CONCEPTS IN INHALATION TOXICOLOGY

Second Edition

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Chapter Eight

Deposition and Clearance of Inhaled Particles

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INTRODUCTION

The biologic effects of inhaled particles are a function of their disposition. This, in turn, depends upon their patterns of deposition, i.e., the sites within which they initially come into contact with airway epithelial surfaces and the amounts removed from the inhaled air at these sites, and clearance, i.e., the rates and routes by which deposited particles are physically removed from the respiratory tract. For materials, such as irritants, which exert their action upon surface contact, the initial deposition is the predicator of toxic response. In many other cases, however, it is the net result of deposition and clearance—namely retention, i.e., the amount of particles remaining in the respiratory tract at specific times after exposure—which influences toxicity. This chapter provides an overview of the processes by which airborne particles are deposited within and cleared from the respiratory tract.

DEPOSITION OF INHALED PARTICLES

Deposition Mechanisms

There are five significant mechanisms by which particles may deposit in the respiratory tract. These are impaction, sedimentation, Brownian diffusion,

electrostatic precipitation, and interception; they are depicted schematically in Fig. 1.

Impaction is the inertial deposition of a particle onto an airway surface. It occurs when the particle's momentum prevents it from changing course in an area where there is a rapid change in the direction of bulk airflow. Impaction is the main mechanism by which particles having diameters ≥ 0.5 μm deposit in the upper respiratory tract and at or near tracheobronchial tree branching points. The probability of impaction increases with increasing air velocity, rate of breathing, particle size, and density.

Sedimentation is deposition due to gravity. When the gravitational force on an airborne particle is balanced by the total of forces due to air buoyancy and air resistance, the particle will fall out of the air stream at a constant rate—the terminal settling velocity. The probability of sedimentation is proportional to the particle's residence time in the airway, particle size, and density and decreases with increasing breathing rate. Sedimentation is an important deposition mechanism for particles with diameters ≥ 0.5 μm which penetrate to airways where air velocity is relative low, e.g., mid to small bronchi and bronchioles.

Submicrometer-sized particles (especially ultrafines, which are those having diameters < 0.1 μm) acquire a random motion due to bombardment by surrounding air molecules. This motion may then result in particle contact with the airway wall. The displacement sustained by the particle is a function of a parameter known as the diffusion coefficient and is inversely related to particle size (specifically cross-sectional area) but is independent of particle density. The probability of deposition by diffusion increases with increasing particle residence time within the airway, and diffusion is a major deposition mechanism where bulk flow is low or absent, e.g., bronchioles and the pulmo-

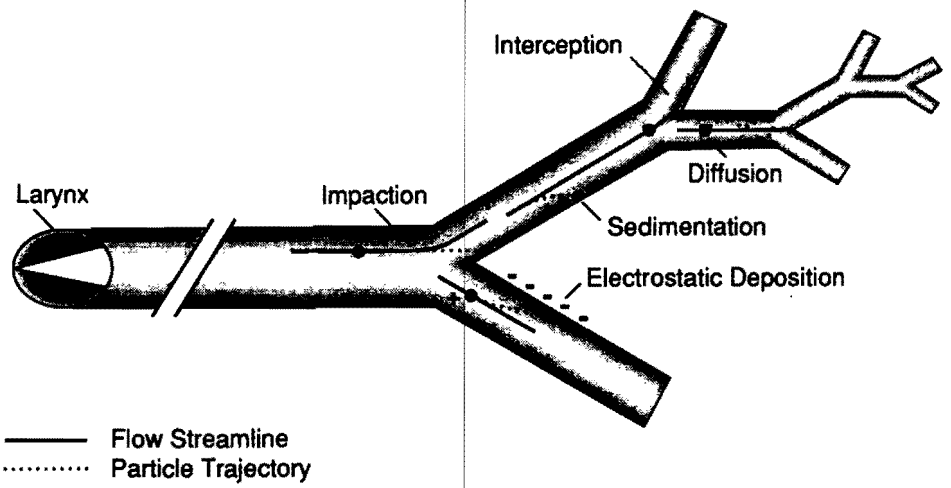


Figure 1 Schematic diagram of particle deposition mechanisms.

nary region (alveolated airways). However, extremely small ultrafine particles can show significant deposition in the upper respiratory tract, the trachea and larger bronchi. This likely occurs by turbulent diffusion.

Some freshly generated particles can be electrically charged and may exhibit enhanced deposition over that expected from size alone. This can be due to image charges induced on the surface of the airway by these particles, and/or to space-charge effects whereby repulsion of particles containing like charges results in increased migration towards the airway wall. The effect of charge on deposition is inversely proportional to particle size and airflow rate. Since most ambient particles become neutralized naturally due to the presence of air ions, electrostatic deposition is generally a minor contributor to overall particle collection by the respiratory tract. It may, however, be important in some laboratory studies.

Interception is a significant deposition mechanism for fibrous particles, which are those having length to diameter ratios > 3:1. While fibers are also subject to all of the same deposition mechanisms as are more spherical or compact particles, they have the additional possibility of deposition when an edge contacts, or intercepts, an airway wall. The probability of interception increases as airway diameter decreases, but it can also be fairly significant in both the upper respiratory tract and upper tracheobronchial tree. While interception probability increases with increasing fiber length, the aerodynamic behavior of a fiber and impaction/sedimentation probability is more influenced by fiber diameter.

Factors Controlling Deposition

The extent and loci of particle deposition depend upon various controlling factors (Table 1). These are characteristics of the inhaled particles, geometry of the respiratory tract, and breathing pattern.

Characteristics of Inhaled Particles From the discussion above, it should be evident that the major particle characteristic which influences deposition is size. But it is important that this be expressed in the proper manner. The deposition probability for particles with geometric diameters $\gtrsim 0.5$ μm is governed largely by their equivalent aerodynamic diameter (D_{ae}), while the deposition probability for smaller particles is governed by actual physical diameter. It therefore follows that aerodynamic diameter is the most appropriate size parameter for describing particles subject to deposition by sedimentation and impaction, but not diffusion. Since particles are generally inhaled not singly, but as constituents of aerosols, the mass median aerodynamic diameter (MMAD) is an appropriate parameter to use for those aerosols in which most particles have actual diameters $\gtrsim 0.5$ μm, while the median size of aerosols containing particles with diameters less than this

Table 1 Some Factors That May Control or Affect Particle Deposition

Particle characteristics
Geometric size
Shape
Density
Hygroscopicity
Electrical charge
Respiratory tract geometry
Airway caliber
Airway branching pattern
Path length to terminal airways
Ventilation
Mode of breathing—oral, nasal, oronasal
Respiratory rate
Tidal volume
Flow rate and velocities
Interlobular distribution of ventilation
Length of respiratory pauses
Other factors
Irritant exposure
Respiratory tract disease
Growth from newborn to adult
Aging from maturity (?)
Gender (?)

should be expressed in terms of a diffusion diameter, such as thermodynamic equivalent diameter, or by using actual geometric size.

The distribution of particle sizes within an aerosol, which is generally characterized as either monodisperse ($\sigma_g = 1.2$) or polydisperse ($\sigma_g > 1$), is also important in terms of ultimate deposition pattern. If the σ_g of a polydisperse aerosol is < 2, the total amount of deposition within the respiratory tract will probably not differ substantially from that for a monodisperse aerosol having the same median size (Diu and Yu, 1983). However, size distribution is critical in determining the spatial pattern of deposition, since the latter depends upon the sequential removal of particles within each region of the respiratory tract which, in turn, depends upon the actual particle sizes present within the aerosol. For example, when the deposition (in hamsters) of a monodisperse and a polydisperse aerosol having similar median aerodynamic sizes was compared (Thomas and Raabe, 1978), the latter was found to deposit to a greater extent in the upper respiratory tract due to the presence of a certain fraction of large particles that were effectively removed by impaction. Total respiratory tract deposition of the two aerosols (expressed as a percentage of the amount inhaled) was comparable.

A particle characteristic which may dynamically alter its size after inhalation is hygroscopicity. Hygroscopic particles will grow substantially while

they are still airborne within the respiratory tract and will deposit according to their hydrated (rather than their initial dry) size.

