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ORIGINAL ARTICLE

New developments in aerosol dosimetry

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Abstract
Dosimetry provides information linking environmental exposures to sites of deposition, removal from these sites, and translocation of deposited materials. Dosimetry also aids in extrapolating laboratory animal and *in vitro* data to humans. Recent progress has shed light on: properties of particles in relation to their fates in the body; influence of age, gender, body size, and lung diseases on inhaled particle doses; particle movement to the brain via the olfactory nerves; and particle deposition hot spots in the respiratory tract. Ultrafine size has emerged as an important dosimetric characteristic. Particle count, composition, and surface properties are recognized as potentially important toxicology-related considerations. Differences in body size influence airway sizes, inhaled particle deposition, specific ventilation, and specific doses (e.g. per unit body mass). Related to body size, age, gender, species, and strain are also dosimetric considerations. Diseases, such as chronic obstructive pulmonary disease (COPD) and bronchitis, produce uneven doses within the respiratory tract. Traditional concepts of the translocation and clearance of deposited particles have been challenged. Ultrafine particles can translocate to the brain via olfactory nerves, and from the lung to other organs. The clearance rates of particles from tracheobronchial airways are slowed by respiratory tract infections, but newer evidence implies that slow particle clearance from this region also exists in healthy lungs. Finally, hot spots of particle deposition are seen in hollow models, lung tissue, and dosimetric simulations. Local doses to groups of epithelial cells can be much greater than those to surrounding cells. The new insights challenge dosimetry scientists.

Keyword:

Introduction and methods

Recent interest in the health effects of air pollution has stimulated several important developments in understanding the dosimetry of inhaled particles (e.g. U.S. EPA, 2009). Among these developments, several new insights on the fates of inhaled particles that challenge previous dogmas are worthy of note. This review covers some of the emerging dosimetry-related progress that is relevant to interpreting toxicological and epidemiological studies of particulate air pollutants. In particular, particle properties (especially in the ultrafine regime), exposed individual characteristics (e.g. body size, age, gender, race, and respiratory diseases), olfactory-to-brain translocation, slow bronchial clearance, and particle deposition hot spots are addressed in this mini-review. Representative scientific publications identified by searching key journals augmented by using the above topics as key words for searches using the ISI Web of knowledge[SM] are briefly reviewed. Because the emerging literature on

particle dosimetry is vast, many potentially relevant works are not included in this focused mini-review.

Relevant particle properties

Dose metrics
For the purpose of understanding the doses delivered to subjects inhaling air-pollutant particles, the concept of a *dose metric* (also called an *indicator*) has emerged. An ideal dose metric has the following properties: it is measurable; it is expressible in physical and temporal scientific units; and it has a *causal relationship* to one or more biological responses (e.g. it exhibits dose–response relationships). Many dose metrics that are commonly used today do not fulfill all of these criteria, but they fulfill current needs for information. Table 1 lists some of the current and proposed metrics that are applied to air-pollutant particles. Note that the listed metrics are not mutually exclusive, nor are they always related to identifiable adverse biological responses. For example, it

Table 1. ome particle-related metrics that may apply to the effects of inhaled air-pollutant particles.

Mass fractions related to aerodynamic or other size intervals (e.g. PM_{10}, $PM_{2.5}$, $PM_{1.0}$, and $PM_{0.1}$)

Particle volume

Particle count

Surface area (e.g. BET surface), or projected area

Surface reactivity or crystallinity

Chemical composition (e.g. metals, acids, etc.)

