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CONTEMPORARY ISSUES IN PBPK/PD MODELING SESSION

COMPARISON OF HUMAN AND RODENT LUNG DOSIMETRY MODELS FOR PARTICLE CLEARANCE AND RETENTION

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ABSTRACT

Interspecies differences in the kinetics and/or mechanisms of particle retention can influence the amount and location of particle retention in the lungs, which can also influence the tissue response to a given particle burden. Dosimetric models may be used to adjust for differences in the exposure-dose relationships in different species, thus allowing for comparison of lung responses at equivalent doses. Although the rat is one of the most frequently used animal models for assessing the risk of exposures to hazardous substances in humans, few data are available for comparison of human and animal responses to inhaled particles. A biologically-based human dosimetric lung model was developed to describe the fate of respirable particles in the lungs of humans, using data from U.S. coal miners and assumptions about the overloading of alveolar

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clearance from studies in rats. This model includes alveolar, interstitial, and hilar lymph node compartments. The form of the model that provides the best fit to the lung dust burden data in these coal miners includes a first-order interstitialization process and either no dose-dependent decline in alveolar clearance or much less decline than expected from rodent studies. These findings are consistent with the particle retention patterns observed previously in the lungs of primates. This human lung dosimetry model is useful for investigating the factors that may influence the relationships between the airborne particle exposure, lung dust burden, and fibrotic lung disease.

INTRODUCTION

Particulate air pollution is an important issue in public health. Studies have shown associations between exposure to airborne particulates and adverse health effects in both environmental and occupational settings. In the environment, short-term exposures to high levels of particulate pollutants have been associated with exacerbation of existing cardiovascular and respiratory conditions, and with increased hospital admissions and mortality among susceptible individuals.[1] Long-term exposure to airborne particulates has also been shown to be a risk factor for chronic respiratory diseases.[2] In the occupational environment, the population at risk is generally considered to be healthier because they are actively working adults; however, the exposure concentrations in the workplace are often higher as well. Particle-related occupational respiratory diseases have been reported for many occupations, and include chronic obstructive pulmonary disease, fibrosis, and lung cancer.[3,4]

The particles of concern in this study are those that deposit in the alveolar (gas-exchange) region of the lungs. These particles, conventionally measured as the respirable mass fraction, have diameters less than 10 μm. In the alveolar region, the primary mechanism for particle clearance is phagocytosis (engulfment) of particles by alveolar macrophage cells.[5] The macrophages then carry the particles to the tracheobronchial region, where they are cleared from the lungs via the mucociliary ''escalator.'' This is followed by either clearance from the body by cough, or ingestion. In the alveoli, particles that escape macrophage-mediated clearance can enter the interstitium of the lungs, where they may be retained or slowly cleared to the lung-associated lymph nodes. Clearance of particles from the alveolar region in humans is relatively slow, with clearance half-times of months to years.[6]

Studies in rodents are frequently used in risk assessment; yet recent studies have led to questions about the reliability of the rat as a model for predicting particle-related lung diseases in humans. In rats exposed via chronic inhalation to high concentrations of various types of poorly soluble,

respirable particles, alveolar clearance becomes impaired with increasing dose, and the rate of particle accumulation exceeds that expected from first-order clearance kinetics.[7,8,9,10] According to first-order kinetics, a steady-state lung dust burden would be achieved when the rate of deposition equals the rate of clearance. The departure from first-order kinetics observed in rodents has been called "overloading" of lung clearance. Morrow[11] hypothesized that overloading can be described as the volume of particles phagocytosed by alveolar macrophages that impairs their mobility (6% at initial impairment; 60% at maximum impairment). Consistent with this hypothesis, clearance studies in rodents have shown that as the particulate volume in the lungs increases, the first-order clearance rate coefficient (d^{-1}) declines. At a lung burden of 10 mg/g lung tissue (unit density dust), the clearance rate coefficient had declined to less than 10% of its initial value.[10] In rats, overloading doses have been associated with pathological responses including chronic inflammation, fibrosis, and lung tumors.[12,13]

In humans, the overloading of lung clearance of particles has not been demonstrated. However, a study of lung dust burdens in retired coal miners indicates that clearance rates are reduced.[14] In that study, lung clearance measurements using magnetopneumography indicated that little or no measurable clearance occurred during the first two years of retirement. This finding in humans is consistent with the observation of particle overloading in the lungs of rodents, in which clearance becomes impaired at high lung dust burdens and continues to be impaired after exposure ceases. Although the impairment of alveolar clearance has been observed to increase with increasing lung dust burden in rodents, the relationship between lung dust burden and clearance has not been quantitatively described in humans. The mechanism leading to reduced clearance in coal miners as observed in the Freedman and Robertson study[14] is not known. Those findings are also consistent with a sequestration process, e.g., in which particles are transferred as a first-order process to the interstitial region of the lungs and retained.

The objective of this paper is to provide an overview of a model developed to investigate the kinetics of particle clearance and retention in the lungs of humans.[15] The data used to develop this model included the exposure histories and lung and lymph node dust burdens from an archival dataset of U.S. coal miners.[16] The process of overloading of alveolar clearance, as observed in rats, was evaluated for fit to these human data. Several models describing the plausible mechanisms of particle retention and clearance in humans were initially investigated, including: (1) overloading as observed in rat lungs; (2) particle sequestration in the lung interstitium; and (3) a combination of both processes. The fits of these models to the coal miner data were evaluated using statistical methods to determine which mechanism may best describe the particle clearance kinetics in the lungs of these humans.

