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Retention Modeling of Diesel Exhaust Particles in Rats and Humans

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Includes the Commentary of the Institute's Health Review Committee

Research Report Number 40

HEALTH EFFECTS INSTITUTE

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TABLE OF CONTENTS

Research Report Number 40

Retention Modeling of Diesel Exhaust Particles in Rats and Humans

INVESTIGATORS' REPORT C. P. Yu and K. J. Yoon

HEALTH REVIEW COMMITTEE'S COMMENTARY Health Effects Institute

Retention Modeling of Diesel Exhaust Particles in Rats and Humans

C. P. Yu[1] and K. J. Yoon

ABSTRACT

The objective of this study was to predict the lung burden in rats and humans of diesel exhaust particles from automobile emissions by means of a mathematical model. We previously developed a model to predict the deposition of diesel exhaust particles in the lungs of these species. In this study, the clearance and retention of diesel exhaust particles deposited in the lung are examined.

A diesel particle is composed of a carbonaceous core (soot) and adsorbed organics. These materials can be removed from the lung after deposition by two mechanisms: (1) mechanical clearance, provided by mucociliary transport in the ciliated airways as well as macrophage phagocytosis and migration in the nonciliated airways, and (2) clearance by dissolution. To study the clearance of diesel exhaust particles from the lung, we used a compartmental model consisting of four anatomical compartments: nasopharyngeal, tracheobronchial, alveolar, and the lung-associated lymph node compartments. We also assumed a particle model made up of material components according to the characteristics of clearance: (1) a carbonaceous core of about 80 percent of particle mass, (2) slowly cleared organics of about 10 percent of particle mass, and (3) fast-cleared organics accounting for the remaining 10 percent of particle mass.

The kinetic equations of the retention model were first developed for Fischer-344 rats. The transport rates of each material component of diesel exhaust particles (soot, slowly cleared organics, and fast-cleared organics) were derived using available experimental data and several mathematical approximations. The lung burden results calculated from the model showed that although the organics were cleared at nearly constant rates, the alveolar clearance rate of diesel soot decreased with increasing lung burden. This is consistent with existing experimental observations. At low lung burdens, the alveolar clearance rate of diesel soot was a constant, equal to the normal clearance rate controlled by macrophage migration to the mucociliary escalator, whereas at high lung burdens, the clearance rate was determined principally by transport to the lymphatic system.

The retention model of diesel exhaust particles for rats was extrapolated to humans of different age groups, from birth to adulthood. To derive the transport rates for the human model, the mechanical clearance from the alveolar region of the lung was assumed to be dependent on the specific particulate burden on the alveolar surface. The reduction in the mechanical clearance in adult humans caused by exposure to high concentrations of diesel exhaust was found to be much less than that observed in rats. The reduction in children was greater than that in adults. For clearance by dissolution, the transport rates were assumed to be the same for humans and rats.

We combined the retention and deposition models for diesel exhaust particles to compute the accumulated mass of diesel soot and the associated organics in various compartments of the human lung under different exposure conditions. The lung burdens of both diesel soot and the associated organics were found to be much higher in humans than in rats for the same period of exposure because of the higher particle intake and slower clearance rate in humans. The reduction in clearance caused by excessive lung burdens would not occur in humans if the exposure concentration were kept below 0.05 mg/m^3. Also, it was found that for the same exposure, the lung burden per unit of lung weight was higher in children and reached a maximum at about five years of age. These results are of use in assessing the health risk of exposure to diesel exhaust particles.

INTRODUCTION

Diesel-powered motor vehicles provide considerably higher fuel economy and reduced exhaust emissions of carbon monoxide and hydrocarbons than do equally performing gasoline engines. However, they also produce significantly more particulate matter. These particles consist principally of a combustion-generated carbonaceous core on which various amounts of solvent-extractable organic compounds are adsorbed. Some of these compounds are carcinogens and mutagens (Schuetzle 1983).

The health effects of exposure to diesel exhaust have been of public concern for many years and continue to be, given the potentially increased use of diesel engines in future forms of transportation. Long-term exposure of animals to high concentrations of inhaled diesel exhaust conducted at different laboratories have shown that there is an accumulation of diesel soot (Chan et al. 1981, 1984; Griffis et al. 1983;

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Heinrich et al. 1986; Wolff et al. 1987; Strom et al. 1988), formation of DNA adducts (Wolff et al. 1986), and incidence of tumors (Brightwell et al. 1986; Ishinishi et al. 1986; Iwai et al. 1986; Stöber 1986; Mauderly et al. 1987) in the lungs of rats. No carcinogenic effects of diesel exhaust were observed in hamsters (Heinrich et al. 1982, 1986), and conflicting results were reported in mice (Orthoefer et al. 1981; Pepelko 1982; Heinrich et al. 1986).

Controlled experiments of diesel exposure have not been conducted on humans. Epidemiological studies on the health effects of diesel exhaust are inconclusive. A study by the British Medical Research Council, which evaluated London bus workers, claimed that diesel exhaust posed no serious threat to public health (Waller 1980). However, other studies conducted more recently (Harris 1983; Garshick et al. 1988) appear to show a definite relationship between exposure and lung cancer risk. Despite all these uncertainties, it is clear that the potential hazards of diesel exhaust are directly related to diesel concentration and duration of exposure. Because exposure to the gas phase of diesel exhaust does not result in tumor formation (Heinrich et al. 1986), work has focused on the effects of the particulate phase. Central to any risk assessment of the particulate phase is knowledge of the amount of inhaled particles deposited in the lung during an exposure and the subsequent fate of the particulate-phase components after deposition.

Mathematical models have often been used to complement experimental studies of the deposition and clearance of inhaled particles in the lungs. They not only enhance our understanding of the exposure-dose-response relationship for rats, but also provide a quantitative basis for extrapolating the data to humans. The deposition of diesel particles in laboratory species and humans was investigated using mathematical models in a previous study (Yu and Xu 1987b; see also Yu and Xu 1986, 1987a; Xu and Yu 1987). The predicted deposition results in animals from this study were verified by actual experimental data. Although modeling studies on clearance and retention have been conducted previously by many investigators (for a review see Morrow and Yu 1985; Oberdorster 1989), few studies dealt specifically with diesel exhaust (Soderholm 1982; Strom et al. 1988). In these studies, efforts were made to simulate the measured accumulations of diesel soot in rat lungs at high inhaled concentrations using mathematical models. The clearance of the particle-associated organics from the lung was not addressed. Because the organics contain certain polycyclic aromatic hydrocarbons that are mutagenic (Lewtas 1983; Brooks et al. 1984) and carcinogenic (El-Bayoumy et al. 1984), there is a critical need to establish a complete retention model that simulates the transport and removal of both diesel soot and the associated organics in the lung.

SPECIFIC AIMS

The specific aims of this study were to develop a mathematical retention model of diesel exhaust particles (DEPs)[2] in the lungs of rats on the basis of available experimental data, and to extrapolate this model from rats to humans for predictive uses. The model would consider two special features of clearance for DEPs: (1) the composition of the particle, that is, carbonaceous core and the associated organics, and (2) the reduction of the clearance rate of diesel soot at high lung burdens. The retention model developed in this study, in conjunction with the deposition model of DEPs developed earlier, would then be used to calculate accumulations of different material components of DEPs in various anatomical compartments of the lung during exposure.

METHODS

PARTICLE MODEL FOR CLEARANCE STUDY

Diesel exhaust particles are irregularly shaped aggregates with a mass median aerodynamic diameter (MMAD) of approximately 0.2 μm. The adsorbed organics generally account for 10 to 30 percent of the particle mass. The exact size distribution of DEPs and the amounts and specific composition of the adsorbed organic compounds depend on many factors including engine design, fuels used, engine operating conditions, and thermodynamic processes that occur during exhaust. Extensive reviews of the physical and chemical characteristics of DEPs were made, respectively, by Amann and Siegla (1982) and Schuetzle (1983).

To develop a mathematical model that simulates the deposition and clearance of DEPs in the lung, appropriate particle models characterizing a diesel particle must first be introduced. In the deposition study, we employed an equivalent sphere model for diesel soot with different aerodynamic, diffusional, and interceptional diameters to simulate the dynamics and deposition of DEPs by various mechanisms (Yu and Xu 1987b). In the present clearance study, we assumed that a diesel particle was composed of three material components according to their characteristic clearance rates: (1) a carbonaceous core of approximately 80 percent of particle mass, (2) adsorbed organics slowly cleared from the lung of about 10 percent of particle mass, and (3) adsorbed organics quickly cleared from the lung accounting for the remaining 10 percent of particle mass. The presence of two discrete organic phases in the particle model was suggested by observations that the removal of the

[2] A list of abbreviations appears at the end of this report for your reference.

particle-associated organics from the lung exhibited a biphasic clearance curve (Sun et al. 1984; Bond et al. 1986). This curve represents two major kinetic clearance phenomena: a fast phase of organic washout with a half-time of a few hours and a slow phase with a half-time that is a few hundred times longer. The detailed components involved in each phase of the clearance are not known. It is possible that the fast phase consists of organics that are leached out primarily by diffusion mechanisms while the slow phase might include any or all of the following components: (1) organics that are "loosened" before they are released; (2) organics that have become intercalated in the carbon core, which impedes release; (3) organics that are associated for longer periods of time due to hydrophobic interaction with other organic phase materials; (4) organics that have been ingested by macrophages, and as a result, effectively remain in the lung for a longer period of time due to metabolism by the macrophage—metabolites formed may interact with other cellular components; and (5) organics that have directly acted on cellular components, for example, by forming covalent bonds with DNA to form adducts.

The above distinction of the organic components is largely mechanistic, and it does not specifically imply the actual component nature of the organics adsorbed on the carbonaceous core. However, this distinction is necessary in appreciating the dual-phase nature of DEPs. For aerosols made of pure organics, such as benzo[*a*]pyrene (B*a*P) and nitropyrene (NP), in the same size range of DEPs, Sun and colleagues (1984) and Bond and associates (1986) observed a nearly monophasic clearance curve. This might be explained by the absence of intercalative phenomena (2) and of hydrophobic interaction imposed by a heterogeneous mixture of organics (3). The measurement of a pure organic might also neglect that quantity that has become intracellular (4) or covalently bound (5).

RETENTION MODEL AND KINETIC EQUATIONS

Diesel exhaust particles are removed from the lung by two principal mechanisms: (1) mechanical clearance, provided by mucociliary transport in the ciliated airways, macrophage phagocytosis, and migration in the nonciliated airways, and (2) clearance by dissolution. Under normal circumstances, diesel soot is removed by mechanical transport, and the particle-associated organics are removed by dissolution. To study the transport and removal of DEPs from the lungs, we used a compartmental 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 1. In addition, we used two outside compartments, the blood (*B*) and gastrointestinal tract (*G*). The alveolar compartment in the model is

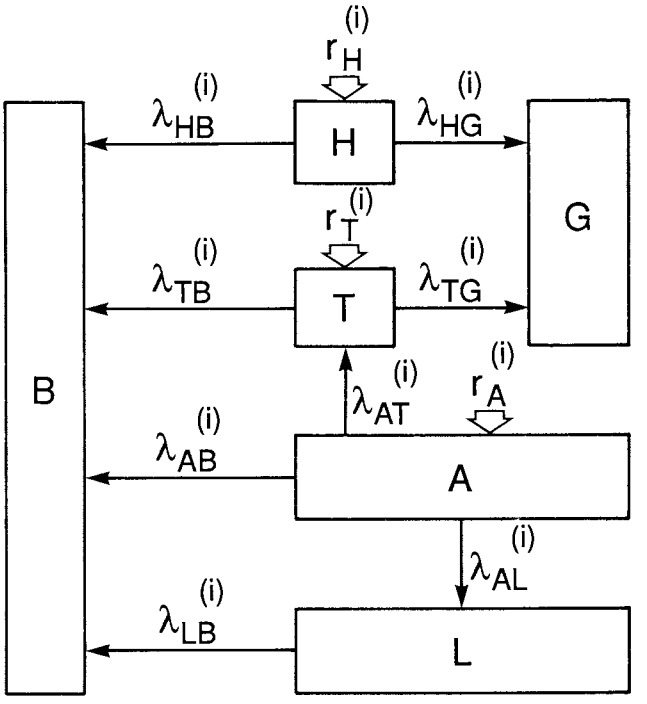

Figure 1. Compartmental model of diesel particle retention. H = head; T = tracheobronchial; A = alveolar; L = lung-associated lymph nodes; B = blood; G = gastrointestinal tract; $\lambda^{(i)}$ terms are the transport rates for the compartments indicated in the subscript; and $r^{(i)}$ terms are the mass deposition rates for the compartments indicated in the subscript.

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 the two outside compartments in the model therefore provides a complete description of all clearance processes involved.

In Figure 1, $r_H^{(i)}$, $r_T^{(i)}$, and $r_A^{(i)}$ are, respectively, the mass deposition rates of DEP material component i (i = 1 [core], 2 [slowly cleared organics], and 3 [fast-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.

Let the mass fraction of material component i of a diesel particle be f_i. Then

$$r_H^{(i)} = f_i r_H , \quad (1)$$

$$r_T^{(i)} = f_i r_T , \quad (2)$$

$$r_A^{(i)} = f_i r_A , \quad (3)$$

where r_H, r_T, and r_A are, respectively, the total mass deposition rates of DEPs in the H, T, and A compartments, determined from the equations

$$r_H = C(TV)(RF)(DF)_H , \quad (4)$$

$$r_T = C(TV)(RF)(DF)_T , \quad (5)$$

$$r_A = C(TV)(RF)(DF)_A . \quad (6)$$

In equations 4 through 6, C is the mass concentration of DEPs in the air, TV is the tidal volume, RF is the respiratory frequency, and $(DF)_H$, $(DF)_T$, and $(DF)_A$ are, respectively, the deposition fractions of DEPs in H, T, and A compartments over a respiratory cycle. The values of $(DF)_H$, $(DF)_T$, and $(DF)_A$, which vary with particle size, breathing conditions, and lung architecture, were determined from our deposition model (Yu and Xu 1987b).

The differential equations for $m_X^{(i)}$, the mass of material component i in compartment X, as a function of exposure time t can be written as

Head (H)

$$dm_H^{(i)}/dt = r_H^{(i)} - \lambda_{HG}^{(i)} m_H^{(i)} - \lambda_{HB}^{(i)} m_H^{(i)} , \quad (7)$$

Tracheobronchial (T)

$$dm_T^{(i)}/dt = r_T^{(i)} + \lambda_{AT}^{(i)} m_A^{(i)} - \lambda_{TG}^{(i)} m_T^{(i)} - \lambda_{TB}^{(i)} m_T^{(i)} , \quad (8)$$

Alveolar (A)

$$dm_A^{(i)}/dt = r_A^{(i)} - \lambda_{AT}^{(i)} m_A^{(i)} - \lambda_{AL}^{(i)} m_A^{(i)} - \lambda_{AB}^{(i)} m_A^{(i)} , \quad (9)$$

Lymph nodes (L)

$$dm_L^{(i)}/dt = \lambda_{AL}^{(i)} m_A^{(i)} - \lambda_{LB}^{(i)} m_L^{(i)} . \quad (10)$$

Equation 9 may also be written as

$$dm_A^{(i)}/dt = r_A^{(i)} - \lambda_A^{(i)} m_A^{(i)} , \quad (11)$$

where

$$\lambda_A^{(i)} = \lambda_{AT}^{(i)} + \lambda_{AL}^{(i)} + \lambda_{AB}^{(i)} \quad (12)$$

is the total clearance rate of material component i from the alveolar compartment.

The total mass of the particle-associated organics in compartment X is the sum of $m_X^{(2)}$ and $m_X^{(3)}$, and the total mass of DEPs in compartment X is equal to

$$m_X = m_X^{(1)} + m_X^{(2)} + m_X^{(3)} . \quad (13)$$

The lung burdens of diesel soot (core) and organics are defined, respectively, as

$$m_{Lung}^{(1)} = m_T^{(1)} + m_A^{(1)} , \quad (14)$$

$$m_{Lung}^{(2+3)} = m_T^{(2)} + m_A^{(2)} + m_T^{(3)} + m_A^{(3)} . \quad (15)$$

Because the clearance of diesel soot from compartment T is much faster than from compartment A, $m_T^{(1)} \ll m_A^{(1)}$ a short time after exposure, and equation 14 leads to

$$m_{Lung}^{(1)} \cong m_A^{(1)} . \quad (16)$$

Solutions to equations 7 through 10 can be obtained once all the transport rates $\lambda_{XY}^{(i)}$ are known. When $\lambda_{XY}^{(i)}$ are constant, which is the case with linear kinetics, equations 7 through 10 will have solutions that increase with time at the beginning of exposure but eventually saturate and reach a steady-state value. This is the classic retention model developed by the International Commission on Radiological Protection (ICRP) (1979). However, experimental data have shown that when rats were exposed to DEPs at high concentrations for a prolonged period, the diesel soot accumulated in various peribronchial and subpleural regions in the lungs and the long-term clearance was impaired (Chan et al. 1981, 1984; Griffis et al. 1983; Oberdorster et al. 1984; Heinrich et al. 1986; Wolff et al. 1987; Strom et al. 1988). No such change was observed regarding mucociliary clearance (Wolff et al. 1987). The reduction in the ability to clear particles from the deep lung at high lung burdens was also observed for other insoluble particles (Ferin and Feldstein 1978; Vincent et al. 1987; Muhle et al. 1988; Strom et al. 1989), as shown in Figure 2. This is called the overload effect. Although the real cause of this effect is presently unknown, Morrow (1988) postulated that it was due to a decrease in alveolar macrophage mobility caused by an excessive number of particle-laden cells, as well as by the volumetric increase of cell size due to phagocytized particles, rather than by the direct toxic effects of the particles. A functional relationship between the alveolar clearance rate and the lung burden has been derived mathematically on the basis of this hypothesis (Yu et al. 1989).

