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Comparison of Human Lung Dosimetry Models: Implications for Risk Assessment

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In this study we have compared several human lung dosimetry models and predicted particle burdens in the lungs and lymph nodes of humans with working lifetime exposures to airborne particulates. The focus of this study was the clearance and retention of poorly soluble particles in the alveolar (gas exchange) region of the lungs. The models evaluated include those developed for exposure to radioactive particles and coal mine dust and a rat-based overload model extrapolated to humans. Results show that the predicted mean particle burden in the lungs varies by as much as two orders of magnitude among the different models. These findings indicate that risk estimates for particle-related lung diseases in humans could differ considerably depending on the choice of lung dosimetry model. Further evaluation is needed to investigate which kinetic model features best predict human lung particle burdens over a range of particle sizes, types and exposure levels and to investigate issues of variability and uncertainty.

Keywords: dosimetry models; toxicokinetics; particles; lung burden; risk assessment

INTRODUCTION

Several models have been developed to estimate the internal dose of particles in the lungs of humans. Recent models (Yu *et al*., 1991; ICRP, 1994; NCRP, 1997; Hseih and Yu, 1998; Kuempel *et al*., 2001a,b) have been evaluated in this study; both simulated occupational exposures and actual exposure data in US coal miners have been used to predict particle lung burdens from each model. All of these models incorporate information on pulmonary clearance rate coefficients measured in studies of humans inhaling low doses of radiolabeled respirable particles (see, for example, Bailey *et al.*, 1985). Yet, the model structures vary, reflecting differences in assumptions about the biological and kinetic factors that influence the clearance and retention of particles in human lungs.

The focus of these model evaluations is on clearance and retention of respirable particles in the alveolar (gas exchange) region of human lungs. Particles that deposit in the alveoli may be engulfed by macrophages and cleared to the tracheobronchial region, where they enter the mucociliary clearance path and are either cleared from the body by expectoration or swallowed into the gastrointestinal tract (Bohning and Lippmann, 1992). Particles may also be cleared to the lung-associated (hilar) lymph nodes. Particles retained in the lungs or lymph nodes represent the internal dose (or particle burden) at a given time. Estimating the dose of particles in human lungs is important for investigations of the nature and shape of dose–response relationships and quantifying the risk of occupational lung diseases.

MATERIALS AND METHODS

Diagrams of the model features are provided in Fig. 1. Models were coded in MATLAB (Mathworks, 1999) from the mathematical equations provided in the published papers. These models describe the particle mass transfer over time in the lungs and (in some models) the lung-associated lymph nodes. The model input is the airborne particle exposure as concentration and duration (either simulated or actual exposures) and the model output is the predicted dose in the lungs or lung-associated lymph nodes over time (both during and after occupational exposure). The particle deposition mass fraction was assumed to be constant throughout the exposure period in all models. A particle mass median aerodynamic diameter of 5 μm and associated alveolar deposition frac-

