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Aerosol Dosimetry Considerations

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Dose considerations are among the most fundamental concepts of toxicology, and inhalation toxicology is no exception; expression of the full-range of possible effects—from no effects (or beneficial effects) to adverse effects to fatal effects—is seen to unfold as the dose is increased for essentially all inhaled substances. Dose-response considerations are key in establishing permissible exposures in occupational and nonoccupational environments.

Even when the exposures are identical, some individuals (or groups of individuals) receive larger or smaller doses than those received by the average person. It is reasonable to expect that individuals/groups that receive the greatest doses are also at greater risk. High-dose and high-risk groups are sometimes referred to as "potentially sensitive subpopulations." It is clear that dose alone does not explain all adverse responses, because concurrent illness, genetic makeup, exposure history, and other factors modify susceptibility.

Defining "dose" for inhaled aerosol particles

For inhaled particles, the concept of dose can be relatively complicated in that it may relate to several quantities. The exposure dose (D_e) is

$$D_e = C \bullet T \quad (1)$$

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in which C is the average airborne aerosol concentration (eg, particle mass or count per unit volume of air or other relevant metric) and T is the duration of exposure. The inhaled dose (D_i) is

$$D_i = C \bullet T \bullet V_m \bullet I \quad (2)$$

in which V_m is the ventilation per unit time and I is the inhalability (sampling efficiency of the nose/mouth). The total deposited dose (D_d) is

$$D_d = C \bullet T \bullet V_m \bullet I \bullet DF_t \quad (3)$$

in which DF_t is the total respiratory tract deposition fraction. The regional deposited dose (D_r) is

$$D_r = C \bullet T \bullet V_m \bullet I \bullet DF_r \quad (4)$$

in which DF_r is the deposition fraction in the region of interest (eg, nose, tracheobronchial tree, or pulmonary zone). The amount deposited per unit surface area in the region of interest D_{rsa} is

$$D_{rsa} = C \bullet T \bullet V_m \bullet I \bullet DF_r/S_r \quad (5)$$

in which S_r is the surface area of the region of interest.

For the purposes of understanding the health effects of inhaled particles, equations (4) and (5) are usually the most important. Simpler concepts of dose, such as that described in equation (1), are often used in toxicology and epidemiology, however. When the inhalability, deposition fractions, and surface areas are included in dosimetry considerations, the aid of a specialist trained in inhalation toxicology is useful.

In this article, fundamental concepts of aerosol dosimetry and some applications related to the health effects of inhaled particles are considered. The topics covered include useful definitions, including the aerodynamic diameter of aerosol particles, how inhaled particles deposit in the human respiratory tract, models for calculating inhaled aerosol deposition, factors that increase aerosol deposition doses (eg, exercise, body size, and respiratory disease), and particle clearance. Some current challenges, unsolved problems, and speculations related to inhaled aerosol dosimetry also are presented.

Aerosol basics

Useful definitions

An aerosol is a two-phase system that consists of finely divided condensed matter (solids or liquids) suspended in a gas, which is usually air

(which also includes co-pollutant gases and vapors). The essential characteristic of an aerosol system is that it is relatively time-stable. That is, the suspended particles do not rapidly settle out of the suspending gas. This characteristic limits the upper size of particles that can exist in an aerosol. Particles with diameters (aerodynamic diameters) that are larger than 100 μm settle out rapidly and are the largest particles that are generally considered by aerosol scientists. The lower limit of particle size is less clearly defined. When particles are smaller than approximately 0.001 μm in diameter (geometric diameter), they contain so few atoms and have such large surface-to-volume ratios that they tend to evaporate and re-form in the air. The particle diameter range of 0.001 to 100 μm is usually considered by aerosol scientists. This broad size range covers four regimes in physics; the free-molecule regime (in which diffusion dominates particle motion), the continuum regime (in which gravitational forces and particle inertia dominate motion), and two intermediate regimes (which are transitional with respect to particle motion).

The aerodynamic diameter (D_{ae}) is an important concept in inhalation toxicology. The aerodynamic diameter (also the aerodynamic equivalent diameter) is the physical diameter of a smooth sphere with a density of 1 g/cm^3 that has the same terminal settling velocity in still air (under standard laboratory conditions) as the particle in question. For example, a solid gold smooth spherical particle with a physical diameter of 1 μm has an aerodynamic diameter of approximately 4.4 μm because of the density of gold (19.3 g/cm^3). For smooth spheres $D_{ae} = D_p \bullet (P_p)^{1/2}$, in which D_p is the physical diameter, and ρ_p is the particle density. The aerodynamic diameter of a particle influences several important kinetic properties, such as its settling rate and inertial behavior when in motion.