Respiratory Tract Geometry Respiratory tract structure affects particle deposition in many ways. For example, airway diameter sets the displacement required for a particle to contact a surface, while the cross-section determines the air velocity and type of flow for a given inspiratory flow rate. Furthermore, flow characteristics depend upon branching angle and branching pattern. Differences in pathway lengths within different lung lobes may affect regional deposition. For example, if particles subject to impaction or sedimentation are inhaled, those lobes with the shortest average path length between the trachea and terminal bronchioles may have the highest pulmonary region concentration of deposition. On the other hand, differences in regional deposition become less obvious for ultrafine particles, which tend to deposit more evenly in all lobes regardless of path length, but rather in proportion to relative ventilation.

The tracheobronchial airways and alveoli show a considerable degree of size variability between different individuals. This is likely the primary factor responsible for the large inter-individual differences in deposition which are observed experimentally (Heyder et al., 1982).

Ventilation Pattern and Mode of Inhalation The pattern of breathing during particle exposure influences the sites and relative amounts of regional deposition. For example, exercise or other enhanced activity may result in increased respiratory rate and tidal volume and increased linear air velocities within the conducting airways. This would tend to enhance impaction, but decrease deposition due to sedimentation and diffusion. While total deposition within the respiratory tract may increase with exercise for particles $>$ 0.2–0.5 μm in diameter (Harbison and Brain, 1983; Zeltner et al., 1991), a shift in the deposition pattern towards the upper respiratory tract and central bronchi and away from more distal conducting airways and the pulmonary region can occur (Bennett et al., 1985; Morgan et al., 1984). Increased linear velocities may also result in the development of turbulence, which tends to enhance deposition of such particles. On the other hand, the deposition of ultrafine particles within the upper respiratory tract and tracheobronchial tree decreases as flow rate increases, and exercise may not increase total respiratory tract deposition of these particles even though it does result in greater numbers inhaled (Hesseltine et al., 1986).

Tidal volume, i.e., the volume of air inhaled during a single breath, affects regional deposition by determining the depth of penetration of inspired air. For a constant breathing frequency, an increase in tidal volume would result in deeper penetration of inhaled particles, with a potential increase in deposition in the smaller conducting airways and pulmonary region. Alterations in tidal volume may also dramatically affect total respiratory

tract deposition. For example, a doubling in tidal volume from 1.4 ml to 2.8 ml in the rat was predicted to increase the deposition of a 1 μm (median D_{ae}) aerosol by 7 times (Schum and Yeh, 1980). Finally, respiratory frequency and the duration of respiratory pauses influences sedimentation or diffusion deposition by affecting particle residence time in relatively still air.

A significant change that occurs in humans when activity level increases is a switch in the mode of breathing from nasal to oronasal (combined oral and nasal breathing). Since the nasal passages are more efficient than the oral in removing inhaled particles, even a partial bypassing of the nose could increase particle penetration into the lungs. Toxicological studies using aerosols may employ a variety of inhalation devices and protocols. When evaluating and comparing such studies, it is important to consider the effects of exposure technique upon subsequent deposition. Just as critical is assessment of the relationship between deposition in obligate nasal breathing experimental animals to humans breathing via the mouth.

Factors Modifying Deposition

Various factors may alter deposition patterns compared to those occurring in normal, healthy adult individuals—the group most commonly used in toxicologic assessments. As outlined in Table 1, these include previous or coexposure to airborne irritants, lung disease, and growth, all of which can affect deposition by changing its controlling parameters, namely ventilation pattern and/or airway geometry.

Irritant inhalation-induced bronchoconstriction would tend to increase impaction deposition in the upper bronchial tree. Likewise, deposition may be altered due to disease. Bronchial obstruction associated with various pulmonary diseases tends to increase total respiratory tract deposition via enhanced deposition within the upper respiratory tract and tracheobronchial tree (especially for particles > 1 μm), even though peripheral deposition may be reduced. The deposition of ultrafine particles is also increased in obstructive lung disease due to increased residence time and to flow perturbations resulting from reductions in airway lumen calibre. On the other hand, deposition may be entirely eliminated in portions of the lungs due to ventilation impairments (Thomson and Short, 1969; Thomson and Pavia, 1974; Lourenco et al., 1972).

Structural alterations in the lungs may affect deposition. For example, rodents with enzyme-induced emphysema showed a reduced deposition compared to normal controls (Damon et al., 1983; Hahn and Hobbs, 1979). This was likely due to an increase in alveolar size, resulting in greater distances to deposit on a surface and a concomitant reduction in pulmonary region deposition efficiency (Brain and Valberg, 1979). On the other hand, inhaled particles deposited more distally in rats with a fibrotic disease, i.e., coal or silica derived pneumoconiosis, than in normal animals (Heppelston, 1963).

One of the current concerns in inhalation toxicology involves differences in deposition between children and adults. A number of attempts have been made to estimate the influence upon deposition of anatomical and ventilatory changes during postnatal growth in humans (e.g., Hofmann, 1982; Crawford, 1982; Phalen et al., 1991). They indicate that the relative effectiveness of the major deposition mechanisms differs at various times during growth and that this, in turn, may alter regional deposition patterns. Taking into account anatomical differences and the greater ventilation per unit body weight in children, the deposition fractions for some particle sizes, especially those > 1 μm, within certain regions of the growing respiratory tract could be quite different, sometimes well above those found based upon studies with adults. Such differences would become even more significant when deposition is expressed on a per unit surface area basis. Since there are also regional differences in clearance rates, this infers that the dose to specific lung compartments from some inhaled particles may vary with age from newborn to adult Anatomical changes with aging post-maturity may also affect deposition for particles > 1 μm, increasing pulmonary region deposition in older adults compared to younger adults (Phalen et al., 1991). On the other hand, the deposition of ultrafine particles may not show dramatic differences between children and adults, nor with aging (Phalen et al., 1991; Swift et al., 1992).

Any differences in deposition between children and adults may be influenced by activity levels due to the manner by which breathing pattern changes. For example, increased ventilation with increasing activity in children occurs to a greater extent by increased respiratory frequency, while adults show greater increases in tidal volume. Since increased frequency is associated with decreased deposition of particles > 1 μm in diameter, the greater total respiratory tract deposition with increasing activity levels seen in adults is not seen in young children, and the latter may actually show somewhat of a decline (Becquemin et al., 1991).

Deposition within the Human Respiratory Tract

The deposition of particles within the human respiratory tract can be assessed with a number of techniques (Valberg, 1985). Unfortunately, the use of different experimental methods and assumptions results in considerable variations in reported values. Figs. 2A–D present experimentally determined values for spherical particle deposition within the human respiratory tract as a function of the median size of the inhaled aerosol. All values are expressed as deposition efficiency—the percentage deposition of the total amount inhaled.

Fig. 2A shows the pattern for overall respiratory tract deposition. Note the deposition minima over the 0.2–0.5 μm size range, with increasing deposition with increasing size for larger particles and with decreasing size for smaller