METHODS

Coal Miner Lung Data

The data used in this study are of 131 former coal miners who died between 1959 and 1973, for whom lung dust burdens were measured (of these, 58 miners also had hilar lymph node dust burden data).[17] These individuals represent a subset of approximately 700 miners who were autopsied at Beckley Appalachian Regional Hospital in Beckley, West Virginia by the late Werner Laqueur, M.D.[16] Pneumoconiosis disease type and severity were determined using whole lung serial sections. Data on each individual miner's work history include: the types of mining jobs and the duration worked in each job; the mean concentration of respirable coal mine dust by job (based on a 1968-1971 survey)[18]; and the duration of employment in nonmining jobs, unemployment, and retirement. Smoking history was available for most (89%, n = 116) of the 131 miners in this study.

Dosimetry Model Development

The human lung dosimetry model developed in this study was based on both biological plausibility (inclusion of the major sites of particle deposition, clearance, and retention in the alveolar region of the lungs), and on parsimony (with consideration of the available data). The final model includes alveolar, interstitial, and hilar lymph node compartments. It describes the kinetics of particle mass transfer among these compartments and clearance from the lungs via the tracheobronchi. The equations for these models were solved using Advanced Continuous Simulation Language (ACSL).[19] Initial parameter values were obtained from human and animal data in the literature (Table 1). The available human data include average values for the alveolar deposition fraction by particle size, the amount of air inhaled per day with heavy work,[6] and an average first-order rate coefficient for lung clearance.[20] The rat data used in this model consist of quantitative information on the dose-dependent decline in the first-order lung clearance rate coefficient based on various studies in rats inhaling airborne respirable particles.[10] These rat lung clearance data, along with the volumetric hypo-thesis of overloading,[11] were used to estimate the human-equivalent critical lung dust burden for use in this model.[15] As expected from the rata data, this human model allows for the dose-dependent decline in alveolar macrophage-mediated clearance once lung dust burden exceeds the critical burden. Parameter values from a previous rat lung dosimetry models[21] were used to estimate the initial values of the rate coefficients for particle mass transfer to the

Table I. Parameters of the Three-Compartment Human Lung Dosimetry Model, by Kinetic Process

Abbreviation	Value	Description (and reference, if applicable)
		Deposition
F_D	0.12	Fractional deposition for 5 μm particles, mouth breathing, at inhalation rate of 1.7 m^3/hr (ICRP[6])
V_I	13.5	Volume of air inhaled in 8-hour (mg^3/day), heavy work (ICRP[6])
d	250	Days/years exposed (5 days/week $\times$ 50 weeks/year)
C_I	varies[a]	Concentration inhaled of airborne respirable coal mine dust (mg/m^3)
		First-Order Clearance or Mass Transfer
K_T	0.001	Rate coefficient for alveolar macrophage-mediated clearance of particle mass to tracheobronchial region of lungs (day^{-1}) (Bailey et al.[20])
K_I	4.7×10^{-4}	Rate coefficient for transfer of particle mass to interstitial region of lungs (day^{-1})
K_{LN}	1.0×10^{-5}	Rate coefficient for transfer of particle mass to lung-associated (hilar) lymph nodes (day^{-1})
		Overload
B	0	Influences the rate of dose-dependent decline in K_T and the value of K_T at M_{max}.
C	1	Influences the shape of the dose-dependent decline in K_T.
M_{min}	1.05×10^2	Human-equivalent minimum lung burden (mg), derived from average volume of particles in alveolar macrophages associated with decline in K_T below the initial value in rodent studies (Bellman et al.[10])
M_{max}	1.05×10^5	Human-equivalent minimum lung burden (mg), based on average volume of particles in alveolar macrophage associated with decline to approximately 10% of the initial value of K_T in rodent studies (Bellman et al.[10])

[a] Based on individual miners' work history data.

interstitium and lymph nodes in the three-compartment human lung dosimetry model.

A one-compartment lung model was constructed first because it represents the simplest form for describing particle retention in the lungs and for evaluating overloading of lung clearance. This simple model structure is similar to previous models developed in rats, which have been used for extrapolation to humans.[22,23] In the one-compartment model, the lung is represented as a single compartment, with particle clearance to the tracheobronchi and hilar lymph nodes combined. Overload is described as a dose-dependent decline in the rate of alveolar clearance, using an exponential decay function to modify the first-order clearance rate coefficient when the lung dust burden exceeds a critical dose. Similar functional forms have been

used by Yu et al.[22] and Tran et al.[21] In this model, the clearance rate (mg/yr) of particles from the alveolar to the tracheobronchial region of the lungs, R_T, is defined as:

$$R_T = K_T \times \exp\{-B[(M_A - M_{min})/(M_{max} - M_{min})]^C\} \times M_A$$

where K_T is the first-order clearance rate coefficient (in units of d^{-1}, then multiplied by 365 to convert to yr^{-1}). M_A is the mass of particles (mg) in the alveolar region of the lungs at time (t). Overload of alveolar macrophage-mediated clearance is described by the exponential decay function $\exp\{-B[(M_L - M_{min})/(M_{max} - M_{min})]^C\}$. This expression represents the dose-dependent modifier of K_T. M_{min} and M_{max} represent the minimum and maximum critical lung dust burdens in humans, based on extrapolation from rat data to humans, as described above. According to this overload expression, when the retained lung dust burden reaches M_{max}, K_T is reduced from its initial value by an amount determined by B. When $M_L \leq M_{min}$, the value of this expression is 1, and thus K_T is not modified. When $M_L > M_{min}$, this expression takes on values between 0 and 1, as determined by B. The extent of overloading (e.g., 50% or 90% used in this study) is defined as the percentage reduction in K_T occurring at M_{max}. C influences the shape of the exponential expression. The complete mathematical equations for this model are provided elsewhere.[15]

