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Methodological issues of using observational human data in lung dosimetry models for particulates

Eileen D. Kuempel[a,*], Chi-Lang Tran[b], A. John Bailer[a,c], Randall J. Smith[a], David A. Dankovic[a], Leslie T. Stayner[a]

[a] *National Institute for Occupational Safety and Health, Cincinnati, OH, USA*
[b] *Institute for Occupational Medicine, Edinburgh, Scotland, UK*
[c] *Miami University, Oxford, OH, USA*

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Abstract

Introduction: The use of human data to calibrate and validate a physiologically based pharmacokinetic (PBPK) model has the clear advantage of pertaining to the species of interest, namely humans. A challenge in using these data is their often sparse, heterogeneous nature, which may require special methods. Approaches for evaluating sources of variability and uncertainty in a human lung dosimetry model are described in this study. *Methods:* A multivariate optimization procedure was used to fit a dosimetry model to data of 131 U.S. coal miners. These data include workplace exposures and end-of-life particle burdens in the lungs and hilar lymph nodes. Uncertainty in model structure was investigated by fitting various model forms for particle clearance and sequestration of particles in the lung interstitium. A sensitivity analysis was performed to determine which model parameters had the most influence on model output. Distributions of clearance parameters were estimated by fitting the model to each individual's data, and this information was used to predict inter-individual differences in lung particle burdens at given exposures. The influence of smoking history, race and pulmonary fibrosis on the individual's estimated clearance parameters was also evaluated. *Results:* The model structure that provided the best fit to these coal miner data includes a first-order interstitialization process and no dose-dependent decline in alveolar clearance. The parameter that had the largest influence on model output is fractional deposition. Race and fibrosis severity category were statistically significant predictors of individual's estimated alveolar clearance rate coefficients ($P < 0.03$ and

* Corresponding author. Tel.: +1-513-533-8363; fax: +1-513-533-8224.
E-mail address: ekuempel@cdc.gov (E.D. Kuempel).

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$P < 0.01$–0.06, respectively), but smoking history (ever, never) was not ($P < 0.4$). Adjustments for these group differences provided some improvement in the dosimetry model fit (up to 25% reduction in the mean squared error), although unexplained inter-individual differences made up the largest source of variability. Lung burdens were inversely associated with the miners' estimated clearance parameters, e.g. individuals with slower estimated clearance had higher observed lung burdens. *Conclusions:* The methods described in this study were used to examine issues of uncertainty in the model structure and variability of the miners' estimated clearance parameters. Estimated individual clearance had a large influence on predicted lung burden, which would also affect disease risk. These findings are useful for risk assessment, by providing estimates of the distribution of lung burdens expected under given exposure conditions.

Keywords: Lung dosimetry modeling; Risk assessment; Particles

1. Introduction

In the continuum from exposure to disease, a physiologically-based pharmacokinetic (PBPK) or dosimetry model describes the relationship between external exposure to a toxicant and the internal dose (Fig. 1). An advantage of a PBPK model is that the kinetic mechanisms influencing the uptake, metabolism, and elimination of a toxicant in the body can be quantitatively described. If these physiological processes are capacity-limited or become impaired (e.g. overloading of lung clearance), then using external exposure to estimate disease risk would result in less accurate or less reliable predictions compared to using internal dose. The biological mechanisms influencing the relationship between internal dose and disease are sometimes described using a pharmacodynamic (PD) model; however, data are usually inadequate for the development of PD models of toxins, particularly in humans. More often in risk assessment, a PBPK model developed in rodents is extrapolated to humans to estimate a human-equivalent internal dose. This is achieved by using the rodent PBPK model with human-appropriate parameters, either based on human data or scaled to humans (e.g. using an allometric relationship). Then, using the assumption of equivalent tissue sensitivity in both species, the dose–response relationship seen in rodents is assumed to apply to humans with equivalent estimated doses. If adequate human data are available, disease risk may be estimated using a statistical model to describe the exposure–response relationship, or a human PBPK model may be developed to estimate internal dose, which is then used to predict disease.

