PARTICLE OVERLOAD IN THE RAT LUNG AND LUNG CANCER
Implications for Human Risk Assessment

Proceedings of a Conference Held at the Massachusetts Institute of Technology on March 29 and 30, 1995

Supported by a grant from the Environmental Health Association of the United States Carbon Black Industry and the European Committee for the Assessment of Biological Effects of Carbon Black

Editors

Joe L. Mauderly, DVM, Lovelace Inhalation Toxicology Research Institute, Albuquerque, New Mexico, USA

Robert J. McCunney, MD, Environmental Medical Service, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA

1996

EXTRAPOLATION MODELING OF PARTICLE DEPOSITION AND RETENTION FROM RATS TO HUMANS

C. P. Yu

Department of Mechanical and Aerospace Engineering, State University of New York at Buffalo, Amherst, New York, USA

Rodents have often been used as surrogates for humans to study biological responses from exposure to airborne particles. To interpret experimental data of rodent studies and to extrapolate results to potential human exposures, interspecies comparisons of particle dosimetry in the lung are necessary. This article deals with dosimetry studies in humans and rats by mathematical models using diesel exhaust particles as an example exposure material. The diesel particle was modeled as a submicrometer-sized particle consisting of a carbonaceous core and associated organics. The dosimetry results showed that total and alveolar deposition fractions in a breathing cycle in humans and rats were similar, but there were large differences between the two species in deposition rate and in particle retention per gram of lung. A new formula was also derived from existing experimental data for the alveolar clearance rate in rats at high lung burdens. This formula was extrapolated to humans based upon a hypothesis previously proposed by Morrow (1988) that clearance impairment at high lung burdens is related to the volumetric fraction of the retained particles in alveolar macrophages. Several predicted human lung burden results are presented.

Biological responses from exposure to airborne particles are related closely to the dose delivered to the target tissue. To interpret experimental data from inhalation studies in rodents and to extrapolate results to human exposures, an understanding of particle dosimetry in the respiratory tracts of rodents and humans is required. Because of the differences in airway structure, airway size, and minute ventilation, humans and rodents usually exhibit different deposition patterns. The deposition rate per gram of lung in rodents can be either higher or lower than in the human, depending upon the size, shape, and mass density of inhaled particles. In addition, inhaled particles can be removed or cleared from the lung's epithelial surfaces once deposited. For insoluble particles, the macrophage-mediated removal rate in rodents is much faster than in humans. The combined deposition and clearance processes may result in considerable differences in particle retention in the lung between humans and rodents. These differences must be taken into account when the biological data are extrapolated from rodents to humans for risk assessment.

T. H. Hsieh performed all the calculations needed in this article. His effort is greatly appreciated.

Address correspondence to C. P. Yu, Department of Mechanical and Aerospace Engineering, State University of New York at Buffalo, Amherst, NY 14260, USA.

Mathematical models have often been used to complement experimental results of deposition and clearance of inhaled particles in the lungs. They not only enhance our understandings of exposure–dose–response relationship for rodents, but also provide a quantitative basis for extrapolating the data to humans. This article presents the processes that are involved in developing mathematical models, using diesel exhaust particles as an example. The rat is the only rodent species considered in the modeling because most diesel exposure experiments were performed in rats and there are sufficient data available for model development and validation.

MODEL DEVELOPMENT

Particle Model

The processes for developing mathematical dosimetry models for humans and rats are shown in Figure 1. First, a particles model that describes the size and structure of the particle under consideration must be established. For diesel exhaust particles, Yu and Xu (1986) proposed that these particles could be modeled as cluster aggregates consisting of many solid primary particles with a bulk density about 1.5 g/cm^3 and a packing density of 0.3. The size distribution of diesel exhaust particles and the amounts of specific organic compounds associated with the particles depend upon many factors including engine design, fuel used, engine operation conditions, and thermo-

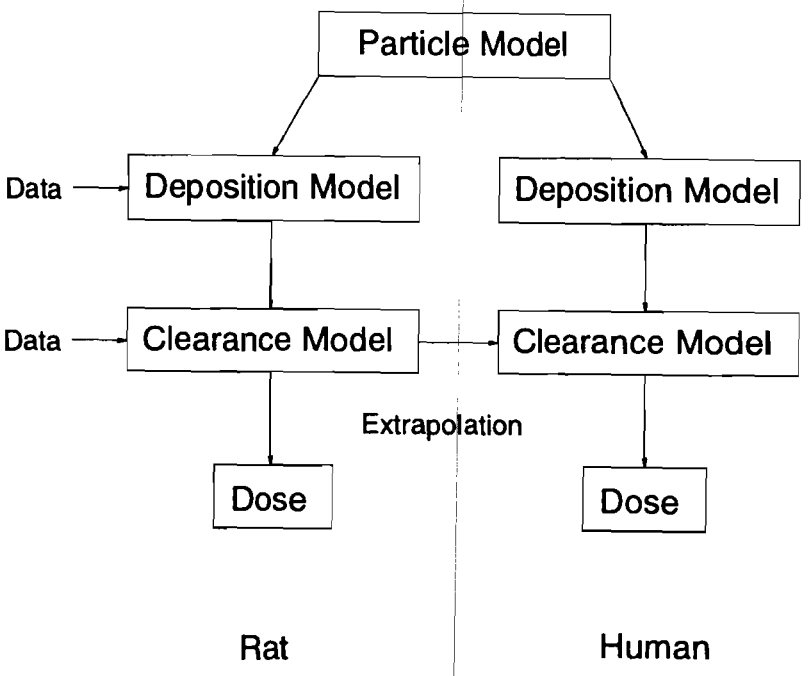

FIGURE 1. Flow diagram for developing mathematical dosimetry models of inhaled particles for humans and rats.

