Respiratory Deposition and Inhalability of Monodisperse Aerosols in Long-Evans Rats

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Because of limitations on conducting exposure experiments using human subjects to evaluate adverse health effects, the deposition and fate of airborne particles in animals are often studied. The results of such studies are extrapolated to humans to estimate equivalent dose and subsequent response. In this article, particle inhalability and respiratory deposition of micron-size particles are determined for female Long-Evans rats. Monodisperse aerosols were generated from a solution of radiolabeled iron chloride ($^{59}$FeCl$_3$). Long-Evans rats were exposed to the radiolabeled particles in a Cannon nose-only exposure tower to determine head, lung lobar, and total lung deposition fractions. Particle deposition fractions in a hypothetical situation, when all particles are inhalable, were found from an experimentally validated deposition model. Particle inhalability in a Cannon nose-only exposure scenario was obtained by comparing the measured deposition fractions with the predicted values for the case of 100% inhalability. Particle deposition fraction and inhalability were compared with data available in the literature. For large particles, the measured deposition fraction was lower than the literature values. Consequently, our inhalability estimates were found to be lower than previously published values. The findings here will directly affect health risk assessments in humans from exposure to airborne particles. The deposition results will improve the database on particle deposition in the lung airways of rats, and inhalability information will improve the accuracy of rat-to-human data extrapolation.

Key Words: aerosol; deposition; inhalability; Long-Evans rats; mathematical modeling.

The adverse health effects of exposure to airborne particulate matter (PM), particularly among sensitive subpopulations, have been recognized in recent years (Bascom et al., 1996; Brunkereef et al., 1995; Dockery and Pope, 1994; Hruba et al., 2001; Jedrychowski et al., 1999; McConnell et al., 1999; Norris et al., 1999; Pope et al., 1995a,b; Roemer et al., 2000; Schwartz, 1994; Schwartz and Neas, 2000). To assess potential health risks of PM exposure, one must first determine the initial deposition and subsequent clearance of inhaled material. Studies have been conducted to measure the fate of PM in animals and humans. In addition, morphologically based mathematical models have been developed to predict and extrapolate dose (deposition plus clearance) across species from animals to humans. Predictive models are particularly useful when data are not available and conducting experiments is not feasible. Dosimetry models can be tied to biological end points to construct comprehensive, biologically based dose-response models for use in PM risk assessment.

To exert harmful effects, inhaled particles must deposit in lung airways and translocate to various sites and organs in the body to yield response. Thus the fate of inhaled particles in the respiratory tract, as the initial port of entry in the body, is a critical first step toward realistic risk assessment for exposure to airborne particles. Due to ethical obligations or legal restrictions, studies in humans are limited. There is a wealth of information in the literature on exposure studies using rodents to study and model deposition, translocation, and response. However, weak links exist in the process of extrapolation of animal results to humans. For example, there are uncertainties regarding the selection of a relevant dose-metric between humans and animals. The uncertainties arise from differences in airway morphology, biological sensitivities, and breathing parameters. Equivalent rather than identical exposure scenarios are required to yield an equal dose in animals and humans since particles completely inhalable by humans may be only partially inhalable by rodents. In addition, nasal filtration, which controls the number of particles that reach the deep lung and are available for deposition, may vary considerably between humans and rodents. Thus, information on particle inhalability and regional deposition in rodents is critical in studying the adverse health effects posed to humans from exposure to airborne particles and to performing appropriate risk analyses. Regional deposition fractions can be found from direct measurements, and information on particle inhalability can be obtained from particle deposition studies in control studies. Particle inhalability is found by comparing particle deposition fractions between scenarios where particles are all inhalable and a fraction of particles are inhalable.

