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A Biomathematical Model of Particle Clearance and Retention in the Lungs of Coal Miners

I. Model Development

Eileen D. Kuempel,*,[1] Ellen J. O'Flaherty,[1] Leslie T. Stayner,* Randall J. Smith,*
Francis H. Y. Green,† and Val Vallyathan†

*Education and Information Division, Risk Evaluation Branch, National Institute for Occupational Safety and Health, Cincinnati, Ohio 45226-1998; †Department of Pathology, University of Calgary, Calgary, Alberta, Canada; and ‡Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Morgantown,West Virginia

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To understand better the factors influencing the relationships among airborne particle exposure, lung burden, and fibrotic lung disease, we developed a biologically based kinetic model to predict the long-term retention of particles in the lungs of coal miners. This model includes alveolar, interstitial, and hilar lymph node compartments. The 131 miners in this study had worked in the Beckley, West Virginia, area and died during the 1960s. The data used to develop this model include exposure to respirable coal mine dust by intensity and duration within each job, lung and lymph node dust burdens at autopsy, pathological classification of fibrotic lung disease, and smoking history. Initial parameter estimates for this model were based on both human and animal data of particle deposition and clearance and on the biological and physical factors influencing these processes. Parameter estimation and model fit to the data were determined using least squares. Results show that the end-of-life lung dust burdens in these coal miners were substantially higher than expected from first-order clearance kinetics, yet lower than expected from the overloading of alveolar clearance predicted from rodent studies. The best-fitting and most parsimonious model includes processes for first-order alveolar-macrophage-mediated clearance and transfer of particles to the lung interstitium. These results are consistent with the particle retention patterns observed previously in the lungs of primates. The findings indicate that rodent models extrapolated to humans, without adjustment for the kinetic differences in particle clearance and retention, would be inadequate for predicting lung dust burdens in humans. Also, this human lung kinetic model predicts greater retained lung dust burdens from occupational exposure than predicted from current human models based on lower exposure data. This model is useful for risk assessment of particle-induced lung diseases, by estimating equivalent internal doses in rodents and humans and predicting lung burdens in humans with occupational dust exposures.

INTRODUCTION

A biomathematical dosimetry model describes the relationship between the external exposure and the internal dose. In this study, the model describes the relationship between the respirable particles in the air a worker breathes and the retained mass of particles in the lungs and lung-associated (hilar) lymph nodes. Internal dose estimates may better predict disease development than external exposure estimates because of the interaction between the contaminant and the target tissue. If the relationship between external exposure and internal dose is not proportional (as in capacity-limited metabolism or clearance), then exposure would be a poor surrogate for internal dose. Rodent studies suggest that particle clearance from the lungs can become impaired due to overloading of alveolar-macrophage-mediated clearance. If overloading occurs in humans, then workers' external exposures to particles may provide a poor estimate of their internal dose (i.e., lung dust burden). Alternatively, if the kinetic processes influencing particle disposition in the lungs of humans and rodents are not related by a standard scaling factor (e.g., allometric), then the extrapolation of a rodent dosimetry model to humans may provide a poor estimate of the internal dose in humans at a given exposure. A human lung dosimetry model can be used to improve dose estimation in either of these situations. It can be used directly (without interspecies extrapolation) to predict

[1] Affiliation at time of this study: College of Medicine, Department of Environmental Health, University of Cincinnati, Cincinnati, OH.

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human doses associated with given exposures. It also provides a biological and empirical basis for determining equivalent doses across species, which should improve the accuracy of estimating dose and disease risk in humans.

Many biomathematical exposure–dose models for particles have been developed using data from experimental studies in rodents (e.g., Thomas, 1972; Vincent *et al.*, 1987; Strom *et al.*, 1988; Yu *et al.*, 1991; Stöber *et al.*, 1989; Bellman *et al.*, 1994; Katsnelson *et al.*, 1994; Tran *et al.*, 1997). Some have also been extrapolated to humans (Smith, 1985; Yu *et al.*, 1991; Yu, 1996). Human models have been developed by the ICRP (1994) and NCRP (1997) to describe particle deposition, clearance, and retention in the entire human respiratory tract. Those models are based largely on experimental studies in human using radiolabeled tracer particles. A portion of these models describe particle deposition and clearance in the gas-exchange region of the lungs, which is the site of interest in this study. The ICRP model includes three first-order clearance compartments in the alveolar/interstitial (AI) region; a fixed proportion of respirable particles depositing in each compartment is assigned (30, 60, and 10% for AI_1, AI_2, and AI_3), and the corresponding first-order clearance rate coefficients are 0.02, 0.001, and 0.0001 day^{-1}, respectively. The three AI compartments do not directly reflect lung anatomy, but are based on measurements of the activity remaining in the lungs up to 1 year after inhalation of low-solubility, radioactive particles. The NCRP model describes the pulmonary region of the lungs as a single compartment (first-order clearance rate coefficient 0.006 day^{-1} in the first 200 days and 0.001 day^{-1} thereafter). Both models include terms for particle transport to the tracheobronchial region and translocation to the lymph node compartments. In the ICRP model, lymph node transfer occurs only from AI_3 (first-order clearance rate coefficient 0.00002 day^{-1}). Faster lymph node transfer is assumed in the NCRP model (first-order clearance rate coefficient 0.0001 day^{-1}).

The human lung model developed in this study focuses on the gas-exchange region of the lungs, where respirable particles (aerodynamic diameter $< 10\ \mu m$) can deposit. This model includes three compartments, including alveolar, interstitial, and lung-associated (hilar) lymph nodes (Fig. 1). It describes the kinetics of mass transfer of particles among these compartments. A principal difference in this model compared to the ICRP and NCRP models is that it treats the alveolar and interstitial regions of the lung as separate compartments, which reflects both the biological structure of the lungs and the disposition of particles in these regions. The biological events that occur in these compartments are as follows.

When particles deposit in the alveolar region, the primary mechanism for particle clearance is phagocytosis by alveolar macrophages. The macrophages transport the particles to the tracheobronchi, where they are removed from the lungs by mucociliary clearance (Bohning and Lippmann, 1992). Particles may be cleared from the tracheobronchi by cough, or they may be swallowed and enter the gastrointestinal tract. Phagocytosed particles may also remain in the alveolar region, causing lysis of macrophages and contributing to pulmonary inflammation (Newman, 1992). Particles that escape alveolar-macrophage-mediated clearance can penetrate the epithelial cell barrier (depending on size) into the interstitium of the lungs, where they may be very slowly cleared to the lung-associated lymph vessels, which drain into the hilar lymph nodes (Leak, 1977). Particle transfer from the interstitium to the lymph nodes occurs by engulfment of particles into pulmonary lymphatic endothelial cells, where they enter the lymphatic vessels as free particles, or by phagocytosis and transfer by interstitial macrophages (Leak, 1977). Particles may also be transported to the lymph nodes by alveolar macrophages (Newman, 1992). The dosimetric model developed here describes the mass transfer of particles among the lung and lymph node

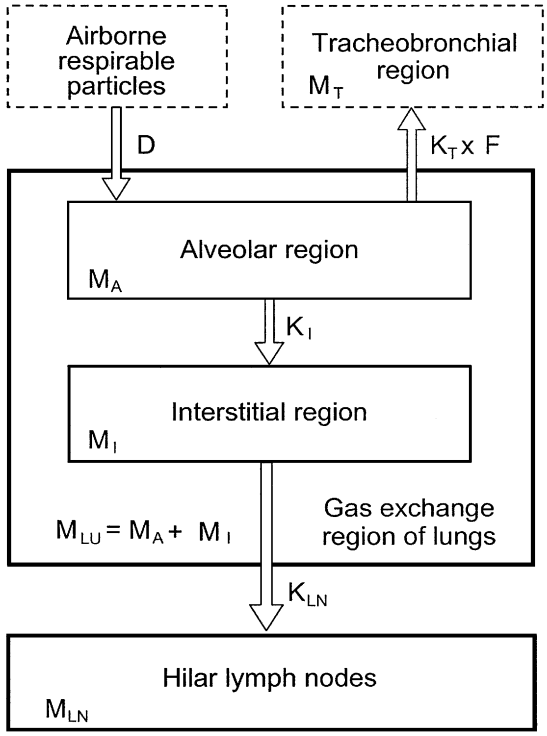

FIG. 1. Three-compartment human lung dosimetry model. D, dose rate of deposited particles; first-order rate coefficients include alveolar-macrophage-mediated clearance of particles to the tracheobronchial region (K_T), transfer of particles into the pulmonary interstitium (K_I), and translocation of particles to the hilar lymph nodes (K_{LN}); F is an exponential decay function that describes overloading as a dose-dependent decline in K_T; and M is the particle mass in a given lung region, including that cleared to the tracheobronchial region (M_T), or retained in the alveolar (M_A), interstitial (M_I), gas-exchange (M_{LU}), or hilar lymph node (M_{LN}) regions.

compartments. Material that is not cleared from the lungs is retained and represents the particle burden at any given time, which is a measure of internal dose.

This model was used to evaluate the biological processes that may influence particle clearance and retention in the lungs of humans. The direct use of human data, when available, avoids the uncertainty associated with interspecies extrapolation. It enables comparison with animal models, which are more commonly used in risk assessment. Rodent studies have shown that the chronic inhalation of various types of insoluble, respirable particles can lead to the impairment, or overloading, of lung clearance (Le Bouffant, 1971; Bolton *et al.*, 1983; Wolff *et al.*, 1987; Strom *et al.*, 1988; Bellmann *et al.*, 1991; Muhle *et al.*, 1998). In rats with overloading doses, there is increased penetration of particles through the epithelium into the interstitium, as well as increased transfer of particles to the lymph nodes (Muhle *et al.*, 1990). Pathological responses associated with overloaded lung burdens in rats include persistent inflammation, fibrosis, and lung tumors (Muhle *et al.*, 1991; Heinrich *et al.*, 1995). It is not known whether overloading of lung clearance occurs in humans and thus whether the findings from animal studies are predictive of exposure–dose relationships in humans. It is also not known whether human disease responses to respirable, insoluble particles are associated with overloading.