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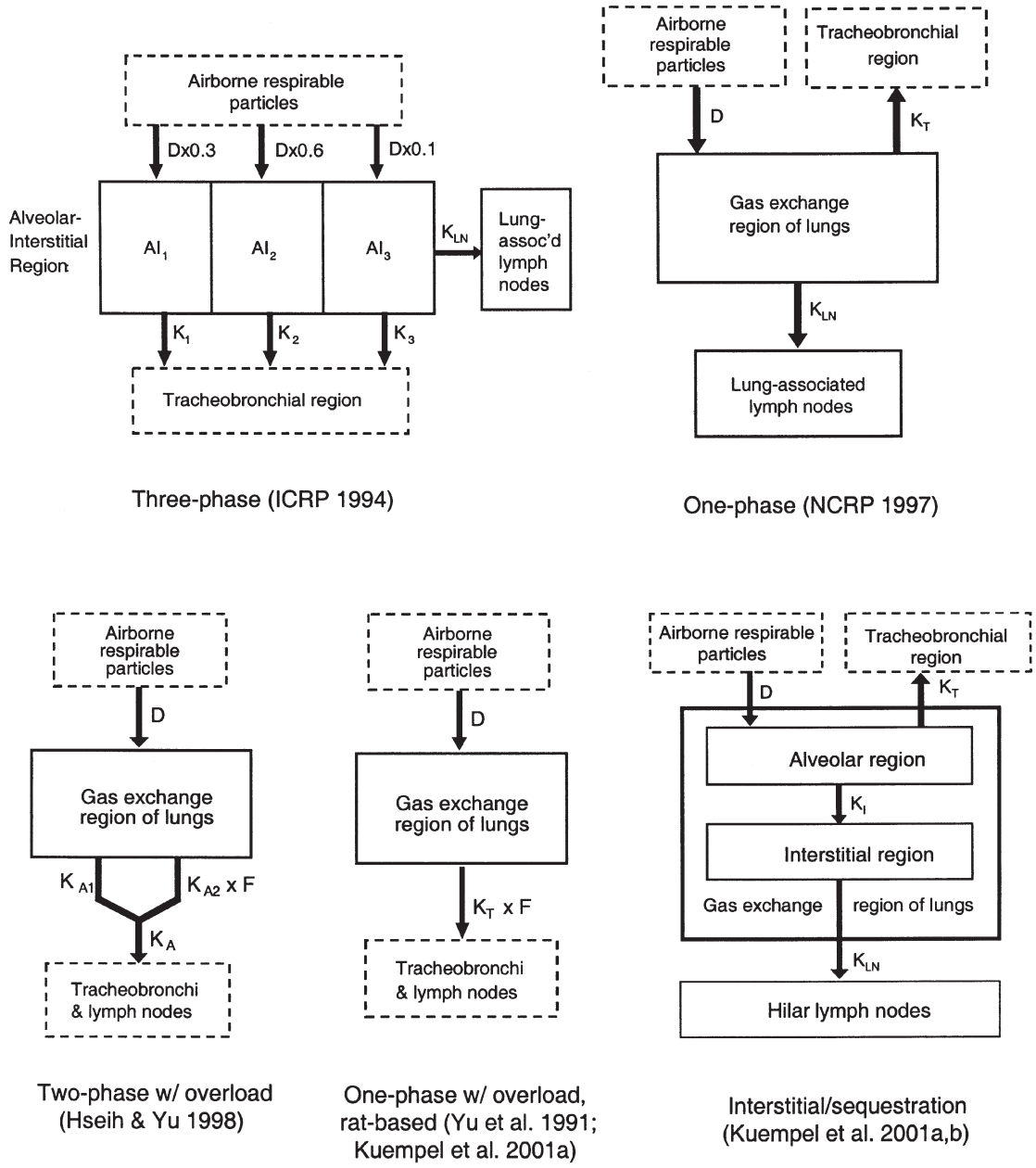

Fig. 1. Model diagrams of particle mass transfer in human lungs. D, deposited dose; K, rate coefficient; F, dose-dependent exponential decay function to describe overloading. See original papers for full mathematical descriptions.

tion (0.12 or 0.13, mouth breathing) (ICRP, 1994) were assumed; the reference worker inhalation rate (9.6 m^3 air breathed/8 h day) was assumed for the simulations and heavy work (13.5 m^3/8 h day) was assumed for the coal miner data.