When adequate human data are available for developing a PBPK model, information can be gained on the kinetic mechanisms that may influence disease risk. These biologically-based models can provide improved estimates of toxicant dose, and the use of human data to develop these models avoids the uncertainty of extrapolation across species. Human-based PBPK models can also be used to assess the validity of models based on experimental animal data. Yet, the human population is inherently more variable, both in genetics and environmental conditions, than inbred rodent strains used in controlled experimental studies. Finally, a human-based PBPK model can be used to characterize inter-individual variability in kinetic parameters. However, there are challenges in using human observational (vs. experimental) data. These data are often sparse and heterogeneous, and they may have been collected originally for purposes other than PBPK modeling (and therefore may not be optimal for this purpose). Unlike experimental studies in animals in which conditions are carefully controlled, observational studies of toxicant exposures in humans often rely on estimates of exposures, and must characterize (rather than control) the traits of the study population (age, smoking habits, etc). In using these data, it is necessary to evaluate the influence of other factors, including confounders or effect-modifiers, which may influence the exposure–dose relationship. There is often uncertainty in the exposure estimates, as when an individual's true exposure differs from the assigned average exposure, or when historical reconstruction of exposures is required. In using

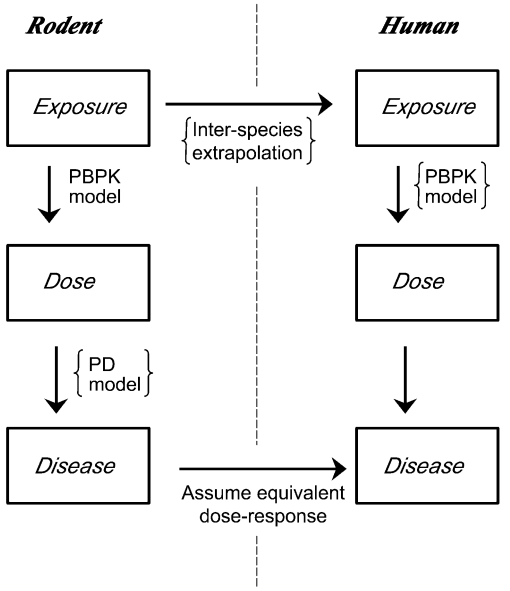

Fig. 1. Biomathematical modeling approaches for predicting disease risk in humans with occupational exposure to respirable particles. The first step is to estimate equivalent doses in humans and rodents. If sufficient exposure–dose data are available in humans (as for coal dust), then a PBPK (physiologically-based pharmacokinetic) model, describing the relationship between airborne exposure and lung particle burden, can be developed in humans. If sufficient data are available for rodents but not humans, then the rodent PBPK model is extrapolated to humans. The second step is to estimate the dose–response relationship. If adequate data are available in rodents, then a PD (pharmacodynamic) model may be developed (it is less likely that these data are available in humans). The default assumption in risk assessment, in the absence of other information, is that tissue sensitivity is equivalent in both species, meaning that the disease response will be the same at equivalent doses.

human data in PBPK modeling, methods are needed to quantitatively evaluate uncertainty and variability in the data and model output.

Issues of uncertainty and variability should be addressed for all models. This may be problematic in PBPK models using observational human data (e.g. epidemiological) because these models are relatively uncommon, and standard techniques for dealing with these issues have not yet been developed. Uncertainty and variability, as they relate to PBPK modeling, have been defined by Clewell and Andersen (1996). Uncertainty is 'the possible error in estimating the true value of a parameter for a representative (average) animal or human.' Variability refers to the 'inter-individual differences' that represent biological variation in a population. Although uncertainty can be reduced by additional information or experimental study, variability cannot be reduced but can be characterized or quantified. The most important source of variability in PBPK modeling is often the natural distribution of a characteristic in a population (i.e. differences among individuals), but another component is intra-individual variability (i.e. differences in the individual, such as changes in a physiological attribute over time, including possible changes related to toxicant exposure).