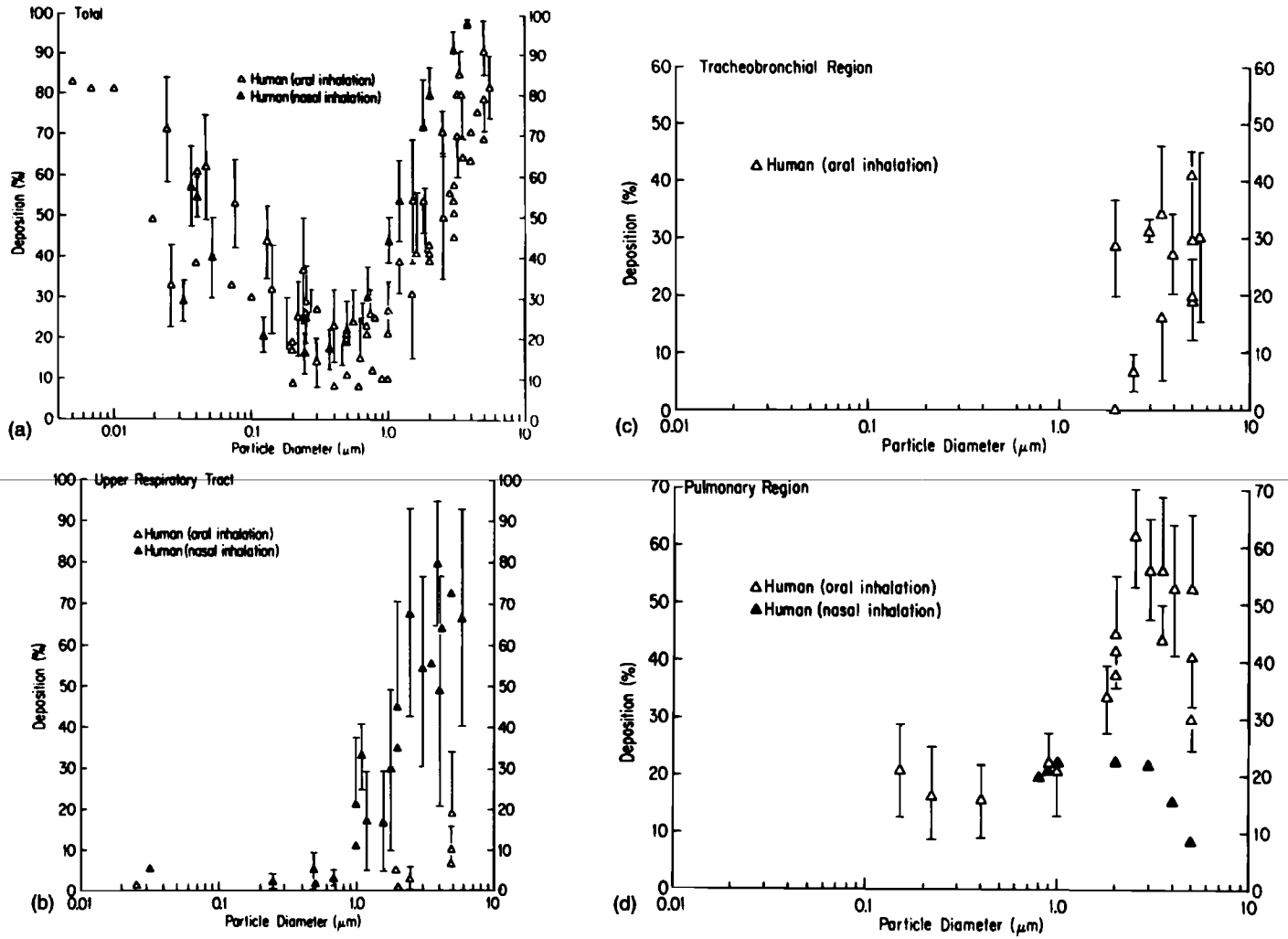


Figure 2 Particle deposition in the human respiratory tract. Deposition efficiency, i.e., the percentage deposition of the amount inhaled, is plotted as a function of particle size for: (a) total respiratory tract; (b) upper respiratory tract; (c) tracheobronchial tree; and (d) pulmonary region. Particle diameters are aerodynamic for those ≥ 0.5 μm and diffusion equivalent for those <0.5 μm. (Based upon data compiled by Schlesinger, 1985b, with additional data from Tu and Knudson, 1984; Wilson et al., 1985; Schiller et al., 1988; Heyder et al., 1986; Anderson et al., 1990; Becquemin et al., 1991).

ones. As previously discussed, particles with diameters $\gtrsim 0.5$ μm are subject to impaction and sedimentation, while the deposition of those $\lesssim 0.1$ μm is diffusion dominated. Particles with diameters between these values are minimally influenced by all three mechanisms and tend to have relatively prolonged suspension times in the inhaled air. They undergo minimal deposition after inhalation, and most are carried out of the respiratory tract in the exhaled air.

The effect of breathing mode upon deposition is evident from Fig. 2A. Inhalation via the nose results in greater total deposition than does oral inhalation for particles with diameters > 0.5 μm. This is due to enhanced collection in the upper respiratory tract with the former. On the other hand, there is little apparent difference in total deposition between nasal or oral breathing for those particles with diameters between 0.02–0.5 μm. For particles $<$ 0.5 μm, an increase in total deposition with nose compared to mouth breathing also occurs, but the difference is smaller, amounting to ~ 5% for particles with diameters of 0.005 μm (Schiller et al., 1988).

The effects of hygroscopicity upon deposition deserves mention. If Fig. 2A is examined, it is evident that hygroscopic particles inhaled at 0.1–0.5 μm diameter would tend to show a decrease in total deposition if they grow to < 0.5 μm and will show a deposition increase only if their final hydrated diameter is > 1 μm. On the other hand, since particles > 5 μm may only minimally grow in one respiratory cycle, they may not show an increase in deposition at all compared to nonhygroscopic material (Ferron, 1988). Hygroscopic particles inhaled at 0.2–0.5 μm may show substantial changes in their deposition probability, particularly in the tracheobronchial and pulmonary regions.

Fig. 2B shows the pattern of deposition in the upper respiratory tract—the larynx and airways above it. Again, it is evident that nasal inhalation results in enhanced deposition compared to oral. The greater the deposition in the head, the less is the amount available for removal in the lungs. Thus, the extent of collection in the upper respiratory tract affects deposition in more distal regions.

Figure 2C depicts deposition in the tracheobronchial tree. There appears not to be as well a defined relationship between deposition and particle size as in other regions. Fractional tracheobronchial deposition is relatively constant over a wide particle size range.

Deposition in the pulmonary region is shown in Figure 2D. With oral inhalation, deposition increases with particle size after a minimum at ~ 0.5 μm. With nasal breathing, on the other hand, deposition tends to decrease with increasing particle size. The removal of particles in more proximal airways determines the shape of these pulmonary curves. For example, increased upper respiratory and tracheobronchial deposition would be associated with a reduction of pulmonary deposition. Thus, nasal breathing results in less pulmonary penetration of larger particles and a lesser fraction of deposition for entering aerosol than does oral inhalation. Thus, in the latter

case, the peak for pulmonary deposition shifts upwards to a larger sized particle and is more pronounced. With nasal breathing, on the other hand, there is relatively constant pulmonary deposition over a wider particle size range.

The deposition of ultrafine particles is of great interest in inhalation studies since these particles present a large surface area for potential adsorption of other toxicants for delivery to the respiratory tract. There are a few inhalation studies in humans using ultrafine aerosols in the diameter range of 0.1–0.01 μm, and less for smaller sizes. The latter is partly due to technical difficulties in producing high quality monodisperse aerosols within this size range in sufficient quantity to allow evaluation of deposition. From Fig. 2A, it can be seen that total respiratory tract deposition increases as particle size decreases below 0.2 μm.

The regional deposition of ultrafine particles in humans has been examined using only mathematical and physical models (Cheng et al., 1991; 1988; 1993; NRC, 1991; Swift et al., 1992). These indicate that as particle size decreases below 0.2 μm, deposition within the upper respiratory tract and tracheobronchial tree increases substantially, while deposition within the pulmonary region is progressively reduced. Deposition efficiency in the nasal passages can be quite high, reaching over 80% for particles below about 0.002 μm, from a low of about 2% for particles in the 0.1–0.2 μm size range. Similar to larger particles, the deposition efficiency for ultrafine particles within the upper respiratory tract with oral breathing is somewhat less than that with nasal breathing. Estimates suggest that oral deposition is likely to be 70–90% of nasal deposition for comparable inspiratory flow rates.

The deposition efficiencies presented in Fig. 2 are for spherical or compact particles. Due to the potential toxicity of fibrous particle shapes, experimental fiber deposition data in humans is not available. However, studies in animals and use of mathematical and physical models provide some general indication of deposition patterns (Asgharian and Yu, 1988; 1989; Sussman et al., 1991; Hammad et al., 1982; Morgan et al., 1977). Long fibers (> 10 μm) tend to show enhanced deposition in the tracheobronchial tree, and reduced deposition in the pulmonary region, compared to shorter fibers. But fibers which are very long (e.g., > 50 μm) and thin (e.g., < 0.5 μm) can reach distal conducting airways, and significant amounts of such particles can deposit in the pulmonary region. But the deposition of fibers is much more complex than that for spherical particles. For example, the shape of the former is important, since straight fibers penetrate more distally than do curly ones.

Localized Patterns of Deposition

Particle deposition may not occur in a homogeneous manner along airway surfaces. Specific patterns of enhanced local deposition are important in determining the dose, which depends on the surface density of deposition. Nonuniformity implies that the initial dose delivered to specific sites may be

greater than that occurring if a uniform density of surface deposit is assumed. This is important for inhaled particles which affect tissues on contact, e.g., irritants, and may be a factor in the site selectivity of certain diseases, e.g., bronchogenic carcinoma (Schlesinger and Lippmann, 1978).