The lack of inhalability information on airborne particles could increase the variability of the deposition data as well as introduce errors in interspecies dosimetric comparisons. For

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nasal breathing, particle inhalability is essentially the sampling or aspiration efficiency of the nasal opening and generally limits the number of particles entering the respiratory tract (Vincent, 2002). Inhalability, therefore, depends in part on the size and orientation of the nasal opening and is different between humans and animals. Particles that are completely inhalable by people may be only partially inhalable by animals. Realistic extrapolation of deposition data from animals to humans should include an inhalability adjustment. There is considerable information on the inhalability (or aspiration efficiency) in humans (Aitken et al., 1999; Breyesse and Swift, 1990; Erdal and Esmen, 1995; Hsu and Swift, 1999; Kennedy and Hinds, 2002; Ogden and Birkett, 1977; Vincent and Armbruster, 1981; Vincent et al., 1990). However, additional studies are necessary to correlate inhalability, since particle aerodynamic properties and subject breathing parameters are both important in determining inhalability.

The database on particle inhalability in animals is inadequate. No experimental study has been designed specifically for determining inhalability. The study by Menache et al. (1995a) is the only study to date that offers inhalability adjustment curves, which were based on the particle deposition data of Raabe et al. (1988) for various laboratory animal species. Since particles larger than 3.5 μm showed a decrease in total deposition, Menache et al. (1995a) assumed that these particles deposited completely in the lung and that the ratio of the internal dose to inhaled mass represented particle inhalability. Due to the lack of sufficient data across particle size, the data of various rodents were combined to calculate a single inhalability curve.

Due to experimental difficulties associated with measurement of particle deposition, few studies have addressed both the deposition of fine and coarse inhalable particles in rats. Chen et al. (1989) measured regional, lobar, and total deposition of cigarette smoke in Fischer-344 rats, exposed nose-only, for 25 min a day for 5 days. Dahlbäck and Eirefelt (1994) and Dahlbäck et al. (1989) exposed male Sprague-Dawley rats to particles in a nose-only tower for 10 min and measured total deposition fraction and distribution in the lung. Raabe et al. (1977, 1988) studied deposition of various sized particles in different regions of the respiratory tracts of common laboratory species, including Long-Evans rats. These carefully conducted studies did not measure minute ventilation of the test animals (Raabe et al., 1988), which is essential for a precise assessment of deposition. For large particles, deposition in the head region is largely by impaction. This means that losses mainly depend on the particle Stokes number, which, in turn, depends directly on the animal’s ventilatory parameters. Raabe et al. (1977, 1988) used allometric equations to determine breathing rates rather than measuring the animal’s ventilatory parameters. In addition, since particle clearance in most nasal regions is rapid, particle deposition studies have to be of short duration. This requires a generation system that produces a high concentration of monodisperse particles (10⁶/cm³) to give measurable deposition during this period. In the aforementioned studies, some of these points were not addressed fully, thereby increasing variability of the results.

A number of studies have been published on modeling particle deposition in the rat lung. These models are semiempirical (Menache et al., 1995b), stochastic (Koblinger et al., 1995), or deterministic (Schum and Yeh, 1980; Yu and Xu, 1986). Deterministic models are most often typical-path, and are therefore based on symmetric lung structures. Typical-path deposition models cannot address variation of dose among different airways at a given generation. Anjilvel and Asgharian (1995) introduced a new generation of the mathematical model of particle deposition in the lung. They calculated particle deposition using a multiple-path analogy operative for any lung geometry structure. This model gave a more realistic prediction of deposition, since variations of deposition among different airways of the lung were innately calculated. The deposition model calculated particle deposition in every airway of the lower respiratory tract (LRT) from the information on breathing rate, lung parameters (e.g., airway length and diameter, branching angle), and deposition efficiencies per airway. Site-specific, lobar, regional, and total deposition fractions were calculated by adding deposition fractions of the individual airways.

Realistic PM deposition and clearance models for animals that incorporate physical phenomena require accurate lung geometries as input. Although one of the most commonly used laboratory animals is the rat, a set of structural data comprising the entire respiratory tract for any strain of rat is currently not available. Different strains of rats have been used for measurements of structure in different regions of the respiratory tract. For example, a detailed reconstruction of nasal geometry was developed for the Fischer 344 rat (Kimbell et al., 1993), while numerous anatomical measurements of the conducting airways of a Long-Evans rat were made by Raabe et al. (1976). In addition, the acinar region, for which structural data are extremely difficult to obtain, has been reconstructed for Sprague-Dawley and CD-1 rats (Mercer and Crapo, 1988).

