

COMPARATIVE DEPOSITION OF INHALED AEROSOLS IN EXPERIMENTAL ANIMALS AND HUMANS: A REVIEW

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The biological effects of inhaled aerosols are often related to their site(s) of deposition within the respiratory tract. However, deposition patterns may differ between humans and those experimental animals commonly used in inhalation toxicology studies, making cross-species risk extrapolations difficult. This paper reviews the factors that control deposition and synthesizes much of the available data on comparative regional deposition.

INTRODUCTION

A basic goal of inhalation toxicologic studies using aerosols is to relate the dose to the lung, or following absorption to other organs, with exposures to a given inhaled concentration of particles having certain physicochemical characteristics. However, the biological effect(s) may be more directly related to the quantitative pattern of deposition within various regions of the respiratory tract than to the environmental concentration. This is because the regional pattern of deposition efficiency determines not only the initial lung tissue dose, but also the specific pathways and rates by which deposited particles are ultimately cleared and redistributed.

Different species of experimental animals are used in aerosol inhalation toxicology studies, with the ultimate goal being extrapolation of the results to humans. To apply these results to human risk assessment, however, it is essential to consider differences in regional deposition

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patterns. Various species exposed to the same aerosol may not receive identical doses in comparable respiratory tract regions; thus, selection of species may, in fact, influence not only the estimated lung dose, but also the endpoint of interest and its relation to potential human health effects.

Most deposition studies using experimental animals measured total, rather than regional, deposition; there are more data for humans in this regard as well. This paper attempts to synthesize the available total and regional deposition data for both experimental animals and humans. The goal is not necessarily to come to some definitive conclusion as to which animal is a good surrogate for humans, but rather to allow initial deposition distributions to be estimated and compared between species to provide for more successful risk assessment judgements.

DEPOSITION MECHANISMS AND THEIR CONTROLLING FACTORS

Specific Deposition Mechanisms

The significant mechanisms by which particles may deposit in the respiratory tract are impaction (inertial deposition), sedimentation (gravitational deposition), Brownian diffusion, interception, and electrostatic precipitation. The relative contribution of each depends on characteristics of the inhaled particles, as well as on breathing patterns and respiratory-tract anatomy.

Impaction onto an airway surface may occur when a particle's momentum prevents it from changing course in an area where there is a rapid change in the direction of bulk airflow. It is the main deposition mechanism in the upper respiratory tract, i.e., above the trachea, and at or near bronchial branching points. The probability of impaction increases with increasing air velocity, rate of breathing, and particle size.

Sedimentation results when the gravitational force on a particle is balanced by the total of forces due to air buoyancy and air resistance; inspired particles will then fall out of the air stream at a constant rate. Thus, this is an important deposition mechanism in small airways having low air velocity. The probability of sedimentation is proportional to residence time in the airway and to particle size, and decreases with increasing breathing rate.

Submicron-sized airborne particles have imparted to them a random motion due to bombardment by surrounding gas molecules; this motion may then result in these particles coming into contact with the airway wall. The effectiveness of Brownian motion is inversely proportional to particle diameters for those particles $< \sim 0.5 \mu\text{m}$ (Lippmann, 1977), and is generally important in bronchioles and alveoli, and at bronchial airway bifurcations. Molecular-sized particles may deposit by diffusion in the upper respiratory tract, trachea, and larger bronchi.

Interception, which is a significant deposition mechanism for fibrous particles, occurs when the edge of a particle contacts the airway wall. This may result if the particle length is similar to the airway diameter.

Test aerosols formed via evaporation of aqueous droplets can be electrically charged, and many experimental deposition studies used such aerosols without charge neutralization. Charged particles may exhibit enhanced deposition due to (1) image charges induced on the surface of the airways by these particles, and/or (2) space-charge effects, whereby repulsion of particles containing like charges results in increased migration toward the airway wall. The effect of charge on deposition increases with decreasing particle size and decreasing air flow rate.

Factors Controlling Deposition

An understanding of the extent and loci of deposition in various species requires knowledge of those underlying factors that control it. These are (1) characteristics of the inhaled particles, e.g., size, distribution, shape, electrical charge, density, hygroscopicity; (2) anatomy of the respiratory tract, e.g., lung size, branching pattern, airway diameters, lengths, angles of branching; and (3) breathing pattern, e.g., frequency, depth, flow rate. Since factors (2) and (3) often differ greatly between species, the distribution of dose due to inhaled aerosols may also differ. Biological variability is the dominant factor affecting comparisons at comparable aerosol size, overwhelming all but extreme differences in other aerosol characteristics. Even in studies using individuals of the same species, anatomic and physiological—i.e., breathing—parameters are highly variable characteristics of the individual, while particle size is usually a more tightly controllable factor.

Particle characteristics. The size of inhaled particles is a critical factor in affecting the site of their deposition, since it determines operating mechanisms and extent of penetration into the lungs. Thus, resultant biological effects are, to some extent, particle size-dependent. Size may be expressed in various ways. For spherical particles, actual measured diameter is unambiguous, but for nonspherical or irregularly shaped particles, some "effective" diameter may be more appropriate. Thus, such particles are often described in terms of equivalent spheres, on the basis of equal volume, mass, or aerodynamic drag.