dynamic processes that occur during exhaust. Measurements showed that the size distribution is approximately lognormal, with MMAD varying from 0.1 to 5.4 μm and σ_g varying from 1.8 to over 4 (Chan et al., 1981, 1984; Cheng et al., 1984). The adsorbed organics generally account for 10–30% of the particle mass. To study the clearance characteristics of diesel exhaust particles, Yu et al. (1991) assumed that a representative diesel particle has a MMAD = 0.2 μm and σ_g = 2.3 and is composed of three material components: (1) a carbonaceous core representing approximately 80% of the particle mass, (2) absorbed organics slowly cleared from the lung representing about 10% of the particle mass, and (3) absorbed organics quickly cleared from the lung accounting for the remaining 10% of the particle mass. The presence of two discrete organic phases in the particle model was suggested by the observations that the removal of the particle-associated organics from the rat lung exhibited a biphasic clearance curve (Sun et al., 1984; Bond et al., 1986).

Deposition Model

Deposition in the airways is a process governed by physical principles alone. It involves mechanics of air and particle motion in a given airway geometry. There are five mechanisms that cause particle deposition within the respiratory tract. These are impaction, sedimentation, diffusion, interception, and electrostatic precipitation. Because particle size is very small compared to the size of the smallest airways, interception is normally insignificant, except for long, elongated particles. Electrostatic precipitation occurs only for freshly generated particles. Thus, for a compact particle in charge equilibrium, the first three mechanisms are most important for deposition. The relative contributions of these mechanisms to deposition in an airway, however, depend on particle size and flow rate, as well as the size and location of the airway in the respiratory tract. In the case of diesel exhaust particles, diffusion is probably the predominant deposition mechanism because of the particle size range. But large particles in the exhaust, although they make up a small number fraction of all particles, may also contribute significantly to mass deposition by impaction and settling mechanisms.

In the development of deposition models for humans and rats, the airway geometry and ventilation conditions must be known. Lung models for human adults have been proposed by Weibel (1963) and others (Olson et al., 1970; Hansen & Ampaya, 1975; Yeh & Schum, 1980). For rats, the only lung model available is by Schum and Yeh (1980). Although the number of airway generations is similar in the human and rat lung models, the airway size and number of airways in each generation differ dramatically between the two species. Humans have much larger airway size and higher airway numbers than rats. The total airway volume of the human is about 500 times greater than that of the rat. There is also a large difference in the ventilation conditions between the two species. Table 1 gives a comparison of several anatomical and physiological parameters between humans and rats.

TABLE 1. Comparison of anatomical and physiological parameters between humans and rats

Parameter	Human	Rat	Human/Rat
Body weight (kg)	70	0.3	233
Lung weight (g)	10^3	1.48	676
Airway volume (cm^3)	3.2×10^3	6.5	492
Airway surface area (cm^2)[a]	6.27×10^5	5.5×10^3	114
Number of alveolar macrophages (AM)[b]	7×10^9	2.6×10^7	269
AM volume (μm^3)[b]	2.5×10^3	10^3	2.5
Total AM volume (mm^3)[b]	1.75×10^4	26	673
Tidal volume (cm^3)	5×10^2	2.74	182
Breathing frequency (min^{-1})	14	98	0.14
Minute ventilation (cm^3/min)	7×10^3	2.68×10^2	26

[a]Calculated from Weibel's model (1963) for humans and Yeh and Schum's model (1980) for rats.
[b]Adopted from Dethloff and Lehnert (1987).

A deposition model of diesel exhaust particles in the respiratory tract for humans and rats was developed by Yu and Xu (1986). Using the ventilation conditions listed in Table 1 and the particle model for diesel exhaust particles described earlier, Xu and Yu (1987) calculated deposition fractions in different regions of the respiratory tract of the rat based upon the lung model of Schum and Yeh (1980). The modeling results for MMAD = 0.1–0.15 μm, σ_g = 1.8–1.9 were in good agreement with the experimental data obtained by Chan et al. (1981) (see Table 2). This suggests that the particle and deposition models used in the calculation are appropriate models. For the representative particle size considered in this study (MMAD = 0.2 μm, σ_g = 2.3), calculated mass deposition fractions in different regions of the respiratory tract for rats and humans from the deposition model of Yu and Xu (1986) are shown in Table 3. In the alveolar region, the deposition fraction of diesel exhaust particles in rats differs only by 0.4% from that in humans despite large differences in airway size.