In the upper respiratory tract, enhanced deposition occurs at areas characterized by constrictions, directional changes and high air velocities, e.g., the larynx, oropharyngeal bend, and nasal turbinates (Swift, 1981; Swift and Proctor, 1988). Likewise, the deposition of aerosols in the tracheobronchial tree is not homogeneous. In humans, air turbulence produced by the larynx results in enhanced localized deposition in the upper trachea and larger bronchi, while deposition is also greatly enhanced at bronchial bifurcations, especially along the carinal ridges, relative to the tubular airway segments (Schlesinger et al., 1982). This occurs for spherical particles > 0.5 μm diameter due to impaction, and for fibers due to both impaction and interception (Asgharian and Yu, 1989). However, enhanced deposition at bifurcations is also seen with submicrometer particles having diameters down to about 0.1 μm (Cohen et al., 1988). This is due to turbulent diffusion. As particle size decreases further, the effects of localized flow patterns upon particle behavior become less important, and more uniform deposition along airway surfaces occurs (Gradon and Orlicki, 1990). Thus, there may be a particle size below which enhanced deposition at bifurcations and other sites becomes insignificant. For example, no enhanced deposition of 0.04 μm particles was found at bifurcations in a cast of the human upper bronchial tree (Cohen et al., 1988).

The experimental conditions employed in the numerous tracheobronchial microdistribution studies varied widely, yet the relative enhancement distribution among the airways was found to be quite similar, suggesting that local patterns of deposition within the larger bronchi may be fairly insensitive to particle sizes > 0.1 μm and to air flow rates. It also appears that the proportional distribution of deposition in specific airways is relatively constant over a wide range of particle sizes and total lung deposition efficiencies (Schlesinger and Lippmann, 1978), as is the distribution of deposition in the various lobes of the lungs (Raabe et al., 1977).

There are a few data on localized deposition patterns for the pulmonary region. Fibers show nonuniform deposition in distal airways of animals, preferentially depositing on bifurcations of alveolar ducts near the bronchioalveolar junction (Brody and Roe, 1983; Warheit and Hartsky, 1990). While this has yet to be demonstrated in human lungs, the presence of early fiber-related lesions in similar regions suggests that it may occur in these as well (Brody and Yu, 1989).

Comparative Aspects of Deposition

Various animals are employed in experimental aerosol inhalation toxicology studies, with the ultimate goal being extrapolation to humans. To adequately

apply the results to human risk assessment, however, it is essential to consider interspecies differences in total and regional deposition patterns. Since different species exposed to the same aerosol may not receive identical doses in comparable respiratory tract regions, and clearance processes are regionally distinct as will be discussed, the selection of a particular species may influence the estimated human lung (or systemic) dose as well as its relation to potential health effects.

Comparable deposition mechanisms operate for humans and animals, but the degree of similarity in deposition between different species may depend to some extent upon the deposition mechanism which predominates. For example, it has been suggested that interspecies particle deposition probabilities would be similar for sedimentation, but a function of body weight for diffusion (Stauffer, 1975).

Figures 3A–D present particle deposition profiles for a number of experimental animals. It is evident that there are few data on regional deposition of ultrafine particles. One study in the rat indicated that, at a normal inspiratory flow rate, nasal airway deposition efficiency ranged from 6% for 0.1 μm particles to 58% for 0.005 μm particles (Gerde et al., 1991). This is fairly comparable to values for humans indicated by studies in physical model systems, as discussed above.

In evaluating studies with aerosols, the amount of deposition expressed merely as a percentage of the total inhaled, i.e., deposition efficiency, may not be adequate information for relating results between species. For example, total respiratory tract deposition for the same size particle can be quite similar in humans and many experimental animals (Fig. 3A). It, therefore, follows that deposition efficiency is independent of body (or lung) size (McMahon et al., 1977; Brain and Mensah, 1983). However, different species exposed to identical particles at the same exposure concentration will not receive the same initial mass deposition. If the total amount of deposition is divided by body (or lung) weight, smaller animals would receive greater initial particle burdens per unit weight per unit exposure time than would larger ones. For example, the initial deposition of 1 μm particles in the rat will be 5–10 times that of humans, and in the dog 3 times that of humans, if deposition is calculated on a per unit lung or body weight basis (Phalen et al., 1977).

Humans differ from most other mammals used in inhalation toxicologic studies in various aspects of respiratory tract anatomy. But the implications of this to particle deposition have not been adequately appreciated One major interspecies difference is bronchial tree branching pattern (Schlesinger and McFadden, 1981). Humans show a relatively symmetrical dichotomous branching, while most quadrupeds have a highly asymmetric monopodial pattern. This can affect particle microdistribution patterns, in that the tendency for enhanced deposition noted at human airway bifurcations is reduced in monopodial branching systems (Schlesinger, 1980). Furthermore, branching pattern also influences the depth of particle penetration within the

bronchial tree due to its effect upon airflow characteristics (Fang et al., 1993). However, the influence of interspecies anatomical differences upon deposition may depend upon particle type. For fibers, for example, the path length and number of branching divisions modulates deposition more than the branching angle or pattern. Thus, deposition of fibers in rodents may be quite relevant to that in humans (Pinkerton et al., 1986).

Interspecies anatomical differences in the upper respiratory tract can also influence deposition patterns. The greater complexity of the nasal passages in rodents compared to primates results in the bulk of impaction deposition occurring more anteriorly in the nasal passages of the former (Gooya and Patra, 1986; Schreider, 1986). Furthermore, rodents would tend to have consistently high deposition in the upper respiratory tract since they are obligate nasal breathers.

In the pulmonary region, alveolar size varies between species. This may be reflected by differences in the probability of deposition by diffusion and sedimentation due to differences in the distance between airborne particles and airway walls.

CLEARANCE OF DEPOSITED PARTICLES

Clearance Mechanisms

Particles which deposit upon airway surfaces may be cleared from the respiratory tract completely or may be translocated to other sites within this system. Clearance mechanisms are regionally distinct in terms of both specific routes (outlined in Table 2) and kinetics. Mechanisms are either absorptive, i.e., dissolution, or nonabsorptive, i.e., mechanical transport of intact particles, and these may occur simultaneously or with temporal variations. It should be mentioned that particle solubility in terms of clearance refers to

Table 2 Respiratory Tract Clearance Mechanisms

Upper respiratory tract
Mucociliary transport
Sneezing
Nose wiping and blowing
Dissolution (for soluble particles)
Tracheobronchial tree
Mucociliary transport
Endocytosis by macrophages/epithelial cells
Coughing
Dissolution (for soluble particles)
Pulmonary region
Macrophages, epithelial cells
Interstitial pathways
Dissolution (for soluble and "insoluble" particles)

