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Application of Markov chain Monte Carlo analysis to biomathematical modeling of respirable dust in US and UK coal miners

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ABSTRACT

A biomathematical model was previously developed to describe the long-term clearance and retention of particles in the lungs of coal miners. The model structure was evaluated and parameters were estimated in two data sets, one from the United States and one from the United Kingdom. The three-compartment model structure consists of deposition of inhaled particles in the alveolar region, competing processes of either clearance from the alveolar region or translocation to the lung interstitial region, and very slow, irreversible sequestration of interstitialized material in the lung-associated lymph nodes. Point estimates of model parameter values were estimated separately for the two data sets. In the current effort, Bayesian population analysis using Markov chain Monte Carlo simulation was used to recalibrate the model while improving assessments of parameter variability and uncertainty. When model parameters were calibrated simultaneously to the two data sets, agreement between the derived parameters for the two groups was very good, and the central tendency values were similar to those derived from the deterministic approach. These findings are relevant to the proposed update of the ICRP human respiratory tract model with revisions to the alveolar-interstitial region based on this long-term particle clearance and retention model.

1. Introduction

A biomathematical model was previously developed to describe the long-term clearance and retention of particles in the lungs of coal miners, which included separate evaluations of model structure and model parameter calibration[1] in two data sets, one from the United States (US) and one from the United Kingdom (UK) (Kuempel et al., 2001a,b; Tran and Buchanan, 2000). The model structure consists of deposition of inhaled particles in the pulmonary (alveolar) region, clearance from the alveolar region to the tracheobronchial region or translocation to the lung interstitium, and irreversible sequestration of interstitialized material. Each of these processes was described as first order. The structure of this three-compartment sequestration model describes additional processes that were not captured in a simple one-compartment model (Kuempel, 2000). Previous analyses also showed that the process of dose-dependent overloading of lung clearance as observed in rats did not adequately fit the coal miner data (Kuempel, 2000; Kuempel et al., 2001a; Tran and Buchanan, 2000). This three-compartment sequestration model has been shown to best predict the long-term retention behavior observed in US and UK coal miners and (more recently) in workers with relatively low exposure to radioactive cobalt or plutonium (Gregoratto et al., 2010, 2011). In contrast, other first-order human lung clearance models (NCRP, 1997; ICRP, 1994) were shown to underpredict the human retained lung particle burden data (Kuempel and Tran, 2002). In addition, a rat-based model (extrapolated to humans) with normal first-order clearance followed by dose-dependent impairment of clearance (overloading) (Hsieh and Yu, 1998) both underestimated the human retained lung dose at low exposures and overestimated the lung dose at higher exposures (Kuempel and Tran, 2002).

The model structure in Kuempel et al. (2001a) was recently adopted by the International Commission on Radiological Protection (ICRP) to describe the long-term clearance and retention of inhaled particles in the alveolar-interstitial region of the human respiratory tract model (HRTM) (Bailey et al., 2007, 2008) [draft revision of the ICRP (1994) model and comments on the draft available at: http://www.icrp.org/page.asp?id = 155)]. This model structure is considered to be physiologically more realistic and provides

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[1] The term "calibration" in biokinetic modeling generally means the estimation and optimization of the model parameter values. When multiple data sets are available, some of the data may be used for model "calibration," and the others for validation of the original values (e.g., Chiu et al., 2009).

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a simpler model that adequately represents the long-term retained lung dose in humans in several studies (described in Gregoratto et al., 2010). The initial model development and parameter estimates were based on a US coal miner autopsy study (Kuempel, 2000), and the model structure was independently evaluated and validated using UK coal miner data (Tran and Buchanan, 2000). The model calibration was also performed separately, and different point estimates of the optimal parameters were obtained for each of these data sets.

To facilitate implementation in the HRTM update, it is of interest to examine whether these differences in the US and UK parameter estimates are systematic, or whether these best-fit point estimates are consistent with a single distribution of values for each parameter in the larger population. The optimal point estimates of the model parameters were originally estimated separately in each data set by identifying those parameter values that minimizing the mean squared error (MSE) in fitting the model to the data (Kuempel, 2000; Kuempel et al., 2001a; Tran and Buchanan, 2000). In addition to point estimates, the current analysis provides estimates of the distributions of parameter values, which are needed to characterize the variability in predicted lung burdens in the human population.

For the current analysis, Bayesian population analysis using Markov chain Monte Carlo (MCMC) simulation is considered an appropriate method for calibrating this particle clearance and retention model. This approach permits parameters to be simultaneously calibrated for multiple data sets using uninformative prior parameter distributions that minimize bias (Bernillon and Bois, 2000; Lunn et al., 2009; Jonsson and Johanson, 2003; Hack, 2006; Hack et al., 2006). Distributions were estimated for the parameters in this three-compartment model, rather than point estimates, to provide information on variability in the lung dose estimates in the population. This analysis also helps to reduce uncertainty in human lung dose estimation by better characterizing the distribution in the parameters influencing the long-term clearance and retention of inhaled particles in the lungs.