Following evaluation of the capabilities of the one-compartment model to describe the data, a three-compartment lung model was developed (Figure 1; Table I). The three-compartment model incorporates both overloading of alveolar macrophage-mediated clearance (as in the

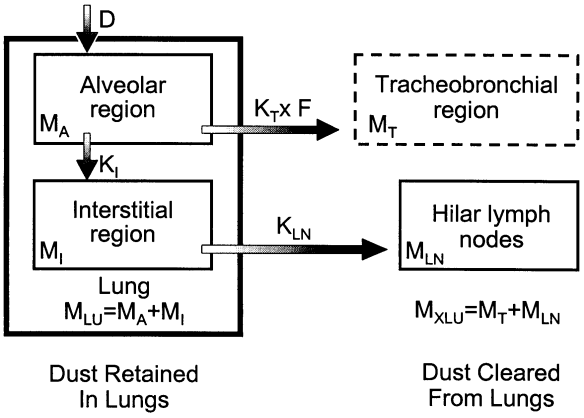

Figure 1. Illustration of three-compartment model for particle retention in the lungs. ***Key:*** **D:** dose rate of deposited particles; **M:** mass of dust in the alveoli (A), interstitium (I), Lungs (LU), or hilar lymph nodes (LN); $\mathbf{K_T}$**:** first-order alveolar clearance rate coefficient; $\mathbf{K_I}$**:** first-order interstitial transfer rate coefficient; **F:** dose-dependent modifying factor; $\mathbf{K_{LN}}$**:** first-order lymph node clearance rate coefficient; $\mathbf{M_T}$**:** mass of dust in the tracheobronchi; $\mathbf{M_{XLU}}$**:** mass of dust cleared from lungs.

one-compartment model) and sequestration processes (via the addition of the interstitial compartment), as well as an additional clearance path from the lung interstitium to the hilar lymph nodes. This model represents the biological processes of particle deposition, clearance, and retention in the deep lung. The lung compartments, particle masses, and rate coefficients are illustrated in Figure 1. In this model, particle deposition into the alveolar region of the lungs occurs at an assumed constant rate (D, in Figure 1). Particle clearance from the alveoli, via alveolar macrophages, is represented as a first-order process (coefficient K_T, in Figure 1) at lung dust burdens below the critical lung dust burden (M_{min}, in Table I). At higher lung dust burdens, the model allows for the dose-dependent decline in alveolar clearance (when F modifies K_T, in Figure 1). Transfer of dust to the interstitium occurs as a first-order process (coefficient K_I), such that even at low lung dust burdens a constant fraction of the dust deposited in the alveoli enters the interstitium. Clearance of dust from the interstitium occurs via the lymphatics at a relatively slow rate (coefficient K_{LN}); thus the interstitialized dust is essentially sequestered.

Parameter Estimation and Model Fitting

Before fitting the human lung dosimetry model to the coal miner data, these data were divided into two groups, by stratified random data allocation,[24] with one group used to develop the model (2/3 of data) and the other reserved for later testing the model (1/3 of data). These strata were based on smoking status and cumulative exposure. Following the model development and validation, all the data were combined (n = 131), and the lung and lymph node dust burdens were predicted for each miner (using the parameter values that provided the best average fit among miners in the development data set). Residuals analyses were conducted to compare the model predictions with the data. In addition, a subgroup of 11 miners whose post-exposure duration was zero (because they had died while still employed in mining) were investigated separately to describe the accumulation of dust in the lungs, without the uncertainty about the clearance pattern in the post-exposure period.

Model parameter values that provided optimum fits to the lung dust burden data were determined using a statistical optimization approach. Individual work histories were used to develop dust exposure scenarios for each coal miner. These exposure estimates were used to provide model predictions of the particle mass burdens in the lungs and hilar lymph nodes as a function of time for each miner. For a given set of parameter values, the end-of-life lung and lymph node burden predictions were compared to the measured values, using a least squares criterion–the mean

squared error (MSE).[25] A trial-and-error approach was used to scan the parameter values, within biologically meaningful ranges of parameter value, based primarily on data in the literature. Model fitting was considered complete when the MSEs for the lung and lymph node dust burdens improved less than 1% compared to the previous parameter values.

The parameter estimation approach involved iteratively varying the initial rate coefficients to obtain values that provided the best fit to the data. The interstitial and lymph node rate coefficients were varied first, and the overload assumptions were then evaluated. Because the average parameter values are not known with certainty, and there may not be a unique set of parameter values that reasonably fit the data, the parameter values for first-order clearance and for transfer to the interstitium and the lymph nodes were allowed to vary in the overload models. This was done to enhance the possibility of detecting an overload effect and to avoid excluding the overload assumption due to *a priori* parameter values, i.e., those selected as providing best fit to the data in the model without overloading.

The best-fitting model, based on least squares, was used to generate predicted lung and lymph node dust burdens for each individual. The predicted lung dust burdens were then evaluated in a statistical dose-response (logistic regression) model for fibrotic lung disease and compared to measured lung dust burden as a predictor of that disease.

RESULTS

Description of Coal Miner Data

The characteristics of miners in this data set have been described previously.[26] Briefly, miner's individual cumulative exposures to respirable coal mine dust were generally high (mean duration = 36.0 years, and mean intensity = 3.0 mg/m^3), although similar to a 45-year working lifetime at the current U.S. coal dust standard of 2 mg/m^3. Lung dust burdens were also high (mean total dust lung burden = 13.8 mg/g tissue), as compared to the mean total dust lung burden of 10 mg/g tissue associated with maximum overloading of lung clearance in rats.[10,11] Most miners had fibrotic lung disease at the end of their lives; the percentage of miners with macules, micronodules, macronodules, or progressive massive fibrosis was 84, 77, 47, and 30%, respectively. All miners were males, and most were white (66%), while 31% were black and 3% were other races. Mean values for work history and dust burden variables, within cumulative exposure groups, are provided in Table 2. These exposure groups, computed as the tertiles of the distribution of cumulative exposures, were used in evaluating model fit among miners with different exposure histories.