In this study, a PBPK or dosimetry model is described for the clearance and retention of respirable particles in the lungs of humans. Methods are described for evaluating the sources of uncertainty in the model structure and mean parameter values, and for estimating the variability in key parameters amongst individuals and their influence on model predictions.

2. Methods

The model development began by describing the lung as a single compartment with an expression for the overloading, or dose-dependent decline, of alveolar clearance (Fig. 2a); this structure was based on existing data and models in rodents (e.g., Bellmann et al., 1991; Yu et al., 1991). When the one-compartment lung model was shown not to provide adequate fit to the human data, the model was expanded to include interstitial and lung associated (hilar) lymph node compartments.

This three-compartment model better reflects the biological structure of the human lungs by including the major sites for particle disposition in the pulmonary or gas-exchange region (Fig. 2b). The model describes the first-order kinetics of particle mass transfer (thus organ volumes do not enter into the model). The kinetic processes include: (1) alveolar macrophage-mediated clearance from the alveoli to the tracheobronchial

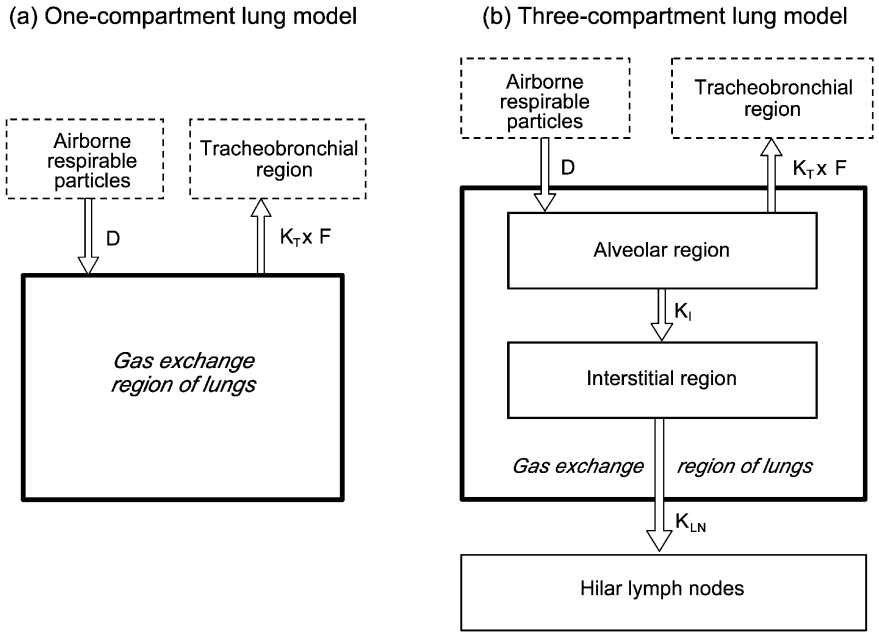

Fig. 2. Comparison of (a) one-compartment and (b) three-compartment human lung dosimetry models. The parameter D is the dose rate of particles deposited in the alveolar or gas-exchange region of the lungs. The first-order rate coefficients include alveolar-macrophage mediated clearance of particles to the tracheobronchial region (K_T, units of d^{-1}), transfer of particles into the pulmonary interstitium (K_I, d^{-1}), and translocation of particles to the hilar lymph nodes, (K_{LN}, d^{-1}); and F (unitless) is an exponential decay function that describes overloading, i.e., dose-dependent decline in K_T.

region, where particles may be cleared from the body by cough or by being swallowed into the gastrointestinal tract; (2) transfer of particles that escape phagocytosis and clearance by macrophages into the lung interstitium, where they are essentially sequestered; and (3) very slow translocation of particles from the interstitium to the lung-associated (hilar) lymph nodes (via engulfment of particles by pulmonary lymphatic endothelial cells or by interstitial macrophages).

