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

II. Evaluation of Variability and Uncertainty

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The objective of this study is to investigate the sources of variability and uncertainty in a previously developed human lung dosimetry model. That three-compartment model describes the retention and clearance kinetics of respirable particles in the gas-exchange region of the lungs. It was calibrated using exposure histories and lung dust burden data in U.S. coal miners. A multivariate parameter estimation and optimization method was developed for fitting the dosimetry model to these human data. Models with various assumptions about overloading of alveolar clearance and interstitialization (sequestration) of particles were evaluated. Variability in the estimated clearance rate coefficients was assessed empirically by fitting the model to groups' and to each miner's data. Distributions of lung and lymph node particle burdens were computed at working lifetime exposures, using the variability in the estimated individual clearance rate coefficients. These findings confirm those of the earlier analysis; i.e., the best-fitting exposure–dose model to these data has substantial interstitialization/sequestration of particles and no dose-dependent decline in alveolar clearance. Among miners with different characteristics for smoking, disease, and race, the group median estimated alveolar clearance rate coefficients varied by a factor of approximately 4. Adjustment for these group differences provided some improvement in the dosimetry model fit to all miners (up to 25% reduction in MSE), although unexplained interindividual differences made up the largest source of variability. The predicted mean lung and lymph node particle burdens at age 75 after exposure to respirable coal mine dust at 2 mg/m^2 for a 45-year working lifetime were 12 g (5th and 95th percentiles, 3.0–26 g) and 1.9 g (0.26–5.3), respectively. This study provides quantitative information on variability in particle retention and clearance kinetics in humans. It is useful for risk assessment by providing estimated lung dust burdens associated with occupational exposure to respirable particles.

INTRODUCTION

In the preceding paper, we describe the development of a human lung dosimetry model representing the clearance and retention of particles in coal miners' lungs (this journal; Kuempel *et al*., 2001). In that study, the process of overloading of alveolar-macrophage-mediated clearance, as observed in rodents (Morrow, 1988), was considered in these human data. The model form that best fit the coal miner data includes an interstitial/sequestration compartment, no dose-dependent decline in alveolar-macrophage-mediated clearance, and very slow particle clearance to the lung-associated (hilar) lymph nodes. Thus, to adequately describe the end-of-life lung dust burdens in these miners, the dosimetry model required a sequestration process (thought to represent interstitialization), but did not require overloading as defined by the rodent data.

Observed differences in clearance and retention of particles in humans and rodents illustrate the utility of a biologically based dosimetry model to describe the kinetic relationship between external exposure and internal dose. A first step in using the rodent data to assess the risk of particle-related lung diseases in humans is to estimate equivalent doses in animals and humans. However, few quantitative data are available in humans to investigate the adequacy of the rodent models for estimating a human-equivalent dose. These data in coal miners have provided an opportunity to investigate the kinetic processes of particle retention and clearance in human lungs and to compare these findings to those from rodent studies. Given the scarcity of human data of particle exposures and lung burdens, the

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findings from this human lung dosimetry model in coal miners is also relevant to estimating interspecies differences in the clearance and retention of other poorly soluble, respirable particles. Finally, these findings provide a basis for comparison with existing human models (e.g., ICRP, 1994; NCRP, 1997) developed using data of lower particle exposures.

In applying the model to other cohorts, it will be of interest to examine not only the mean predictions of the model, but also to provide estimates of uncertainty and variability in the model predictions. Uncertainty in biologically based kinetic models can be defined as "the possible error in estimating the 'true' value of a parameter for a representative ('average') animal or human," whereas variability in these models generally represents the "interindividual differences" (Clewell and Andersen, 1996). Thus, uncertainty can be reduced by additional information from experimental studies, but variability primarily reflects the biological variation in a population, which in humans is often considerable.

In this study, we evaluate sources of uncertainty in the structure and the mean parameter values of the human lung dosimetry model described in the preceding paper (this journal; Kuempel *et al*., 2001), using a multivariate optimization approach we developed for sparse, heterogenous data. We evaluate the robustness of our putative "best-fit" parameter estimates by testing the sensitivity of the model to plausible changes in key parameter values. To evaluate interindividual variability, we develop empirical estimates of the population variability associated with key model parameters. We use these estimates to derive distributions of the model-predicted lung and lymph node dust burdens, in the whole cohort and among miners stratified by smoking habits, race, and severity of pulmonary fibrosis.

METHODS

A description of the human lung dosimetry model and the data used to calibrate this model are provided in the preceding paper (Kuempel *et al*., 2001). Briefly, working lifetime exposure histories, lung dust burdens, and pathological classifications of pulmonary fibrosis at autopsy were available for 131 U.S. coal miners (Vallyathan *et al*., 1996). Of these, 57 miners also had data on dust burden in the lung-associated (hilar) lymph nodes. The time course of the individual miners' estimated inhalation exposures to respirable coal mine dust provided the input for the dosimetry model, which describes the kinetics of particle clearance and retention in the gas-exchange region of human lungs. Initial model parameter values were based on data from the literature in humans (Bailey *et al*., 1985) and rodents (Bellmann *et al*., 1991; Tran *et al*., 1997). Parameter estimation and optimization of the model fit to the data was performed initially by determining the parameter values that minimized the mean squared error (MSE) for lung burden, using a systematic grid search approach in ACSL (1997). The group-fit parameter values from that earlier analysis are provided in the preceding paper (Kuempel *et al*., 2001).

Optimization of Parameter Estimates

The MSE was also used in the current analysis to evaluate the goodness-of-fit of the dosimetry model to the coal miner lung and lymph node dust burden data. The MSE was selected because least squares is a well-known method of fitting models to normally distributed data, which is a reasonable assumption for these data (Kuempel, 1997). In this study, the MSE values represent the sum of the MSEs for lung and lymph node burdens:

$$\mathrm{MSE}_{\mathrm{total}} = \frac{\sum(\mathrm{Obs}_{\mathrm{L}} - \mathrm{Pred}_{\mathrm{L}})^2 + \sum(\mathrm{Obs}_{\mathrm{LN}} - \mathrm{Pred}_{\mathrm{LN}})^2}{n}, \quad (1)$$

where $\mathrm{Obs}_{\mathrm{L}}$ and $\mathrm{Pred}_{\mathrm{L}}$ are the observed and predicted lung particle mass burdens, respectively; $\mathrm{Obs}_{\mathrm{LN}}$ and $\mathrm{Pred}_{\mathrm{LN}}$ are the observed and predicted lymph node particle mass burdens, respectively; and n is the sample size of the data (i.e., miners with both lung and lymph node data). The total mean bias (defined as the mean of the residuals, i.e., observed minus predicted values for the lung and lymph node burdens) was also computed to provide an indication of how close, on average, the predicted values were to the observed. The total MSE, as defined above, was the objective function used in the multivariate optimization procedure.

A multivariate approach to parameter estimation and optimization was developed for this study (Tran and Buchanan, 2000) using MATLAB (1999). In this procedure, the initial parameter values and the individual data are passed through several program files (known as m-files in MATLAB), including the optimization routine (e.g., fmins), the objective function to be optimized (i.e., total MSE or sum of the MSEs for the lung and lymph node burdens, in a specified number of miners), and the ordinary differential equation (ODE) solver (e.g., ODE45), to the three-compartment lung dosimetry model containing the differential equations describing the mass transfer of particles in the lungs over time. Numerical integration was performed using the Runge–Kutta algorithm for solving a system of nonstiff, ordinary differential equations (MATLAB, 1999). The model predictions (i.e., end-of-life lung and lymph node particle burdens) are then passed back to the objective function to compute the total MSE, which is evaluated by the optimization routine. The optimization routine uses the Nelder–Mead simplex (direct search) method to perform unconstrained optimization of the initial parameter values, by minimizing the function of several variables, and attempting to

return a vector that is a local minimizer of the objective function near the starting vector (MATLAB, 1999). This approach was used to optimize the model fit to the whole group of miners with both lung and lymph node dust burden data ($n = 57$), to groups stratified on common characteristics (including race, smoking status, and fibrosis severity) and to individuals. Lung and lymph node lymph node particle burdens were predicted from the model using whole group-fit and strata-fit parameter values. For the model fits to the individuals' data, the objective function being minimized was the sum of the squared residuals for each individual's lung and lymph node burdens. The purpose of these individual fits was to determine the required amount of variability in the parameter values such that the residual error from fitting the model to the data is equal to nearly zero.