Table II. Work History and Dust Burden Data among Coal Miners in this Study, within Cumulative Exposure Groups[a]

Variable	*Mean (standard deviation)*		
	Group 1 (n = 44)	**Group 2** (n = 44)	**Group 3** (n = 43)
Exposure to respirable coal mine dust			
Cumulative (mg-yr/m^3)	67.7 (13.5)	102.6 (9.7)	154.3 (40.2)
Duration (years)	26.8 (7.3)	35.6 (6.2)	44.4 (7.6)
Intensity (mg/m^3)	2.6 (0.5)	2.9 (0.6)	3.5 (1.1)
Post-exposure duration (years)	10.0 (7.7)	10.2 (6.7)	10.2 (5.9)
Age (years)			
Start mining	25.0 (7.8)	21.2 (6.8)	16.7 (6.3)
Retirement	52.5 (8.3)	57.8 (5.5)	61.6 (4.3)
Death	62.6 (10.2)	68.0 (8.2)	71.8 (8.8)
Total dust lung burden (g)	12.1 (7.5)	12.5 (8.1)	17.0 (7.8)
Total dust lymph node burden (g)[b]	1.16 (0.76)	1.51 (0.96)	1.98 (1.37)

[a] Computed as the tertiles of the distribution of cumulative exposures (mg/m^3): group 1: 30- < 85; group 2: 85- < 120; group 3: 120-309.
[b] Number of miners with lymph node data: group 1 (n = 16); group 2 (n = 22); group 3 (n = 20).

Human Lung Dosimetry Models

One-compartment model

The effect of varying the lung clearance assumptions is illustrated for the one-compartment lung model in Figure 2. In this figure, model simulations are compared with the end-of-life mean lung dust burden values for miners in each of the three exposure groups (using a subset of smokers in the development data set). The average exposure histories among miners in each group were used as the input values for these model simulations (i.e., intensity and duration of exposure to respirable coal mine dust, and ages of starting work in mining, retirement, and death). In the model using the initial first-order clearance rate constant from Bailey et al.[20] of 0.001 d^{-1} (clearance half-time of 693 days), the end-of-life mean lung dust burdens were substantially underpredicted among miners in all three cumulative exposure groups (Figure 2a). When the clearance rate constant was reduced from 0.001 d^{-1} to 0.00013 d^{-1}, the model-predicted lung dust burden was improved (MSE reduced nearly 5-fold); however this model also predicts that considerable clearance would occur in the post-exposure period (Figure 2b), which is inconsistent with previous analyses[26] and lung clearance measurements in coal miners.[14] Finally, the one-compartment overload model (90% reduction in first-

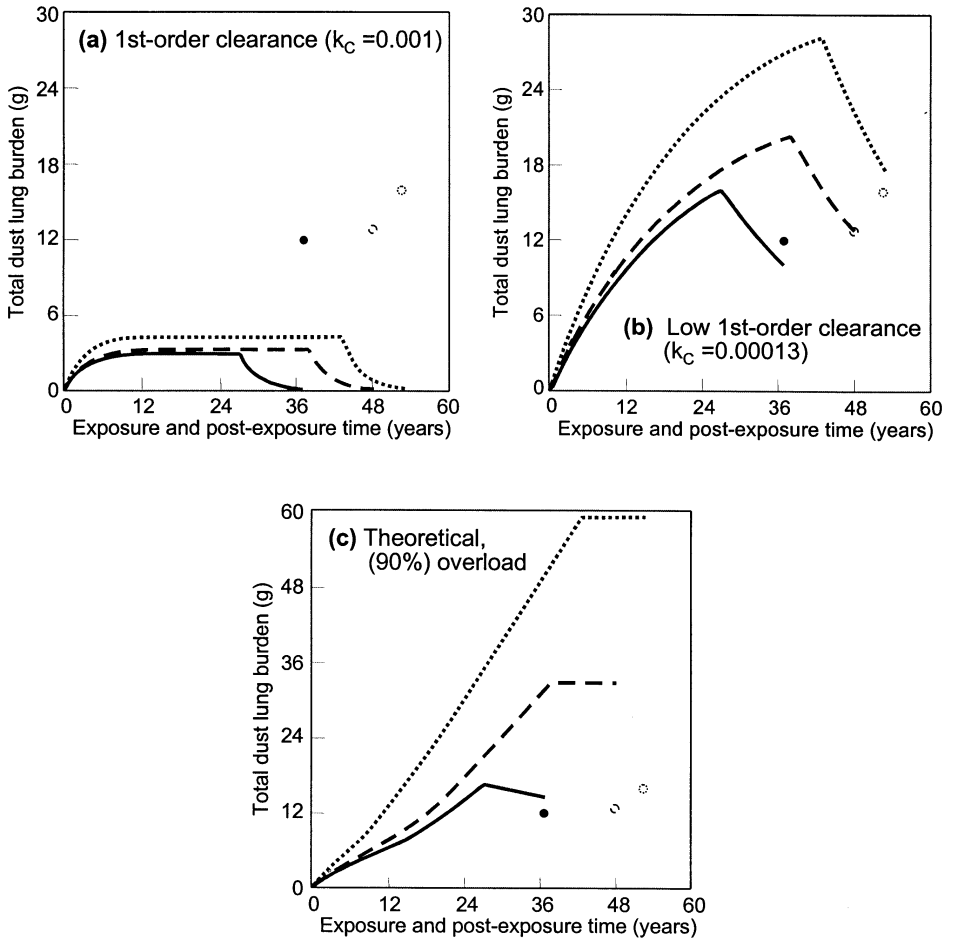

Figure 2. Predicted and measured mean total dust lung burden in various one-compartment models, among smokers in development data set (n = 69). ***Key:*** Cumulative exposure tertiles (mg-yr/m^3): Low (30- < 85) _____ ; Medium (85- < 120) _ _ _ ; High (120-309) . . . . . .