TABLE 2. Calculated regional mass deposition fractions of diesel exhaust particles in rats by Xu and Yu (1987) and comparison with experimental data by Chan et al. (1981)

Compartment	Data (%)	Prediction (%)
Head	NA	6.0–6.8
Tracheobronchial	4	3.1–4.6
Alveolar	11	10.3–13.4
Total	15–17	13.5–17.9

Note. The measured particle sizes in the experiment are MMAD = 0.1–0.15 μm and σ_g = 1.8–1.9.

TABLE 3. Calculated regional mass deposition fractions of diesel exhaust particles for humans and rats

Compartment	Rat	Human
Head	0.091	0.046
Tracheobronchial	0.024	0.047
Alveolar	0.119	0.099
Total	0.234	0.192

Note. The particle size used in the calculation is MMAD = 0.2 μm and $\sigma_g = 2.3$.

For risk assessment, a comparison of minute dose between rats and humans at the same exposure concentration is useful. Considering a concentration of 1 mg/m^3, the minute dose per gram of lung in the alveolar region of the lung for rats and humans were calculated to be 4.24×10^{-2} and 1.34×10^{-3} μg/min, respectively. Thus, rats will receive a dose rate per gram of lung about 32 times higher than humans.

Clearance Model

Deposited particles are removed from the lung by two principal mechanisms: (1) mechanical clearance, provided by mucociliary transport in the ciliated airways and macrophage phagocytosis and migration in the nonciliated airways, and (2) clearance by dissolution. For diesel exhaust particles, the carbon core is removed principally by mechanical transport and the particle-associated organics are removed by dissolution. To study the transport and removal of diesel exhaust particles from the lungs, Yu et al. (1991) used a compartment model consisting of four anatomical compartments: the nasopharyngeal or head (H), tracheobronchial (T), alveolar (A), and lung-associated lymph node (L) compartments, as shown in Figure 2. In addition, they used two outside compartments, the blood (B) and gastrointestinal tract (G). The alveolar compartment in the model is obviously the most important compartment for long-term retention studies. However, for short-term consideration, retention in other lung compartments may also be significant. The presence of these lung compartments and two outside compartments in the model therefore provides a complete description of all clearance pathways involved.

In Figure 2, $r_H^{(i)}$, $r_T^{(i)}$, and $r_A^{(i)}$ are, respectively, the mass deposition rates of material component i ($i = 1$, carbon core; $i = 2$, slowly cleared organics; and $i = 3$, quickly cleared organics) in the head, tracheobronchial, and alveolar compartments, and $\lambda_{XY}^{(i)}$ represents the transport rate of material component i from compartment X to compartment Y. The value of $\lambda_{XY}^{(i)}$ for rats can be either determined from the measured diesel particle mass burden $m_X^{(i)}$ and $m_Y^{(i)}$ in an inhalation study or estimated from previous data obtained for other types of particles. The kinetic equations that describe the mass of material

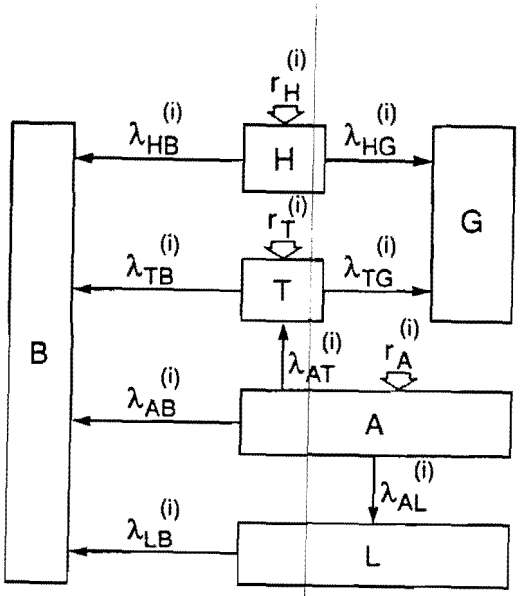

FIGURE 2. Compartmental model of particle retention. H, head; T, tracheobronchial; A, alveolar; L, lung-associated lymph nodes; B, blood; G, gastrointestinal tract; $\lambda^{(i)}$ terms are the transport rates for the compartments indicated the subscript; and $r^{(i)}$ terms are the mass deposition rates for the compartments indicated in the subscript.

component i, $m_X^{(i)}$ in compartment X, as a function of exposure time t were derived by Yu et al. (1991). For compartment A, the equation is

$$\frac{dm_A^{(i)}}{dt} = r_A^{(i)} - (\lambda_{AT}^{(i)} + \lambda_{AL}^{(i)} + \lambda_{AB}^{(i)})\, m_A^{(i)}$$
$$= r_A^{(i)} - \lambda_A^{(i)} m_A^{(i)} \qquad (1)$$

where

$$\lambda_A^{(i)} = \lambda_{AT}^{(i)} + \lambda_{AL}^{(i)} + \lambda_{AB}^{(i)} \qquad (2)$$

is the total clearance rate from compartment A through all three pathways.