Because the objective of this study was to evaluate clearance and retention kinetics, the rate coefficients allowed to vary in the model included alveolar-macrophage-mediated clearance to the tracheobronchi (K_T), transfer of particles into the interstitium (K_I), and translocation of particles to the hilar lymph nodes (K_{LN}). The fractional deposition and the ventilation rate were fixed to average values obtained from the literature (ICRP, 1994), as described in the preceding paper. In some analyses, optimization of K_T, K_I, and K_{LN} was performed at varying levels of another parameter (B), which regulates the amount of dose-dependent decline in alveolar clearance (overloading). To fit the model to the individuals' data, K_T and K_{LN} were optimized, and K_I was set at the group-fit value (Table 1). The model fits to the individuals' data were limited to fitting two parameters to avoid overparameterization due to limited data for each miner (i.e., end-of-life lung and lymph node dust burdens and assumed zero burdens at the start of exposure).

TABLE 1
Comparison of Best-Fitting Clearance Parameter Values, by Approach

Parameter	Original (ACSL) group fit[a]	Multivariate optimization (MATLAB)[b]		
		Group fit	Mean of individual fits	Median of individual fits
K_T	1×10^{-3}	9.96×10^{-4}	1.28×10^{-3}	8.81×10^{-4} [c]
K_I	4.7×10^{-4}	4.54×10^{-4}	4.54×10^{-4} [d]	4.54×10^{-4} [d]
K_{LN}	1×10^{-5}	1.04×10^{-5}	1.44×10^{-5}	1.16×10^{-5} [e]

[a] Other model parameters set to values in Table 7 (no-overload model) in preceding paper (Kuempel *et al.*, 2001).

[b] Optimization to data for 57 miners with hilar lymph node dust burden data.

[c] 5th and 95th percentiles of K_T distribution: 1.08×10^{-4} and 4.44×10^{-3}.

[d] Constant (i.e., two-parameter optimization of model fit to the individuals' data).

[e] 5th and 95th percentiles of K_{LN} distribution: 2.84×10^{-6} and 3.97×10^{-5}.

Evaluation of Uncertainty in the Model Structure and Parameters

Uncertainty in the model structure and group-fit parameter values was investigated by systematically evaluating alternative model forms. In the earlier analysis, two key features of the human lung dosimetry model were identified. These are (1) no dose-dependent decline in alveolar-macrophage-mediated clearance (i.e., no "overloading") and (2) first-order sequestration, thought to represent the interstitialization of particles. Because verification of these possible mechanisms is critical for accurately describing the kinetics of particle retention and clearance in humans, and for extrapolating from the rodent models to estimate human-equivalent dose, additional analyses of these processes were performed in this study using a multivariate optimization approach.

Overloading was investigated in this study as a dose-dependent decline in the alveolar-macrophage-mediated clearance rate. This was performed by determining model fit to the data with different values for the extent of the dose-dependent decline in K_T (equations in preceding paper; Kuempel *et al.*, 2001). A multivariate optimization was then performed, allowing the clearance rate coefficients (K_T, K_I, and K_{LN}) to vary to obtain an optimal model fit at each level of overloading. This approach increases the opportunity for detecting an overloading effect in these data, by varying the other parameters to best fit the data at a specified level of overloading.

Sequestration, or interstitialization, was investigated using two approaches. The first approach was to evaluate uncertainty in the group-fit value for first-order interstitialization by fixing K_I at values above and below the original best-fit K_I value and then optimizing the model fit by allowing K_T and K_{LN} to vary. The rate of postexposure clearance (i.e., during retirement) predicted from each model was also evaluated; and clearance rate curves were plotted and evaluated with consideration of the earlier finding of no detectable clearance of dust from miners' lungs during retirement. The second approach was to evaluate uncertainty in the description of K_I as a first-order process. This analysis also provided an empirical correction for the observed trend in the lung dust burden residuals in the original model, by fitting a higher-order expression for the interstitialization rate coefficient. The value of K_I was optimized within the cumulative exposure tertiles as a first look at whether K_I is dose-dependent. The range of cumulative exposures in these tertiles were 30 to <85, 85 to <120, and 120 to 309 mg-year/m^3, respectively, for the lowest, middle, and highest groups. Next, the model structure itself was revised by expressing K_I as

a dose-dependent rate coefficient, K_{I2}:

$$K_{I2} = K_I \times \exp(-B_2 \times M_I), \quad (2)$$

where K_I is the first-order rate coefficient for interstitialization, M_I is the particle mass in the interstitium at any time t, and B_2 determines the rate of decline in K_I with increasing interstitial burden. The reason for this form of the expression is the downward trend observed in the residuals (toward overpredicting lung burden among miners with higher observed lung burdens). This model was fit to all miners with lymph node dust burden data ($n = 57$) by multivariate optimization of K_I, B_2, and K_{LN}. Starting values for these parameters were, respectively, 1×10^{-3} (based on the results from the fitting K_I within the cumulative exposure tertiles), 0 (results in multiplying K_I by a factor of 1 or no dose-dependent decline), and 1×10^{-5} (original value). The revised model (with optimized parameter values) was then run using all miners' data ($n = 131$); and the residuals pattern, MSE, and mean bias were reevaluated.

An additional analysis to investigate sources of bias in the residuals was performed to determine the influence of the four "outliers" (identified in the preceding paper) on the group-fit parameter values and their contribution to the observed trend in the lung burden residuals. These four miners had the highest estimated cumulative exposures in the study (>200 mg-year/m^3) yet had relatively low lung dust burdens; these miners' data were visibly distinct from the rest of the data. After omitting the four miners, the model was refit to the reduced data set by multivariate optimization of K_T, K_I, and K_{LN}. The optimization was performed in the reduced subset of miners with lymph node data ($n = 55$), and the optimized model was then run using all miners in the reduced data set ($n = 127$).

Sensitivity of the best-fitting dosimetry model to plausible changes in the deposition and clearance rate coefficients was investigated by systematically modifying the deposition and clearance parameter values (F_D, K_T, K_I, and K_{LN}) and evaluating the resulting model predictions and fits. The percentage of change in output associated with a given percentage of change in input (10%) was also computed.

Evaluation of Variability in Parameter Estimates

The interindividual variability in alveolar and lymph node particle clearance was estimated by optimizing the model fit to each individual, as described above. The distributions of estimated individual values of K_T and K_{LN} were computed and compared among miners with different characteristics. In addition, optimization of the rate coefficients for K_T, K_I, and K_{LN} was performed in small groups (strata) of miners, based on smoking habits, race, and fibrosis severity. Because of the limited size of the data set (57 miners with lymph node data), it was not possible to create strata for all combinations of these characteristics. Therefore, we used linear regression models (Neter *et al*., 1989; SAS, 1996) to investigate the extent to which certain characteristics of these miners may explain the estimated variability in the clearance rate coefficients. In these regression models, K_T and K_{LN} were treated as the response variables, and miners' characteristics were the predictors. The principal predictors examined included smoking habits (as an indicator variable, 1 = ever smoker or unknown; 0 = never smoker); race (as an indicator variable, 1 = black; 0 = white/other); and fibrosis category of highest severity at end of life (as indicator variables (1 = yes; 0 = no) for micronodules, macronodules, and progressive massive fibrosis; the comparison group was miners with either macules only or no fibrosis).