Another process that can result in higher lung dust burdens than expected from first-order clearance is sequestration, the retention of some portion of dust that is unavailable for clearance (Soderholm, 1981). Sequestration may occur as a first-order process at any exposure (Vincent *et al.*, 1987; Jones *et al.*, 1988b) or as a consequence of the overloading of alveolar-macrophage-mediated clearance (Tran *et al.*, 1997; Stöber *et al.*, 1989). Thus, lung dust burdens that exceed the steady-state burden expected with simple first-order clearance could be due to sequestration, overloading, or a combination of both processes. In this human dosimetric lung model, the importance of these kinetic processes was explored and compared to the findings from the rat studies. The hypotheses investigated in this study are in humans with long-term occupational exposures to respirable, insoluble particles, the end-of-life lung dust burdens are best described by a model with (1) rodent-based overloading of alveolar clearance, (2) sequestration of particles in the interstitium, or (3) a combination of both processes.

METHODS

Data Description

The original data set is based on approximately 600 former coal miners who were autopsied at Beckley Appalachian Regional Hospital in Beckley, West Virginia, between 1959 and 1973. These cases were collected systematically from consecutive autopsies by the late Werner Laqueur, M.D. A subgroup of 430 miners was analyzed previously, and results were reported on agreement of fibrosis determinations from radiographic and pathologic examination (Attfield *et al.*, 1994; Vallyathan *et al.*, 1996). The miners included in this study are from the subgroup of 141 miners with lung dust burden data. These miners had died during 1962 to 1968, and lung tissue samples were collected and analyzed sequentially. Whole lung serial sections were used for pathologic evaluation of the disease type and severity of pneumoconioses, emphysema, and lung cancer (Vallyathan *et al.*, 1996). The percentage (g/100 g dry lung tissue) and composition (coal, noncoal, silica, and total) of dust in the lungs were determined in laboratory analyses of the lung tissue (Crable *et al.*, 1967, 1968; Carlberg *et al.*, 1971; Sweet *et al.*, 1974), described below. For 58 of these miners, data on the percentage and composition of dust in the hilar lymph nodes were also available.

A gravimetric method was used to determine the concentrations of coal, noncoal, and total dust (Crable *et al.*, 1967, 1968). Digestion and washing procedures were used to remove the lung tissue, leaving the particulate matter as a residue. This residue was then dried at 110°C to a constant weight, which represented the total mass of dust in the tissue sample, and then ashed at 380°C. The amount of coal dust was determined as the mass lost during ashing, while the noncoal mass was that portion remaining after ashing. The silica content in the noncoal fraction was determined by X-ray diffraction or spectrophotometric methods (Carlberg *et al.*, 1971; Sweet *et al.*, 1974) (silica data are available for 110 of the 131 miners). The resulting dust burdens were expressed as mass concentration (g dust/100 g dry tissue). For the dosimetric modeling, the dust burden in the whole lung was needed. Thus, to compute this from the mass concentration data available, estimates of the lung weights were needed. The whole lung wet weights were available, but this information was not used because those values are greatly influenced by the cause of death and the time between death and autopsy. Ideally, one would want the whole lung dry weights, but these data were not available. Therefore, the standard reference value of 1000 g for the lung wet weight was assumed, and the dry lung tissue weight was assumed to the standard be 20% of the wet tissue weight (ICRP, 1975). Some height and weight data were available (for about half of the miners), but this information was not used to adjust lung weight because it was incomplete and because these factors were considered to have less influence on lung weight than fibrosis, which fills in lung air spaces and is more dense than normal lung tissue. To determine the possible influence of using a standard lung weight, an analysis was done later to compare the fit of the dosimetry model among miners with

severe fibrosis (progressive massive fibrosis or PMF) to the model fit among the other miners (see Results). The data available on the lymph node dust burdens were also expressed as mass concentration (mg/g dry tissue). A standard reference value of 15 g was assumed for the wet weight of the hilar lymph nodes (ICRP, 1975). This standard value was used for miners with normal, unenlarged nodes, but most of the coal miners in this study had recorded enlargement of hilar lymph nodes. For those miners, the lymph nodes were assumed to be five times the normal size, an estimate based on observations during the pathological examinations of these coal miners by two coauthors (F.H.Y.G. and V.V.). No published data were found on the dry-to-wet tissue weights for hilar lymph nodes; however, a value of 33% dry tissue weight was assumed based on unpublished data from pathological examinations of coal miners by coauthors F.H.Y.G. and V.V. For the dosimetry modeling, the mass concentration values for lung and lymph nodes were converted to total mass of particles (mg) in the whole organ, and results are reported as total particle mass in grams (g).

Occupational histories had been obtained previously from a standardized questionnaire sent to the next-of-kin soon after the miner's death, from clinical records, and from coal mine company records (Vallyathan *et al.*, 1996). These data include date of first employment in mining, job titles and dates worked, dates unemployed and/or employed in nonmining jobs, date of retirement, and total number of years in mining. Working lifetime exposure to respirable coal mine dust was estimated for each miner using the individual's work history data and job-specific estimates of the mean airborne dust concentration. These measurements of the airborne dust concentration were taken during a sampling survey by the former U.S. Bureau of Mines (BOM) during 1968 and 1969 in 29 underground coal mines throughout the United States (Jacobson, 1971). Approximately 4300 gravimetric samples of airborne respirable dust were collected. These BOM data include samples for at least 10 shifts for certain jobs (e.g., coal face jobs), but fewer or no samples for other underground or surface jobs. For those jobs, the mean concentrations estimates were based on samples collected from 1970 to 1972 by mine operators as part of a mandated sampling program administered by the Mine Safety and Health Administration (MSHA) (Attfield and Morring, 1992). The mass median aerodynamic diameter (MMAD) of the respirable coal mine dust is approximately 5 μm (SD 2.1 μm) (Jones *et al.*, 1988a; Burkhart *et al.*, 1987). The particle size distributions in U.S. mines were shown to not vary significantly across jobs or mining methods, although mine-to-mine differences were observed (Seixas *et al.*, 1995). These findings suggest that for miners with the same estimated airborne exposure, the fractional deposition of particles in their lungs would be similar, even if they worked in different types of jobs or with different mining methods (which have changed over time). Assuming miners worked in various mines throughout their careers, the mine-to-mine differences could contribute to variability to the exposure–dose relationships.

The minimum data required for inclusion of a miner in this study were lung dust burden, duration of employment in mining, at least one mining job title (to assign intensity of exposure), and pathological grading of fibrosis. Of the 141 miners with lung dust burden data, 131 had sufficient data for inclusion in this study. Of the 131 miners, 58 also had hilar lymph node dust burden data. Additional data required for the dosimetric modeling were the dates and/or ages at retirement and death (needed to compute the postexposure duration). Three of the 131 miners did not have this additional data (1 of whom did have hilar lymph node data) and were omitted from the model calibration. Thus, 128 and 57 miners were used in the modeling. When the calibrated model was used for prediction of lung and lymph node burdens, those 3 miners were included by assuming they had the postexposure duration equal to the mean values for the whole group.

Model Development

As part of the early model development, a one-compartment model was constructed because it is the simplest model for describing particle retention in the lungs (Kuempel, 2000). In that model clearance was described by a single rate coefficient, with alveolar macrophage-mediated clearance and translocation to the lymph nodes combined. Model forms with either linear or dose-dependent clearance were evaluated. After determining that the one-compartment model was inadequate to describe the particle clearance and retention in these coal miners, we developed a three-compartment lung model (Fig. 1). This model includes two lung compartments (alveolar and interstitial) and a lung-associated lymph node compartment. The main principles guiding the development of this model were biological plausibility and parsimony. Three compartments is the minimum number compatible with what is known about the mechanisms of clearance and retention of inhaled respirable particles. A description of the model parameters is provided in Table 1. The input for this dosimetric model is the individual miners' work history data (including intensity and duration of exposure in each job and duration not employed in mining or retired). The model output is predicted particle mass burden in the lungs and lymph nodes as a function of time.

The model was developed using the software Advanced Continuous Simulation Language (ACSL, 1995). The mass balance (input minus output) was evaluated and determined to be acceptable (i.e., virtually zero) before proceeding with model calibration, in which

TABLE 1
Description of Variables and Constants in Three-Compartment Human Lung Dosimetry Model

Abbreviation	Units	Description
F_D	None	Fractional deposition of airborne respirable dust in alveolar region
V_I	m^3/day	Volume of air inhaled in an 8-h day, heavy work
d	Days/year	Days exposed/year
C_I	mg/m^3	Mean concentration of respirable coal mine dust inhaled, by job[a]
D	Years	Duration of exposure, by job[a]
K_T	Day^{-1}	Rate coefficient, alveolar-macrophage-mediated clearance to tracheobronchi
K_I	Day^{-1}	Rate coefficient, transfer from alveoli to interstitium
K_{LN}	Day^{-1}	Rate coefficient, translocation from interstitium to hilar lymph nodes
F	None	Exponential decay function, does-dependent reduction in K_T
B	None	Slope modifier of F
C	None	Shape modifier of F
M_{min}	mg	Minimum lung dust burden associated with beginning of dose-dependent decline in K_T
M_{max}	mg	Maximum lung dust burden associated with leveling off of dose-dependent decline in K_T

[a] Individual work history data for each miner (input data).

the optimum parameter values were determined. The model was calibrated using the coal miner data described above. These data were initially divided into two groups, one group for developing the model (two-thirds of the data, $n = 87$) and the other for testing it (one-third of the data, $n = 44$), using stratified random data allocation (RANUNI function, SAS, 1996). The strata were based on smoking status and cumulative exposure, both of which were expected *a priori* to influence particle clearance and retention. Following model calibration, the model was tested using the reserved data. Then, all the data were combined ($n = 131$) to generate model predictions of lung and lymph node dust burdens and to do residuals analysis of the model fit to the data.