Oxidative potential

Complex makeup (e.g. organic and inorganic components)

Mobility and distribution within the body

Fractal dimension

Electrical properties (e.g. zeta potential)

Dissolution rates in biological media

Particle volatility

Shape (e.g. aspect ratio of poorly soluble fibers)

Allergenicity, infectivity, irritancy, odor (odor may be especially important for dogs and rodents)

Biochemical reactions and reaction products

Presence of co-pollutants

Temporal changes in exposure level (e.g. spikes in air-pollutant concentrations)

History of exposures

Table 2. Representative peer-reviewed journals that include particle dosimetric topics

Aerosol Science and Technology

Applied Occupational and Environmental Hygiene

Atmospheric Environment

Archives of Environmental and Occupational Health

Biomarkers

Environmental Health Perspectives

Experimental Lung Research

Health Physics (for both radioactive and nonradioactive particles)

Inhalation Toxicology

Journal of Aerosol Science

Journal of Applied Physiology

Journal of Aerosol Medicine and Pulmonary Drug Delivery

Journal of Aerosol Science

Journal of Drug Targeting

Journal of Occupational and Environmental Hygiene

Respiration Physiology

The Annals of Occupational Hygiene

Toxicological Sciences

can be safely assumed that some modest particle exposures are necessary for maintaining robust respiratory tract defense mechanisms, even though such exposures in sufficient concentrations will negatively affect some individuals. Biological systems are responsive to short- and long-term environmental changes (e.g. day-to-day variations in air-pollutant levels), including activation of defense mechanisms that may have both beneficial and adverse effects on the whole organism. Identifying the most important metrics is a current challenge to air pollution scientists and regulators (Schwarze et al., 2006; Giechaskiel et al., 2009; Lippmann, 2010).

Biological targets

Closely associated with the concept of a dose metric, is the concept of a *biological target*. A biological target may be anatomical (e.g. a cell type, tissue, organ, or organ system), or physiological (e.g. an essential biological process, or a function such as learning, memory, or athletic performance). Accordingly, the number of potential biological targets and the associated metrics that are related to these targets are essentially uncountable given the current state of knowledge. As a result, it is fair to say that the current understanding of the effects of air pollutants is still in an early stage; perhaps where chemistry was before the introduction of the Periodic Table. The ultimate challenges faced by those who pursue air-pollutant dosimetry are formidable. Tables 2 and 3 list just some of the peer-reviewed journals and recent monographs that address particle dosimetry in one form or another.

Particle size

Particle size a primary property that affects the initial deposition patterns inhaled particles. Physical bodies, other than smooth solid spheres, do not have unique diameters.

Therefore, definitions of particle diameter are either derived from *measurable dimensions* (e.g. the average or ratio of the largest and smallest dimensions, or the average of several randomly oriented dimensions) or so-called *equivalent diameters* (such as the aerodynamic equivalent diameter, or the diffusion equivalent diameter). When collections of particles are encountered, statistical distributions of size-related parameters must be considered. Typically, mass median, volume median, surface median, and count median diameters are used along with the associated geometric standard deviations (GSDs) when the particle distribution is approximated by a lognormal function. These, and other definitions of particle diameter are described in several monographs (Cox & Wathes, 1995; Vincent, 1995; Hinds, 1999; Brown et al., 2000; Ruzer & Harley, 2005; Hickey, 2007).

Important particle properties that are relevant to dosimetry considerations are dependent on the particle's diameter. Tables 4 and 5 display some of these properties for ideal solid spherical particles that have densities of $1\,g/cm^3$. The tables illustrate important principles, but real-life particles may differ in their characteristics. It is important to note that the surface areas shown in Table 4 are rarely applicable to real air-pollutant particles. Such particles (except those that are liquid) can have surface areas that are one or more orders of magnitude larger than those of equivalent diameter smooth spheres. Rough or complex surfaces, cracks, and internal voids in solid environmental particles can add significantly to their surface areas. The real surfaces are the ones that interact with the air prior to inhalation and with biological media after they deposit. The specific surface areas (ratios of surface area to mass) of real particles also depend on their *effective densities* (which may be less than the "handbook" densities of their primary components). For example, the specific surface area of 10-µm diameter charcoal particles can be 8 million cm^2/g, instead of the value for smooth 10-µm spheres of 6000 cm^2/g, as shown in Table 4. Therefore, if the surface areas of environmental particles are required,

Table 3. Some recent monographs that include dosimetry topics.

Brown LM, Collings N, Harrison RM, Maynard AD, Maynard RL. 2000. Ultrafine Particles in the Atmosphere. Imperial College Press. London.

