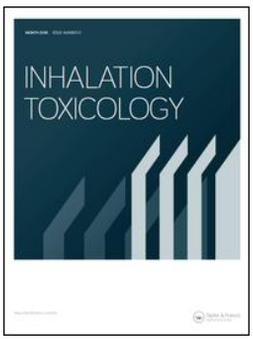

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EVALUATION OF PARTICLE CLEARANCE AND RETENTION KINETICS IN THE LUNGS OF U.S. COAL MINERS

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Rodent studies are frequently used to assess risk in humans, yet it is not known whether the overloading of lung clearance, as observed in rodents, occurs in humans, or whether overloading is related to particle-related lung diseases in humans. The objective of this study is to develop a biologically based mathematical model to describe the retention and clearance of respirable coal mine dust in the lungs of humans. A human dosimetric lung model was developed that includes alveolar, interstitial, and hilar lymph-node compartments. The model describes the particle mass transfer kinetics among these compartments and clearance via the tracheobronchi. The model was calibrated using data in U.S. coal miners, including individual working lifetime exposure histories and lung and lymph-node particle burdens. The model fit to the human data was evaluated using a least-squared error criterion. The end-of-life lung dust burdens of all coal miners in this study were substantially greater than expected from a simple, linear first-order model with effective clearance, yet their lung and lymph-node dust burdens were lower than expected from the rodent-based overload model, particularly at higher exposures. The best fitting model included a predominant first-order interstitial compartment, in which the particles are essentially sequestered (with very slow clearance to the lymph nodes), and a first-order alveolar clearance compartment with

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either no dose-dependent decline (overloading) or much less than expected from the rodent studies. These findings are consistent with the findings from magnetopneumography studies of clearance in retired miners and from studies of particle retention patterns in rodents and primates. This human dosimetric lung model is useful for evaluating the kinetic differences of particle retention in humans and rodents, and for evaluating the lung doses in humans given different exposure scenarios.

Many studies on inhaled particle toxicity have been conducted in rodents, but questions remain on whether the observed disease responses are applicable to humans. Although the overloading of macrophage-mediated particle clearance (Morrow, 1988) has been observed in rodents (Bellmann et al., 1991), overloading has not been demonstrated in humans. A first step in assessing the risk of particle-related disease in humans from the rodent studies is to estimate equivalent doses in animals and humans. Dosimetric models, which can explicitly incorporate experimental and physiological data, describe the quantitative relationship between external exposure to a substance and the internal dose and can assist with the estimation of equivalent doses across species.

In this article, we describe a human dosimetry lung model we developed and calibrated using data of U.S. coal miners. We used this model to investigate the kinetics of particle clearance and retention, and overloading of alveolar clearance, in these miners.

The data used for this study are from an autopsy data set of approximately 700 U.S. coal miners, who died in 1957–1971, and for whom pathology and radiographic disease categories have been described previously (Vallyathan et al., 1996). The 131 miners included in this study had data on mass of particles in the lungs, and 57 of these miners also had data on mass of particles in the hilar lymph nodes. Information on miners' work and exposure histories was used to predict the miners' end-of-life lung and lymph-node dust burdens using this model. Results are reported here for miners with both lung and lymph-node dust burden data.

A dosimetric model was developed to describe the kinetics of particle clearance and retention in the gas-exchange region of human lungs. The structure of this model was based on inclusion of the major sites of particle deposition, clearance, and retention in the deep lungs, and on parsimony given the available data. The model structure includes alveolar, interstitial, and hilar lymph-node compartments (Figure 1), and the model describes the particle mass transfer among these compartments and clearance via the tracheobronchi. 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). A human-equivalent expression for nonlinear dose-dependent decline in the first-order alveolar clearance rate coefficient was derived using extrapolation from rodent data and the volumetric hypothesis for overloading (Morrow, 1988). The data used to calibrate the model include individual working lifetime exposure histories and end-of life particle burdens in the lungs and hilar lymph nodes.