Particle motion

To understand the deposition efficiencies of inhaled aerosol particles, a consideration of particle motion is helpful. Table 1 shows the rate of movement of particles in still air and the time required to travel 1 cm (T_{1cm}) from an original release point.

Consider a person inhaling the various particles in Table 1 in which movement away from the inhaled air stream by even a fraction of a centimeter may cause the particles to touch an airway wall and deposit (the sticking coefficient for a particle touching an airway surface = 1; that is, if it touches, it sticks). It is clear that the smallest particles depart the air stream and deposit by diffusion, and the largest particles deposit by sedimentation (and by inertial motion, which is related to particle mass). The net result is that inhaled particle deposition efficiency curves are U-shaped (ie, the large and the small particles have high deposition efficiencies, and particles between 0.1 and 1.0 μm in diameter have the lowest deposition efficiencies). A minimum in the total respiratory tract deposition efficiency occurs for particles that are approximately 0.3 μm

Table 1
Movement of spherical particles of density 1 g/cm^3 and the time required for a displacement of 1 cm in still air

Diameter (μm)	Settling velocity (cm/s)	Diffusion velocity (cm/s)	T_{1cm} via settling	T_{1cm} via diffusion
100	25	6.9×10^{-5}	0.04 sec	4 h
10	0.31	2.2×10^{-4}	3.2 sec	76 min
1	3.5×10^{-3}	7.4×10^{-3}	4.7 min	23 min
0.1	8.6×10^{-5}	3.7×10^{-3}	3.2 h	4.5 min
0.01	6.7×10^{-6}	3.3×10^{-2}	1.7 d	30 sec
0.001	6.5×10^{-7}	0.32	18 d	3.1 sec

Data from Hinds WC. Aerosol technology. 2nd edition. New York: John Wiley and Sons; 1999. p. 459.

in diameter; under ordinary resting conditions more than 80% of these inhaled particles typically are exhaled without depositing.

Inhaled particle deposition and clearance

Inhaled particle deposition curves

Inhaled particle deposition curves describe the probability of deposition of inhaled particles as a function of particle diameter. One such curve, for an adult man performing light work (10 L/min ventilation), is shown in Fig. 1A [1]. Four curves are shown, one for total deposition (anywhere in the respiratory tract), one for deposition in the nose/oral cavity/pharynges/larynx, one for deposition in the tracheobronchial region, and one for deposition in the alveolarized, pulmonary (P) region. Although the four curves are not simple, each has a minimum deposition efficiency somewhere between 0.1 and 1.0 μm diameter particles. Each of the four curves also has a peak on either side of the minimum, which is produced by the effects of diffusion, sedimentation, and impaction. Equation (2) introduced the concept of inhalability, which relates to the fact that large particles are difficult to inhale (because they are settling out of the air entering the nose or mouth). Fig. 1B shows inhaled deposition curves as corrected for inhalability [1]. Note that 100 μm diameter particles are only 50% inhalable, as seen by their total deposition efficiency changing from 100% in Fig. 1A to 50% in Fig. 1B. These curves, which have been obtained by many clinical measurements and mathematical modeling [2,3], apply only to the standard man.

Many factors have an effect on the inhaled particle deposition curves; level of exercise, age, body size, respiratory disease, and even normal population variability (in anatomy or physiology) shift the curves one way or another. Fortunately, it is not necessary to have hundreds of such curves on hand, because computer software is available to perform inhaled particle deposition calculations for nearly all cases of interest [2,4,5]. The software MPPD1 is particularly useful, because it is free (from CIIT, 2005), covers