The model was calibrated using data of working lifetime exposures to respirable coal mine dust and end-of-life lung and lymph node particle (dust) burdens in 131 U.S. coal miners. Miners' exposures were estimated from individual work histories and job-specific measurements of mean airborne respirable dust concentrations (Attfield and Morring, 1992). These miners are a subset of a larger pathology study of approximately 700 miners (Vallyathan et al., 1996), and represent all of the miners with lung dust burden and work history data. Of the 131 miners, 57 miners also had data on the dust burden in the hilar lymph nodes. The data used in this study are the total dust burdens, which include various types of particles, primarily coal, but also silica and other mineral dusts (Kuempel et al., 1997). The time course of the individual miner's estimated exposures to respirable coal mine dust provide the input for the dosimetry model, and the model output includes the predicted lung and lymph node dust burdens for individuals or groups at any point in time, during exposure and after leaving work as coal miners.

Initial model parameters were based on data from the literature in humans (Bailey et al., 1985; ICRP, 1994) and animals (Bellmann et al., 1991; Tran et al., 1997). The parameter estimation and model fit to the data was performed using a multivariate optimization procedure in Matlab (Matlab, 1999; Kuempel et al., 2000). Least squares was used to ascertain model fit to the data by determining the parameter values that minimize the mean squared error (MSE), which is the mean of the squared differences in observed and model-predicted dust burdens (then summed

for dust burdens in the lungs and hilar lymph nodes). The mean bias of the model was also calculated as the mean difference in the observed and predicted values. Uncertainty in model structure was investigated by fitting various model forms with plausible mathematical expressions for particle clearance and retention in the lungs. These included descriptions for the volumetric overloading of alveolar-macrophage mediated particle clearance, as observed in rodent studies (Morrow, 1988; Bellmann et al., 1991; Tran et al., 1997), and the sequestration of particles in the lung interstitium, which is consistent with observations from studies in non-human primates and humans [Nikula et al., 1997, 2001 (in press)]. A sensitivity analysis was performed to determine the influence of small changes ($\pm 10\%$) in key parameters on the model output. This was performed on one parameter at a time, while holding all other parameters constant. The model input consisted of the individuals' exposure histories, and the model output corresponded to the predicted lung and lymph node dust burdens of each miner at the end of life. The changes in the predicted mean dust burdens were computed.

The distributions of individuals' parameter values for alveolar-macrophage mediated clearance of particles to the tracheobronchial region (K_T, units of d^{-1}) and translocation of particles from the lung interstitium to the hilar lymph nodes (K_{LN}, d^{-1}) were estimated by fitting the model to each miner's data. Other parameters in the model include a rate coefficient for particle transfer to the interstitium (K_I, d^{-1}) and fractional deposition (F_D, unitless), which is the particle mass fraction (by aerodynamic diameter) that deposits into the alveolar region of the lungs. The value for K_I was empirically determined using these data, and the value for F_D is based on human data available in the literature (ICRP, 1994). These model parameters have been described in detail previously (Kuempel, 2000). The influence of certain factors (smoking history, race and severity of pulmonary fibrosis) on individual estimates of K_T was examined by linear regression modeling, with K_T as the response variable and these factors as covariates. The information on inter-individual variability in alveolar clearance was used to predict the distributions of lung and lymph node particle burdens for miners with a given exposure history, but with differences in clearance.

3. Results

The model structure that provided the best fit to the coal miner data includes three compartments with first-order processes for alveolar clearance of particles, interstitialization, and translocation to lymph nodes (Table 1). The inclusion of the interstitial and lymph node compartments was shown to significantly improve the fit of the model to the data compared to a one-compartment lung model ($P < 0.0001$, based on an F-test). In both the one- and three-compartment models, first-order clearance provided significantly better fit than the models with overloading, i.e. dose-dependent decline, of alveolar clearance. These improvements in model fit are also seen in the three- to fourfold reduction in the MSE (Table 1). The predicted end-of-life particle

Table 1
Comparison of fit of one- and three-compartment models to data, in miners with hilar lymph node data ($n = 57$)

Model	MSE[a]	Mean bias (g)
One-compartment (lung)		
First-order clearance	278	+16.0
Overloading of alveolar clearance	832	−17.0
Three-compartment (alveolar, interstitial and hilar lymph node compartments)		
First-order clearance	94	+0.99
Overload of alveolar clearance	358	−7.2

[a] Mean squared error.