Experimental data for $\lambda_A^{(1)}$ for diesel exhaust particles and other insoluble particles showed that $\lambda_A^{(i)}$ decreased with $m_A^{(1)}$ or particle volume $V_A^{(1)}$, as shown in Figure 3. This is the so-called overload effect. Although the real cause of this effect is presently not fully understood, Morrow (1988) postulated that it was due to a decrease in alveolar macrophage mobility caused by phagocytosis of an excessive number of particles, as well as by volumetric increase of macrophage size due to the phagocytized particles. On the basis of this hypothesis, several mechanistic models have recently been proposed to explain the experimental findings (Yu et al., 1989; Stober et al., 1990). These models divide the alveolar region of the lung into several compartments to account for various pathways of particle translocation and clear-

ance in this region. The rate in each pathway may vary with particle loading, resulting in an overall change of the alveolar clearance rate with lung burden. However, because large numbers of transport rates are involved in these models, a ready extrapolation to humans is not currently possible.

Another approach to model the impairment of $\lambda_A^{(1)}$ at high $m_A^{(1)}$ in clearance is to use an empirical equation of $\lambda_A^{(1)}$ as a function of $m_A^{(1)}$ or $V_A^{(1)}$, derived from the experimental data. Such an approach was adopted by Yu et al. (1991). The empirical equation for $\lambda_A^{(1)}$ derived by Yu et al. (1991) was based upon the data for diesel exhaust particles from a single study by Strom et al. (1988). A more accurate expression can be obtained by using all the data in Figure 3. This gives

$$\frac{\lambda_A^{(1)}}{\lambda_{A0}^{(1)}} = \exp\left[-7.16\left(\frac{V_A^{(1)}}{V_{AM}}\right)^{0.95}\right] \tag{3}$$

where $\lambda_{A0}^{(1)} = 0.0128\ \text{day}^{-1}$ is the alveolar clearance rate at $V_A^{(1)} \to 0$, and V_{AM} is the total volume of alveolar macrophages and is equal to 26 mm^3 for rats (Table 1). At a lung burden of 1.5 mg/lung, $V_A^{(1)} = 1\ \text{mm}^3$. The value of $\lambda_A^{(1)}$ is reduced by 28% according to Eq. (3).

The alveolar clearance rates of particle-associated organics $\lambda_A^{(2)}$ and $\lambda_A^{(3)}$ were determined by Yu et al. (1991) using the experimental data of Sun et al.

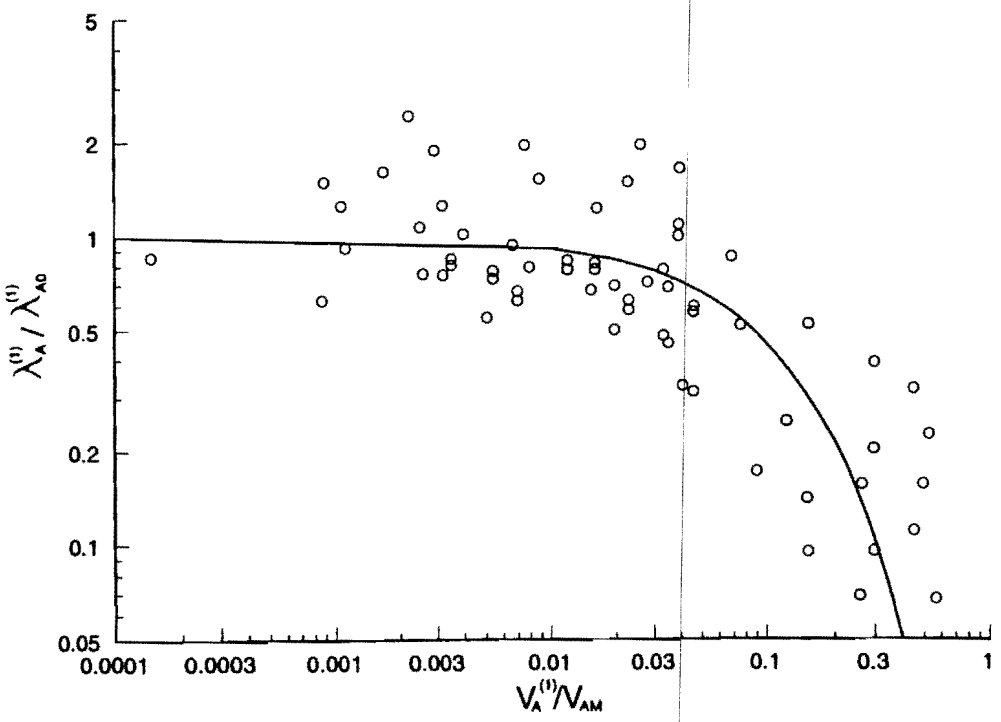

FIGURE 3. Variation of $\lambda_A^{(1)}/\lambda_{A0}^{(1)}$ as a function of $V_A^{(1)}/V_{AM}$ for insoluble particles. Data (open circles) were from various studies and compiled by Yu et al. (1989). The solid line is Eq. (3).

