Title
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Publication Date
2016-09-01

DOI
10.1016/j.jaerosci.2015.12.008

Journal of Aerosol Science 99 (2016) 7–13

Contents lists available at ScienceDirect

Journal of Aerosol Science

journal homepage: www.elsevier.com/locate/jaerosci

The evolution of inhaled particle dose modeling: A review

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ARTICLE INFO

Available online 27 April 2016

Keywords:
Inhaled particles
Dose models
Computational fluid dynamics
PBPK models
Historical developments
Local particle deposition

ABSTRACT

Inhaled aerosol dose models play critical roles in medicine, the regulation of air pollutants and basic research. The models fall into several categories: traditional, computational fluid dynamical (CFD), physiologically based pharmacokinetic (PBPK), empirical, semi-empirical, and "reference". Each type of model has its strengths and weaknesses, so multiple models are commonly used for practical applications. Aerosol dose models combine information on aerosol behavior and the anatomy and physiology of exposed human and laboratory animal subjects. Similar models are used for in-vitro studies. Several notable advances have been made in aerosol dose modeling in the past 80 years. The pioneers include Walter Findeisen, who in 1935 published the first traditional model and established the structure of modern models. His model combined aerosol behavior with simplified respiratory tract structures. Ewald Weibel established morphometric techniques for the lung in 1963 that are still used to develop data for modeling today. Advances in scanning techniques have similarly contributed to the knowledge of respiratory tract structure and its use in aerosol dose modeling. Several scientists and research groups have developed and advanced traditional, CFD, and PBPK models. Current issues under study include understanding individual and species differences; examining localized particle deposition; modeling non-ideal aerosols and nanoparticle behavior; linking the regions of the respiratory tract airways from nasal–oral to alveolar; and developing sophisticated supporting software. Although a complete history of inhaled aerosol dose modeling is far too extensive to cover here, selected highlights are described in this paper.

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http://dx.doi.org/10.1016/j.jaerosci.2015.12.008
0021-8502/

1. Introduction to inhaled particle dose modeling

1.1. Inhaled particle doses

In general toxicology, "dose" is usually related to a specific biological target (e.g., a potentially responsive organism, organ, tissue, cell, etc.), and the dose might be normalized to a property of the target (e.g., its mass, surface area, etc.). For example, oral medications are often administered on the basis of body weight. In inhalation toxicology, the exposure agent is delivered to the subject in the air, is inhaled (i.e., the inhalable fraction) and a portion initially deposits in the respiratory tract. After deposition, the biological targets may be in the respiratory tract or elsewhere as a result of absorption distribution, metabolism, and excretion (ADME) processes. A general overview of airborne particle human inhalation, deposition, and clearance has been provided by Raabe (1982). The primary objective in inhalation toxicology is to find relationships between the amounts of exposure agents and their effects, which may be either beneficial or adverse. Aerosol exposures can be intentional or incidental, and the subjects may be humans, laboratory animals, cell cultures, etc. Inhaled agents of interest include medications, air contaminants, and substances that are used to study in the laboratory basic aspects of physiology and anatomy. The focus of this paper is on inhaled particles rather than inhaled gases and vapors.

1.2. Inhaled particle dose models

Inhaled particle dose models have evolved over the past 80 years, largely in order to predict or understand the health-related effects of inhaled agents in quantifiable terms. A key concept in modeling is the "dose metric", which is any measurable property of the exposure agent (e.g., particle size distribution, mass, surface area, oxidative potential, etc.) that when controlled will modulate the biological effects. Although there is a tendency to find "the correct metric", in fact all of the relevant metrics will act simultaneously. The biological effects are thus modified by several properties of the inhaled particles, as well as by the exposure characteristics, the exposed species, and the status of the exposed subject during the initial exposure and afterward. Other factors, such as co-inhaled agents, environmental conditions, and subject behavior during and after exposure may modify the effects. Additionally, individual subjects will respond differently to each of the various exposure metrics. These variations must be considered by dose modelers.