Two of the models evaluated were originally developed to describe the clearance kinetics of radioactive particles in the human respiratory tract (ICRP, 1994; NCRP, 1997). The ICRP model includes three sub-compartments in the alveolar/interstitial region, each with first order clearance (Fig. 1). The fraction of the total deposited respirable particle mass is divided among these sub-compartments, which also have different first order clearance rate coefficients (K) representing three-phase pulmonary clearance (K = 0.02, 0.001 and 0.00001 per day). Clearance to the lymph nodes occurs from the slowest clearing sub-compartment (K = 0.00002 per day). The NCRP model includes a single alveolar compartment with a first order clearance rate coefficient (K differs with time since exposure; 0.06 per day for <200 days and 0.001 per day by 200 days) and a lymph node com-

partment (K = 0.0001 per day). The two overload models include an expression that modifies the first order clearance rate coefficient when the lung burden exceeds a minimum critical dose, representing the dose-dependent decline in alveolar–macrophage-mediated clearance. One of these models was developed from an interspecies comparison of particle clearance data (Hseih and Yu, 1998). It includes two-phase alveolar clearance, in which the proportion of clearance via the slower path increases with dose (initial K values of 0.027 and 0.0014 per day). Clearance to the lymph nodes is not described separately, but included in the alveolar clearance expression. The other overload model was based on rat data and extrapolated to humans (Yu *et al.*, 1991; Kuempel *et al.*, 2001a). It includes a first order alveolar clearance rate coefficient to the tracheobronchial region and lymph nodes (initial K value of 0.001 per day). The final model evaluated was developed using data for occupational dust exposures in coal miners (Kuempel *et al.*, 2001a,b). It has first order processes for alveolar clearance to the tracheobronchial region (K_T = 0.001 per day) and transfer of particles to the lung interstitial tissue (K_I = 0.00045 per day), where particles are essentially sequestered, with very slow clearance to the lymph nodes (K_{LN} = 0.00001 per day).

Using each model, the mean particle lung burdens were first predicted over time, from age 18 to 75, by assuming simulated exposures to a mean concentration of 0.05 or 5 mg/m^3 over a 45 yr working lifetime (assuming retirement at age 63). For most models only point estimates of the clearance parameters were available. In the interstitial/sequestration model, the 5th and 95th percentiles of the distribution of estimated individual alveolar clearance rate coefficients in the US coal miner population (representing slower or faster clearance) were also used to estimate lung burdens (Kuempel *et al.*, 2001b). Secondly, all models were evaluated for fit to the individual exposure and lung burden data for US coal miners. Model fits were determined using the mean squared error (MSE), which is the average of the squared differences in observed and predicted burdens in the lungs and hilar lymph nodes. For the interstitial/sequestration model the parameter values derived from UK coal miner data (Tran and Buchanan, 2000) were used to evaluate model fit to the US data.

RESULTS

The first comparison of the model predictions is shown in Fig. 2, which illustrates the predicted internal particle dose in the lungs at two simulated average airborne particle concentrations. The predicted mean particle burden in the lungs varies by more than an order of magnitude among the different models at the end of exposure (age 63) and by several orders of magnitude at 12 yr post-exposure. The models based on first order clearance give predictions linearly related to exposure level, but the overload-based models predict relatively higher burdens at the higher exposures. The two-phase model with overload gives the lowest predicted burdens at both concentrations because the overload effect in that model does not occur until higher concentrations (~7 mg/m^3 in these exposure scenarios).

Table 1 shows the second comparison of the model predictions, which indicates how well the predictions from each model fit the end of life lung and lymph node particle burdens in US coal miners. The smaller values of MSE indicate better overall fit of that model to the data. Also provided is the mean predicted lung burden from the interstitial/sequestration model that was originally fitted to these data (and lung burdens predicted for individuals in the 5th and 95th percentiles of the distribution of estimated pulmonary clearance rate coefficients). The model that was inde-