(1984) for benzo[a]pyrene (BaP) and Bond et al. (1986) for nitropyrene (NP). Because the organics are bound to particles, these rates are also a function of $m_A^{(1)}$. For low $m_A^{(1)}$ or weak binding, the approximate values of $\lambda_A^{(2)}$ and $\lambda_A^{(3)}$ are

$$\lambda_A^{(2)} \cong 0.0288 \text{ day}^{-1} \tag{4}$$

$$\lambda_A^{(3)} \cong 15.7 \text{ day}^{-1} \tag{5}$$

Equations (3)–(5) are to be used in Eq. (1) for calculating $m_A^{(i)}$ at a given exposure rate. When the exposure rate is sufficiently high, lung overload condition will occur due to the effect of Eq. (3).

EXTRAPOLATION OF RAT CLEARANCE MODEL TO HUMANS

Experimental data on deposition and clearance of diesel exhaust particles in humans are not available. In order to estimate the lung burden of these particles for human exposures, the retention model for rats was extrapolated to humans. The kinetic equation that determines $m_A^{(i)}$ during exposure was a version of Eq. (1) in which $r_A^{(i)}$ was replaced by the deposition rate in humans. The values of $\lambda_A^{(i)}$ in this equation were unknown, however, and they were determined by extrapolating the rat's results. Schanker et al. (1986) demonstrated that the lung clearance rate of inhaled lipophilic compounds was independent of species. We may therefore assume that $\lambda_A^{(2)}$ and $\lambda_A^{(3)}$ for humans are about the same as for rats. In contrast, the clearance rate of the carbon core was species dependent. Differences in the alveolar clearance rates of insoluble particles at low lung burdens among species were observed in numerous studies (e.g., Bailey et al., 1982, 1985; Snipes et al., 1983, 1989). Respective retention half-times ranged from about 50 to 100 days in rats, mice, and hamsters to several hundred days in dogs, guinea pigs, and humans. The reason for such a large interspecies difference is not yet understood. The number of respiratory bronchioles, particle deposition pattern, clearance pathway length, and alveolar macrophage number and mobility may all contribute to the differences. Assuming that the carbon core is cleared from the human lung as other insoluble particles are, we obtained a value of $\lambda_{A0}^{(1)} = 0.00169 \text{ day}^{-1}$ for humans using the data of Bailey et al. (1982). This is about 7.6 times less than the value of $\lambda_{A0}^{(1)}$ observed for rats.

There are, as yet, no data available on the change in alveolar clearance due to excessive lung burdens in humans. Although human exposures to environmental diesel exhaust are not likely to result in lung overload, such a condition may occur in occupational settings. It is therefore necessary to derive relationships between clearance rates and lung burdens in order to determine the exposure conditions under which overload might occur. Yu et al. (1991) assumed that the mechanical clearance rate of carbon core for

humans varied with the specific particulate dose to the alveolar surface in the same proportion as in the rats, while the dissolution rate of the particle-associated organics was species independent. A different approach is proposed here for the carbon core. We assume that Eq. (3) is valid for all species; that is, the clearance rate slows down when the alveolar particle volume $V_A^{(1)}$ reaches a significant fraction of V_{AM}. This is consistent with the hypothesis of Morrow (1988) for lung overload, but it requires experimental justification by future studies. For humans, Table 1 gives $V_{AM} = 1.75 \times 10^4$ mm^3, which is 673 times higher than the rat value. Thus, for same $V_A^{(1)}$, the reduction of $\lambda_A^{(1)}$ in humans due to higher lung burdens is much smaller than that in rats.

MODELING RESULTS

Equation (1) was used to calculate alveolar lung burdens of the carbon core and the particle-associated organics in humans and rats using the values of $\lambda_A^{(i)}$ given by Eqs. (3)–(5). The calculations were based on nose breathing at a tidal volume and breathing rate shown in Table 1. The particle conditions used were again 0.2 μm MMAD with $\sigma_g = 2.3$, and mass fractions of the strongly and weakly bound organics were each 10%.

Figures 4 and 5 show, respectively, the results of the carbon core and particle-associated organics for a 2-yr continuous exposure (8 h/day and 5 days/wk) at particle concentration of 1 mg/m^3. The diesel soot burden in