Donaldson K, Borm P, Eds. 2007. Particle Toxicology. CRC Press, Boca Raton, FL.

Gardner DE, Ed. 2006. Toxicology of the Lung, 4th ed. CRC Press, Boca Raton, FL.

Gehr P, Heyder J, Eds. 2000. Particle–Lung Interactions. Marcel Dekker, New York, NY.

Hickey AJ, Ed. 2007. Inhalation Aerosols: Physical and Biological Basis for Therapy, 2nd ed. Informa Healthcare, New York, NY.

ICRP (International Commission on Radiological Protection, Task Group of Committee 2). 1994. Human Respiratory Tract Model for Radiological Protection, Publication 66. Pergamon Press, New York, NY.

Martonen TB, Ed. 2001. Medical Applications of Computer Modeling: Respiratory System. WIT Press, Southampton, UK.

Mauderly JL, McCunney RJ, Eds. 1996. Particle Overload in the Rat Lung and Lung Cancer: Implications for Human Risk Assessment. Taylor & Francis, Washington, DC.

McClellan RO, Henderson RF, Eds. 1995. Concepts in Inhalation Toxicology, 2nd ed. Taylor & Francis, Washington, DC.

Miller FJ, Ed. 1995. Nasal Toxicity and Dosimetry of Inhaled Xenobiotics: Implications for Human Health. Taylor & Francis, Washington, DC.

NCRP (National Council on Radiation Protection and Measurements). 1997. Deposition Retention and Dosimetry of Inhaled Radioactive Substances, NCRP Report No. 125. National Council on Radiation Protection and Measurements, Bethesda, MD.

Ruzer LS, Harley NH, Eds. 2005. Aerosols Handbook: Measurement, Dosimetry, and Health Effects. CRC Press, Boca Raton, FL.

U.S. EPA. 2009. Integrated Science Assessment for Particulate Matter, EPA/600/R-08/139F. U.S. Environmental Protection Agency. Research Triangle Park, NC, Chapter 4. Dosimetry.

Table 4. Some physical properties of smooth solid spherical particles (density = 1 g/cm³) that relate to their dosimetry.

Individual particles			
Diameter (µm)	Mass (g)	Surface area (cm²)	Surface/mass (cm²/g)
0.01	5.2×10^{-19}	3.1×10^{-12}	6×10^6
0.1	5.2×10^{-16}	3.1×10^{-10}	6×10^5
1.0	5.2×10^{-13}	3.1×10^{-8}	6×10^4
10.0	5.2×10^{-10}	3.1×10^{-6}	6×10^3
100.0	5.2×10^{-7}	3.1×10^{-4}	6×10^2
One microgram of particles			
Diameter (µm)	Number of particles	Surface area (cm²)	Surface/mass (cm²/g)
0.01	1.9×10^{12}	6	6×10^6
0.1	1.9×10^9	6×10^{-1}	6×10^5
1.0	1.9×10^6	6×10^{-2}	6×10^4
10.0	1.9×10^3	6×10^{-3}	6×10^3
100.0	1.9	6×10^{-4}	6×10^2

Table 5. Displacements of ideal smooth spherical particles (density = 1 g/cm³) in still air.

Diameter (µm)	Settling (cm/s)	Diffusion (cm/s)
0.01	6.9×10^{-6}	3.3×10^{-2}
0.1	8.8×10^{-5}	3.7×10^{-3}
1.0	3.5×10^{-3}	7.4×10^{-4}
10.0	3.1×10^{-1}	2.2×10^{-4}
100.0	2.5×10^1	6.9×10^{-5}

Source: Hinds (1999, Appendix A11b).

they must be measured (e.g. by the BET method; Brunauer et al., 1938; Schmid et al., 2009).