A subgroup of miners ($n = 11$) whose post-exposure duration was equal to zero (because they died while employed as coal miners) was evaluated separately. Evaluating the model fit to these miners' data provides information on the buildup of dust in the lungs without the additional unknown of clearance during the postexposure (retirement) period. The model fits and parameter values for these miners were compared to those for miners who had both exposure and postexposure experience.

Model Equations and Description

The equations for the three-compartment human lung model are provided below. The model describes the kinetics of particle mass transfer in the lungs. Mathematically, it consists of a series of nonlinear differential equations that are integrated over time to predict individuals' lung and lymph node particle burdens. The sources and values of the initial parameter values are described in the section "Model-Fitting and Parameter Estimation."

The rate of change of particle mass in the alveoli (M_A) at any time (t) is defined as

$$dM_A/dt = R_D - R_T - R_I, \tag{1}$$

where R_D is the deposition rate (mg/year) of inhaled, respirable particles into the alveoli (described in Eq. 2). R_T is the clearance rate (mg/year) of particles from the alveoli to the tracheobronchi (Eq. 3). R_I is the transfer rate (mg/year) of particles from the alveoli into the interstitium (Eq. 5).

$$R_D = F_D \times C_I \times V_I \times d, \tag{2}$$

where F_D is the fractional deposition (fraction of the inhaled particle mass that is deposited in the alveolar region of the lungs, C_I is the airborne concentration of dust inhaled (mg/m^3), V_I is the volume of air inhaled in an 8-h workday (m^3/day), and d is the days worked per year (days/year) (estimated as 5 days/week × 50 weeks/year).

$$R_T = K_T \times 365 \times F \times M_A, \tag{3}$$

where K_T is the first-order rate coefficient (day^{-1}) for particle clearance from the alveoli to the tracheobronchi. M_A is defined in Eq. (1), 365 is the days per year to convert R_T to units of $year^{-1}$, and F is defined in Eq. (4).

$$F = 1 \quad \text{when} \quad M_A \le M_{min} \tag{4a}$$

$$F = \exp\{-B[(M_A - M_{min})/(M_{max} - M_{min})]^C\} \quad \text{when} \quad M_A > M_{min}. \tag{4b}$$

F is a dose-dependent modifying factor of K_T. M_{min} and M_{max} are constants representing the human-equivalent minimum and maximum critical lung dust burdens at which the dose-dependent decline in the alveolar clearance rate coefficient begins and reaches a maximum, respectively, as predicted from rodent studies (see next section); M_A is defined in Eq. (1). When $M_A \le M_{min}$, F is set equal to 1; when $M_A > M_{min}$, F equals a value (between 0 and 1) that is determined by B. C is a shape parameter (set to 1 in this model).

$$R_I = K_I \times 365 \times M_A, \tag{5}$$

where K_I is the first-order rate coefficient (day^{-1}) for transfer of particles from the interstitium to the

lung-associated (hilar) lymph nodes. M_A is defined in Eq. (1), and 365 converts R_I to units of year^{-1}. The rate of change of particle mass in the interstitium (M_I) at any time (t) is defined as

$$dM_I/dt = R_I - R_{LN}, \quad (6)$$

where R_I is defined in Eqs. (1) and (5). R_{LN} is the translocation rate (mg/year) of particles from the interstitium to the lung-associated (hilar) lymph nodes, as follows:

$$R_{LN} = K_{LN} \times 365 \times M_I, \quad (7)$$

where K_{LN} is the first-order rate coefficient (day^{-1}) for translocation of particles from the interstitium to the hilar lymph nodes. M_I is defined in Eq. (6), and 365 converts R_{LN} to units of year^{-1}.

The rate of change of particle mass in the hilar lymph nodes (M_{LN}) at any time (t) is defined as

$$dM_{LN}/dt = R_{LN}, \quad (8)$$

where R_{LN} is defined in Eq. (7).

The mass of particles at time (T) in any compartment is determined from the integral of the rate of change of particle mass in that compartment:

Alveoli:

$$M_A(T) = \int_0^T (R_D - R_T - R_I)\, dt \quad (9)$$

Interstitium:

$$M_I(T) = \int_0^T (R_I - R_{LN})\, dt \quad (10)$$

Hilar lymph nodes:

$$M_{LN}(T) = \int_0^T (R_{LN})\, dt, \quad (11)$$

where integration occurs from time 0 to t, and the terms of Eqs. (9)–(11) are described in Eqs. (1)–(8).

For clarity of the model comparisons, we also describe the preliminary one-compartment model. It is a simplification of the three-compartment model and has some common features. Essentially, the three-compartment model reduces to the one-compartment lung model when K_I is set to zero. In the one-compartment model, Eq. (1) simplifies to

$$dM_L/dt = R_D - R_C, \quad (12)$$

where M_L is the particle mass in the whole lungs, R_D was defined in Eq. (1), and R_C is the total clearance rate (mg/year), i.e., clearance from the alveoli to the tracheobronchi and lung-associated lymph nodes.

Equations (2)–(4b) are identical in the one-compartment model, except that M_L is substituted for M_A and K_C and R_C are substituted for K_T and R_T. Equations (5)–(8) are omitted. Equation (9) simplifies to the following, and Eqs. (10) and (11) are omitted:

$$M_L(T) \int_0^T (R_D - R_C)\, dt, \quad (13)$$

where the terms are described in Eqs. (1) and (12).

The mathematical equations in the three-compartment model better reflect the biological structures and kinetic processes in human lungs which influence respirable particle clearance and retention. The accumulation of dust in the alveolar compartment is determined by rates of particle deposition, alveolar-macrophage-mediated clearance, and transfer of particles into the interstitium (Eq. (1)). The deposition of particles in the alveolar compartment is assumed to occur at a rate proportional to the concentration in inhaled air, i.e., a first-order process (Eq. (2)). Once deposited in the alveolar compartment, particles are coated by lung fluid (lipid surfactant) and rapidly phagocytosed by alveolar macrophages (Bohning and Lippmann, 1992). The presence of foreign material stimulates the recruitment of additional macrophages, which are derived from monocytes in the bone marrow and enter the lung interstitium through the blood; macrophages mature in the interstitium and then move out onto the alveolar surface (Bohning and Lippmann, 1992). Although the macrophage recruitment rate would be important for describing clearance of particles in short-term exposures, it was not considered in this model because all of the miners had long-term exposures (mean duration of 36 years), and it was therefore assumed that a steady-state alveolar macrophage cell population would have been achieved. This model describes alveolar-macrophage-mediated clearance as a first-order process at lung burdens below those potentially causing impairment of clearance (Eq. (3)). At higher lung dust burdens, alveolar-macrophage-mediated clearance can be described as dose-dependent, declining exponentially (Eq. (4)). The model also assumes that some particles will escape phagocytosis by alveolar macrophages and enter the interstitium at a constant rate (Eq. (5)); this will occur even at low lung dust burdens, below the estimated human-equivalent dose associated with overloading of alveolar clearance. This assumption of a first-order process for interstitialization is evaluated in the next paper (this journal; Kuempel *et al.*, 2001). The accumulation of dust in the interstitium is described by the difference in the rates of particles entering from the alveoli

and particles leaving to the lung-associated lymph nodes (Eq. (6)). The rate of particle translocation to the lymph nodes is also assumed to be first-order (Eq. (7)), and the accumulation of particles in the lymph nodes occurs only by particles passing through the interstitium (Eq. (8)). The rate coefficients for these processes are estimated by the model-fitting and parameter estimation, as reported under Results. The model equations also enable prediction of the amount of dust in the lung and lymph node compartments at any point in time (Eqs. (9)–(11)).

Human-Equivalent Critical Lung Dust Burdens

Overloading of alveolar clearance is expressed above as a dose-dependent exponential decay function (Eq. (4)), which modifies the first-order alveolar clearance rate coefficient (K_T). The basis for this expression is the studies of rodents exposed to various poorly soluble, respirable particles. These studies show that as the lung particle burden increases, the clearance rate coefficient declines (Fig. 2 of Bellmann *et al.*, 1991). These results of the lung dust burdens associated with overloading of alveolar clearance in rats are used to estimate the equivalent lung dust burdens in humans. These calculations account for interspecies differences in the number and volume of macrophages, as well as differences in the density of particles used in the rat studies and the density of respirable coal mine dust. These human-equivalent critical lung dust burdens provide a basis for comparing the extent of overloading of alveolar-macrophage-mediated clearance in rodents and humans.

Critical lung dust burdens in rats. Bellmann *et al.* (1991) show that the alveolar clearance rate coefficient decreases with increasing lung dust burden in rats exposed to various types of inhaled particles. When the lung dust burden exceeds approximately 100 μg (equivalent to 100 nl for unit density dust), the rate coefficient begins to decline. When the lung dust burden reaches approximately 10,000 μg, the clearance rate coefficient has declined to approximately 10% of its initial value. For unit density dust (1 g/ml), the retained mass (μg) is equal to the retained volume (nl).