Table 2
Observed and predicted mean total dust lung burden (g) with various clearance assumptions

	Whole cohort ($n = 131$)[a]	Ever smokers ($n = 91$)	Never smokers ($n = 24$)
Total deposited[b]	43.1	42.6	50.8
Observed[c]	13.8	13.2	16.4
Predicted by:			
1-compartment model, no overload	0.6	0.4	0.7
3-compartment model, with interstitialization but no overload	12.8	12.6	14.6

[a] Smoking history was unknown for 16 miners.
[b] Total working lifetime particle deposition in alveolar region predicted from three-compartment model and miners' exposure histories.
[c] Observed particle burden in lungs at autopsy.

burden in the lungs of these miners differs considerably in these models (Table 2). The total mass of particles predicted to be deposited in the lungs of these miners is 40–50 g on average, amongst miners in the whole cohort, ever smokers, or never smokers; while the amount retained (i.e. not cleared) in the lungs of these miners at autopsy was 13–16 g. The one-compartment, first-order clearance model predicts that less than 1 g of dust would remain in these miners' lungs. The three-compartment model provides much closer predictions (approx. 90% of the observed mean lung burdens), although it still tends to underestimate the burden. Refinements to the model are being investigated in further analyses.

A sensitivity analysis shows that F_D is the parameter which has the largest influence on model output for lung dust burden (Fig. 3); a 10% change in the value of F_D results in a 9–10% change in the predicted lung dust burden (and an

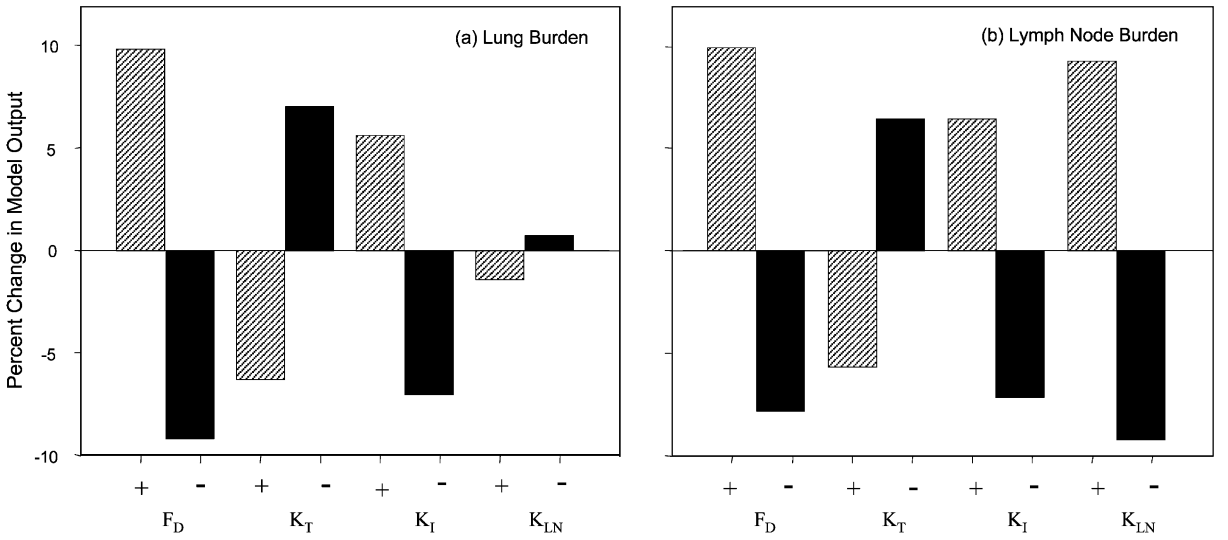

Fig. 3. Sensitivity of the human three-compartment lung model to small changes in key parameters. This is represented as the percentage change in the model output for either (a) lung or (b) lymph node particle burden following a 10% change (either increased +, or decreased −) in a particular parameter whilst holding all other parameters constant (among miners with both lung and hilar lymph node burden data, $n = 57$). The parameter F_D equals fractional deposition. The first-order rate coefficients are: K_T, alveolar macrophage mediated clearance to the tracheobronchial region; K_I, transfer of particles into the interstitium; and K_{LN}, translocation of particles into the lung-associated (hilar) lymph nodes.