Prediction of Lung and Lymph Node Burdens

The three-compartment human lung dosimetry model was used to predict lung and lymph node dust burdens in these miners. Two approaches were used. First, both the whole group-fit and the strata-specific model parameter values for K_T, K_I, and K_{LN} were used, along with each miner's exposure data as input in the model. Predictions were then generated of miners' lung and lymph node dust burdens over time and at the end of life. Second, the dosimetry model was used to predict the distribution of lung and lymph node dust burdens among miners at age 75 with a given exposure history, while allowing individual differences in estimated clearance (using estimated individual values of K_T and K_{LN}). The exposure scenario selected here was 2 mg/m^3 of respirable coal mine dust for a 45-year working lifetime because it represents the current U.S. exposure limit for coal mine dust and a full working lifetime typically used in occupational risk assessment (NIOSH, 1995). By using the pairs of K_T and K_{LN} values for each individual, the correlation between K_T and K_{LN} was inherently taken into account in this approach.

RESULTS

Parameter Estimation

The estimated values of the clearance rate coefficients in the group or individual data are compared in Table 1, for both the grid search method in the original study (using ACSL) and the multivariate optimization approach in this study (using MATLAB). The results of both approaches are quite similar. The mean parameter values based on the group fits were nearly identical, and the median of the individual fits were similar. The values based on the mean of the individual fits were higher, due to the right-skewness in the distributions.

TABLE 2
Multivariate Optimization of Clearance Parameters in the Three-Compartment Model with Various Levels of Alveolar-Macrophage-Mediated Clearance Overloading, among Miners with Lymph Node Data, $n = 57$

Amount of overload (%)	B[a]	Optimized parameter values			MSE	P value[b]
		K_T	K_I	K_{LN}		
0[c]	0	9.36×10^{-4}	4.31×10^{-4}	1.05×10^{-5}	93.9	[d]
10	0.1	1.01×10^{-3}	4.51×10^{-4}	9.69×10^{-6}	95.5	0.4
20	0.22	1.08×10^{-3}	4.58×10^{-4}	1.03×10^{-5}	97.1	0.2
30	0.36	1.09×10^{-3}	4.44×10^{-4}	1.03×10^{-5}	99.7	0.08
40	0.51	1.17×10^{-3}	4.53×10^{-4}	9.81×10^{-6}	102	0.04
50[e]	0.69	1.10×10^{-3}	1.04×10^{-4}	1.34×10^{-5}	234	<0.0001

[a] In the dosimetry model, the value of B describes the extent of the overloading of the alveolar-macrophage-mediated clearance parameter, K_T, at any given alveolar dust burden (M_A). This occurs because alveolar-macrophage-mediated clearance is described by the product of K_T and a dose-dependent modifying factor, $F = \exp\{-B[(M_A - M_{min})/(M_{max} - M_{min})]\}$, in which M_{min} and M_{max} are the lung dust burdens at which K_T is expected, based on extrapolation from rodent studies, to begin to decline and to reach maximum decrement.

[b] P values determined using an F test (in which the test statistic is referenced to an F distribution) (Jennrich and Ralston, 1979).

[c] The optimized clearance parameter values at $B = 0$ differ slightly compared to Table 1, MATLAB group fit, because there the original ACSL group-fit parameter values were used as the initial values for the MATLAB optimization, including B, which was not optimized but set at 0.0001, giving 99.99% of initial K_T at M_{max} (compared to 100% of initial K_T at M_{max} for $B = 0$).

[d] Not applicable; this is comparison model.

[e] Models with 60% or greater overloading of lung clearance did not converge.

Uncertainty and Sensitivity Analyses

Uncertainty in the dosimetry model structure and parameter values was investigated in several analyses. Table 2 shows the results of an analysis to evaluate whether there is any evidence of overloading of alveolar clearance in these human data. In this analysis, the parameter that governs the extent of dose-dependent decline in alveolar-macrophage-mediated clearance (B) was set at fixed values, and the optimal model fit at each fixed value of B was determined by allowing K_T, K_I, and K_{LN} to vary multivariately. The results show that the model fit becomes increasingly worse (i.e., MSE increases) as the assumed amount of overloading increases. These results confirm the findings of the earlier study—that the best-fitting model includes interstitialization/sequestration of particles but no dose-dependent decline in alveolar clearance.

Another area of uncertainty relates to the relative size of the interstitial/sequestration compartment and whether alternative assumptions about the rate of particle interstitialization/sequestration might be reasonable for predicting the end-of-life lung and lymph node dust burdens in these miners. To investigate the influence of alternative values for the interstitialization rate coefficient, K_I was set to values above and below the original (default) value, and the optimal model fit was determined by allowing K_T and K_{LN} to vary. Similar model fits (i.e., similar MSE) are obtained in models with K_I varying by factors of 4 above and below the original K_I (data not shown). However, the models with K_I below the original value predict a substantial decline (over 40%) in the lung dust burden during retirement; and the models with higher K_I underpredict the mean end-of-life lung dust burden (possibly due to the larger K_T values in these models, the burden did not build up as high). The original value for K_I provides predictions that are more consistent with the earlier findings of no detectable postexposure clearance in these miners (Kuempel *et al.*, 2001) and little or no detectable clearance during retirement in other U.S. coal miners (Freedman and Robinson, 1988). This analysis also provides information on the correlation between K_T and K_I. As the fixed value of K_I is increased or decreased, the optimal value of K_T also increases or decreases, respectively, by nearly the same amount. The Pearson correlation coefficient for K_T and K_I is 0.99 ($P < 0.0001$). In contrast, K_{LN} was not significantly correlated with either K_T or K_I (correlation coefficient is -0.6; $P = 0.2$).

Reported next are the results of analyses to investigate the trend in the lung dust burden residuals. In the analyses in the reduced data set ($n = 127$) without the four outliers, the optimized parameter values for K_T, K_I, and K_{LN} are 8.8×10^{-4}, 5.1×10^{-4}, and 1.0×10^{-5}, respectively. Compared to the optimized model fit to the full data, the model fit to the reduced data was improved by approximately 15% in MSE (from 81.1 to 69.6) and by >90% in mean bias (from 1.57 to 0.13). Next we evaluated the possibility of a dose-dependent K_I. First looking at K_I in the cumulative exposure tertiles, the values were 1.0×10^{-3}, 5.5×10^{-4}, and 3.6×10^{-4}, for the low, middle, and high tertiles, respectively. These results indicate that the optimized K_I values decrease with increasing cumulative exposure. We therefore modified the model structure to include dose-dependent decline in interstitialization (as described under Methods). The

TABLE 3
Sensitivity of Best Group-Fit Model Parameters for Deposition and Clearance, Among Miners and Lymph Node Data ($n = 57$)

Parameter and specified change from initial value[a]	Mean squared error	Mean bias (g)	Mean predicted lung dust burden (g)	Percentage of change in output with 10% change in input[b]	Mean predicted lymph node dust burden (g)	Percentage of change in output with 10% change in input[c]
Default values[d]	95.2	+0.99	14.2	[e]	1.41	[e]
$F_D + 10\%$	101.0	−0.59	15.6	+9.8	1.55	+9.9
$F_D - 10\%$	95.5	+2.3	12.9	−9.2	1.30	−7.8
$K_T + 10\%$	94.0	+2.0	13.3	−6.3	1.33	−5.7
$K_T - 10\%$	98.6	−0.15	15.2	+7.0	1.50	+6.4
$K_I + 10\%$	98.1	+0.03	15.0	+5.6	1.50	+6.4
$K_I - 10\%$	93.8	+2.0	13.2	−7.0	1.31	−7.1
$K_{LN} + 10\%$	95.0	+1.0	14.0	−1.4	1.54	+9.2
$K_{LN} - 10\%$	95.5	+1.0	14.3	+0.7	1.28	−9.2