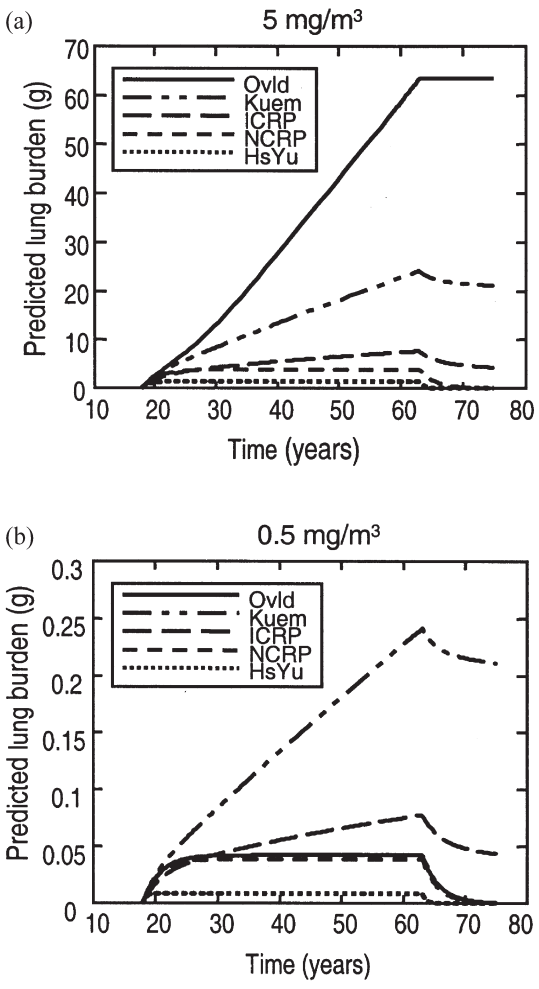

Fig. 2. Predicted lung burden by model, assuming a 45 yr working lifetime at two mean concentrations.

Table 1. Comparison of model fit to US coal miner data

	Mean lung burden (g)	Mean lymph node burden (g)	Mean squared error (MSE)
Model predictions			
Three-phase (ICRP 94)	3.4	0.75	205
One-phase (NCRP 97)	0.49	4.1	287
Two-phase with overload (Hseih and Yu)	3.3	NA	540
One-phase with overload (rat-based)	34	NA	828
Interstitial/sequestration (UK parameters)	10	1.6	105
Interstitial/sequestration (US parameters)	14 (3.8–34)	1.4 (0.41–3.1)	95
Observed lung burden (US miners)	15 ± 8.4[a]	1.6 ± 1.1[a]	NA

NA, not applicable.
[a]Standard deviation.

pendently fitted to the UK data provides the best fit to the US coal miner data, although the mean lung burden is underpredicted by a factor of 0.5 and the mean lymph node burdens agree. The ICRP model provides the next best fit, but the mean predicted lung burden is just below the 5th percentile of the distribution of estimated lung burdens in the US data. The ICRP model predicted lymph node burden two times lower than the actual value, but within the 5th to 95th percentiles. The NCRP model underestimates the mean lung burden by more than an order of magnitude and overpredicts the lymph node burden. The rat-based overload model overpredicts the mean lung burden by a factor of only approximately two, but that model provides a poor fit overall (largest MSE). The two-phase overload model underpredicts the lung burden by a factor of four to five and provides poor overall fit to the data (large MSE).

DISCUSSION

Differences in the model structures (Fig. 1) represent differences in assumptions about the biological and kinetic factors that affect particle retention and clearance in human lungs. These models also provide substantially different predictions of internal particle dose. The simple, first order model structures of the NCRP and rat-based overload models give similar predictions at low simulated exposures. However, at high simulated exposures they differ considerably, when effective clearance continues in the NCRP model and decreasing clearance occurs in the rat-based overload model. Both models provide poor predictions of the coal miner lung burden, with the worst prediction from the NCRP model. This finding suggests that some portion of the particles deposited in the coal miners' lungs are cleared at a slower rate than allowed for in the NCRP model. The ICRP model, which assumes that 10% of the deposited dose is cleared very slowly (retention half-time of ~20 years), predicts nearly one-quarter of the mean end of life lung burden in coal miners. This suggests that an even greater proportion of the deposited dose may be cleared very slowly in coal miners lungs. The interstitial/sequestration model structure, which was calibrated using coal miner data, accounts for the higher lung burdens by including a path for particle transfer to the interstitium. This model structure, fitted to UK coal miner data, predicts just two-thirds of the mean end of life lung burden in US coal miners, indicating possible differences among individuals or exposure estimates. The interstitial/sequestration model structure is consistent with findings from other studies, which showed either very slow or no measured particle clearance in the lungs of retired coal miners (Freedman and Robinson, 1988) and which found that the interstitial region was the predominant site for pulmonary particle retention in humans (Nikula *et al.*, 2001).