Inhaled particle dose models fall into six categories as shown in Table 1. Each type of model has its own characteristics and historical development, and each has its applications, strengths, and weaknesses. Thus each modeling approach is useful, but none is perfect for understanding the effects of inhaled agents in different applications. Models for predicting the deposition patterns of inhaled aerosol particles depend on developments in particle physics and the biological systems that are under consideration. Selected model types will be described in the following sections.

Table 1
Inhaled particle dose deposition model types.

Model type	Description	Comments
Traditional (Findeisen-type)	Particle deposition mechanisms are applied to simplified anatomical geometries and airflows	Useful when major deposition mechanisms and realistic anatomical and physiological data are used
Computational fluid dynamical (CFD)	Fluid flows are "solved" for discrete volume and boundary conditions, and particle trajectories are tracked to provide deposition sites and amounts	Provide detailed deposition patterns and can use actual anatomical scanning data
Physiologically based pharmacokinetic (PBPK)	Multi-compartment models that describe kinetics of absorption, distribution, metabolism, excretion, and storage (ADMES) of inhaled agents	Useful for describing internal fates of inhaled agents in multiple species, and making extrapolations
Empirical	Experimental data displayed in tables, figures, or fitted equations	Applicability is limited to matching the study conditions
Semi-empirical	Experimental data are used to generate equations that include particle, fluid, and biological parameters	Can be used to extrapolate the data to new cases
"Reference"	Inhaled particle dose models that apply to a reference man, woman, child, etc.	Widely used in medical, occupational, and environmental applications

1.3. Early understanding

Prior to 1900 there was a general recognition of the importance of the doses of inhaled infectious and non-infectious aerosol particles in producing adverse effects (Thomas, 1882; White, 1902). But it was a later seminal paper by Findeisen (1935) that initially brought aerosol physics and respiratory system biology together for calculating inhaled aerosol doses. He envisioned the bronchial tree and alveoli as cylindrical tubes and spherical sacs, and modeled 4 deposition mechanisms (diffusion, sedimentation, inertia, and interception). An assumption, still valid today, is that any particle that touches an airway surface will irreversibly deposit (i.e. the sticking coefficient is 1.0). Findeisen's respiratory tract model had 9 portions (trachea, 4 levels of bronchi, terminal bronchioles, respiratory bronchioles, alveolar ducts, and alveolar sacs). Neither the nose nor the mouth were included in his model. He described the model structure and results, and demonstrated reasonable agreement with the limited experimental data from excised lungs of a dog, calf and sheep that was available in 1935. In summarizing his results, he noted that large, presumably solid unit density (1 g/cm^3) spherical, particles (diameter 60 μm) deposit mainly in the trachea and larger bronchi (in the absence of any upper airways), smaller particles (about 2 μm diameter) deposit mainly in the respiratory regions, particles 0.2–0.6 μm in diameter are mostly exhaled, and very small particles (e.g., 0.06 μm diameter) have greater total deposition than the other small particles. The familiar U-shaped curve for inhaled particle deposition efficiency vs. particle diameter was thus established. Findeisen's paper was the first to put anatomy, respiration, and aerosol behavior together to make and test quantitative dose predictions. This type of aerosol particle dose modeling may be called “traditional” or “Findeisen-type”. Landahl (1950a, 1950b) improved on Findeisen's model by (1) adding several anatomical structures (e.g., nose, mouth, pharynx, and additional alveolar ducts); and (2) modeling several breathing patterns and additional particle sizes. Thus, modeling included upper airways, and recognized that deposition in upper airways was greater in nasal than in oral breathing.

Davies (1949) described the state of knowledge in his time on inhaled particle doses, covering sites of action, effects of particle size, the available experimental data, and “nasal filtration”. Although the nose may be a somewhat protective filter for the rest of the respiratory tract, unfortunately the importance of potential nasal injury from inhaled substances may not be adequately appreciated. The importance of nasal toxicity was described in a collection of 20 articles in *Nasal Toxicity and Dosimetry of Inhaled Xenobiotics* (Miller, 1995).