Table 3
Clearance parameter values, in model fit to group or individual data[a]

Parameter	Group-fit value[b]	Individual-fit values [median, (5th, 95th percentiles)]
Alveolar-macrophage mediated (K_T)	1×10^{-3}	8.81×10^{-4} (1.08×10^{-4}, 4.44×10^{-3})
Interstitialization (K_I)	4.5×10^{-4}	4.54×10^{-4} [c]
Transfer to hilar lymph nodes (K_{LN})	1×10^{-5}	1.16×10^{-5} (2.84×10^{-6}, 3.97×10^{-5})

[a] Among miners with hilar lymph node data ($n = 57$).
[b] Multivariate (three-parameter) optimization of model fit to group data, using Matlab (1999).
[c] Constant (i.e., two-parameter optimization of model fit to the individuals' data).

8–9% change in predicted lymph node dust burden). The model is less sensitive to small changes in alveolar clearance and interstitialization parameters; a 10% change in K_T and K_I results in a 5–7% change in the predicted lung and lymph dust burdens. The model output for lung dust burden is fairly robust to changes in the lymph node clearance rate coefficient; a 10% change in K_{LN} leads to an approximately 1% change in lung burden. Changes in K_{LN} have greater influence on the model output for lymph node dust burden (9–10% change).

Two separate, parameter estimation approaches provided similar best-fitting values for the clearance rate coefficients (Table 3). The parameter estimates obtained from fitting the model to the group data by multivariate optimization of K_T, K_I and K_{LN} are consistent with those obtained by fitting the model to the individuals' data (optimizing only on K_T and K_{LN} to avoid over-parameterization). The latter approach also provides information on the distributions of estimated clearance parameter values among individuals, which are described by the 5th, 50th and 95th percentiles (Table 3).

Some of the inter-individual variability in the clearance rate coefficients was associated with certain factors, i.e. smoking status, race and severity of fibrosis. Table 4 shows the results of linear regression modeling of K_T. In each model,

Table 4
Predictors of estimated individual alveolar clearance rate coefficient (K_T) in linear regression models, among miners with hilar lymph node data ($n = 57$)

Model	Estimated coefficient	Standard error	*P*-value
Smoking status			
Intercept (never smoker)	0.00102	0.000611	0.02
Smoking status (ever/unknown)	0.000352	0.000454	0.4
Race			
Intercept (white/other)	0.00153	0.000196	0.0001
Race (black)	−0.000828	0.000378	0.03
Pulmonary fibrosis severity, highest category[a,b]			
Intercept (macules)	0.00215	0.000357	0.0001
Micronodules	−0.000871	0.000461	0.06
Macronodules	−0.00151	0.000564	0.01
PMF[c]	−0.00106	0.000461	0.03

[a] Fibrosis classification described in Vallyathan et al. (1996).
[b] Test for all fibrosis categories, compared to macule group: $P = 0.03$.
[c] Progressive massive fibrosis.

Table 5
Comparison of three-compartment model fits to stratified data[a]

Group	MSE[b]	% reduction in MSE
Whole group	95	NA
Strata		
Smoking status	91	4
Race	79	17
Smoking and race	70	26
Fibrosis category	80	16
Smoking, race and fibrosis category	75	21

[a] Miners with hilar lymph node data ($n = 57$).
[b] Mean squared error.