Despite progress on particle deposition in the lungs of rats, a significant data gap remains to be filled. A unified dataset on lung structure in a given strain of rat is desirable. Particle deposition in various regions of the lung, as well as inhalability fraction, must be established. This article details a study conducted to measure deposition and inhalability of particles in the respiratory tract of the Long-Evans rat, which was selected for this study because of the availability of anatomical data for its conducting airways and because this data set was used in a mathematical dosimetry model to calculate particle deposition in the rat lung (Anjilvel and Asgharian, 1995). Particle deposition fraction in the nasal passages and in various lobes and regions of the Long-Evans rat lung was measured following a nose-only exposure to radiolabeled monodisperse particles. Rat inhalability fraction was obtained by comparing lung deposition measurements with predictions.
MATERIALS AND METHODS

Animals. Fifty-five female Long-Evans rats were obtained from Charles River Breeding Laboratories (Raleigh, NC). The rats were certified to be free of respiratory disease and had a mean body weight of 298 g (± 24 g). Animals were housed, two per cage, in 48 × 27 × 20-cm polycarbonate cages with Alpha-dri bedding (Shepherd Specialties Paper, Kalamazoo, MI). The temperature in the animal rooms was maintained at 20 ± 5°C, with a relative humidity of 50 ± 15%. Animals were kept on a 12-h light cycle (0700–1900 h). Food (NIH-07 pelleted diet, Zeigler Bros., Gardener’s Point, PA) and reverse-osmosis water were provided ad libitum.

Aerosol generation and characterization. A condensation monodisperse aerosol generator (CMAG) (Model 3475; TSI Inc., St. Paul, MN) was used that produced monodisperse, radiolabeled aerosols with aerodynamic diameters ranging from 0.9 to 4.2 μm (0.9, 1.3, 1.9, 2, 2.3, 2.6, 2.7, 3.1, 3.4, 3.6, and 4.2 μm). Aerosol diameters had an average geometric standard deviation \( \sigma_g \) of 1.12 (all values of \( \sigma_g \) were less than 1.18), reflecting monodisperse aerosols. Radiolabeled particles were formed in the CMAG by heterogeneous condensation of triphenyl phosphate (TPP) with a density of 0.95 g/cm³ (Tomaides et al., 1971) onto radioactive iron chloride seed particles. Iron chloride solution with gamma-emitting \(^{59}\text{Fe}\) of 44.6 days half-life and a specific activity of about 20–30 mCi/mg was purchased from Perkin Elmer Life Sciences, Inc. (Boston, MA) as iron chloride in 0.5 M hydrochloric acid.

The \(^{59}\text{Fe}\) solution was transferred to an atomizer inside the CMAG and diluted with distilled water to a concentration of 12 to 16 mg/L. Compressed air was delivered to the atomizer using a setting of 60 psi. The resulting aerosol was diffusion-dried and then bubbled through a temperature-controlled saturator containing heated TPP. The mixture of dry \(^{59}\text{Fe}\) seed aerosol and TPP vapor leaving the saturator entered a condensation chimney where TPP condensed into particles with a radioactive \(^{59}\text{Fe}\) core. Monodisperse aerosol was sampled from the condensation chimney and delivered to the exposure system. Desired particle sizes were achieved by controlling the concentration of TPP vapor and \(^{59}\text{Fe}\) seed aerosol in the condensation chimney. Particle size was monitored during animal exposures with an aerodynamic particle sizer (APS) (Model 3320; TSI Inc., St. Paul, MN).

Exposure system. A schematic diagram of the exposure apparatus is shown in Figure 1. Aerosol, pumped from the CMAG by a peristaltic pump (Masterflex® Model No. 7565, Cole Parmer Instrument Co, Chicago, IL), was combined with filtered air generated with a house air source and delivered at a constant flow rate using a mass flow controller (MKS Instruments, Model 246B, Andover, MA). A fraction of this flow was diverted to an APS; the remaining flow, approximately 4.5 l/min, was delivered to a 52-port, Cannon nose-only tower (Lab Products, Maywood, NJ). Seven ports of the tower were used for experimental purposes (5 for animal exposure, one for a filter sample, and one for a pressure gauge); the unused ports were plugged. Therefore approximately 640 mℓ/min of aerosol flow was delivered to each port.