In order to compare deposition data obtained using particles of different materials, some "normalized" diameter must be used, the most common of which is aerodynamic equivalent diameter (D_{ae}). Aerodynamic diameter is defined as the diameter of a spherical particle having unit density that has the same settling velocity from an airstream as the particle in question. Thus, particles that have higher than unit density will have actual diameters smaller than their D_{ae} . Aerodynamic diameter is the most appropriate unit for describing deposition by impaction and sedimentation, but not for diffusion, since the latter is independent of particle shape and density, being related only to actual physical size.

Particles are inhaled not singly, but as aerosols. An aerosol has a size distribution, characterized as monodisperse or polydisperse; the distri-

bution generally depends on the technique of generation. The size distribution of an aerosol is usually expressed aerodynamically in terms of mass, as mass median aerodynamic diameter (MMAD); radioactive aerosol size distributions are often expressed as activity median aerodynamic diameter (AMAD). Monodisperse aerosols consist of particles that are all essentially the same size; they are characterized by a common operational distinction, i.e., having a geometric standard deviation (σ_g) < 1.2 . In polydisperse aerosols, particles of widely different sizes may be present, with $\sigma_g \geq 1.2$.

Respiratory-tract anatomy. It is obvious that the respiratory system of humans and that of various experimental animals differ anatomically in many quantitative as well as qualitative ways. (Schreider and Raabe, 1981; Schlesinger, 1980; Phalen, 1984). Certain aspects of gross and subgross anatomy have been studied in numerous species. For example, there is variability in the structure of nasal passages, bronchial path lengths between trachea and alveoli, in lung lobation and lobulation, pleural thickness, and the relative degree of alveolarization.

One of the most dramatic differences between humans and the commonly used experimental animals is the pattern of airway branching in the tracheobronchial tree (Schlesinger and McFadden, 1981; Phalen, 1984). Humans exhibit a relatively regular dichotomous pattern, while most experimental animals have an irregular dichotomous pattern termed monopodial. In a dichotomous branching system, one branch (the "parent") divides, giving rise to two branches (the "daughters"). If both of the daughters have the same diameter and length and branch off the parent at the same angle, the mode of division is known as regular. If the two daughters differ from each other in one or more dimensions, the mode of branching is termed irregular, the extreme case of which is known as monopody. In a monopodial branching system, the larger-diameter daughter may not be easily distinguishable from the parent, since the change in diameter and direction from the parent to the major daughter may be negligible, while the smaller-diameter branch appears to originate laterally from the parent.

Airway geometry affects particle deposition in various ways. For example, the diameter sets the necessary displacement by the particle before it contacts an airway surface, cross-section determines the air velocity for a given flow rate, and variations in diameter and branching patterns affect mixing between tidal and reserve air. Convective mixing can be a dominant factor determining deposition efficiency for particles with $D_{ae} < \sim 2 \mu\text{m}$.

Alveolar size also differs, especially between humans and common experimental species (Tenney and Remmers, 1963; Weibel, 1963). Since particles with $D_{ae} > \sim 1 \mu\text{m}$ that reach the alveoli will probably have a high probability of deposition by sedimentation, and different-size alveoli would have different characteristics as sedimentation chambers, the

alveolar regions of various species may have dissimilar deposition efficiencies.

Aside from any interspecies differences, tracheobronchial airways and alveoli show a considerable degree of intraspecific size variability. In fact, variability in airway dimensions is probably the primary factor responsible for intraindividual deposition variability within one species (Heyder et al., 1982). Thus, it should have a great effect on interspecific patterns.

Respiratory parameters. The pattern of respiration during aerosol exposure influences regional deposition, since breathing volume and frequency determine the mean flow rates in each region of the respiratory tract, which, in turn, influence the effectiveness of each deposition mechanism. The degree and extent of turbulent flow in the upper respiratory tract and larger bronchi may differ between species. Turbulence would tend to enhance particle deposition, the degree of potentiation depending on particle size (Schlesinger et al., 1982). In all species, however, flow is always laminar in the smaller conducting airways and is viscous in the alveoli.

Variations in ventilatory patterns and rate can alter the regional distribution of deposition without necessarily changing the total amount depositing. Rapid breathing is often associated with increased deposition of larger particles in the upper respiratory tract, compared to slow, deep breathing (Valberg et al., 1982).

Tidal volume affects deposition, since it determines how deeply into the lungs the inspired air penetrates. For any constant breathing frequency, a large tidal volume would result in deeper penetration of inhaled aerosol, with a potentially increased deposition fraction in the alveolar region. On the other hand, small tidal volumes may result in lower alveolar deposition, since less aerosol reaches the distal lung.

COMPARATIVE DEPOSITION OF INHALED AEROSOLS IN EXPERIMENTAL ANIMALS AND HUMANS

Factors Influencing Comparisons

Comparisons between available studies are often difficult, since certain basic parameters are needed in order to perform valid intercomparisons and one or more of them are often not available from many studies. Some of the important factors that must be considered in any comparison are discussed next.

Size distribution of particles. Different methods were often used to measure size distributions of aerosols that differed widely in physical characteristics. For an aerosol with a given particle size distribution, mass deposition probability is closely correlated with the MMAD (or AMAD) of the distribution; thus, the figures in this paper are presented in terms of D_{ae} for aerosols with median sizes $\geq 0.5 \mu\text{m}$. For median sizes $< 0.5 \mu\text{m}$, when sedimentation and impaction are not important, some effective

diffusion diameter is used, since this type of parameter tends to better relate to deposition probability for this size range (Wolff et al., 1982).

