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Development of a biomathematical lung model to describe the exposure-dose relationship for inhaled dust among U.K. coal miners

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The aim of this study was to investigate exposure-dose relationships in humans with working lifetime exposures to respirable particulates, by using a bio-mathematical exposure-dose model to predict lung and lymph node dust burdens in coalminers with long-term exposure to respirable dust. To meet this aim, statistical and mathematical modelling techniques were used to analyse data from an autopsy study of UK miners held at the Institute of Occupational Medicine.

In this study, we validated an existing lung dosimetry model for consistency with observed human lung and lymph burden data. The results of our test suggested that, for humans, the sequestration of dusts in the interstitial compartment is a more prominent feature than the retention of dust due to overload that is observed in animal studies. Modelling and statistical analyses have shown that quartz is more likely to be retained in the lung and lymph nodes than the non-quartz fraction of lung burden and that the quartz fraction may play an important role in the development of PMF. The results of statistical analyses have also shown that the translocation to the lymph nodes is not simply a linear function of lung burden, but may terminate beyond a threshold in lung burden. Our assessment of the variation in the model parameters yielded a distribution of values for the clearance rate and the translocation rate to the lymph nodes respectively. While other sources of uncertainty (e.g. uncertainty in exposure estimation) were not investigated in this study, the results suggested that variability can be quantified and incorporated in the current modelling framework. This approach may be useful for assessing risk in humans to dust exposure.

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SUMMARY

The aim of this study was to investigate exposure-dose relationships in humans with working lifetime exposures to respirable particulates, by using a bio-mathematical exposure-dose model to predict lung and lymph node dust burdens in coalminers with long-term exposure to respirable dust. The bio-mathematical model was developed by Kuempel *et al.* (1999). The model parameters were estimated from data available in the US, consisting of exposure histories and lung dust burden data in an autopsy study of US coalminers (the US model).

Specifically, the objectives of this study were:

(a) to validate, and, if necessary, extend the bio-mathematical model by testing its consistency with autopsy data for UK miners held at the Institute of Occupational Medicine;

(b) to evaluate the relevance in humans of the overloading of particle clearance in the lungs, as observed in animal studies, using this model and the UK data set;

(c) to use the current model and the UK data set to describe the kinetics of retention and clearance of the quartz fraction of the total dust in the lungs.

Meeting these objectives will allow us to stimulate and support development of knowledge of the adverse health effects of exposure to respirable particles and to advance the fields of risk assessment methodology, pulmonary toxicology and occupational health.

Chapter 1 focuses on the statistical analysis of the autopsy data to inform the later development of the exposure-dose model. The main findings from the statistical analysis were:

i. Comparing the exposure-dose relationships across subjects with different pathology at autopsy showed that, for a given cumulative exposure, there was a clear trend of increasing retained lung dust burdens from those with soft macules (M) to those with fibrotic nodules (F) and, in turn to those with PMF. However, it is not possible to deduce with certainty whether those with the highest burdens were more likely to develop PMF or, whether those who developed PMF subsequently accumulated burden at a greater rate than those without PMF, or whether both of these occurred.

ii. Among those of similar pathology, there was little difference in average lung dust burdens among those exposed to different lower rank coals. However, among those with PMF, burdens among those mining the highest rank coal were noticeably higher relative to the lower rank coals. This could reflect increased accumulation of this type of coal in the lungs of miners with PMF or suggest that the non-coal component of the dust, which is lower in high rank coal, has an important role in the development of PMF. The most important non-coal component with implications for lung health is silica.

iii. There was no evidence, given the large variability in retained burdens at any given exposure, that retained lung dust burden was anything other than linearly related to cumulative dust exposure.

iv. The relationship between disease status and lung burden at autopsy suggested that progression from the soft macules (M) occurs at lung burdens lower than 10g. However, due to the roughly constant proportion of cases of small fibrotic lesions (F), the results suggest that some subjects progressed relatively quickly to large fibrotic lesions (PMF) while others remained in category F.

v. A clear non-linear trend was observed in the relationship between lymph node and lung dust burdens at autopsy suggesting that lymph burdens increased with lung burdens to a limit of, on average, 3 g. At lung burdens higher than the lowest level corresponding to the onset of this lymph node limit value, i.e. approximately 20 g, subjects were most likely to be diagnosed as PMF. Beyond this limit, a significant minority were diagnosed as having small fibrotic lesions (F), but virtually none were diagnosed with only soft macules (M).