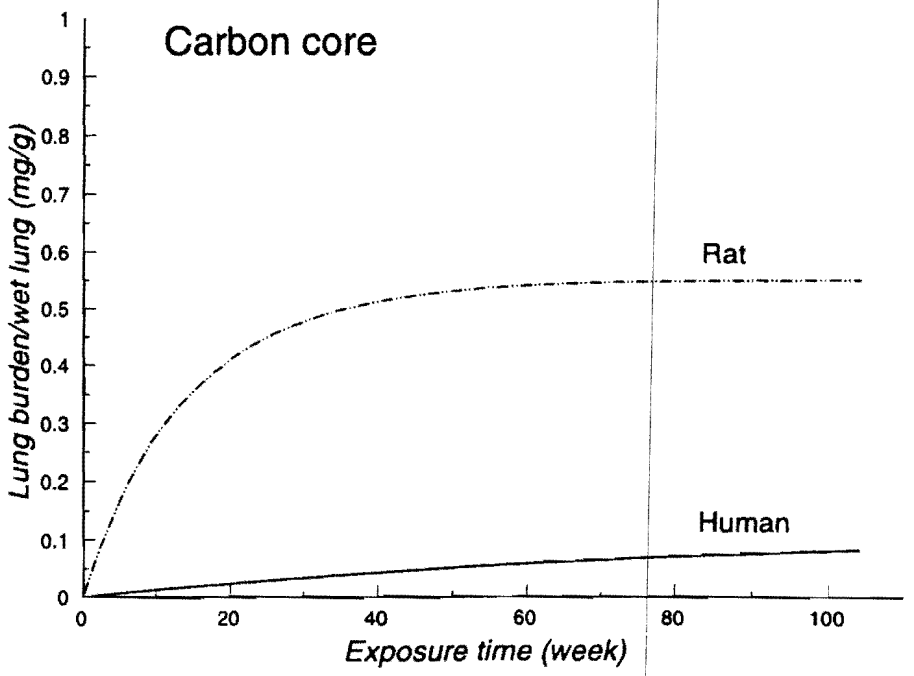

FIGURE 4. Calculated lung burdens of the carbon core of diesel exhaust particles in humans and rats for a 2-yr continuous exposure (8 h/day, 5 days/wk) at particle concentration of 1 mg/m^3.

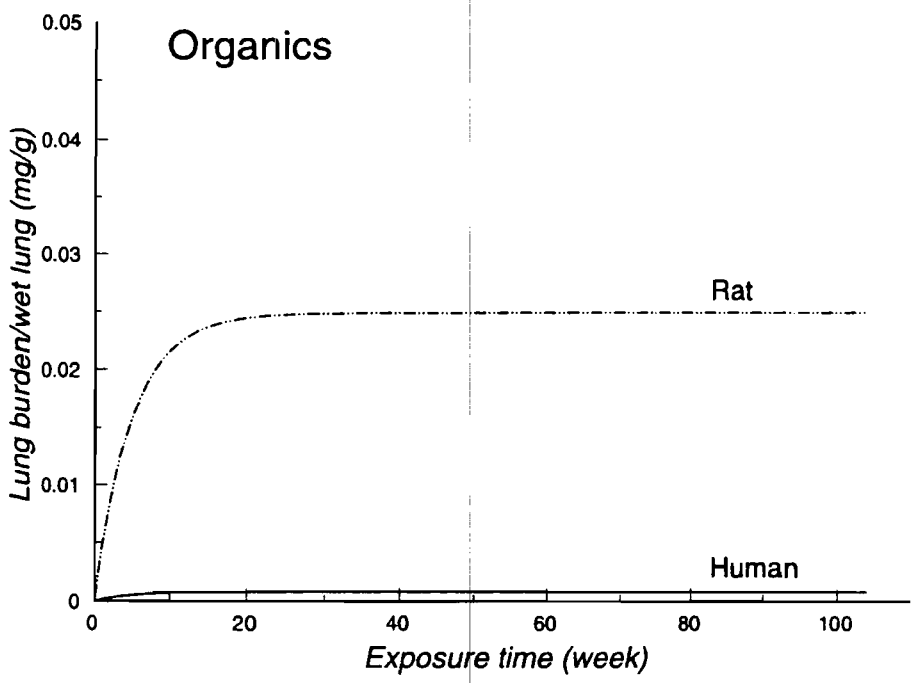

FIGURE 5. Calculated lung burdens of the particle-associated organics of diesel exhaust particles in humans and rats for a 2-yr continuous exposure (8 h/day, 5 days/wk) at particle concentration of 1 mg/m^3.

humans per gram of lung was calculated to be 0.078 mg after 2 yr of exposure versus 0.78 mg found in rats. For organics, the respective values of humans and rats are 0.78×10^{-3} mg and 0.033 mg per gram of lung. Thus, when exposed to the same concentration of diesel exhaust, the specific lung burdens in humans are about 10 times smaller for the carbon core and 43 times smaller for organics than that in rats.

To predict the effect of lung overload in humans, the lung burden of the carbon core per unit concentration of diesel exhaust was calculated in humans using concentrations 0.1 mg/m^3 and 1.0 mg/m^3 for two different exposure patterns, (A) 24 h/day and 7 days/wk, and (B) 8 h/day and 5 days/wk, simulating environmental and occupational exposure conditions. The results are shown in Figure 6 for a 10-yr exposure period. In this model, the lung burdens reached approximately steady-state values during exposure. Due to differences in the amount of particle intake, the steady-state lung burdens per unit concentration were higher for exposure pattern (A). Also, increasing particle concentration from 0.1 to 1 mg/m^3 increased the lung burden per unit concentration. However, the increase was not noticeable for exposure pattern (B). The dependence of lung burden on particle concentration is caused by the reduction of alveolar clearance rate at high lung burdens given by Eq. (3). The results in Figure 6 are slightly lower than that predicted earlier by Yu et al. (1991) in humans using a lung surface area extrapolation relationship from the data of rats.