The displacement velocities of particles in still air at normal atmospheric pressure are shown in Table 5. Such displacement velocities are important for calculating aerosol settling rates and for modeling deposition efficiencies in confined spaces, including pipes, filters, rooms, and respiratory tract airways. Deposition occurs when particles leave air streams and contact surfaces because their sticking coefficients are normally 1.0 (i.e., 100%). Settling and diffusion are only two of many mechanisms that cause inhaled particles to depart from airstreams and deposit in the respiratory tract. Large particles, such as long fibers, can physically touch airway surfaces and also deposit by the interception mechanism (Sturm & Hofmann, 2006). Inertial deposition, which is related to the sedimentation rates of particles, occurs at bends, obstructions, and bifurcations in the respiratory tract when the air velocity is appreciable. Electrically charged particles can also deposit with greater efficiencies than noncharged particles, if they carry sufficient charge levels. Other, usually minor, mechanisms can affect the deposition efficiencies of inhaled particles (e.g. via thermal, transpirational, and magnetic phenomena). Currently-used mechanistic particle dosimetry models include settling, impaction, diffusion, and sometimes interception mechanisms (ICRP, 1994; NCRP 1997; Sturm & Hofmann, 2006; Finlay & Martin, 2008; Kane et al., 2010).

Particle size is also important for dosimetric considerations post-deposition in the respiratory tract. Because of their large specific surface areas, ultrafine particles (diameters ≤ 0.1 µm) are now seen as an important class. Particle size influences the rates of dissolution in biological fluids, rates of uptake by lung macrophages and other cells, and translocation from the lungs to other sites in the body after they have deposited in the respiratory tract (e.g. ICRP, 1994; Dorman et al., 2001; Fechter et al., 2002; Oberdörster et al., 2004; Elder et al., 2006; Kreyling et al., 2006a,b; Schmid et al., 2009). It is important to note that *nanoengineered particles*, especially those designed for medical applications, may have unique interactions with biological systems (Maynard & Kuempel, 2005; Sayes et al., 2007; Geiser & Kreyling, 2010). Such particles may target extrapulmonary sites, have designed toxicities, and trigger various biochemical reactions. Thus, they must be evaluated dosimetrically on a case-by-case basis.

Body size, age, gender, and disease

Body size

The vast majority of knowledge on particle dosimetry applies to 70-kg body mass healthy young adult males (i.e., the

reference man). Dosimetric information is also available for children, females, some diseased individuals, and several species that are commonly used in toxicological studies (Schlesinger, 1985; Newton, 1995; Phalen et al., 2008; Phalen & Mendez, 2009). Yet, the available information is inadequate for performing dosimetric evaluations for the great variety of humans who are environmentally exposed. Also, recent research indicates that even within a species of laboratory animal, anatomical and physiological differences in strains can significantly influence the deposition efficiencies of inhaled aerosols (Oldham & Phalen, 2002; Moss & Oldham, 2006; Saxena et al., 2009). Strictly speaking, ideal dosimetric evaluations should be performed for individuals, whether they are humans or laboratory animals.

Allometric relationships that describe the effects of body size on airway dimensions and ventilation parameters are commonly used for dosimetric calculations. Such relationships have been recently reviewed (Alexander et al., 2008). This review, which focused on various strains of dogs, monkeys, mice, and rats, recommended a single relationship for estimating the particulate delivered dose (DD).

$$DD = C \times RMV \times D \times IF/BW$$

where C is the concentration of a substance in the air, RMV is the volume of air inhaled per minute, D is the duration of exposure, IF is the fraction by weight of particles that are inhaled (i.e., inhalability, which is the sampling efficiency of the subject), and BW is the body weight (more strictly the body mass) of the subject. A formula for the RMV as a function of body mass was also provided, and other published algorithms (that include various sizes of humans, and several other mammals) were presented. Allometric relationships also have applications in those epidemiological studies that have acquired body weights for their subjects. The minute ventilation, and hence the delivered dose, will vary significantly among subjects with different body size, including children (ICRP, 1994; Ginsberg et al., 2008). Jarabek et al. (2005) presented methods for dose extrapolations among various species based on current knowledge.