Chapter 2 focuses on the validation of the US model and the extension of the model to describe the retention and clearance of the quartz and non-quartz fraction of the lung and lymph node burdens of UK coalminers. The US study investigated three hypotheses, each with a different parameter set regarding the extent of the overloading of clearance mechanisms. The hypotheses were: (1) 'Severe Overload', when 90 percent of the clearance rate became impaired; (2) 'Moderate Overload', with 50 percent impairment of clearance; (3) 'No Overload with high sequestration', in which alveolar clearance is effective but the amount of dust in the alveolar region is small in proportion to the amount retained in the interstitial region. The main results from the mathematical modelling were:

i. As in the US study, the model representing hypothesis (3) gave the lowest mean square error for lung and lymph node burden and therefore, according to this criterion, was most consistent with the autopsy data. However, the model with hypothesis 2 ('50 percent overload') gave mean square error values which were comparable and a smaller bias for lung burden. The model for the hypothesis 1 ('90% overload') gave the worst predictions when compared to UK data. Thus, our findings with the UK data have confirmed the early findings when the same hypotheses were tested with the US data.

ii. For quartz, a lower clearance rate, K_t, and a higher translocation rate to the lymph node, K_{ln}, (than the original rates of the model of hypothesis 3) should be used to describe the retention and clearance of the quartz fraction. This finding is consistent with the animal data on quartz.

iii. A routine written in MATLAB™ script was developed to estimate K_t and K_{ln} for each individual miner. This routine involves solving a system of differential equations describing the retention and clearance of coalmine dusts in the human lungs for each individual miner and selecting the best fit parameters (K_t and K_{ln}) for each individual using an optimisation routine which minimises the total mean square error.

iv. Applying this algorithm to both the quartz and non-quartz fraction of the lung and lymph node burdens data available for each UK coalminers, almost a perfect fit was obtained for each individual miner's data. A distribution of values for each parameter (K_t and K_{ln}) was obtained and summary statistics (arithmetic and geometric mean of the estimated parameters) calculated. For the quartz fraction, Summary statistics for K_t, whether based on the arithmetic or geometric mean of K_t, gave an average value smaller than the original reported value for effective clearance. Similarly, the average values for K_{ln} were higher than the originally assigned value for total dust. These findings appeared to confirm our original expectation on the toxicity of quartz. For the non-quartz fraction, the values for the average parameters were generally close to the values used in the original model (hypothesis 3).

In this study, we have tested a lung dosimetry model for consistency with observed human lung and lymph burden data. The results of our test suggested that, for humans, the sequestration of dusts in the interstitial compartment is a more prominent feature than the retention of dust due to overload that is observed in animal studies. Modelling and statistical analyses have shown that quartz is more likely to be retained in the lung and lymph nodes than the non-quartz fraction of lung burden and that the quartz fraction may play an important role in the development of PMF. The results of statistical analyses have also shown that the translocation to the lymph nodes is not simply a linear function of lung burden, but may terminate beyond a threshold in lung burden. Our assessment of the variation in the model parameters yielded a distribution of values for the clearance rate, K_t, and the translocation rate to the lymph nodes K_{ln} respectively. While other sources of uncertainty (e.g. uncertainty in exposure estimation) were not investigated in this study, our results suggested that variability can be quantified and incorporated in the current modelling framework. This approach may be useful for assessing risk in humans to dust exposure.