[a] F_D, fractional deposition. First-order rate coefficients: K_T, alveolar-macrophage-mediated clearance of paticles to the tracheobronchi; K_I, transfer of particles to the interstitium; K_{LN}, translocation of particles to the hilar lymph nodes.
[b] Output is mean predicted lung burden.
[c] Output is mean predicted lymph node burden.
[d] $F_D = 0.12$; $K_T = 8.8 \times 10^{-4}$ day^{-1}; $K_I = 4.5 \times 10^{-4}$ day^{-1}; $K_{LN} = 1.0 \times 10^{-5}$ day^{-1}.
[e] Not applicable because percent change is relative to the default values.

optimized parameter values for K_I, B_2, and K_{LN} in the revised model (with dose-dependent decline in interstitialization) are 9.8×10^{-4}, 8.0×10^{-5}, and 9.9×10^{-6}, respectively. In this revised model, when the predicted interstitial lung dust burden reaches 10 g (10,000 mg in model), the value of the dose-dependent rate coefficient, K_{I2}, is approximately equal to the original first-order value of K_I (4.5×10^{-4}); at lower interstitial particle burdens, K_{I2} is greater than the original K_I, while at higher burdens, K_{I2} is smaller, declining to half the original value at 18 g. Compared to the original model, the revised model shows a 15% reduction in the MSE (from 81.1 to 69.8) and a 60% reduction in the mean bias (from 1.57 to 0.65). The revised model provides similar improvement to the original model without the four outliers.

Sensitivity of the dosimetry model fit and output to small changes in the deposition and clearance parameters is shown in Table 3. The results show that the model is fairly robust to 10% changes in the clearance parameters. It is most sensitive to changes in the fractional deposition (F_D); a 10% increase or decrease in F_D gave changes in model output of +9.8% or −9.2% for lung dust burden and +9.9% or −7.8% for lymph node dust burden. Changes in the lymph node clearance rate coefficient had a large influence on the model output for lymph node dust burden, but not for lung dust burden. A 10% change in K_{LN} gave a ±9.2% change in lymph node burden, but led to only an approximately 1% change in predicted lung dust burden. Changes in the alveolar clearance or interstitialization rate coefficients had moderate influence; a 10% change in these parameters produced changes from 5.6 to 7.1% in lung or lymph node burdens. As expected, the direction of change in output is opposite for K_T and K_I,; that is, an increase in K_T leads to a decrease in both lung and lymph node burdens, while an increase in K_I leads to an increase in these burdens.

Variability in Parameter Estimates

Interindividual variability in alveolar and lymph node clearance rate coefficients is illustrated in Table 4. The median values of K_T and K_{LN} (and 5th and 95th percentiles of the distributions) are provided for miners within strata based on smoking habits, race, and fibrosis severity at the time of death. Although differences of up to a factor of four are seen in the median clearance parameters across these strata, the differences are small relative to the large remaining variability in the data. Figures 1a and 1b show that when the model is fit to the group of miners with lymph node data ($n = 57$), using constant group-fit parameter values, the residual variability is large, and there is a trend for underprediction among miners with low predicted lung dust burdens (and low cumulative exposures). This is consistent with the residual plot for the full data set in the earlier paper. The residual variability from the group model fits is essentially eliminated when individuals are allowed to have their own clearance rate coefficients for K_T and K_{LN} (Figs. 2a and 2b).

The extent to which miners' characteristics may explain the variability in the estimated clearance rate

TABLE 4
Estimated Alveolar Clearance Rate Coefficient, by Characteristic, among Miners with Lymph Node Data[a]

Characteristic	Median K_T (day^{-1}) (5th, 95th percentiles)	Median K_{LN} (day^{-1}) (5th, 95th percentiles)
All miners ($n = 56$)[b]	8.8×10^{-4} (1.1×10^{-4}, 4.4×10^{-3})	1.2×10^{-5} (2.8×10^{-6}, 4.0×10^{-5})
Smoking habit		
Ever ($n = 44$), unknown ($n = 2$)	9.4×10^{-4} (1.2×10^{-4}, 4.6×10^{-3})	1.2×10^{-5} (3.4×10^{-6}, 4.0×10^{-5})
Never ($n = 10$)	5.3×10^{-4} (1.0×10^{-4}, 4.5×10^{-3})	1.4×10^{-5} (2.6×10^{-6}, 2.4×10^{-5})
Race		
Black ($n = 15$)	4.3×10^{-4} (0, 1.2×10^{-3})	1.3×10^{-5} (4.6×10^{-6}, 3.1×10^{-5})
White ($n = 40$), other ($n = 1$)	1.0×10^{-3} (1.2×10^{-4}, 4.5×10^{-3})	1.2×10^{-5} (4.6×10^{-6}, 3.1×10^{-5})
Fibrosis, highest, severity classification at autopsy		
Macules ($n = 12$)[c]	2.0×10^{-3} (2.1×10^{-5}, 4.6×10^{-3})	7.8×10^{-6} (4.6×10^{-6}, 3.1×10^{-5})
Micronodules ($n = 18$)	9.7×10^{-4} (1.6×10^{-4}, 4.2×10^{-3})	1.3×10^{-5} (1.7×10^{-6}, 4.0×10^{-5})
Macronodules ($n = 8$)	5.2×10^{-4} (1.6×10^{-4}, 4.2×10^{-3})	1.1×10^{-5} (3.4×10^{-6}, 4.2×10^{-5})
Progressive massive fibrosis ($n = 18$)	8.8×10^{-4} (1.0×10^{-4}, 3.5×10^{-3})	1.4×10^{-5} (2.6×10^{-6}, 6.1×10^{-5})

[a] Based on fitting the model to individuals' data, with optimization on K_T and K_{LN} (K_I fixed at 4.5×10^{-4}; other parameters fixed at values in Table 7 (no-overload model) of Kuempel *et al.* (2001)).
[b] Excludes one miner with a negative estimated K_T.
[c] Includes one miner without fibrosis.

coefficients are shown using two approaches: (1) optimizing the dosimetry model fit to the stratified data and (2) linear regression modeling with the clearance rate coefficients as the response (due to sample size restrictions on the strata). Results of multivariate optimization of K_T, K_I, and K_{LN} within strata based on smoking habits, race, or fibrosis categories are provided in Table 5. The largest changes in the optimal parameter values were in K_T and K_I, while relatively small changes in K_{LN} were necessary for optimal model fits within these strata. Since most miners were white (Caucasian) smokers, the parameter values obtained from fitting the model in this strata are similar to the whole group-fit parameter values. As the severity of fibrosis increases, K_T tends to decrease and K_I tends to increase. The group-fit parameter values in Table 5 are generally similar to the median of the individual-fit values of K_T and K_{LN} (Table 4). Although the number of parameters allowed to vary differed in the two approaches, the trends across groups are consistent. Results of a linear regression model with K_T as the response variable and smoking, race, and fibrosis as the predictor variables are given in Table 6. Additional models with predictor variables of height, weight, duration of retirement, or age at death, retirement, or start of work in mining were evaluated; however, none of these factors was a significant predictor of K_T (all P values <0.3). A log transform of K_T was also evaluated because of the observed skewness in the K_T distribution; however, that model was not used because the