Many studies with humans used monodisperse aerosols, allowing direct comparison between reported particle sizes. In studies with experimental animals, however, polydisperse aerosols were often used. Since these may consist of particles of widely different sizes, it is often difficult to evaluate deposition based upon the median size alone. However, it is necessary to include some of these latter studies, since the existing data base includes a substantial amount derived using such aerosols.

Respiratory parameters during exposure. Respiratory parameters were not always measured during aerosol exposure. Some studies used estimates of tidal volumes, among others, to derive some index of inhaled volume. Although it is ideal to relate deposition of particles $\geq 0.5 \mu\text{m}$ to some flow parameter, the lack of such information in many studies with experimental animals precludes this. Thus, in this review, deposition is related solely to aerosol size. Since breathing pattern may vary from one individual to another, as well as from day to day in one individual, and since some experimental animals are much more variable in this pattern than are humans, much of the variability in the reported data is due to this lack of ability to normalize for specific respiratory parameters during exposure. For example, Schum and Yeh (1980), using a mathematical model, predicted that in the rat, a change in tidal volume from 1.4 ml to 2.8 ml will increase the total deposition of a $1\text{-}\mu\text{m}$ (median D_{ae}) aerosol by 7 times, and that for one having median D_{ae} of $0.2 \mu\text{m}$ over 50 times.

Another parameter that is rarely controlled, but will affect regional deposition by influencing the depth of penetration of the tidal air as well as airway caliber, is the ratio of functional residual capacity (FRC) to total lung capacity (TLC). It has been predicted that as FRC/TLC increases, deposition would decrease (Schum and Yeh, 1980). In humans, Davies et al. (1972) observed increasing deposition of $0.5\text{-}\mu\text{m}$ particles with decreasing expiratory reserve volume during breathing at a constant tidal volume.

In general, studies with humans were conducted under protocols that often varied tidal volume and breathing frequency on some schedule, or the subject at least attempted to standardize each breath. Studies with experimental animals involved a wider variation in respiratory exposure conditions—e.g., spontaneously breathing versus controlled breathing, anesthetized versus nonanesthetized, etc. In addition, different levels of sedation were used in various experiments.

Deposition measurement techniques. Deposition refers to the initial collection of inhaled aerosol in the respiratory tract. Regional deposition refers to the percentage of initial deposition occurring within defined regions. One problem in comparing the available studies is that different definitions of each respiratory tract region were used, and different methods to estimate total and regional deposition have been employed. Such differences may result in variation in reported deposition values

within the same species, even under otherwise identical exposure conditions.

Total deposition is often estimated by comparing the amount of aerosol in the inhaled air to that in the exhaled air; the difference represents the amount deposited. By making assumptions about mixing and dead space, estimates of regional deposition may be obtained using measurements of the concentration of aerosol in different volume fractions of the expired air.

If radioactively tagged particles are used, initial and regional deposition values may be obtained by measuring retention at various times postexposure. In this case, regional deposition is usually functionally defined, based on subsequent clearance. For example, it is often assumed that any aerosol remaining in the thorax at 20-24 h after exposure is in the alveolar region, and that tracheobronchial deposition, therefore, was accounted for by the amount cleared from the lungs prior to this time. Upper-respiratory-tract deposition is obtained by measurements of head retention immediately after exposure. Since this region clears rapidly, even the first measurement may be lower than the actual initial deposition; accordingly, some investigators include the initial measurement of material in the gastrointestinal tract in their reported value for upper respiratory deposition. In addition, the upper respiratory tract, as defined in various studies, may have included any or all of the following anatomic regions: nasopharynx, oropharynx, larynx, or upper trachea.

Another technique for deposition analysis involves chemical and/or radiologic assay of tissues or whole organs obtained by dissection after exposure. Obtaining accurate initial deposition values would require immediate sacrifice, and the assumption of no particle translocation prior to or during dissection, especially if reliable values for upper-respiratory-tract deposition are to be obtained.

Mode of aerosol inhalation. Inhalation studies may involve various exposure techniques, e.g., nasal or oral delivery using a mask, oral delivery via a tube placed in the mouth and extending to the pharynx, nasal delivery via catheters placed in the nasal passages, or delivery directly to the lungs via tracheal intubation. In comparing regional deposition fractions between species, or even in different studies using the same species, the results may be affected by the exposure route and delivery technique employed.

In a study with dogs, for example, inhalations of a 1.0- μm aerosol at identical respiratory frequencies via either a mouthpiece or an endotracheal tube were performed (Swift et al., 1977a). A slightly higher lung deposition fraction was observed with mouthpiece inhalation [range (dependent on tidal volume) = 24-29%] compared to the tube (range = 20-27%). Breathing through an oral tube may result in less retention in the upper respiratory tract than would normal mouth breathing. In a study with humans, Wolfsdorf et al. (1969) compared the deposition of 2.8- and

6.0- μm water droplets following inhalation via mask or oral tube. The latter resulted in a reduction of upper respiratory deposition compared to mask breathing by approximately 37% for the smaller particles, and 39% for the larger. In human exposure tests, it has been found that even the specific configuration of the mouthpiece used in oral exposures can affect the extent of deposition in the upper respiratory tract and, thus, the degree of penetration into the lungs (Heyder et al., 1980).