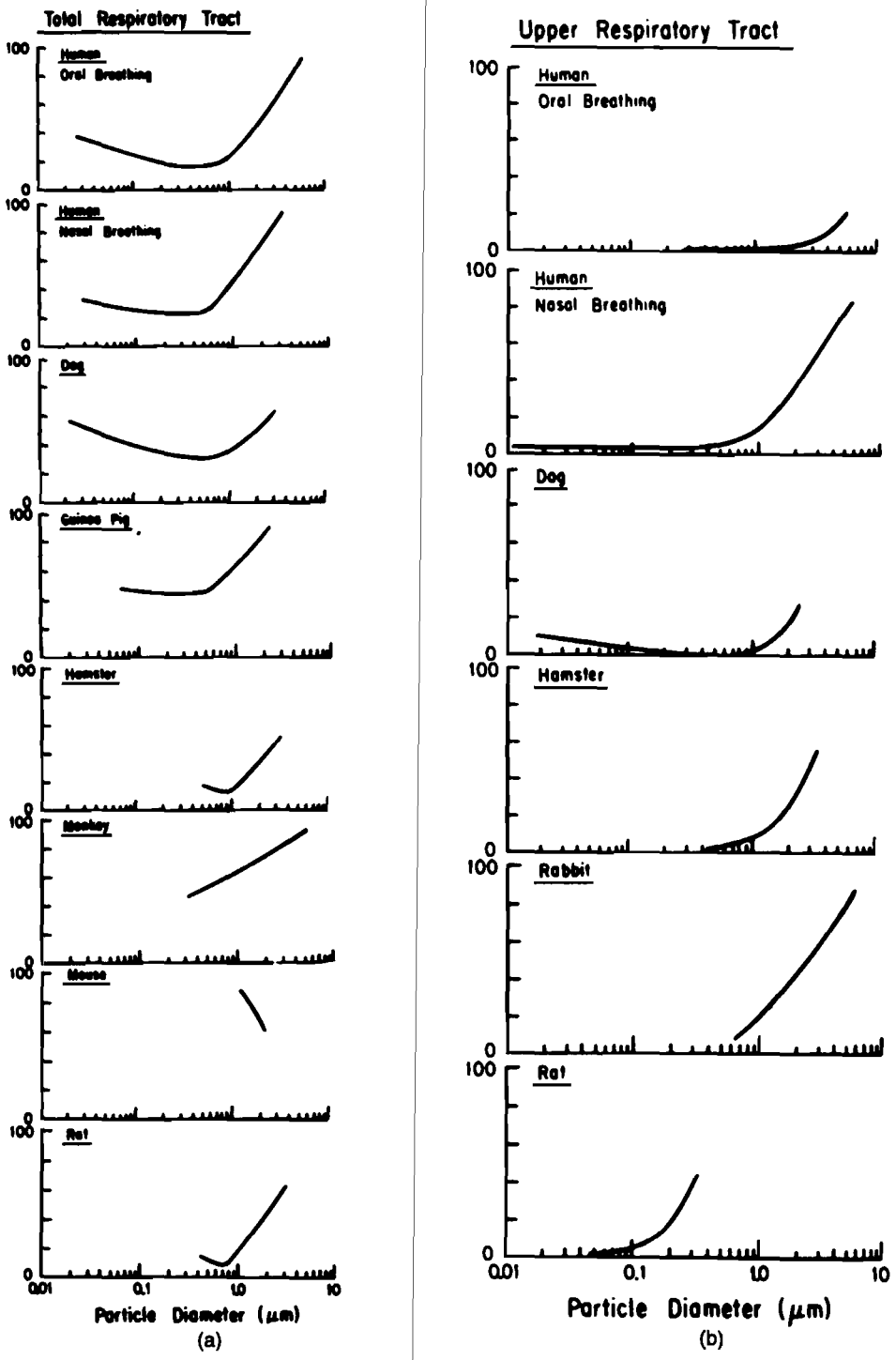
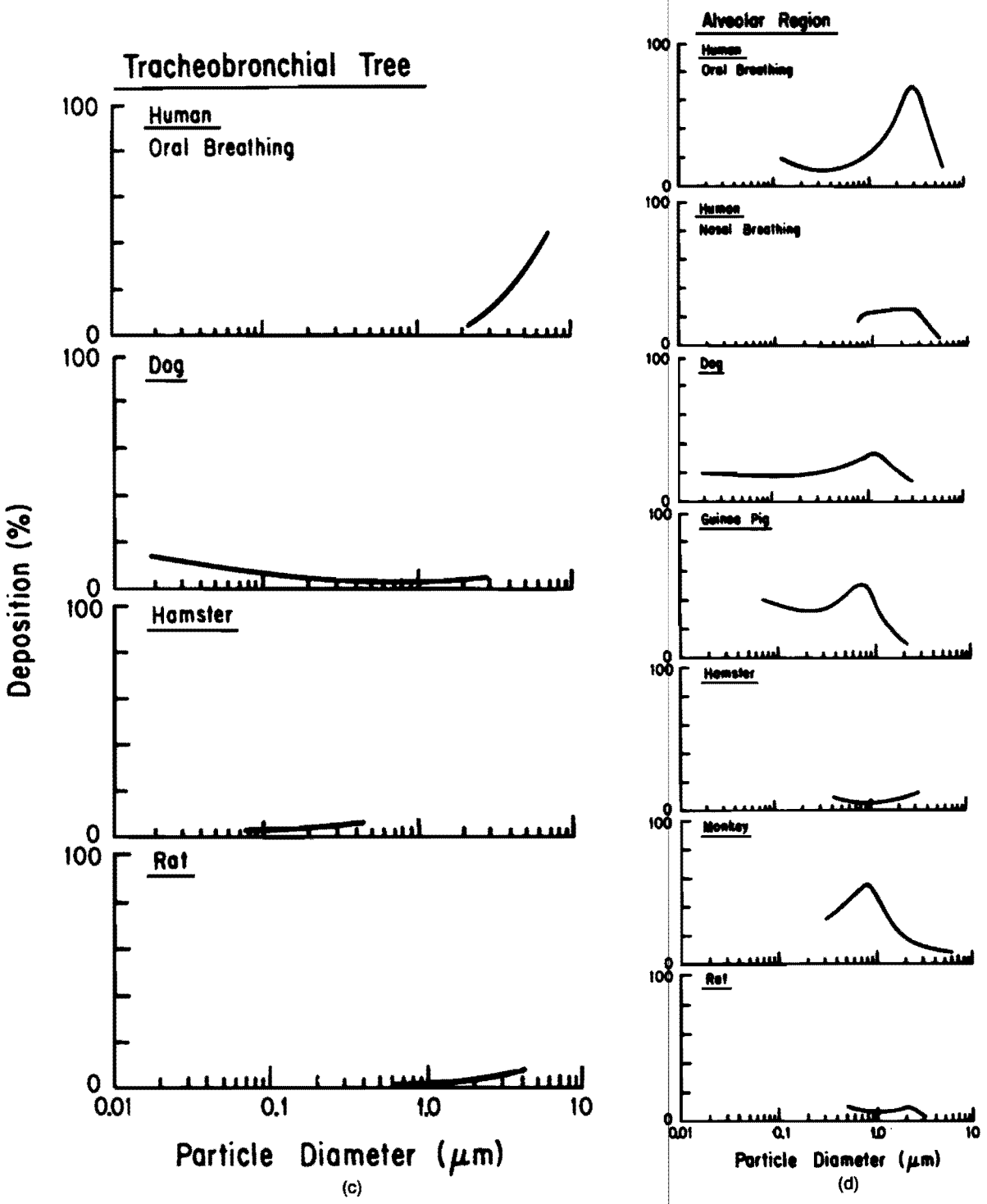


Figure 3 Particle deposition efficiencies for experimental animals often used in inhalation toxicological protocols plotted as a function of particle size for (a) total respiratory tract, (b) upper respiratory tract, (c) tracheobronchial tree, and (d) pulmonary re-



gion. Each curve represents an eye fit through mean values (or centers of ranges) of the data compiled by Schlesinger (1985b). Similar curves for humans are shown for comparison. Particle diameters are aerodynamic for those ≥0.5 μm and diffusion equivalent for those <0.5 μm.

solubility *in vivo* within respiratory tract fluids. Thus, an insoluble particle is considered to be one whose rate of clearance by dissolution is insignificant compared to its rate of clearance by mechanical processes. For the most part, all deposited particles clear by the same mechanisms whether they are fibers or compact spheres, with their ultimate fate a function of deposition site, physicochemical properties (including any toxicity), and deposited concentration.

Upper Respiratory Tract Clearance of insoluble particles deposited in the nasal passages occurs via mucociliary transport, and the general flow of mucus is backwards—towards the nasopharynx. The epithelium in the most anterior portion of the nasal passages is not ciliated, and the mucus flow distal to this is forward, clearing deposited material to a site where removal is by sneezing, wiping, or blowing (extrinsic clearance). Soluble material deposited on the nasal epithelium will be accessible to underlying cells if it can diffuse them through the mucus prior to removal via mucociliary transport. Since there is a rich vasculature in the nose, uptake into the blood may occur rapidly.

Clearance of insoluble particles deposited in the oral passages is by swallowing into the gastrointestinal tract. Soluble particles are likely rapidly absorbed after deposition (Swift and Proctor, 1986).

Tracheobronchial Tree Like the nasal passages, insoluble particles deposited on tracheobronchial tree surfaces are cleared primarily by mucociliary transport, with the net movement of fluid towards the oropharynx. Some insoluble particles may traverse the epithelium by endocytotic processes, entering the peribronchial region (Masse et al., 1974; Sorokin and Brain, 1975). Clearance may also occur following phagocytosis by airway macrophages, located on or beneath the mucus lining throughout the bronchial tree, which then move cephalad on the mucociliary blanket, or via macrophages which enter the airway lumen from the bronchial or bronchiolar mucosa (Robertson, 1980). Soluble particles may be absorbed through the mucus layer, into the blood, via intercellular pathways between epithelial cell tight junctions or by active or passive transcellular transport mechanisms.

The bronchial surfaces are not homogeneous; there are openings of daughter bronchi and normal islands of non-ciliated cells at bifurcation regions. In the latter, the usual progress of mucus movement is interrupted, and bifurcations may be sites of relatively retarded clearance. The efficiency with which non-ciliated obstacles are traversed is dependent upon the traction of the mucus layer.

Pulmonary Region Clearance from the pulmonary region occurs via a number of mechanisms and pathways, but the relative importance of each is not always certain.