1. STATISTICAL ANALYSIS OF AUTOPSY DATA

1.1 INTRODUCTION

1.1.1 Background

Studies into the effects of inhaled coalmine dust on miners' lungs have naturally had to rely principally on radiographic evidence of lung disease among working and retired miners. When estimates of exposure have been available, this has allowed the effects of exposure to be analysed in relation to the presence of radiographic abnormality. This type of analysis has been a central component of the Pneumoconiosis Field Research (PFR) programme set up by the British National Coal Board in the 1950's. Within the PFR, regular radiographic surveys on working miners in selected pits across the country were carried out concurrently with a programme of detailed dust sampling and analysis linked to occupational records (e.g. Hurley *et al*, 1982; Hurley *et al*, 1987; Soutar and Hurley, 1986).

There have been earlier studies that have reported pathological analysis of lung dust content at autopsy. However, early studies of miners lungs from South Wales and North West England (Faulds *et al*, 1959, Spink *et al*, 1963) revealed substantial differences between the amount and composition (e.g. ash content) of retained dust in the lungs of men working in different coalfields in the UK. Further studies also suggested that the rate at which dust accumulated in the lungs was related to coal rank and that miners with evidence of PMF at autopsy had accumulated dust at a faster rate than those without evidence of PMF (Bergman, 1972). In the absence of measured dust exposure for the men involved, these early studies had analysed dust accumulation in relation to working time only.

With the availability in the mid-1970's of lung autopsy data for miners who had been part of the PFR, came the opportunity to study retained dust burden and composition in relation to detailed exposure histories, at least as far back as the start of the PFR programme in the early 1950's.

Chapman and Ruckley (1985) described microanalyses of the dust content of lesions and hilar lymph nodes dissected from the lungs of 49 PFR miners. They found the highest mean dust content within nodules and massive fibrosis. A much greater quartz composition in the lymph nodes relative to the lung was presented as evidence of the lymphotrophic nature of inhaled quartz. Ruckley *et al* (1984) examined the pathology and dust content in the lungs of 261 miners in relation to routine chest radiographs taken within 4 years prior to death. They found that the composition of the dust, in addition to the mass, was an important factor in determining the appearances of radiographic abnormalities.

Douglas *et al* (1986) reported on a study of the pathology and recovered dust from the lung of 430 miners in relation to estimates of cumulative dust exposure derived from the PFR. Based on pathological examination, miners were categorised into three groups: those with evidence of fibrosis, split into cases with large (>10mm) fibrotic nodules ('PMF') and those with small (<10 mm) fibrotic nodules ('F'), and those without evidence of fibrosis but only small focal dust deposits ('M'). They found that the mass of lung dust increased from groups M to F to PMF across all coal ranks, even though cumulative dust exposure was not significantly different across the three groups. They found that the ash and, in particular, the quartz content of lung dust was greater among men working with low rank coal, particularly in those with evidence of fibrosis. Correspondingly, in miners of low rank coal they found evidence that, relative to the ash/quartz content of the dust to which they were exposed, there had been enhanced deposition and/or selective retention of the mineral components in the lung, more so among those with evidence of fibrosis.

Kuempel *et al* (1997) reported on a study of the lung content of 131 US coal miners who mined in an area primarily consisting of highly volatile bituminous coal. Exposures were derived from occupational histories, determined retrospectively from next-of-kin interviews, and job-specific concentration measurements. They found an approximately linear relationship between cumulative dust exposure and retained lung burden and evidence of greater retained burdens among non-smokers. In addition, there was no evidence of any post-exposure clearance based on comparison of lung burdens of miners similarly exposed, but with different times since last exposure.

This current chapter reports a later re-analysis of the data reported by Douglas *et al* both to verify and update the analyses originally reported, and to carry out some additional analyses in relation to new research questions.

1.2 OBJECTIVES

The work reported in this chapter forms part of a wider study into the exposure-dose relationships in humans exposed over their working lifetimes to respirable particulates. The overall aim of the study was to construct a biomathematical exposure-dose model to predict lung and lymph node burdens in a sample of coal miners with long-term exposure to respirable coal mine dust.