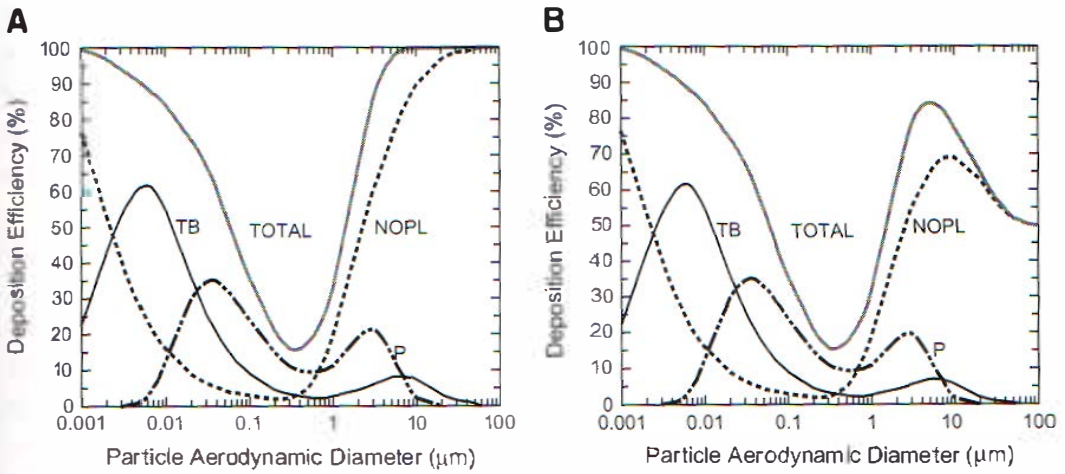

Fig. 1. Particle deposition curves in the average adult man. NOPL, naso-oro-pharyngo-laryngeal region; TB, tracheobronchial region; P, pulmonary region. Part A is uncorrected for inhalability, and part B is corrected for inhalability. (*From* Phalen RF. The particulate air pollution controversy. Boston: Kluwer Academic Publishers; 2002. p. 60; with kind permission of Springer Science and Business Media.)

humans and rats, allows input of particle size distribution data, age, ventilation, and other important variables, and is relatively user-friendly.

Local particle deposition hot spots

The preceding information relates to averaged deposition doses in the respiratory tract or specific regions, such as the nasal, tracheobronchial, or alveolarized airways. For many purposes, such averaged doses are sufficient. If local doses (eg, within portions of bronchial tubes) are of interest, however, different models and more detailed laboratory measurements must be consulted. There is a great deal of convincing evidence that inhaled particle deposition is nonuniform. The analysis of mammalian lung samples shows that particles deposit and are retained preferentially at thousands of points in the respiratory tract, especially at the bifurcating regions of the tracheobronchial airways [6–8]. The locations and intensities of these hot spots of particle deposition have been modeled successfully using computational fluid dynamics techniques [9–13]. Depending on the size of the hot spot, local dose enhancement factors of 100 or more over the doses to nearby surfaces are seen. Although the health significance of these high local doses is still uncertain, it is likely that in some individuals their impact on adverse health outcomes may be significant. Such hot spots also have implications for particle doses used in in vitro toxicology studies.

Other factors that may increase inhaled particle doses

Healthy and diseased individuals can belong to subpopulations that receive greater than average doses from inhaled particles. These high-dose

subpopulations include (1) otherwise normal people who have airway anatomies/breathing characteristics that are extreme in the healthy population distribution, (2) very young, very small, or obese individuals (who have high V_m in relation to their lung sizes), (3) people who have lung diseases that produce uneven airflow patterns, (4) people who are engaged in exercise, (5) people with impaired particle clearance, and (6) people who are exposed in close proximity to local particle sources. The inhaled particle deposition curves shown in Fig. 1 actually represent population averages, and some members of the population have much greater deposition efficiencies than the average individual [14]. In these individuals, factors of two or even three multiples of the average particle deposition may be seen. These high-dose individuals are expected to potentially be at higher risk than are individuals with average or lower doses.

The effects of age and body size on inhaled particle deposition can be significant. It is well known that smaller mammals tend to have higher ventilation rates per unit body mass (because of increased metabolism as a result of loss of body heat) than normal sized individuals. Newborns and neonates, for example, can have inhaled particle deposition rates in the tracheobronchial region per kilogram of body mass that are nearly ten times greater than that for adults [15,16], and obesity can lead to even greater particle deposition in children [17].

Exercise can increase greatly the volume of air inhaled per unit time and nearly proportionately increase particle doses. Various states of exertion can increase the rate of intake of air by large amounts, as shown in Table 2.

