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REVIEW ARTICLE

Deposition of aerosol particles in human lungs: *in vivo* measurement and modelling

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Abstract

The deposition dose and site of inhaled particles within the lung are the key determinants in health risk assessment of particulate pollutants. Accurate dose estimation, however, is a formidable task because aerosol transport and deposition in the lung are governed by many factors whose precise workings are often not fully understood. *In vivo* human data obtained under controlled environment are most important and provide the primary basis of estimating lung doses. The existing database, however, is not sufficient to cover widely varying exposure conditions encountered during daily activities. Mathematical models thus are used to fill the gap or to extend the range of experimental data and are further used as a tool for analysing the exposure–dose relationship under varying inhalation conditions. In this report we briefly review and discuss our recent studies of *in vivo* measurement of inhaled particles in normal subjects, subsequent analysis of the data for empirical modelling and an improved mathematical model that can be used for a wide range of applications.

Keywords: *Aerosol deposition; lung dose; inhalation; particulate matter; mathematical model*

Introduction

Deposition of inhaled particles in the lung is one of the key factors for assessing toxic effects of airborne pollutant particles on the one hand and for evaluating the efficacy of inhalant drug aerosols on the other. Lung deposition is governed primarily by particle size, breathing pattern and lung morphology. Estimating accurate doses in real-life situations, however, is a formidable task because the factors affecting lung deposition vary widely in time and space and specific values of each factor may or may not be known at the time of exposure. Dose estimation is primarily based on *in vivo* human data obtained under controlled inhalation conditions. Many earlier studies have reported lung deposition values measured in healthy adult subjects (Heyder et al. 1986, Stahlhofen et al. 1989). The scope of the studies, however, is limited to a small number of subjects and a few typical breathing patterns. In our recent studies, lung deposition was measured in a large number of subjects of both men and women and for a wide range of particle sizes and breathing patterns (Jaques & Kim 2000, Kim & Hu 2006). Regional deposition was also measured using a novel serial bolus delivery method showing detailed deposition distribution patterns along the sequential volume compartments of the respiratory airways (Kim et al. 1996, Kim & Jaques 2000).

The experimental data, however, are still limited to selected conditions of both particle size and breathing pattern, and the data gap is often filled by predicted values from mathematical models. Many mathematical models have been reported that vary in design and sophistication and the models have shown reasonable agreement with experimental data available at the time of testing (Taulbee & Yu 1975, Hofmann & Koblinger 1990, Asgharian et al. 2001, Goo & Kim 2002). All models, however, need to be validated continuously as new experimental data become available. Most of earlier mathematical models are somewhat uncertain in accuracy, particularly for nano-size and ultrafine

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particles whose experimental data were not available then. Recently, we have developed a dynamic mathematical model utilizing improved transport equations, particularly for nano-size particles, and model results have shown excellent agreement with experimental data (Choi & Kim 2007).

The purpose of this study was to present the selected results of our recent studies of both *in vivo* experiments and mathematical modelling for deposition of inhaled particles in normal adult subjects and to discuss briefly the significance of lung dosimetry in health risk assessment of exposure to particulate pollutants.

In vivo measurement

Total deposition in healthy men and women

In measuring total lung deposition, subjects inhale monodispersed aerosols with a prescribed breathing pattern displayed on the computer screen while respiratory flow rates and aerosol concentrations are continuously monitored and analysed *in situ*. Total deposition fractions (TDF) then are determined by $(N_i - N_e)/N_i$ where N_i and N_e is the total number of particles inhaled and exhaled, respectively. The method is well established and has been used for decades. In our recent studies we generated monodispersed oil aerosols in the size range from 0.04 to 5 μm in diameter and TDF was measured in 22 healthy adult subjects. A wide range of breathing patterns was used to cover individual variability and activity patterns: tidal volume $(V_t) = 350 - 1500$ ml and breathing frequency $(f) = 5–30$ breaths min^{-1} (Jaques & Kim 2000, Kim & Hu 2006).