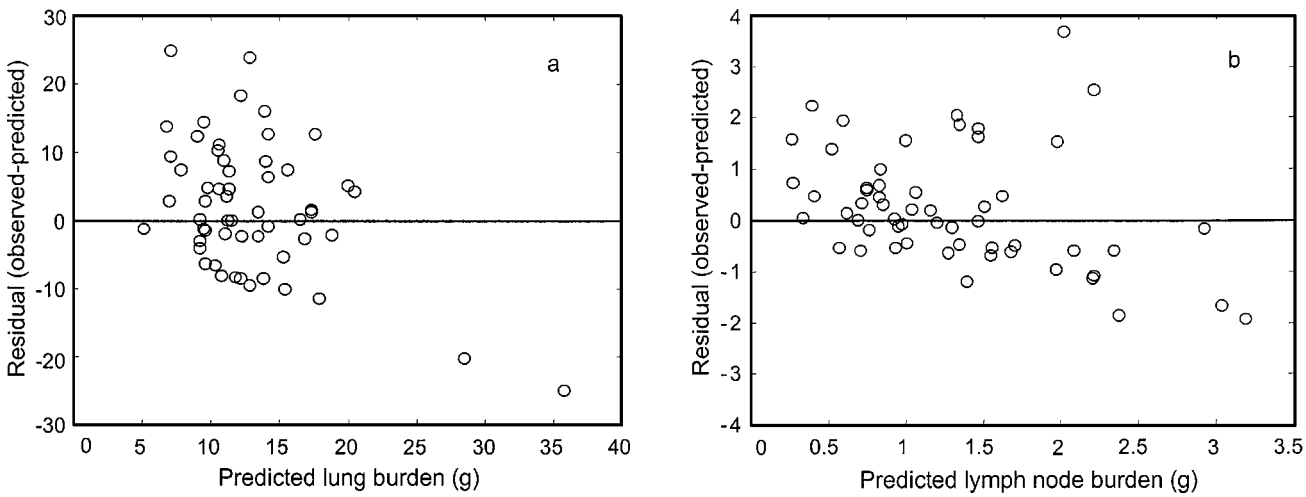

FIG. 1. Residuals for the total dust burden in the (a) lungs and (b) hilar lymph nodes, based on fitting the human lung dosimetry model to the group ($n = 57$).

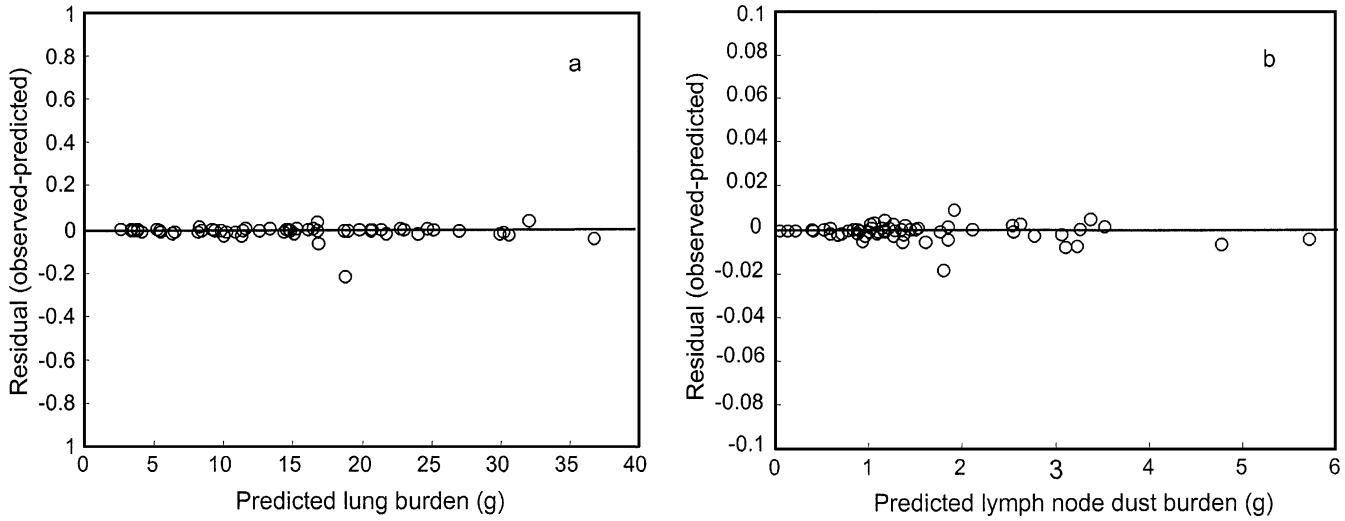

FIG. 2. Residuals for total dust burden in the (a) lungs and (b) hilar lymph nodes, based on fitting the human lung dosimetry model to individuals.

residuals of untransformed K_T model appeared approximately normal and because the untransformed K_T model provided better fit than the log-transformed model. The linear regression models with K_{LN} as the response variable revealed that none of the factors evaluated was a significant predictor (all P values <0.5); thus, K_{LN} was not adjusted based on the regression results.

In lieu of using constant parameter values for all individuals, the strata-specific parameter values for K_T, K_I, and K_{LN} were used in model fits to the whole group; likewise, the results of the regression analyses were used to predict K_T for each miner (based on that individual's data on smoking status, race, or fibrosis category) (Table 6). Table 7 provides a comparison of the dosimetry model fits using either these stratified parameter values, the group-fit values, or the individual-fit values. The models with the strata-specific parameter values provide modest improvement in fit to the data (up to 25% reduction in MSE) compared to the models with the group-fit parameter values. Two different whole group-fit values are shown, one with K_T based

TABLE 5
Optimized Clearance Parameters[a] in Stratified Groups, among Miners with Lymph Node Data

Group	K_T	K_I	K_{LN}
Whole group ($n = 57$)	9.36×10^{-4}	4.31×10^{-4}	1.05×10^{-5}
Smoking status			
Ever smoker ($n = 45$) or unknown ($n = 2$)	1.04×10^{-3}	4.53×10^{-4}	1.00×10^{-5}
Never smoker ($n = 10$)[b]	7.81×10^{-4}	5.20×10^{-4}	1.06×10^{-5}
Race			
Black ($n = 16$)	6.04×10^{-4}	5.58×10^{-4}	1.11×10^{-5}
White ($n = 40$) or other ($n = 1$)	1.07×10^{-3}	4.06×10^{-4}	1.01×10^{-5}
Race and smoking status			
White smoker ($n = 36$)	1.07×10^{-3}	3.69×10^{-4}	1.14×10^{-5}
Black smoker ($n = 11$)[b]	4.88×10^{-4}	5.48×10^{-4}	9.93×10^{-6}
White nonsmoker ($n = 5$)	7.44×10^{-4}	5.17×10^{-4}	9.78×10^{-6}
Black nonsmoker ($n = 5$)	1.10×10^{-4}	1.22×10^{-5}	2.95×10^{-5}
Fibrosis, highest severity classification at autopsy			
Macules ($n = 12$)	1.18×10^{-3}	3.31×10^{-4}	1.07×10^{-5}
Micronodules ($n = 18$)	1.09×10^{-3}	3.60×10^{-4}	1.13×10^{-5}
Macronodules ($n = 9$)	6.06×10^{-4}	5.56×10^{-4}	1.10×10^{-5}
Progressive massive fibrosis ($n = 18$)	8.42×10^{-4}	4.96×10^{-4}	1.05×10^{-5}

[a] Rate coefficients: K_T, alveolar-macrophage-mediated clearance of particles to the tracheobronchi; K_I, transfer of particles to interstitium; K_{LN}, translocation of particles to hilar lymph nodes.
[b] Model failed to converge at tolerance limits of 1×10^{-4}; did converge at 1×10^{-3}.

