patients with obstructive disease is heterogeneous, with an enhancement of deposition in various local regions.[234-236]

5. Modeling Disease

Several models of particle deposition have been developed that specifically address disease. Segal et al.[237] modeled particle deposition in patients with COPD, using a modified deterministic model.[7,33] This work investigated the dependence of deposition pattern on the severity of disease. In addition, Martonen et al. simulated particle deposition in cystic fibrosis. This study found a proximal shift in particle deposition with severity of obstruction.[238-240] More recently, Martonen et al.[224] have simulated the effect of asthma on particle deposition patterns, comparing their results with data from imaging studies of asthma patients.

The United States Environmental Protection Agency (U.S. EPA) has identified people suffering from respiratory disease as a sensitive subpopulation needing particular consideration in risk assessment of particulate matter and in the establishment of air pollution standards.[241] Therefore, more advanced models of particle deposition for a variety of diseases are needed.

H. AGE

Age can be a significant factor influencing the deposition and distribution of particles in the human lung, likely due to the differences in airway geometry and ventilation between children and adults. Studies of airway geometry as a function of age are presented by Ménache and Graham,[242] Hofmann et al.,[244] and Martonen et al.[243] Age has also been shown to affect percentage of nasal breathing,[245] thus affecting amount of particulate matter that make it to the human lung. Bennett et al.[246] showed that children have enhanced upper airway deposition of coarse particles when compared to adults, but that total deposition amounts are comparable.

Several studies have modeled aerosol deposition as a function of human subject age. Martonen et al.[243] found that modeled total deposition within the human lung decreased with increasing age from 7 months to 30 years. In addition, Isaacs and Martonen[247] compared modeled lung deposition results for children with available experimental data. Using the International Commission on Radiological Protection (ICRP) 66 model,[22] Harvey and Hamby[248] found that for 1 μm particles, deposition and regional distribution varied by age, with extrathoracic deposition increasing significantly in younger age groups (young children and infants) which have smaller respiratory airway sizes. Hoffman et al.[244] showed that particle deposition does indeed depend on lung morphology and that dose per surface area decreases from 7 months of age to adulthood.

The U.S. EPA has also identified children as a sensitive subpopulation requiring additional consideration in the establishment of air quality standards.[241] Therefore, the development of particle deposition models for children is of particular importance. A model of particle deposition in a developing human lung has also been developed.[249] It was predicted that

children may receive a localized PM dose three times that of adults. Such models will be of great use in both inhalation toxicology and inhalation therapy.

VI. THEORY AND EXPERIMENT

Many different types of experimental protocols have been developed to measure particle deposition in the respiratory system. An overview of several of these methods will be presented, and a discussion of how the resulting data can be compared with particle deposition will be presented.

A. PREDICTIONS OF PARTICLE DEPOSITION

Simulation studies can be used to predict the deposition of inhaled particles on differing spatial scales of resolution. Models can be developed which predict total respiratory system deposition or deposition in each of the regional (i.e. extrathoracic, tracheobronchial, or pulmonary) compartments. In addition, models can predict deposition efficiencies in each individual airway generation, or simulate the dose to a specific anatomical location (e.g. a carinal ridge or airway wall) within a respiratory passage. The level of detail desired and the type of experimental data available for model validation should govern the selection or development of an appropriate model for a given research purpose.

B. PARTICLE DEPOSITION MEASURMENTS

Much work has been done in attempting to quantify the deposition of particles in respiratory airways, encompassing a wide range of approaches and techniques. We provide an overview of aerosol deposition measurements that have been performed in casts, animal models, and human subjects. Comprehensive reviews of experimental measurements of respiratory particle deposition have been presented by Martonen,[8] Sweeny and Brain,[250] and Kim.[251]

