Journal of the Air & Waste Management Association
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uawm20

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Published online: 27 Dec 2011.

To cite this article: Cynthia J. Musante & Ted B. Martonen (2000) Computer Simulations of Particle Deposition in the Developing Human Lung, Journal of the Air & Waste Management Association, 50:8, 1426-1432, DOI: 10.1080/10473289.2000.10464176

To link to this article: http://dx.doi.org/10.1080/10473289.2000.10464176

TECHNICAL PAPER

ISSN 1047-3289 *J. Air & Waste Manage. Assoc.* **50**:1426-1432

Computer Simulations of Particle Deposition in the Developing Human Lung

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ABSTRACT

An age-dependent theoretical model has been developed to predict PM dosimetry in children's lungs. Computer codes have been written that describe the dimensions of individual airways and the geometry of branching airway networks within developing lungs. Breathing parameters have also been formulated as functions of subject age. Our computer simulations suggest that particle size, age, and activity level markedly affect deposition patterns of inhaled air pollutants. For example, the predicted lung deposition fraction is 38% in an adult but is nearly twice as high (73%) in a 7-month-old for 2-μm particles inhaled during heavy breathing. Tracheobronchial (TB) and pulmonary (or alveolated airways, P) deposition patterns may also be calculated using the model. Due to different clearance processes in the TB and P airways (i.e., mucociliary transport and macrophage action, respectively), the determination of compartmental dose is important for PM risk assessment analyses. Furthermore, the results of such simulations may aid in the setting of regulatory standards for air pollutants, as the data provide a scientific basis for estimating dose delivered to a designated sensitive subpopulation (children).

IMPLICATIONS

Children have been identified as a sensitive subpopulation to be addressed in the determination of regulatory standards for air pollutants. To aid in this process, we have developed an age-dependent mathematical model that describes the behavior and fate of inhaled particles in human lungs. Our results suggest that when differences in deposition fraction, ventilation rate, and cumulative airway surface area are taken into account, children may receive a localized dose that is 3 times higher than adults receive. Therefore, children may experience increased injury to the cells that line the respiratory tract as compared with adults in the same exposure environment.

INTRODUCTION

Children have been identified as a sensitive subpopulation to be addressed in the determination of regulatory standards for air pollutants.[1] For a variety of reasons, however, experimental data describing the deposition patterns of inhaled PM in children are rare.[2] In the pharmaceutical industry, where the administration of aerosolized drugs to children is increasing, age-dependent dosimetry information is also lacking.[3] The limited data available suggest that children have greater deposition efficiencies than adults under resting conditions,[4,5] a factor that may contribute to increased health risk from airborne substances.

To aid in the risk assessment process, we have developed an age-dependent mathematical model that describes the behavior and fate of inhaled particles in human lungs. Knowledge of particle deposition and clearance is a first step in understanding the biological mechanisms that lead to adverse health effects. Therefore, the model, which has been validated by comparison with experimental data from adult subjects, may provide additional insight into health risks associated with inhalation exposure to PM.

METHODS

A physiologically realistic mathematical model describing particle deposition in the developing human lung has previously been reported.[6] Age-dependent lung morphologies are based on the descriptions of Hofmann[7] for the tracheobronchial (TB) airways and of Dunnill[8] for the alveolated, or pulmonary (P), region. The number of TB airways is considered fixed at birth, but the number of P airways changes as the lung develops. We refer the reader to other age-dependent lung morphologies and particle deposition codes that have been proposed[9–11] and comparisons that have been summarized elsewhere.[6]

Data in Table 1 were used to simulate sedentary and heavy human activity levels and corresponding variations

Table 1. Definition of age-dependent breathing patterns for sedentary and heavy human activity levels.

	Sedentary		Heavy	
Age (months)	Flow Rate (mL/sec)	Tidal Vol. (mL)	Flow Rate (mL/sec)	Tidal Vol. (mL)
7	49	42	600	222
22	78	84	810	308
48	112	152	1070	460
98	159	266	1368	903
360	234	500	2007	2449

in respiratory parameters as a function of age. The values are based on equations formulated by Hofmann.[7,11]

A variety of monodisperse aerosols were studied, ranging from 0.25 to 5.0 μm unit density spheres. These particle diameters were chosen to reflect typical constituents of ambient PM. Deposition of a polydisperse aerosol with a log-normal particle size distribution was also considered. The residual oil fly ash (ROFA) aerosol, an emission source particulate pollutant, was assumed to have a mass median aerodynamic diameter of 1.95 μm, a geometric standard deviation of 2.19, and a count median diameter of 0.53 (assuming a particle density of 0.34 g/cm^3).

RESULTS AND DISCUSSION

Monodisperse Aerosol Deposition

Lung (L = TB + P), TB, and P deposition fractions are shown in Figures 1–3, respectively, as a function of particle diameter and subject age for sedentary breathing conditions. Corresponding charts for increased (heavy) activity are given in Figures 4–6. Deposition fractions are mass-based (assuming unit densities and spherical particles), and are normalized to the amount entering the trachea. This normalization was performed because the experimental data used as comparison with the original dosimetry model for adults were presented in that format.