The volumetric overload hypothesis of Morrow (1988, 1992) was used to describe overloading in rats, and an equivalent description was used for humans. Morrow (1988) hypothesized that alveolar macrophages have a volumetric limit for particle engulfment, above which macrophage mobility begins to progressively decline, until both mobility and clearance essentially cease. Support for this volumetric overload hypothesis was reported by Oberdörster *et al.* (1992), in which increased retention times were observed for larger (10.3 μm diameter) compared to smaller (3.3 μm) radiolabled microspheres. Morrow (1988) provided estimates of the average volume of dust associated with overloading from data on the lung dust burden (mass), the density of the dust, and the average number and volume of alveolar macrophages in rat lungs. A similar approach is described here. Table 2 provides values for the number and volume of alveolar macrophages in the lungs of humans and rats. At the 100-nl minimum critical lung dust burden in rats, 0.4% is the average percentage of macrophage volume filled with dust of unit density (100 nl/2.6×10^4 nl). This represents the average volume of dust in a macrophage when clearance begins to slow down. It is much lower than the 6% average alveolar macrophage (AM) volume estimated by Morrow (1988) for unit density dust. The value of 6% is equivalent to 1560 nl ($0.06 \times 2.6 \times 10^4$ nl), and Fig. 2 from Bellmann *et al.* (1991) clearly shows that at 1500 nl (or 1500 μg for unit density dust), the clearance rate coefficient has already declined to approximately 0.0045 or 41% of its initial value. By similar calculations, the maximum critical lung dust burden in rats is estimated to be 40% of the alveolar macrophage volume. This value is much closer to the 60% reported by Morrow (1988). The values of 40 to 60% correspond to retained lung dust burdens of 10,000 and 15,000 μg, respectively, the region where k appears to reach a minimum constant value (in Fig. 2 of Bellmann *et al.* (1991)). Table 3 includes the values used in computing the critical lung dust burdens in rats.

Critical lung dust burdens in humans. The critical lung dust burdens in humans are computed by

TABLE 2
Average Number and Volume of Alveolar Macrophages (AM) in the Lungs of Humans and Rats

	Volume of single AM (μm^3)	Number of AMs in lungs	Volume of AM pool (μm^3)[a]	Volume of AM pool (nl)[b]
Human	2500[c,d]	7.0×10^9[c,e]	1.75×10^{13}	1.75×10^7
Rat	1000[c,f]	2.6×10^7[c,g]	2.6×10^{10}	2.6×10^4

[a] Computed as (volume of single AM) × (total number of AM).
[b] Computed as volume of AM pool (μm^3) × ($1\,cm^3/1 \times 10^{12}\,\mu m^3$) ($1\,ml/cm^3$)($1 \times 10^6$ nl/ml).
[c] Oberdörster (1995), who cites Crapo *et al.* (1983) and Dethloff and Lehnert (1988).
[d] Other values reported for AM cell volume in humans: 3195 μm^3 (males) (Lapp *et al.*, 1991) and 1474 μm^3 (males and females) (Stone *et al.*, 1992).
[e] Other values reported for AM number in humans (males and female): 6.0×10^9 (Stone *et al.*, 1992) and 2.3×10^{10} (Crapo *et al.*, 1982).
[f] Other values reported for AM cell volume in rats (male): 1525 μm^3 (Long–Evans hooded) (Castranova *et al.*, 1979); 639 μm^3 (Fischer 344) and 1,058 μm^3 (Sprague–Dawley) (Crapo *et al.*, 1983; Stone *et al.*, 1992).
[g] Other values reported for AM number in rats (male): 2.7×10^7 (Fischer 344) and 2.9×10^7 (Sprague–Dawley) (Crapo *et al.*, 1983; Stone *et al.*, 1992); 1.3×10^7 (Fischer 344) (Lehnert *et al.*, 1985); and 2.1×10^7 (Long–Evans hooded) (Lehnert and Morrow 1985).

TABLE 3

Values Used in Computing the Minimum (M_{min}) and Maximum (M_{max}) Critical Lung Dust Burdens in Humans and Rats

	Critical volume or mass of dust in AM[a,b]	Average percentage of AM dust-filled	Average weight of lungs (g)	Lung dust concentration (mg/g wet tissue)
Rats			1.5	
M_{min}	100 nl	0.4		0.07
M_{max}	10,000 nl	40		6.7
Humans			1000	
M_{min}	105 mg	0.4		0.105
M_{max}	10,500 mg	40		10.5

[a] Estimated from Fig. 2 in Bellmann *et al.* (1991).

[b] For rats, critical volumes and lung dust concentrations are computed for unit density dust. For humans, critical masses and dust concentrations are computed for coal dust with a density of 1.5 g/ml.

assuming the same average volume of dust as in rat alveolar macrophages associated with overloading. Different values for the mass of human lungs, the alveolar macrophage number and volume in humans, and the density of respirable coal mine dust were used in these calculations (Tables 2 and 3). In humans, the equivalent minimum critical lung dust burden as a volume is calculated to be 0.07 ml ($0.004 \times 1.75 \times 10^7$ nl $\times$ 1 ml/10^6 nl) for unit density dust. The density of coal dust in the which miners in this study were exposed was calculated to be $\rho = 1.5$ (Kuempel, 1997). Thus, the human-equivalent minimum critical lung dust burden in these miners is estimated to be 105 mg (0.07 ml $\times$ 1.5 g/ml $\times$ 1000 mg/g). By similar computation, the human-equivalent maximum critical lung dust burden for coal dust is estimated to be 10,500 mg.

Model-Fitting and Parameter Estimation

Initial model parameter values were based on data available in the literature. Some of these parameters were fixed, while others were allowed to vary to optimize the model fit to the data. The fixed values include fractional deposition (F_D) in the alveolar region of the lungs for particles with mass median aerodynamic diameter of 5 μm, assuming mouth breathing at inhalation rate of 1.7 m^3/hr (ICRP, 1994); the volume of air inhaled (V_I) in an 8-h workday (m^3/day), for heavy work, defined as 7 h of light exercise and 1 h of heavy exercise, for a reference worker (Caucasian, age 30 years, height 176 cm, weight 73 kg) (ICRP, 1994)); and d is the days worked per year (days/year) (estimated as 5 days/week $\times$ 50 weeks/year). The fixed parameters in the expression describing the overloading of alveolar clearance include the estimated human-equivalent lung dust burdens associated with the beginning of decline in the alveolar clearance rate coefficient and the leveling-off of that decline (M_{min} and M_{max}, respectively, in Eq. (4) above).

The parameter values that were allowed to vary in optimizing the fit of the model to the data are provided in Table 4. Because a primary objective was to evaluate

TABLE 4

Description of Initial Values Rate Coefficients for Clearance and Retention Allowed to Vary in Optimising Fit of the Three-Compartment Human Lung Dosimetry Model to the Coal Miner Data

Abbreviation[a]	Range evaluated	Source of values
K_T	1×10^{-4}–4×10^{-3} (day^{-1})	Freedman and Robinson (1988), 1.98×10^{-4} day^{-1} ($t_{1/2} = 3501$ days) in coal miners (half this value was also evaluated); Bohning *et al.* (1982), 2.0×10^{-3} day^{-1} ($t_{1/2} = 296$ days); Bailey *et al.* (1985), 1×10^{-3} day^{-1} ($t_{1/2} = 693$ days) and 4×10^{-3} day^{-1} ($t_{1/2} = 173$ days).
K_I	3×10^{-5}–3×10^{-2} (day^{-1})	Values estimated from modeling of rat data (following values evaluated and a factor of 10 lower for estimated human equivalency): Kuempel (1997), Appendix K, 3×10^{-4} and 2×10^{-3} day^{-1} in three-compartment rat model reduced from nine-compartment rat model (Tran *et al.*, 1997); Stöber *et al.* (1989) and Tran *et al.* (1997), 3×10^{-2} day^{-1}.
K_{LN}	5×10^{-6}–5×10^{-3} (day^{-1})	Values estimated from modeling of rat data (following values evaluated and a factor of 10 lower for estimated human equivalency): Cuddihy *et al.* (1979) and Thomas (1972), 1×10^{-4} day^{-1} (half this value was also evaluated); Snipes *et al.* (1983), 2×10^{-4} day^{-1}; Kuempel (1997), Appendix K, 4×10^{-3} day^{-1} in three-compartment rat model reduced from nine-compartment rat model (Tran *et al.*, 1997); Stöber *et al.* (1989) and Tran *et al.* (1997), 5×10^{-3} day^{-1}.
B	1×10^{-4} – 2.3	Associated with 0.01 to 90% reduction in the initial value of K_T at M_{max},[a] based on a human-equivalent expression for the overloading of alveolar-macrophage-mediated clearance observed in rodent studies (Bellmann *et al.*, 1991).[b]

[a] Defined in Table 1.