1. Casts and Models

Particle deposition measurements have been performed in models and replica casts of both human and animal lungs. Such studies provide a means of examining particle deposition airway by airway in realistic geometries. In addition, deposition studies in casts can be reproduced, and particles of different sizes and characteristics may be studied serially under the same conditions. Replica cast studies have been performed in the human tracheobronchial region,[27,252-254] in canine lungs,[253] and in nasal passages.[255,256] Other studies have been performed using laryngeal casts combined with a silicone rubber model of the tracheobronchial airways.[257,258] Deposition data obtained in this silicone model at a flow rate of 15 L/min are shown in Figure 9 for 2 particle sizes. Deposition in a TB replica cast[259] is also shown. In this figure, the ratio of the amount of aerosol deposited in a single generation to the amount entering the cast is plotted. Note that good agreement between the replica cast and the silcone model results were obtained. Table 3 summarizes localized (ie. bifurcation) deposition from the two silicone model studies for several particle sizes at three different flow rates. Specifically, the table contains the bifurcation deposition ratio B_d, where

$$B_d = \frac{\text{(aerosol mass deposited within a bifurcation) / (bifurcation surface area)}}{\text{(total aerosol mass deposited within the two airways of a generation, including the shared bifurcation) / (total airway and bifurcation surface area)}} \quad (9)$$

Note that in most cases the deposition in the bifurcation zone is enhanced in relation to the adjacent airways. For example, at a flow rate of 60 L/min the deposition of 8.7 μm particles at the third generation bifurcation is three times greater than that in the adjacent airway segments. The values of B_d of less than one may be due to large regions of the bifurcations site having 0 deposition, as observed by Schlesinger et al.[260]

Recently, advances in stereolithography and "3D printing" techniques have allowed for the rapid development of plastic (resin) or polymer models from medical images for use in deposition studies. Such models include the Premature Infant Nose Throat (PrINT) model,[260] an MRI-based polymer model, and the Sophia Anatomical Infant Nose –Throat model.[261] In addition, Giesel et al.[262] presented a method of rapidly prototyping models of the upper (generations 0-5) tracheobronchial airways using CT scanning and laser sintering.

2. Deposition Patterns Deduced from Clearance Studies

Experimental methods have been developed in which the regional deposition of particles is deduced from measurement of the time-course of clearance of particles from the thorax.[134] Specifically, radiolabeled particles are inhaled, and a whole body counter is used to measure the amount of radioactive activity in the stomach, chest, and extrathoracic regions. Since the removal of particles (by mucociliary clearance) in the tracheobronchial region occurs at a faster rate than removal (by macrophagic clearance) in the pulmonary region, deposition in the two regions can be deduced from the two-part slope of a normalized retention curve for the thorax.

3. Light-Scattering Methods

Traditionally, total deposition of particles in the respiratory tract has been quantified using light scattering photometry to compare the concentration of particles in the inhaled and exhaled air.[134,251,263,264] When a monodisperse aerosol is used, and ventilation is simultaneously measured, the deposition fraction in the respiratory system can be calculated. However, photometry cannot distinguish between differences in inspiratory and expiratory aerosol concentration and changes in aerosol size distribution, therefore, these methods are inappropriate for polydisperse or hygroscopic aerosols.[251] Rosati et al.[265] have developed a light-scattering,

particle-sizing system that may be the best option for determining total deposition of polydisperse aerosols in the respiratory tract. This system also has the potential to be applied to hygroscopic aerosols as it can determine particle sizes of inhaled and exhaled aerosols, and works well for varying-sized polydisperse aerosols.[265,266]

4. Imaging Studies

Radionuclide imaging has been widely used to measure both the concentration and spatial distribution of inhaled aerosols. In these studies, particles are tagged with a radioisotope (such as ^{99m}Tc) and then inhaled. Two-dimensional (2D, planar) or three-dimensional (3D) imaging modalities can then be used to measure the radioisotope emissions from specific locations within the body.

Planar gamma cameras can be used to obtain projections of the spatial distribution of inhaled radiolabeled aerosols. These images may be useful in predicting total deposition within the lung or extrathoracic passages, but the 2D nature of the images may obscure important deposition patterns.[267] Planar imaging studies have been performed for a variety of inhaled aerosols.[133,269,270] To assist in the interpretation of planar gamma camera data, Martonen et al.[269,270] have developed methods to associate regions of images (Figure 10A) with computer models of the human lung (Figure 10B). The computer model serves as a template to be superimposed on actual images thus permitting the generational airway composition within the central (C), intermediate (I), and peripheral (P) zones of planar images to be predicted (Figure 10C). Tossici-Bolt[271,272] et al. have recently described methods of constructing three-dimensional representations of aerosol deposition from planar scintigraphic images