For sedentary breathing and each monodisperse aerosol considered, the predicted lung deposition fraction was highest for the 22- and 48-month-olds, and lowest for the adult. This was in contrast to heavy respiratory activity, wherein lung deposition generally decreased with age for each particle size category.

TB deposition also decreased with age, for both ventilatory states. P deposition was generally highest for the 48- and 98-month-olds under resting conditions, but was an increasing function of age during enhanced respiration.

The effect of physical activity level on PM deposition was largely dependent upon particle size. For example, when going from a resting to an active state within a particular age group, TB deposition decreased by approximately one-half for 0.25-μm particles, but increased nearly 2-fold for an aerosol composed of 5-μm particles. The former effect (i.e., halving) is due to the reduction in residence times of particles within the conducting airways, resulting

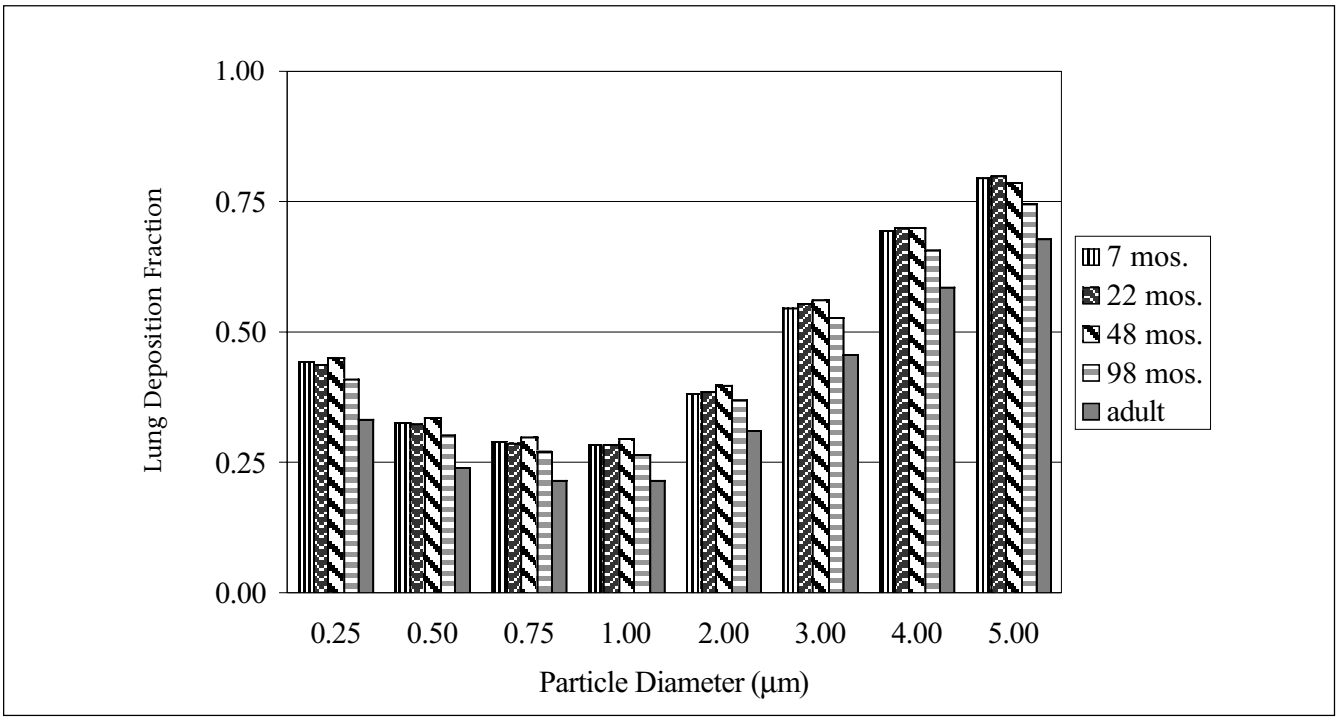

Figure 1. Lung (TB and P) deposition in the developing human lung under sedentary conditions (see Table 1).