the estimated coefficient for the intercept represents the value of K_T for the referent group (i.e. never smoker, white/other or macules). The coefficients for the comparison groups represent the adjustment in K_T for a given group (calculated by addition of the coefficients for that group and the intercept). These results indicate that K_T is greater (i.e. faster clearance) among miners with less severe fibrosis, whites and smokers. Although race ($P < 0.03$) and severity of fibrosis at the time of death ($P < 0.01$–0.06, by fibrosis category) are statistically significant predictors of K_T, smoking history is not ($P < 0.4$). The model combining all of these covariates was statistically significant ($P = 0.04$), but most variables were no longer individually significant. Other factors (e.g. height, weight, or age at starting work in mining, retirement, or death) were also evaluated and found not to be predictors of K_T (all P-values > 0.3). Linear regression models were evaluated for K_{LN}, but that rate coefficient was found not to be predicted by any of these factors (all P-values > 0.5). This result, and the sensitivity analysis result that lung burden predictions were relatively unaffected by K_{LN}, are the reasons that only the value of K_T was adjusted in the dosimetry model for miners with differences in race, smoking status, and fibrosis severity. When K_T was adjusted for these group differences, improvement in the fit of the dosimetry model to the data was seen as a 4–26% reduction in the MSE (Table 5).

Table 6 shows the predicted lung dust burdens when the model incorporates the estimated differences in miners' rates of particle clearance from the lungs. Lung burden predictions are provided for various ages and exposure conditions. Estimated clearance rates of slow, median, or fast are represented by the 5th, 50th and 95th percentiles of the distribution of K_T. For miners

Table 6
Predicted lung particle burdens in the lungs, by age and lung clearance rate, assuming exposure to respirable coal mine dust at 1 or 2 mg/m^3 [a,b,c]

Age (years)	Slow clearance	Median clearance	Fast clearance
Mean exposure concentration: 1 mg / m^3			
30	4.2	2.2	0.64
45	8.9	4.1	1.2
63	14	6.3	1.8
78	13	5.4	1.5
Mean exposure concentration: 2 mg / m^3			
30	8.4	4.3	1.3
45	18	8.2	2.3
63	28	12	3.5
78	26	11	2.9

[a] Based on fitting three-compartment human lung dosimetry model to individuals' data (among miners with hilar lymph node burden data).
[b] Assuming individuals begin work in coal mining at age 18, work 45 years, retire at age 63, and die at age 78.
[c] The alveolar macrophage-mediated clearance rate coefficient (K_T) is assumed to equal either the 5th, 50th, or 95th percentile of the distribution of estimated individual values, which corresponds to the designation of slow, median, and fast clearance, respectively.

with 12 years of exposure (starting at age 18 years) to a mean concentration of 1 mg/m^3 respirable coal mine dust, the predicted lung dust burden is 2.2 g for miners with the median estimated clearance rate, and it is 0.64 or 4.2 g, respectively, for miners with fast or slow estimated clearance. As seen by comparing lung burdens at ages 63 and 78, most of the particle mass in the miners' lungs at retirement age is predicted to remain in the lungs after exposure ends.

4. Discussion

The findings from this study show that a rodent-based model with overloading of alveolar clearance is inadequate for predicting the end-of-life lung and lymph node dust burdens in these miners. That model overpredicts miners' lung dust burdens; and a simple, one-compartment model (with first-order clearance) underpredicts miners' lung burdens (Tables 1 and 2). A three-compartment human lung dosimetry model (Fig. 2) provides a significantly improved fit to these data. An implication of these findings is that a PBPK model which does not account for an interstitialization or sequestration process would be inadequate for predicting the lung dust burdens in humans with occupational exposures to poorly soluble, respirable particles such as coal dust. The accurate estimation of retained particle burden in the lungs is important because the internal dose is associated with disease development. Lung dust burden was shown to be a stronger predictor of the pulmonary fibrosis in these coal miners than was cumulative exposure to respirable coalmine dust (Kuempel et al., 1997).

When the three-compartment model was fitted to the individuals' data, virtually all of the variability and bias was eliminated; that is, the predicted lung and lymph node dust burdens were virtually identical to the observed values (Kuempel et al., 2000). This is not unexpected, given that the model is being custom-fit to each miner; although it does indicate that the model is flexible enough to accommodate the inter-individual differences. It is important to compare the distributions of clearance parameters estimated using this approach (Table 3) with other data in the literature to determine whether biologically unreasonable parameter values were required to fit each miner's data. The findings show that the distribution of the individual estimated alveolar clearance rate coefficient is, in fact, consistent with other data in the literature (Bailey et al., 1985; Philipson et al., 1985). Although we are not aware of any data in the literature on a rate coefficient for particle interstitialization in humans, the model predictions are qualitatively consistent with findings of the observed pattern of particle interstitialization in the lungs of humans and non-human primates (Nikula et al., 1997, 2001 — in press). In addition, the distribution of estimated values for K_{LN} is similar to that for K_T.