[b] Derivation of human-equivalent values from rodent data provided under Methods.

clearance kinetics of particles in humans, including the possibility of overloading of alveolar clearance as observed in rodents, the deposition parameters were fixed at the average human values in the literature, and the clearance parameters were iteratively varied to determine the best fit of the model to the data. A systematic grid search approach was used to determine the parameter values that provided the best fit of the model to the data. Biologically plausible ranges in which to search for alternatives to the initial parameter values were also based on data from the literature (Table 4). The rate coefficients for the alveolar macrophage-medicated, interstitial, and lymph node rate compartments were varied first, and then overloading (dose-dependent decline in alveolar-macrophage-mediated clearance) of different amounts was evaluated. The slope factor (B) for the exponential decay function (F, Eq. (4)) was set at values associated with specified levels of overloading. In the "no overload" model, the value for B was set to 0.0001, which gives a value of F=0.9999 when $M_A = M_{max}$ (10.5 g); thus, the first-order clearance rate coefficient (K_T) retains 99.99% of its initial value at that lung dust burden. Likewise, the "50% overload" model is determined by assuming $B = 0.69$, which leads to $F = 0.50$ at $M_A = M_{max}$, and K_T reduced to 50% of its initial value. The "90% overload" model has $B = 2.3$, resulting in $F = 0.10$ at M_{max}, and K_T reduced by 90%. In fitting the overload models, the parameter values for first-order alveolar clearance and transfer to the interstitium and the lymph nodes were allowed to vary to optimize the fit to the overload model structure. Given the likelihood that there is a distribution of values for these parameters in the population and that alternative values may also provide reasonable fit to the group data, we did not restrict the "overload" model to the original parameter set. Thus, this approach enhanced the possibility of detecting an overload effect in these human data. In the second paper (this journal; Kuempel *et al.*, 2001), we explore the sensitivity of the model predictions to alternative parameter values.

Using the individual miners' work history data, the model-predicted lung and lymph node dust burdens were generated for a given set of parameter values. These predicted burdens were quantitatively compared to the observed burdens by computing the mean squared error (MSE) of the observed burdens. The MSE is a least squares criterion and a well-known method of fitting models to normally distributed data (Neter *et al.*, 1989). The assumption of normality was examined previously and found to be reasonable (Kuempel, 1997). The MSE, which was computed separately for the lung and lymph node dust burdens in this study, is defined as

$$\mathrm{MSE} = \frac{\sum(\mathrm{Bur}_{obs} - \mathrm{Bur}_{pred})^2}{n},$$

where Bur_{obs} and Bur_{pred} are the observed and predicted dust burdens, respectively, in either the lungs or the hilar lymph nodes, and n is the sample size of the data.

Model fitting was considered complete when the MSEs for the lungs and lymph nodes improved less than 1% compared to the previous parameter values. The set of parameter values that minimized the MSE was considered to be optimal. Residual analyses were used to evaluate variability and bias in the model-predicted lung dust burdens, among all miners and within groups of miners with differences in factors that may influence the retention of dust in the lungs (e.g., cumulative exposure, smoking history, and disease status). These residuals were plotted for evaluation of trends, and Bartlett's test for homogeneity of variance was performed for each of those factors. The best-fitting model was used to generate predicted lung and lymph node dust burdens for each individual.

RESULTS

Characteristics of the miners in this study ($n = 131$) are given in Table 5. The mean concentration of total dust (i.e., coal, noncoal, and silica) in miners' lungs was 13.8 mg/g wet tissue. Assuming an average lung weight of 1000 g, this is equivalent to a mean particle mass burden of 13.8 g in the whole lungs. The dust burdens in these miners' lungs ranged from 2.6 to 36 g. Most of the miners were smokers (69%). On average, the ever smokers had lower cumulative exposures to respirable coal mine dust (due to shorter duration, with similar intensity of exposure), retired earlier, and died at younger ages than did the never smokers. Coal dust lung burden was statistically significantly lower among smokers than nonsmokers ($P < 0.01$), although noncoal, silica, and total dust lung burden were not (all P values $>$ 0.1). Disease response was high in the entire cohort. Just 3% (4/131) of the miners had no fibrosis, and 16% (21/131) had macules of slight severity only. Differences in pathological responses between the ever smokers and the never smokers were not statistically significant (P values = 0.09–0.7).

The preliminary one-compartment lung model was found to be inadequate to describe the end-of-life lung dust burdens in these miners. The simple, first-order model with the clearance rate coefficient from human data in the literature (Bailey *et al.*, 1985) provided poor fit to these coal miner data; this rate coefficient of 1×10^{-3} corresponds to a retention half-time of 693 days. That model underestimated substantially the lung dust burden (in g), and the MSE for that model was 238 in the data that was randomly selected to develop (or calibrate) the dosimetry model. Reducing that clearance rate coefficient to 1.3×10^{-4} (corresponding to a retention half-time of 5330 days) substantially

TABLE 5
Characteristics of Autopsy Study Population of U.S. Miners[a]

Variable (units)	Smokers ($n=91$)	Nonsmokers ($n=24$)	Whole cohort ($n=131$)	Lymph node subset ($n=57$)
		Mean (SD)		
Age(years)				
Start of mining	20 (7.1)	20 (8.3)	21 (7.8)	19.8 (6.4)
Retirement	56 (7.4)	61 (6.9)	57 (7.3)	56.9 (7.4)
Death	66 (9.4)	74 (9.0)	67 (9.8)	66.3 (9.2)
Exposure to respirable coal mine dust				
Cumulative (mg-year/m^3)	108.4 (42.7)	122.1 (49.0)	107.8 (43.4)	112.7 (45.4)
Duration (years)	36.2 (9.6)	40.8 (10.6)	36.0 (10.0)	36.3 (9.1)
Intensity (mg/m^3)	3.0 (0.9)	2.9 (0.6)	3.0 (0.8)	3.1 (1.0)
Postexposure duration (years)	9.8 (6.5)	12.8 (6.7)	10.3 (6.7)	9.4 (5.8)
Total dust burden (g)				
Lungs	13.5 (8.0)	16.4 (8.5)	13.8 (8.0)	15.0 (8.4)
Hilar lymph nodes[b]	1.46 (1.1)	2.06 (1.1)	NA	1.57 (1.1)
		Percentage (count)		
Pathological response[c]				
No disease	1 (1)	8 (2)	3 (4)	2 (1)
Macules	87 (79)	83 (20)	84 (110)	82 (47)
Micronodules	79 (72)	75 (18)	77 (101)	79 (45)
Macronodules	42 (38)	58 (14)	47 (61)	47 (27)
PMF	24 (22)	42 (10)	30 (39)	32 (18)
Race (%)				
White	73 (66)	46 (11)	66 (86)	70 (40)
Black	25 (23)	54 (13)	31 (41)	28 (16)
Other	2 (2)	0 (0)	3 (4)	2 (1)

[a] Of the 131 miners in the study, 16 miners had unknown smoking status; 58 miners had lymph node dust burden data, of which 46 were smokers, 10 were nonsmokers, and 2 had unknown smoking status (one miner had missing data for the postexposure duration and was omitted from the lymph node subset).
[b] Data on particle mass burden in the hilar lymph nodes were available only for the miners included in the lymph node subset.
[c] Macules, moderate severity or greater; micronodules, macronodules, and PMF, slight severity or greater; details of disease pathological classification provided in Vallyathan *et al.* (1996) and Green and Laqueur (1980).

improved the model fit (MSE = 100). However, that model structure was inadequate because it predicted that approximately 40% of the dust in miners' lungs at retirement would be cleared by the time of death. This is inconsistent with a previous finding in these data of no measurable postexposure dust clearance (Kuempel *et al.*, 1997) and little or no clearance observed during retirement in another study of coal miners (Freedman and Robinson, 1988). The one-compartment model with overloading of lung clearance was also inadequate to fit these data. The rodent-based 90% overload model overpredicted the lung dust burdens in these miners, and this overprediction increased with increasing cumulative exposure. The MSE for the 90% overload model was 860, and the MSE for the 50% overload model was 295. Similar model results were obtained among the 11 miners who died while employed as coal miners.

These results show that although the simple, first-order model substantially underpredicts these miners' lung dust burdens, the rodent-based overload model substantially and systematically overpredicts their lung burdens. Further, the one-compartment model structure is inadequate to describe the pattern of dust retention observed in previous studies and to predict these miners' end-of-life lung dust burdens. The three-compartment model was therefore developed because of these results indicating the need for a sequestration process to explain the higher lung burdens at low exposures. The three-compartment model structure also better reflects the biological structure of the lungs, as described earlier.

The three-compartment model that provides the best fit to these data has no overloading of alveolar-macrophage-mediated clearance (lowest MSE in Table 6 and generally in Table 7). The improved fit of the three-compartment model compared to the one-compartment model was highly statistically significant for both the no-overload and the overload forms (P values < 0.0001). This was determined in an F test (Jennrich and Ralston, 1979) of whether the additional model parameters in the three-compartment model significantly improved the fit to the data. In the three-compartment model, the model form with 50% overload provided nearly as good a fit as the no-overload model, using the approach of allowing the parameter values

TABLE 6
Comparison of the Fit of the Three-Compartment Lung Dosimetry Models, with Different Degrees of Overloading, in the Development and Test Data Sets

	Mean squared error for lung dust burden (g)			
	Ever smokers		Never smokers	
Degree of overloading of alveolar clearance	Development data set ($n=69$)[a]	Test data set ($n=35$)[b]	Development data set ($n=16$)	Test data set ($n=8$)
No overloading	72	75	108	101
50% overloading	78	76	111	105
90% overloading	294	102	260	126

[a] Two of the 71 miners were omitted due to incomplete data for determining postexposure duration (i.e., time between leaving mining and death).
[b] One of the 36 miners was omitted due to incomplete data for determining postexposure duration.

for alveolar clearance and interstitialization to vary to accommodate the dose-dependent decline. Although the MSEs were only slightly lower (indicating better model fit) in the no-overload model compared to the 50% overload model, this difference was statistically significant among smokers ($P=0.02$) but not among nonsmokers ($P=0.4$) (Table 6). However, even with allowing adjustment of alveolar and interstitial parameters, the 90% overload model was a poor fit. Compared to the 90% overload model, the improved fit of the no-overload model was highly statistically significant among both smokers (P values < 0.0001) and nonsmokers ($P=0.0005$). In the data reserved to test the models, the same patterns were observed, although the contrast is less (Table 6).