The continuous buildup of DEPs in the lung at high lung burdens during a prolonged exposure cannot be predicted by the classic ICRP model. A revised model, designed spe-

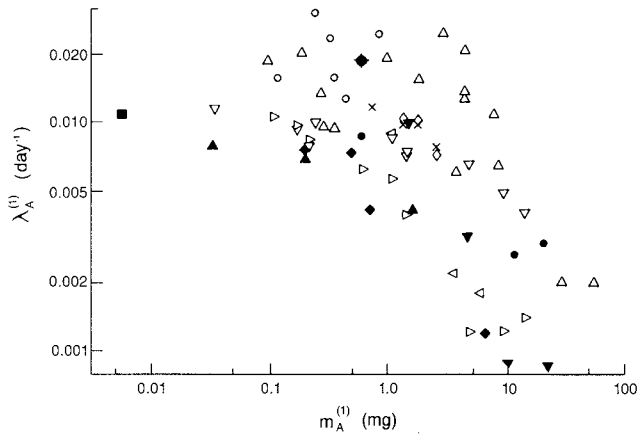

Figure 2. Comparison of $\lambda_A^{(1)}$ as a function of m_A in rats between DEPs and other insoluble particles based on the data from ■ Chan and coworkers (1981), ◆ Chan and coworkers (1984), ▲ Griffis and associates (1983), ◆ Oberdorster and colleagues (1984), ● Wolff and associates (1987), ▼ Strom and colleagues (1988) for DEPs; and data from ○ Ferin and Feldstein (1978), △ Vincent and coworkers (1987), ×, ▷, ▽, ◇ Muhle and associates (1988), and ◁ Strom and colleagues (1989) for other insoluble particles.

cifically for DEP removal from the lung, was proposed by Soderholm (1982) and improved by Strom and associates (1988). This model subdivided the alveolar region into two compartments on the basis of the physiology of clearance. The first compartment was associated with mobile, phagocytic macrophages and was called the macrophage compartment, and the second was identified by slowly moving, clustered, particle-laden macrophages and, therefore, was called the sequestering compartment. Although both compartments eliminate DEPs to the lymph nodes, the macrophage compartment also eliminates DEPs via mucociliary transport in the tracheobronchial tree to the gastrointestinal tract and to the sequestering compartment. Through the laborious task of fitting the calculated results from their model with experimental data, Strom and coworkers (1988) were able to find a set of transport rates between various compartments that give the best data fit. However, the uniqueness of their solution cannot be guaranteed because of the larger number of transport rates involved. The increased number of transport rates also prevents a ready extrapolation of the model to humans.

In the retention model proposed in Figure 1, the buildup of lung burdens and the introduction of overload effects were simulated mathematically using a single compartment for the alveolar region of the lung. The effect of sequestration was accounted for by a set of variable transport rates $\lambda_{AT}^{(i)}$, $\lambda_{AL}^{(i)}$, and $\lambda_{A}^{(i)}$ from this compartment such that $\lambda_{AT}^{(i)}$, $\lambda_{AL}^{(i)}$, and $\lambda_{A}^{(i)}$ are functions of m_A, which is the total mass of DEPs in compartment A. Without the hypothetical sequestering compartment in the model, the kinetic equations for transport of material (soot and organics) are considerably simplified, and are more readily used for interspecies extrapolation. The transport rates $\lambda_{A}^{(i)}$and $\lambda_{AL}^{(i)}$ in equations 7 through 10 can be determined directly from experimental data on lung and lymph node burdens, and $\lambda_{AT}^{(i)}$ and $\lambda_{AB}^{(i)}$ can be determined from equation 12.

SOLUTIONS TO KINETIC EQUATIONS

Equation 11 is a nonlinear differential equation of $m_A^{(i)}$ with known function of $\lambda_A^{(i)}$. For diesel soot, this equation becomes

$$dm_A^{(1)}/dt = r_A^{(1)} - \lambda_A^{(1)}(m_A)m_A^{(1)} . \quad (17)$$

Because clearance of the particle-associated organics is much faster than clearance of diesel soot, $m_A^{(2)}$ and $m_A^{(3)}$ constitute only a very small fraction of the total particle mass (less than one percent) after a long exposure, and we may consider $\lambda_A^{(1)}$ as a function of $m_A^{(1)}$ alone. Equation 17 is then reduced to a differential equation with $m_A^{(1)}$ as the only dependent variable.

For a constant $r_A^{(1)}$, equation 17 has a few simple solutions at limiting cases. At the beginning of an exposure, $\lambda_A^{(1)}m_A^{(1)}$ in equation 17 is much smaller than $r_A^{(1)}$ and the solution of equation 17 takes the form of

$$m_A^{(1)} = m_{A0}^{(1)} + r_A^{(1)}t , \quad (18)$$

where $m_{A0}^{(1)}$ is the value of $m_A^{(1)}$ at $t = 0$. Equation 18 represents a linear buildup of $m_A^{(1)}$ with time. This solution prevails for a long period of time if the soot concentration is high, a result observed in many experiments conducted at high levels of exposure (for example, Wolff et al. 1986). After longer periods of exposure, however, $\lambda_A^{(1)}m_A^{(1)}$ eventually reaches the value of $r_A^{(1)}$ and equation 17 has a steady state solution of

$$m_A^{(1)} = \frac{r_A^{(1)}}{\lambda_{A\infty}^{(1)}} , \quad (19)$$

where $\lambda_{A\infty}^{(1)}$ is the value of $\lambda_A^{(1)}$ as time approaches infinity. In this case, particle intake is balanced by removal due to clearance. The time required to reach the steady state increases with the exposure concentration.

The general solution to equation 17 for constant $r_A^{(1)}$ at any time, t, can be obtained by the separation of variables to give

$$\int_0^{m_A^{(1)}} \frac{dm_A^{(1)}}{r_A^{(1)} - \lambda_A^{(1)}m_A^{(1)}} = t . \quad (20)$$

If $r_A^{(1)}$ is an arbitrary function of t, equation 17 must be solved numerically such as by a Runge-Kutta method (Press et al. 1989). Once $m_A^{(1)}$ is found, the other kinetic equations 7 through 10 for both diesel soot and the particle-associated organics can be solved readily, since they are linear equations. The solutions to these equations for constant $r_H^{(i)}$, $r_T^{(i)}$, and $r_A^{(i)}$ are given in Appendix A.

The transport rates $\lambda_{XY}^{(i)}$ in the retention model formulated above need to be determined from experimental data. For instance, if the data for $m_X^{(i)}$ in every compartment during an exposure are known, $\lambda_{XY}^{(i)}$ can be determined from this information using the retention model. Up to the present time, a complete set of data is not available for both diesel soot and the particle-associated organics from a single exposure experiment. In this study, the transport rates of diesel soot and organics for rats were derived separately from the best data available to date. Because these data did not provide information for all transport rates, several approximations were used in the derivation.

DERIVATION OF TRANSPORT RATES OF DIESEL SOOT IN RATS

The transport rates of diesel soot in rats were derived using the lung burden and lymph node burden data from

a single experiment by Strom and colleagues (1988). Because other investigators (Griffis et al. 1983; Chan et al. 1984; Heinrich et al. 1986; Wolff et al. 1986) did not measure burden outside of the lung, data from these studies are not sufficient to determine the transport rates of diesel soot from compartment A to the other compartments in the retention model.

In the experiments of Strom and associates (1988), male Fischer-344 rats were exposed to diesel exhaust diluted to a nominal mass concentration of 6 mg/m^3 for 20 hours/day and 7 days/week for anywhere from 3 to 84 days. Animals were killed for as long as a year after exposure in order to obtain lung and lymph node burdens that would elucidate the mass dependency of particle retention. The experimental data showed that the lung burden accumulated in a nearly linear manner for the first 12 weeks of exposure, but approximated an exponential decline during the postexposure period, as shown in Figure 3. The magnitude of decline, however, decreased with the initial postexposure lung burden. To make the clearance more apparent, lung burdens were normalized by their initial postexposure values and were plotted as the percentage of retained mass in the lungs versus postexposure time, as shown in Figure 4. The lymph node burdens during postexposure were also measured and found to be strongly dependent on the initial postexposure lung burden (Figure 5).

To derive the expressions for $\lambda_A^{(1)}$ and $\lambda_{AL}^{(1)}$ as functions of $m_A^{(1)}$ from these data, we assumed a clearance model during postexposure in which $\lambda_A^{(1)}$ and $\lambda_{AL}^{(1)}$ depended only on the value of $m_A^{(1)}$ at the beginning of postexposure, $m_{Ap}^{(1)}$. The reason for this assumption is that the $m_A^{(1)}$ did not decrease

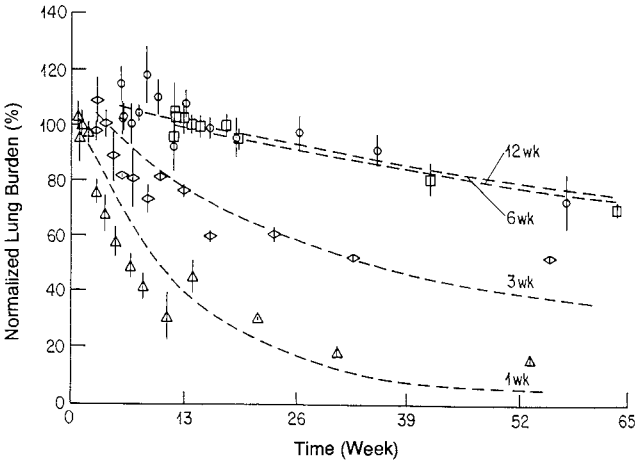

Figure 4. Experimental and predicted normalized lung burdens of rats exposed to DEPs at a concentration of 6.0 mg/m^3 for different exposure spans. The dashed lines are the predicted burdens during postexposure. The symbols represent the experimental data from Strom and colleagues (1988).

significantly over the postexposure period for each of the four postexposure experiments, but the differences between the initial postexposure lung burdens were much larger. Under this assumption, equation 17 can be written as

$$dm_A^{(1)}/dt = -\lambda_A(m_{Ap}^{(1)})m_A^{(1)}, \qquad (21)$$

and the solution to equation 21 is

$$m_A^{(1)}/m_{Ap}^{(1)} = \exp[-\lambda_A(m_{Ap}^{(1)})(t - t_p)], \qquad (22)$$

where t_p is the time at which the postexposure period starts and $m_{Ap}^{(1)}$ is the alveolar burden of diesel soot at t =

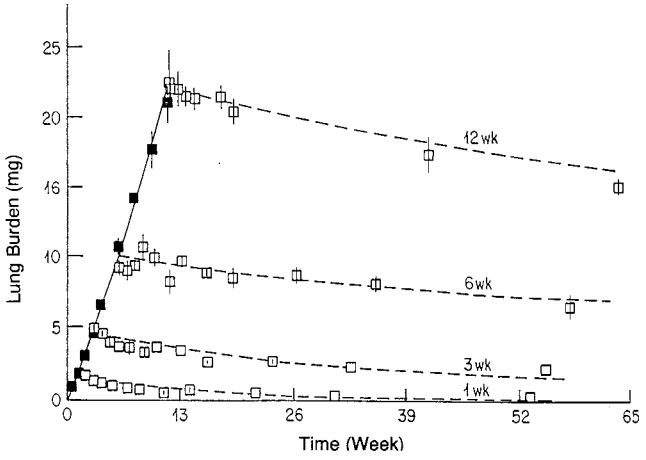

Figure 3. Experimental and predicted lung burdens of rats exposed to DEPs at a concentration of 6.0 mg/m^3 for 1, 3, 6, or 12 weeks. The solid line represents the predicted burdens during exposure and the dashed lines represent those during postexposure. Particle characteristics and exposure pattern are explained in the text. The symbols represent the experimental data from Strom and colleagues (1988).

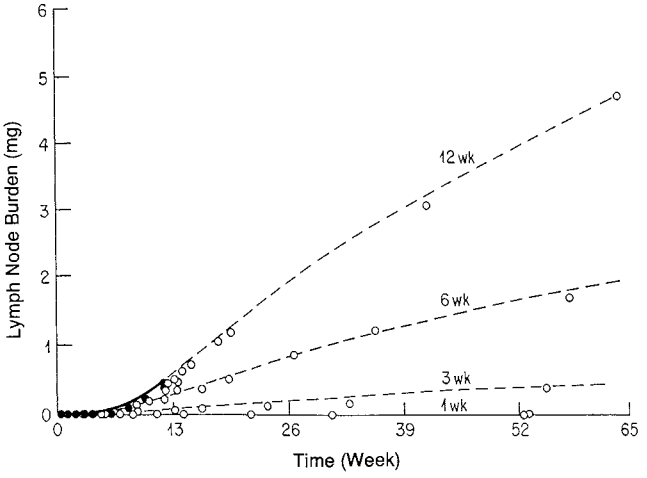

Figure 5. Experimental and predicted lymph node burdens of rats exposed to DEPs at a concentration of 6.0 mg/m^3 for 1, 3, 6, or 12 weeks. The solid line represents the predicted burdens during exposure and the dashed lines represent those during postexposure. Particle characteristics and exposure pattern are explained in the text. The symbols represent the experimental data from Strom and colleagues (1988).

t_p. Equation 22 was used to fit the individual data in Figure 3 by means of a nonlinear regression procedure (Dixon 1985). This procedure minimized the function $\sum_i (y_i - y_{ci})^2/y_i^2$ where y_i is the lung burden and y_{ci} is the calculated lung burden. The best statistical fits of the data resulted in four different values of $\lambda_A^{(1)}$, each corresponding to a given value of $m_{Ap}^{(1)}$, shown in Table 1.

The functional relationship between $\lambda_A^{(1)}$ and $m_{Ap}^{(1)}$ can be described by an exponential function of the form

$$\lambda_A^{(1)} = a \exp\left[-b(m_{Ap}^{(1)})^c\right] + d \text{ day}^{-1}, \quad (23)$$

where $m_{Ap}^{(1)}$ is expressed in milligrams, and the constants a, b, c, and d were found to be 0.012, 0.11, 1.76, and 0.00086, respectively, from the four sets of values of $\lambda_A^{(1)}$ and $m_{Ap}^{(1)}$. During exposure, equation 23 is modified by replacing $m_{Ap}^{(1)}$ with $m_A^{(1)}$, because $\lambda_A^{(1)}$ depends on the instantaneous value of $m_A^{(1)}$. It follows that

$$\lambda_A^{(1)} = 0.012 \exp\left[-0.11(m_A^{(1)})^{1.76}\right] + 0.00086 \text{ day}^{-1}. \quad (24)$$

Although derived at high levels of exposure, equation 24 can be utilized under any exposure condition. For the special case of low levels of exposure, $m_A^{(1)}$ should remain low and is limited to the steady-state value of

$$m_A^{(1)} = \frac{r_A^{(1)}}{\lambda_{A0}^{(1)}}, \quad (25)$$

where $\lambda_{A0}^{(1)} = 0.0129 \text{ day}^{-1}$ is the value of $\lambda_A^{(1)}$ obtained from equation 24 as $m_A^{(1)} \to 0$. In this case, the overload condition will never be reached.

To derive an expression for $\lambda_{AL}^{(1)}$ as a function of $m_A^{(1)}$ from the data for lymph node burden shown in Figure 5, we used the solution of equation 10 for diesel soot during postexposure. This solution is

$$m_L^{(1)} = \exp(-\lambda_{LB}^{(1)}t)\left[\int_{t_p}^{t} \lambda_{AL}^{(1)} m_A^{(1)} \exp(\lambda_{LB}^{(1)}t)dt + m_{Lp}^{(1)} \exp(\lambda_{LB}^{(1)}t_p)\right], \quad (26)$$

where $m_{Lp}^{(1)}$ is the lymph node burden of diesel soot at $t = t_p$.

Table 1. Values of $\lambda_A^{(1)}$ Derived from the Diesel Soot Retention Experiment of Strom and Colleagues (1988)

$m_{Ap}^{(i)}$ (mg)	$\lambda_A^{(1)}$ (day^{-1})
1.3	10.94×10^{-3}
4.8	2.97×10^{-3}
10	8.81×10^{-4}
22	8.60×10^{-4}

As in the derivation of $\lambda_A^{(1)}$, we again assumed that $\lambda_{AL}^{(1)}$ was only a function of $m_{Ap}^{(1)}$ because $m_A^{(1)}$ did not vary appreciably during postexposure. After substitution for $m_A^{(1)}$ in equation 22, equation 26 becomes

$$m_L^{(1)} - m_{Lp}^{(1)} \exp[-\lambda_{LB}^{(1)}(t - t_p)] = -\frac{m_{Ap}^{(1)}\lambda_{AL}^{(1)}}{\lambda_A^{(1)} - \lambda_{LB}^{(1)}} [\exp(-\lambda_A^{(1)}(t - t_p)) - \exp(-\lambda_{LB}^{(1)}(t - t_p))]. \quad (27)$$

There are no data currently available on the transport of diesel soot from various lung compartments to blood. Because of the small particle size, it is conceivable that the soot particles may penetrate the alveolar wall and enter the blood stream. Assuming this, we have

$$\lambda_{AB}^{(1)} = \lambda_{LB}^{(1)} = \text{constant}. \quad (28)$$

In addition, the mechanical transport of diesel soot from compartment A to compartment T was assumed to stop completely at very high $m_A^{(1)}$, that is,

$$\lim_{m_A^{(1)} \to \infty} \lambda_{AT}^{(1)} = 0. \quad (29)$$

Then, from equation 12, we obtain

$$\lambda_{AB}^{(1)} = \lim_{m_A^{(1)} \to \infty} (\lambda_A^{(1)} - \lambda_{AT}^{(1)} - \lambda_{AL}^{(1)}) = \lim_{m_A^{(1)} \to \infty} (\lambda_A^{(1)} - \lambda_{AL}^{(1)}). \quad (30)$$

With the use of equation 28, equation 27 becomes

$$m_L^{(1)} - m_{Lp}^{(1)} \exp[-\lambda_{AB}^{(1)}(t - t_p)] = -\frac{m_{Ap}^{(1)}\lambda_{AL}^{(1)}}{\lambda_A^{(1)} - \lambda_{AB}^{(1)}} [\exp(-\lambda_A^{(1)}(t - t_p)) - \exp(-\lambda_{AB}^{(1)}(t - t_p))]. \quad (31)$$

Again, as for $\lambda_A^{(1)}$, an exponential function was used to approximate the relationship between $\lambda_{AL}^{(1)}$ and $m_A^{(1)}$, and we have

$$\lambda_{AL}^{(1)} = \alpha \exp\left[-\beta(m_{Ap}^{(1)})^\gamma\right] + \delta. \quad (32)$$

Therefore, $\lambda_{AB}^{(1)} = d - \delta$. Equation 31 was used to compute α, β, γ, and δ from the best fits of four sets of data points for lymph node burden at different $m_{Lp}^{(1)}$, shown in Figure 5, following the same procedures used in determining $\lambda_A^{(1)}$. The values of α, β, γ, and δ were found to be -0.00068, 0.046, 1.62, and 0.00068, respectively. Thus,

$$\lambda_{AB}^{(1)} = d - \delta = 0.00018 \text{ day}^{-1}, \quad (33)$$

and during exposure

$$\lambda_{AL}^{(1)} = -0.00068 \exp\left[-0.046(m_A^{(1)})^{1.62}\right] + 0.00068 \text{ day}^{-1}. \quad (34)$$

Substituting equations 24, 33, and 34 into equation 12, we obtain

$$\lambda_{AT}^{(1)} = \lambda_{A}^{(1)} - \lambda_{AL}^{(1)} - \lambda_{AB}^{(1)}$$
$$= 0.012 \exp\left[-0.11(m_A^{(1)})^{1.76}\right] + 0.00068$$
$$\exp\left[-0.046\ (m_A^{(1)})^{1.62}\right] \text{ day}^{-1} . \quad (35)$$

The derived expressions for $\lambda_A^{(1)}$, $\lambda_{AL}^{(1)}$, $\lambda_{AT}^{(1)}$, and $\lambda_{AB}^{(1)}$ are plotted in Figure 6. It is apparent that the major component of $\lambda_A^{(1)}$ is $\lambda_{AT}^{(1)}$ when $m_A^{(1)}$ is smaller than 4 mg, and that $\lambda_A^{(1)}$ is dominated by $\lambda_{AL}^{(1)}$ when $m_A^{(1)}$ is larger than 12 mg.