Lung diseases, such as chronic obstructive pulmonary disease and asthma, can increase the deposition doses from inhaled particles in several

Table 2
Body mass, height, and minute ventilation at three levels of activity for selected ages

			Minute Ventilation (L)[a]		
Age (y)	Mass (kg)	Height (cm)	Low activity	Light exercise	Heavy exercise
0	3.3	50	1.5	3.0	8.9
2	13.0	88	2.8	5.5	16.4
4	16.4	104	3.2	6.3	19.0
6	22.0	115	3.9	7.8	23.2
8	27.0	127	4.5	9.1	27.1
10	34.0	138	5.4	10.8	32.4
12	43.0	150	6.6	13.1	39.3
14	54.0	162	8.0	15.9	47.8
16	63.0	170	9.1	18.2	54.6
18	70.0	175	10.0	20.0	60.0

[a] Terminology used for describing ventilation is arbitrary because no standard accepted definitions exist.

Adapted from Phalen RF, Oldham MJ, Kleinman MT, et al. Tracheobronchial deposition predictions for infants, children and adolescents. Ann Occup Hyg 1988;32(Suppl 1):11–21; with permission of the Oxford University Press.

ways; they can increase the total volume of air inhaled for a given level of physical activity, they can decrease the portion of the lung that is ventilated, and they can greatly increase the nonuniformity of particle deposition [18–22]. These factors combine to place persons with lung disease in the unfavorable category of a high-dose plus a potentially high-risk subpopulation.

Impaired particle clearance, in general, does not increase the initial deposition doses, but it does increase the integrated doses to those tissues that have slow particle clearance rates. The three main factors associated with impaired clearance are (1) normal variations in clearance rates, (2) acute infections, such as influenza, and (3) chronic diseases that are associated with poor particle clearance [23–25]. Persons with poor particle clearance usually augment normal clearance mechanisms with coughing. Coughing fits, which are characterized by numerous rapid coughs separated by long intervals of eupnea, can effectively move mucus and trapped particles up the airways generation by generation to a point at which they are swallowed. As a rule of thumb, each cough can be expected to move mucus accumulations upward one generation, which is why coughing fits are required to eliminate deeply lying mucus.

Another important factor that increases particle deposition relates to exposure in close proximity to particle sources. For example, exposure downwind from and near busy roads—or other areas of high particle concentrations—can lead to exposures that are significantly greater than would be expected on the basis of central air monitoring data [26,27]. Likewise, exposures that take place near certain industrial sources, construction sites, or during some personal activities (eg, vacuuming, composting, smoking, wood working) can significantly increase personal exposures.

Controlling doses in high-risk individuals

If one considers the simultaneous occurrence of several of the foregoing exposure factors, it is easy to envision the highest risk individuals. For example, a young or overweight person with chronic obstructive lung disease (or another lung disease) who also has an acute respiratory tract infection, is engaged in exercise, and is exposed near a busy road can receive enormous doses in comparison to the average individual. Attempting to protect such rare, but unlucky, individuals by tightening regional air standards may be difficult, unduly expensive (in terms of direct costs and indirect economic impacts), or simply impossible. For this reason, high air pollution alerts that encourage individual protective behavioral changes probably always will be needed. Such behavioral changes include curtailing physical activity, seeking cleaner environments (eg, air-conditioned structures), reducing certain personal activities that generate pollutants, using indoor air cleaners, and even taking doctor-recommended medications that prevent significant or life-threatening responses (eg, acute asthma attacks).

Challenges and unsolved problems

Although much is known regarding the dosimetry of inhaled particles, various significant challenges remain. Most importantly, it is still difficult to predict individual exposures confidently. Most of the scientific knowledge and available particle dosimetry software relates to normal individuals. Certainly, a high priority for research is to increase the database to include the effects of age, body size, and disease states on inhaled particle doses and to incorporate this information into the available dosimetry software. Similarly, more information on personal exposures, as opposed to reliance on fixed aerosol monitors, is needed. Progress in this area requires the development of inexpensive, lightweight particle monitors that can be comfortably worn for long periods by potentially high-risk subpopulations and individuals. More data are needed to better define the full range of personal activities that generate excessive particle exposures.

A serious complication in defining particle exposures relates to defining the proper dose metrics. A useful dose metric is one that measures the important (ie, mechanistically associated with adverse health effects) properties of inhaled particles in a reliable reproducible manner. Several particle properties have been considered with respect to the dose metrics. Particle mass within a defined particle size range is most commonly used, but particle count, particle surface area, and particle chemistry are also recognized as being important in certain circumstances [1]. Probably any measurable particle property (eg, size, mass, count, surface area, aspect ratio, fractal dimension, acidity, oxidative capacity, solubility, and catalytic activity) has some potentially adverse impact on some people. The presence of gaseous/vaporous co-pollutants cannot be ignored. Considerable sustained research is needed to define and evaluate the many potential dose metrics. Only when such research is substantially completed will it be possible to confidently propose effective and cost-efficient air quality regulations.