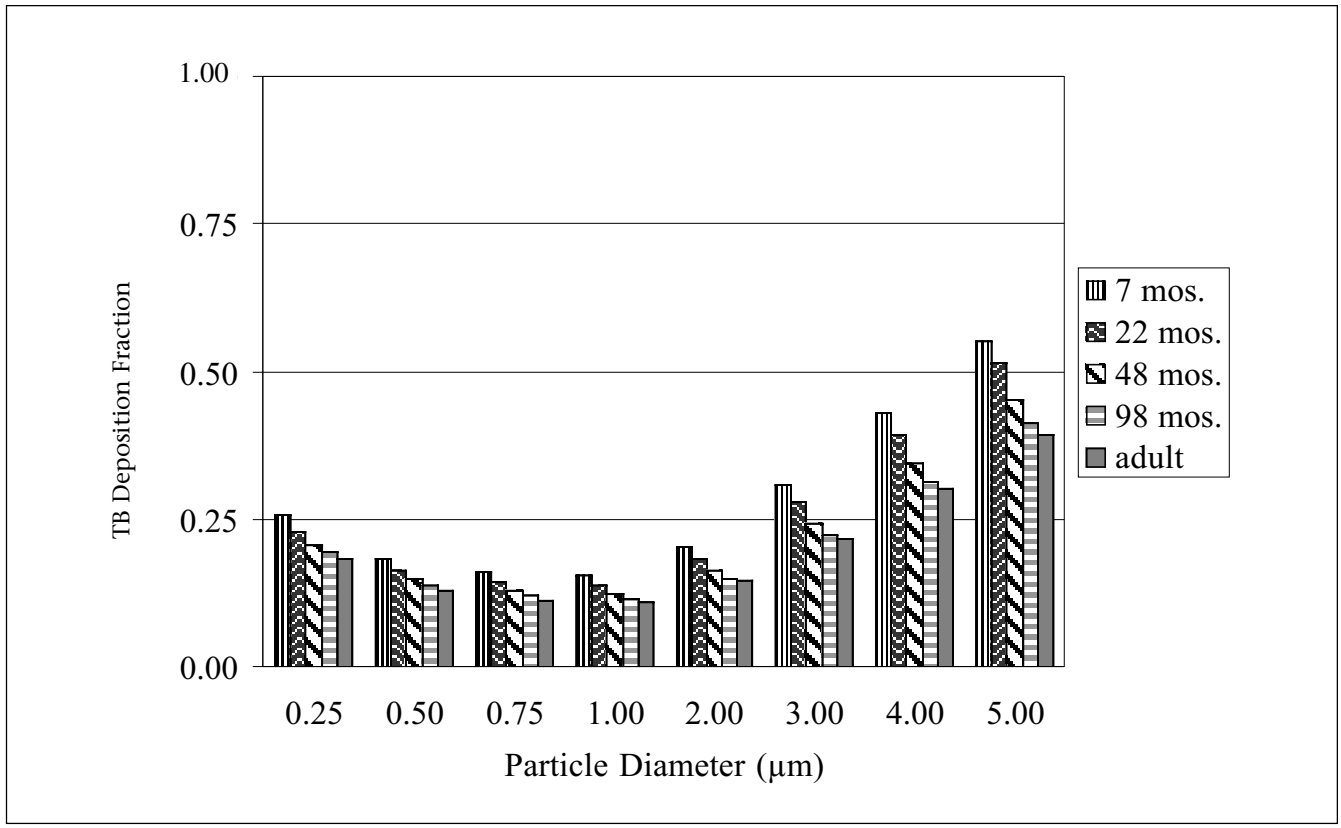

Figure 2. TB deposition in the developing human lung under sedentary conditions (see Table 1).