An alternative approach to deriving the expressions for $\lambda_{AL}^{(1)}$ and $\lambda_{AT}^{(1)}$ is to assume that $\lambda_{AB}^{(1)} = 0$ (perfectly insoluble) instead of using equation 29. Because $\lambda_{AB}^{(1)}$ constitutes only a very small fraction of $\lambda_A^{(1)}$, this approach would change the lung burden calculation only slightly (less than 1.5 percent). Thus, the current approach is adequate and also offers a more general description of the clearance process.

To further illustrate the dependence of alveolar clearance rate $\lambda_A^{(1)}$ on particulate mass burden in the lungs, we plotted $\lambda_A^{(1)}/\lambda_{A0}^{(1)}$ versus $m_A^{(1)}$ per gram of lung in Figure 7, where, again, $\lambda_{A0}^{(1)}$ is the value of $\lambda_A^{(1)}$ for the limiting case of $m_A^{(1)} \to 0$. This permitted comparison between the alveolar clearance rate given by equation 24 and rates obtained from other studies of diesel soot retention (Griffis et al. 1983; Chan et al. 1984; Heinrich et al. 1986; Wolff et al. 1986) because only the ratio $\lambda_A^{(1)}/\lambda_{A0}^{(1)}$ was measured in some of these studies. Figure 7 shows that all data are consistent in that $\lambda_A^{(1)}/\lambda_{A0}^{(1)}$ decreases with increasing $m_A^{(1)}$, but there are substantial differences in magnitude among different studies.

DERIVATION OF TRANSPORT RATES OF PARTICLE-ASSOCIATED ORGANICS IN RATS

The clearance rates of particle-associated organics for rats were derived from the retention data of Sun and colleagues

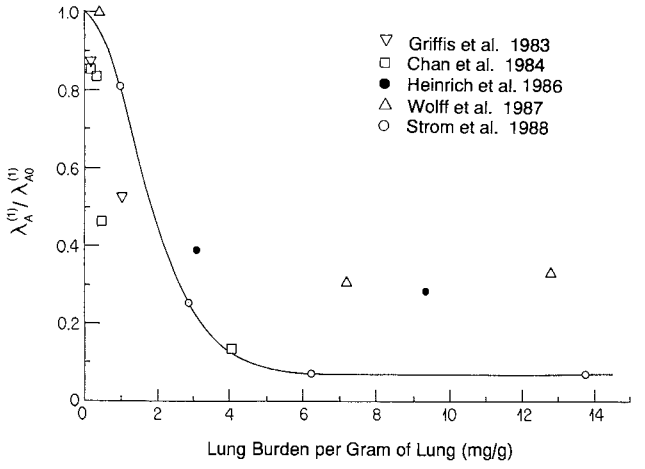

Figure 6. Dependence of dimensionless clearance rate $\lambda_A^{(1)}/\lambda_{A0}^{(1)}$ on $m_A^{(1)}$ per gram of lung. The solid line represents the theoretical results from equation 24. The symbols are the data points from various sources. The lung weight is assumed to be 1.5 g.

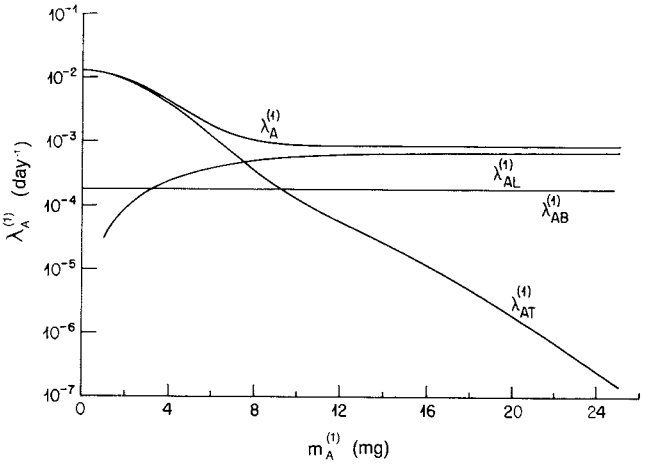

Figure 7. Variation of transport rates $\lambda_A^{(1)}$, $\lambda_{AL}^{(1)}$, $\lambda_{AT}^{(1)}$, and $\lambda_{AB}^{(1)}$ with $m_A^{(1)}$.

(1984) for BaP and the data of Bond and coworkers (1986) for NP adsorbed on diesel particles. The results of these measurements may be written in the following mathematical form:

$$\frac{m_A^{(2)} + m_A^{(3)}}{m_{Ap}^{(2)} + m_{Ap}^{(3)}} = \frac{f_2}{f_2 + f_3} \exp(-\lambda_A^{(2)} t) + \frac{f_3}{f_2 + f_3} \exp(-\lambda_A^{(3)} t) , \quad (36)$$

where $m_{Ap}^{(2)}$ and $m_{Ap}^{(3)}$ are, respectively, the values of $m_A^{(2)}$ and $m_A^{(3)}$ at the time at which the postexposure period starts, and

$$\lambda_A^{(2)} = \lambda_{AT}^{(2)} + \lambda_{AB}^{(2)} + \lambda_{AL}^{(2)} , \quad (37)$$

and

$$\lambda_A^{(3)} = \lambda_{AT}^{(3)} + \lambda_{AB}^{(3)} + \lambda_{AL}^{(3)} . \quad (38)$$

At low lung burdens, we have

$$\lambda_{AT}^{(2)} = \lambda_{AT}^{(3)} = \lambda_{AT}^{(1)} = \lambda_{AT0}^{(1)} , \quad (39)$$

$$\lambda_{A0}^{(2)} = \lambda_{AT0}^{(2)} + \lambda_{AB}^{(2)} + \lambda_{AL}^{(2)} , \quad (40)$$

and

$$\lambda_{A0}^{(3)} = \lambda_{AT0}^{(3)} + \lambda_{AB}^{(3)} + \lambda_{AL}^{(3)} , \quad (41)$$

where $\lambda_{AT0}^{(1)} = 0.0127$ day^{-1} is the value of $\lambda_{AT}^{(1)}$ at $m_A^{(1)} \to 0$ calculated from equation 35. If we further assume that

$$\lambda_{AB}^{(2)} = 4\lambda_{AL}^{(2)} , \quad (42)$$

and

$$\lambda_{AB}^{(3)} = 4\lambda_{AL}^{(3)} , \quad (43)$$

which are the relationships suggested by the ICRP model (1979) for soluble particles, we obtain from equations 40 and 41

$$\lambda_{AB}^{(2)} = \frac{4}{5}(\lambda_{A0}^{(2)} - \lambda_{AT0}^{(2)}) , \quad (44)$$

and

$$\lambda_{AB}^{(3)} = \frac{4}{5}(\lambda_{A0}^{(3)} - \lambda_{AT0}^{(3)}) . \quad (45)$$

Equations 37 through 45 determine $\lambda_{AT}^{(2)}$, $\lambda_{AT}^{(3)}$, $\lambda_{AB}^{(2)}$, $\lambda_{AB}^{(3)}$, $\lambda_{AL}^{(2)}$, and $\lambda_{AL}^{(3)}$ for given measured values of $\lambda_{A0}^{(2)}$ and $\lambda_{A0}^{(3)}$.

The transport rates of particle-associated organics in DEPs were determined in the manner described above. Because the $\lambda_{A0}^{(2)}$ and $\lambda_{A0}^{(3)}$ of all the organics adsorbed on the particle have not been measured experimentally, the mean of the transport rates of the particle-associated BaP and NP measured by Sun and associates (1984) and Bond and colleagues (1986) were used as the representative transport rates of the organics. This led to

$$\lambda_{A0}^{(2)} = 0.0288 \text{ day}^{-1} , \quad (46)$$

and

$$\lambda_{A0}^{(3)} = 15.7 \text{ day}^{-1} . \quad (47)$$

The final results for particle-associated organics are

$$\lambda_{AB}^{(2)} = 4\lambda_{AL}^{(2)} = 0.0129 \text{ day}^{-1} , \quad (48)$$

$$\lambda_{AB}^{(3)} = 4\lambda_{AB}^{(3)} = 12.55 \text{ day}^{-1} , \quad (49)$$

$$\lambda_{AT}^{(2)} = \lambda_{AT}^{(3)} = \lambda_{AT}^{(1)} = 0.012 \exp\left[-0.11(m_A^{(1)})^{1.76}\right] + 0.00068 \exp\left[-0.046(m_A^{(1)})^{1.62}\right] \text{ day}^{-1} , \quad (50)$$

$$\lambda_A^{(2)} = 0.0161 + 0.012 \exp\left[-0.11(m_A^{(1)})^{1.76}\right] + 0.00068 \exp\left[-0.046(m_A^{(1)})^{1.62}\right] \text{ day}^{-1} , \quad (51)$$

and

$$\lambda_A^{(3)} = 15.7 + 0.012 \exp\left[-0.11(m_A^{(1)})^{1.76}\right] + 0.00068 \exp\left[-0.046(m_A^{(1)})^{1.62}\right] \cong 15.7 \text{ day}^{-1} . \quad (52)$$

Other approximations for the transport rates of particle-associated organics are

$$\lambda_{HB}^{(2)} = \lambda_{TB}^{(2)} = \lambda_{LB}^{(2)} = \lambda_{AB}^{(2)} , \quad (53)$$

and

$$\lambda_{HB}^{(3)} = \lambda_{TB}^{(3)} = \lambda_{LB}^{(3)} = \lambda_{AB}^{(3)} . \quad (54)$$

The remaining transport rates in our model were not critical to the model development and were estimated from the data of Chan and colleagues (1981) and the ICRP model (1979). These are

$$\lambda_{HG}^{(i)} = 1.73 \text{ day}^{-1} , \quad i = 1,2,3 \quad (55)$$

and

$$\lambda_{TG}^{(i)} = 0.693 \text{ day}^{-1} , \quad i = 1,2,3 . \quad (56)$$

Appendix B lists all the transport rates of diesel soot and particle-associated organics derived for rats. It should be emphasized that except for the values of $\lambda_{A0}^{(2)}$, $\lambda_{A0}^{(3)}$, $\lambda_{HG}^{(i)}$, and $\lambda_{TG}^{(i)}$, which are given by equations 46, 47, 55, and 56, respectively, all other $\lambda_{XY}^{(i)}$ were derived using experimental data. The derivations were based on reasonable assumptions that, in any case, do not contribute significantly in magnitude to the value of $\lambda_A^{(i)}$. For simulating the existing experiments and predicting the results of lung burden under new conditions, the retention model presented above will prove to be valuable. The structure of the retention model is designed to permit ready modifications that can accommodate newer, more detailed, compartmental data and analyze additional transport rates.

METHOD OF EXTRAPOLATION TO HUMANS

Experimental data on the deposition and clearance of DEPs in humans are not available. In order to estimate the lung burden of DEPs for human exposure, we must extrapolate the retention model from rats to humans. The extrapolation method consists of two steps. The first step is to determine the deposition rates $r_X^{(i)}$ for humans. This work was previously reported (Yu and Xu 1987b). In the second step, we derived a set of transport rates ($\lambda_{XY}^{(i)}$) for humans. Although it is known that many physiological time constants, such as respiratory frequency and metabolic rate, are body-size dependent, the transport rates of particle-associated organics are believed to be insensitive to body size. The lung clearance rate of inhaled lipophilic compounds was shown to be dependent only on their lipid/water partition coefficients and to be independent of species (Schanker et al. 1986). In contrast, the transport rates of diesel soot were species dependent. Differences in the alveolar clearance rates of insoluble particles at low lung burdens among species were observed in numerous previous studies (for example, Snipes et al. 1983; Bailey et al. 1985a,b; Snipes and McClellan 1985). 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 such a difference. Assuming that diesel soot 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 from Bailey and associates (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 exposure to environmental diesel exhaust is not likely to result in lung overload, it is desirable to derive relationships between the transport rates and lung burdens in order to determine the exposure conditions under which overload might occur. From equation 24, it is seen that $\lambda_A^{(1)}$ for rats consists of two terms, macrophage-mediated mechanical clearance and clearance by dissolution. The first term depends on the lung burden $m_A^{(1)}$, whereas the second term does not. To extrapolate this relationship to humans, we assumed that the mechanical clearance term for humans varied with the specific particulate dose to the alveolar surface in the same proportion as in rats, while the dissolution clearance term was species independent. This assumption resulted in the following expression for $\lambda_A^{(1)}$ in humans:

$$\lambda_A^{(1)} = \frac{a}{P} \exp\left[- b(m_A^{(1)}/S)^c \right] + d \qquad (57)$$

where P is a constant derived from the human-rat ratio of the alveolar clearance rate at low lung burdens, and S is the ratio of the pulmonary surface area between humans and rats. Equation 57 implies that rats and humans have equivalent degrees of biological response in the lung to the same specific surface dose of inhaled DEPs.

In equation 57, S could have been taken to be the ratio of macrophage numbers in the respective species' lung fields for extrapolation. However, the number of macrophages is highly variable and no data reliably quantify such numbers. The value of P was obtained by letting $\lambda_A^{(1)} \rightarrow \lambda_{A0}^{(1)} = 0.00169$ day^{-1} as $m_A^{(1)} \rightarrow 0$ in equation 57. This led to $P = 14.4$. Also, we found $S = 148$ using data from the anatomical lung model of Yeh and Schum (1980) for rats and the Weibel (1963) model for human adults. For humans 25 years of age or younger, we assumed the same value for P, but S was obtained from the lung model for young humans (Yu and Xu 1987b). The values of S for different ages are shown in Table 2.

The expressions for other transport rates that have a lung burden–dependent term were extrapolated from rats to humans in a similar manner, and the constant terms remained unchanged. Appendix C shows all the transport rates derived for the human model used in the retention study.

Table 2. Ratio of Pulmonary Surface Areas Between Humans and Rats (S) for Different Ages of Humans

Age (years)	S
0	4.99
1	17.3
2	27.6
3	36.7
4	44.7
5	51.9
6	58.5
7	64.6
8	70.4
9	76.0
10	81.4
11	86.6
12	91.6
13	96.4
14	101
15	106
16	110
17	115
18	119
19	123
20	128
21	132
22	136
23	140
24	144
25	148

RESULTS

SIMULATION OF RAT EXPERIMENTS

To test the accuracy of our model, the transport rates listed in Appendix B were used in equations 7 through 10 to calculate the retention of diesel soot in the rat lung, and these values were compared with the data on lung burden and lymph node burden obtained by Strom and colleagues (1988). The particle deposition rates r_H, r_T, and r_A were computed from the deposition model for rats (Yu and Xu 1987b). A particle size of 0.19 μm MMAD and a geometric standard deviation, σ_g, of 2.3 (as used in Strom's experiment) were used in the calculation. The respiratory parameters for rats were based on their weight and were calculated using the following correlations of minute volume, respiratory frequency, and growth curve data.

$$\text{Minute Volume} = 0.9W \text{ (cm}^3\text{/min)} \qquad (58)$$

$$\text{Respiratory Frequency} = 475W^{-0.3} \text{ (L/min)} \qquad (59)$$

in which W is the body weight (in grams) as determined from the equation

$$W = 5 + 537T/(100 + T), \text{ for } T \geq 56 \text{ days}, \qquad (60)$$

where T is the age of the rat measured in days.

Equation 58 was obtained from Mauderly's data (1986) for rats ranging in age from three months to two years, equation 60 was obtained from the data of Strom and colleagues (1988), and equation 59 was determined from the best fit of the experimental deposition data. Figures 3, 4, and 5 show the calculated lung burden of diesel soot ($m_A^{(1)} + m_T^{(1)}$), the normalized lung burden, and the lymph node burden, respectively, for the experiment by Strom and associates (1988) using animals exposed to DEPs at 6 mg/m^3 for 1, 3, 6, and 12 weeks; exposure in all cases was 7 days/week and 20 hours/day. The solid lines represent the calculated accumulation of particles during the continuous exposure phase and the dashed lines indicate calculated postexposure retention. The agreement between the calculated and the experimental data for both lung and lymph node burdens during and after the exposure periods was very good.

Comparison of the model calculation and the retention data of particle-associated B*a*P in rats obtained by Sun and colleagues (1984) is shown in Figure 8. The calculated retention is shown by the solid line. The experiment of Sun and associates consisted of a 30-minute exposure to diesel particles coated with ^{3}H-benzo[*a*]pyrene (^{3}H-B*a*P) at a concentration of 4 to 6 μg/m^3 of air, followed by a postexposure period of more than 25 days. The fast and slow phases of ^{3}H-B*a*P clearance half-times were found to be 0.03 day and 18 days, respectively. These correspond to $\lambda_{A0}^{(2)} = 0.0385$ day^{-1} and $\lambda_{A0}^{(3)} = 23.1$ day^{-1} in our model. Figure 8 shows that the calculated retention is in excellent agreement with the experimental data obtained by Sun and coworkers (1984).

The good agreement between the calculated results and the experimental data for both diesel soot and particle-associated B*a*P is not surprising because these data were used in the derivation of the transport rates in the retention model. The comparisons provide, nonetheless, a check of the accuracy of the deposition model and ensure that all approximations used in the derivation were reasonable. The ultimate success of the model will depend on future experimental validation.

COMPARISON BETWEEN RATS AND HUMANS

To gain an understanding of the differences in the lung and lymph node burdens between rats and humans under the same exposure conditions, we calculated these quantities in humans of different ages exposed via nose breathing for a 12-week period of exposure to DEPs, followed by a postexposure period under the same particle conditions and exposure pattern described in Figures 3 through 5. The transport rates used in the calculation for humans were those listed in Appendix C and the deposition rates r_H, r_T, and r_A were computed from the deposition model (Yu and Xu 1987b).

Figures 9 and 10 show, respectively, the lung burden and lymph node burden results. The dashed lines are the corresponding calculated burdens in rats that we plotted in Figures 3 and 5. The lung burdens and lymph node burdens of both diesel soot and the associated organics were much larger in humans than in rats. This is attributed to the large minute volume of DEPs inhaled by humans. Figures 9 and 10 also show that human adults have the highest burdens, and that a decrease in the various burdens occurs with decreasing age because of the decrease in minute ventilation.