2. Materials and methods

2.1. Key data sets and model structure

The US data are from a study by the late Werner Laqueur, M.D., who systematically collected approximately 600 cases from consecutive autopsies at Beckley Appalachian Regional Hospital in West Virginia. Lung dust burden was measured for 141 of these coal miners, who were autopsied between 1962 and 1968. Of the 141 miners, 128 miners had the minimal information specified in the original model parameter calibration, which included (in addition to the lung dust burden), the duration of employment in mining, the mining job history (to assign job-specific exposure concentration), and the dates and/or ages at retirement and death (to compute the post-exposure duration) (Kuempel et al., 2001a). Of these, 57 miners also had data on the lung-associated lymph node dust burden. The work histories were derived from questionnaires provided to the next-of-kin, clinical records, and mine company records (Kuempel et al., 2001a). In the current analysis, an additional 8 individuals were omitted due to discrepancies in tabulated values for ages, work experience, and death, which resulted in 120 US coal miners with lung burden, and 54 with lymph node data, for this MCMC-based parameter estimation.

The miners in the UK study were participants in the British National Coal Board's Pneumoconiosis Field Research program, which was set up in the 1950s, with lung autopsy dust burden data becoming available in the 1970s (Tran and Buchanan, 2000). Usable data (i.e., information on exposure, lung burden, age) was available for 514 individuals in the British study. For 115 of these individuals, lymph node dust burden data were also available (Tran and Buchanan, 2000).

Briefly, the model structure (illustrated in Fig. 1) consisted of the deposition of inhaled dust in the alveolar (gas-exchange) region; the competing processes of either particle clearance from the alveolar region (rate: *KT*) or particle translocation to the interstitial region (rate: KI); and the very slow (irreversible) translocation of interstitialized material in the hilar (lung-associated) lymph nodes (rate: KLN) The original parameter estimation for this model was performed using a systematic grid search within biologically plausible ranges of KT, KI, and KLN (identified from human and animal studies in the literature; Table 4 of Kuempel et al., 2001a). In addition, a fixed value of the average alveolar deposition fraction (ICRP, 1994) was estimated on the reported airborne coal mine particle size data (Jones et al., 1988a; Burkhart et al., 1987). The clearance parameters were then iteratively varied to determine the best fit of the model to the data (Kuempel et al., 2001a). The optimal parameter values were estimated as those that minimized the MSE in fitting the model to the data. Evaluation of the evidence for possible dose-dependent KT was a focus of the original model development (Kuempel, 2000; Kuempel et al., 2001a). In the best-fitting model, each of these processes is described as first-order because the inclusion of biomathematical equations describing varying degrees of dose-dependent impairment of alveolar clearance (KT) did not improve the model fit to either the US or the UK data (Kuempel, 2000; Tran and Buchanan, 2000). The equations describing the model and parameters (both original and updated) are provided in Appendix A.

2.2. Model implementation/model calibration

The previously used model code (Kuempel et al., 2001a,b) was adapted to the conventions for MCSim (version 5.3.1). Extensive reformatting was conducted on the input files. The UK files in particular required extensive preprocessing because of greater detail in the exposure histories (i.e., several changes in exposure concen-

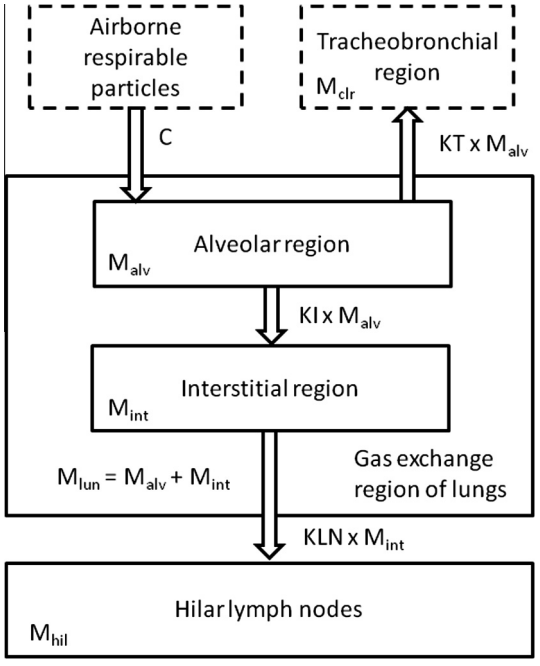

Fig. 1. Structure of the three-compartment biomathematical model for long-term clearance and retention of particles in the lungs of coal miners.