This chapter focuses on the statistical analysis of the autopsy data to inform the later development of the exposure-dose model. The objectives of this statistical analysis were to:

i. summarise the pathology and exposure characteristics of the group of miners selected;

ii. determine the distribution of years since last exposure to death within the study group;

iii. investigate, using statistical regression models, any nonlinearity in the relationship between cumulative exposure and retained lung burden;

iv. evaluate possible differences in this relationship between smokers and non-smokers and the effect of years since last exposure;

v. investigate the relationship between retained dust in the lymph nodes and in the lung.

1.3 METHODS

1.3.1 Study sample

Douglas *et al* (1986) described a study using the lungs of 430 miners, all males, who had been included in the PFR programme of exposure measurement. The vast majority (n=414) of the lungs were obtained from the Pneumoconiosis Medical Panels which were set up to collect the lungs of as many ex-miners as possible who had taken part in the PFR medical surveys while alive. Since most the lungs collected by the Medical Panels were from men with some evidence of CWP, an attempt was made to supplement the numbers of lungs obtained from miners with little of no evidence of CWP. Therefore, the remaining miners' lungs were obtained from pathologists working from hospitals in the vicinity of PFR collieries. Consequently, the lungs analysed were not representative of coal miners, or even PFR miners, as a whole, but over-represent miners with evidence of lung disease that is related to their inhaled dust exposure.

The 430 miners analysed by Douglas *et al* represent a subgroup of over 500 lungs from PFR miners for which lung dust data was available. However, only in this subgroup are pathology results available and therefore only this subgroup have been analysed here. In addition although only estimates of cumulative dust exposure were required for statistical analysis of lung dust burdens, the later mathematical model required additional exposure history and other details (e.g date of birth) as input variables. To ensure consistency of subjects between statistical analysis and model development phases of the study, seven subjects for whom these additional variables were missing were excluded from analysis to give a study group of 423 subjects.

1.3.2 Lung burdens

A pathological examination was carried out on the lungs. Full details are presented in Davis *et al* (1979). During this examination, lungs were categorised into three pathological types labelled M, F and PMF, similar to those described in Douglas *et al* (1986). Lungs in the 'M' group showed only focal dust deposits (soft macules) without any macroscopic evidence of fibrosis. Lungs labelled 'F' contained, in addition, one or more fibrotic dusted lesion of diameter between 1mm and 9mm, while lungs labelled PMF showed fibrotic dusted lesions of diameter 10mm or more.

Following pathological examination, either the right or left lung was used for lung dust analysis and correction factors applied to take account of ventilation differences. Full details are presented in Davis *et al* (1979). After weighting, the dust content was ashed and composition of quartz, kaolin and mica determined by infra-red spectrometry.

1.3.3 Lymph burdens

Hilar lymph nodes were dissected from a subset of the total available PFR lungs (Ruckley *et al*, 1981). The proportions of coal and ash were available for the lymph nodes for 120 of the 423 subjects included in the analysis. However, the dry weights of the lymph nodes were not available. Therefore, an estimated dry weight of 25 g for lymph node tissue (Kuempel, 1997) was substituted for each miner to allow estimation of the mass of dust in the lymph nodes from records of amount of dust per gm of dry lymph node.

1.3.4 Dust exposure

The PFR programme consisted of regular sampling of respirable dust concentrations and composition at 24 collieries starting in 1954, continuing at 10 collieries throughout the 1970's. Simultaneously, attendance time records, linked to the payroll, and specific to occupational groups defined during sampling, were kept for most of the miners working at these collieries until their eventual closure in the late 1970's and early 1980's. This allowed precise estimates of cumulative dust exposure to be made for individual miners during the three decades that the PFR was in operation. For periods prior to start of the PFR, or when men spent time away from the colliery, work histories were obtained using a questionnaire at subsequent health surveys. This component of a miner's working time was described as 'unmeasured' in PFR jargon. More details can be found in the many publications stemming from PFR research (e.g. Hurley *et al*, 1982; Hurley *et al*, 1987; Soutar and Hurley, 1986, Miller *et al*, 1981, Miller *et al*, 1997).