1.4. Recent Findeisen-type models of inhaled aerosol deposition and clearance

A major advance was made by the Task Group on Lung Dynamics of the International Commission on Radiological Protection (ICRP), (Morrow, Bates, Fish, Hatch, & Mercer, 1966). The Task Group used Pattle's (1961) empirical formula for nasal deposition, developed a similar model for oral deposition, separated the tracheobronchial (TB) and pulmonary (P) regions, considered lognormal aerosol size distributions, addressed hygroscopic and electrically-charged aerosols, and described particle clearance and its dependence on classes of particle solubility. This model was well received, and it established the modern approach for Findeisen-type aerosol deposition models. Many improvements in the details and scope of such models would follow the Task Group Lung Model (e.g., ICRP, 1994; NCRP, 1997; Wang, 2011).

Raabe, Yeh, Schum, and Phalen (1976) used Weibel's (1963) approach for TB morphometry, but introduced the idea of basing airway measurements on realistic in-situ lung casts in a state of normal inflation for acquiring the specific quantitative data required for input into mathematical aerosol deposition models (i.e., airway lengths, diameters, branching and gravity angles). They published single-pathway anatomical models of linked airway generations for humans, dogs, rats, and hamsters (Raabe et al., 1976). Single- or typical-path anatomies were then used for individual lung lobes to perform aerosol deposition calculations (e.g., Yeh & Schum, 1980). Later, conjectural lung anatomies allowed large numbers of pathways to be developed from the Raabe et al. data, the Weibel data, and other anatomical data sets (Hofmann, 2011).

The International Commission on Radiological Protection (ICRP, 1994) and the National Council on Radiation Protection and Measurements (NCRP, 1997) published major reports describing substantial models that included the entire airways of adults and children, a range of ventilation levels, a broad range of particle diameters (0.001–100 μm), and particle clearance phenomena. The ICRP and NCRP models were accompanied by software for inhaled aerosol particle dose calculations. Due to the complexity of use, and the fact that the NCRP and ICRP models produced different dosimetry results in some cases, these models have not received wide general usage.

Several investigators developed similar, more user-friendly dosimetry software, e.g., the Multiple Path Particle Dosimetry (MPPD) model (Asgharian, Hofmann, & Bergmann, 2001; Asgharian, Price, & Hofmann, 2006; Price, Asgharian, Miller, Cassee, & de Winter-Sorkina, 2002) that is periodically updated and widely used today. MPPD is currently available for free download from Applied Research Associates, Inc. (http://www.ara.com/products/mppd.htm; Accessed 4/29/2016). The current model allows selection of particle size, exposure conditions, and biological input data for Sprague–Dawley rats, rhesus monkeys, mice, pigs, sheep and humans. This allows simulations of particle deposition for a variety of ventilation states and subject ages exposed to aerosols with realistic properties.

2. Respiratory tract anatomy and physiology

By 1900 the human respiratory tract was well understood with respect to gross and cellular anatomy and its varied breathing patterns. This understanding also covered particle clearance mechanisms including the actions of mucus, cilia, lymph, and phagocytic cells (Thomas, 1882; White, 1902).

Weibel (1963) advanced anatomical understanding by publishing detailed 23-generation symmetrical and asymmetrical airway models of the human tracheobronchial (TB) and alveolar (pulmonary, P) regions. He introduced quantitative airway morphometry methods that are still used and that have been improved upon by other anatomists and modelers. In recent years Weibel's methods have led to quantitative data on a variety of mammals as well as the respiratory tract changes associated with post-natal development and aging. Hofmann (2011) reviewed the development of morphometric data for particle deposition modeling, including simulations of population variability from the data of Weibel (1963), Raabe et al. (1976), and others. Currently, modelers have access to a substantial number of quantitative physiological and anatomical data sets (e.g., Asgharian et al., 2001, 2006, 2012; Corley, Kabilan, & Kuprat, 2012; Newton, 1995, Chapter 5; Yeh & Schum, 1980). Also, medical scanning techniques are often used to define respiratory airways for aerosol deposition modeling (Corley et al., 2012; Rostami, 2009).