TABLE 6
Predictors of Estimated Individual Alveolar Clearance Rate Coefficient (K_T) in Linear Regression Model, among Miners with Lymph Node Data, $n = 56$[a]

Model[b]	Estimated coefficient	Standard error	P value
Intercept	0.00205	0.000559	<0.01
Fibrosis (comparison group: macules)[c]			
Micronodules	−0.000777	0.000462	0.09
Macronodules	−0.00135	0.000576	0.02
Progressive massive fibrosis	−0.000838	0.000481	0.09
Smoking status	0.000158	0.000462	0.70
Race	−0.000582	0.000395	0.10

[a] One miner with estimated negative K_T was omitted.
[b] $R^2 = 0.18$.
[c] Test for all disease categories (3 degrees of freedom), $P < 0.05$.

TABLE 7

Comparison of the Fit of the Three-Compartment Lung Dosimetry Model for Respirable Particle Retention and Clearance to Data for Whole Group, Individuals, and Small Groups (Strata), among Miners with Lymph Node Data ($n = 57$)

Model fitting approach	Mean squared error	Mean bias (g)	Predicted mean lung dust burden (g)[a]	Predicted mean lymph node dust burden (g)[b]
Whole group fit, using either				
Median individual K_T[c]	95.2	+0.99	14.2	1.41
Group optimization[d]	93.9	+2.04	13.2	1.38
Individual fit	0.00103	−0.00740	15.0	1.57
Stratified fit, by				
Smoking status[e]	94.4	+1.83	13.4	1.34
Race[e, f]	79.4	+1.46	13.7	1.44
Smoking and race[e]	70.1	+1.64	13.6	1.32
Fibrosis category[e]	80.0	+1.70	13.4	1.50
Fibrosis, smoking, and race[f, g]	74.6	+3.17	12.2	1.24

[a] Observed mean total dust lung burden, 15.0 g.
[b] Observed mean total dust lymph node burden, 1.57 g.
[c] $K_T = 8.8 \times 10^{-4}$; $K_I = 4.5 \times 10^{-4}$; $K_{LN} = 1.0 \times 10^{-5}$.
[d] $K_T = 9.36 \times 10^{-4}$; $K_I = 4.31 \times 10^{-4}$; $K_{LN} = 1.05 \times 10^{-5}$.
[e] Clearance parameter values based on optimization of K_T, K_I, and K_{LN} within indicated strata (Table 5).
[g] Clearance parameter value based on regression modeling of K_T (Table 6).
[f] Statistically significant improvement (at $P < 0.05$) of dosimetry model fit to the lung and lymph node burden data, compared to the whole group optimization model; based on approximate F tests (Jennrich and Ralston, 1979).

on the median of the individual estimated values of K_T (and default values for K_I and K_{LN}) and the other based on optimization of K_T, K_I, and K_{LN} in the whole group. These models provide similar fit to the data.

Prediction of Lung and Lymph Node Burdens

Using miners' individual exposure data and the group-fit parameter values, the predicted mean lung dust burden among all miners ($n = 131$) at autopsy is 12 g (5th and 95th percentiles, 5.8 and 20 g). The revised model with dose-dependent decline in interstitialization gave similar predictions: mean lung dust burden of 13 g (5th and 95th percentiles, 7.6 and 19 g).

Model predictions were also generated by allowing individual differences in clearance, for a given exposure. The estimated individual values of K_T and K_{LN} were used, along with a simulated exposure scenario of 2 mg/m^3 for 45 years and simulated age of death at 75 years. Predictions were made for lung and lymph node dust burdens among all miners with lymph node data ($n = 57$) and among these miners stratified by smoking habits, race, and fibrosis severity. Percentiles (median, 5th, and 95th) of the distributions are shown in Table 8. The end-of-life lung and lymph node dust burdens are predicted to be higher among never smokers and blacks than among smokers and whites with the same exposures. A trend is seen in increasing predicted lung and lymph node dust burdens among miners with increasing severity of fibrosis, at the same estimated lifetime dust exposure, except for PMF, where predicted lung and lymph node burdens are lower.

The total dust lung burden predicted over time (from the beginning of work in mining through retirement to the end of life) is shown in Fig. 3, utilizing information on the estimated interindividual variability in alveolar and lymph node clearance (K_T and K_{LN}). The working lifetime exposure to respirable coal mine dust was assumed to be 2 mg/m^3 for 45 years and ages at starting work, retirement, and death of 18, 63, and 75 years, respectively. The central curve represents the predicted lung dust burden over time among miners with K_T and K_{LN} at the median, while the 5th and 95th percentiles represent the predicted lung burdens among miners with K_T and K_{LN} values in the tails of those distributions.

DISCUSSION

The findings of this study confirm those of the earlier study (this journal; Kuempel *et al.*, 2001) with regard to the model structure and mean parameter values. This study also provides quantitative estimates of the interindividual variability in the clearance parameters and explores some of the factors that contribute to that variability.

Model Uncertainty and Sensitivity

A principal finding of both studies is the importance of a particle sequestration process (attributed to

TABLE 8
Predicted Particle Burdens in the Lungs and Hilar Lymph Nodes at Age 75, Assuming Exposure to Respirable Coal Mine Dust at 2 mg/m^3 for 45 Years, Based on Three-Compartment Human Lung Dosimetry Model[a]

Group	Predicted median lung burden (g) (5th, 95th percentiles)	Predicted median lymph node burden (g) (5th, 95th percentiles)
All miners ($n = 56$)[b]	10.73 (2.95, 25.9)	1.36 (0.26, 5.31)
Smoking habit		
Ever ($n = 44$), unknown ($n = 2$)	10.45 (2.81, 23.7)	1.24 (0.32, 4.78)
Never ($n = 10$)	13.74 (4.76, 27.4)	2.13 (0.36, 4.54)
Race		
Black ($n = 15$)	16.21 (5.71, 24.7)	2.39 (0.75, 6.44)
White ($n = 40$), other ($n = 1$)	10.04 (2.73, 26.8)	1.19 (0.22, 3.49)
Fibrosis category, highest severity classification at autopsy		
Macules ($n = 12$)[c]	6.64 (2.46, 29.1)	1.15 (0.14, 4.03)
Micronodules ($n = 18$)	10.18 (2.98, 20.5)	1.49 (0.45, 6.14)
Macronodules ($n = 8$)	14.19 (9.15, 19.4)	1.56 (0.70, 6.40)
Progressive massive fibrosis ($n = 18$)	10.06 (3.42, 26.1)	1.22 (0.64, 3.27)

[a] Among miners with lymph node burden data.
[b] Excludes one miner with estimated negative K_T.
[c] Includes one miner without fibrosis.

interstitialization) in determining the end-of-life lung particle burdens in these U.S. coal miners. These analyses also show that including dose-dependent decline in alveolar clearance (overloading) does not improve the model fit to the data. These findings differ from those observed in rodent models, where overloading is important kinetically in explaining the reduced clearance with increased lung dust burden. Some rodent models that include overloading but not sequestration have been extrapolated to predict lung particle burden in humans (e.g., Yu *et al*., 1991). That model structure would tend to underpredict the human lung burdens at lower exposures and overpredict them at higher exposures, compared to predictions from this human lung dosimetry model. Other rodent models include both overloading and sequestration processes (with alveolar sequestration and interstitialization defined separately), as well as several subcompartments representing cell populations in the lungs (Tran *et al*., 1997; Stöber *et al*., 1989); however, data on many of these parameter values are not generally available in humans. This human lung dosimetry model is similar in structure to those models, although the parameter values differ (including zero for the parameter governing overloading) and some subcompartments are combined (e.g., interstitialization and alveolar sequestration). The more prominent interstitialization/sequestration component of this human model, compared to the rodent models, is consistent with the findings of histological lung studies in humans (Nikula *et al*., 2001) and nonhuman primates (Nikula *et al*., 1997). A utility of developing and validating lung dosimetry models in both humans and rodents, where data are available, is that the interspecies differences in the kinetics of particle disposition in the lungs can be taken into account when predicting human internal dose from rodent data. In addition, the findings from this human lung dosimetry model, based on working lifetime dust exposures in coal miners, also provides information relevant to the current human lung dosimetry models (e.g., ICRP, 1994; NCRP, 1997).