Aerosol from one port of the nose-only tower was collected on a 47-mm glass filter (0.5 μm Prefilter, Osmonics Inc., Minnetonka, MN) during exposure. A constant flow rate through the filter was maintained using a mass flow controller and house vacuum source. A slightly negative pressure (−2.5 mm of water) was maintained in the nose-only tower by controlling the vacuum pump on the tower with a rotameter and monitoring pressure in one port (Fig. 1) with a differential pressure gauge (Magnehelic®, Dwyer Instrument Co., Michigan City, IN).

Five female Long-Evans rats were loaded into nose-only tubes (Skornik Plethysmograph, CH Technologies Inc., Westwood, NJ) 10–15 min prior to an exposure event. An exposure event involved exposing 5 rats to a single size of monodisperse, radiolabeled aerosols for a given period of time. A total of 11 exposure events were conducted. The length of exposure ranged from 10 to 17.5 min, with an average of 12 min. Exposures times were chosen to enable depositing sufficient radioactivity for detection in airway tissues while minimizing the time for nasal and TB clearance. Immediately following cessation of exposure, animals were killed by CO₂ asphyxiation, and relevant tissues (i.e., nasal passage, larynx, esophagus, trachea, lung lobes, stomach, and duodenum) were dissected. The dissection involved isolating an entire lobe or region of the respiratory or digestive tract, not just a representative sample; total activity in a lobe or region was counted and used to estimate deposition.

Breathing measurements. Animal respiratory parameters were monitored for a 5-min period prior to aerosol exposure and continuously during exposure. Each animal was placed in a nose-only tube with an opening through a screen pneumotachograph in the back end of the tube. The animal’s nose was led through a latex collar placed near the nose-only tube entrance, creating an airtight seal (Fig. 2). During breathing, contraction and expansion of the animal’s thorax forced air into and out of the chamber through the pneumotachograph, thereby causing periodic changes in chamber pressure. Measurements of respiration were made using a conventional data acquisition system (Busasco Electronics, Sharon, CT) by monitoring fluctuations in chamber pressure and calibrating pressure fluctuations to volume displacements.

Deposition fraction. Following exposure and necropsy, deposited gamma radioactivity was measured in dissected tissues by scintillation counting. A 7.62-cm NaI(Tl) detector was used in a computer-controlled gamma counting system (Cobra Model 5003, Packard Instrument Company, Downers Grove, IL). Energy emissions between 940 and 1400 keV were measured in each tube for 2 min. Energy emitted outside this range was not related to \(^{59}\text{Fe}\), whose principal gamma photons are 1099 (56%) and 1292 (44%) keV. Background radiation was accounted for by subtracting the activity measured in an empty sample tube from that measured in each tissue sample.

Each dissected tissue was placed in a single sample tube except for the nasopharynx and stomach. Since these tissues were each too large to fit into a single sample tube, the nasopharynx and stomach tissues were split into two tubes. Tissue samples were stored at −20°C before analysis.

Deposition fraction of inhaled material per breath of animal is a unique quantity as long as breathing parameters and lung geometry remain the same.
Deposition fraction is defined as the amount of material deposited in the tissue divided by the amount of the material inhaled. Deposition fraction depends on particle aerodynamic properties, lung geometry, and breathing parameters of each animal and varies among different regions of the lung. Deposition fraction is determined by dividing the activity counted in each tissue sample by the activity counted on the filter sample that collected aerosol from the exposure atmosphere. The following formula, which accounts for differences in sampling rate of the animals and filter sample, was used to calculate the deposition fraction:

\[
DF_i = \frac{A_i Q_{fs}}{A_{fs} MV t_{fs} t_{exp}}
\]

where \(DF_i\) is the deposition fraction in the \(i\)th airway, \(A_i\) the activity in the \(i\)th airway, \(A_{fs}\) the activity on the filter sample, \(Q_{fs}\) the filter sample flow rate, \(MV\) the animal minute volume, \(t_{fs}\) the filter sampling time, and \(t_{exp}\) the exposure time.