The nasal passages are more efficient than the oral cavity in removing inhaled particles. Thus, if exposure bypasses the nose, increased lung deposition could result. A major factor influencing the relative difference in upper-respiratory-tract deposition efficiency between nasal and oral breathing is aerosol particle size distribution, since larger-sized particles would be more effectively filtered in the nose than would smaller ones (Schlesinger et al., 1983). For a polydisperse aerosol, oral inhalation could result in an increased number of larger particles penetrating the upper respiratory tract and reaching the lungs, compared to inhalation via the nose. Thus, both the actual amount and the size distribution of an aerosol entering the lungs would differ.

Basis for Comparisons

There has been no recent systematic comparison of regional deposition patterns between common experimental animals used in inhalation toxicologic studies and humans. Because of the factors just discussed, deposition studies reported in the literature were not all included in this survey, since the objective was to make intercomparisons as valid as possible. In any case, extrapolation between species must be performed with appropriate caution, since deposition data obtained under one set of experimental conditions may differ from data that would have been obtained under other conditions. The ground rules for inclusion of data in this review were as follows:

1. Only experimentally derived deposition values are presented in the figures; these must have been directly reported, or have been capable of accurate conversion to some common basis. Values derived from mathematical modeling studies were not used.

2. Only studies where regional deposition values as a function of amount of aerosol inhaled were provided, or could be derived, were included. This requirement limited those studies that could be used, since most described regional fractions as a percentage of total deposition rather than in terms of amount inhaled.

3. Only studies using nonhygroscopic, nonviable, nonfibrous aerosols were included. An aerodynamic size (or its equivalent) must either have been given, or must have been able to be derived, for particles $\geq 0.5 \mu\text{m}$; for aerosols with diameters $< 0.5 \mu\text{m}$, some diffusion-related diameter must have been available.

4. Although aerosols in some studies were not charge-neutralized, data using these were included. Electrical charges could increase deposition in certain regions over uncharged aerosols of the same size, and could also account for some of the variability between different studies using the same species with similarly sized particles.

Deposition Data

The deposition data are shown in Figs. 1-4; the key indicating the original sources is given in Table 1. All values are, unless otherwise stated, means, with standard deviations when available, and are expressed as a percentage of inhaled aerosol. In addition, all deposition data for the

TABLE 1. Key to Symbols Used in Figures

Human Deposition Panels		Animal Deposition Panels	
Lippmann and Albert (1969)	○	Kanapilly et al. (1982)	▲
Stahlhofen et al. (1981)	□	Wolff et al. (1982)	■
Chan and Lippmann (1980)	△	Wolff et al. (1981)	◆
Foord et al. (1977)	◇	Cuddihy et al. (1973)	●
Altshuler et al. (1966) ^a	◊	McMahon et al. (1977) ^e	
Heyder et al. (1980)	●	Palm et al. (1956)	△
Chan and Lippmann (1980) ^b	—	Raabe et al. (1977)	□
Lippmann and Altshuler (1976) ^b	- - -	Thomas and Raabe (1978)	◇
Lippmann and Altshuler (1976) ^c	- · - · -	Yeh et al. (1980)	○
Swift et al. (1977b) ^d	■	Moores et al. (1980)	▼
Hounam et al. (1969)	▲	Johnson and Zeimer (1971) ^f	▽
Heyder and Rudolf (1977)	◆	Boyland et al. (1947)	▲
Lippmann (1970)	▼	Davies (1946)	▣
Pattle (1961)	●	Gibb and Morrow (1962)	●
Giacomelli-Maltoni et al. (1972)	⊙	Craig and Buschbom (1975)	⊙
George and Breslin (1967)	▣	Davies (1946) ^g	◇
Landahl et al. (1952)	▲		
Altshuler et al. (1957)	◆		
Heyder et al. (1973)	▼		
Heyder et al. (1975)	⊙		
Landahl et al. (1951)	◐		
Heyder et al. (1982)	▣		
Muir and Davies (1967)	◆		
Martens and Jacobi (1974) ^d	⊙		
Lippmann (1977) ^b	- - -		

^a Mean and range of reported values.
^b Eyefit median through reported data.
^c Estimated deposition based upon difference in measured URT deposition under nose and mouth breathing.
^d Data based on one subject only.
^e Range of reported values.
^f Median and range of reported values.
^g Median.