PREDICTED BURDENS IN HUMANS

Extensive calculations were performed to predict the

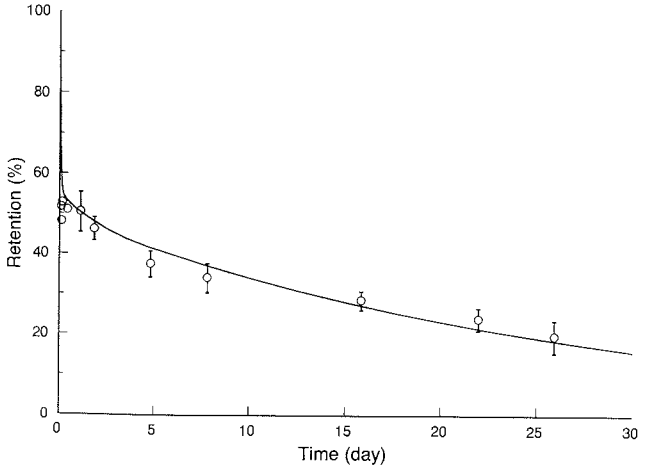

Figure 8. Comparison between the calculated lung retention (solid line) and the experimental data (data points with error bars) obtained by Sun and coworkers (1984) for the particle-associated B*a*P in rats.

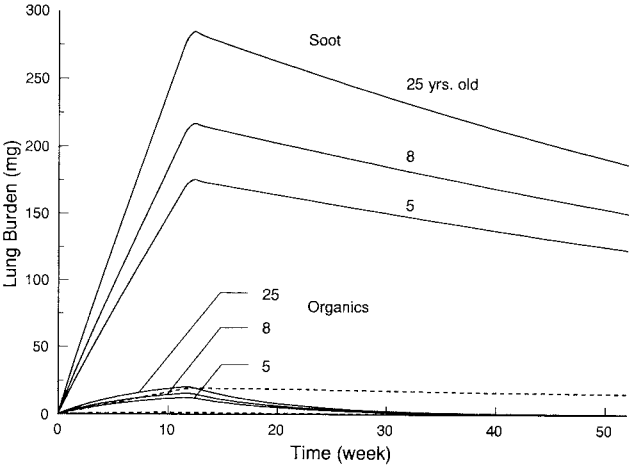

Figure 9. Calculated lung burdens in humans of different ages exposed via nose breathing to DEPs at 6 mg/m^3 for 12 weeks at 20 hours/day and 7 days/week. Dashed lines are the corresponding burdens in rats.

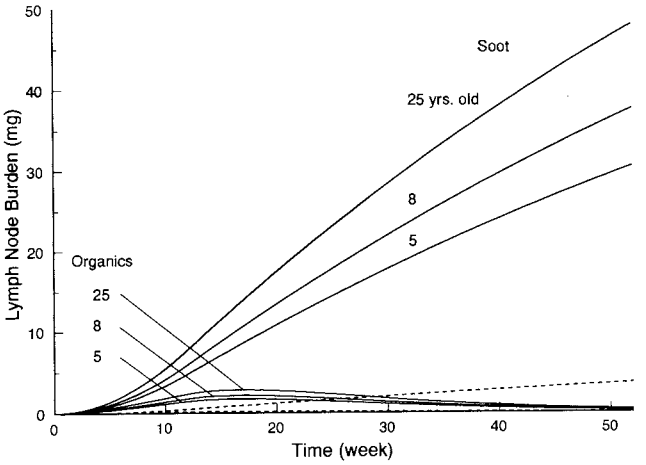

Figure 10. Calculated lymph node burdens in humans of different ages exposed via nose breathing to DEPs at 6 mg/m^3 for 12 weeks at 20 hours/day and 7 days/week. Dashed lines are the corresponding burdens in rats.

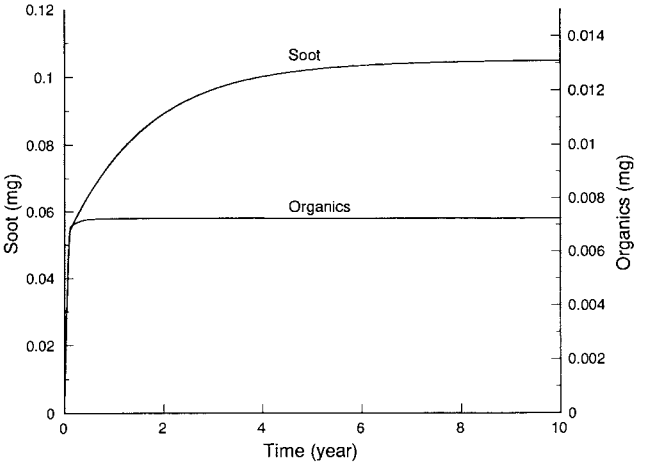

Figure 12. Calculated tracheobronchial burdens in human adults exposed to DEPs at 0.1 mg/m^3 for up to 10 years at 24 hours/day and 7 days/week.

lung burdens of diesel soot and the associated organics under different exposure conditions. The calculations were based on nose breathing for humans of different ages at the normal tidal volume and breathing rate described previously (Yu and Xu 1987b). The particle conditions used in the calculation were, again, 0.2 μm MMAD with σ_g = 2.3, and the mass fractions of the strongly and weakly bound organics were each 10 percent ($f_2 = f_3 = 0.1$).

Burdens in Various Anatomical Compartments

To gain an overall understanding of the intercompartmental transport of diesel soot and the associated organics, we calculated the burdens of these materials in each anatomical compartment for human adults, as shown in Figures 11 through 14. The exposure conditions for the cal-

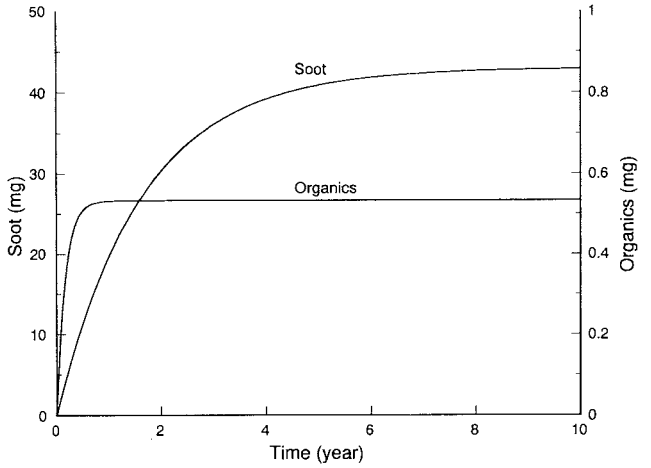

Figure 13. Calculated alveolar burdens in human adults exposed to DEPs at 0.1 mg/m^3 for up to 10 years at 24 hours/day and 7 days/week.

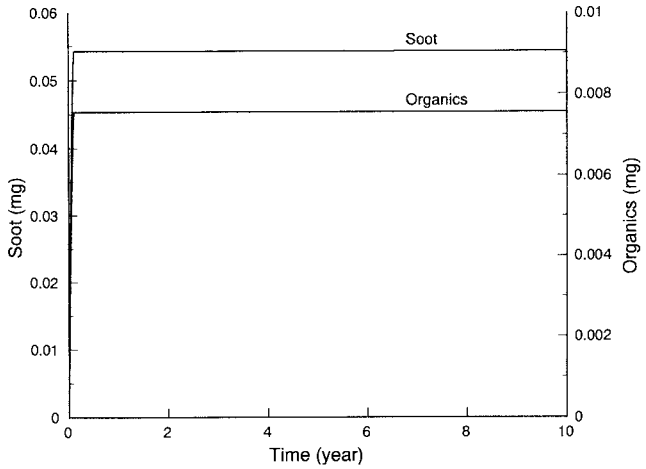

Figure 11. Calculated head burdens in human adults exposed to DEPs at 0.1 mg/m^3 for up to 10 years at 24 hours/day and 7 days/week.

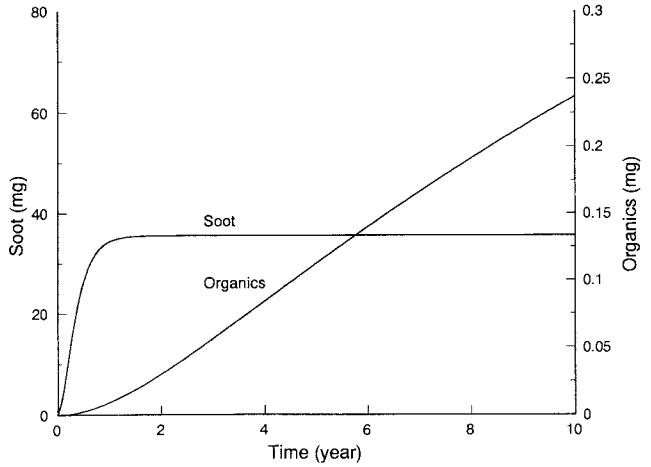

Figure 14. Calculated lymph node burdens in human adults exposed to DEPs at 0.1 mg/m^3 for up to 10 years at 24 hours/day and 7 days/week.

culations were 24 hours/day and 7 days/week at a soot concentration of 0.1 mg/m^3. The organic burdens in the head, tracheobronchial, alveolar, and lymph node compartments all reached their respective steady-state values during exposure. The time required to reach the steady state varied from a few days for the head and tracheobronchial compartments, to a few months for the alveolar and about one year for the lymph node compartment. The mass accumulation of organics in the head and tracheobronchial compartments at the steady state is less than one percent of that in the alveolar compartment. Clearly, the alveolar compartment is most important for magnitude and for long-term clearance.

For diesel soot, the accumulations in the head, tracheobronchial, and alveolar compartments also showed saturation with time, but the time to reach saturation in the tracheobronchial and alveolar compartments was much longer because of the slower particle clearance in the alveolar compartment. Again, the soot burdens in the head and tracheobronchial compartments at the steady state were smaller than one percent of the alveolar burden. In the lymph node compartment, the soot burden increased with time during the first 10-year period of exposure, as shown in Figure 14, because of the extremely small clearance rate from this compartment. Eventually, however, this burden would approach a steady state after 50 to 60 years of continuous exposure.

Effects of Exposure Pattern on Lung Burden

Lung burdens of diesel soot and the associated organics were calculated for different exposure patterns at two soot concentrations, 0.1 mg/m^3 and 1 mg/m^3, for human adults.

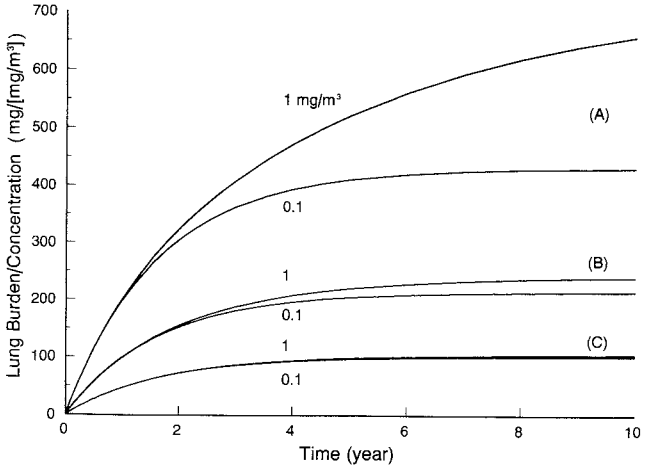

Figure 15. Calculated lung burdens of diesel soot per unit exposure concentration in human adults exposed continuously to DEPs at two different concentrations, 0.1 mg/m^3 and 1.0 mg/m^3. Exposure patterns are (a) 24 hours/day and 7 days/week, (b) 12 hours/day and 7 days/week, and (c) 8 hours/day and 5 days/week.

The results of the lung burden per unit concentration are shown in Figures 15 and 16. The exposure patterns used in the calculation were (A) 24 hours/day and 7 days/week, (B) 12 hours/day and 7 days/week, and (C) 8 hours/day and 5 days/week, simulating environmental and occupational exposure conditions. The results show that the lung burdens of both diesel soot and the associated organics reached a steady-state value during exposure. Due to differences in the amount of particle intake, the steady-state lung burdens per unit concentration were the highest for exposure pattern A and the lowest for exposure pattern C. Also, increasing soot concentration from 0.1 to 1 mg/m^3 increased the lung burden per unit concentration. However, the increase

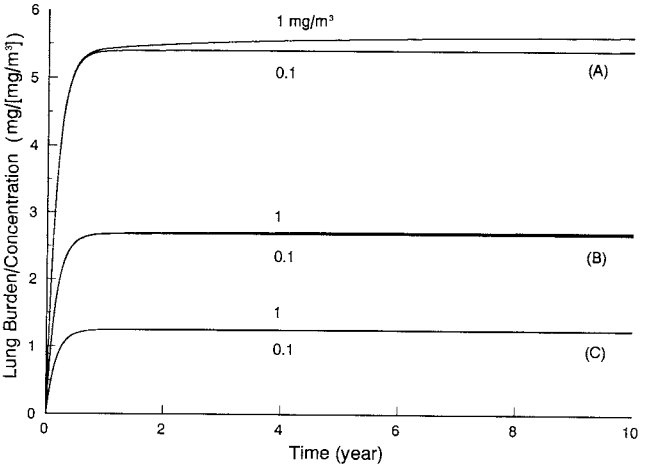

Figure 16. Calculated lung burdens of the particle-associated organics per unit exposure concentration in human adults exposed continuously to DEPs at two different concentrations, 0.1 mg/m^3 and 1.0 mg/m^3. Exposure patterns are (a) 24 hours/day and 7 days/week, (b) 12 hours/day and 7 days/week, and (c) 8 hours/day and 5 days/week.

was not noticeable for exposure pattern C. The dependence of lung burden on the soot concentration is caused by the reduction of the alveolar clearance rate at high lung burdens discussed above.

Effect of Age on Lung Burden

To illustrate the effect of age on lung burden, we calculated the lung burden of diesel soot and the associated organics per unit concentration per unit lung weight. The lung weight data at different ages were those reported by Snyder and colleagues (1975). The exposure pattern used in the calculation was 24 hours/day and 7 days/week for a period of one year at the two soot concentrations, 0.1 mg/m^3 and 1 mg/m^3. Figures 17 and 18 depict the results. On a unit lung weight basis, the lung burdens of both soot and the organics were functions of age, and the maximum lung

burdens occurred at approximately five years of age. Again, for any given age, the lung burden per unit concentration was slightly higher at 1 mg/m^3 than at 0.1 mg/m^3.

Effect of Soot Concentration on Lung Clearance

The increase in lung burden per unit concentration due to the reduction in the lung clearance rate at high soot concentrations in humans (shown in Figures 15 through 18) is further illustrated in Figures 19 and 20, where the normalized alveolar clearance rate, $\lambda_A^{(1)}/\lambda_{A0}^{(1)}$, is plotted versus soot concentration. Figure 19 depicts this result for human adults at the end of a continuous exposure of 1, 5, and 10 years for two exposure patterns: (1) 24 hours/day and 7 days/week and (2) 8 hours/day and 5 days/week. The decrease of $\lambda_A^{(1)}/\lambda_{A0}^{(1)}$ with concentration varied with exposure pattern and total time of exposure. Because of a higher particle intake into the lung, a continuous exposure pattern of 24 hours/day and 7 days/week resulted in a faster decline of the clearance rate with increasing concentration than the occupational exposure pattern of 8 hours/day and 5 days/week. A longer exposure period also led to a greater reduction in the clearance rate. Figure 19 also shows that when the soot concentration was below 0.05 mg/m^3, the clearance in human adults was not affected regardless of the length of exposure.

Figure 20 shows the dependence of $\lambda_A^{(1)}/\lambda_{A0}^{(1)}$ on concentration for humans of different ages at continuous exposure for one year. The reduction in clearance was more pronounced at young ages. However, below a concentration of 0.05 mg/m^3, reduction did not occur at any ages.

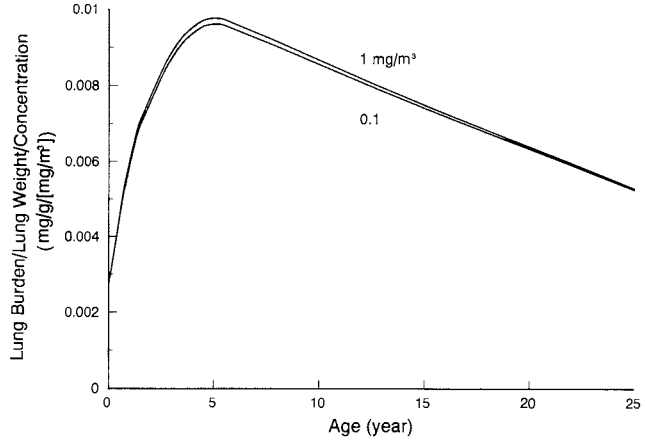

Figure 17. Calculated lung burdens of diesel soot per gram of lung per unit exposure concentration in humans of different ages exposed continuously for one year to DEPs of two different concentrations, 0.1 mg/m^3 and 1.0 mg/m^3, for 24 hours/day and 7 days/week.

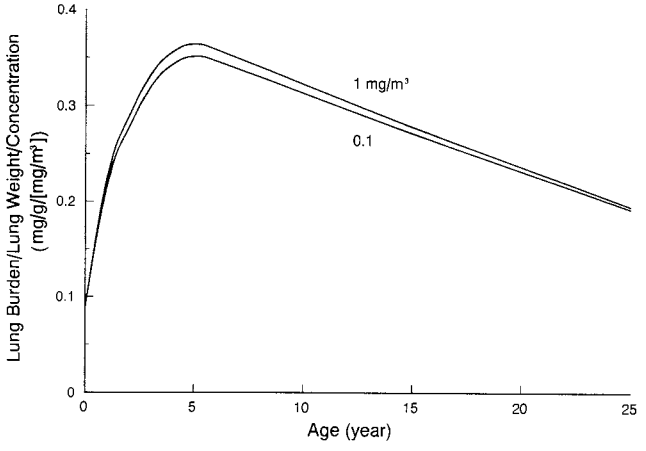

Figure 18. Calculated lung burdens of the particle-associated organics per gram of lung per unit exposure concentration in humans of different ages exposed continuously for one year to DEPs of two different concentrations, 0.1 mg/m^3 and 1.0 mg/m^3, for 24 hours/day and 7 days/week.

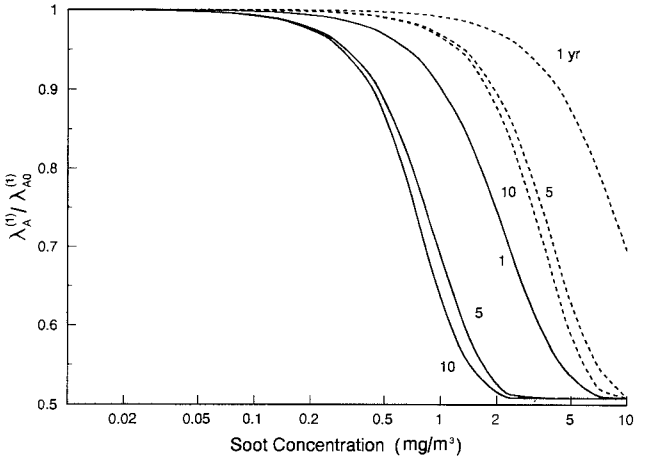

Figure 19. Normalized clearance rate of diesel soot, $\lambda_A^{(1)}/\lambda_{A0}^{(1)}$, versus soot concentration in human adults at the end of a continuous exposure of 1, 5, and 10 years. Solid lines represent an exposure pattern of 24 hours/day and 7 days/week and dashed lines represent 8 hours/day and 5 days/week.