Gender

As a group, women differ from men with respect to their total and regional particle deposition efficiencies (Bennett et al., 1996; Kim & Hu, 2006; U.S. EPA, 2009). On the average, adult women have smaller nasal, laryngeal, and tracheobronchial airways than men, which all will serve to produce a shift toward a more-proximal deposition pattern. Three general consequences of this shift in deposition are: greater total deposition; more rapid particle clearance rates; and reduced deposition in the deep-lung (primarily alveolar) airways. Yet, the smaller body sizes of women also produce lower airflow rates than men at a given level of physical exertion, which tends to offset the total deposition and the more-proximal deposition pattern. There is a need for additional data on particle deposition on adult men and women who have the same body sizes and levels of exertion, in order to identify effects that can be attributed to gender alone. As previously noted, individual dosimetric calculations are superior than those for groups.

Race

Race as a factor in aerosol deposition has mainly been approached with respect to nasal deposition efficiencies, and the partitioning of airflow (oral vs. nasal flows) during exercise. Bennett and Zeman (2005) and Bennett et al. (2003) measured the nasal deposition efficiencies and oral–nasal partitioning using 1 and 2 µm (mass median aerodynamic diameter) particles in African American (A) and Caucasian (C) young adult men and women. Measurements were made with the subjects resting and during light exercise. Nasal airflow resistance in C was more than two times greater than that in A, and C noses were longer and had more elliptical entrances than those of A. As expected, the group-averaged nasal deposition efficiency was significantly greater in C than in A during light exercise, but no difference was observed at rest. Also, C had a greater fraction of oral airflow during exercise than did A, which would tend to decrease the total aerosol deposition in the head airways of A in comparison with C. The authors concluded that in spite of the reduced nasal collection efficiencies in A, it was not possible to draw conclusions with respect to the comparative (C vs. A) toxicological responses for particulate matter doses to the nose or to the lower respiratory tract. However, the authors recommended that racial differences in upper airways should be considered in modeling doses from air-pollutant exposures. More research on racial differences in aerosol dosimetry is needed, as race may be an important modifier of responses to air pollutants.

Children

Dosimetric modeling for children inhaling both gases and particles has been recently reviewed (Ginsberg et al., 2005, 2008; Foos & Sonawane, 2008; Foos et al., 2008). Children have age-dependent airway sizes, ventilation patterns, and time-activity behaviors, all of which potentially increase their air-pollutant doses over those of adults. In addition, young children (e.g. under 3 years of age) are developmentally immature, which can alter their toxicological and immunological responses to inhaled materials. The smaller airways of children (e.g. birth to 10 years) predict a shift to more-proximal deposition of particles. This effect is offset by their lower airflow rates. Also, because of their smaller body masses, specific deposition rates are larger on a body mass basis (Ginsberg et al., 2005, 2008). For dosimetry modeling purposes, Ménache et al. (2008) reviewed airway geometry models for the age range of 3 months to 21 years. The authors noted the need for additional information during the period of lung development, particularly for those aged 3 years and younger. Isaacs and Martonen (2005) reviewed and compared the modeled and experimental particle deposition data on children. They concluded that agreement was good, and that the dose per unit surface area of the respiratory tract is greater in children than in adults. One can conclude that the particle deposition dose models for children are relatively

well-developed. However, understanding the fates of particles post-deposition will require additional research.

Respiratory tract disease

That some lung diseases alter airflow distribution, aerosol deposition, and particle clearance rates has been appreciated for several decades. Acute respiratory tract infections, which occur two to three times yearly in adults, significantly impair particle clearance, sometimes for 6–8 weeks. Old age *per se* was not seen to alter the total deposition of ultrafine particles (0.04 to 0.1 µm in diameter), in groups of healthy adults aged 69 ± 5 years vs. 31 ± 4 years (Kim & Jaques, 2005). Smaldone (2001) also concluded that aging *per se* did not alter particle deposition. This finding is relevant in light of observations that elderly subjects are more susceptible to the adverse effects of air pollutants (U.S. EPA, 2009). It is reasonable to assume that this observed susceptibility is due to the effects of lung and cardiovascular diseases in older individuals. Svartengren et al. (2005) reported that long-term small bronchial clearance of 6-µm diameter particles was negatively correlated to age in healthy subjects aged 19–81 years. Age is obviously a difficult parameter to incorporate in dosimetric calculations.