Recently, three-dimensional tomographic imaging modalities have been applied to the study of particle deposition patterns. Both 3D single photon emission computed tomography

(SPECT)[268,273 ,274] and positron emission tomography (PET)[275-277] have been employed in particle deposition studies. Three-dimensional methods provide a powerful means of associating particle deposition with distinct local regions within the respiratory system. In a series of papers, Martonen, Fleming, and coworkers[273,278-282] have recently presented computational methods for correlating the individual airways of a lung morphology model with the voxels of 3D SPECT images. These methods provide a means of validating 3D CFPD and deposition models using SPECT data while simultaneously providing a framework for predictive laboratory studies of targeted aerosol delivery. In practice, the computer model may be superimposed on the voxels of a SPECT image to allow a quantification of particle deposition. Figure 11 shows an example SPECT image and a detailed view of the airway composition of an associated voxel.

5. Microdosimetry

In the experimental methods described above, particle deposition may be measured by region (e.g. by clearance studies) or airway-by-airway (e.g in casts). However, in the study of the health risks associated with inhaled particles, it is desirable to obtain deposition measurements at ever finer levels of spatial resolution, measuring the dose to individual airway structures or cells. Unfortunately, there is little such data available. Schlesinger et al.[259] performed local deposition studies of 8 μm particles in a cast of an airway bifurcation. After the aerosols were deposited, the airway cast (Figure 12) was cut open and a microscope was used to count the number of particles in 1-mm-square regions of the bifucation surface. Panels A and B of Figure 12 show their results for constant flow rates of 15 and 60 L/min, respectively. There is a definite “hot-spot” of deposition at the carinal ridge at 15 L/min, and this area becomes wider with increasing flow rate. In addition, Martonen[283] presented a qualitative description of the local concentrations of 6.7 μm ammonium fluorescein particles in several generations of a

bifurcating cast at a constant flow rate. Following the deposition of the particles, the cast was cut open and the distribution of the particles was imaged (Figure 13). Note the "hot spots" of particles at the carinal ridges. Additional studies of the dosimetry or microdosimetry of inhaled particles would be of great use in the validation of CFPD studies.

C. COMPARISON OF MODELING AND DATA

Validation of deposition modeling results with experimental data is a crucial step in the modeling process. Studies comparing simulated particle deposition predictions with experimental results exist for a wide variety of models. In these studies, simulations of total and compartmental particle deposition have been examined, with many particle sizes being considered. Stahlhofen et al.[20] presented a comprehensive overview and summary of large amount of experimentally obtained particle deposition data, providing a resource for many subsequent modeling investigations.

In the study of the fate of inhaled particles, one must be aware that inherent uncertainties exist in both experimental data and in model simulations. For example, uncertainty and error may be imparted into experimental data by uncertainties in the measurement of flow rates, particle size distributions, or experimental deposition measurements, or by intersubject variability in these measurements.[20] Uncertainty in model simulations may depend on one or more of the following: 1) observational errors in any model input parameters, 2) natural (i.e. intersubject of intra-subject) variation of model input parameters, 3) the validity of the underlying theory of the model or any simplifying assumptions, 4) any approximation errors imparted by the computational numerical methods, or 5) round–off errors imparted by limitations of the computer hardware or software being used. Therefore, any comparisons of model and data should be undertaken with the sources of uncertainty in both the experimental system and

modeling method in mind, and research aimed at explaining and/or controlling variability and uncertainty should be ongoing.

1. Simulations of Total Particle Deposition

Comparison of total deposition predictions with experimental data have been performed for both stochastic and deterministic models. Hoffmann and Koblinger[284] presented a comparison between their estimated total deposition, as predicted by their stochastic model, and that obtained from a variety of experimental sources as a function of particle size. They also considered mouth versus oral breathing and breathing pattern in their comparisons. In general, they found good agreement between the model and experiment at all particle sizes.