The exposure time, filter sampling time, and flow rate were set during each exposure event. These values plus the measurements of \(A_i, A_{fs}\), and animal breathing parameters were used in Equation (1) to determine the deposition fraction in each animal per exposure event.

**RESULTS AND DISCUSSION**

Since both impaction and sedimentation mechanisms contribute to the deposition of fine and coarse particles in the lung, particle deposition in the lung depends on several parameters such as particle diameter, breathing parameters, and particle inhalability. Particle deposition in the lung of a single animal can be justifiably plotted as a function of particle diameter when other variables just mentioned remain constant. The deposition fractions in the left lung and caudal, medial, cranial, and accessory lobes of the right lung were plotted against particle aerodynamic diameter in Figures 3A–3E. Deposition patterns were similar among the lobes of the lung. Consistent with model predictions (Anjilvel and Asgharian, 1995), particle deposition is expected to increase with particle diameter, reach a maximum, and decline thereafter due to the filtering effects of the upper respiratory tract. This trend was also observed in the deposition measurements of Raabe et al. (1988) in Fischer 344 rats (Menache et al., 1995a). A general trend was observed (Figs. 3A–3E) despite intersubject variability, differences in breathing parameters, and particle inhalability in particular, which somewhat smeared the expected pattern of deposition fraction with particle diameter.

Each lobe of the lung received a different amount of deposition since deposition correlates with lobar volume. This is evident by comparing mean deposition fractions in different lobes of the lung (Fig. 3). Basically, the left lung received higher deposition than each lobe of the right lung. In the right lung, the caudal and accessory lobes had the highest and lowest deposition, respectively. Depositions in the right medial and right cranial lobes were similar. This information is useful in
the lobe selection for dissection to study physical and biological end points.

The mean and standard deviation of the head and lung deposition fractions in Long-Evans rats were plotted against particle diameter (Fig. 4). Head deposition fractions showed an increase followed by a decrease with particle size. Variability in the data prevented identifying the particle size at which maximum head deposition fraction was achieved. Most deposition occurred in the nasal passages. Due to strong filtering in the head and inertial losses in the upper airways of the LRT, particle deposition in the lung appeared to remain relatively constant. The lung deposition fraction was below 10% for most particle sizes. Considerable variation in deposition results was observed, since each animal had different breathing parameters and head orientation in the nose-only tube, which would alter particle inhalability.

Total deposition fraction results in the respiratory tract were compared with the results of Raabe et al. (1977, 1988). The initial data of Raabe et al. (1988) showed a decrease in deposition with particle size for particles larger than about 3 or 4 μm but was adjusted to 100% deposition. Menache et al. (1995a) used the original data of Raabe et al. (1988) and recalculated deposition fractions. The values given by Menache et al. (1995a) are shown here in Figure 5, along with the results of the present study. There was a good agreement between the results for particles of submicron and micron size. For particles of 3 to 10 μm, however, the deposition values of Menache et al. (1995a) were significantly greater than those of the current study. An uncertainty in the recalculated values of Raabe et al. (1988) by Menache et al. (1995a) arose from the lack of breathing-parameter measurements that were required to calculate the amount of inhaled material. Instead, the authors used the expression by Guyton (1947), which was for a resting animal, to estimate breathing parameters. This equation underestimates an animal’s minute ventilation during a nose-only exposure. The minute ventilation in the study of Raabe et al. (1988) was calculated to vary between 85 and 140 cm³/min, which is clearly lower than our measurements (Table 1) despite animals in the two studies having similar weights. The measured breathing parameters in Table 1 are consistent with the measurements of Mauderly (1986). The deposition data of Menache et al. (1995a) are probably high due to underestimation of animal breathing parameters, which resulted in underprediction of inhaled dose and over-prediction of deposition fraction.

Our findings as well as others (Dahlbäck and Eirefelt, 1994; Raabe et al., 1988) showed a decrease in total particle deposition, with increasing particle size for micron-size particles.