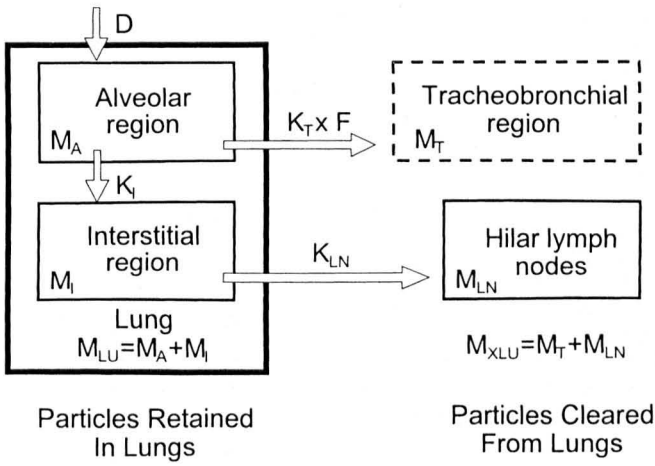

FIGURE 1. Illustration of three-compartment human lung dosimetry model for particle clearance and retention. Key: D, dose rate of deposited particles; M, mass of dust in the alveoli (A), interstitium (I), lungs (LU), or hilar lymph nodes (LN); K_T, first-order alveolar clearance rate coefficient; K_I, first-order interstitial transfer rate coefficient; F, dose-dependent modifying factor; K_{LN}, first-order lymph-node clearance rate coefficient; M_T, mass of dust in the tracheobronchi; M_{XLU}, mass of dust cleared from lungs. From Kuempel (2000), by courtesy of Marcel Dekker, Inc.

Optimization of the model fit to the data was performed by determining the parameter values that minimized the mean squared error (Kuempel, 2000), first using a systematic grid search approach in ACSL (1997) and then using an automated, multivariate approach (Tran et al., 1999) in MATLAB (1999). Using the latter approach, the model was also fitted to individual miners to generate distributions of estimated parameter values for alveolar macrophage-mediated clearance to the tracheobronchi (K_T) and particle transfer to the hilar lymph nodes (K_{LN}).

The end-of-life lung dust burdens of all coal miners in this study are substantially greater than expected from a simple, first-order clearance model (Table 1). The mean retained total dust lung burden represents approximately 4% of the mean cumulative airborne respirable coal mine dust exposure, and one-third of the total dust predicted to have been deposited in the lungs (Table 1).

The model that best describes the end-of-life lung and lymph-node dust burdens in these miners includes a predominant first-order interstitial compartment, in which the particles are essentially sequestered (with slow clearance to the lymph nodes), and a first-order alveolar macrophage-mediated clearance compartment, with either no dose-dependent decline in that rate coefficient or much less than expected from the rodent studies (Table 2). The estimated values of the clearance rate coefficients, using either the grid search method (ACSL) or numerical optimization (MATLAB), are quite similar (Table 3).

The distribution of estimated individual values of the alveolar clearance rate coefficient (K_T) has a median of 8.8×10^{-4} (5th and 95th percentiles of

TABLE 1. Measured Mean Airborne Dust Exposure and Measured and Predicted Mean Total Dust Lung Burden, with Various Clearance Assumptions ($n = 57$ Miners with Lymph-Node Data)

	Working lifetime airborne dust exposure (g)[a]	Lung dust burden (g)	Hilar lymph-node dust burden (g)
Measured	380	15.0	1.57
Predicted, assuming[b]:			
No alveolar clearance	[c]	41.7	3.60
Simple, first-order clearance	[c]	0.58	0
First-order alveolar clearance and interstitialization/sequestration	[c]	14.2	1.41

[a]Calculated from mean cumulative exposure of 112.7 mg-yr/m^3, and assuming 13.5 m^3 volume of air inhaled per 8-h day (ICRP, 1994), and 250 days/yr exposure.
[b]Alveolar fractional deposition of 0.12 (ICRP, 1994).
[c]Not applicable.