Theoretical predictions of total particle deposition obtained using the deterministic model of Martonen et al.[7,33] are compared with the experimental data of Heyder et al.[285] in Figure 14. The deposition formulae presented in Chapter VI form the foundation of this model. For the given ventilatory conditions, the predicted total deposition fractions are in relatively good agreement with the experimental data over a wide range of particle sizes. However, there are some systematic differences between the model predictions and the data, namely an overestimation of the total deposition fraction at larger particle sizes. Other comparisons of this deterministic model to human subject data have been performed by Segal et al.[286] More recently, Rosati et al.[108] used the total respiratory tract deposition of Kim and Hu[287] to assess total deposition results for a combined nose-lung CFPD model.

2. Simulations of Compartmental Particle Deposition

a. Extrathoracic

Due to the complex geometries present in the oral and nasal regions (e.g. the nasal geometry depicted in Fig. 4), little theoretical modeling has been done in the extrathoracic compartment. Simple analytical models were developed early on for the nose,[288] but as the complexity of the nasal passages was recognized, and more experimental data was published,[289] it became apparent that more complex models were needed. Experimental deposition data has also been reported for the oral cavity,[27, 134,290] and analytical models have been developed.[291] Historically, most of the modeling that has been done for the nose[289,292,293] and mouth[292] region has been empirical in nature. Recently, CFPD has offered an alternative approach to the simulation of particle deposition in the extrathoracic passages, while at the same time advancements have been made in the manufacture of replica models of the tortuous extrathoracic airways for use in deposition experiments. Kelly et al. described the deposition of both coarse[294] and ultrafine[295] particles in stereolithography-based plastic nasal model. Their experimental results have been compared (with good agreement) to results obtained in CFPD models by Schroeter et al.[77] and Tian et al.[75] Similar comparisons have been done in the oral cavity as well. The mouth deposition efficiencies predicted by Xi et al.[71] in a realistic mouth geometry using CFPD compared well with the experiment results obtained by Cheng et al.[296] in a cast of the human mouth.

b. Tracheobronchial

Hoffmann and Koblinger[284]compared their simulated tracheobronchial deposition values with the experimental data of Heyder et al.[285] For particle sizes of 0.05-1 μm, their model

predicted deposition in the tracheobronchial region of 1-11%, while zero measured deposition was reported by Heyder et al. It was hypothesized that these differences were due to inherent limitations of the definition of different regions in the model.

Theoretical predictions of tracheobronchial deposition fraction for the model of Martonen[7,33] are plotted versus corresponding experimental data in Figure 15. Again, relatively good agreement between theory and average experimental data was observed over the range of particle sizes investigated, suggesting that the physics of the inhaled particles are being adequately simulated.

There have been many comparisons of CFPD models of the tracheobronchial airways (either idealized or physiologically-realistic models) with experimental data collected in physical models of branching networks. While these comparisons don't consider *in vivo* experimental data, they can be useful in validating CFPD methods. For example, Kim and Fisher[297] described deposition in a series of physical tubes. Their results have been used to validate the CFPD models of Farkas et al., [298] which were performed in geometrically similar configurations.

c. Pulmonary

Hoffmann and Koblinger[284] also compared their simulated pulmonary deposition values with the experimental data of Heyder et al.;[285] their model very closely predicted measured values in the pulmonary region. Results from the deterministic model of Martonen[7,33] for the pulmonary region are plotted against the experimental data of Heyder et al. in Figure 16. While generally good agreement was seen between theory and experiment over the particle sizes simulated, these was a noticeable shift of the predicted deposition with respect to the experimental data. Such a systematic trend in the model bears further investigation.

3. Simulations of Particle Distribution Generation-By-Generation

Figure 17 depicts particle deposition by generation as predicted by the model of Martonen[7,33] for a variety of ventilatory conditions. At higher flow rates (Figure 17C), the model predicts enhanced deposition of large particles in the tracheobronchial airways. Experimental measurements of deposition generation-by-generation are scarce, and additional accurate cast studies would be particularly useful in validating such simulations.