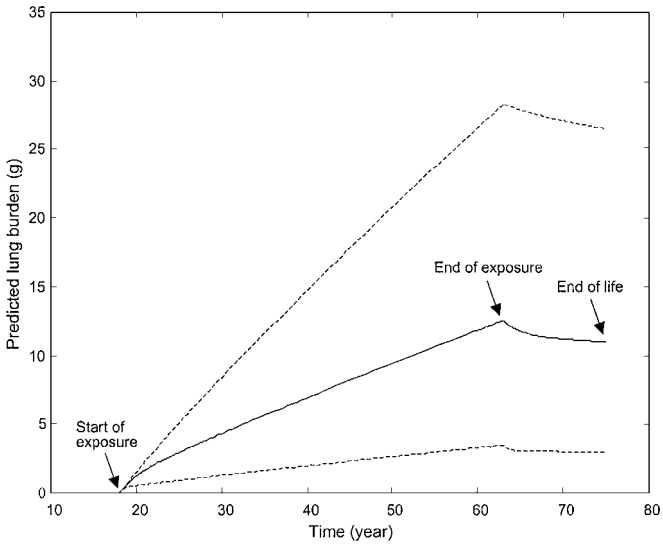

FIG. 3. Predicted mean total dust lung burden, assuming exposure to respirable coal mine dust at 2 mg/m^3 for 45 years, using the mean group-fit parameter values; confidence bounds were derived using the 5th and 95th percentiles of the distribution of estimated individual values of the alveolar-macrophage-mediated clearance rate coefficient.

We performed several evaluations of the variability and uncertainty in this human lung dosimetry model. First, we wanted to investigate whether there are reasonable adjustments in the model form or parameter values that would reduce the residual bias, which was observed as a tendency for the model to underpredict

the lung dust burdens among miners with lower cumulative exposure and to slightly overpredict the lung dust burdens among miners with higher cumulative exposures. One possible explanation for residual bias is an inadequate model structure. To reduce the residual bias in this model, it would be necessary to increase the predicted lung burden among miners with low exposures and decrease the predicted lung burdens among miners with high exposures. This would occur, for example, if the model allowed for faster macrophage-mediated clearance with increasing lung dose. However, it is assumed that alveolar macrophage number in the lungs would be at steady state in these miners with long-term exposures, and faster macrophage clearance with increasing dose is also contradictory to the rodent overloading data. Another possibility would be to decrease the particle interstitialization rate with increasing dose. A hypothesis for such a mechanism is that as the fibrotic response increases, in response to the increasing lung dose, the lung epithelium becomes less penetrable by particles in the alveolar lumen. We are not aware of any published findings to either support or refute this possible mechanism. However, a utility of a biologically based dosimetry model is to investigate possible mechanisms, as was done here, and to suggest areas for possible further experimental study. The findings from this revised model structure (i.e., to allow decline in the rate of interstitialization with increasing particle burden) show a 60% reduction in mean bias and a 15% reduction in the MSE. This improvement is similar to that obtained when the four outliers were removed, as described next.

A second possible explanation for the trend in the residuals it the influence of the four outliers on the model fit to the data. When the four miners with the highest estimated cumulative exposures (and relatively low lung dust burdens) were omitted and the original model was refit to the reduced data, an even greater reduction in mean bias was seen (92%). These findings demonstrate that the four outliers have a strong influence on the model fit to the data and contribute substantially to the observed trend in the lung burden residuals. Thus, revising the model to reduce interstitialization at high lung burdens does not seem justified, as it would serve mostly to explain just a few "outlying" data points. An investigation of those four miners' work histories revealed no apparent anomalies to support removing them from the data set, and it is possible that those miners had unusually low particle deposition or unusually high clearance. Their estimated alveolar clearance rate coefficients ($\sim 4 \times 10^{-3}$ each for the two outliers with lymph node data) were near the upper 95th percentile of the distribution, and their values were within a factor of two of the individuals' values reported in the Bailey *et al*. (1985) study of humans without dusty jobs. Thus, their data values are not implausible. Although their inclusion increases the mean bias, which generally is not desirable, it should be noted that the optimized model parameter values are similar whether or not the four outliers are included. In addition, the predicted lung burdens are similar using either the original model or the revised model (i.e., dose-dependent change in interstitialization rate).

These findings confirm that the current model structure is the best to describe these coal miner data. Further investigations using other data sets would provide an additional basis for evaluating possible alternative model structures. This could help reduce the uncertainty about the key kinetic mechanisms influencing long-term clearance and retention of respirable particle in human lungs. It is noteworthy that there was no evidence in these coal miner data of a lesser rate of particle interstitialization at lower exposures and lung burdens; instead, either a first-order or a dose-dependent decline provided the best fit to the data. These findings differ from those of some rodent studies and models, in which interstitialization increases after the lung burden exceeds a critical dose (i.e., at overloading) (Muhle *et al*., 1990; Tran *et al*., 1997), as discussed above.

A third possible explanation for the observed trend in the lung burden residuals is random errors in exposure estimation, leading to attenuation (dampening toward the null) of the exposure–response relationship (Fuller, 1987). The individual exposure intensities were estimated from mean values of job-specific measurements based on airborne samples taken in the late 1960s, after the time most of these miners had been working in the mines (Attfield and Morring, 1992a). Thus, the extent to which a miner's true exposure differs from the assigned average exposure will introduce error in the exposure estimation. It is worth noting that these exposure estimates also have been used in other studies of U.S. coal miners and have shown statistically significant exposure response for fibrosis (Attfield and Morring, 1992b; Kuempel *et al*., 1995). Yet, attenuation would also cause the exposure–dose relationship to spread out, such that at low exposures the estimated value would tend to be lower than the true value; and at high exposures, the estimated value would tend to be higher than the true value. Because a given amount of error would represent a larger proportion of the total exposure at low exposures than at high exposures, it is reasonable to expect that the influence of a constant error would be greater among miners with low exposures. An assumption of constant error variance appears to be consistent with the residuals, which do not show heteroscedasticity. Since the estimated exposure data are used in the dosimetry model to predict lung dust burdens, the effect of underestimating the true exposure would be to underestimate the lung burden (and likewise—overestimating exposure would overestimate lung burden). This explanation is consistent with the observed trend in lung burden residuals, in which the

lung dust burdens are generally underestimated among miners with lower exposure estimates, and to a lesser extent overestimated among miners with higher exposure estimates. In summary, the group fit parameter values in the human lung dosimetry model provide reasonable fit to these coal miner data. Attempts to reduce variability and bias, either by assigning group-specific parameter values or by modifying the three-compartment model structure, provided only modest improvements. This contrasts with the substantial improvement observed in the fit of the three-compartment model vs one-compartment model, as discussed in the preceding paper.