Nonabsorptive clearance processes, shown schematically in Fig. 4, are

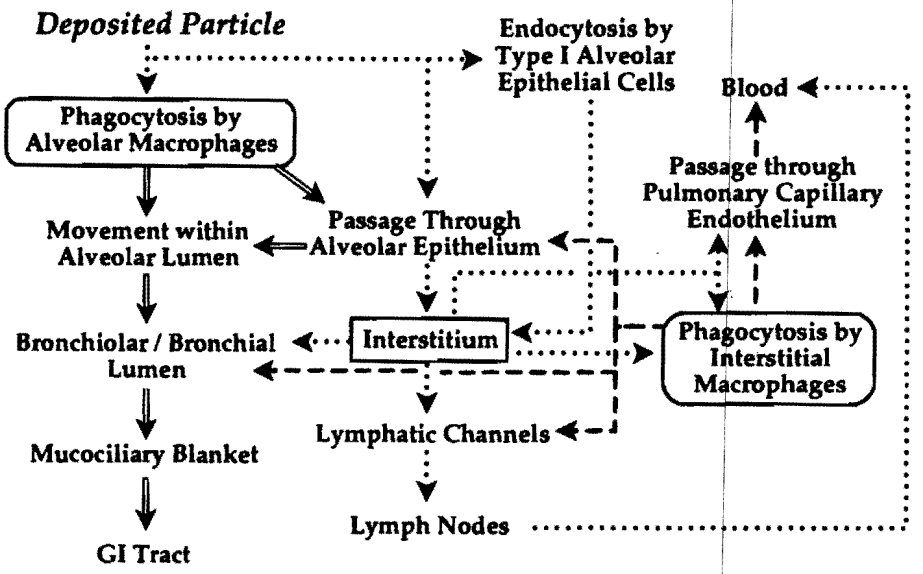


Figure 4 Diagram of known and suspected mechanical clearance pathways for insoluble particles depositing in the pulmonary region. (Dissolution is not included.)

mediated primarily via alveolar macrophages. These cells reside on the alveolar epithelium, and phagocytize and transport deposited material which they contact by random motion or, more likely, via directed migration under the influence of local chemotactic factors. Some deposited particles may be translocated to areas where macrophages congregate, due to pressure gradients or via capillary action within the alveolar surfactant lining (Schurch et al., 1990; Parra et al., 1986).

Alveolar macrophages normally comprise ~3–5% of the total alveolar cells in healthy (nonsmoking) humans and other mammals (Gehr, 1984), and represent the largest subpopulation of nonvascular macrophages in the respiratory tract (Lehnert, 1992). However, the actual cell count is influenced by particle loading. Low numbers of deposited particles may not result in an increase in cell number, but above some level macrophage numbers increase proportionally to particle number until a saturation point is reached (Adamson and Bowden, 1981; Brain, 1971). Since the magnitude of this increase is related more to the number of deposited particles than to total deposition by weight, equivalent masses of an identical deposited substance may not produce the same response if particle sizes differ. Thus, smaller particles tend to result in a greater elevation in cell number than larger ones.

Particle-laden macrophages may be cleared from the pulmonary region along a number of pathways. The primary route is cephalad transport via the mucociliary system after the cells reach the distal terminus of the mucus blanket. However, the manner by which macrophages actually attain this is not certain. The possibilities are:

Chance encounter;

Passive movement along the alveolar surface due to surface tension gradients between the alveoli and conducting airways;

Directed locomotion along a gradient produced by chemotactic factors released by macrophages ingesting deposited material (Sorokin and Brain, 1975; Kilburn, 1968); or

Passage through the alveolar epithelium and the interstitium (Brundelet, 1965; Green, 1973; Corry et al., 1984; Harmsen et al., 1985).

Some cells which follow interstitial clearance pathways are likely resident interstitial macrophages which have ingested free particles transported through the alveolar epithelium, probably via endocytosis by Type I pneumocytes (Brody et al., 1981; Bowden and Adamson, 1948). Such endocytosis is often seen for fibers that cannot be fully ingested by alveolar macrophages. Particle-laden interstitial macrophages can also migrate across the alveolar epithelium, becoming part of the alveolar macrophage cell population.

Macrophages which are not cleared via the bronchial tree may actively migrate within the interstitium to a nearby lymphatic channel or, along with uningested particles, be carried in the flow of interstitial fluid towards and into the lymphatic system (Harmsen et al., 1985). Passive entry into lymphatic vessels is fairly easy since the vessels have loosely connected endothelial cells with wide intercellular junctions (Lauweryns and Baert, 1974). Lymphatic endothelium may also actively engulf particles from the surrounding interstitium (Leak, 1980). Particles within the lymphatic system may be translocated to tracheobronchial lymph nodes, which often become reservoirs of retained material. Particles penetrating the nodes and subsequently reaching the postnodal lymphatic circulation may enter the blood.

Uningested particles or macrophages in the interstitium may traverse the alveolar-capillary endothelium, directly entering the blood (Raabe, 1982; Holt, 1981). Endocytosis by endothelial cells followed by exocytosis into the vessel lumen seems, however, to be restricted to particles <0.1 μm, and may increase with increasing lung burden (Lee et al., 1989; Oberdörster, 1988). Once in the systemic circulation, transmigrated macrophages, as well as free particles, can travel to extrapulmonary organs. Some species have pulmonary intravascular macrophages which can remove particles from circulating blood (Warner and Brain, 1990) and which may play some role in the clearance of material deposited in the alveoli.

Free particles and macrophages within the interstitium may travel to perivenous, peribronchiolar or subpleural sites, where they become trapped and increase the particle burden. The migration and grouping of particles and macrophages within the lungs can lead to the redistribution of initially diffuse deposits into focal aggregates (Heppleston, 1953). Some particles, notably fibers, can be found in the pleural space, often within macrophages which have migrated across the visceral pleura (Sebastien et al., 1977; Hager-

strand and Siefert, 1973). Resident pleural macrophages do occur, but any role in clearance is not known.

During clearance, particles can be redistributed within the alveolar macrophage population (Lehnert, 1992). One mechanism is by death of the macrophage and the release of free particles to the epithelium followed by uptake by other macrophages. Some of these newly freed particles may, however, translocate to other clearance routes.

Clearance by the absorptive mechanism involves dissolution in the alveolar fluid, followed by transport through the epithelium and into the interstitium, and diffusion into the lymph or blood. Some soluble particles translocated to and trapped in interstitial sites may be absorbed there. Although the factors affecting the dissolution of deposited particles are poorly understood, it is influenced by the particle's surface-to-volume ratio and other surface properties (Morrow, 1973; Mercer, 1967). Thus, materials generally considered to be relatively insoluble may have high dissolution rates and short dissolution half times if the particle size is small.

Some deposited particles may undergo dissolution after phagocytic uptake by macrophages. For example, metals may dissolve in the acidic milieu of the phagolysosomes (Lundborg et al., 1985). It is, however, not certain whether the dissolved material then emigrates from the macrophage. Finally, some particles can bind to epithelial cell or other cell components, delaying clearance from the lungs.

Fibrous particles deposited in the pulmonary region may be additionally subject to a process of disintegration, which involves the subdivision of a large particle into smaller segments. This can occur by leaching within the fibrous structure which then fractures, or by surface etching, resulting in a change in the external dimensions of the fiber. Some fiber types break up by length; others will disintegrate into smaller diameter particles (Lippmann, 1992).

Clearance Kinetics

Although deposited particles may be cleared completely from the respiratory tract, the actual time frame over which this occurs affects dose delivered to the respiratory tract, and to extrapulmonary organs. Particle-tissue contact and subsequent dose in the upper respiratory tract and tracheobronchial tree are often limited by the rapid clearance from these regions and are, thus, proportional to toxicant concentration and exposure duration. On the other hand, the dose from material deposited in the pulmonary region is highly dependent upon the characteristics of both the particle matrix and any substances associated with it.

Various experimental techniques have been used to assess clearance rates in both humans and experimental animals (Schlesinger, 1985a). Because of technical differences and the fact that measured rates are strongly influenced

by the specific methodology, comparisons between studies are often difficult to perform. However, regional clearance rates, i.e., the fraction of the deposit which is cleared per unit time, are well defined functional characteristics of an individual human or experimental animal when repeated tests are performed under the same conditions. But, as with deposition, there is a substantial degree of inter-individual variability.

Upper Respiratory Tract Mucus flow rates in the posterior nasal passages are highly nonuniform. Regional velocities in the healthy adult human may range from < 2 to > 20 mm/min (Proctor, 1980), with the fastest flow occurring in the midportion of the nasal passages. The median rate is about 5 mm/min. The overall result is a mean transport time for insoluble particles over the entire region of ~ 10–20 minutes (Stanley et al., 1985; Rutland and Cole, 1981).