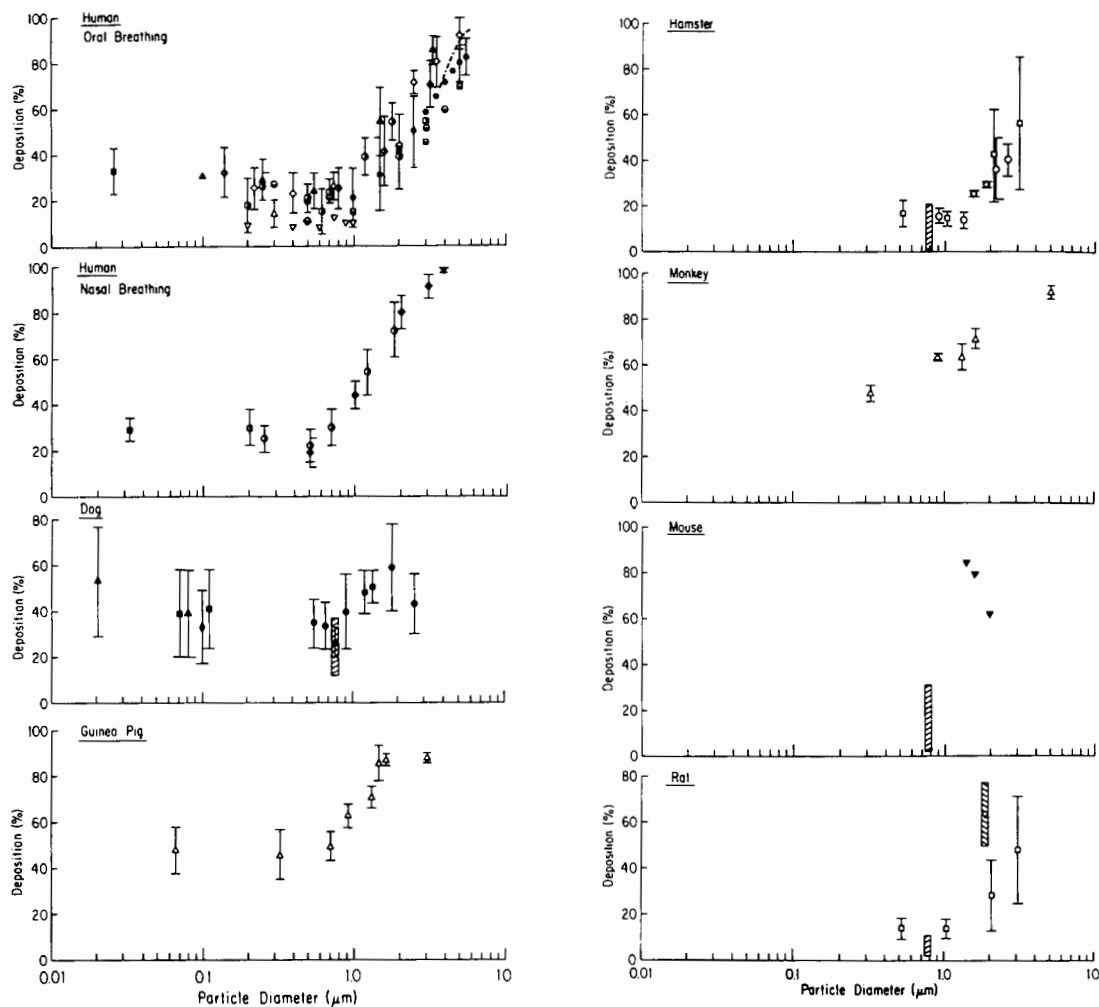


FIGURE 1. Total Respiratory-tract deposition.

experimental animals were based upon nasal breathing. Particle sizes $\geq 0.5 \mu\text{m}$ are MMAD or AMAD, while those $< 0.5 \mu\text{m}$ are a diffusion-equivalent size.

Total deposition. Figure 1 presents data for total respiratory-tract deposition. For humans, nasal inhalation results in greater deposition in the respiratory tract than oral exposures for aerosols with median diameters $> 0.5 \mu\text{m}$; this is due to enhanced upper-respiratory-tract deposition with the former mode. Both dog and guinea pig exhibit greater total deposition than nasal-breathing humans for aerosols $\leq 1 \mu\text{m}$, while for those $> 1 \mu\text{m}$, the dog shows less deposition than, and the guinea pig is similar to, humans. On the other hand, both rat and hamster show less total deposition than humans throughout the available particle size range. The monkey (*Macaca mulatta* and *M. cynomologus*) shows greater deposition than humans for particle sizes $< 1 \mu\text{m}$, and has a similar pattern for those $\geq 1 \mu\text{m}$.

Although there may be broad similarities in the patterns of total

deposition for experimental animals and humans, certain factors relevant to actual dose must be considered. If interspecific differences in breathing parameters and body weight are taken into account, it becomes evident that although some small animals may deposit less total mass of aerosol per unit exposure time than larger animals if each were exposed to the same aerosol size and concentration, the former will receive a greater deposition per unit body (or lung) weight per unit time than will the latter (Stauffer, 1975; Phalen et al., 1977). For example, for particles with D_{ae} of $1 \mu\text{m}$, the rat is predicted to receive an initial dose 5-10 times that of humans, and dogs 3 times that of humans, if deposition is calculated on a per unit organ or body weight basis (Phalen et al., 1977). This type of extrapolation is risky, however, since the actual amount of deposition may be different from that predicted due to avoidance behavior by animals during the exposure (Phalen et al., 1977).

Some interspecific differences in total deposition may be due to variations in airway size. Thus, what is termed a "respirable" aerosol may be species-dependent. For example, the limited data for mice indicate a decrease in total deposition with increasing particle size. This may occur because the larger sizes were less "respirable" by this small animal than by larger animals (Thomas, 1969).

Regional deposition. Figure 2 shows upper-respiratory-tract (URT) deposition. The data indicate substantial variability between different species, as well as large differences between individuals of the same species. A large part of the latter may be due to nasal geometry variation, which is known to occur in otherwise equivalent animals (Brain and Valberg, 1979), as well as to different breathing patterns during exposure. Note the large intraspecies variability in URT deposition at the large particle sizes subject to inertial impaction. This variability is likely responsible for a large portion of the intraspecies variation in total respiratory-tract deposition (Stahlhofen et al., 1981; Heyder et al., 1982).

The extent of URT removal may vary depending upon whether the aerosol used is mono- or polydisperse. For example, Thomas and Raabe (1978) compared the deposition in hamsters of $1.53\text{-}\mu\text{m}$ (AMAD) monodisperse aluminosilicate particles and a polydisperse aerosol of montmorillonite clay having a similar AMAD ($1.87 \mu\text{m}$). The major difference was that the latter deposited to a greater extent in the URT, due to the presence of a certain percentage of larger particles that were effectively removed by impaction. Total lung deposition of the two aerosols, expressed as a percentage of inhaled aerosol, was the same.