TABLE 2. Comparison of Fit of One- and Three-Compartment Models to Data, by Amount of Alveolar Clearance Overloading (Miners with Lymph-Node Data, $n = 57$)

Model	MSE	Bias (g)
One-compartment (lung)		
No overload	278	+16.0
50% Overload	362	+14.0
90% Overload	832	−17.0
Three-compartment (alveolar, interstitial/sequestration, hilar lymph nodes)		
No overload	94	+0.99
50% Overload	116	+0.40
90% Overload	358	−7.2

TABLE 3. Best-Fitting Clearance Parameter Values, by Optimization Approach (Group Fit to Miners with Lymph-Node Data, $n = 57$)

Parameter	Systematic grid search (ACSL)	Automated, numeric integration (MATLAB)
Alveolar-macrophage mediated (K_T)	1×10^{-3}	9.68×10^{-4}
Interstitialization (K_I)	4.7×10^{-4}	4.54×10^{-4}
Transfer to hilar lymph nodes (K_{LN})	1×10^{-5}	1.04×10^{-5}

1.1×10^{-4} and 4.4×10^{-3}); the distribution of estimated individual values of the coefficient for particle transfer to the hilar lymph nodes has a median of 1.2×10^{-5} (5th and 95th percentiles of 2.8×10^{-6} and 4.0×10^{-5}). Among miners with different characteristics for smoking, disease, and race, the median estimated K_T varies by a factor of approximately four (Table 4), but the median estimated K_{LN} is similar across these groups (results not shown).

TABLE 4. Estimated Alveolar Clearance Rate Coefficient, by Characteristic, among Miners with Lymph-Node Data ($n = 57$)

Characteristic	Median K_T (day^{-1})	5th, 95th Percentiles
Smoking habit		
Ever ($n = 45$)	0.0020	0.00012, 0.0044
Never ($n = 10$), unknown ($n = 2$)	0.00051	0.00010, 0.0045
Race		
Black ($n = 16$)	0.00043	0, 0.0012
White ($n = 40$), other ($n = 1$)	0.0010	0.00012, 0.0045
Disease, pathological classification of fibrosis[a,b]		
Macules ($n = 11$)	0.0020	0.000021, 0.0046
Micronodules ($n = 18$)	0.00097	0.00016, 0.0042
Macronodules ($n = 9$)	0.00052	−0.00014, 0.0012
Progressive massive fibrosis ($n = 18$)	0.00088	0.00010, 0.0035

[a]Vallyathan et al. (1996).
[b]One miner (among $n = 57$) was classified as not having fibrosis.

A principal finding of this study is the importance of including the process of interstitialization/sequestration of particles in the dosimetric model to predict the end-of-life lung particle burdens in these coal miners. This finding is consistent with several previous studies. In an earlier analysis of these data using a statistical regression model, there was no measurable reduction of particle burdens in the lungs of these miners during retirement (Kuempel et al., 1997). In a magnetopneumography study in retired U.S. coal miners, alveolar clearance was reduced in some miners and below detection in others (Freedman & Robinson, 1988). A study of lung retention patterns for coal dust and/or diesel exhaust particulate showed that particle retention was greater in the interstitium of nonhuman primates than in rodents (Nikula et al., 1997).

Other findings are also consistent with previous studies. The percentage of the working lifetime airborne mass of respirable coal mine dust that was retained (as total particle mass) in the lungs at the end of life was similar in these U.S. coal miners and in U.K. coal miners (Davis et al., 1977), approximately 4% and 5%, respectively. The distribution of estimated individual values for the first-order alveolar clearance rate coefficient is comparable to that measured in a study of long-term particle retention in humans without dusty jobs (Bailey et al., 1985). Finally, the estimated clearance parameters in this model are consistent with those obtained in an independent data set of U.K. coal miners (Tran et al., 1999).

An implication of these findings is that a compartmental kinetic model that does not describe an interstitial/sequestration process may be inadequate for predicting the retained lung dust burdens in these miners, and possibly in other workers with working lifetime exposures to respirable, poorly soluble particles. Similarly, rodent models that do not include an interstitial compartment may provide poor estimates of long-term particle retention if used for extrapolation to humans. The development of an automated optimization approach for

these sparse, heterogeneous data provides a method for objectively fitting the model, as well as making it feasible to investigate interindividual variability in certain model parameters. This approach of human lung dosimetry modeling is promising for use in the development and application of risk assessment methods for occupational exposure to respirable particles.

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