Chronic obstructive pulmonary disease (COPD), a leading worldwide cause of death and illness, is actually a group of diseases. Emphysema, chronic bronchitis, cigarette smoking, and lung damage from chronic asthmatic bronchitis can all lead to the blockage of airflow and thus contribute to COPD. The implications of COPD to particle deposition (Meyer et al., 2003; Phalen et al., 2006) and clearance (Smaldone et al., 1993; Scheuch et al., 2008) are significant. Severe COPD can result in increased total ventilation rates with 50%, or much less, of the lung volume receiving airflow. Thus, particle deposition rates in the ventilated airways can be 4-fold higher compared with normals (Phalen et al., 2006). Particle clearance in COPD can be slowed in the tracheobronchial region. However, quantifying the slower clearance is difficult due to the significant variation (ranging from normal to 3-fold slower) in patients (Scheuch et al., 2008). This slower clearance may be limited to the larger bronchial airways, as earlier studies by Smaldone et al. (1993) and a more recent one by Brown et al. (2002) indicated that clearance from peripheral airways was normal in COPD patients.

The ICRP (1994) recommended modifications to their bronchial clearance model to account for disease states. Among the conditions that slowed bronchial clearance were: asthma, bronchial cancer, chronic bronchitis, cystic fibrosis, immotile cilia syndrome, influenza, and cigarette smoking. Each condition was given a default numerical modifier to adjust the default clearance rates in dosimetric evaluations. However, knowledge about individuals when available will be superior to default data, which apply only to populations.

Nose-to-brain transport

Perhaps the most important new development in inhaled particle dosimetry is the realization that ultrafine particles depositing on olfactory epithelium can be transported intact to the olfactory bulbs of the brain via the olfactory nerves (U.S. EPA, 2009; Oberdörster, 2010). The potential importance of this pathway is significant, but toxicological implications are yet to be understood (Doty, 2008, 2009; Oberdörster et al., 2004, 2009; Oberdörster, 2010). This olfactory transport mechanism is a reminder of the species differences with respect to the relative surface area of the nasal olfactory mucosa in humans compared with that in the most common laboratory animals (e.g. 5% of the nasal surface in humans vs. 50% in rodents). Humans are visually oriented, but many other mammals are odor-oriented, which could make the odor of pollutants an important trigger for cardiopulmonary responses in rats, mice, and dogs in inhalation studies of urban air pollutants.

The olfactory epithelium in humans has receptor cells (tall ciliated neurons), interspersed with subepithelial secretory glands, and support, basal, and goblet epithelial cells. The olfactory region is covered by mucus, and cell turnover is relatively rapid, with a half-time of a few weeks (Ganong, 1999). On their basal ends, the receptor cells have long axons (nerve fibers) that join and pass through the cribriform plate (a bony shelf that separates the nasal epithelium from the brain) and synapse with mitral neurons in a region of the brain called the olfactory bulb. Mitral cells conduct signals to other regions of the brain (e.g. the olfactory cortex) to provide for odor sensation and odor memory. For particles depositing on the olfactory mucosa to reach the brain, they must penetrate the coating mucus layer, be taken up by receptor cells, and travel to the olfactory bulbs along neurons that penetrate through the perforated bony cribriform plate. Transport of deposited particles between (instead of through) the olfactory epithelial cells is unlikely, unless the tight cell-to-cell adhesions are disrupted (e.g. as by chemical destruction).