![FIG. 4. Regional head and lung deposition fraction of particles in Long-Evans rats as a function of particle diameter. Each measurement indicates the mean particle deposition fraction (± standard deviation) for five animals, each having different breathing rates.](image1)

![FIG. 5. Comparison of total deposition fraction with available relevant data in the literature. Values provided by Menache et al. (1995a) are recalculation of the measurements made by Raabe et al. (1988).](image2)

**TABLE 1**

<table>
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<tr>
<th>Average of the Animal Breathing Parameters for Each Exposure Event</th>
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<tr>
<td><strong>Particle diameter (μm)</strong></td>
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*Note. Values are average ± standard deviation.*
This trend can be readily explained in terms of particle inhalability (Menache et al., 1995a). When the particle exceeds a certain size in a given breathing scenario, the inertia reduces the probability of a given-sized particle entering the respiratory tract. The inhalability (or aspiration efficiency) can be calculated from comparison of the deposition measurements with theoretical prediction of deposition at different sizes. Menache et al. (1995a) assumed that particles larger than 3.5 μm had 100% deposition in the respiratory tract, and thus inhalability was computed as the ratio of deposited to inhaled material for particles larger than 3.5 μm. However, particle size transition from 100% inhalable to partially inhalable does not necessarily start at 100% deposition fraction. The analyses neglected the group of particles that have deposition fractions of less than 100% but were partially inhalable. Deposition measurements for the entire inhalable size range are necessary to accurately assess inhalability. The study of Raabe et al. (1988) used few particle sizes and excluded particle sizes in the interval from 1 to 3 μm.

Inhaled particle concentration may be less than that in the exposure air for fine and coarse particles. Particle inhalability depends on particle size as well as on breathing parameters and is calculated using the following equation,

\[ IF = \frac{DF}{\Delta} \] (2)

where DF and Δ are the measured and theoretical (100% inhalable) lung regional or total deposition fractions (see Appendix for derivation). Values for Δ can be found from studies where 100% of particles are inhalable or, alternatively, from experimentally validated mathematical models.

Anjilvel and Asgharian (1995) introduced a mathematical model of particle deposition in the lungs of rats based on the morphometric lung measurements of Long-Evans rats (Raabe et al., 1976). The model was used here to calculate Δ based on the measured breathing parameters of the animals in the study. Inhalability was calculated from Equation 2 and plotted against the inertial parameter \( \rho d^2 Q \) in Figure 6, where \( \rho \) is particle density, \( d \) is particle diameter, and \( Q \) is inhalation flow rate. The parameter \( \rho d^2 Q \) combines particle diameter and breathing parameters and is a measure of particle inertia. Due to experimental variability, a number of calculated inhalability values were higher than 100%. These values were not included here. The calculated inhalability fractions showed variability with \( \rho d^2 Q \), but there was a decline in inhalability with increasing \( \rho d^2 Q \). A predictive model of inhalability in Long-Evans rats was found by fitting a function of the form similar to that given by Menache et al. (1995a) to the data.

\[ IF = 1 - \frac{1}{1 + \alpha(\rho d^2 Q)^\beta} \] (3)

Equation 3 has the same functional form as that of Menache et al. (1995a), with the difference of dependence on \( \rho d^2 Q \) in place of particle diameter. Fitting Equation 3 to the measurements yielded \( \alpha = 19.87 \) and \( \beta = -0.7466 \) with \( r^2 = 0.46 \). This equation has the right behavior by approaching 1 for small particles and 0 for large particles. While some studies in humans suggested that inhalability reached a plateau for sufficiently large particles (Aitken et al., 1999; Chung and Dunn-Rankin, 1992; Erdal and Esmen, 1995), this equation showed that inhalability became negligible around 50 μm.