In humans, nasal inhalation results in enhanced URT deposition compared to oral inhalation. In all species shown, the available data indicate increases in deposition with increasing particle size above $1 \mu\text{m}$, although the apparent "rate" of deposition increase is not the same. Thus, in humans and dogs, deposition appears to plateau somewhat for sizes $> 2 \mu\text{m}$, while hamster, rat, and rabbit show rapidly increasing deposition.

The data indicate that URT deposition in nasal breathing humans for

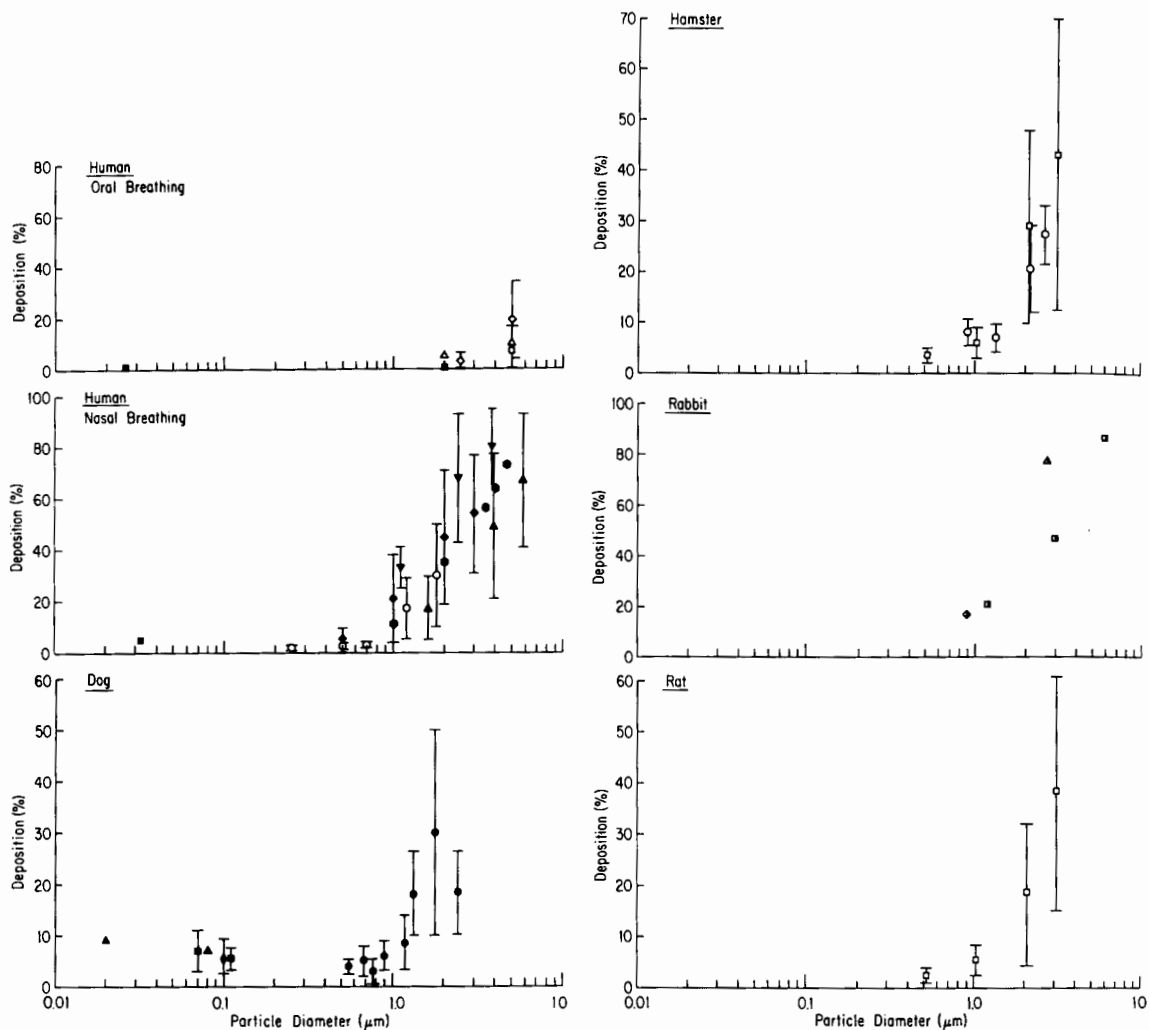


FIGURE 2. Upper-respiratory-tract deposition.

particles $> 1 \mu\text{m}$ is greater than in the experimental animals. This is not necessarily expected, since the nasal passages of the latter are more intricate than are those in humans and therefore should be more efficient particle collectors. However, the actual observations may be a reflection of exposure conditions. For example, many of the studies with experimental animals were performed under sedation or anesthesia, which would result in a rate of breathing slower than that of normal, awake animals. On the other hand, the human data are based upon studies in spontaneously breathing individuals. Since the dominant mechanism for deposition of particles $> 1 \mu\text{m}$ in the URT is impaction, low flow rates should reduce deposition efficiency. Since smaller particles can penetrate the URT at all flow rates, deposition for these is similar in all species. If URT deposition was plotted in a manner that would normalize for flow, the experimental animals would probably show greater URT deposition efficiency for larger particles than would humans at equivalent size-flow normalization parameters.