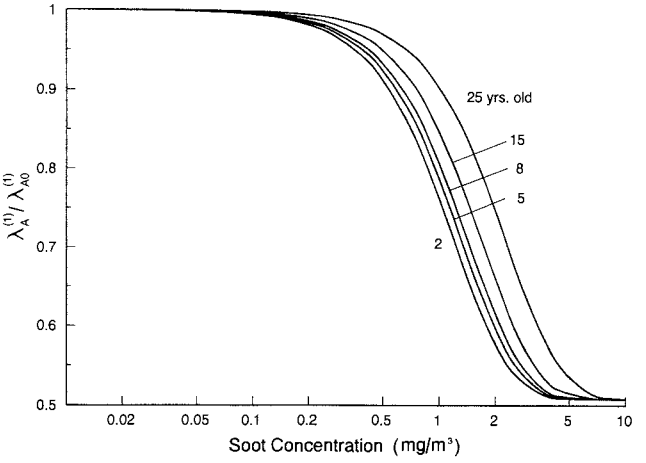

Figure 20. Normalized clearance rate of diesel soot, $\lambda_A^{(1)}/\lambda_{A0}^{(1)}$, versus soot concentration in humans of different ages at the end of a one-year continuous exposure of 24 hours/day and 7 days/week.

Lung Burdens for Exposure over a Life Span

The lung burdens of diesel soot and the associated organics were also calculated for exposure over a life span, from birth to adulthood, for a continuous exposure pattern at concentration levels of 0.1 mg/m^3 and 1 mg/m^3. Lung burdens per unit concentration are depicted in Figures 21 and 22. The accumulation of both diesel soot and the associated organics in the lung increased with age from birth to about 23 years of age, and decreased slightly to a steady-state value beyond this age. At a soot concentration of 1 mg/m^3, the maximum lung burden of diesel soot was found to be about 800 mg and the associated organics approximately 6 mg.

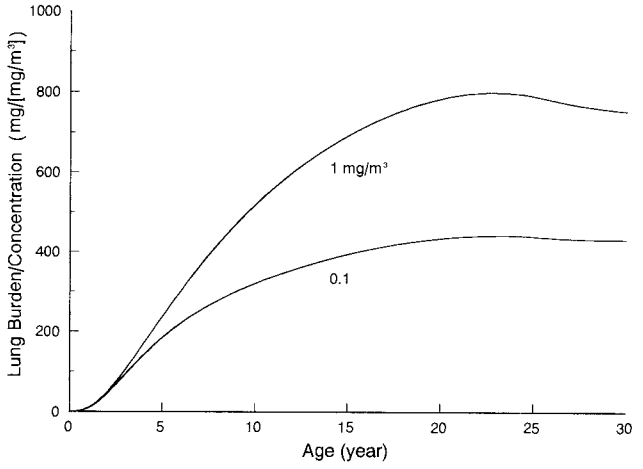

Figure 21. Calculated lung burdens of diesel soot per unit exposure concentration in humans at two different concentrations, 0.1 mg/m^3 and 1.0 mg/m^3, for exposure to DEPs over a life span, from birth to adulthood, at 12 hours/day and 7 days/week.

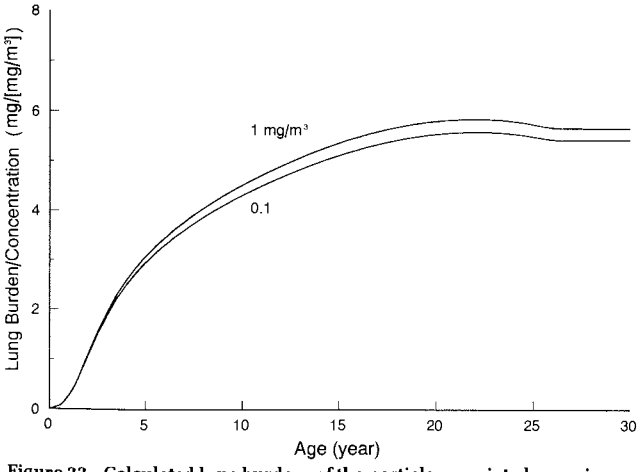

Figure 22. Calculated lung burdens of the particle-associated organics per unit exposure concentration in humans at two concentration levels, 0.1 mg/m^3 and 1.0 mg/m^3, for exposure to DEPs over a life span, from birth to adulthood, at 12 hours/day and 7 days/week.

PARAMETRIC STUDY OF RETENTION MODEL

The retention model of DEPs in humans, presented above, consists of a large number of parameters that characterize the size and composition of diesel particles, the structure and dimension of the respiratory tract, the ventilation conditions of the subject, and the clearance half-times of diesel soot and the particle-associated organics. Any single or combined changes of these parameters from their normal values in the model would result in a change in the predicted lung burden. We conducted a parametric study of the retention model to investigate the effects of each individual parameter on calculated lung burden in human adults. The exposure pattern chosen for this study was 24 hours/day and 7 days/week for a period of 10 years at a constant soot concentration of 0.1 mg/m^3. The effects of each individual parameter on the accumulation of diesel soot and the associated organics in the lung at the end of exposure are summarized below.

Effect of Particle Characteristics

The parameters that govern the size distribution of DEPs are MMAD and σ_g. Figures 23 and 24 show, respectively, the effects of these parameters on lung burden for varying MMAD (0.1 to 0.3 μm) and σ_g (1.2 to 4.6). Increasing MMAD led to a reduction in the lung burden of both diesel soot and the associated organics, while increasing σ_g produced the opposite effect. The changes in lung burden in both cases were caused by changes in the particle intake rate into the lung during exposure.

Other particle parameters that affect lung burden are the mass fraction of the particle-associated organics, $f_2 + f_3$,

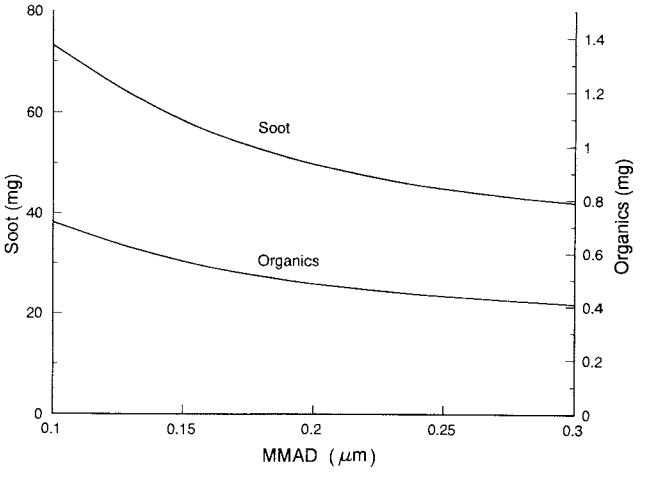

Figure 23. Calculated lung burdens in human adults versus MMAD for exposure to DEPs at 0.1 mg/m^3 for 10 years at 24 hours/day and 7 days/week. Parameters used in the calculation are σ_g = 2.3, f_2 = 0.1, f_3 = 0.1; tidal volume = 500 cm^3, respiratory frequency = 14 min^{-1}; and Weibel's lung model, and lung volume = 3,200 cm^3.

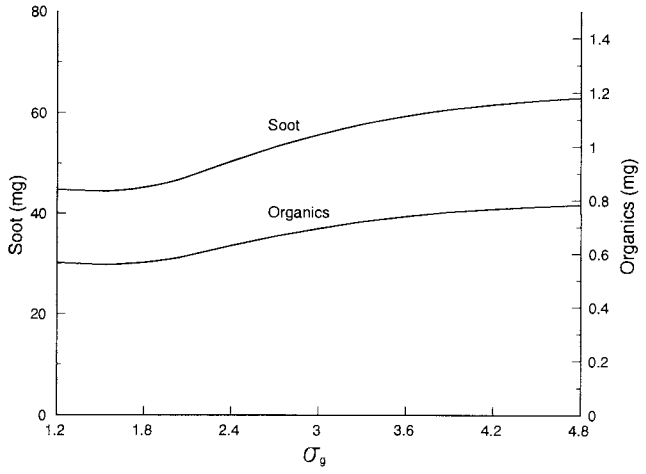

Figure 24. Calculated lung burdens in human adults versus σ_g for exposure to DEPs at 0.1 mg/m^3 for 10 years at 24 hours/day and 7 days/week. Parameters used in the calculation are MMAD = 0.2 μm, f_2 = 0.1, f_3 = 0.1; tidal volume = 500 cm^3, respiratory frequency = 14 min^{-1}; and Weibel's lung model, and lung volume = 3,200 cm^3.

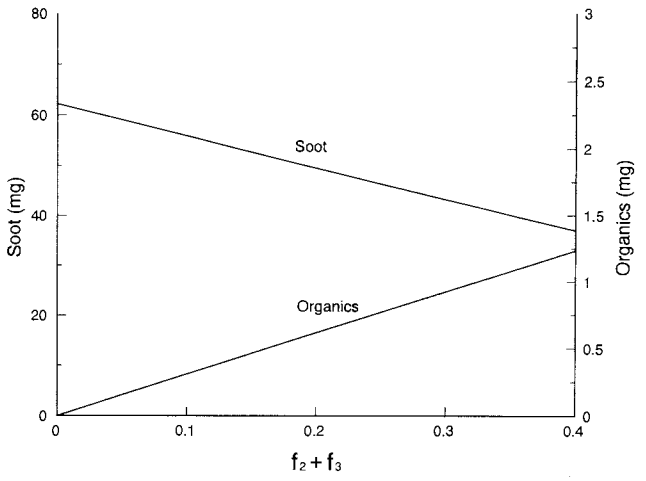

Figure 25. Calculated lung burdens in human adults versus $f_2 + f_3$ for exposure to DEPs at 0.1 mg/m^3 for 10 years at 24 hours/day and 7 days/week. Parameters used in the calculation are MMAD = 0.2 μm, σ_g = 2.3, $f_2 = f_3$; tidal volume = 500 cm^3, respiratory frequency = 14 min^{-1}; and Weibel's lung model, and lung volume = 3,200 cm^3.

and the mass ratio of fast-cleared organics to the total organics, $f_3/(f_2 + f_3)$. The lung burden results that illustrated the effects of these parameters are shown, respectively, in Figures 25 and 26. Figure 25 shows that when the organics mass fraction, $f_2 + f_3$, increased, the lung burden of diesel soot decreased and that of the organics increased. Figure 26 shows that for a constant organic mass fraction $f_2 + f_3 = 0.2$ with variable f_2 and f_3, the lung burden of diesel soot remained constant and the organics burden decreased as the ratio of $f_3/(f_2 + f_3)$ increased.

Effect of Ventilation Conditions

The changes in lung burden due to variations in tidal volume and respiratory frequency are depicted in Figures 27 and 28. Increasing any one of these ventilation parameters increased the lung burden, but the increase was much smaller with respect to respiratory frequency than to tidal volume. This small increase in lung burden was a result of the decrease in deposition efficiency as respiratory frequency increased, despite a higher total amount of DEPs inhaled.

The mode of breathing has only a minor effect on lung burden; switching from nose breathing to mouth breathing does not produce any appreciable change in the amount of particle intake into the lung (Yu and Xu 1987b). All lung burden results presented in this study are for nose breathing.

Effect of Lung Volume and Lung Structure

For a given lung structure, the lung burden of DEPs was affected by lung volume in two special ways: (1) the deposition efficiency or particle intake into the lung decreased with lung volume, and (2) the overloading effect of clearance was reduced as the lung volume increased. Although the second effect was not appreciable at a soot concentration of 0.1 mg/m^3, both effects led to a smaller lung burden at large lung volume, as shown in Figure 29.

At a given lung volume, the use of different lung models also led to different lung burden predictions. The lung burden results of diesel soot and the associated organics as a function of the exposure time are shown, respectively, in

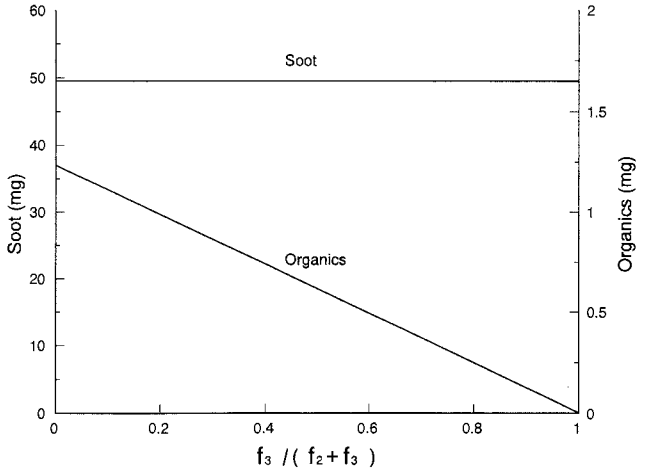

Figure 26. Calculated lung burdens in human adults versus $f_3/(f_2 + f_3)$ for exposure to DEPs at 0.1 mg/m^3 for 10 years at 24 hours/day and 7 days/week. Parameters used in the calculation are MMAD = 0.2 μm, σ_g = 2.3, $f_2 + f_3$ = 0.2; tidal volume = 500 cm^3, respiratory frequency = 14 min^{-1}; and Weibel's lung model, and lung volume = 3,200 cm^3.

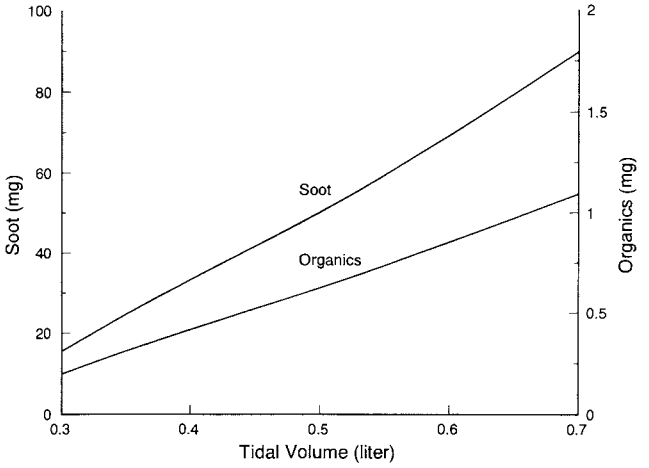

Figure 27. Calculated lung burdens in human adults versus tidal volume in liters for exposure to DEPs at 0.1 mg/m^3 for 10 years at 24 hours/day and 7 days/week. Parameters used in the calculation are MMAD = 0.2 μm, σ_g = 2.3, f_2 = 0.1, f_3 = 0.1; respiratory frequency = 14 min^{-1}; and Weibel's lung model, and lung volume = 3,200 cm^3.

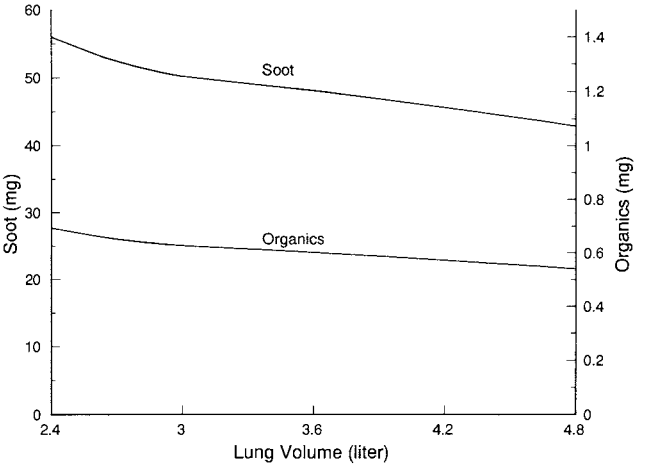

Figure 29. Calculated lung burdens in human adults versus lung volume in liters for exposure to DEPs at 0.1 mg/m^3 for 10 years at 24 hours/day and 7 days/week. Parameters used in the calculation are MMAD = 0.19 μm, σ_g = 2.3, f_2 = 0.1, f_3 = 0.1; tidal volume = 500 cm^3, respiratory frequency = 14 min^{-1}; and Weibel's lung model.

Figures 30 and 31, for four different lung models of human adults developed by Weibel (1963), Olson and colleagues (1970), Hansen and Ampaya (1975), and Yeh and Schum (1980). The lung model of Weibel is equivalent to the age-dependent lung model evaluated at 25 years of age used earlier in this study. Major differences between the other three lung models and Weibel's model were discussed previously (Yu and Xu 1987b).

Figures 30 and 31 show that the lung burdens (of soot and the associated organics) calculated from the lung model of Hansen and Ampaya were the highest among all lung models, the burdens from the model of Olson and associates were the lowest, and the results from the other two models were intermediate. These differences can be attributed to the different deposition efficiencies of DEPs in these lung models.

Effect of Transport Rates

Transport rates have an obvious effect on the retention of DEPs in the lung after deposition. Because we were mainly concerned with the long-term clearance of diesel soot and the associated organics, only the effects of two transport

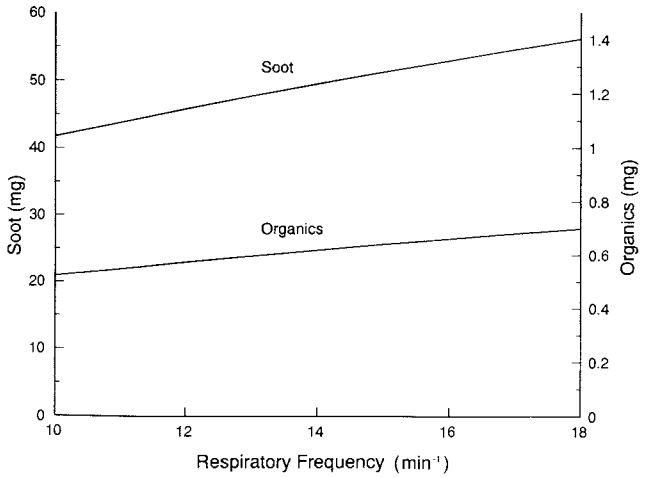

Figure 28. Calculated lung burdens in human adults versus respiratory frequency in breaths min^{-1} for exposure to DEPs at 0.1 mg/m^3 for 10 years at 24 hours/day and 7 days/week. Parameters used in the calculation are MMAD = 0.2 μm, σ_g = 2.3, f_2 = 0.1, f_3 = 0.1; tidal volume = 500 cm^3; and Weibel's lung model, and lung volume = 3,200 cm^3.