Some information is available on how the properties of inhaled particles influence their translocation from the olfactory epithelium to the brain. Dissolved metals (e.g. aluminum, cobalt, manganese, nickel, and zinc), and intact particles (e.g. carbon, ferric oxide, gold, manganese oxide, titanium dioxide, polystyrene, and viruses) smaller in diameter than about 50 nm have been observed to translocate to the olfactory bulb in instillation and inhalation studies in several species, including humans (Brodie and Elvidge, 1934; Tjalve & Henriksson, 1999; Fechter et al., 2002; Oberdörster et al., 2004, 2009; Elder et al., 2006; Kreyling et al., 2006a,b; Doty, 2008, 2009; Matsui et al., 2009; Mistry et al., 2009; U.S. EPA, 2009; Geiser & Kreyling, 2010; Oberdörster, 2010). The important role of transporter proteins in facilitating the olfactory nerve transport of solutes has been reviewed (Genter et al., 2009). Also, coatings on intact particles can facilitate their nose-to-brain olfactory transport (Mistry et al., 2009; Oberdörster et al., 2009). Once in the olfactory bulb, the subsequent translocation to other regions of the brain is possible, but generalizations as to the extent to which this may occur are still uncertain (Oberdörster, 2010). There is a clear need for additional

experimental information that can be used to support dosimetric calculations.

Oberdörster (2010) reviewed the safety assessment for nanoengineered particles for medical applications. He concluded that such particles should be evaluated in relation to their "biological activity," instead of their "physicochemical category." Kreyling et al. (2006a,b), Sayes et al. (2007), Teeguarden et al. (2007), Warheit (2008), and Geiser and Kreyling (2010) provided reviews that support Oberdörster's conclusions. Size, solubility, and surface properties must all be taken into account in dosimetric and toxicological studies of such particles.

Slow bronchial clearance

Clearance rates of inhaled particles that deposit on the tracheobronchial airways are key data in dosimetric calculations. Although the slowing effects of acute infections and lung disease on tracheobronchial clearance rates are well-known, it is clear that slow bronchial clearance occurs in healthy lungs as well (ICRP, 1994; Kreyling et al., 2006a,b; Smith et al., 2008; U.S. EPA, 2009). The usual assumption that the tracheobronchial tree completely clears all particles within 24 h is incorrect. The mechanisms for slow bronchial clearance of particles include: epithelial damage, mucus stasis, mucus retrograde flow, transport to the mucus subphase, and uptake by resident cells. The ICRP "Human Respiratory Tract Model for Radiological Protection" (ICRP, 1994) used two default clearance half-times of 23 and 70 days to represent slow bronchial clearance and particle sequestration, respectively. Particle size was the parameter used to assign fractions of deposited particles that had normal or slow clearance. Smaller particles were associated with slower clearance. The slow clearance rates and associated particle sizes largely came from instillation studies in rodents, and bolus inhalations in humans in which the particles were introduced in a small volume (e.g. 50 cm^3) at the end of each breath. The assumption was that these particles would deposit only on ciliated airways (and none on alveolarized airways). More recent studies have indicated that the slow tracheobronchial clearance was most likely due to particles depositing beyond the ciliated tracheobronchial airways (Svartengren et al., 2001, 2004; Bailey et al., 2007, 2008; Smith et al., 2008). In addition, Philipson et al. (2000) found that two particles with different physical diameters (6 and 4.5 μm), but similar aerodynamic sizes (6.2 and 6.4 μm), did not have different clearance rates when inhaled by humans. Smith et al. (2008) performed similar studies using radiolabeled aerodynamically similar polystyrene particles (density = 1.05 g/cm^3) and gold particles (density = 19.3 g/cm^3) inhaled by human volunteers. No differences were seen in clearance rates although both particles had aerodynamic diameters of 5 μm, and they were inhaled simultaneously. Thus, it appears that the issue of particle size-dependent slow bronchial clearance is less clear than previously assumed. Still, as noted earlier, there are many circumstances in which the clearance of particles

depositing in the tracheobronchial airways is not complete within 24 h.