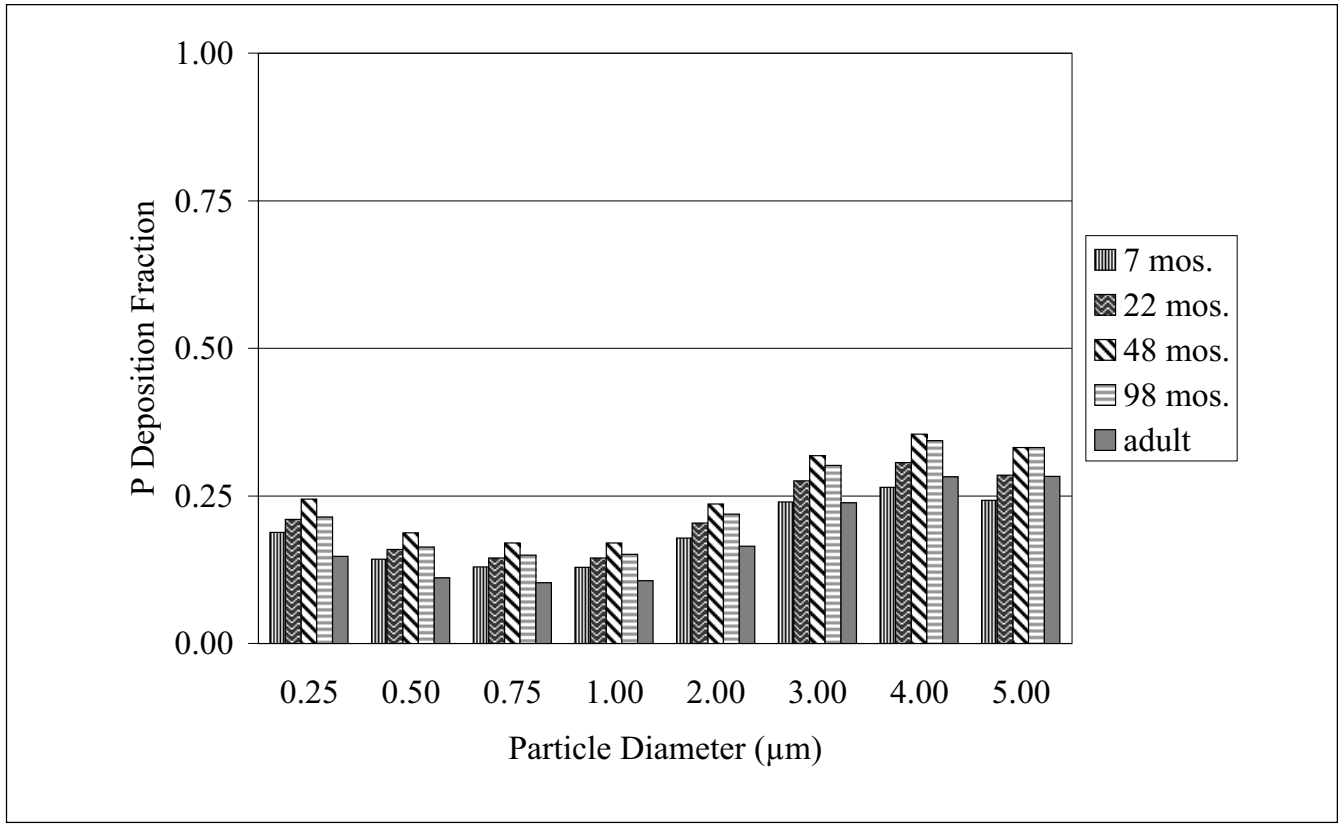

Figure 3. P (alveolated airways) deposition in the developing human lung under sedentary conditions (see Table 1).

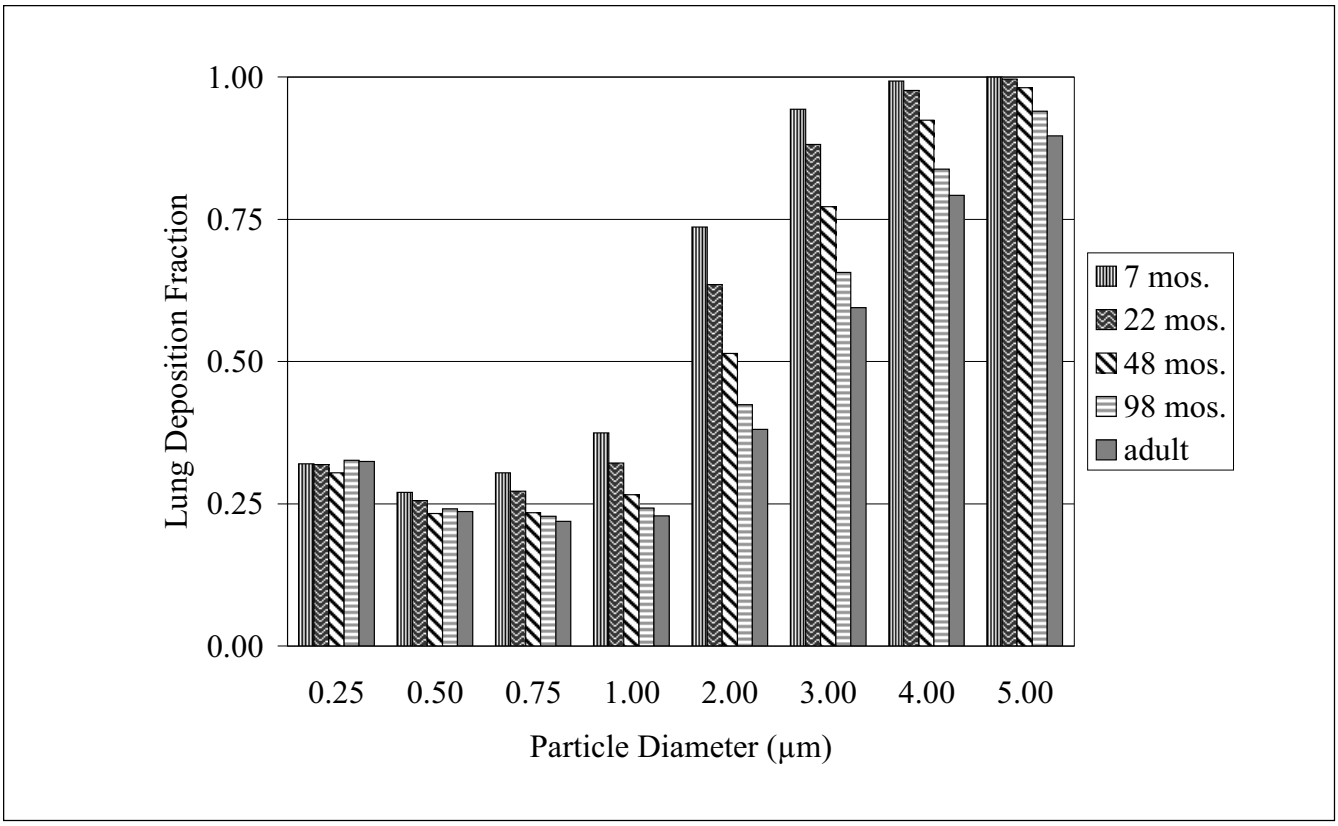

Figure 4. Lung deposition in the developing human lung under increased (heavy) activity (see Table 1).