Particles which deposit in the nonciliated anterior portion of the nasal passages may be cleared slowly (1–2 mm/hr) by mucus moved by traction due to more distal cilia (Hilding, 1963). Since this may take upwards of 12 hours, such deposits are usually more effectively removed by sneezing, wiping, or nose blowing, in which case clearance may occur in under 30 minutes (Morrow, 1977; Fry and Black, 1973).

Tracheobronchial Tree Mucus transport in the tracheobronchial tree occurs at different rates in different local regions. The velocity of mucus movement is fastest in the trachea, and it becomes progressively slower in more distal airways. Measured rates in the human trachea range from 4–20 mm/minute, depending upon the experimental technique used. Anesthesia and/or invasive procedures affect transport, resulting in observed rates which are apparently slower than normal. In unanesthetized, healthy nonsmokers using noninvasive procedures, average tracheal mucus transport rates have been measured at 4.3–5.7 mm/minute (Leikauf et al., 1981, 1984; Yeates et al., 1975, 1981b; Foster et al., 1980). Furthermore, the rate of insoluble particle transport seems to be independent of the nature—shape, size, and composition—of the material being cleared (Man et al., 1980).

The mean mucus velocity in the human main bronchi has been experimentally found to be ~ 2.4 mm/minute (Foster et al., 1980). While rates of movement in smaller airways cannot be directly measured, those in human medium bronchi have been estimated at between 0.2–1.3 mm/minute and those in the most distal ciliated airways as low as 0.001 mm/minute (Yeates and Aspin, 1978; Morrow et al., 1967b).

The total duration of bronchial clearance, or some other time parameter, is often used as an index of mucociliary function. In healthy adult nonsmoking humans, 90% of insoluble particles depositing on the tracheobronchial tree will be cleared from 2.5 to 20 per hour after deposition, depending upon the individual subject and the size of the particles (Albert et al., 1973). The

latter does not affect surface transport, but does affect the depth of particle penetration and deposition and the subsequent pathway length for clearance. Due to differences in regional transport rates, clearance times from different regions of the bronchial tree will differ. In most cases, however, removal of a tracheobronchial deposit will generally be 99% completed 48 hours after exposure (Bailey et al., 1985a).

Studies with both rodents and humans have indicated that a small fraction (~ 1%) of insoluble material may be retained for a prolonged period of time within the upper respiratory tract (nasal passages) or tracheobronchial tree (Patrick and Stirling, 1977; Gore and Patrick, 1982; Watson and Brain, 1979; Radford and Martell, 1977). The mechanism(s) underlying this long-term retention is unknown, but may involve endocytosis by epithelial cells with subsequent translocation into deeper tissue, or merely passive movement into this tissue. The retained particles may eventually be cleared to regional lymph nodes, but with a long half time that may be > 80 days (Patrick, 1989; Oghiso and Matsuoka, 1979).

Long-term tracheobronchial retention patterns are not uniform. There appears to be an enhancement at bifurcation regions (Cohen et al., 1988; Radford and Martell, 1977; Henshaw and Fews, 1984), perhaps the result of both greater deposition and ineffectual mucus clearance within these areas. Thus, doses calculated based upon uniform surface retention density may be misleading, especially if the material is, toxicologically, slow acting. Soluble material may also undergo long-term retention in ciliated airways due to binding to cells or macromolecules.

Pulmonary Region Clearance kinetics in the pulmonary region are not definitively understood, although particles deposited there generally remain longer than those deposited in airways cleared by mucociliary transport. There are limited data on rates in humans, while within any species rates vary widely due to different properties of the particles used in the various studies. Furthermore, some of these studies employed high concentrations of insoluble particles, which may itself have interfered with normal clearance mechanisms, producing rates different from those which would occur at lower exposure levels. Prolonged exposure to high particle concentrations is associated with what is termed particle "overload." This is a nonspecific effect noted in experimental studies using many different kinds of insoluble particles, including fibers, and results in clearance slowing or stasis, with an associated inflammation and aggregation of macrophages in the lungs. (Muhle et al., 1990; Lehnert, 1990). While it is, however, likely to be of little relevance for most "real world" exposures to humans, it is of concern in interpreting some long-term experimental exposure data.

There are numerous pathways of pulmonary region clearance which may depend upon the nature of the particles being cleared. Thus, kinetic generalizations are hard to make, especially since the manner in which particle char-

acteristics affect kinetics is not resolved. Nevertheless, pulmonary region clearance can be described as a multiphasic process. Each component is considered to represent removal by a different mechanism or pathway, characterized by increasing half times of clearance with time postexposure. For example, an initial fast phase, which has a half time of ~ 2–6 weeks, presumably represents rapid clearance via macrophages, while a phase of prolonged clearance, with a half time of months to years, represents removal by dissolution. This latter is extremely variable, but it likely dominates the long-term clearance of relatively insoluble particles (Kreyling et al., 1988). An intermediate phase with a half time on the order of months may represent a slower phase of macrophage clearance via interstitial pathways.

Clearance of inert, insoluble particles in healthy, nonsmoking humans has been generally observed to consist of two phases, the first having a half-time measured in days, and the second in hundreds of days. Table 3 presents half times for the longer second phase of clearance as reported in a number of studies. Although wide variations in clearance times reflect a dependence upon the nature of the deposited material, e.g., particle size, once dissolution is accounted for, mechanical removal to the gastrointestinal tract and/or lymphatic system appears to be independent of size, especially for particles < 5 μm (Snipes et al., 1983). Although not evident from Table 3, there is considerable intersubject variability in the clearance rates of identical particles, which appears to increase with time postexposure (Philipson et al., 1985; Bailey et al., 1985a). The large differences in clearance kinetics among different individuals suggest that equivalent chronic exposures to insoluble particles may result in large variations in respiratory tract burdens.

Although the kinetics of overall clearance from the pulmonary region have been assessed to some extent, much less is known concerning relative

Table 3 Long-term Particle Clearance from the Pulmonary Region in Nonsmoking Humans

Particle		Clearance half-time*	
Material	Size(μm)	(days)	Reference
Polystyrene latex	5.0	150–300	Booker et al., 1967
Polystyrene latex	5.0	144–340	Newton et al., 1978
Polystyrene latex	0.5	33–602	Jammett et al., 1978
Polystyrene latex	3.6	296	Bohning et al., 1982
Teflon	4	200–2500	Philipson et al., 1985
Aluminosilicate	1.2	330	Bailey et al., 1982
Aluminosilicate	3.9	420	Bailey et al., 1982
Iron oxide (Fe_2O_3)	0.8	62	Morrow et al., 1967a,b
Iron oxide (Fe_2O_3)	0.1	270	Waite & Ramsden, 1971
Iron oxide (Fe_3O_4)	2.8	70	Cohen et al., 1979

*Represents the half-time of clearance for the slowest phase observed

rates along specific pathways. The usual initial step in clearance, i.e., uptake of deposited particles by alveolar macrophages, is very rapid. Unless the particles are cytotoxic or very large, ingestion by macrophages occurs within 24 hours of a single inhalation (Naumann and Schlesinger, 1986; Lehnert and Morrow, 1985). But the actual rate of subsequent macrophage clearance is not certain. Perhaps 5% or less of their total number is translocated from the lungs each day (Lehnert and Morrow, 1985; Masse et al., 1974). The actual time for the clearance of particle-laden alveolar macrophages via their main route (the mucociliary system) depends upon the site of uptake relative to the distal terminus of the mucus blanket at the bronchiolar level. Furthermore, clearance pathways and subsequent kinetics may depend to some extent upon particle size. For example, ultrafine particles < 0.02 μm are less effectively phagocytosed than are larger ones (Oberdörster, 1993). But once ingestion occurs, alveolar macrophage-mediated kinetics are independent of the particle involved as long as solubility and cytotoxicity are low.