4. Simulations of Local Particle Deposition

Experimental data describing the local airway concentrations of inhaled particles are relatively scarce, and are mainly derived from observations of cadaver airways and cast studies. Therefore, it is challenging to validate CFPD studies of local particle deposition in all except very simple geometries, although predicted accumulations of particles at carinal ridges have been shown consistent with experimental observations.[54] Recent efforts by Martonen and coworkers[280,281] present a methodology for associating individual airways of a branching lung morphology model with specific voxels of a corresponding SPECT image, thereby allowing for the comparison of simulated deposition with actual deposition measurements.

Some CFPD studies have also compared local deposition patterns with experimental data. Isaacs et al.[64] created a CFPD model of a tracheal bifurcation, based on the geometry of the cast system of Schlesinger et al.[299] Modeled particle deposition results in the localized “hotspot” region of the bifurcation were favorably compared with the experimental results obtained in the cast.

VII. APPLICATIONS OF DEPOSITION MODELS

A. EXPOSURE AND RISK ASSESSMENT

Aerosol particle deposition models can provide a quantitative estimate of the amount of material deposited in the lungs under certain conditions. The ability to provide a mechanistic link between human exposure to pollutants and intake dose received has a potential role in the assessment of risk associated with inhaled particulate matter. Several stochastic human exposure models developed and used by the U.S. Environmental Protection Agency have recently been updated to incorporate aerosol dosimetry models. These models include the Air Pollutants Exposure (APEX) model[300,301] of EPA's Office of Air Quality Planning and Standards and SHEDS-PM,[302] a stochastic exposure model developed by EPA's Office of Research and Development (ORD).

In both APEX and SHEDS-PM, census and other input data are used to create a simulated population of the area being studied (usually a U.S. city, urban area, or state). A year-long time series of pollutant exposures (the PM concentration being encountered) are then estimated for each simulated person based on ambient air quality data, housing characteristics, and human activity data. The exposure time series are combined with other physiological characteristics of the simulated person and particle composition information, and used as input to a modified version of the empirical ICRP dosimetry model[22] to predict population distributions of deposited particle doses. These dosimetry algorithms may be useful in future risk assessments of PM. An example of a population dose distribution curve is provided in Figure 18.

Other particle dosimetry models are also being used in other EPA efforts to associate human pollutant exposures and doses with health effects. The Exposure Model for Individuals (EMI)[303] is being developed by ORD for use in interpreting individual-level data (e.g., questionnaires)

collected in a number of air pollution cohort health studies. Similar to APEX and SHEDS, EMI also contains an exposure calculation module, but in this case the exposures are predicted not for a simulated population, but rather for a targeted group of real individuals. The exposure module will be coupled with the MPPD particle dosimetry model[304] and a particle clearance algorithm to estimate a time-series of particle doses for the individuals being studied. Both the exposure and dose estimates produced by EMI will then be used in conjunction with epidemiological models to assess correlations with negative health outcomes.

B. DESIGN OF INHALED PHARMACEUTICALS AND DELIVERY SYSTEMS

One of the most promising applications of aerosol deposition modeling is in the design of optimized pharmaceutical aerosols and associated delivery systems. Computational models, especially CFPD models, have the potential to predict the ideal particle properties, inhalation patterns, and aerosol intake conditions (such as velocities or spatial distributions) for targeting the delivery of mass to the therapeutically relevant portions of the respiratory system. Typically, this means reducing deposition in the extrathoracic airways so that the drug can reach either the smooth muscle-lined airways of the lungs (for asthma therapies) or the pulmonary region (for systemic treatments), although in the case of some therapies (like nasal sprays) deposition in the extrathoracic region may be desirable.

In addition to their pure predictive power, deposition models can also be used to interpret observed deposition patterns produced by drug de livery systems, such as dry power inhalers (DPIs), nebulizers, and pressured metered-dose inhalers (pMDIs). The use of models in conjunction with *in vitro* and *in vivo* experiments can illuminate mechanistic reasons for differences in inhaler performance.