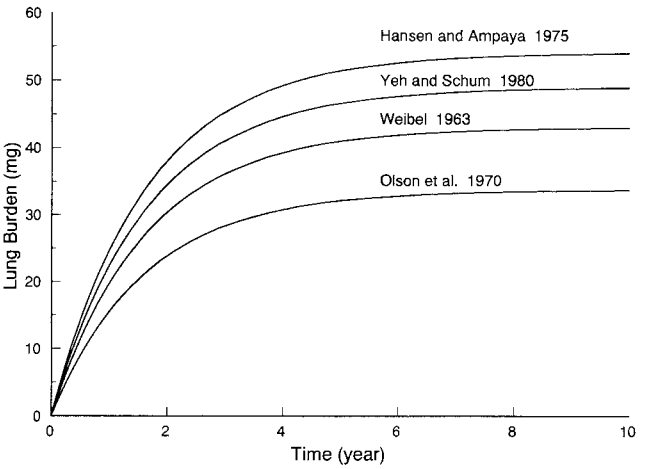

Figure 30. Calculated lung burdens of diesel soot in human adults for four different lung models for exposure to DEPs at 0.1 mg/m^3 for up to 10 years at 24 hours/day and 7 days/week. Parameters used in the calculation are MMAD = 0.2 μm, σ_g = 2.3, f_2 = 0.1, f_3 = 0.1; tidal volume = 500 cm^3, respiratory frequency = 14 min^{-1}; and lung volume = 3,200 cm^3.

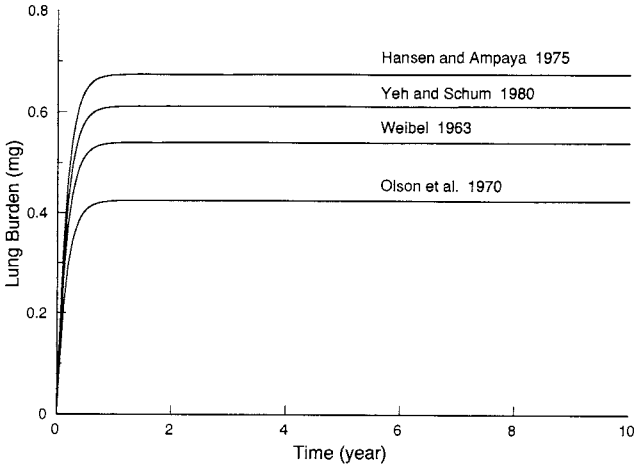

Figure 31. Calculated lung burdens of particle-associated organics in human adults for four different lung models for exposure to DEPs at 0.1 mg/m^3 for 10 years at 24 hours/day and 7 days/week. Parameters used in the calculation are MMAD = 0.2 μm, σ_g = 2.3, f_2 = 0.1, f_3 = 0.1; tidal volume = 500 cm^3, respiratory frequency = 14 min^{-1}; and lung volume = 3,200 cm^3.

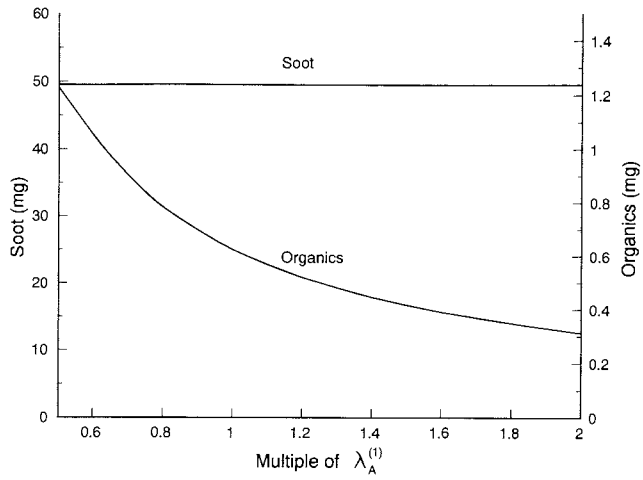

Figure 33. Calculated lung burdens in human adults versus a multiple of $\lambda_A^{(2)}$ for exposure to DEPs at 0.1 mg/m^3 for 10 years at 24 hours/day and 7 days/week. Parameters used in the calculation are MMAD = 0.2 μm, σ_g = 2.3, f_2 = 0.1, f_3 = 0.1; tidal volume = 500 cm^3, respiratory frequency = 14 min^{-1}; and Weibel's lung model, and lung volume = 3,200 cm^3.

rates, $\lambda_A^{(1)}$and $\lambda_A^{(2)}$, were studied. The variation in the value of $\lambda_A^{(1)}$ from different studies was shown earlier, in Figure 7. This difference is equivalent to about a factor of 2 at low lung burden but can be as high as 3 to 4 at high burden. Because the lung burden for human exposure is normally low, we used a multiple of 0.5 to 2 for the uncertainty in $\lambda_A^{(1)}$ to examine how such variation affected the lung burden. We also used the same multiple for the variation of $\lambda_A^{(2)}$. Figures 32 and 33 show, respectively, the lung burden results for diesel soot and the associated organics versus the multiples of $\lambda_A^{(1)}$ and $\lambda_A^{(2)}$ used in the calculation. As expected, increasing the multiple of $\lambda_{A0}^{(1)}$ reduced the lung burden of diesel soot with practically no change in the organics burden (Figure 32), whereas just the opposite occurred when the multiple of $\lambda_A^{(2)}$ was increased (Figure 33).

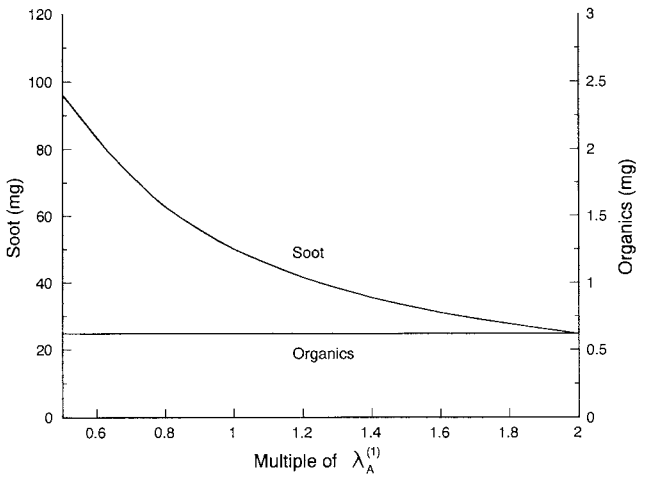

Figure 32. Calculated lung burdens in human adults versus a multiple of $\lambda_A^{(1)}$ for exposure to DEPs at 0.1 mg/m^3 for 10 years at 24 hours/day and 7 days/week. Parameters used in the calculation are MMAD = 0.2 μm, σ_g = 2.3, f_2 = 0.1, f_3 = 0.1; tidal volume = 500 cm^3, respiratory frequency = 14 min^{-1}; and Weibel's lung model, and lung volume = 3,200 cm^3.

DISCUSSION AND CONCLUSIONS

The retention model of DEPs presented above offers an in-depth picture of material transport between various anatomical compartments and the removal of diesel soot and associated organics from the lung. The most difficult and crucial task in developing such a retention model was the determination of the intercompartmental transport rates for each material component. Usually, it is the knowledge of the transport rates that dictates the structure and sophistication of a model.

The multicompartmental retention model that we propose in this study can be utilized for both fast and slow clearance of diesel soot and associated organics from the lung. The value of this model lies in its completeness and versatility. It helps elucidate the system dynamics and provides a useful tool for simulation and prediction. However, because our major concern with DEPs was with their long-term accumulation in the lung, most quantitative results presented in this study centered on this special case. In the development of the retention model, we made a major effort to derive the transport rates associated with the alveolar compartment using the limited experimental data available for rats. In our model, these alveolar transport rates, as well as the transport rates associated with the other compartments, can be modified easily should additional animal or

human data become available. Furthermore, the particle-associated organics defined in this study represent a general term that consists of a mixture of organic compounds with uncertain proportions, including B*a*P and NP. It is conceivable that different organic compounds have different transport rates. In our model, however, we used the mean of the transport rates of particle-associated B*a*P and NP as representative transport rates because only these rates are known at this time. Our retention model can readily be extended to consider the lung clearance of each specific organic component if its transport rate is known.

The reduction of diesel soot at high lung burdens by mechanical clearance was extrapolated from rats to humans in the model by assuming that the magnitude of response to particle loading is the same for any species at a given specific dose. This assumption was necessary because no data presently exist on the relationship between mechanical transport rates and lung burden in humans. We also assumed that there were no species differences in the transport rates of the particle-associated organics, again because of the lack of human data. Future measurements are called for to clarify all these points.

The calculated lung burdens are consistent with previous experimental observations and demonstrate the following:

1. When diesel particles are deposited in the lung, the carbonaceous soot and the particle-associated organics are cleared from the lung in different proportions and to different degrees.
2. The particle-associated organics of DEPs can be divided into two components according to their clearance half-time. The component with a short clearance half-time of a few hours corresponds to the organics leached out primarily by diffusion-driven mechanisms, whereas the other component has a clearance half-time of a few hundred hours and includes all those organics that are characterized by more complex interactions with other components of the DEPs, the clearance system, or the deposition surface itself.
3. Diesel particles deposited in the head and tracheobronchial airways are quickly removed, principally by the combined mechanisms of mucociliary transport and dissolution. The fast-cleared organics are cleared by dissolution in a matter of hours, while slowly cleared organics are cleared by mucociliary transport in a matter of days.
4. In the alveolar region of the lung, the removal of the particle-associated organics is controlled by dissolution, whereas macrophage phagocytosis and migration are responsible for the removal of diesel soot.
5. Because of their fast clearance rates in the tracheobronchial compartment, the accumulation of both diesel soot and the associated organics in this region of the lung constitutes less than one percent of the total lung burden after a long exposure.
6. Exposure to diesel exhaust has no effect on mucociliary clearance; however, the alveolar clearance rate of diesel soot is reduced as a result of high particle burden in the lung. For rats, the alveolar clearance rate of diesel soot is reduced by about 10 percent at a lung burden of 1 mg/g of wet lung and by approximately 95 percent when the lung burden exceeds 8 mg/g. At this point, macrophage-mediated clearance is practically nonexistent.
7. The clearance of diesel soot from the alveolar region of the lung is due to its transport to the tracheobronchial, lymph node, and blood compartments. At low lung burden, transport to the tracheobronchial region is dominant, whereas at high burden, transport is principally through the lymphatic system.

Several new conclusions may also be drawn from this model study:

1. When humans and rats are exposed to DEPs for the same period of time, the lung burdens of diesel soot and the associated organics are much larger in humans than in rats. This is due to the higher particle intake and slower clearance rate in humans.
2. During a continuous exposure, the lung burdens of diesel soot 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, but the increase for diesel soot is much larger than for the organics. At low concentrations, these increases are negligible.
3. When children and adult humans are exposed to equal concentrations of DEPs, the reduction in alveolar clearance of diesel soot due to high lung burden is greater in children than in adults. For a continuous exposure of up to 10 years, the alveolar clearance rate in adults is not affected if the exposure soot concentration remains below 0.05 mg/m^3. This threshold concentration decreases slightly with age.
4. The accumulation of both diesel soot and the associated organics in the human lung varies with age due to the differences in particle intake and clearance rates. Per unit lung weight, the accumulations for a one-year continuous exposure reach a maximum at about five years of age.

Finally, it must be realized that the lung burden of DEPs calculated from the retention model depends on a large number of parameters that include particle size and composition, individual lung structure and breathing condition, and exposure pattern and concentration. It is important that

these parameters are known accurately before reliable lung burden estimates can be made from the retention model developed in this study.

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APPENDIX A. Kinetic Equations for Diesel Soot and Particle-Associated Organics and Their Solutions

The differential equations for $m_X^{(i)}$ and their solutions as a function of exposure time, t, can be written as (for i = 1, 2, and 3):

Head (H)

$$dm_H^{(i)}/dt = r_H^{(i)} - \lambda_{HG}^{(i)} m_H^{(i)} - \lambda_{HB}^{(i)} m_H^{(i)} = r_H^{(i)} - \lambda_H^{(i)} m_H^{(i)} \quad \text{(A.1)}$$

where

$$\lambda_H^{(i)} = \lambda_{HG}^{(i)} + \lambda_{HB}^{(i)} \quad \text{(A.2)}$$

$$m_H^{(i)} = r_H^{(i)}/\lambda_H^{(i)} + (m_{H0}^{(i)} - r_H^{(i)}/\lambda_H^{(i)}) \exp(-\lambda_H^{(i)} t) \quad \text{(A.3)}$$

Tracheobronchial (T)

$$dm_T^{(i)}/dt = r_T^{(i)} + \lambda_{AT}^{(i)} m_A^{(i)} - \lambda_{TG}^{(i)} m_T^{(i)} - \lambda_{TB}^{(i)} m_T^{(i)} = r_T^{(i)} - \lambda_T^{(i)} m_T^{(i)} + \lambda_{AT}^{(i)} m_A^{(i)} \quad \text{(A.4)}$$

where

$$\lambda_T^{(i)} = \lambda_{TG}^{(i)} + \lambda_{TB}^{(i)} \quad \text{(A.5)}$$

$$m_T^{(i)} = \exp(-\lambda_T^{(i)} t) \int_0^t (r_T^{(i)} + \lambda_{AT}^{(i)} m_A^{(i)}) \exp(\lambda_T^{(i)} t) dt + m_{T0}^{(i)} \quad \text{(A.6)}$$

Alveolar (A)

$$dm_A^{(i)}/dt = r_A^{(i)} - \lambda_{AT}^{(i)} m_A^{(i)} - \lambda_{AL}^{(i)} m_A^{(i)} - \lambda_{AB}^{(i)} m_A^{(i)} = r_A^{(i)} - \lambda_A^{(i)} m_A^{(i)} \quad \text{(A.7)}$$

where

$$\lambda_A^{(i)} = \lambda_{AT}^{(i)} + \lambda_{AL}^{(i)} + \lambda_{AB}^{(i)} \quad \text{(A.8)}$$

$$\int_0^{m_A^{(i)}} \frac{dm_A^{(i)}}{r_A^{(i)} - \lambda_A^{(i)} m_A^{(i)}} = t \quad \text{(A.9)}$$

Lymph nodes (L)

$$dm_L^{(i)}/dt = \lambda_{AL}^{(i)} m_A^{(i)} - \lambda_{LB}^{(i)} m_L^{(i)} \quad \text{(A.10)}$$

$$m_L^{(i)} = \exp(-\lambda_{LB}^{(i)} t) \int_0^t \lambda_{AL}^{(i)} m_A^{(i)} \exp(\lambda_{LB}^{(i)} t) dt + m_{L0}^{(i)} \quad \text{(A.11)}$$

where $m_X^{(i)}$ is the mass of component i in X compartment and $r_X^{(i)}$ is the mass intake rate of component i to X compartment calculated from a deposition model of DEPs (Yu and Xu 1987b). The total mass of the particle-associated organics in compartment X is the sum of $m_X^{(2)}$ and $m_X^{(3)}$, and the total mass of DEPs in compartment X is equal to

$$m_X = m_X^{(1)} + m_X^{(2)} + m_X^{(3)}. \quad \text{(A.12)}$$

APPENDIX B. Transport Rates of Diesel Soot and Particle-Associated Organics in Rats

The values of $\lambda_{XY}^{(i)}$ (in day^{-1}) that we adopted from the literature and used in the model calculation for rats are listed below:

$\lambda_{HG}^{(i)} = 1.73, \quad i = 1, 2, 3$ (Chan et al. 1981; ICRP 1979)

$\lambda_{TG}^{(i)} = 0.693, \quad i = 1, 2, 3$ (Chan et al. 1981)

$\lambda_{A0}^{(1)} = 0.0129$ (Strom et al. 1988)

$\lambda_{A0}^{(2)} = 0.0288$ (Sun et al. 1984; Bond et al. 1986)

$\lambda_{A0}^{(3)} = 15.7$ (Sun et al. 1984; Bond et al. 1986)

$\lambda_{AB}^{(i)} = 4\lambda_{AL}^{(i)} \quad i = 2, 3$ (ICRP 1979)

The following values of $\lambda_{XY}^{(i)}$ were derived using the experimental data of lung burden and lymph node burden:

$$\lambda_{AT}^{(i)} = 0.012 \exp(-0.11\, m_A^{1.76}) + 0.00068 \exp(-0.046\, m_A^{1.62}), \quad i = 1, 2, 3$$

$$\lambda_{AL}^{(1)} = 0.00068[1 - \exp(-0.046\, m_A^{1.62})]$$

$$\lambda_{HB}^{(1)} = \lambda_{TB}^{(1)} = \lambda_{LB}^{(1)} = \lambda_{AB}^{(1)} = 0.00018$$

$$\lambda_{HB}^{(2)} = \lambda_{TB}^{(2)} = \lambda_{LB}^{(2)} = \lambda_{AB}^{(2)} = 0.0129$$

$$\lambda_{HB}^{(3)} = \lambda_{TB}^{(3)} = \lambda_{LB}^{(3)} = \lambda_{AB}^{(3)} = 12.55$$

$$\lambda_{A}^{(i)} = \lambda_{AT}^{(i)} + \lambda_{AL}^{(i)} + \lambda_{AB}^{(i)} \quad i = 1, 2, 3$$

$$\lambda_{A}^{(1)} = 0.012 \exp(-0.11\, m_A^{1.76}) + 0.00086$$

$$\lambda_{A}^{(2)} = 0.012 \exp(-0.11\, m_A^{1.76}) + 0.00068 \exp(-0.046\, m_A^{1.62}) + 0.0161$$

$$\lambda_{A}^{(3)} = 0.012 \exp(-0.11\, m_A^{1.76}) + 0.00068 \exp(-0.046\, m_A^{1.62}) + 15.7$$

where $m_A \cong m_A^{(1)}$ is the particulate burden (in milligrams) in the alveolar compartment.

APPENDIX C. Transport Rates of Diesel Soot and Particle-Associated Organics in Humans

The values of $\lambda_{XY}^{(i)}$ (in day^{-1}) that we adopted from the literature and used in the model calculation for humans are listed below:

$\lambda_{HG}^{(i)} = 1.73, \quad i = 1, 2, 3$ (Chan et al. 1981; ICRP 1979)

$\lambda_{TG}^{(i)} = 0.693, \quad i = 1, 2, 3$ (Chan et al. 1981; ICRP 1979)

$\lambda_{A0}^{(1)} = 0.00169$ (Bailey et al. 1982)

$\lambda_{A0}^{(2)} = 0.0288$ (Sun et al. 1984; Bond et al. 1986)

$\lambda_{A0}^{(3)} = 15.7$ (Sun et al. 1984; Bond et al. 1986)

$\lambda_{AB}^{(i)} = 4\lambda_{AL}^{(i)} \quad i = 2, 3$ (ICRP 1979)

The following values of $\lambda_{XY}^{(i)}$ were derived by extrapolating the results of rats:

$$\lambda_{AT}^{(i)} = (1/P)[0.012 \exp(-0.11(m_A/S)^{1.76}) + 0.00068 \exp(-0.046(m_A/S)^{1.62})], \quad i = 1, 2, 3$$

$$\lambda_{AL}^{(1)} = 0.00068[1 - (1/P) \exp(-0.046(m_A/S)^{1.62})]$$

$$\lambda_{HB}^{(1)} = \lambda_{TB}^{(1)} = \lambda_{LB}^{(1)} = \lambda_{AB}^{(1)} = 0.00018$$

$$\lambda_{HB}^{(2)} = \lambda_{TB}^{(2)} = \lambda_{LB}^{(2)} = \lambda_{AB}^{(2)} = 0.0129$$

$$\lambda_{HB}^{(3)} = \lambda_{TB}^{(3)} = \lambda_{LB}^{(3)} = \lambda_{AB}^{(3)} = 12.55$$

$$\lambda_{A}^{(i)} = \lambda_{AT}^{(i)} + \lambda_{AL}^{(i)} + \lambda_{AB}^{(i)}$$

$$\lambda_{A}^{(1)} = (1/P)[0.012 \exp(-0.11(m_A/S)^{1.76})] + 0.00086$$

$$\lambda_{A}^{(2)} = (1/P)[0.012 \exp(-0.11(m_A/S)^{1.76}) + 0.00068 \exp(-0.046(m_A/S)^{1.62})] + 0.0161$$

$$\lambda_{A}^{(3)} = (1/P)[0.012 \exp(-0.11(m_A/S)^{1.76}) + 0.00068 \exp(-0.046(m_A/S)^{1.62})] + 15.7$$

where $m_A \cong m_A^{(1)}$ is the particulate burden (in milligrams) in the alveolar compartment, $P = 14.4$, and S is the pulmonary surface area ratio given in Table 2.