CONCLUSIONS

The materials just presented offer a description of processes involved in modeling the deposition and clearance of inhaled particles in humans and rats. The most difficult and crucial task in the modeling process was the determination of the intercompartmental transport rates for each material component of the particle. Usually it is the knowledge of the transport rates that dictates the structure and sophistication of a model.

Because the transport rates are readily measured in rodents, extrapolation of these rates to humans was necessary in developing the human retention model. In the example of diesel exhaust particles discussed in this article, the extrapolation was made by assuming that reduction of alveolar macrophage clearance at high lung burdens was a function of the volumetric fraction of the retained particles in alveolar macrophages and was independent of species. It was also assumed that there were no species differences in the dissolution rates of the particle-associated organics. Future studies are called for to justify these assumptions.

Another important consideration that has not been addressed is variability. All the parameters used in the model study are single numbers that were determined from limited available data. For example, the carbon core clearance rate $\lambda_A^{(1)}$ was obtained by best fitting the available data for insoluble particles, and $\lambda_A^{(2)}$ and $\lambda_A^{(3)}$ were chosen from the data for two specific

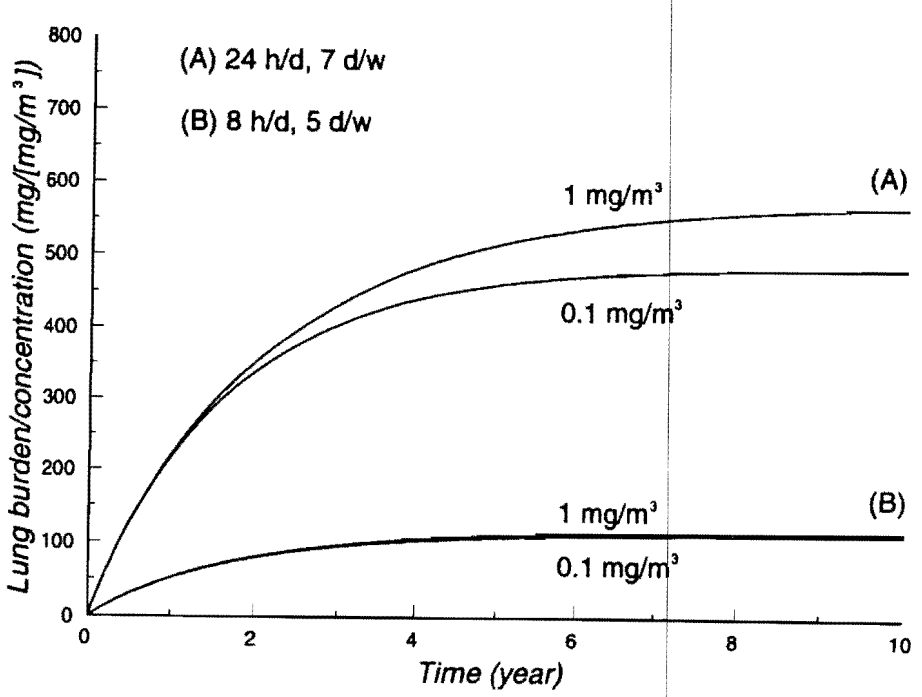

FIGURE 6. Calculated lung burdens of the carbon core of diesel exhaust particles per unit exposure concentration in humans at concentrations of 0.1 and 1.0 mg/m³. Exposure patterns are (A) 24 h/day, 7 days/wk, and (B) 8 h/day, 5 days/wk.

organic compounds. The extent to which they are representative of reality has a high degree of uncertainty. In addition, other factors such as age, preexisting disease, and smoking habit can also affect deposition, clearance, and retention. Thus, the results of lung burden for humans presented in this paper should be interpreted with care.

Several conclusions can be drawn from the modeling results of diesel exhaust particles in humans and rats:

1. Because of the differences in airway structure, airway size, and ventilation conditions, the particle deposition rate per gram of lung in rats is about 32 times higher than in humans.
2. When humans and rats are exposed to diesel exhaust for the same period of time, the lung burdens of the carbon core and the associated organics per gram of lung are much higher in rats than in humans, although humans have a slower alveolar clearance rate for the carbon core.
3. During a continuous exposure, the lung burdens of the carbon core and the associated organics will eventually reach a steady state, even at high concentrations. The steady-state burden per unit concentration generally increases with the concentration, due to the overload effect.
4. Modeling results suggest that excessive particle accumulation may begin to be apparent in humans, due to lung overload, at particle concentrations of approximately 1 mg/m^3 and greater with chronic exposures.