Using the coal rank classification scheme used by the then National Coal Board, collieries could be divided into four rank categories (A,B,C,D), with A of highest rank and D lowest. High rank coal consisted of a high carbon content (over 90%) while low rank coals were associated with an increasing volatile content. Coal rank was related to geographical region within the UK, with the highest rank coals in South Wales and low rank coals in the Midlands, North Wales, North England and Scotland.

Years since last exposure to autopsy for each subject was estimated from work history information as follows. Times worked for each miner were stored by the approximately 5-year periods between health surveys, labelled the inter-survey period (ISP). The last ISP in which a man had recorded time worked was identified. This time, recorded in hours was divided by the number of hours in a standard working year, 1740 hours, to give an estimated number of years spent in employment during the ISP. Assuming this time was spent in a single continuous block of full-time employment, the date of last exposure was estimated by adding the number of years to the known start date of the ISP.

1.3.5 Statistical methods

Standard regression methods were used to investigate the effect of pathology, rank and smoking status on lung dust content adjusting for the effect of cumulative exposure. To analyse in more detail the shape of the relationship between cumulative exposure and lung dust burden, cubic smoothing splines (Hastie and Tibshirani, 1990) were fitted in place of linear terms within pathology categories in an additive model. The smoothness of the splines is controlled by a smoothing parameter called the effective degrees of freedom which was selected by eye as a trade off between detecting local trends in the data and not introducing excessive and implausible variability to the fitted function. By default a value of 4 effective d.f. was used. Regression models and additive models were fitted using Genstat version 5 for Windows (Genstat 5 Committee, 1993). Cubic smoothing splines were also used to investigate the relationship between lymph node and lung burdens.

The proportion of those in various pathology categories was plotted against dose and exposure variables using the nonparametric kernel density method of Copas (1983) using a normal kernel with the degree of smoothing controlled by the bandwidth parameter. The value of this parameter was taken to be a fixed multiple of the average difference between successive points along the axis of the explanatory variable.

1.4 RESULTS

1.4.1 Characteristics of study sample

Almost all the men whose lungs were analysed died between 1972 and 1977. The remaining two subjects died in the mid 1960's. The 423 subjects included in the analysis were spread across the 24 phase 1 PFR collieries, and were approximately evenly split between high rank (57%) and low rank (43%) collieries. Table 1.1 shows the distribution of age at death among the autopsy subjects studied. the mean age at death was 67 years (SD 7.7 years) and only a small proportion (14%) were less than 60 years at death. Smoking status was based on the information recorded at the most recent PFR health survey attended prior to death. For the 344 men with smoking information last recorded at the 2nd or 3rd round of PFR surveys this meant that knowledge of smoking status was only known generally ten years or more prior to death. Smoking status had been recorded for 401 (95%) of subjects of whom 363 (86%) were known to have been current or ex- smokers at the last survey where the information was available.

Men were assigned into pathology categories based on examination of the lungs at autopsy. Using the categories described earlier, the numbers of men assigned to the M, F, and PMF categories were 89 (21%), 172 (41%) and 162 (38%) respectively.

Figure 1.1 shows a histogram of the distribution of estimated years since last exposure to death. This shows that, although for nearly half of the subjects studied, deaths occurred less than 2 years since last exposure, for a significant minority over ten years had elapsed.

Summaries of the lung and lymph dust and quartz burdens are shown in Table 1.2. The mean lung dust burden was 14.4 g (SD 11.7) while the mean lymph dust burden, among the subset for which lymph data were available, was 2.3 g (SD 1.0). The lymph burdens were estimated assuming an average value of 25 g for the dry weight of the lymph nodes of each man. The quartz content was generally low in the mines in which the men worked and this is reflected in the mean lung quartz burden of 0.8 mg (SD 0.8) equivalent to 5.8% of the mean dust burden.