ABOUT THE AUTHORS

C. P. Yu is Professor and former Chairman of the Department of Mechanical and Aerospace Engineering at the State University of New York at Buffalo. He received his Ph.D. from Purdue University in 1964. In 1972, Dr. Yu spent a sabbatical leave at the University of Essex, England, and worked with Dr. C. N. Davies on aerosol deposition in human airways. Dr. Yu's primary research interests include the development of theoretical descriptions of aerosol deposition and the application of deposition models to various anatomical situations.

K. J. Yoon obtained his B.Sc. in mechanical engineering from National Seoul University in 1981. He was awarded a Ph.D. in 1989 in mechanical and aerospace engineering, from the State University of New York at Buffalo for his work in mathematical modeling of lung clearance. His research interests have been the deposition and clearance of inhaled environmental pollutants and the risk analysis of human exposure. He is currently with Hyundai Motor Corporation, Seoul, Korea.

PUBLICATIONS RESULTING FROM THIS RESEARCH

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ABBREVIATIONS

B*a*P	benzo[*a*]pyrene
DEPs	diesel exhaust particles
^{3}H-B*a*P	[^{3}H]benzo[*a*]pyrene
MMAD	mass median aerodynamic diameter
NP	nitropyrene
ICRP	International Commission on Radiological Protection
σ_g	geometric standard deviation

INTRODUCTION

A Request for Applications (RFA 83-3), which solicited proposals for "Dose of Airborne Pollutants to Target Tissues," was issued by the Health Effects Institute (HEI) in the summer of 1983. In response to the RFA, Dr. C. P. Yu from the State University of New York at Buffalo submitted a proposal entitled "Predictive Models for Deposition of Inhaled Diesel Exhaust Particles in Humans and Laboratory Species." This study was completed in June 1986, and was published as HEI Research Report No. 10. In January 1986, Dr. Yu submitted to the HEI a renewal application entitled "Determination of Lung Dose of Diesel Exhaust Particles." The HEI approved the two-year study, which began in April 1987. Total expenditures for the two-year project were $144,918. The Investigators' Report was received at the HEI in July 1989 and accepted by the Health Review Committee in April 1990. During the review of the Investigators' Report, the Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in the Investigators' Report and in the Review Committee's Commentary. The Health Review Committee's Commentary is intended to place the Investigators' Report in perspective, as an aid to the sponsors of the HEI and to the public.

REGULATORY BACKGROUND

The U.S. Environmental Protection Agency (EPA) sets emissions standards for diesel engines and vehicles under Section 202 of the Clean Air Act, as amended in 1990. Section 202(a)(1) directs the Administrator of the EPA to "prescribe (and from time to time revise) . . . standards applicable to the emission of any air pollutant from any class or classes of new motor vehicles or new motor vehicle engines, which in his judgment cause, or contribute to, air pollution which may reasonably be anticipated to endanger public health or welfare." Section 202(a)(3)(A)(i) specifically directs the Administrator to set standards for the "emissions of carbon monoxide, hydrocarbons, oxides of nitrogen and particulate matter from classes of heavy-duty vehicles and engines. . . ."

The EPA has taken a variety of regulatory actions with respect to diesel engines and vehicles under the authority given it by Section 202(a)(1) and 202(a)(3)(A)(i) of the Act. For instance, the EPA has set emissions standards for both heavy-duty and light-duty trucks. These emissions standards initially are made applicable to all engines and vehicles produced in a given model year. Engines and vehicles of the same class that are produced in succeeding years must also comply with these existing standards unless the EPA establishes a new set of standards.

The EPA issued emissions standards for diesel-fueled heavy-duty engines and vehicles in 1980 that specified limits for hydrocarbons, carbon monoxide, and oxides of nitrogen applicable to heavy-duty engines and vehicles produced during the 1985 model year, and in 1985 added limits on particulate matter emissions for the 1988 model year. The EPA also set emissions standards for the 1991 and 1994 model years. The EPA revised those standards most recently in 1989.

With respect to light-duty trucks, the EPA issued emissions standards for the 1985 model year in 1980 that specified limits for the emission of hydrocarbons, carbon monoxide, oxides of nitrogen, and particulate matter. New standards were later promulgated for the 1987, 1988, 1990, and 1991 model years. The EPA set standards applicable to the 1991 model year in 1988 and revised them most recently in 1989.

The 1990 Amendments to the Clean Air Act included several provisions that deal with diesel engines and vehicles. Section 202(a)(3)(B)(ii), as amended, requires that, beginning in 1998, all diesel-fueled heavy-duty trucks not emit more than 4.0 grams per brake horse power-hour (g/bhp-hour). Section 202(a)(3)(B)(ii) sets new emissions standards for oxides of nitrogen produced from diesel-powered heavy-duty trucks. Section 292(j) authorizes the Administrator to promulgate regulations for carbon monoxide emissions from various classes of vehicles when operated at cold temperatures. Section 219 requires the use of certain low-polluting fuels in urban buses in cities that have not met certain emissions standards. Section 231 requires the Administrator to oversee a study to determine whether or not ethanol and high erucic rapeseed oil might be used as an "alternative to diesel fuel."

The development of models that estimate retention and predict lung burdens of diesel particles can contribute to an increased understanding of the risks to humans from exposure to diesel engine exhaust. These models can contribute also to informed decision-making with respect to standards under the Clean Air Act.

SCIENTIFIC BACKGROUND

The health effects of diesel engine emissions are of con-

cern for several reasons, including the respirable size of the diesel exhaust particle, the genotoxicity of a number of chemicals associated with the particle (Claxton 1983; Lewtas 1983), and the recent reports of pulmonary carcinogenicity of diesel engine exhaust in rats (Brightwell et al. 1986; Heinrich et al. 1986; Ishinishi et al. 1986; Iwai et al. 1986; Mauderly et al. 1986). Also, several epidemiological studies suggest an association between chronic exposure to diesel engine exhaust and an increased risk of lung and bladder cancer in humans (Silverman et al. 1986; Steenland 1986; Garshick et al. 1987, 1988). It is important to note, however, that obtaining an accurate assessment of exposure has been a major limitation in the interpretation of epidemiological studies. In addition to the difficulties in estimating exposure to diesel engine exhaust, several particulate agents, most notably cigarette smoke, confound the estimates. After reviewing the genotoxicity, carcinogenicity, and epidemiological data, the International Agency for Research on Cancer evaluated diesel engine exhaust as "probably carcinogenic to humans" (International Agency for Research on Cancer 1989). In the United States, the National Institute for Occupational Safety and Health (1988) has recommended that whole diesel exhaust be regarded as a "potential occupational carcinogen."

The major focus of concern with exposure to diesel engine exhaust has been carcinogenicity. However, noncarcinogenic histologic and cytologic effects also have been noted in animal studies. After subchronic and chronic exposure to diesel emissions, an inflammatory cell response occurs (Mauderly et al. 1981; White and Garg 1981; Heinrich et al. 1986; Lewis et al. 1986; McClellan et al. 1986). Particle-laden macrophages accumulate in the alveoli and peribronchial regions (Wiester et al. 1980; Karagianes et al. 1981; Mauderly et al. 1981; White and Garg 1981; Pepelko 1982; Plopper et al. 1983; Heinrich et al. 1986). Hyperplasia of bronchiolar and alveolar type II epithelial cells, as well as thickening of alveolar walls, have been reported (Wiester et al. 1980; White and Garg 1981; Kaplan et al. 1982; Pepelko 1982; Plopper et al. 1983; Heinrich et al. 1986; Ishinishi et al. 1986; Lewis et al. 1986). Fibrotic (Karagianes et al. 1981; Hyde et al. 1985; Heinrich et al. 1986; Lewis et al. 1986; McClellan et al. 1986) and emphysematous (Karagianes et al. 1981; Heinrich et al. 1986) lesions have been noted. The relationship of these observations to chronic lung disease remains to be determined.

The overall assessment of the health effects of exposure to diesel engine exhaust involves the sum of numerous complex variables, such as the extent of exposure, target-tissue dose, toxicity of the original and metabolized agent or agents, and variations in host susceptibility. When relating ambient exposures to potential human health effects, determining the dose of diesel particulate matter to pulmonary tissues is critical. Without measurements or accurate estimates of dose, it is difficult to extrapolate findings from animal studies, evaluate exposure in epidemiological studies, or assess individual variability.

Airborne particles of respirable size are inhaled and deposited onto respiratory tract surfaces (reviewed by Schlesinger 1988). Several physical, chemical, and biological processes act upon the deposited material to remove it from the lungs. In the airways, insoluble particles are cleared to the oropharynx primarily by the movement of surface mucus propelled by the ciliated epithelial cells; this process is termed mucociliary clearance. Soluble particles may dissolve and diffuse into the circulation. Both of these processes are fairly rapid, and the majority of deposited material in the airways is removed within 24 to 48 hours. Particles that reach the alveolar region of the lung are cleared more slowly and by different pathways. Some particles are taken up by alveolar macrophages, which, in turn, migrate onto airway surfaces and exit the lung by way of the mucociliary system. Alternatively, particle-laden macrophages, as well as free particles, may enter the pulmonary interstitium and make their way to the lung-associated lymph nodes. The clearance half-life of material deposited in the alveolar region ranges from weeks to months, depending on the route of exit from the lung. If material reaches the pulmonary lymph nodes, the residence time increases from months to years.

Deposited particles that are not cleared from the lungs remain sequestered in pulmonary tissues. In healthy individuals exposed to small amounts of particles, pulmonary clearance mechanisms are usually effective in removing the majority of the deposited material. However, if the lung is unable to clear particles faster than the rate at which they are deposited, the particles accumulate; this phenomenon is termed particle overloading. The significance of particle overloading is that, with longer retention times, the dose of toxic compounds to pulmonary tissues potentially increases. In summary, deposition and clearance are interrelated processes, and if deposition exceeds clearance, the balance is termed retention. These processes influence the local dose to target tissues, and hence, the toxic response to inhaled particulate matter.

Diesel exhaust particles are composed of a dense carbonaceous core. Combustion-derived organic compounds are adsorbed to this core. It is assumed that the clearance kinetics of diesel exhaust particles from the respiratory tract are similar to those of insoluble particles. After an acute exposure to diesel engine exhaust, the removal of particles from rat pulmonary surfaces follows a biphasic pattern, indicating that mucociliary transport and macrophage-

mediated transport are likely to be the predominant clearance mechanisms (Chan et al. 1981). Under conditions of high exposure levels, overloading has been demonstrated in rodents. A threshold concentration has not been determined, but clearance from the alveolar region is impaired in studies in which diesel exhaust particle concentrations are greater than 1 mg/m^3 (Vostal et al. 1982; Griffis et al. 1983; Chan et al. 1984; Wolff et al. 1987). Furthermore, the extent to which alveolar clearance is impaired depends on the initial particle burden: the greater the particulate concentration, the slower the clearance (Chan et al. 1984).

The disposition of the adsorbed organics also needs to be considered (reviewed by Sun et al. 1988). For those adsorbed organic compounds that remain associated with the carbon core during clearance, clearance kinetics are the same as those of the particle. Clearance rates vary for those organic compounds released from the particle. Dissociated compounds may pass into the circulation. Alternatively, they can be taken up by respiratory tract tissues or pulmonary macrophages and be metabolized. Metabolism may lead either to activation or degradation of the parent compound.

The determination of tissue doses of diesel exhaust particles has important implications when trying to elucidate mechanisms of toxicity. It is not known if the mechanisms operative at high exposure levels, which are usually used in animal studies, also operate at low levels, which may be more representative of human exposures. For example, several mechanisms have been proposed to account for the carcinogenic response observed in rodents. The deposition and clearance of the adsorbed organics, some of which are mutagens and carcinogens, are affected by their association with the diesel particle (reviewed by Sun et al. 1988). The deposition sites and clearance mechanisms are different, clearance rates are slower, and retention times are longer for particle-associated organics than for aerosols of pure compounds. Recently, considerable attention has been focused on the influence of particle overloading. The induction of respiratory tract carcinomas in rats has occurred only with high exposure concentrations of 3.5 mg or more of diesel particles/m^3. It has been suggested that under conditions of particle overload, the increased retention of particle-associated organic compounds may increase the bioavailability of genotoxic compounds, thus increasing the risk of a tumorigenic response (Heinrich et al. 1986). However, the actual bioavailability of adsorbed organic compounds has not been determined. Their prolonged presence in the lungs may or may not be significant as long as they remain adherent to particle surfaces. The physical-chemical factors that govern desorption and subsequent bioavailability of genotoxic compounds are poorly understood. In addition, the uptake and metabolism of released organics by macrophages and epithelial tissues have not been well characterized.

In addition to genotoxic mechanisms, nongenotoxic mechanisms may play a role in a tumorigenic response. After chronic exposure of rats to diesel engine exhaust, hyperplasia of bronchiolar and alveolar type II epithelial cells has been observed (Wiester et al. 1980; White and Garg 1981; Pepelko 1982; Plopper et al. 1983; Heinrich et al. 1986; Ishinishi et al. 1986; Lewis et al. 1986). Increased epithelial proliferation may increase susceptibility to tumor induction, thus contributing to the observed tumor incidence in chronic inhalation studies (reviewed by Ames and Gold 1990). Therefore, the determination of tissue doses that induce cell renewal also may be relevant.

Mechanisms that cause noncarcinogenic effects are not well understood, but the inability of the lungs to clear deposited diesel particles appears to play a role. The cellular changes described above do not occur at low particle concentrations. Such changes are associated with the reduction of pulmonary clearance and the accumulation of macrophages filled with ingested particles. The relationships among particle overloading, macrophage aggregation, and conditions such as inflammation, cellular proliferation, fibrosis, or emphysema are not known.

Thus, in order to assess the health risks from exposure to diesel engine exhaust, it is important to determine the retention time and sites of accumulation of the particles and associated organic compounds. Animal studies have focused primarily on the deposition, clearance, and retention of diesel exhaust particles, but have not measured directly the dose of particles to the cells and tissues of the respiratory tract (Chan et al. 1981; Griffis et al. 1983; Lee et al. 1983; Chan et al. 1984; Wolff et al. 1986). Data on the fate of combustion-derived organics are not available, although studies on the disposition of organic compounds experimentally adsorbed onto diesel exhaust particles (Sun et al. 1984; Ball and King 1985; Bond et al. 1986) or other insoluble particles (Wolff 1989; Wolff et al. 1989) have been conducted. No data on clearance kinetics and retention, of either diesel particles or associated organics, are available on humans. However, tissue doses can be estimated by constructing dosimetry models that utilize experimental data obtained from animals. The accuracy of the model will depend, in part, on taking into account the complexity of the routes, rates, and mechanisms of clearance.

JUSTIFICATION FOR THE STUDY

The health effects of inhaled particles and gases from mo-

bile source emissions are of central concern to the HEI. Considerable attention has been given to the evaluation of biological responses caused by emission products, but less effort has been devoted to the quantification of dose. However, without an accurate measurement or estimation of dose, descriptions of responses are of diminished value. In an earlier project funded by the HEI, Yu and Xu (1987) made theoretical calculations of lung deposition to predict the amount and distribution of particulate material deposited in the lungs during inhalation from a given airborne diesel exhaust particle concentration. However, tissue dose is determined not only by the distribution of deposition, but also by clearance times and pathways of redistribution among cells and tissues. Thus, additional modeling research was needed to describe clearance, retention, and total lung burdens.

For the current study, Dr. Yu proposed to determine the lung burden of diesel engine exhaust particles under various exposure conditions. Mathematical modeling first would be done in rats and then extrapolated to humans. The investigator proposed to develop a nonlinear model for clearance kinetics, which describes clearance as a function of lung burden over time, and then to develop a retention model for diesel exhaust particles. Using this retention model and the deposition model developed in his previous study, Dr. Yu would then predict total lung burden of particulate material.

The HEI Research Committee considered that the development of a reliable mathematical model of clearance, taking into account the nonlinear nature of clearance processes, was an important contribution to dosimetry modeling. Estimates of diesel-particle burdens are necessary for the assessment of diesel engine exhaust exposure. Thus, the goals of Dr. Yu's proposal were considered worthy and, because of his qualifications and experience, attainable.

STUDY OBJECTIVES

The objective of this project was to extend a previously developed model for deposition of inhaled diesel exhaust particles (Yu and Xu 1987) to include clearance kinetics and retention. The investigators sought to develop a mathematical retention model based on available experimental data in rats and then to extrapolate this model from rats to humans.

A critical feature of the theoretical model was the consideration of the diesel exhaust particle as tripartite with regard to its clearance characteristics. The description of the particle included a carbonaceous core (which the investigators refer to as soot), a rapidly cleared organic fraction with a short retention time, and a slowly cleared organic fraction with a long retention time. The division of the organics into slowly cleared and rapidly cleared components was based on the observations that the concentration of inhaled particle-associated organic compounds in the lungs decreases along a concave, biphasic curve (Sun et al. 1984; Bond et al. 1986). A biphasic disappearance of the associated organics is consistent with a single species of organics passing though two compartments on its way out of the lung. A biphasic disappearance curve is also consistent with two distinct species clearing independently at different rates. The physical transport of the particle was modeled in four anatomical compartments: the nasopharyngeal, tracheobronchial, alveolar, and lymph node regions. Equations were developed for the role of each of these compartments in the clearance of the three components of the diesel exhaust particle. The model was based on experimental data collected by Strom and coworkers (1988) in Fischer rats and was extended to humans. The retention model was based on exposures to diesel exhaust particles at 6 mg/m^3 for 20 hours/day and 7 days/week.

Once developed, the retention model was combined with the investigators' deposition model (Yu and Xu 1987), and burdens of diesel soot and associated organics were calculated. Exposure conditions of the model were varied, and their effects on estimated burdens were examined. The effects of diesel particle concentrations (0.1 mg/m^3 and 1.0 mg/m^3), exposure pattern (continuous and intermittent), and age on lung burdens of diesel soot and associated organics were calculated. In addition, the effect of diesel particle concentration on lung clearance, intercompartmental transport, and the accumulation of lung burdens over time were evaluated.