Challenges also exist with respect to defining and using better laboratory animal models for aerosol toxicity research. Several advances in developing health-compromised animal models have been valuable [28–35], but establishing their relationships to human diseases remains problematic. An important issue with all laboratory animals relates to species differences in particle deposition and clearance [1]. Great care must be taken in selecting such models, but they are clearly essential for conducting particle toxicity studies.

To improve the quality of data that are available for epidemiologic analyses, information on body mass and height, physical activity patterns, lifestyle factors (eg, smoking status), health status, place of residence (eg, urban or rural), personal activities and hobbies, and other dosimetry-related data should be collected, as should the usual demographic descriptors (eg, gender, age, education, and income). The quality of epidemiologic findings is enhanced by defining more clearly the (often rare) individuals in potentially susceptible subpopulations who are at significant risk of experiencing

the adverse effects of exposures to particles. From a clearer understanding of dose-response associations among high-risk individuals, it will be more feasible to devise appropriate public health interventions for protection of high-risk subpopulations from the effects of exposures to particles.

A particularly interesting problem related to dose-response relationships is that for a given dose, the response can depend on the previous recent exposure history. Previous exposure, or lack thereof, alternatively can produce either adaptation or sensitization. For example, in short-term time series epidemiologic studies, statistically significant responses are often associated with increases, or increments, in particle concentrations, as opposed to levels of particles [36]. For example, associations (between adverse outcomes and particle measures) are seen when 3- to 5-day averages in particle concentrations are used as measures of exposure. This implies that previous exposure to cleaner air may intensify the adverse effects on some (perhaps many) individuals. Why this might occur is unclear; perhaps short-term loss of normal defenses is occurring. Although this issue is not strictly a dosimetry problem, it relates to how dose is interpreted. Possible long-term adaptation to aerosols and the potential physiologic costs of such require additional research.

An unsettled area in inhalation toxicology and dosimetry research involves the health effects of low doses (minimally polluted air). Specifically, can the effects of such low doses be extrapolated from observations at moderate doses? Can the air actually be too clean, in that exposed populations may be unable to tolerate future unavoidable higher particle exposures? Are low levels of air pollutants even beneficial to overall health, as related to possible hormetic effects [37]? A recently introduced scientific journal, *Dose-Respones* [38], publishes papers related to low-dose exposures and their effects.

Summary

Dosimetric considerations are clearly essential to an adequate understanding of the health effects of inhaled particulate air pollutants. Defining exposure in terms of C • T is not adequate, because it ignores such important factors as volume of air inspired, aerosol inhalability, deposition efficiency, uniformity of deposition, local deposition intensities (eg, deposited dose per unit surface area), and the actions of particle clearance/redistribution mechanisms. By considering these and other potentially important dose-related factors, it may be possible to identify high-risk individuals within potentially susceptible subpopulations. When an individual is at high risk (because of disease or genetic or exposure history factors) and receives unusually high doses (because of anatomic, physiologic, and environmental factors), he or she is likely to be the most severely harmed. Some of the factors that predispose individuals to receiving high doses and being at high risk are identified, and others are still under investigation. It is important that these factors be more thoroughly incorporated into epidemiologic

and human clinical investigations, so that individuals most severely affected can be identified clearly and protected appropriately. Otherwise, increasingly restrictive and costly particle control strategies may be pursued without significant net benefits to public health.

Research intended to identify the more harmful particulate agents, combinations, and temporal exposure effects requires the use of laboratory animal models in the foreseeable future. Understanding species differences in particle deposition and clearance is fundamental to the use of such investigations. More is known about species differences in healthy animals than in health-compromised ones. Additional research on such compromised animal models is needed.

Difficult problems remain in understanding the effects of low doses and the effects of mixtures and intermittent high- and low-level exposures. Until more is learned about these problems, it is difficult to have confidence in the effects of control strategies based on finding acceptable air concentrations of air pollutants one by one.

Current coordinated research efforts are underway worldwide to better understand the potential adverse health effects of current particle exposures. The Committee on Research Priorities for Airborne Particulate Matter of the National Research Council has defined many important issues (including dosimetric ones) and a logical sequence of research activities to better understand them [39]. The identified National Research Council research agenda is a long-term proposition that provides important guidance to many research communities.

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