The inhalability fraction computed by Equation 3 was compared with the results of Menache et al. (1995a) in Figure 7 for various particle sizes. Equation 3 was plotted for slow, normal,
and fast breathing, corresponding to a minute ventilation of 3.33 cm$^3$/s, 7.14 cm$^3$/s, and 14 cm$^3$/s respectively. The inhalability prediction of Menache et al. (1995a) gave a higher prediction of inhalability, because their expression was based on the deposition data of Raabe et al. (1988), which overestimated deposition (Fig. 4). Raabe et al. (1988) also used a different exposure system for which particle inhalability could have been different, depending on the orientation of incoming exposure air with respect to the nose of the animals.

The study presented here provides data on lobar and regional deposition of particles in Long-Evans rats. The results can be used to advance and validate lung deposition models and correlate dose with biological effects in animals. The information on particle inhalability helps with data extrapolation to humans, where it has an impact on multiple disciplines (e.g., the regulatory arena for desiring to minimize the deposition of the inhaled pollutant and the pharmaceutical industry for maximizing deposition of a therapeutic drug by selecting certain particle sizes).

Summary

Deposition of radiolabeled monodisperse particles in the lungs of Long-Evans rats was measured following a short exposure to particles ranging in size from 0.9 to 4.2 μm in a Cannon nose-only exposure system. The breathing rates for all the animals were measured during the exposure and were used to calculate the lobar and regional deposition fractions. Deposition patterns were found to be similar among the various lobes, giving a maximum deposition for particles near 3.5 μm. The caudal and accessory lobes gave the highest and lowest deposition of particles in the right lung, while the medial and cranial had similar deposition falling between the two limits. Our deposition fractions agreed with the literature values for particles smaller than 3 μm but fell short of those for larger particles, because the breathing parameters used to calculate deposition were low and resulted in overestimation of deposition values. The particle deposition fraction decreased with particle size because of an inhalability limitation that increased with particle size. A new expression based on the deposition results was introduced for inhalability fraction prediction. This expression predicted smaller inhalability of particles than the previously used results of Menache et al. (1995a). The difference in inhalability results was attributed to the difference in deposition datasets used to construct the inhalability curves.

APPENDIX

An increase in particle size makes it more difficult for a particle to enter the respiratory tract on inhalation. Only a fraction of particles in the inhaled air will be able to make it into the respiratory tract. The transport of the particles in a compartmental representation of the respiratory tract is depicted in Figure A-1. Due to partial inhalability, particle concentration initially decreases from the concentration in the exposure air, $C_a$, to that entering the body, $C_1$. Particle inhalability fraction is thus

\[ IF = \frac{C_i}{C_a} \]  \hspace{1cm} (A1)

Particles enter the head airways at $C_i$, and exit at $C_1$, enter the lung and exit at concentration $C_2$, and enter the head region again before exiting the respiratory tract at a concentration $C_3$. Since $C_3$ is larger than $C_1$, measured deposition fraction, DF, is smaller than theoretical deposition fraction $\Delta$ when a fraction of the airborne particles enters the respiratory tract. Deposition fractions for the entire respiratory tract are calculated as below:

\[ \Delta_t = 1 - \frac{C_i}{C_3} \]  \hspace{1cm} (A2)

\[ DF_t = \frac{C_i - C_1}{C_i} \]  \hspace{1cm} (A3)

where subscript t denotes total deposition fraction. Taking the ratio of equations A2 and A3 and replacing $C_i/C_3$ with IF from equation 1 gives

\[ IF = \frac{DF_t}{\Delta_t} \]  \hspace{1cm} (A4)

The theoretical and measured deposition fractions in the lung compartment are

\[ \Delta_L = \frac{C_i - C_2}{C_i} \]  \hspace{1cm} (A5)

\[ DF_L = \frac{C_i - C_2}{C_o} \]  \hspace{1cm} (A6)

Taking the ratio and inserting the definition of inhalability fraction yields

\[ IF = \frac{DF_L}{\Delta_L} \]  \hspace{1cm} (A7)

Similarly, the inhalability fraction using the head compartment deposition fractions can be shown to be

\[ IF = \frac{DF_h}{\Delta_h} \]  \hspace{1cm} (A8)

The measurements for regional and total deposition fraction, along with the predicted deposition fractions for 100% particle inhalability, were used in equations A4, A7, and A8 to calculate inhalability fractions.

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