order clearance) overpredicted the mean lung dust burdens of miners in all cumulative exposure groups; and this overprediction became systematically worse in the higher cumulative exposure groups (Figure 2c). These model simulations using average exposure data values are consistent with the statistical evaluations of model fits using each individual's exposure data (discussed with Figure 4).

Three-Compartment Model

The three-compartment models evaluated included those with and without overloading of lung clearance. The model that provided the best

Table III. Best fitting Parameter Values[a] in Three-Compartment Human Lung Dosimetry Models with and without Overloading of Alveolar Clearance[b]

Parameter[c]	90% Overload	50% Overload	No Overload
K_T	1.4×10^{-3}	1.5×10^{-3}	1.0×10^{-3}
K_I	3×10^{-4}	7.0×10^{-4}	4.7×10^{-4}
K_{LN}	1×10^{-5}	1×10^{-5}	1×10^{-5}
B	2.3	0.69	0

[a] Based on least squares (Table IV).
[b] Extent of overloading refers to the percentage decline in K_T at M_{max}, which is governed by the value of B (Table I).
[c] Parameter description provided in Table I.

Table IV. Mean Squared Errors for Model-Predicted Total Dust Burdens (g) in the Lungs and Lymph Nodes, in Three-Compartment Models with and without Overloading of Alveolar Clearance[a]

Compartment	90% overload	50% overload	No overload
	All miners ($n = 128$)[b]		
Lungs	231	85.8	79.3
	Subset of miners with lymph node data ($n = 57$)[b]		
Lungs	354	106	94.7
Lymph Nodes	2.15	1.39	1.31
	Subset of miners with post-exposure duration equal to zero ($n = 11$)		
Lungs	148	68.9	70.0

[a] Extent of overloading refers to the percentage decline in K_T at M_{max} (Table I). Model parameter values are provided in Table III.
[b] Three miners, including one with lymph node data, were omitted because no data on post-exposure duration were available for them.

fit to the lung and lymph node dust burden data included the first-order transfer of dust to the interstitium (rate constant of 4.7×10^{-4} d^{-1}) and the lymph nodes (1.0×10^{-5} d^{-1}), as well as first-order alveolar macrophage-mediated clearance (1.0×10^{-3} d^{-1}) with no dose-dependent decline (Tables III and IV). The trends in the MSE values are consistent, across the data subgroups, in the models with or without overloading (Table IV). The behavior of the three-compartment model is also illustrated using group mean data (Figure 3), which is consistent with the MSEs and residuals plots (discussed below). The best-fitting model fits reasonably well to the lung dust burden data among miners in the middle exposure group; but it slightly overpredicts the lung dust burdens among miners in the high exposure group; and it substantially underpredicts the lung dust burdens of miners in the low exposure group (Figure 3a). The lymph node dust

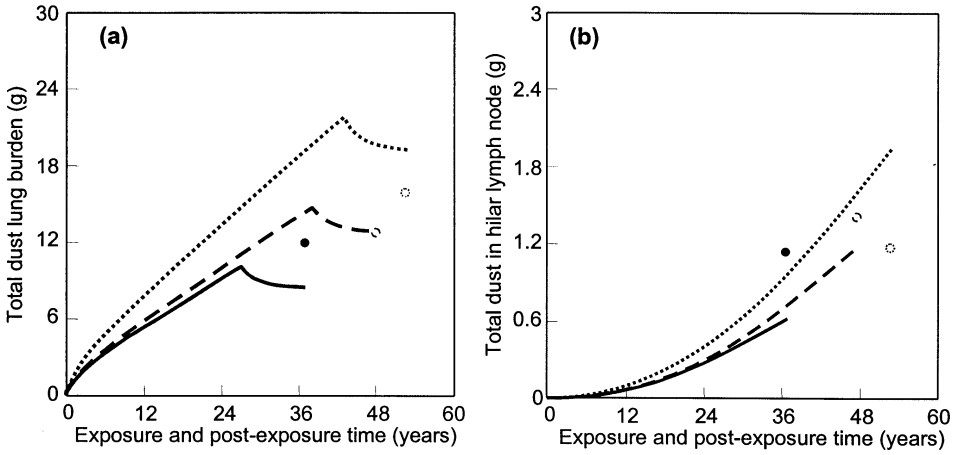

Figure 3. Predicted and measured mean total dust burden in the (a) lungs or (b) hilar lymph nodes, within cumulative exposure tertiles (mg-yr/m^3): Low (30-<85) _____ ; Medium (85-<120) _ _ _ ; High (120-309) . . . . . . Based on three-compartment model, with first-order interstitialization ($k_I = 4.7 \times 10^{-4}$) and alveolar macrophage-mediated clearance ($k_T = 1.0 \times 10^{-3}$), among smokers in development data set (n = 69).