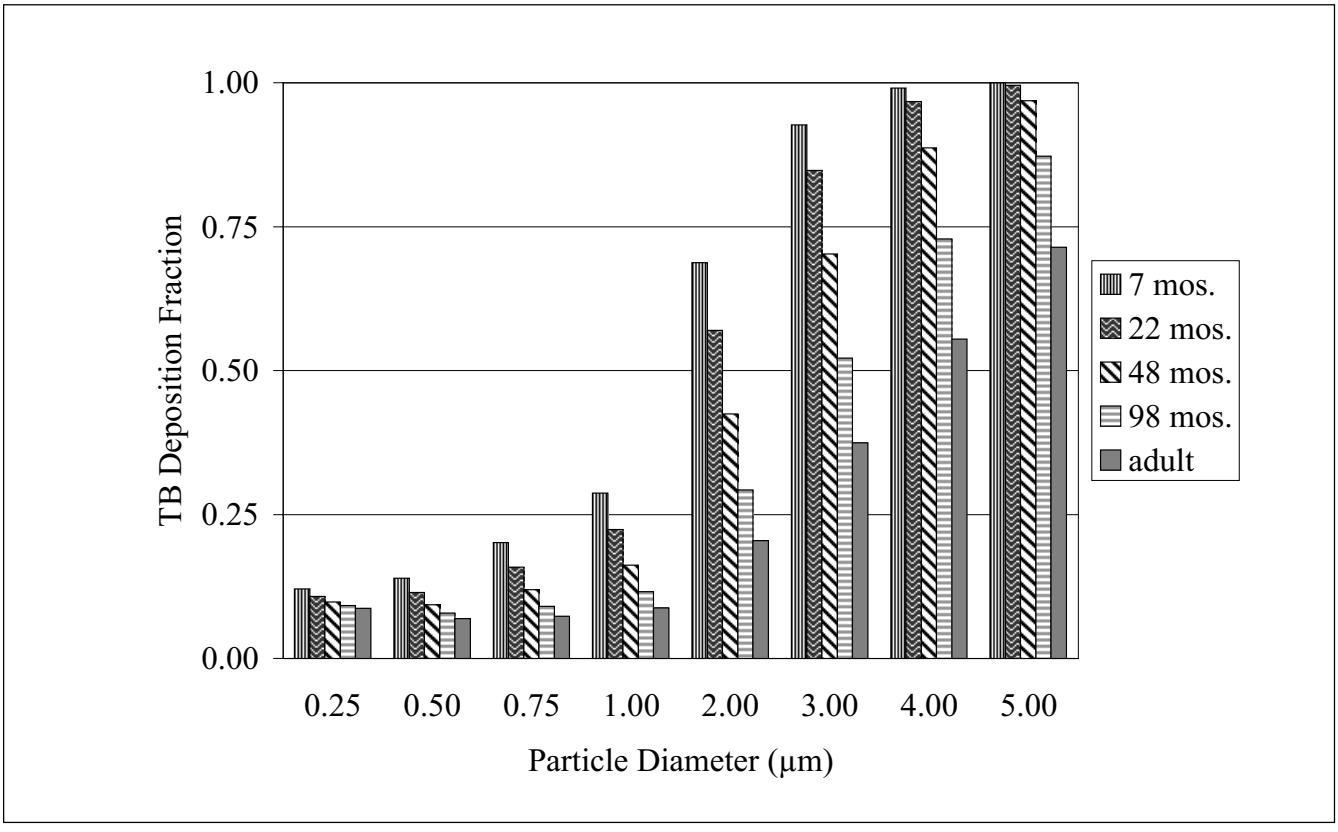

Figure 5. TB deposition in the developing human lung under increased (heavy) activity (see Table 1).