Interindividual Variability Evaluations

In the analyses to estimate interindividual variability in the model clearance parameters, both the variability and the bias in the group-fit model residuals are "explained" by fitting the model to the individuals' data. Although it is expected that fitting the model to each individual's data would provide a nearly perfect fit, it is important to find that the distribution of K_T values observed is biologically reasonable and consistent with other human data. This distribution of estimated individual K_T values is similar to the findings in a small study of long-term particle retention in humans (12 males with no history of lung disorder); the pulmonary clearance rate coefficient for 4-μm particles among individuals in that study varied from 3.5×10^{-5} to 1.8×10^{-3} (Bailey *et al*., 1985). Although we are not aware of any human data with which to compare the distribution of the estimated individual K_{LN} values, the spread in that distribution is similar to that for K_T. Yet, the mean and median K_{LN} values are approximately 1 order of magnitude lower than the lymph node clearance rate coefficient estimated in dogs by Cuddihy *et al*. (1979) (1×10^{-4} day^{-1}) and Snipes *et al*. (1983) (2×10^{-4} day^{-1}). This could be due to interspecies differences, or it could reflect a saturation of lymph node clearance in these miners (possibly resulting in a lower average lymph node clearance rate coefficient). Either way, this may be of minor concern with regard to the model predictions because the observed mean total dust lymph node burdens are a relatively small proportion of the retained dust (on average 1% of the observed mean total dust lung burdens). However, it may be of concern for disease prediction. For example, the reduced clearance of particles to the lymph nodes at high lung burdens has been suggested to be a factor in the development of fibrosis in humans (Seaton and Cherrie, 1998) and has also been reported in rats (Creutzenberg *et al*., 1990). Consistent with these findings is the observed leveling off of the lymph node dust burden among miners with higher lung dust burdens and the decline in the individuals' estimated K_{LN} values with increasing lung burden (results not shown). Possible dose-dependent changes in lymph node clearance is an area for further study and modeling efforts.

It is quite likely that the distributions of estimated individual K_T and K_{LN} values include variability and uncertainty that could be attributed to other model parameters, but this cannot be teased out of these data. For example, it is known that there is also variability in the deposition of particles in human lungs (ICRP, 1994). Although investigation of the variability in fractional deposition was not an objective of this study, it is an area that could be evaluated further to better describe the sources of variability in the estimated individual clearance rate coefficients. Also, both the deposition and the clearance rate coefficients are likely to change over time within individuals, due to factors such as aging and disease development (Bohning *et al*., 1982), but no data were available in this study to evaluate such intraindividual changes. An additional source of uncertainty in the distributions of estimated individual clearance rate coefficients is possible error in exposure estimation, as discussed above. Despite the possible sources of variability and uncertainty, the distributions of the clearance parameters estimated in this study are both biologically reasonable and consistent with existing data in the literature (Bailey *et al*., 1985). These findings are also quite similar to those obtained in testing the model on an independent data set of UK coal miners with more complete information on exposures to both respirable coal mine dust and respirable crystalline silica (Tran and Buchanan, 2000). Thus, the estimated distributions appear to be reasonable approximations of the variability in the model parameter values and in the resulting model predictions of lung and lymph node particle burdens. The analyses of between-group differences in model parameters show that approximately 25% of the residual variability in the whole-group fit model may be explained by interindividual differences in smoking habits, race, and fibrosis severity at the end of life. This indicates that most of the residual variability is due to other, unknown interindividual factors.

Predicted Lung and Lymph Node Dust Burdens

Because an objective of this study is to use these findings to predict lung burdens in other populations of workers exposed to respirable particles, it is of interest to provide estimates of both the mean and the distribution of predicted lung and lymph node dust burdens. It is useful to determine whether the distributions of predicted dust burdens vary among individuals with different characteristics, for which data may be available in other populations. The predicted median lung and lymph node dust burdens were found to differ among miners with differences in smoking habits, race, or fibrosis severity, although the within-group

variability is large. These strata-specific differences may represent biological differences and/or systematic errors in exposure estimation or other factors. The pattern seen with disease is consistent with biological expectations; i.e., miners with increasingly severe fibrosis also generally have increasing lung and lymph node particle burdens. Miners with greater deposition or slower clearance would be expected to retain more dust in the lungs at a given exposure and therefore would be more likely to develop disease. Alternatively, the disease process might have caused reduced clearance, resulting in increased lung dust retention. There is no way to determine the time course with these data, nor to distinguish between these scenarios; both are plausible hypotheses. The higher predicted mean lung dust burden in ever smokers is consistent with an earlier study (Kuempel *et al*., 1997), in which the observed total dust lung burden in ever smokers was statistically significantly lower than in never smokers with the same cumulative exposure. Since alveolar clearance has been shown to be reduced among smokers, we proposed in the earlier study that smokers may deposit less dust in the deep lungs due to mucus hypersecretion in the airways and increased cough. The higher predicted lung burdens among blacks is also consistent with the results of the earlier analyses; that is, blacks had statistically significantly higher lung dust burdens than whites at the same estimated cumulative exposure. Because physiological differences in the lungs due to race are relatively small (ICRP, 1994) compared to the differences observed here, other explanations are also possible. The observed pattern is consistent with a systematic underestimation of exposures among blacks, which could have occurred, for example, if they had worked in dustier conditions than whites with the same assigned job category. Since it is not known, based on this study alone, to what extent the strata-specific differences in clearance parameters represent biological or other factors, it appears to be most reasonable at this stage to use the group best-fit parameter values to predict the lung dust burden of another population and to also estimate the variability in these predictions. For miners with a given exposure history, there is a range of approximately an order of magnitude between the 5th and 95th percentiles of the distribution of the predicted lung burdens (not to be confused with 95% confidence intervals on the predicted mean lung burden, which would be narrower and of less utility for characterizing variability in the population). This finding suggests that estimates of the interindividual variability in the kinetics of particle retention in the lungs could have a large impact on the predicted amount of dust retained in the lungs. This variability should be considered when estimating doses or predicting disease risks in another population.

In interpreting the relevance of these findings to current working conditions, it is necessary to evaluate whether the exposures experienced by miners in this study are representative of current exposures. The mean cumulative exposure of 108 mg-year/m^3 (3 mg/m^3 for 36 years) of miners in this study is actually similar to the 90 mg-year/m^3 (2 mg/m^3 for 45 years) expected for miners exposed for a full working lifetime at the current standard (NIOSH, 1995). The current working lifetime exposures are within the range of these cumulative exposure data and therefore do not require extrapolation. This lung dosimetry model may also provide a biological basis for predicting lung burdens in workers with exposures to other dusts of similar size distribution, shape, solubility, and toxicity. However, the model has not been tested on other types of particles, and certain model revisions would be required (e.g., to account for solubility).

A clear advantage of using human data in developing and validating a dosimetry model is that it avoids the uncertainty of extrapolation across species. However, it is not known whether these findings would be relevant at lower exposures in humans, which may require extrapolation beyond the range of the data. When rodent bioassay data are used, it is also necessary to extrapolate from high to low exposures, in addition to the cross-species extrapolation. An advantage of a biologically based model, such as this human lung dosimetry model, is that the parameters can be experimentally determined, either in human or in animal studies. A biologically based model also provides an opportunity to evaluate subgroups of the population for factors that may influence particle retention and disease risk, as has been illustrated here. This information potentially can be used in assessing risk to sensitive subpopulations, who may have greater deposition or reduced clearance of particles due to environmental and/or genetic factors.

CONCLUSIONS

This study has examined the sources of variability and uncertainty in the lung and lymph node dust burdens predicted from a human lung dosimetry model, using the input data of respirable coal mine dust exposures in U.S. coal miners. Using a multivariate optimization approach, we have confirmed the model structure and mean parameter values described in the preceding paper. First-order sequestration/interstitialization and alveolar clearance (no overload) are the kinetic processes in this lung dosimetry model that best fit these coal miner data. Sources of variability and bias in the residuals have been identified and quantified. This has enabled prediction of lung and lymph node dust burdens for all miners in the study and for miners stratified by smoking habits, race, and severity of pulmonary fibrosis. This human lung dosimetry model has potential for use in estimating the lung burdens in workers exposed to other poorly soluble, respirable

particles of low toxicity for which human data are not available.

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