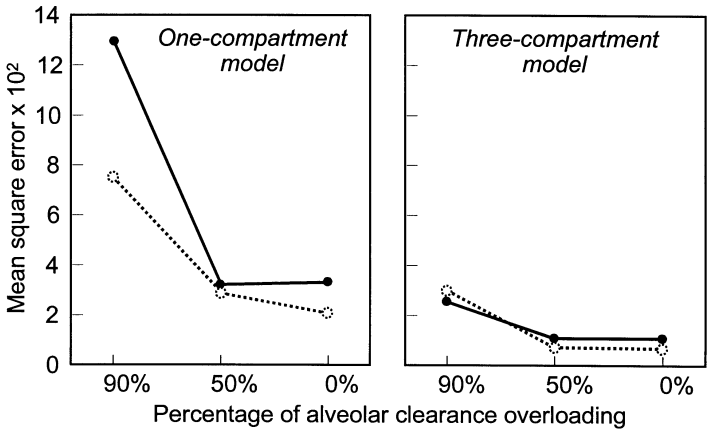

Figure 4. Comparison of the mean square error (MSE) of the predicted total dust lung burdens from the one- and three-compartment models, among ever smokers (n = 69) _____ , and never smokers (n = 16) . . . . . in the development data set.

burdens are somewhat underpredicted in the low and medium exposure groups and overpredicted in the high exposure group (Figure 3b).

Comparison of the MSEs for the one- and three-compartment models, with varying overload assumptions, is shown in Figure 4. Substantial improvement in model fit to the total dust lung burden data was observed in the three-compartment models compared to the one-compartment models, among both ever smokers and never smokers.

The MSEs for the three- vs. one-compartment model decreased by a factor of 2.5 to 5, depending on the assumed degree of overloading (Figure 4).

Following development of the three-compartment model, the model was tested using the remaining 1/3 of the data from the 131 coal miners. A similar pattern of model fit was observed in both the development and test data sets (data not shown). That is, the no overload or 50% overload models provide similar fit and the theoretical (90%) overloading model gave the poorest fit, although the contrast in the MSEs was less in the smaller test data set than in the development data set.

A residuals plot for total dust lung burden by cumulative exposure tertile (Figure 5a) confirms the MSE findings (Table IV) and the three-compartment model behavior illustrated in Figure 3. That is, the best-fitting model tends to underpredict the lung dust burdens of miners in the low cumulative exposure group (residuals are generally greater than zero); it provides an unbiased fit to the lung dust burdens of miners in the middle exposure group (residuals are approximately equally distributed above and below zero); and it tends to overpredict the lung dust burdens of miners in the high exposure group (residuals generally lie below zero). Closer inspection of the high exposure group, however, shows that residuals for most miners in this group are approximately equally distributed above and below zero, while the residuals for the four miners with the highest predicted values (who also had the highest cumulative exposures, all $>200\,\text{mg-yr/m}^3$) are considerably below zero. A statistical test for inhomogeneity of variance indicated no statistically significant difference among the cumulative exposure groups, either with all miners ($p = 0.2$) or with the four ''outliers'' omitted ($p = 0.9$).

Residuals for the total dust burdens in the hilar lymph nodes are shown in Figure 5b. In general, the lymph node dust burdens were underpredicted, as observed by the residuals being generally greater than zero. There is some suggestion of inhomogeneity of variance in the predicted lymph node dust burdens for miners in the high cumulative exposure group (trend of widening range in residuals at higher exposures), although fewer miners had lymph node dust burden data ($n = 58$).

Figure 6 illustrates the total dust masses in various lung compartments, based on a simulation of exposure to $2\,\text{mg/m}^3$ for 45 years, using the three-compartment model with first-order interstitialization and alveolar clearance (no overload). In this exposure scenario, the retained lung dust burden consists almost entirely of the interstitialized dust mass, while the mass in the alveolar region is cleared by the end of the post-exposure period. The mass cleared to the tracheobronchial region rises until the alveolar dust mass is completely cleared. The mass in the lymph nodes continues to increase, even during the post-exposure period.

The three-compartment model with first-order interstitialization and alveolar clearance (no overload) was used to generate predicted lung and