Although many experimental animals are obligate nasal breathers, large anatomical differences occur between species, resulting in differences in URT deposition due to geometrical and/or resultant air flow differences. Asset et al. (1956) examined URT deposition in the rabbit, dog, and guinea pig under identical exposure conditions by drawing an aerosol of 1.3- μm (MMD) triphenyl phosphate spheres through the nose and collecting it below the larynx of dead animals. The air flow rate used was the average velocity obtained during a single inspiration of a normally breathing animal, so the velocity of aerosol entering the nares differed between animals. The results were as follows, expressed as mean penetration of inhaled aerosol through the URT:

Rabbit	$92 \pm 7\%$
Dog	$85 \pm 2\%$
Guinea pig	$76 \pm 10\%$

These data highlight relative differences in URT collection likely due to anatomically related flow differences.

The less the deposition in the URT, the greater is the amount of aerosol available for removal in the lungs. Thus, the extent of URT removal may affect deposition patterns in distal regions.

For the tracheobronchial tree (TB), only very limited data are available for deposition in experimental animals; these are shown in Fig. 3. The data for TB deposition in nasal breathing humans are too few to permit development of a size-efficiency relationship. The panels indicate that the percentage of inhaled aerosol which is removed in the TB tree is greater in the orally breathing human than in nasal breathing dog, hamster, or rat, at least in the limited region where there is particle size overlap. As mentioned previously, a lower TB deposition in experimental animals may be a reflection of greater URT deposition. On the other hand, the differences may be due to greater turbulence in airflow in the upper bronchial tree in humans, and/or to differences in airway branching patterns.

The larger size of human bronchial airways compared to those in most experimental animals results in higher Reynolds numbers for the same flow velocities in the former. As a result, turbulent flow may occur in large airways in humans at moderate to high rates of ventilation and can contribute greatly to particle deposition, but should be rare or absent in monopodial branching systems. Another anatomic difference between humans and experimental animals may also contribute to relatively less upper bronchial airway deposition in the latter. The animals' tracheas are much longer in relation to their diameters than is the human trachea. Thus, the turbulence introduced by jet flow through the larynx is much less likely to persist into the bronchi and contribute to particle deposition in the lungs of the former, since a long trachea facilitates the establishment of a more parabolic flow profile.

In all cases, especially in the experimental animals, there is not as well a defined relation between deposition and particle size as that observed in

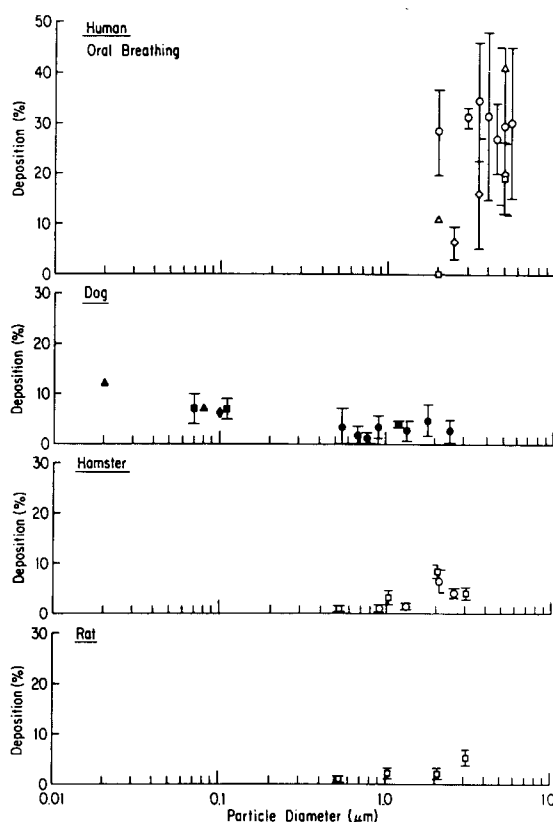


FIGURE 3. Tracheobronchial-tree deposition.

other respiratory tract regions. However, TB deposition does appear to decrease as particle size decreases from $\sim 5 \mu\text{m}$ to $2 \mu\text{m}$. This relative insensitivity of efficiency with size may be a function of the monopodial branching pattern in the experimental animals. In this system, airways having considerable diameter differences may be found in the same branching level, and at the same distance from the trachea. In humans, the sizes of airways in any generation are more similar. Thus, a monopodial system could result in a constant size-deposition relationship over a fairly wide particle size range.

Deposition in the alveolar (AV) region (i.e., distal to the last ciliated airway) is shown in Fig. 4. In general, deposition increases as particle diameter decreases, after a minimum deposition is reached. However, removal of aerosol in more proximal airways determines the shape of these curves. Thus, for particles $\geq 1 \mu\text{m}$, increased URT and TB retention results in a reduction of AV deposition occurring more sharply in smaller animals than in humans. This is due not necessarily to a reduced AV deposition efficiency above this size but to the fact that only a small fraction of these large particles reach the lower respiratory tract in these animals due to removal in more proximal regions. Similarly, nasal breathing in humans results in less penetration of larger particles to the alveoli;