3. Computational fluid dynamics models of inhaled particle deposition

Computational fluid dynamics (CFD) models describe the fundamental behavior of fluids by using numerical methods to solve the Navier–Stokes equations that describe the motion of viscous fluids. For aerosol dose modeling, airway structures are divided into small volumetric elements (as in traditional finite element analysis). CFD modeling proceeds in several steps: (1) selecting (or writing) software; (2) defining the boundary (airway walls) conditions; (3) solving airflow fields (by an iteration/convergence process); (4) selecting aerosol particle properties; (5) placing the particles into the airway entrances; and (6) defining particle deposition sites (where particle trajectories intersect airway walls). CFD models for calculating detailed particle deposition in the respiratory tract that emerged in the 1990s represented an important advance (Balásházy & Hofmann, 1993; Ferron et al., 1991; Kimbell, Gross, Joyner, Godo, & Morgan, 1993; Yu, Zhang, & Lessmann, 1996). Kimbell and colleagues were probably the first to mesh a three-dimensional respiratory tract structure used to model the gas flow (in the nose of the rat). Such models have been applied to upper, bronchial, and alveolar airways (Asgharian et al., 2012; Balásházy & Hofmann, 1993; Balásházy, Hofmann, Farkas, & Madas, 2008; Corley et al., 2012; Darquenne, Harrington, & Prisk, 2009; Ferron et al., 1991; Heistracher & Hofmann, 1995; Schroeter, Asgharian, Price, & McClellan, 2013; Zhang, Kleinstreuer, & Kim, 2009;). CFD models have proven useful for calculating detailed deposition patterns, but validation of the results are still under development (Hofmann, 2011; Oldham, Phalen, & Budiman, 2009; Rostami, 2009).

4. Physiologically based pharmacokinetic (PBPK) models

4.1. What are PBPK models?

Physiologically based pharmacokinetic (PBPK) models are based on differential equations that are designed to simulate the absorption, distribution, metabolism, and excretion (ADME) in “compartments” (connected biological regions), usually in whole animals or humans. The input parameters for PBPK models are both inhaled substance-specific and exposed species-specific. Such models depend on knowledge of species specific blood flows that connect the various compartments (e.g., lung, liver, kidney, brain, bone, etc.). For inhaled particles, the initial deposition patterns can be supplied by traditional or CFD models. Subsequent metabolism in the respiratory tract and transport of intact particles and particle constituents to blood and lymph are modeled and distribution to distant compartments computed, including any additional transformations and translocations. PBPK models can also be used to back-calculate values of the input parameters if compartment concentrations of an agent are evaluated through tissue sampling and analysis.

A review of PBPK modeling by Leung (2009) described the model characteristics and historical development. The steps in PBPK modeling are (1) define the problem; (2) select the appropriate tissue compartments; (3) formulate the mathematical equations for the ADME phenomena to be used; (4) define the model parameter values (e.g. blood flows, tissue solubilities, partition constants, metabolism, etc.) and (5) adjust parameter values if needed, validate, and re-formulate the model applying plausible biological mechanisms. Among the applications, Leung (2009) listed were (1) dose modeling for human health risk (e.g., Andersen, 2003); (2) dose selection for laboratory animal experiments; (3) drug discovery; (4) mixture analyses; (5) pre- and post-natal toxicological assessments; (6) occupational exposure limits; and (7) evaluation of personal protective equipment. According to Leung (2009), the first application to an environmental chemical, dieldrin, was published by Lindstrom, Gillet, and Rodecap (1974).

4.2. Applications of PBPK models

Applications of PBPK models to inhaled particles are in a relatively early stage of development. The ICRP (1994) human respiratory tract modeling utilized a compartment model for clearance of particles from the respiratory tract. Although the ICRP clearance and distribution model was not identified as a PBPK approach, uptake, metabolism, and partitioning (e.g., air to aqueous/lipid partitioning in tissues) data were used to calculate time-dependent concentrations of radioactive materials within the respiratory tract, blood, and lymph; providing input data for ADME calculations for other organs and tissues.