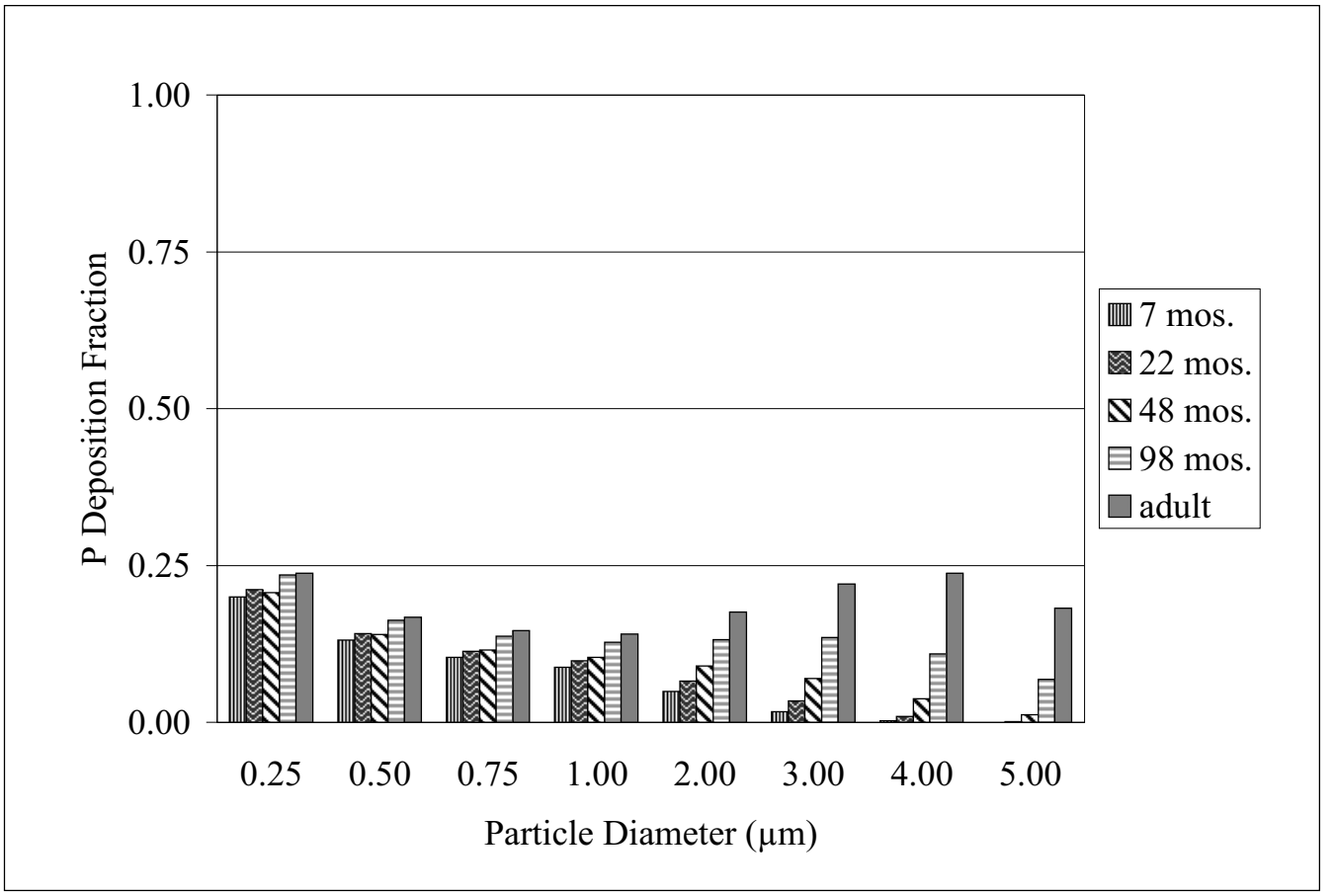

Figure 6. P (alveolated airways) deposition in the developing human lung under increased (heavy) activity (see Table 1).

in decreased probabilities of deposition by diffusion (the primary deposition mechanism for submicron particles). The latter characteristic (i.e., doubling) is due to the increased effectiveness of the inertial impaction mechanism at high flow rates. This, of course, affects the deposition patterns of PM downstream, in distal pulmonary airways. The filtering of the 5-μm particles in the TB region at the higher flow rate resulted in a decrease in P deposition as compared with the sedentary state. For the submicron (0.25 μm) case, because a greater percentage of particles reach the pulmonary region during heavy activity, P deposition fractions for the resting and active states are actually quite similar.

Polydisperse Aerosol Deposition

In Figure 7, deposition of ROFA within the lungs of a 4-year-old subject is shown as a function of respiratory intensity and airway generation. This figure is included to illustrate shifts in regional deposition that may occur with changes in ventilation. For example, based on this data, the predicted mass-based deposition fraction (TB + P) was similar for sedentary (30%) and heavy (35%) conditions, but the regional doses differed considerably. The TB/P ratio, an indicator of uniformity of PM deposition, was 0.676 for the sedentary case and 3.193 for enhanced respiration. This suggests that deposition is skewed toward the alveolated airways under resting conditions but is concentrated in the conducting airways during enhanced ventilation. TB ROFA deposition increased by a factor of 2 during periods of exercise or heavy breathing, while pulmonary deposition decreased. This phenomenon may contribute to the exacerbation of upper respiratory illnesses such as asthma[12] in children exposed to ambient PM. Environmental factors, including physical location, breathing zones, and oxygen consumption, may also lead to greater susceptibility in children.[13]

Care must be taken when making comparisons of deposition between age groups. Our analyses so far have been made in terms of "deposition fraction," defined as the number (or mass) of particles deposited divided by the total number (or mass) of particles entering the trachea. While this term is useful in the study of qualitative differences in aerosol deposition behavior, it is just one component of a complex interplay of parameters affecting quantitative estimates of deposition. Differences in minute ventilation and cumulative airway surface area must also be considered when making predictions of ROFA deposition for PM risk assessments.