Martonen et al.[107] provide a review of the theoretical modeling issues relevant to assessing different types of inhaled pharmaceuticals, and present a methodology for developing a physiologically-based model of the entire upper respiratory system for use in CFPD studies of inhaler performance. Other CFPD models have recently been used to interpret human studies of dry powder inhalation,[305] compare deposition results among different pMDI formulations[306] and between an MDIs and a DPI,[307] evaluate different inhaler mouthpiece configurations,[308,309,310] assess the influence of spray momentum on mouth and throat deposition,[311] and predict the deposition patterns of nasal sprays.[312]

Recently, hygroscopicity has been proposed as the basis for a new method of improving deposition of pharmaceutical aerosols. The method, called enhanced condensational growth (ECG), involves inhaling a submicron-sized aerosolized medication in combination with water vapor. Ideally, the initial small particle size would minimize extrathoracic deposition, while the hygroscopic growth of the particle as it moves into the lung would provide enhanced deposition. Longest and coworkers[313,314] have developed CFPD models to explore the potential of this method.

VIII. SUMMARY

The modeling of particle deposition is of great use in both inhalation toxicology and inhalation therapy. In particular, modeling provides a means of predicting total, regional, and local respiratory system concentrations of inhaled particles, and offers a foundation for development of targeted delivery protocols. In addition, modeling aids in interpreting experimental measurements and advances the understanding of events and variables that cannot be experimentally quantified.

Particle deposition in the human respiratory system is an extremely complex phenomenon, governed by a wide variety of overlapping and interacting factors. Development and validation of increasingly sophisticated computational models that address particle deposition on local and regional scales, and consider both biological variability and realism, will be instrumental in improving the prediction of both the health effects of inhaled particles and the therapeutic value of inhaled pharmaceutics.

VIII. DISCLAIMER

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Table 1 Temperatures and relative humidities (RH) in the human respiratory tract, for both inspiration and expiration. Adapted from *Extrapolation of Dosimetric Relationships for Inhaled Particles and Gases*, Martonen, T. B., Hoffman, W., Eisner, A. D., and Ménache, M. G., The role of particle hygroscopicity in aerosol therapy and inhalation toxicology, Pages 303-316, Copyright 1989, with permission from Elsevier.

Anatomical Location	**Nasal**				**Oral**				**References**
	$T_{insp\ (°C)}$	**$T_{exp(°C)}$**	**RH_{insp}**	**RH_{exp}**	**$T_{insp(°C)}$**	**$T_{exp(°C)}$**	**RH_{insp}**	**RH_{exp}**	
Nasal Passages									
Distance from Nostril									
1.5 cm	28.9 $\pm$ 2.3	-	69 $\pm$ 6.5	-	-	-	-	-	Keck et al.[137]
2.5 cm	30.3 $\pm$ 1.6	-	78.7 $\pm$ 7.2	-	-	-	-	-	Keck et al. [137]
6.0 cm	32.6 $\pm$ 1.5	-	90.3 $\pm$ 5.3	-	-	-	-	-	Keck et al. [137]
Laryngeal cavity	32.3 $\pm$ .8	36.4 $\pm$ .2	98 –99	98-99	30.6 $\pm$ .8	36.2 $\pm$ .3	90	99	Ingelstedt[138]
Airway generation, i									
i=0 (trachea)	34 – 35	36 – 37	-	-	33 - 34	36 – 37	-	-	Cole[139]
i=0 (trachea)	35.3	35.7	98	99.9	-	-	-	-	Perwitzschky[140]
i=0 (trachea)	35.4	36.2	-	-	34.5	35.8	-	-	Verzar et al.[141]
i=0 (trachea)	32.6	35.3	-	-	32.9	34.4	-	-	Herlitzka[142]

i=0 (trachea)	-	-	-	-	26.7	-	82.7	-	Dery et al.[143]
i=0 (trachea)	-	-	-	-	31.4 – 31.9	33.2 – 33.4	73.6 – 80.4	-	Dery[144]
i=0 (trachea)	-	-	-	-	31.2	32.6	-	-	McFadden et al.[145]
i=0 (trachea)	-	-	-	-	32	3	-	-	McFadden et al. [145]
i=0 (trachea)	-	-	-	-	32.2	3	-	-	Dery et al. [143]
i=0 (trachea)	36	36.2	98.3	99.2	-	3	-	-	McRae et al.[146]
i=1 (main)	-	-	-	-	30.6	3.	85.8	-	Dery[144]
i=1 (main)	-	-	-	-	32.2	4	87	-	McFadden et al. [145]
i=2 (lobar)	-	-	-	-	33	-	-	-	McFadden et al. [145]
i=3 (segmental)	-	-	-	-	33.1	-	91.3	-	Dery et al. [143]
i=4 (subsegmental)	-	-	-	-	33.9	3	94.6	-	McFadden et al. [145]
i=4-5	-	-	-	-	33.9	3.	-	-	Dery[144]
i=10-11	-	-	-	-	34.6	7	-	-	McFadden et al. [145]
						3			
						4			
						-			
						-			
						3			
						5			
						3			