Finally, the investigators varied several parameters of the retention model to determine the effects on estimated lung burdens of diesel soot and associated organics. Particle characteristics (mass median aerodynamic diameter, geometric standard deviation, mass fraction of particle-associated organics, and mass ratio of the rapidly cleared organics), ventilation (tidal volume and respiratory frequency), lung volume, lung structure (by using different lung models), and alveolar transport rate were varied, and lung burdens for adult humans were calculated. These parametric analyses used an exposure pattern of 0.1 mg/m^3 for 24 hours/day and 7 days/week for 10 years.

TECHNICAL EVALUATION

ATTAINMENT OF STUDY OBJECTIVES

The investigators developed a retention model for diesel

exhaust particles and associated organics for rats and humans. This retention model was combined with the deposition model developed earlier (Yu and Xu 1987), and lung as well as lymph node burdens for diesel soot and associated organics were calculated. Thus, all the study objectives were attained.

THE MODEL: RESULTS OF CALCULATIONS AND PREDICTIONS

Most of the predictions reached by the investigators are consistent with the experimental results reported in previous studies on clearance in animals. More specifically, calculations of the model showed that alveolar clearance rates of diesel soot, but not organic compounds, decrease with increasing lung burdens. At low lung burdens of diesel soot, mucociliary transport dominates alveolar clearance, whereas at high lung burdens, material is cleared to the lymphatic system. On the basis of calculations of their model, the investigators arrived at four new predictions:

1. After exposure to diesel exhaust particles for the same amount of time, lung burdens of diesel soot and associated organics are greater in humans than in rats.
2. During continuous exposure, the lung burdens of diesel soot and associated organics eventually reach a steady state.
3. After exposure to equal concentrations of diesel exhaust particles, the reductions in alveolar clearance of diesel soot from high lung burdens is greater in children than in adults.
4. The accumulations of diesel soot and associated organics, on a per-unit-of-lung-weight basis, reach a maximum at five years of age.

On the basis of their calculations of dose and the resulting predictions, humans could prove to be more susceptible than rats to toxic effects from diesel exhaust particles, and children may be especially more sensitive than adults.

From the equations and assumptions presented in the Investigators' Report, the predictions drawn appear sound. In this type of mathematical modeling study, however, the predictions are driven strongly by the methods used. Therefore, there are several aspects of the study to consider for refinement:

1. Characteristics of the particle. The descriptions of the three components of the diesel exhaust particle could be improved. Experimental data for the particle-associated organics were derived from studies of radiolabeled 1-nitropyrene (Bond et al. 1986) and benzo[*a*]pyrene (Sun et al. 1984). In those studies, the radiolabeled compounds were adsorbed onto diesel soot particles, and then the coated particles were used for inhalation studies; the release of the radiolabeled compounds from the particle were assumed to predict the desorption of unlabeled combustion-derived organic molecules. This assumption may not be valid because adsorption energy decreases with coverage. Diesel exhaust particles could contain as many as eight layers of adsorbed molecules on their surfaces, causing the adsorption energy of the combustion-derived molecules to change dramatically depending on the number of layers. In addition, evidence suggests that diesel exhaust particles, which have heterogeneous surfaces, selectively retain polar molecules. These studies with radiolabeled molecules do not take into account selective adsorption and, hence, release. Thus, the release of combustion-derived organics may not be analogous to the behavior of compounds applied by passive adsorption.

   The investigators assumed that the amount of organics cleared slowly from the lungs represents 10 percent of the total particle mass. Although the investigators suggested several mechanisms by which organics would be removed from the lungs slowly over time, it should be pointed out that the amount of organics that are tightly bound to the carbon core is probably only 0.1 to 0.2 percent of the total particle mass. Figures 25 and 26 of the Investigators' Report illustrate how the lung burden of soot and associated organics would be affected if the total mass fraction ($f_2 + f_3$) or the mass ratio of fast-cleared organics to total organics ($f_3/f_2 + f_3$) were varied. The reader should refer to these figures in order to estimate lung burdens for different proportions of organics.
2. Exposure conditions. The retention model was based on one pattern of exposure consisting of 6 mg of diesel soot/m^3 for 20 hours/day and 7 days/week, with the emphasis on obtaining a particle-overload condition. The applicability of the model to short, low-level exposures or to intermittent peaks of high-level exposure, both of which are more comparable to human exposure patterns, is unclear. Additional effort could have been directed toward the application of the model to a wider range of exposure patterns. For example, Figure 15 shows that when human adults are exposed to diesel exhaust particles at 0.1 or 1.0 mg/m^3, the accumulation of soot over time becomes disproportionately greater with the higher concentration as the intensity of exposure increases. Also, Figure 19 shows that under intermittent exposure conditions over a 10-year period, the tolerated dose before the normalized alveolar clearance rate starts to decline is five times greater than that under the continuous exposure conditions. These examples illustrate

the value of looking at alternative exposure patterns. Thus, in addition to fitting existing data from experiments that emphasize lung burden and overload, assumptions of the model need to be varied further.

3. Model construction. A critical aspect of the construction of the model is the parameter-fitting exercise conducted on the data from Strom and coworkers (1988). Because many of the numerical parameters were derived from this exercise, the validity of the exercise is important. In most of the postexposure periods from Strom's experiment, alveolar soot mass ($m_A^{(1)}$) declined very little below its initial level ($m_{Ap}^{(1)}$). Therefore, it is difficult to ascertain whether or not the alveolar clearance rate ($\lambda_A^{(1)}$) was a function of the dynamically changing mass ($m_A^{(1)}$) or a function of the maximum mass ($m_{Ap}^{(1)}$, which remains a constant) during the postexposure period. Because using the maximum mass led to a simple exponential decline, it appears that it was chosen for convenience. This choice would be irrelevant if exponential declines fitted the data well, but in fact the fit was poor (see Figure 4). The fit might have been improved by allowing the alveolar clearance rate to depend dynamically on the declining mass of soot.
4. Statistical reliability. The statistical reliability of the gathered, derived, or assumed parameters could have been more thoroughly examined. Goodness-of-fit was not evaluated for the functions forced through the data from Strom and coworkers (1988), on which many of the model parameters were based. No reason was given for the unconventional $1/y^2$ weighting that was used to fit these data. Furthermore, the fitted parameters were reported without standard errors (see Table 1). Similarly, all additional parameters derived from Strom's study or from other studies were reported without any indication of statistical limits. The possibility remains that the propagation of error could make some parameters of the model ill-determined, and thus of limited value. This aspect of variability has not been estimated by the calculation of standard errors, nor has its impact been assessed by sensitivity analysis. Without such an assessment, it is difficult to know if the model is well-determined on the basis of the data from which it was constructed. Thus, the stability, validity, and reliability of the predictions are unclear.
5. Extrapolation assumptions. The extrapolation from rats to humans represents the most interesting and valuable part of the study. The rat-to-human scaling, however, was based on the unconfirmed assumption that mechanical clearance varies with the specific particulate dose to alveolar surface in the same proportion in humans and in rats. All other clearance rates in humans were assumed equal to those in rats. These assumptions, however, are substantial and require validation.
6. Model validation. Incomplete validation of the model is a concern. Although the investigators presented some independent data, some of the validation was circular, in that experimental data were used to construct the model and then were used to validate the model. The absence of abundant experimental data from which the investigators could have drawn emphasizes the need for such studies.

These limitations do not seriously detract from the estimates and usefulness of the model; rather, they should be considered during future revisions of the model and for its use by others. The model generated reasonable qualitative behavior and quantitative results for various body burdens of soot and organic compounds. No paradoxical or extravagant effects were apparent.

The model yielded several interesting numbers, such as the lifelong equilibrated soot accumulation in adult lungs (150 mg for each mg/m^3 of chronic half-day exposure), the ratio of alveolar to tracheobronchial burden (50:1 for organic compounds, 400:1 for diesel soot), and the equilibration time for accumulating lung soot (five to ten years). Comparisons among clearance rates after full-day exposures (24 hours/day and 7 days/week), half-day exposures (12 hours/day and 7 days/week), and work-day exposures (8 hours/day and 5 days/week), which entail a total of 168, 84, and 40 hours/week, respectively, exhibited a ratio of 4:2:1. The lung burdens of diesel soot also exhibited an approximate ratio of 4:2:1 over a 10-year chronic exposure. The exception to this calculation occurred when the effect of overload (that is, high concentrations and full-day exposures) added to the burden on a concentration-specific basis.

Assumptions and approximations are inevitable with an ambitious modeling exercise. The investigators took care to examine the effects that would have resulted if incorrect values had been used for some of their simulations. For example, two crucial parameters, the alveolar soot clearance rate ($\lambda_A^{(1)}$) fitted to the data from Strom and the slower alveolar organic clearance rate ($\lambda_A^{(2)}$) obtained by averaging two values from the literature, were perturbed to determine the effect on the lung burden of soot and organics. The response was approximately inversely proportional; halving the clearance rate doubled the burden, and raising the clearance to 3/2 of the unperturbed value lowered the burden by a factor of 2/3. One important parameter that was not perturbed was the scaling factor for alveolar clearance rate (P) between rats and humans. Extrapolation to humans was acknowledged as the "most tenuous" aspect of the model and is, therefore, a good candidate for sensitivity analyses.

REMAINING UNCERTAINTIES AND IMPLICATIONS FOR FUTURE RESEARCH

The model developed by Yu and Yoon remains to be fully explored. Some of the assumptions need testing. For example, the use of adsorbed radiolabeled compounds as surrogates for combustion-derived organics may not be valid; the organics forming the secondary coating of diesel exhaust particles may not exhibit the same degree of adherence as those organics formed during combustion. Also, some of the rat-to-human scaling factors need validation. The extrapolations were based on lung size and lung surface area; these assumptions could be tested further.

Although the model focuses on the influence of overload on lung burdens, this phenomenon is probably not relevant to most human exposures. The annual mean level of exposure to diesel particulate matter, which represents approximately 3.9 percent of the total suspended particulate emissions, is estimated at less than 3.0 $\mu g/m^3$ (Carey 1987); this level is orders of magnitude less than the value on which the model was constructed. A greater range of exposure conditions, especially those more closely approximating human exposure, should be considered. With intermittent or low-dose exposures, the lungs may clear deposited material adequately. The ultimate impact on tissue dose needs to be estimated under such exposures.

Finally, additional experimental data are needed to validate the model and its predictions. The model could be used to suggest an appropriate experimental design for such studies. In addition to validating the model, experimental studies could be used to explore various components of the model. For example, with overload conditions the model could be simplified by considering the alveolar region only; under such circumstances, the mechanisms of alveolar clearance might be examined empirically.

CONCLUSIONS

The model described in this report addresses the pulmonary disposition of inhaled diesel exhaust particles and the particle-associated organics. The model developed is well considered and executed, clearly presented, and shows a high level of inventiveness and technical proficiency. The investigators took a novel approach in considering the alveolar compartment as a single compartment and the fractional alveolar clearance rate as a function of the existing burden, rather than as a constant. They distinguished between clearance during deposition, which is a function of the instantaneous alveolar mass of soot, and clearance following termination of exposure, which no longer depends on instantaneous levels of soot, but remains at the end-of-exposure level. Different parameters can be inserted into the model, making it dynamic and useful.

Values for lung burdens, which are difficult to obtain experimentally, can be calculated from the model. The estimations of dose and the resulting predictions both support previous findings in animal studies and address new and interesting information on the extrapolations of the animal studies to human exposure scenarios and on the potential susceptibility of preschool children. Calculations of dose suggest that after repeated exposures, the accumulated lung burdens of diesel soot in humans would be higher than in rats, which implies that humans may be more susceptible to toxic effects than are rats. According to the model, adults, who have larger lungs, accumulate more total soot than children in response to a given exposure. Conversely, the lungs of preschool children absorb more soot on a mass-specific basis than do tissues of adults.

As with all models that lack data on many of the physiological processes involving clearance, the validity of this model depends on the accuracy and completeness of the assumptions on which it is based. Most of the concerns are with clarifying the construction of the model and distinguishing between what was assumed and what was derived, so that the limits of the model's inference can be more clearly delineated.

Current application of this model, however, must be approached with great restraint. For example, the extrapolation of a model that assumes overload may not be appropriate for lower exposure conditions. With an understanding of the limitations of that assumption, the model calculation that shows a peak in lung burden per unit of lung weight in the age range of two to six years has important implications for establishing standards for children based on data from adults. Confirmation of this estimation of dose, as well as others generated by the model, should be pursued and tested.

In summary, the model represents a significant contribution to the field and could have a direct bearing on risk assessment as well as implications for public policy. From a risk assessment standpoint, this model sufficiently describes the potential tissue dose of inhaled particles, but the model description for the adsorbed organics may be too simplistic. For example, although the investigators recognized the importance of the binding of organic compounds to macromolecules, they did not provide transport rates; there should be some experimental data on xenobiotic metabolism that could be incorporated into the model. Once modified and validated, the model could provide considerable insight into the dose to target tissues for diesel exhaust particulate matter. Thus, the human health risks from inhaled diesel engine exhaust could be better assessed.

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LIST OF HEI PUBLICATIONS

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Special Reports

Title	Publication Date
Gasoline Vapor Exposure and Human Cancer: Evaluation of Existing Scientific Information and Recommendations for Future Research	September 1985
Automotive Methanol Vapors and Human Health: An Evaluation of Existing Scientific Information and Issues for Future Research	May 1987
Gasoline Vapor Exposure and Human Cancer: Evaluation of Existing Scientific Information and Recommendations for Future Research (Supplement)	January 1988

Research Reports

Report No.	Title	Principal Investigator	Publication Date
1	Estimation of Risk of Glucose 6-Phosphate Dehydrogenase-Deficient Red Cells to Ozone and Nitrogen Dioxide	M. Amoruso	August 1985
2	Disposition and Metabolism of Free and Particle-Associated Nitropyrenes After Inhalation	J. Bond	February 1986
3	Transport of Macromolecules and Particles at Target Sites for Deposition of Air Pollutants	T. Crocker	February 1986
4	The Metabolic Activation and DNA Adducts of Dinitropyrenes	F.A. Beland	August 1986
5	An Investigation into the Effect of a Ceramic Particle Trap on the Chemical Mutagens in Diesel Exhaust	S.T. Bagley	January 1987
6	Effect of Nitrogen Dioxide, Ozone, and Peroxyacetyl Nitrate on Metabolic and Pulmonary Function	D.M. Drechsler-Parks	April 1987
7	DNA Adducts of Nitropyrene Detected by Specific Antibodies	J.D. Groopman	April 1987
8	Effects of Inhaled Nitrogen Dioxide and Diesel Exhaust on Developing Lung	J.L. Mauderly	May 1987
9	Biochemical and Metabolic Response to Nitrogen Dioxide-Induced Endothelial Injury	J.M. Patel	June 1987
10	Predictive Models for Deposition of Inhaled Diesel Exhaust Particles in Humans and Laboratory Species	C.P. Yu	July 1987
11	Effects of Ozone and Nitrogen Dioxide on Human Lung Proteinase Inhibitors	D.A. Johnson	August 1987
12	Neurotoxicity of Prenatal Carbon Monoxide Exposure	L.D. Fechter	September 1987
13	Effects of Nitrogen Dioxide on Alveolar Epithelial Barrier Properties	E.D. Crandall	October 1987
14	The Effects of Ozone and Nitrogen Dioxide on Lung Function in Healthy and Asthmatic Adolescents	J.Q. Koenig	January 1988
15	Susceptibility to Virus Infection with Exposure to Nitrogen Dioxide	T.J. Kulle	January 1988
16	Metabolism and Biological Effects of Nitropyrene and Related Compounds	C.M. King	February 1988

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Research Reports

Report No.	Title	Principal Investigator	Publication Date
17	Studies on the Metabolism and Biological Effects of Nitropyrene and Related Nitro-polycyclic Aromatic Compounds in Diploid Human Fibroblasts	V.M. Maher	March 1988
18	Respiratory Infections in Coal Miners Exposed to Nitrogen Oxides	M. Jacobsen	July 1988
19	Factors Affecting Possible Carcinogenicity of Inhaled Nitropyrene Aerosols	R.K. Wolff	August 1988
20	Modulation of Pulmonary Defense Mechanisms Against Viral and Bacterial Infections by Acute Exposures to Nitrogen Dioxide	G.J. Jakab	October 1988
21	Maximal Aerobic Capacity at Several Ambient Concentrations of Carbon Monoxide at Several Altitudes	S.M. Horvath	December 1988
22	Detection of Paracrine Factors in Oxidant Lung Injury	A.K. Tanswell	February 1989
23	Responses of Susceptible Subpopulations to Nitrogen Dioxide	P.E. Morrow	February 1989
24	Altered Susceptibility to Viral Respiratory Infection During Short-Term Exposure to Nitrogen Dioxide	R.M. Rose	March 1989
25	Acute Effects of Carbon Monoxide Exposure on Individuals with Coronary Artery Disease	HEI Multicenter CO Study Team	November 1989
26	Investigation of a Potential Cotumorigenic Effect of the Dioxides of Nitrogen and Sulfur, and of Diesel-Engine Exhaust, on the Respiratory Tract of Syrian Golden Hamsters	U. Mohr (U. Heinrich)	May 1989
27	Cardiovascular Effects of Chronic Carbon Monoxide and High-Altitude Exposure	J.J. McGrath	July 1989
28	Nitrogen Dioxide and Respiratory Infection: Pilot Investigations	J.M. Samet	September 1989
29	Early Markers of Lung Injury	J.N. Evans	September 1989
30	Influence of Experimental Pulmonary Emphysema on Toxicological Effects from Inhaled Nitrogen Dioxide and Diesel Exhaust	J.L. Mauderly	October 1989
31	DNA Binding by 1-Nitropyrene and Dinitropyrenes in Vitro and in Vivo: Effects of Nitroreductase Induction	F.A. Beland	November 1989
32	Respiratory Carcinogenesis of Nitroaromatics	R.C. Moon	April 1990
33	Markers of Exposure to Diesel Exhaust in Railroad Workers	M.B. Schenker	October 1990
34	Metabolic Activation of Nitropyrene and Diesel Particulate Extracts	A.M. Jeffrey	July 1990
35	Acute Effects of Carbon Monoxide on Cardiac Electrical Stability	R.L. Verrier	October 1990
36	Carbon Monoxide and Lethal Arrhythmias	J.P. Farber	December 1990
37	Oxidant Effects on Rat and Human Lung Proteinase Inhibitors	D.A. Johnson	December 1990
38	Synergistic Effects of Air Pollutants: Ozone Plus a Respirable Aerosol	J.A. Last	January 1991
39	Noninvasive Determination of Respiratory Ozone Absorption: Development of a Fast-Responding Ozone Analyzer	J.S. Ultman	March 1991

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Research Report Number 40 **May 1991**