Results from healthy men are shown in Figure 1 for ultrafine particles and in Figure 2 for micron-size particles. Although not shown in the figures, TDF values in women are similar to those in men in the fine particle range ($d_p = 0.06–3$ μm), but slightly greater in the below or above the range. It is clearly seen in the figures that TDF varies widely with particle size and breathing pattern. For ultrafine particles, TDF decreases with an increase in particle size. But the relationship is opposite for micron particles showing an increase in TDF with increasing particle size. For a given particle size, TDF varies markedly depending on breathing pattern. However, the effects of breathing pattern are not easily delineated because each breathing component (i.e. tidal volume, breathing frequency, respiratory flow rate, respiratory time) operates independently and their effects are often counteractive. In general, TDF increases with deep and slow breathing regardless of particle size. This is because ultrafine and micron particles deposit primarily by diffusion and sedimentation, respectively, and both diffusion and sedimentation are time-dependent mechanisms.

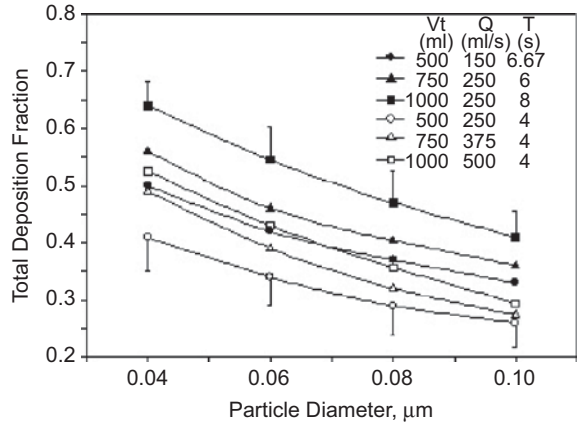

Figure 1. Total deposition fraction of ultrafine particles in healthy men during controlled normal breathing via the mouth.

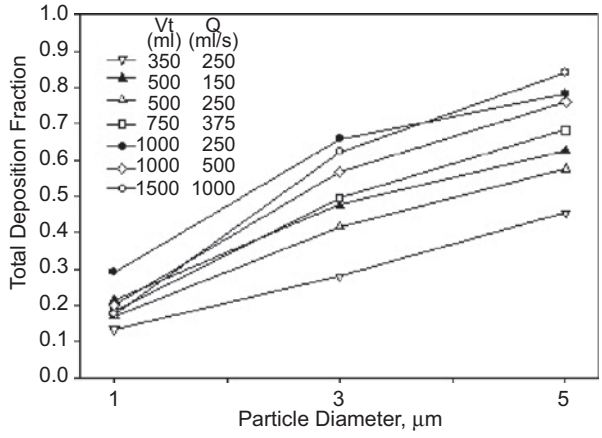

Figure 2. Total deposition fraction of micron-size particles in healthy men during controlled normal breathing via the mouth.

For large micron-size particles, however, inertial impaction becomes an important factor for deposition at fast breathing. Enhanced deposition by inertial impaction at fast breathing compensates for reduced deposition by sedimentation and thus TDF remains relatively unchanged.

Detailed analysis on the roles of each breathing component has been discussed in our previous studies (Kim & Jaques 2000, Kim & Hu 2006). Briefly, TDF is uniquely related with a single composite parameter, X, in the functional form of $TDF = 1 - a/(1 + bX)$ where a and b are index and X is defined by $(DT)^{0.5}V_t^{0.49}$ for ultrafine particles and $d_a^{1.845}V_t^{1.541}Q^{-0.481}$ for micron particles. All data points are collapsed into a single curve as a function of X with very tight correlation ($r^2 = 0.98$). Here, D is the diffusion coefficient of particles, T is the respiratory time, V_t is the tidal volume, d_a is the aerodynamic diameter of particles and Q is the respiratory flow rate. Results suggest that D, T and V_t are equally important for determining TDF of ultrafine particles whereas d_a is most influential for deposition of micron particles. Because the empirical

relationships are based on a wide range of particle size and breathing patterns, one can safely obtain TDF by simply inputting the values of three parameters of interest. The equations are particularly handy and useful when more comprehensive mathematical models are unavailable.