6

Table 2 Hygroscopic growth of various environmental and pharmacological aerosols

Substance	Conditions		Diameter Increase (%)	Source
	T (°C)	RH (%)		
Mainstream cigarette smoke				
0.44 μm		100	65	Kousaka et al.[148]
~0.3 μm		99.5	~60	Li and Hopke[149]
~0.2 μm		99.5	~45	Li and Hopke[149]
-		100	~70	Hicks et al.[150]
NaCl				
0.1 μm	20	90	129	Gysel et al.[151]
0.3-0.5 μm	25	75	~90	Tang et al.[152]
0.3-0.5 μm	25	85	~110	Tang et al. [152]
0.3-0.5 μm	25	98	~280	Tang et al.[152]
$(NH_4)_2SO_4$				
0.05 μm	20	90	66	Gysel et al.[151]
0.1 μm	20	90	68	Gysel et al.[151]
$NaNO_3$				
0.05 μm	20	90	86	Gysel et al.[151]
0.1 μm	20	90	91	Gysel et al.[151]
NH_4HSO_4		98	~220	Tang and Munkelwitz [153]

Cromolyn sodium	98	31	Smith et al.[154]
Metaproterenol sulfate	98	29	Hiller et al.[155]
Isoproterenol sulfate	98	13	Hiller et al.[155]
Beclomethasone dipropionate	98	33	Hiller et al.[156]
Isoproterenol/phynlephedrine	90	24	Kim et al.[155]
Epinephrine	90	11	Kim et al. [155]
Metaproterenol	90	10	Kim et al.[155]
Albuterol	90	8	Kim et al.[155]
Isoetharine/phenylephedrine	90	10	Kim et al.[155]
Triamcinolone	90	17	Kim et al.[155]
Aerodur	98	37	Seemann et al.[158]
Bricanyl	98	144	Seemann et al.[158]
Cromolind	98	48	Seemann et al.[158]
Intal powder	97.4	30	Seemann et al.[158]
Intal composite	97.4	30	Seemann et al.[158]
Atropine sulfate	99.5	160	Peng et al.[159]
Isoproterenol hydrochloride	99.5	186	Peng et al.[159]
Isoproterenol hemisulfate	99.5	142	Peng et al.[159]
Disodium cromoglycate	99.5	26	Peng et al.[159]

Table 3 Bifurcation deposition ratio B_d at different flow rates

Tracheobronchial Model Generation	Q=15 L/min				Q=30 L/min			Q=60 L/min			
	1.9 μm[b]	2.1 μm[a]	3.0 μm[b]	6.7 μm[a]	3.3 μm[a]	3.6 μm[a]	6.8 μm[b]	1.9 μm[a]	6.1 μm[a]	8.7 μm[b]	10.6 μm[b]
1	0.80	0.42	0.51	0.83	0.17	0.25	0.65	0.50	0.84	1.10	1.20
2	1.15	1.08	1.15	0.92	1.08	1.19	1.35	1.30	1.14	1.40	1.52
3	1.50	1.38	1.62	1.36	2.29	1.83	2.31	1.93	1.84	3.05	3.16
4	0.91	0.90	0.87	1.12	1.34	1.47	1.57	1.74	1.46	2.10	1.94
5	1.10	0.85	0.91	1.18	1.48	1.63	1.50	1.63	1.78	1.75	1.60

[a] Martonen[257]

[b] Martonen and Lowe[258]

XI. FIGURE LEGENDS

Figure 1. Cylindrical coordinate system for an arbitrary airway and corresponding velocity components at an arbitary point.