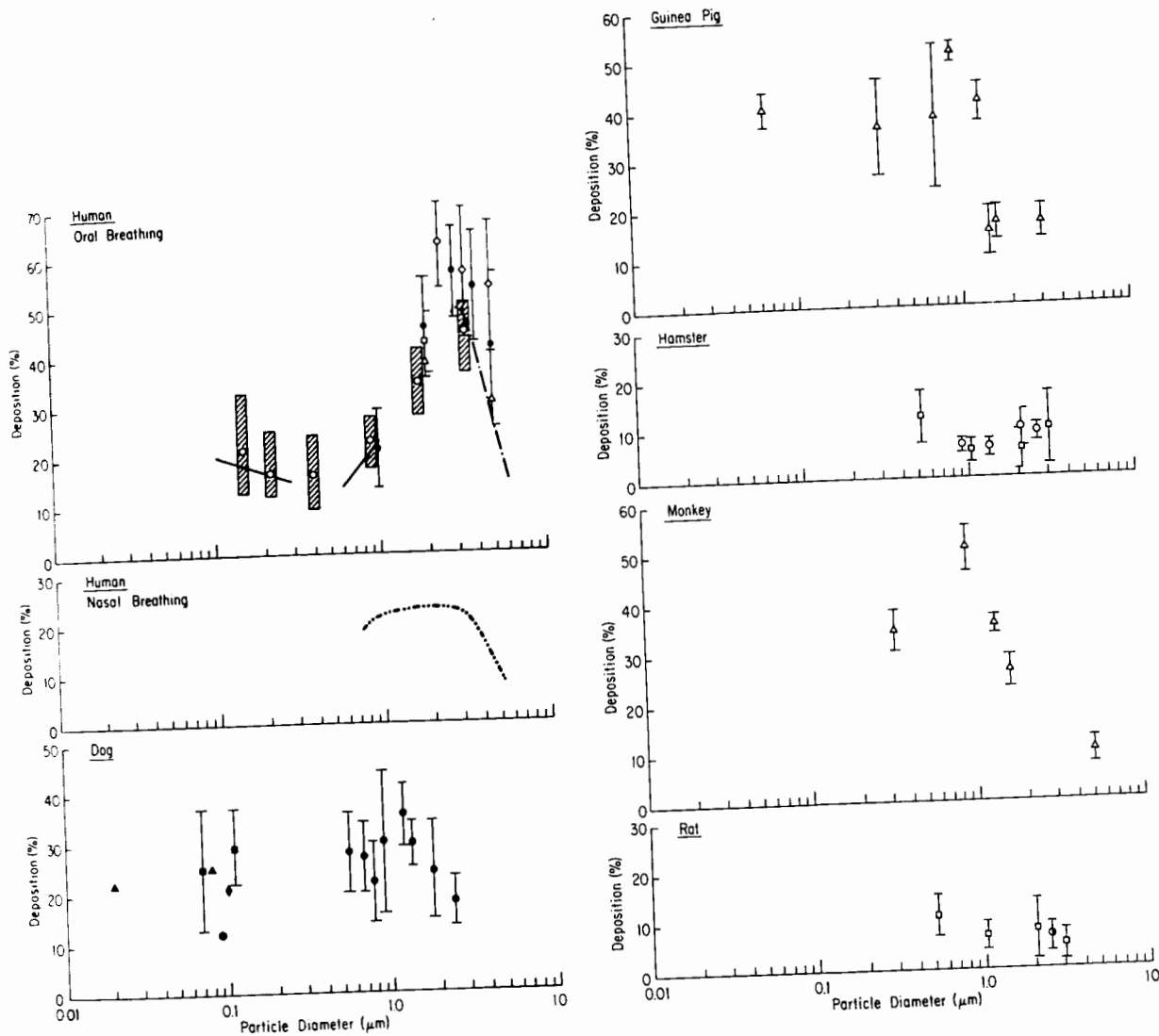


FIGURE 4. Alveolar-region deposition.

thus, there is a lesser fraction of deposition for entering aerosol than for oral inhalation.

Hamster and rat, similar to each other, showed much less alveolar deposition than dog, guinea pig, monkey, or human. Alveolar deposition in nasal-breathing humans is less than these three species, but for oral inhalation, patterns are similar, although the particle size for peak deposition is greater in humans than in the monkey, guinea pig, or dog. This is probably due to the more efficient removal of larger particles in the smaller URT and TB airways of these experimental animals.

CONCLUSIONS

The deposition of inhaled aerosols occurs by similar physical mechanisms in humans and those experimental animals commonly employed in

toxicological analyses. From a critical review of the literature, however, it is evident that interspecific differences in particle size-deposition efficiency relationships may occur in various regions of the respiratory system; these are due to anatomical, physiological as well as experimental factors. Nevertheless, the following generalizations may be made.

1. The relationship between particle size and total respiratory tract deposition is quite similar in humans and most of the experimental animals presented. Deposition increases on both sides of a size minimum, which is at $\sim 0.5\text{-}0.9\ \mu\text{m}$.

2. In all species shown, URT deposition efficiency approaches 0 within the particles size range of $\sim 0.5\text{-}1.0\ \mu\text{m}$. Very small particles ($< 0.1\ \mu\text{m}$), however, may have enhanced URT deposition.

3. The data for TB deposition indicate fairly low, relatively constant efficiencies in this region for the size range of $0.1\text{-}5.0\ \mu\text{m}$, especially in the experimental animals. The apparently low efficiencies may be due to some extent to prior removal in the URT and/or to geometric differences between these animals and humans.

4. Alveolar region deposition efficiency appears to reach a peak at a lower particle size ($\sim 1\ \mu\text{m}$) in experimental animals than in humans ($\sim 2\text{-}4\ \mu\text{m}$).

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