The best-fitting parameter values for each of these models are shown in Table 7, among all miners ($n=131$), miners with hilar lymph node data ($n=57$), and miners with no postexposure time ($n=11$). Because the no-overload three-compartment model with interstitialization was the simplest model that provided the best fit to the data, this model was selected as the best model. The fit of this model is illustrated in Figs. 2a (lung dust burden data) and 2b (lymph node burden data) among miners within tertiles of exposure to respirable coal mine dust. The miners in these tertiles had a mean of 25, 36, and 46 years of exposure in the low, medium, and high tertiles, respectively. The data of individuals who died while employed as miners are also shown; these miners had a mean 30 years of exposure. The mean intensity of exposure was approximately 3 mg/m^3 among miners in each of these groups. The actual model fitting was done by inputting each miner's individual work history data and predicting individuals' lung and lymph node dust burdens. In Fig. 2, the mean values for miners in each tertile were used to illustrate the model predictions for these groups; these mean values included duration and intensity of exposure and ages of starting work in mining, retirement, and death. The model fits well on average the lung burden data of miners in the medium and high exposure tertiles, but it tends to overpredict the lung burden data of miners in the lower exposure tertile. Miners in the lower exposure tertile have higher mean observed lung dust burden than expected by comparison to the lung burdens of miners in the higher

TABLE 7
Optimized Parameter Values and Fit of the Three-Compartment Human Lung Dosimetry Models, by Degree of Overloading of Alveolar-Macrophage-Mediated Clearance

	Parameter value		
Model parameter[a]	No overload	50% overload	90% overload
F_D	0.12	[b]	[b]
V_I (m^3/day)	13.5	[b]	[b]
d (days/year)	250	[b]	[b]
K_T (years)	1×10^{-3}	1.5×10^{-3}	1.4×10^{-3}
K_I (day^{-1})	4.7×10^{-4}	7.0×10^{-4}	3×10^{-4}
K_{LN} (day^{-1})	1×10^{-5}	1×10^{-5}	1×10^{-5}
B (day^{-1})	0.0001	0.69	2.3
C	1	[b]	[b]
M_{min}	1.05×10^{2}	[b]	[b]
M_{max}	1.05×10^{5}	[b]	[b]
Data set	Mean squared error (MSE) for lung dust burden (g) and lymph node burden (if noted)		
All miners ($n=131$)	79.3	85.8	231
Miners with hilar lymph node burden data ($n=57$)	1.31[c]	1.39[c]	2.15[c]
Miners with no post exposure duration ($n=11$)	70.0	68.9	148

[a] Parameter description provided in Table 1.
[b] Fixed at values in no overload model.
[c] MSE for hilar lymph dust node burden (g).

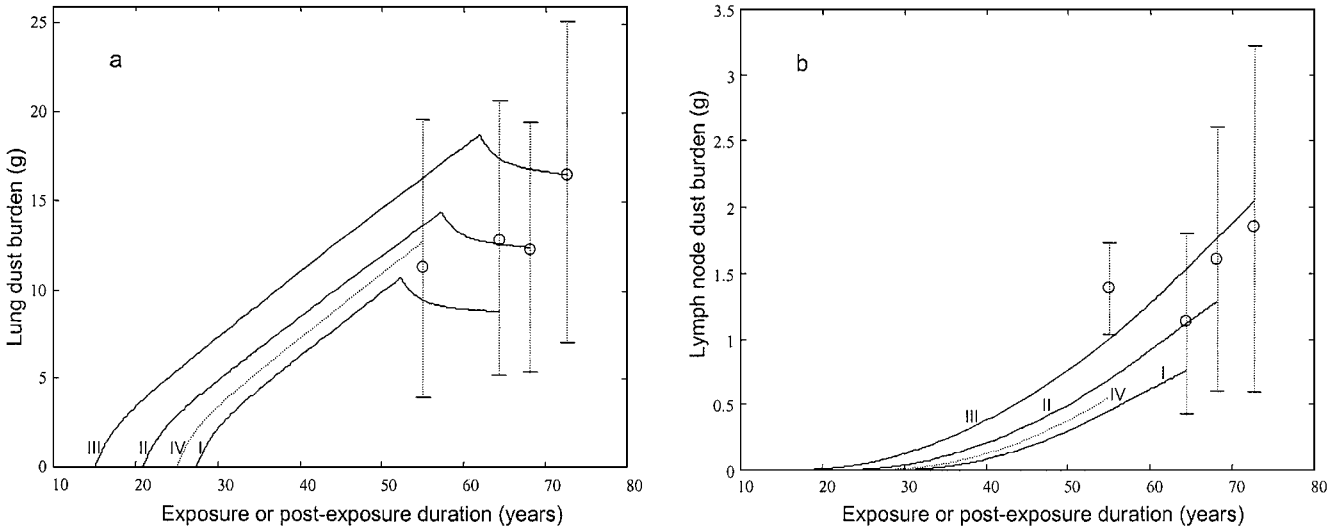

FIG. 2. Relationship between duration of exposure and particle burden retained in the (a) lungs or (b) hilar lymph nodes. Circles are the observed mean lung or lymph node burdens among all miners ($n = 131$), divided into groups based on either the tertiles of the distribution of exposure duration (I–III, $n = 120$) or the miners who died while employed as coal miners (IV, $n = 11$). Error bars are standard deviations of the mean lung or lymph node dust burdens. The mean durations of exposure among miners in these groups are 25 (I), 36 (II), 46 (III), and 30 (IV) years. The input values in the dosimetry model are the mean ages in each group of starting work, retirement, and death and the mean working lifetime concentration of respirable coal mine dust. The lines are the model-predicted mean lung or lymph node burdens among miners in each group. The predicted lung dust burden begins to increase at the beginning of exposure, i.e., starting work in mining (all groups) and then begins to drop slightly at the end of exposure, i.e., retirement (except for group IV with postexposure duration equal to zero). The predicted lymph node dust burdens begin to increase several years after the beginning of exposure and continue to increase until death. The observed lung and lymph node dust burdens were measured at the end of life, and the tissues were obtained at autopsy.

exposure groups. The model overpredicts only slightly the lung burdens of the miners who died when employed as coal miners. The hilar lymph node dust burdens tend to be underpredicted by this model for all miners except those in the high exposure tertile, for whom the model slightly underpredicts the average lymph node dust burden. The lymph node dust burdens among the miners with no postexposure time are underpredicted.

This same pattern is observed in the residual plots in Figs. 3a (lung burden data) and 3b (lymph node burden data) vs cumulative exposure. The model tends to underpredict lung dust burden among miners with low cumulative exposures (seen by the positive

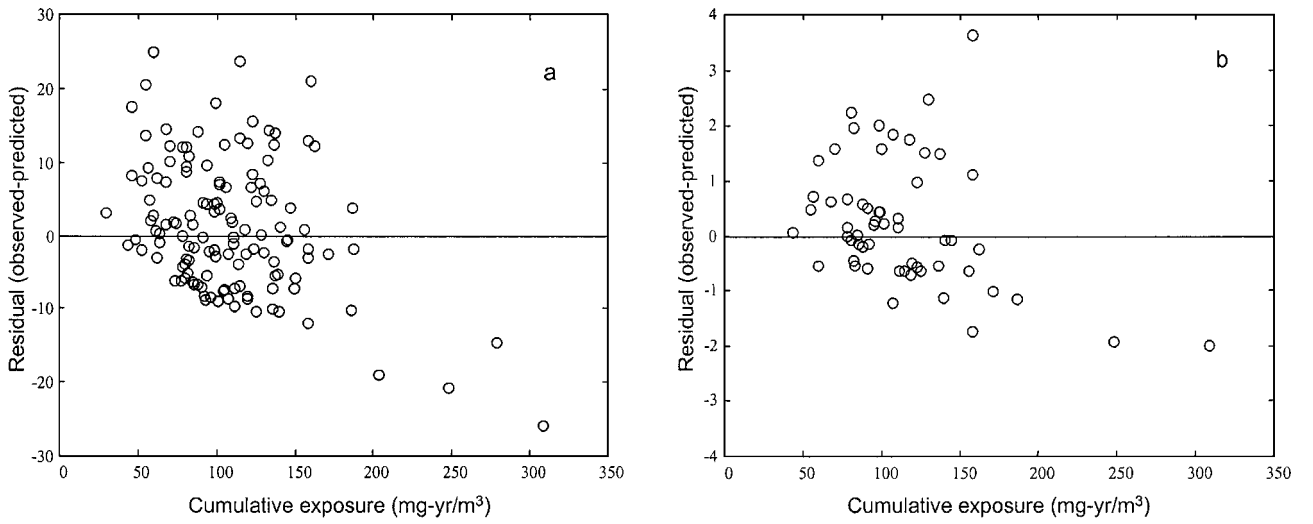

FIG. 3. Residual (observed minus predicted) total dust burden in the (a) lungs ($n = 131$) and (b) hilar lymph nodes ($n = 57$), as related to miners' cumulative exposure to respirable coal mine dust.

residuals). The model fits on average the data of miners with medium or higher cumulative exposures (seen by roughly equally distributed positive and negative residuals). An exception to this is the overprediction of lung burden among the four miners with the highest cumulative exposure (>200 mg-year/m^3) but unexpectedly low lung dust burdens. Additional analyses of the trend in residuals are performed in the second paper (this journal; Kuempel *et al.*, 2001). A statistical test for homogeneity of variance indicated no statistically significant difference among miners grouped in tertiles of the cumulative exposure distribution, either among all 131 miners ($P = 0.2$) or with the four "outliers" omitted ($P = 0.9$). Additional residuals analyses were done for variables that were not included in the model but that could influence the retained lung dust burden. These variables include smoking status, pack-years of smoking, and disease status. The results showed that the lung dust burden residuals were not statistically significantly different among miners with differences in smoking habits (ever smoker, never smoker, or unknown) ($P = 0.5$), nor were there trends in the plot of residuals by pack-years of smoking. Similarly, no trends were observed in a residual plot by disease status (defined as highest severity of fibrosis observed at autopsy). No evidence of heterogeneity of variance was observed in these residuals (all P values > 0.3).