Regional deposition

Traditionally, regional deposition is measured by means of radioaerosol inhalation and subsequent monitoring of clearance of particles from the airways by gamma scintigraphy. The method, however, requires a long experimental time and poses potential hazard from exposure to radioactivity. In the present study we used a novel serial bolus delivery method that does not require radioactive labelling of particles (Kim & Hu 1998, Kim & Jaques 2000). In this method, regional deposition is obtained in each of 10 sequential volumetric compartments at 50 ml intervals starting from the mouth. Conventional three-compartment regional deposition values, extrathoracic, tracheobronchial and alveolar deposition, are also obtained by grouping the sequential volume compartments according to lung anatomy of normal subjects: the upper airway = 0–50 ml, tracheobronchial airways = 50–150 ml and alveolar region = beyond 150 ml. Figure 3 shows local deposition fractions in serial volumetric lung compartments for both ultrafine (d_p = 0.04–0.10 μm) and micron (d_p = 1–5 μm) particles in healthy men during normal breathing via the mouth at V_t = 500 ml and f = 15 breaths min^{-1}. It is noted in the figure that local deposition is highly uneven among different volumetric regions showing peak deposition taking place in the region between 100 and 200 ml depth. Peak deposition sites may shift somewhat to the proximal or distal

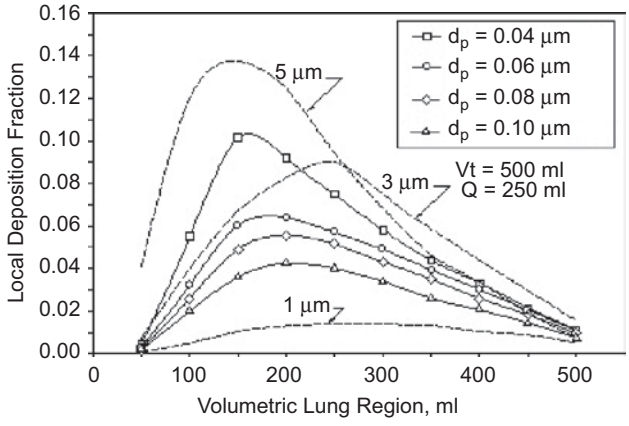

Figure 3. Local deposition fractions in serial volumetric lung compartments (50 ml) of ultrafine (solid line) and micron-size (dashed line) particles in healthy men at tidal volume (V_t) of 500 ml and mean respiratory flow rate (Q) of 250 ml s^{-1}.

regions depending on the breathing pattern, but the basic skewed mound shape of deposition curve may not change. It is particularly worth noting that deposition patterns are similar for both ultrafine and micron particles, indicating that very small ultrafine particles deposit in the same regions as large micron particles. The implications of the results are that effects of exposure to heterogeneous ambient aerosols are likely due to combined effects of different size particles rather than a particular size fraction and that adverse effects may originate from a particular region receiving a high dose of particles.

Mathematical modelling

Although experimental data are most valuable and provide the basis of validating mathematical models, mathematical models allow a wide range of testing that cannot be achieved in experiments. Of a few different approaches, a dynamic single-path model is most robust and versatile. In our recent study, we have attempted to improve the one-dimensional dynamic model by using more realistic alveolar transport scheme, particularly for fine and ultrafine particles (Choi & Kim 2007). In the model, alveolar transport has been treated as a two-dimensional process, and both the axial and radial transport in the alveolar region have been taken into account as the alveoli expand and contract in real time with the breathing cycle. Typical results are shown in Figure 4 for the total (upper panel), tracheobronchial (mid panel) and alveolar (lower panel) deposition in healthy men during normal breathing via the mouth. The results have shown excellent agreement with experimental data available for comparison. The figure shows the characteristic trough-shaped curve for total deposition with minimal deposition taking place at d_p = ~0.5 μm. The curve maintains the same shape but shifts up and down when breathing pattern changes. Tracheobronchial deposition shows dual peaks at d_p = ~0.005 μm and d_p = ~8 μm with minimal values in the size range of d_p = 0.2–1.0 μm. Alveolar deposition shows a characteristic M-shaped curve with two peaks occurring at d_p = 0.02–0.05 μm and d_p = 3–5 μm. Although minimum deposition occurs at d_p = ~0.5 μm as in total and tracheobronchial deposition, the deposition curve is relatively flat over the wide range of particle size indicating that alveolar region is subjected to deposition of both ultrafine and micron particles. Alveolar deposition, however, is essentially zero for very small ultrafine (d_p < ~0.005 μm) and large micron (d_p > ~10 μm) particles. It is also noteworthy that although Figure 4 shows only a few typical datasets, the figure can be easily extended for different breathing patterns and inhalation conditions.