In Figure 8, a comparison of inhalation rate (i.e., aerosol volume inspired per hour), cumulative airway surface

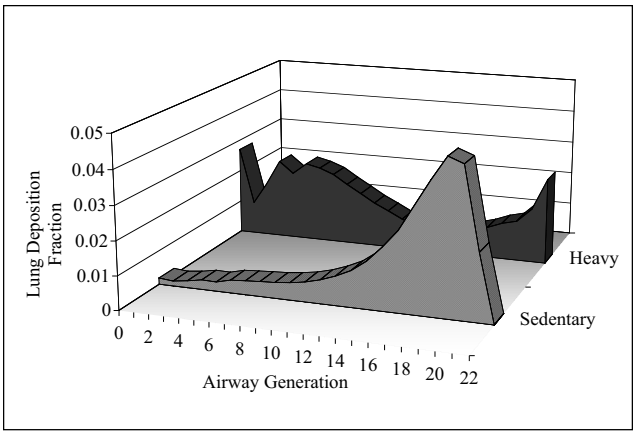

Figure 7. Mass-based deposition fractions for a ROFA aerosol in the lungs of a 4-year-old subject as a function of airway generation and respiratory intensity (see Table 1). The TB region includes generations 0–16, whereas generations 17–23 are considered to be P (alveolated) airways.

area (SA), and lung deposition fraction is given for the ROFA aerosol described above, assuming sedentary breathing conditions. In general, deposition fraction decreases with age, whereas SA and ventilation rate increase with age. To fully understand the complex interaction of these parameters, the data in Figure 8 were used to calculate the mass-based ROFA deposition rate (i.e., the total mass of ROFA deposited per hour) for each age group, assuming an ambient concentration of 65 $\mu g/m^3$. The deposition rate monotonically increased with age, ranging from ~3 µg/hr in the youngest child to 12 µg/hr in the adult. One should consider, however, that the total airway surface area is an order of magnitude higher in the adult model. This has immediate implications for PM risk assessment analyses, as it suggests that although the total body burden of ROFA may be higher in adults, the localized dose (i.e., the mass distribution to the cells that line the respiratory tract) may be lower. This can be seen in Figure 9, where the deposition rate and the normalized deposition rate (i.e., the deposition rate divided by the cumulative airway surface area) are compared for each age group.

Specifically, assuming sedentary activity levels, the ROFA deposition rate is 8 µg/hr for the 4-year-old, compared to 12 µg/hr in the adult, whereas the deposition rate per unit surface area is 3 times higher in the child. This difference in localized ROFA concentration suggests that children may experience increased injury to the cells that line the respiratory tract as compared with an adult in the same exposure environment.

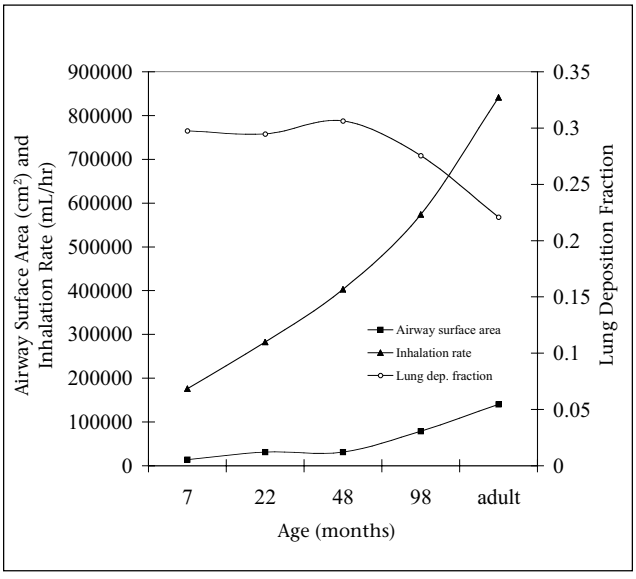

Figure 8. Comparison of ventilation rate, cumulative airway surface area, and mass-based lung deposition fraction for a ROFA aerosol for each age group under resting conditions (see Table 1).

SUMMARY

The physiologically realistic dosimetry model presented herein agrees with experimental data from inhalation exposure experiments in adults. The model has a wide variety of input and output options. Input parameters include aerosol characteristics (e.g., particle size and density), lung morphology (e.g., human or laboratory animal, adult or child), and breathing pattern (e.g., tidal volume and frequency). Data output, in terms of aerosol deposition fractions, may be calculated at desired levels of spatial resolution; that is, lung, compartmental (TB and P), and localized (airway-by-airway).