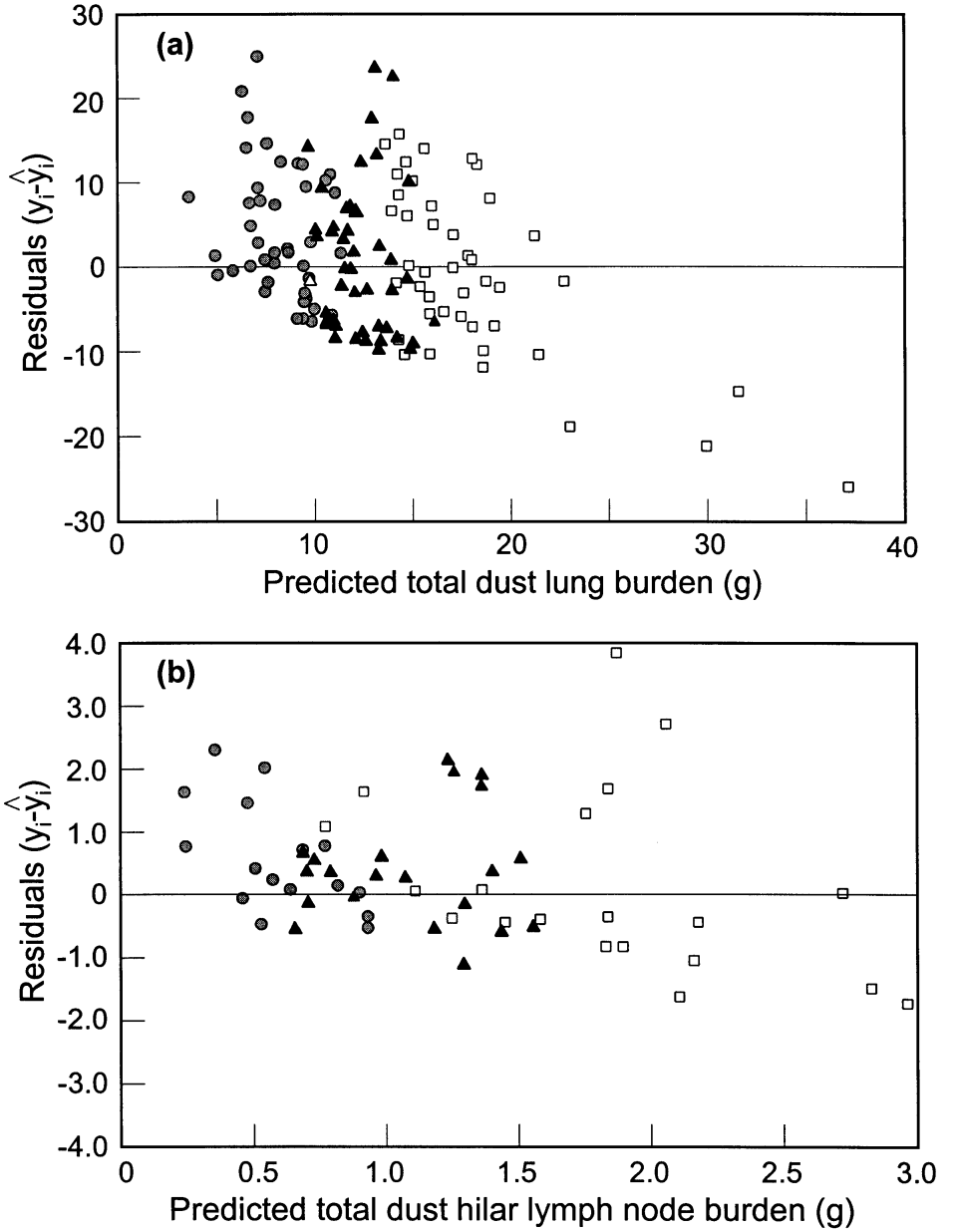

Figure 5. Residual (observed minus predicted) total dust burden in the (a) lungs (n = 128) and (b) hilar lymph nodes (n = 57). ***Key:*** Cumulative exposure tertiles (mg-yr/m^3): ● Low (30- < 85); ▲ Medium (85- < 120); □ High (120-309).

lymph node dust burdens for each miner by separately fitting the model to each miner's individual work history data. Figure 7 shows the probability of fibrotic lung disease, for all four grades of severity, based on the logistic regression models using either measured or predicted lung dust burdens.

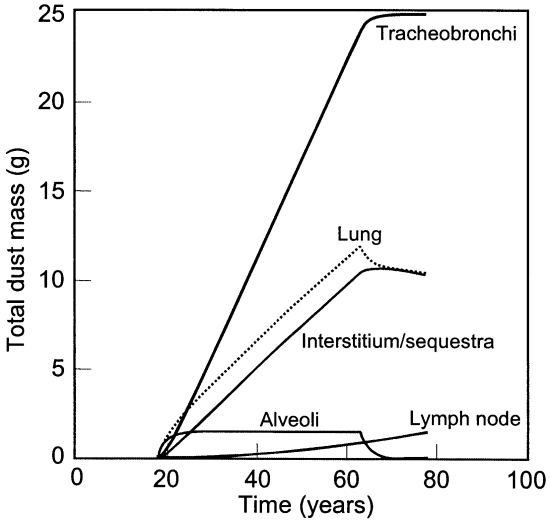

Figure 6. Predicted mass of particles in various lung compartments, assuming exposure to 2 mg/m^3 for 45 years, based on three-compartment model with first-order interstitialization and alveolar clearance (no overload).

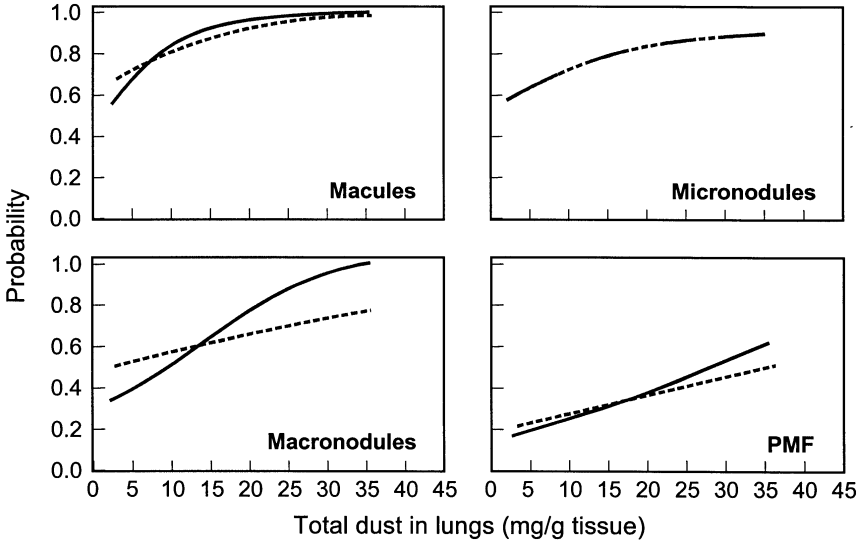

Figure 7. Probability of fibrotic lung disease, by pathological classification, based on measured or predicted total dust lung burden (n = 131). ***Key:*** Measured ——— ; Predicted . . . . . .