Table 8 shows the observed lung and lymph node dust burdens and those predicted from various models; it also gives the estimated airborne mass of dust to which miners were exposed and the estimated mass of dust deposited in the deep lungs. Of the >350 g of airborne respirable dust miners are estimated to have been exposed to, approximately 40 g is estimated to have been deposited in the alveolar region of the lungs, and a mean of 14 to 15 g was observed in the lungs of miners at autopsy. In contrast, a simple, one-compartment model with first-order clearance predicts that most of the dust would have been cleared by the time of death. The ICRP and NCRP models are similar to the one-compartment lung model in that the lung clearance is first-order and there is no pulmonary sequestration; but those models differ by also having a lymph node compartment. The ICRP model actually has three separate first-order alveolar compartments, in which fixed percentages of respirable dust deposit and the first-order clearance rate coefficients differ. The slowly clearing compartment accounts for the higher lung burdens and lower lymph node burdens predicted by the ICRP model than the NCRP model. In contrast to these human models, the rodent-based, one-compartment model with overloading of lung clearance predicts that most of the dust would be retained in the lungs of these miners at the time of death. The three-compartment model with first-order alveolar-macrophage-mediated clearance (no overload) and first-order interstitialization of particles (developed in this study and calibrated to these coal miner data) provides a close fit to the observed data, although the tendency on average is to slightly underpredict the lung and lymph node dust burdens.

Figure 4 illustrates the pattern of particle retention in the various lung compartments over time as

TABLE 8
Observed and Predicted Mean Total Dust Lung Burden, from Models with Various Clearance Assumptions, in the Whole Cohort ($n = 131$) and the Subset of Miners with Lymph Node (LN) Burden Data ($n = 57$)

	Lung dust burden (g)		Hilar lymph note dust burden (g)	
	Whole cohort	LN subset	Whole cohort	LN subset
Observed.[a]	13.8	15.0	[b]	1.57
Predicted, assuming:				
Total deposited in alveolar region (no clearance)[c]	39.3	41.7	3.49	3.60
Simple, first-order clearance, no overload[d] (one-compartment model)	0.584	0.577	[b]	[b]
ICRP (1994) model	3.20	3.39	0.718	0.748
NCRP (1997) model	0.500	0.487	3.84	4.08
Rodent-based overload, 90%[d] (one-compartment model)	30.5	33.6	[b]	[b]
Interstitialization/sequestration and no overload[d] (three-compartment model)	13.4	14.2	1.36	1.41

[a] The observed working lifetime mean airborne dust exposure was 364 g in the whole cohort and 380 g in the subset of miners with lymph node data. These values were calculated from the mean cumulative exposure of 107.8 and 112.7 mg-year/m^3, respectively, and assuming 13.5 m^3 volume of air inhaled per 8-h day (ICRP, 1994) and 250 days/year exposure.
[b] Not applicable.
[c] Assuming alveolar fractional deposition of 0.12 (ICRP, 1994).
[d] Defined under Methods.

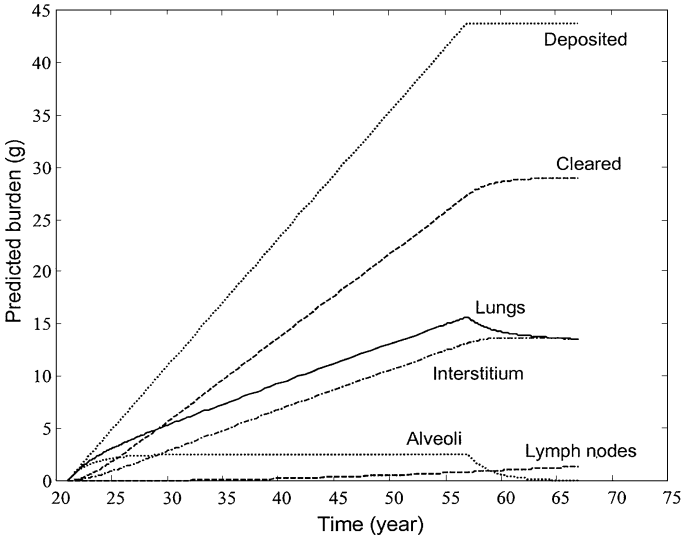

FIG. 4. Predicted mass of particles retained in various lung compartments over time, assuming the mean exposure to respirable coal mine dust among all miners in this study (3 mg/m^3 for 36 years), based on the three-compartment model with first-order interstitialization and alveolar clearance (no overload). "Deposited" refers to the alveolar region of the lungs, and "cleared" means from the alveoli to the mucociliary clearance path in the tracheobronchial region.

predicted by the best-fitting three-compartment model (no-overload), using the average of all miners' data ($n = 131$) as the input. The model predicts that during the first several years, most of the particles in the lungs are in the alveolar region and therefore available for alveolar-macrophage-mediated clearance. Steady state (rate of deposition equals rate of clearance) is achieved in the alveolar region during the first few years, but the dust buildup continues in the interstitial region due to the very slow clearance to the lung-associated lymph nodes. The total dust lung burden is predicted to consist equally of dust in the alveolar and interstitial regions after approximately 8 or 9 years at the exposure rate of these miners, but thereafter an increasing proportion of the total lung dust burden is predicted to be retained in the interstitium. When exposure ends (e.g., retirement), the lung dust burden decreases slightly, reflecting the decline of dust in the alveolar region when dust is no longer being deposited. Several years after exposure ends, nearly all of the dust retained in miners' lungs is predicted to be interstitialized or otherwise sequestered and available only for the relatively slow clearance to the hilar lymph nodes. The amount of dust retained in the hilar lymph nodes steadily increases throughout the exposure and postexposure period.

DISCUSSION

This dosimetric model was developed based on what we know about the structure of the human lungs and the biological and kinetic processes influencing the clearance and retention of respirable, poorly soluble particles. The model was calibrated using existing data in humans with occupational exposures to respirable coal mine dust, and it was validated using a reserved subset of those data. The human data used in this study are necessarily observational in nature and therefore contain much more variability and uncertainty than the data from experimental studies in rodents. In the experimental setting, exposure and other factors are carefully controlled, and animals of the same age and similar genetic makeup are used. A dosimetry model in rodents can then be developed using relatively homogeneous data from controlled experiments. In addition, the mean values for each exposure group are often used in model fitting, which further reduces the apparent variability. In contrast, the human data are inherently variable. Humans are genetically diverse; lifestyles differ, including differences in diet and nutritional status, smoking habits, and occupational or nonoccupational exposures to hazardous substances. All of these factors may influence the clearance and retention of dust from occupational exposures and contribute to the observed variability in model predictions. As described earlier, the occupational exposures were estimated from dust sampling surveys by job category and from individual work history records. However, gaps and uncertainties in these exposure data could lead to variability and/or bias of the model predictions (this issue is explored further in the second paper (this journal; Kuempel *et al.*, 2001)). Despite the variability and uncertainty, consistent patterns emerge from this study.

Results clearly show that a simple, first-order clearance model is inadequate for describing the end-of-life lung dust burdens. This was observed among all miners regardless of their cumulative exposure to respirable coal mine dust, including those individuals who were employed as coal miners when they died. Actively working coal miners are expected to be among the least likely to have impaired clearance since such impairment may be associated with lung dysfunction and disease that could preclude them from continuing in a physically demanding occupation like mining. In the one-compartment model, reducing the first-order clearance rate coefficient by nearly 1 order of magnitude resulted in improved fit of the one-compartment model to the end-of-life lung dust burdens; however, that model was deemed inadequate because it predicted considerable postexposure clearance, which is inconsistent with the previous studies (Kuempel *et al.*, 1997; Freedman and Robinson, 1988). Interestingly, the reduced rate coefficients (1.3×10^{-4} day^{-1} among miners in the development data and 3.0×10^{-4} day^{-1} among miners postexposure duration equal to zero) are remarkably similar to rate coefficients observed by Freedman and Robinson (1988). In that study, the rate coefficients of 3.62×10^{-4} and 1.98×10^{-4} day^{-1} can be computed from the

retention half-times of 63 and 115 months reported by Freedman and Robinson (which are based on their magnetopneumography measurements after 1 and 2 years, respectively). In an early study of German coal miners, Stöber *et al*. (1967) report a similar first-order clearance rate coefficient (3.8×10^{-4} day^{-1}; computed from the year^{-1} value), based on a simple, first-order clearance model. All of these studies indicate that the retention half-time of respirable particles in the deep lungs in coal miners is many times greater than the 693-day retention half-time (1×10^{-3} day^{-1}) reported for persons without occupational dust exposure, based on measurements taken 200 days after inhalation of radiolabeled tracer particles (Bailey *et al*., 1985).