Recently, PBPK models have seen significant development, including applications to a variety of inhaled aerosols (e.g. nanoaerosols, and volatile particles), using additional species, and interfacing with CFD models of particle deposition (e.g., Corley et al., 2012). Nanoparticles smaller than 10 nm in physical diameter can readily move by diffusion through available pores directly into the blood passing intact through the air-to-blood cellular barrier of the gas-exchange regions of the lungs (Raabe, 1982).

5. Current state of aerosol deposition modeling

Modern inhaled aerosol deposition models are of two basic types: (1) Findeisen-type, but with the full range of realistic anatomical structures and improved particle deposition mechanisms; and (2) CFD type with realistic anatomies, complex flow fields, and tracked particle behaviors. CFD models provide local particle deposition data that can be applied to small groups of airway cells (e.g., Balásházy & Hofmann, 1993; Hofmann & Balásházy, 1991).

Important advances and current issues under study include: (1) individual differences (including different animal species and strains); (2) enhanced local depositions; (3) non-ideal inhaled particles e.g., non-spherical and complex shaped particles; (4) modeling the complexity of the airways, as opposed to typical paths; (5) linking upper and lower airway regions in CFD models; (6) alveolar dynamics effects on aerosol deposition (Balásházy et al., 2008; Darquenne et al., 2009; Lee & Lee, 2003); (7) consideration of secondary effects, such as airway motion, airway surface roughness, impact of collateral ventilation, and effect of disease states (e.g., Martonen, Yang, & Xue, 1994); and (8) improved software for dose calculations. The basic interactions of inhaled particles with tissue elements are an area of current interest (e.g., Gehr & Heyder, 2000), which allows modelers to identify the tissue targets and mechanisms of toxicity of inhaled aerosols.

With limited space, it is not possible to cover the many significant events, let alone the complete history of inhaled aerosols and modeling their doses. Snippets of the story are found in hundreds, if not thousands of published papers and books. For further reading, books by Ensor (2011), Hickey (1996), Hinds (1999), Mercer (1973), Preining and Davis (2000), Ruzer and Harley (2005), and Salem and Katz (2015) are useful. A few sample papers that provide historical perspectives and/or overviews are Davies (1949), Hofmann (2011), Morrow (1980), McClellan (2000, Chapter 9), Martonen, Rosati, and Isaacs (2005), Rostami (2009), Swift (1996), Wang (2011) and Yeh and Schum (1980).

6. Who was W. Findeisen?

Perhaps the greatest contribution to inhaled particle dose modeling was the paper by W. Findeisen titled “Über das Absetzen Kleiner, in der Luft suspendierter Teilchen in der menschliehen Lunge bei der Atmung” (Findeisen, 1935). Two translations of the title are

(1) “The deposition of small air-borne particles in the human lung during respiration” by Stein (1973).
(2) “On lung deposits, through breathing, of small particles suspended in the air” (Robins, 1968, Fort Belvoir Defense Technical Information Center).

A note by Findeisen on the title page of his paper is translated by Robins (1968) as; “I became interested in this work during my activity as a physicist at the Institute for Air Travel Medicine and Climactic Research in Hamburg (Eppondorfer Hospital) during the years 1931–32. For the suggestions and the medical advice I first thank the Director, Prof. Dr. L. Brauer, and Dr. Zeplin.” Admirably, the young physicist sought the advice of medical experts. Findeisen's subsequent publications do not address inhaled aerosols, but deal with fundamental processes in meteorology and their applications to aviation. This interest would lead to his wartime untimely death at age 36 years.

Theodor Robert Walter Findeisen was born July 23, 1909 in Hamburg and presumably died (listed as “missing”) on May 9, 1945 in Prague during a post-war uprising and massacre in which 763 local German residents died. The uprising was the subject of a documentary film, containing actual amateur motion picture footage of the incident: “Killing, the Czech Way”, by Vodraeck (2010). At the time, Findeisen was director of the Research Center of Prague Reich Office for weather service.

Acknowledgments

Support was provided by the University of California Office of the President; the University of California Irvine Conference Support Program; the University of California Irvine Center for Occupational and Environmental Health; the Charles S. Stocking Fund; the U.C. Irvine Foundation Phalen Family Fund (#3500); and the University of California Davis Center for Health and the Environment.

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