Free particles may penetrate into the interstitium (largely by Type I cell endocytosis) within a few hours following deposition (Ferin and Feldstein, 1978; Sorokin and Brain, 1975; Brody et al., 1981). This transepithelial passage seems to increase as particle loading increases, especially to a level above the saturation point for increasing macrophage number (Adamson and Bowden, 1981; Ferin, 1977). It may also be particle-size dependent since insoluble ultrafine particles < 0.05-μm diameter show increased access to and greater lymphatic uptake than larger ones (Oberdörster et al., 1992). Similarly, a depression of phagocytosis by toxic particles or the deposition of large numbers of smaller ultrafine particles may increase the number of free particles in the alveoli, enhancing removal by other routes. In any case, free particles and alveolar macrophages may reach the lymph nodes within a few days after deposition (Lehnert et al., 1988; Harmsen et al., 1985). However, the bulk of translocation to the lymphatic system is very slow, on the order of 0.02–0.003%/day (Snipes, 1989), and elimination from the lymph nodes is even slower, with half times measured in tens of years (Roy, 1989).

Soluble particles depositing in the pulmonary region are rapidly cleared via absorption through the epithelial surface into the blood, but there are few data on dissolution and transfer rates to blood in humans. Actual rates depend upon the size of the particle, i.e., molecular size, with smaller ones clearing faster than larger ones. Some solubilized material may be retained in lung tissue due to binding with cellular components, preventing it from passing into the circulation.

Factors Modifying Clearance

A number of host and environmental factors may modify normal clearance patterns, affecting the dose delivered by exposure to inhaled particles. As

Table 4 Some Factors That May Affect Particle Clearance

Factor	Upper respiratory tract and/or tracheobronchial tree (mucociliary transport)	Pulmonary
Gender	Probably no effect	(?)*
Aging	Possible retardation	(?)
Exercise	Possible acceleration with heavy exercise	Possible acceleration
Irritant exposure	Acceleration or retardation depending on dose	Acceleration or retardation depending on dose
Lung disease		
Chronic bronchitis	Retardation	Retardation
Asthma	Retardation	(?)
Influenza	Retardation	Retardation

*(?) = Effect has not been evaluated

outlined in Table 4, these include aging, gender, workload, disease and irritant inhalation. However, in many cases, the exact role of these factors is not resolved.

The evidence for aging-related effects on mucociliary function in healthy individuals is equivocal, with studies showing either no change or a slowing in clearance function with age after maturity (Goodman et al., 1978; Yeates et al., 1981a). However, it is difficult to determine whether any observed functional decrement was due to aging alone, or to long-term, low-level ambient pollutant exposure (Wanner, 1977).

There are no data to allow assessment of age-related changes in clearance from the pulmonary region. Although functional differences have been found between alveolar macrophages of mature and senescent mice (Esposito and Pennington, 1983), no age-related decline in macrophage function has been seen in humans (Gardner et al., 1981).

There is also insufficient data to assess changes in clearance in the growing lung. Nasal mucociliary clearance time in a group of children (average age 7 years) was found to be ~ 10 min (Passali and Ciampoli, 1985). This is within the range for adults. There is one report of bronchial clearance in children (12 years old), but this was performed in patients hospitalized for renal disease (Huhnerbein et al., 1984).

In terms of gender, no difference in nasal mucociliary clearance rate was observed between male and female children (Passali and Ciampoli, 1985), nor in tracheal transport rates in adults (Yeates et al., 1975). Slower bronchial clearance has been noted when male adults are compared to female adults, but this was attributed to differences in lung size (and resultant clearance pathway length) rather than to inherent gender-related differences in transport velocities (Gerrard et al., 1986).

The effect of increased physical activity upon mucociliary clearance is

also unresolved; the available data indicate no change to a speeding with exercise (Wolff et al., 1977; Pavia, 1984). There are no data concerning changes in pulmonary region clearance with increased activity levels, but CO_2-stimulated hyperpnea (rapid, deep breathing) was found to have no effect on early pulmonary clearance and redistribution of particles (Valberg et al., 1985). Increased tidal volume breathing was noted to increase the rate of particle clearance from the pulmonary region. This was suggested to be due to distension-related evacuation of surfactant into proximal airways resulting in a facilitated movement of particle-laden macrophages or free particles because of the accelerated motion of the alveolar fluid film (John et al., 1994).

Various respiratory tract diseases are associated with clearance alterations. Nasal mucociliary clearance is prolonged in humans with chronic sinusitis, bronchiectasis, or rhinitis (Majima et al., 1983; Stanley et al., 1985) and in cystic fibrosis (Rutland and Cole, 1981). Bronchial mucus transport may be impaired in people with bronchial carcinoma (Matthys et al., 1983), chronic bronchitis (Vastag et al., 1986), asthma (Pavia et al., 1985), and in association with various acute infections (Lourenco et al., 1971; Camner et al., 1979; Puchelle et al., 1980). In certain of these cases, coughing may enhance mucus clearance, but it generally is only effective if excess secretions are present.

Rates of pulmonary-region particle clearance appear to be reduced in humans with chronic obstructive lung disease (Bohning et al., 1982) and in experimental animals with viral infections (Creasia et al., 1973). The viability and functional activity of macrophages was found to be impaired in human asthmatics (Godard et al., 1982). Studies with experimental animals have also found disease-related clearance changes. Hamsters with interstitial fibrosis showed an increased degree of pulmonary clearance (Tryka et al., 1985). Rats with emphysema showed no clearance difference from control (Damon et al., 1983), although the copresence of inflammation resulted in prolonged retention (Hahn and Hobbs, 1979). Inflammation may enhance particle and macrophage penetration through the alveolar epithelium into the interstitium by increasing the permeability of the epithelium and the lymphatic endothelium (Corry et al., 1984). Neutrophils, which are phagocytic cells present in alveoli during inflammation, may contribute to the clearance of particles via the mucociliary system (Bice et al., 1990).

Inhaled irritants, such as cigarette smoke, have been shown to have an effect upon mucociliary clearance function in both humans and experimental animals (Wolff, 1986). Single exposures to a particular material may increase or decrease the overall rate of tracheobronchial clearance, oftentimes depending upon the exposure concentration (Schlesinger, 1986). Alterations in clearance rate following single exposures to moderate concentrations of irritants are generally transient, lasting < 24 hours. However, repeated exposures may result in an increase in intra-individual variability of clearance rate and persistently retarded clearance. The effects of irritant exposure may be enhanced by exercise or by coexposure to other materials.

Acute and chronic exposures to inhaled irritants may also alter pulmonary region clearance (Cohen et al., 1979; Ferin and Leach, 1977; Schlesinger et al., 1986), which may be accelerated or depressed, depending upon the specific material and/or length of exposure. Alterations in alveolar macrophages likely underlie some of the observed changes since numerous irritants have been shown to impair the numbers and functional properties of these cells (Gardner, 1984).

Comparative Aspects of Clearance

As with deposition analyses, the inability to study the retention of certain materials in humans for direct risk assessment requires use of experimental animals. Since dosimetry depends upon clearance rates and routes, adequate toxicologic assessment necessitates that kinetics in these animals be related to those occurring in humans. The basic mechanisms of clearance from the respiratory tract appear to be similar in humans and most other mammals. However, regional clearance rates show substantial variation between species, even for similar particles deposited under comparable exposure conditions (Snipes, 1989). Dissolution rates and rates of transfer of dissolved substances into the blood may or may not be species independent, depending upon certain chemical properties of the deposited material (Griffith et al., 1983; Bailey et al., 1985b; Roy, 1989). For example, lipophilic compounds of comparable molecular weight are cleared from the lungs of various species at the same rate (dependent solely upon solute molecular weight and the lipid/water partition coefficient), but hydrophilic compounds show species differences. On the other hand, there are interspecies differences in rates of mechanical transport, e.g., macrophage-mediated clearance of insoluble particles from the pulmonary region (Bailey et al., 1985b); transport of particles from the pulmonary region to pulmonary lymph nodes (Snipes et al., 1983; Mueller et al., 1990); and mucociliary transport in conducting airways (Felicetti et al., 1981). This is likely to result in species-dependent rate constants for these clearance pathways. Thus, differences in regional (and perhaps total) clearance rates between some species are most likely due to these mechanical processes.

CONCLUSION

The toxic response from inhaled particles is dependent upon both the amount and pattern of deposition and the time frame of persistence in various sites. The deposition of particles on airway surfaces is the result of specific physical mechanisms that are influenced by particle characteristics, airflow patterns, and respiratory tract anatomy. Because regional deposition patterns determine the specific pathways and rates by which particles are ultimately cleared and redistributed, biological effects are often related more

to the quantitative pattern of deposition at specific sites than they are to the total amount depositing in the respiratory tract. Clearance routes and kinetics are a function of the respiratory tract region and, in some cases, lung burden and the physico-chemical properties of the deposited material. The accurate interpretation of results from inhalation toxicological studies employing particles requires an appreciation of those factors which control and affect both their deposition and clearance.

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