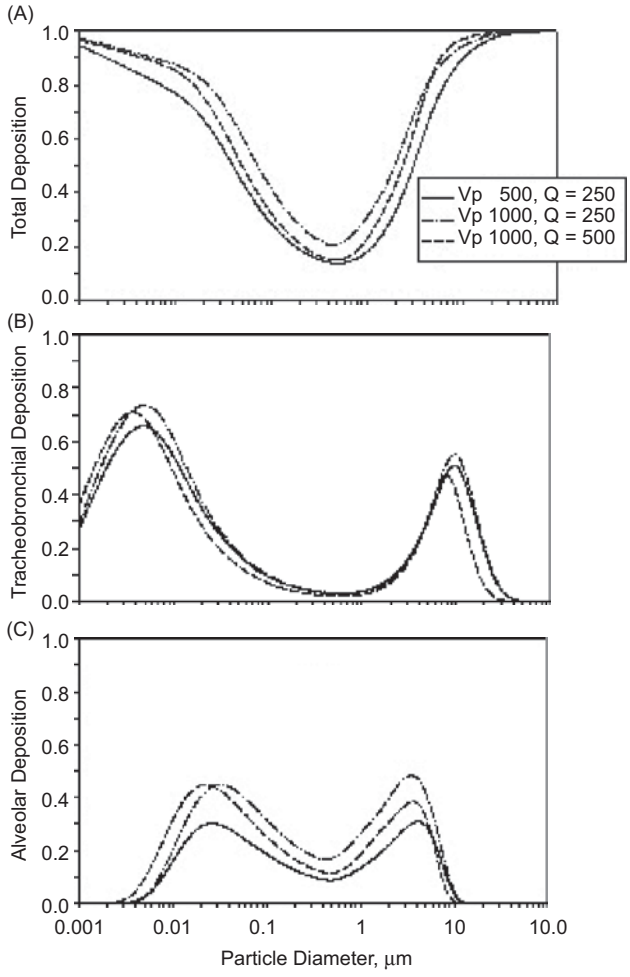

Figure 4. Mathematical model predictions of the total (A), tracheobronchial (B) and alveolar (C) deposition fractions in healthy men during normal breathing via the mouth at three different breathing patterns. V_t is the tidal volume (ml) and Q is the mean respiratory flow rate (ml s^{-1}).

The versatility of the mathematical models allows us to explore the deposition of complex aerosols under varying exposure conditions. Ambient aerosols consist of particles of many different sizes, shapes and chemical components and of particles with varying stability both physically and chemically. Inhalation patterns of individuals also vary considerably depending on their physical as well as health conditions and their lifestyle. Deposition of particles under complex inhalation conditions cannot be predicted based on limited experimental data obtained under simple and well-defined inhalation conditions. Deposition of hygroscopic aerosols or volatile liquid droplets is very different from that of solid and stable particles. Because of the growth of particle size, deposition of hygroscopic particles is expected to increase for micron particles, but decrease for ultrafine particles. In other words, the deposition curves shown in Figure 4 are shifted to the left for hygroscopic particles. The degree of hygroscopicity, however, is difficult to define for ambient particles (Ferron et al. 1988). Dose estimation of aerosols with complex size distribution together with size-specific physicochemical properties is very challenging. However, the real challenge comes from the human factors, particularly lung morphology and distribution of ventilation in abnormal and diseased lungs. In some clinical studies, total deposition has been shown to increase in patients with obstructed airway disease and a good correlation has been found between enhanced deposition and the severity of airway obstruction (Kim & Kang 1997). However, the detailed nature of aerosol transport and deposition in the abnormal lungs remains beyond full comprehension. Once mathematical models have been thoroughly validated with experimental data, the models may be further extended or developed in order to systematically tackle the above issues.

Conclusions

In summary, recent studies of both *in vivo* experiments and modelling have significantly improved our ability to estimate respiratory deposition of inhaled particles in healthy subjects. However, a challenge remains in further improving and refining the present methods in order to handle new types of aerosol emerging from industrial development and natural changes and to tackle unusual conditions of exposure particularly in individuals with obstructive airway disease.

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