Particle deposition hot spots

The deposition patterns of inhaled particles are highly nonuniform in the tracheobronchial tree. Airflow patterns and velocities, along with obstructions to airflow, are some of the causes of deposition *hot spots*. Such areas of high deposition relative to surrounding tissues are particularly prominent at carinas (bifurcation points) in the tracheobronchial tree. This deposition pattern is seen in actual lungs (Churg & Vedal, 1996), hollow airway models, and Computational Fluid Dynamics (CFD) model predictions (e.g. Balásházy et al., 1999, 2003; Phalen et al., 2006). Thus, the presence of deposition hot spots is well-established. The intensities of hot spots, which are described as *enhancement factors* (EFs), are usually quantified as the ratio of particle deposition at a hot spot (per unit tracheobronchial surface area) to the average deposition on surrounding surfaces. The EFs depend on the size of the hot spot in question, which is called the *patch size*. For example, the particle deposition intensity at an airway branch is highest at the center of the branch's carina (e.g. Kleinstreuer & Zhang, 2010). Thus, the largest EF is usually seen at a small patch at the center of a bifurcation of the tracheobronchial tree (Balásházy et al., 1999, 2003). Because impaction is a major mechanism for producing hot spots of deposition, airflow rates and particle aerodynamic diameters correlate strongly with the EFs. Table 6 shows some calculated EFs for an adult male at resting (5 L/min) and exercising (30 L/min) ventilation for three particle diameters using a square patch size of 0.1 mm by 0.1 mm. Such a patch contains ~200 epithelial cells. The largest EF of 380 in the table indicates that the particle deposition dose is nearly 400 times greater than that averaged over the surrounding epithelial surface. For 9-μm diameter particles, Farkas and Balásházy (2008) found EFs of 800 to 1200 for patch sizes containing 1000 bronchial epithelial cells. One unanswered question is: What is the toxicological significance of the greatly enhanced surface deposition? Also, a second unanswered question is: How accurate is the CFD simulation in representing particle deposition *in vivo*? In addition to these questions, the dosimetric implications of hot spots to *in vitro* dosing (e.g. applying particle doses to cell cultures) should be considered (Gerde, 2008). For example, should cell cultures

Table 6. Computational fluid dynamics modeled hot spot enhancement factors (EF) for an adult male at resting (5 L/min) and exercising (30 L/min) ventilation states.

Particle aerodynamic diameter (μm)	Ventilation (l/min)	EF
1	5	107
2	5	110
5	5	115
1	30	80
2	30	190
5	30	380

Source: From Balásházy et al. (2003).

be dosed uniformly in toxicological investigations of inhaled particles, or in a spotty fashion that better simulates *in vivo* particle deposition? If deposition EFs are considered in the tracheobronchial trees of individuals with COPD, the local doses to carinal cells can be several thousand times greater than average bronchial doses in normal individuals (Phalen et al., 2006).

Computational fluid dynamics models present challenges to modelers that do not occur in conventional deterministic dosimetric models. In a review, Rostami (2009) pointed out that CFD models tend to be less accurate (in part because of the many important choices that must be made with respect to fluid properties and particle–fluid interactions), and less capable of modeling the many relevant physiological and environmental conditions. Robinson et al. (2008) also reported that different CFD software packages lacked agreement in particle deposition predictions, and Oldham (2006) and Longest and Oldham (2006) discussed the challenges associated with reconciling CFD model predictions with actual particle deposition data. Yet, CFD modeling represents one of the most significant advancements in modeling the deposition of inhaled particles, especially with respect to local deposition phenomena.

Conclusions

There are several recent significant advancements in the dosimetric modeling of inhaled particles. This mini-review has addressed some of these that are important with respect to their implications to air pollution toxicology and epidemiology investigations. These advancements also present significant new challenges to dosimetry research itself. The concept of appropriate dose metrics has become more complex and more interesting, especially in the realm of ultrafine or nanoparticles (including nanoengineered particles). Such particles can have greater access to extrapulmonary sites, including the brain, than do micron-sized particles. The influence of body size, gender, race, age, and lung diseases on particle dosimetry is, as yet, still poorly appreciated. Slow bronchial clearance of particles deposited on tracheobronchial epithelia is now better understood, although quantitatively less certain than it was a decade ago. Advancements in CFD modeling have provided new insights on the details of local particle deposition phenomena. However, there is much to be learned about differences in specific CFD model packages, and how the model predictions compare with actual human and laboratory animal particle deposition efficiencies and patterns. In sum, the recent advances reviewed here provide both essential insights and significant challenges to those who perform dosimetric evaluations of particulate air pollutants.

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