The only human data available in this study for testing these models were in coal miners, who had relatively high respirable dust exposures. Although the interstitial/sequestration model provides the best fit to these coal miner data, it is not known how representative it is of other occupational exposures. Also, the coal miner data were sparse in the low exposure region, which increases the uncertainty of model fit at low lung burdens. Simulations show substantial differences in predicted lung burdens among the various models at both lower and higher exposures. For risk assessment it would be useful to evaluate these dosimetry models at low exposures, if such data were available. It would also be useful to determine if different respirable particle size fractions (e.g. ultrafines), which differ in deposition fraction, also differ in clearance. The predictions from these human lung kinetics models vary by two orders of magnitude, indicating a large uncertainty in dose estimation, and therefore in human health risk estimation.

CONCLUSIONS

These findings illustrate that estimates of internal particle dose, and therefore disease risk, could differ

substantially due to the choice of human lung dosimetry model. Additional analyses are needed to investigate which kinetics model features would best predict human lung particle dose over a range of respirable particle sizes and exposure levels and to investigate sources of variability and uncertainty.

REFERENCES

Bailey MR, Fry FA, James AC. (1985) Long-term retention of particles in the human respiratory tract. J Aerosol Sci; 16: 295–305.

Bohning DE, Lippmann M. (1992) Particle deposition and pulmonary defense mechanisms. In Rom WN, editor. Environmental and occupational medicine, Ch. 14, Organ system: lung, 2nd edn. Boston, MA: Little, Brown and Co. pp. 171–82.

Freedman AP, Robinson SE. (1988) Noninvasive magnetopneumographic studies of lung dust retention and clearance in coal miners. In Frantz RL, Ramani RV, editors. Respirable dust in the mineral industries: health effects, characterization and control. University Park, PA: Pennsylvania State University Press. pp. 181–6.

Hseih TH, Yu CP. (1998) Two-phase pulmonary clearance of insoluble particles in mammalian species. Inhal Toxicol; 10: 121–30.

ICRP. (1994) Human respiratory tract model for radiological protection, publication no. 66. Tarrytown, NY: Elsevier Science.

Kuempel ED, O'Flaherty EJ, Stayner LT, Smith RJ, Green FHY, Vallyathan V. (2001a) A biomathematical model of particle clearance and retention in the lungs of coal miners: Part I. Model development. Regul Toxicol Pharmacol; 34: 70–88.

Kuempel ED, Tran CL, Smith RJ, Bailer AJ. (2001b) A biomathematical model of particle clearance and retention in the lungs of coal miners: Part II. Evaluation of variability and uncertainty. Regul Toxicol Pharmacol; 34: 89–102.

Mathworks. (1999) MATLAB version 5.3 (release 11). Natick, MA: Mathworks.

NCRP. (1997) Deposition, retention, and dosimetry of inhaled radioactive substances, report no. 125. Bethesda, MD: National Council on Radiation Protection and Measurements.

Nikula KJ, Vallyathan V, Green FHY, Hahn FF. (2001) Influence of dose on the distribution of retained particulate material in rat and human lungs. In Proceedings of Particulate Matter 2000, January 23–28, 2000. Charleston, SC: Air and Waste Management Association.

Tran CL, Buchanan D. (2000) Development of a biomathematical lung model to describe the exposure–dose relationship for inhaled dust among U.K. coal miners, IOM research report TM/00/02. Edinburgh, UK: Institute of Occupational Medicine.

Yu, CP, Yoon KJ, Chen YK. (1991) Retention modeling of diesel exhaust particles in rats and humans. J Aerosol Med; 4: 79–115.