The retention models of diesel exhaust particles in rats and humans presented in this article can be readily modified and applied to other similar types of particles such as carbon black and titanium dioxide. The information needed to develop models for such particles are particle structure and size, mass density, and transport and clearance rates.

REFERENCES

Bailey, M. R., Fry, F. A., and James, A. C. 1982. The long-term clearance kinetics of insoluble particles from the human lung. *Ann. Occup. Hyg.* 26:273–289.

Bailey, M. R., Hodgson, A., and Smith, H. 1985. Respiratory tract retention of relatively insoluble particles in rodents. *J. Aerosol Sci.* 16:279–293.

Bond, J. A., Sun, J. D., Medinsky, M. A., Jones, R. K., and Yeh, H. C. 1986. Deposition, metabolism and excretion of 1-[^{14}C]nitropyrene and 1-[^{14}C]nitropyrene coated on diesel exhaust particles as influenced by exposure concentration. *Toxicol. Appl. Pharmacol.* 85:102–117.

Chan, T. L., Lee, P. S., and Herring, W. E. 1981. Deposition and clearance of inhaled diesel exhaust particles in the respiratory tract of Fischer rats. *J. Appl. Toxicol.* 1:77–82.

Chan, T. L., Lee, P. S., and Herring, W. E. 1984. Pulmonary retention of inhaled diesel particles after prolonged exposures to diesel exhaust. *Fundam. Appl. Toxicol.* 4:624–631.

Cheng, Y. S., Yeh, H. C., Mauderly, J. L., and Mokler, B. V. 1984. Characterization of diesel exhaust in a chronic inhalation study. *Am. Ind. Hyg. Assoc. J.* 45:547–555.

Dethloff, L. A., and Lehnert, B. E. 1987. Compartmental origin of pulmonary macrophages harvested from mechanically disrupted lung tissue. *Exp. Lung Res.* 13:361–383.

Hansen, J. E., and Ampaya, E. P. 1975. Human air space, shape, size, areas and volumes. *J. Appl. Physiol.* 38:990–995.

Morrow, P. E. 1988. Possible mechanisms to explain dust overloading of the lungs. *Fundam. Appl. Toxicol.* 10:369–384.

Olson, D. E., Dart, G. A., and Filley, G. F. 1970. Pressure drop and fluid flow regime of air inspired into the human lung. *J. Appl. Physiol.* 28:482–494.

Schanker, L. S., Mitchell, E. W., and Brown, R. A. 1986. Species comparison of drug absorption from the lung after aerosol inhalation or intratracheal injection. *Environ. Health Perspect.* 47:65–80.

Schum, G. M., and Yeh, H. C. 1980. Theoretical evaluation of particle deposition in anatomical models of mammalian lung airways. *Bull. Math. Biol.* 42:1–15.

Snipes, M. B., Boecker, B. B., and McClellan, R. O. 1983. Retention of monodisperse or polydisperse alluminosilicate particles inhaled by dogs, rats and mice. *Toxicol. Appl. Pharmacol.* 69:345–362.

Snipes, M. B. 1989. Long-term retention and clearance of particles inhaled by mammalian species. *CRC Crit. Rev. Toxicol.* 20:175–211.

Stober, W., Morrow, P. E., and Morawietz, G. 1990. Alveolar retention and clearance of insoluble particles in rats simulated by a new physiologically-oriented compartmental kinetic model. *Fundam. Appl. Toxicol.* 15:329–349.

Strom, K. A., Chan, T. L., and Johnson, J. T. 1988. Pulmonary retention of inhaled submicron particles in rats: Diesel exhaust particles and lung retention model. In *Inhaled particles VI,* eds. J. Dodgson, R. I. McCallum, M. R. Bailey, and D. R. Fisher, pp. 645–658. Oxford, England: Pergamon Press.

Sun, J. D., Wolff, R. K., Kanapilly, G. M., and McClellan, R. O. 1984. Lung retention and metabolic fate of inhaled benzo[a]pyrene associated with diesel exhaust particles. *Toxicol. Appl. Pharmacol.* 73:48–59.

Weibel, E. R. 1963. *Morphometry of the human lung.* Berlin: Springer Verlag.

Xu, G. B., and Yu, C. P. 1987. Deposition of diesel exhaust particle in mammalian lungs. *Aerosol Sci. Technol.* 7:117–123.

Yeh, H. C., and Schum, G. M. 1980. Models of human lung airways and their application to inhaled particle deposition. *Bull. Math. Biol.* 42:461–480.

Yu, C. P., and Xu, G. B. 1986. Predictive models for deposition of diesel exhaust particulates in human and rat lungs. *Aerosol Sci. Technol.* 5:337–347.

Yu, C. P., Chen, Y. K., and Morrow, P. E. 1989. An analysis of alveolar macrophage mobility kinetics at dust overloading of the lung. *Fundam. Appl. Toxicol.* 13:452–459.

Yu, C. P., Yoon, K. J., and Chen, Y. K. 1991. Retention modeling of diesel exhaust particles in rats and humans. *J. Aerosol Med.* 4:79–115.