The finding in this study that the dust is not being cleared from these miners' lungs as a simple first-order process does not seem to be explained by the overloading of lung clearance as observed in rodents with high lung dust burdens. Overload is defined as the dose-dependent decline in alveolar-macrophage-mediated clearance and is described in the model as an exponential decline in the alveolar clearance rate coefficient with increasing lung burden. Indeed, the average concentration of dust in these coal miners' lungs (13.8 mg/g tissue) exceeds that associated with severe impairment of alveolar clearance in rodents (>10 mg dust/g tissue). However, the results clearly show that the one-compartment model (which used only the overloading of alveolar clearance to try to describe the increased lung burdens) was inadequate for predicting the lung dust burdens of these miners. That model overpredicted miners lung dust burdens, and the overprediction increased with increasing cumulative exposure. A possible explanation for these findings, as shown by the modeling, is that sequestration is an important kinetic process influencing particle retention in the lungs of these miners. With sequestration, some portion of the dust is no longer available for normal macrophage-mediated clearance. Inclusion of this process in the model required the addition of another model compartment, which is believed to represent the lung interstitium and is consistent with what is known about the structure and particle retention sites of primate lungs. From the interstitial compartment, clearance occurs very slowly to the lung-associated lymph nodes. The results clearly show that the three-compartment model with first-order processes for alveolar-macrophage-mediated clearance and interstitialization of particles provides the best fit to the lung and lymph node dust burden data. Indeed, the improvement of this three-compartment model over the one-compartment models is highly statistically significant ($P < 0.0001$). This finding supports the hypothesis that particle sequestration is an essential process in describing the disposition of respirable, poorly soluble particles in the lungs of humans with long-term occupational dust exposures.

The results also clearly show that the addition of alveolar clearance overloading to the three-compartment sequestration model did not improve that model fit to the data. Although the MSEs for the 50% overload model were similar to that of the no-overload model (Table 7), suggesting similar model fit, the no-overload model was statistically significantly better in all miners ($P = 0.002$) and miners with lymph node data ($P = 0.01$); the model fits could not be distinguished among the miners who died while employed as miners ($P = 0.7$). These findings were observed despite the modeling approach designed to maximize the possibility of detecting overload by allowing other model parameters to vary in order to accommodate the overload model structure (with dose-dependent decline in alveolar-macrophage-mediated clearance). Thus, there is no evidence from this study that particle clearance and retention are dose-dependent in these miners. The results also showed that, contrary to expectations based on previous findings of increased particle retention time in the lungs of smokers (Bohning *et al*., 1982), smoking had little influence on particle retention or clearance in these miners. Possible explanations are that miners' occupational dust exposures influenced these kinetic processes to a greater extent than smoking or that the smoking information was insufficient (e.g., missing or incomplete and not analyzed by intensity of smoking or pack-years). These findings on particle clearance kinetics of course do not address the issue of smoking as a possible factor in pulmonary disease response.

This three-compartment human lung model was recently tested using an independent data set of UK coal miners (Tran and Buchanan, 2000), and the results are remarkable consistent with this study of U.S. coal miners. It is clear from these findings that if overloading occurs in these coal miners, it occurs to a lesser extent than expected from the rodent studies; and overloading contributes very little relative to an interstitialization or sequestration process in explaining the retained lung dust burdens in these miners.

The absence of an "overload" effect does not imply that these miners had effective clearance. As discussed above, the half-time of respirable particle retention in coal miners' lungs was shown to be 5 to 15 years, compared to less than 2 years in persons without dusty jobs. The increased retention half-time in coal miners is consistent with a substantial portion of the dust being sequestered (e.g., in the interstitium), as predicted from our model. The apparent importance of particle interstitialization in humans is also consistent with the kinetic differences in lung clearance in humans and rats. The first-order rate coefficient for alveolar clearance is approximately 1 order of magnitude faster in rats than in humans (retention half-times on the order of 2 and 24 months, respectively) (Snipes, 1996), and this may allow for greater interstitialization of particles at all lung dust burdens. In the rat, particle sequestration

and transfer to the interstitium and lymph nodes is quite low usually, but these dramatically increase when doses are high enough to cause overloading of alveolar macrophage-mediated clearance. In fact, only in the "overloaded" rat does the lung burden reach concentrations as high as those observed in some humans with occupational dust exposure, such as coal miners.

Studies in humans and nonhuman primates provide support for the importance of interstitialization in particle retention in human lungs. Nikula *et al.* (1997) found in a histological analysis of lung tissue sections from an earlier study that the predominant site for particle retention in the deep lungs was the interstitium in cynomolgus monkeys (vs the alveoli in rats), following 2-year inhalation exposure to 2 mg/m^3 of respirable coal mine dust and/or diesel exhaust particulate. An evaluation of lung serial sections in both coal miners and nonminers showed that the interstitium is also the predominant tissue site for particle retention in the deep lungs of humans (Nikula *et al.*, 2001). In that study, 57, 68, and 91% of the volume density of the retained particulate material was observed, respectively, in the interstitium of nonminers, in coal miners working under the current federal coal dust standard, and in coal miners working under the earlier standard.

These findings indicate that a rodent model extrapolated to humans, without adjustment for the kinetic differences in the particle clearance and retention, would be inadequate for predicting lung dust burdens in humans. These models would potentially underpredict lung dust burdens at low exposures and overpredict burdens at high exposures. Some dosimetry models in rodents describe the lung as one compartment with dose-dependent decline in alveolar-macrophage-mediated clearance (i.e., overloading) (e.g., Yu *et al.*, 1991; Yu and Rappaport, 1997). This model structure, which fits the rodent data well, has also been used in extrapolations to humans (Yu *et al.*, 1991; Yu, 1996). Other lung dosimetry models in rodents have been developed that include both interstitialization and alveolar sequestration, which increase in the model once an overloading lung dust burden is achieved (Stöber *et al.*, 1989; Tran *et al.*, 1997). These models are more complex (approximately nine compartments in each) and include compartments describing cellular processes within the alveoli and interstitium, for which data are generally not available, particularly not in humans. The lung dosimetry model developed in this study using human data is consistent with the structure of the Stöber *et al.* (1989) and Tran *et al.* (1997) models in that the three compartments correspond to the major compartments (without the subcompartments) in those models.

These findings also indicate that current human models (e.g., ICRP, 1994; NCRP, 1997), which were developed primarily to describe the retention of radioactive particles in the human respiratory tract, may substantially underpredict the lifetime retention of respirable particles in the lungs of workers in dusty jobs. The ICRP and NCRP models are based on first-order clearance, and neither includes a pulmonary sequestration compartment. We are currently investigating the structures and predictions of these various models, using additional data sets with both low and high dust exposures. Additional studies are also needed to determine to what extent our model is representative of other populations. Our model was developed for respirable-sized particles of very low solubility. It has not been tested for particles of different solubility or sizes (within the range of those depositing in the gas exchange region, for example, ultrafines), and modifications would be required to include dissolution and possibly particle-size-specific clearance. Both the ICRP (1994) and the NCRP (1997) models include dissolution but assume the same clearance for all particle sizes in a given lung compartment.

Although our three-compartment model represents the major sites for dust disposition in the deep lungs (alveoli, interstitium, and hilar lymph nodes), it is, of necessity, a simplification of the complex biological processes in the lungs in response to inhaled particles. Likewise, the tissues and processes in the lungs do not necessarily fit rigidly into these model compartments. For example, the interstitial compartment could also represent dust that is essentially sequestered in the alveolar compartment, perhaps encapsulated in reticulin and collagen fiber network and then cleared very slowly to the lymph nodes. Even the best-fitting model did not adequately describe the lung dust burdens of miners with low cumulative exposures. A trend in the residuals by cumulative exposure tertile was observed, showing underestimation of the lung dust burdens of miners with low cumulative exposures, although the model fit was good among miners with medium or high cumulative exposures. The lymph node dust burdens were underestimated among miners with low and medium cumulative exposures and overestimated among miners with high cumulative exposures. These findings are opposite to those expected from rodent studies, in which the lung and lymph node dust burdens were underestimated in rats with exposures associated with overloading. A factor that may help to explain the difficulty in fitting the model to the lung dust burden data for miners in the low exposure tertile is that their mean lung dust burden (12.9 g; SD = 7.8 g) is very similar to that in miners in the middle exposure tertile (12.4 g; SD = 7.0 g). This suggests that either there is greater sequestration of dust at low exposures than expected or the "low" exposures are underestimated. Either situation could explain the model's underestimation of the lung dust burdens of miners with lower exposures. Interindividual differences in miners' exposures are primarily determined by their duration of work in mining, as the working lifetime average concentrations of respirable coal mine dust were similar

among all miners (3.0 mg/m^3; S D = 0.8 mg/m^3); however, individuals' job-specific dust concentrations (used in the dosimetry modeling) varied to a greater extent (ranging from <2 to 9 mg/m^3).

This human lung dosimetry model is potentially useful for risk assessment of particle-related lung diseases in humans. It provides a biological approach to lung burden prediction. It can also predict lung burdens among individuals with different exposures, breathing rates, etc. Furthermore, this model can be used to adjust for the kinetic differences in exposure–dose relationships across species so that disease responses can be evaluated at equivalent doses in both species. Other modifications to the model are possible, for example, to expand the deposition portion using particle size distribution data or to describe size- or solubility-dependent differences in particle clearance. Additional evaluation of this model is provided in the accompanying paper (Kuempel *et al.*, 2001), both to investigate sources of uncertainty in the model structure and average parameter values and to attempt to explain the interindividual variability in the observed and predicted lung dust burdens.

CONCLUSIONS

A three-compartment dosimetry model was developed to describe the kinetics of respirable particle clearance and retention in human lungs. The model was calibrated using lung and lymph node dust burden data in U.S. coal miners. This model clearly shows that miners retained more dust in their lungs than expected from a simple, first-order clearance model, and they retained less dust than expected from a rodent-based model with overloading of alveolar clearance. The model that best fit these human data includes a predominant sequestration compartment, which is thought to represent the retention of particles in the lung interstitium. These findings indicate that adjustment for these kinetic differences in particle clearance and retention is required when using rodent data to predict lung disease risks in humans. These findings also suggest that the current human lung models may substantially underestimate the working lifetime lung dust burdens in certain occupational populations.

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