An implication of these distributions of estimated clearance parameters in humans is that for any given exposure to respirable, poorly soluble particles, there will be substantial differences in the retained dose of particles in the lungs. This, in turn, implies that an individual's susceptibility to developing occupational lung disease from a given exposure is determined in part by their individual clearance kinetics. Individual differences in particle deposition, which have been observed in humans (ICRP, 1994), will also influence lung burdens. In this human lung dosimetry model, the deposition rate was fixed at an average value in humans based on the aerodynamic particle size for respirable coal mine dust and average breathing rates in workers (ICRP, 1994; Kuempel, 2000). The sensitivity analysis showed that the model-predicted lung dust burden was most sensitive to changes in F_D (Fig. 3), indicating that additional analyses are needed, which incorporate inter-individual variability in this parameter. Thus, the distributions of estimated clearance parameters are likely to include variability in deposition and other factors, including possible misclassification errors in the estimated exposures. Despite this uncertainty, the distribution of estimated alveolar clearance parameters is consistent with other human data, as mentioned previously. In the dosimetry model with the alveolar clearance parameter adjusted by smoking habit, race, and/or fibrosis severity (Table 4), the reduced variability and improved model fit (Table 5) sug-

gests that these factors are associated with particle clearance from the lungs. The lower K_T values amongst miners with more severe fibrosis is biologically reasonable because it indicates that reduced lung clearance may be either caused by or lead to lung disease. The higher K_T among smokers is inconsistent with other data (ICRP, 1994), but it was not statistically significant, indicating that smoking habits had little influence on estimated clearance in these miners. The lower K_T values among blacks might reflect a systematic underestimation of exposures, rather than an inherent biological difference influencing lung clearance. Most of the variability in estimated alveolar clearance, however, was not associated with these factors but with other, unexplained inter-individual differences. Although the sources of the variability were not completely identified, the methods in this study enabled quantitative estimation of the distribution of individual alveolar clearance parameters. This information was then used to estimate the differences in lung burdens expected among miners with given lifetime exposure scenarios (Table 6). This approach of determining the distribution of an internal dose measure (lung dust burden) is useful for risk assessment because it enables estimation of disease risk over a range of biologically plausible doses in addition to the mean or point estimate of dose.

Some of these inter-individual differences in the estimated clearance parameters could include errors in exposures, as would occur whenever an individual's true exposure differs from the assigned average value. The influence of measurement error in PBPK modeling of human data is an area that has received little attention. An effect of independent additive errors in assigning exposure is that among individuals assigned low exposures, the true exposures are likely to be greater, and our model would tend to underpredict the observed dose. The converse would occur for miners assigned high exposures where the tendency is to overpredict the exposure and the observed dose. This scenario is consistent with earlier analyses that showed a trend of underprediction of lung burdens among most miners with low cumulative exposure (i.e. sum of products of intensity and duration for each individual) and overprediction of lung burdens among some miners with high cumulative exposures (Kuempel, 2000). However, we hasten to acknowledge that there is uncertainty about the structure of the exposure errors, and the influence of the actual error structure may be more complicated. This issue is discussed here to illustrate a potentially important source of uncertainty in using human data in PBPK modeling, which warrants further investigation.

5. Conclusion

The methods in this study helped to address uncertainty in the structure of a human lung dosimetry model developed using data of U.S. coal miners, and provided an approach for estimating inter-individual variability in miners' lung clearance parameters. The findings suggest that individual differences in clearance strongly influence the retained particle burdens, which may in turn influence disease risk. These findings are useful for risk assessment, by providing estimates of the distribution of lung particle burdens expected under given exposure conditions.

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