Dose-response relationships between either model-predicted or measured lung dust burdens and fibrotic lung disease were statistically significant, although the measured lung dust burden was a better predictor of disease, based on model likelihoods.

DISCUSSION

To summarize the findings, first, the simple first-order clearance model (with a lung clearance rate coefficient from a study in humans without occupational dust exposure) predicts that a steady-state lung dust burden would be achieved, and that during the post-exposure period most of the dust would be cleared from the lungs. This model greatly underestimates the lung dust burden in these miners, who have an average end-of-life lung dust burden of 13.8 mg/g tissue. Second, the human overload model (based on impaired clearance observations in rats) overpredicts the lung dust burden in humans, with the overprediction becoming systematically worse at increasing exposures. Finally, the three-compartment model that includes first-order interstitialization/sequestration and alveolar clearance (no overload), provides significantly improved fit to the data, based on least squares analyses. According to this model, most of the particle mass retention in the lungs is in the interstitial/sequestration compartment.

Even in the best-fitting three-compartment model, the lung dust burdens of miners in the low exposure tertile were underpredicted on average. However, there were no additional biologically reasonable revisions that were feasible within the structure of this model. Already, there was no dose-dependent decline in the first-order clearance (thus, no increased retention at the higher exposures), and there was high first-order interstialization (i.e., retention of dust even at lower exposures). This is opposite to the trend expected from overloading, in which the lung dust burden becomes disproportionally high at high exposures. In this study, the lung dust burdens were higher than expected from the model among miners with lower exposures. Given that the mean lung dust burden among miners in the lowest exposure group (12.1 g; standard deviation 7.5 g) was quite similar to the burden among miners in the middle group (12.5 g; standard deviation 8.1 g), it is possible that misclassification of exposures occurred among miners in the lowest exposure group. Alternatively, there may have been a selection effect, in which those miners most susceptible to particle retention and adverse health effects left mining earlier, thus resulting in lower working lifetime exposures among those miners. Some evidence of this is seen in the earlier ages of retirement and death among miners in the lower cumulative exposure group.

Several criteria were used to evaluate the utility of this model. First, this model is biologically plausible. It includes the major compartments for retention and clearance of dust in the alveolar region of the lungs, and the initial parameter values were based primarily on experimentally measured values in humans and animals. Second, a statistically-based approach (least squares) was used to estimate the parameter values and fit the model to the data. Third, the modeling results were consistent using either the subset of data randomly selected to develop the model or the subset reserved to test the

model. Fourth, the findings from this dosimetric model are consistent with other studies.[14,27] Specifically, the model prediction that intersitialization is the predominant mechanism for retention of dust in the human lungs is consistent with a histology study by Nikula et al.[27] In that study, the site of dust retention in the lungs of both nonhuman primates and humans was primarily in the interstitium, while in rats a greater proportion of the total dust mass was retained within the alveoli. Furthermore, an earlier analysis of the data in this study[26] showed no evidence that measurable dust clearance had occurred in the lungs of those miners during retirement. This finding is also consistent with a magnetopneumography study in retired U.S. coal miners in which clearance was greatly reduced in some miners and undetectable in others.[14] Finally, another criterion of model utility was the comparison of measured and model-predicted lung dust burdens as predictors of disease. In the dose-response models (logistic regression), the model-predicted lung dust burdens gave similar predictions of fibrotic lung disease (within four separate severity grades) to those based on the measured lung dust burdens. This suggests that a biologically-based model of particle retention in humans may be useful in estimating risk of disease. The probability of disease predicted at the lower doses reflects the high measured and predicted lung dust burdens and the high occurrence of disease among the miners in this data set. However, the sparse data for miners with low lung dust burdens makes disease prediction in this region less reliable. The lung dust burdens and disease response among these U.S. miners are similar to those reported in a pathology study of U.K. coal miners.[28]

There were several challenges in developing a human lung dosimetry model using these coal dust data.[16] The individual lung and lymph node organ weights for miners were not available, and therefore standard reference values[29] were assumed. The individual work history data were limited, and the amount and quality of the data varied. Although the duration of exposure by mining job was available for each miner (including periods of unemployment or nonmining employment), the estimates for intensity of exposure for each miner were based on the average values, by job category, from a survey of airborne concentrations in the late 1960's.[18] Silica exposures were not available, and silica, which is cytotoxic, may affect both the retention of dust in the lungs and the development of disease. There were no miners in this study with low exposures; thus it was not possible to validate the model predictions at low exposures. Finally, the kinetic parameter values used in these models are average values, which do not reflect the inter-individual variability in these data.

This three-compartment human lung dosimetry model has been shown to be useful for investigating the factors that influence the long-term retention of particles in the lungs of humans. The model predictions are consistent with previous observations of different particle retention patterns in rats and humans, and this model may be useful for quantifying those kinetic differ-

ences. Further research is needed on whether interspecies differences in particle retention sites within the lungs may influence the sensitivity to a given lung dust burden, and influence the disease response. The findings from this study also suggest that a human lung dosimetry model without an interstitialization or sequestration compartment would not be adequate for predicting the end-of-life lung dust burdens in humans, at least not among those with high dust exposures such as coal miners. Other data sets, particularly those including individuals with low exposures, are needed for further validation of this model. A validated human lung dosimetry model may be useful in risk assessment, particularly in the step of estimating the equivalent particulate doses in the lungs of humans and other species in which the toxicity of inhaled particles has been studied. The purpose of this paper was to provide an overview of the development of a lung dosimetry model in coal miners. Additional manuscripts are in preparation to provide further details on the model development, validation, and disease predictions.

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