Although deposition in the thoracic airways is affected by many factors, some specific observations can be made regarding the effects of subject age.

- Lung (TB + P) deposition fraction was generally higher in children than adults. The differences may be significant, depending on particle size, respiratory intensity, and subject age.
- The TB deposition fraction was a monotonically decreasing function of age for both sedentary and heavy respiratory activity levels and all particle sizes considered.
- The P deposition fraction was highest in the 48- and 98-month-old subjects under resting conditions for all particle sizes examined, but was an increasing function of age during enhanced activity.
- For a 4-year-old child, ROFA deposition was skewed toward the alveolated (P) airways under sedentary conditions, but was concentrated in the conducting (TB) airways during heavy activity.
- When ventilation rate and cumulative airway surface area are considered, children may receive a localized dose that is 3 times higher than adults receive.

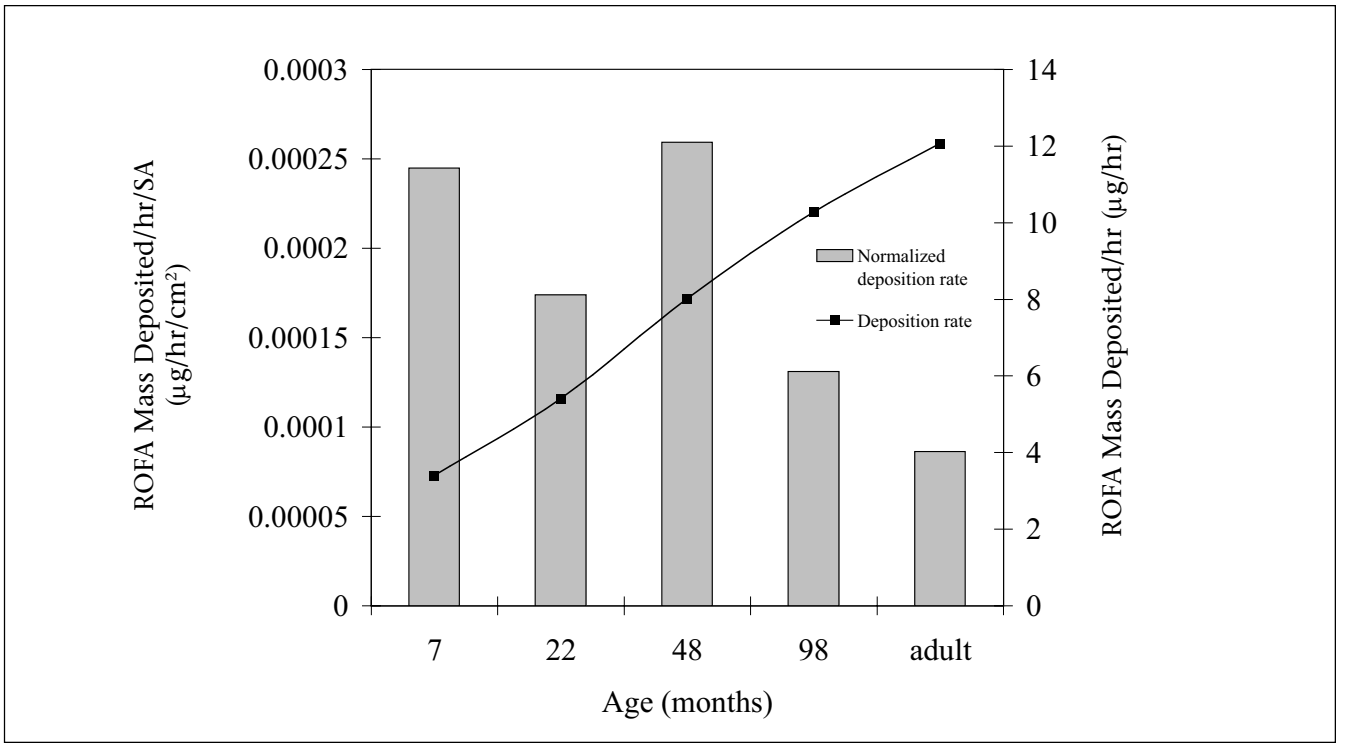

Figure 9. Total ROFA mass deposited in the lung per hour (line plot) normalized to total airway surface area (columns) for each human subject age under resting conditions (see Table 1). The ambient ROFA concentration was assumed to be 65 μg/m³.

These validated theoretical models may provide additional insight into PM distribution in the developing human lung, and may thereby aid in the integration of children into risk assessment protocols for particulate air pollutants.

ACKNOWLEDGMENTS

C.J. Musante was funded by the U.S. Environmental Protection Agency/University of North Carolina Toxicology Research Program, Training Agreement CT902908, with the Curriculum in Toxicology, University of North Carolina at Chapel Hill.

DISCLAIMER

This manuscript has been reviewed in accordance with the policy of the National Health and Environmental Effects Research Laboratory and the U.S. Environmental Protection Agency, and has been approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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