Figure 2. Image of a CFD simulation of secondary velocity currents in the eighth generation of a bifurcating airway, using FLUENT 6.0.

Figure 3. CFPD simulations of particle trajectories in a bifurcating airway using FLUENT 6.0. The flow rate is 120 L/min, and the two panels show trajectories for 2 different sets of initial particle locations.

Figure 4. A branching lung network model (A) and an associated network of voxels (B, not to scale) for analysis of SPECT images of aerosol distribution.

Figure 5. A morphological model of the human nasal passages derived from MRI imaging data. Note the complex cross section of the nasal passage.

Figure 6. The combined extrathoracic and lung airway model of Rosati et al.[108] Deposition of 1 micron particles in a typical lobar path is shown.

Figure 7. Airways and surface features photographed with videobroncoscopy. A. The trachea and the main bronchi with the cartilaginous rings clearly visible. B. A quadruple

bifurcation, indicative of the complex branching pattern of the lung. C. Blunt carinal ridges. D. Sharp carinal ridges. University of Iowa, 1992-2003, reprinted with permission.

Figure 8. Spontaneous (A) and controlled (B) breathing patterns. Note that in spontaneous breathing, rate and tidal volume may vary, while these are constant in controlled breathing.

Figure 9. Deposition of particles in the tracheobronchial region as measured by Martonen[257] using a silicone rubber cast, compared with the replica cast data of Schlesinger et al.,[259] for different particle sizes.

Figure 10. Association of the central, intermediate, and peripheral zones (A) of planar gamma camera images with a corresponding computerized lung branching network model (B). Panel C shows the resulting distribution of lung airways within each zone.

Figure 11. A SPECT image of radiolabeled aerosol distribution in the human lung and an associated voxel of the branching computer model; the composition of airways within the voxel is shown.

Figure 12. Determination of localized deposition by Schlesinger et al.[259] The replica cast, the expanded bifurcation zones, and the resulting measured local deposition are shown. Adapted from Schlesinger et al., *Ann. Occup. Hyg.,* Pergamon Press, 1982, with permission.

Figure 13. Enhanced deposition of 6.7 μm particles at different generations of bifurcations in a replica cast. Adapted from Martonen, T. B. et al., *Am. Ind. Hyg. Assoc. J.*, American Industrial Hygiene Association Press, 1992, with permission.

Figure 14. Model predictions of total deposition determined using the deterministic model of Martonen,[7,33] plotted against experimental data.[285] (A) breathing frequency=30 breaths/min, tidal volume=500 mL, (B) breathing frequency=15 breaths/min, tidal volume=1000 mL, (C) breathing frequency=30 breaths/min, tidal volume=1500 mL.

Figure 15. Model predictions of tracheobronchial deposition determined using the deterministic model of Martonen,[7,33] plotted against experimental data.[285] (A) breathing frequency=30 breaths/min, tidal volume=500 mL, (B) breathing frequency=15 breaths/min, tidal volume=1000 mL, (C) breathing frequency=30 breaths/min, tidal volume=1500 mL.

Figure 16. Model predictions of pulmonary deposition determined using the deterministic model of Martonen,[7,33] plotted against experimental data.[285] (A) breathing frequency=30 breaths/min, tidal volume=500 mL, (B) breathing frequency=15 breaths/min, tidal volume=1000 mL, (C) breathing frequency=30 breaths/min, tidal volume=1500 mL.

Figure 17. Model predictions of particle deposition generation-by-generation determined using the deterministic model of Martonen,[7,33] for a range of particle sizes. (A) breathing frequency=30 breaths/min, tidal volume=500 mL, (B) breathing frequency=15 breaths/min, tidal volume=1000 mL, (C) breathing frequency=30 breaths/min, tidal volume=1500 mL.

Figure 18. Distribution of daily deposited $PM_{2.5}$ dose in a year-long simulation of a population of 15,358 individuals in Philadelphia, PA, both by gender (A) and age (B). These doses were calculated using the SHEDS-PM exposure model,[302] incorporating an adapted version of the ICRP deposition algorithm (with no clearance). These simulations were based on $PM_{2.5}$ air quality data for 2008. Courtesy of Janet Burke, EPA.