Effect of pathology and coal rank

Earlier analyses had indicated that both the pathology category and the rank of the coal mines had an effect on the retained lung burdens (Douglas *et al*, 1986). Regression analyses showed that cumulative dust exposure was positively associated with lung burden and, adjusted for cumulative dust exposure, pathology and rank were statistically significant explanatory variables.

A significant interaction term was found for pathology and rank indicating that the joint effects were not additive (P=0.002). In fact, as can be seen in the two-way table of predicted means (Table 1.3), for a fixed cumulative exposure equal to the sample mean of 256 $g.h.m^{-3}$, the lack of additivity was principally due to the group of miners with PMF working with the highest rank coal. In each rank category, burdens increased from group M to group F to group PMF. However, in rank category A, burdens were higher than expected assuming simple additivity. This high subgroup also explains the significant effect of coal rank, since there is no evidence of a difference between rank categories if miners in rank category A are omitted from the analysis (P=0.91). Although these findings confirm the patterns of lung burden found by Douglas *et al*, in the earlier study no adjustment was made for cumulative dust exposure.

Table 1.3 also shows the estimated linear cumulative dust exposure coefficient, which represents the increase in lung burden (g) per unit ($g.h.m^{-3}$) increase in cumulative dust exposure. Unlike Douglas *et al*, these linear coefficients are adjusted for significant mean differences due to rank and pathology and therefore are not constrained to pass through the origin (burden=0, exposure=0) but assumed different intercept parameters for each pathology/rank combination. The test of equal slopes across all subgroups in the two-way table of rank by pathology was not statistically significant (P=0.48). A pooled estimate of the linear cumulative dust exposure coefficient was 24.4 mg per $g.h.m^{-3}$.

A model was fitted to a subgroup omitting coal rank A miners assuming a constant intercept value for the three pathology groups. Omitting rank A miners meant that the effect of rank could be ignored. This model predicted a higher linear exposure coefficient for the PMF category relative to the M and F categories. However, an F-test of the addition of separate intercepts among the pathology categories was highly significant (P=0.001), corresponding to higher intercepts for PMF and F categories compared to the M category.

1.4.2 Linearity of exposure-burden relationship

The shape of the relationship between cumulative exposure and retained burden was investigated using the subset of miners in the lower rank categories (B,C,D) among which no effect of rank was observed. This allowed exposure-burden analyses to be carried out within each pathology category without regard to differences due to rank which were not significant outside of the highest rank category (see above). To optimise the investigation of the linearity of the exposure-burden relationship, only miners with the most reliable exposure estimates were included. A reliable subset (n=162) was defined to be those with the shortest unmeasured working times estimated by retrospective questionnaire rather than attendance records (< 20%), and average measured hours per day of between 5 and 10 hours. Figure 1.2 shows scatter plots of lung burden against cumulative dust exposure for each of the 3 pathology categories. Graphs show both the estimated linear effect (dashed line) and the cubic smoothing spline (continuous line). This figure highlights the fact that, for the same given exposure, burdens were highest among category PMF followed by category F then category M. However, for the same given exposure, the variation in lung burdens is also higher.

For category F the slope of the linear fit appears to mirror closely the gradient of spline fit which is approximately linear. In category M, the point corresponding to the highest exposure and highest burden appears to have increased the gradient of the linear fit slightly relative to the spline fit across the range of typical exposures (0 to 400 $g.h.m^{-3}$). In category PMF, the point corresponding to the lowest exposure with atypically high burden appears to have reduced the gradient of the linear fit relative to the spline fit across the range of typical exposures. However, in no category is there strong evidence of a substantial non-linear relationship with exposure, although the scatter relative to the group sizes makes detecting trends difficult. Taking the spline fits however, and ignoring the two influential points described above, there is some evidence that the gradient of burden relative to cumulative exposure is higher among the PMF category compared to the less diseased categories.

1.4.3 Effect of smoking and time since last exposure

The effects of smoking status and time since last exposure on the exposure-burden relationship were investigated using regression analyses on the subset of subjects reported above, and in particular, the category showing least lung disease (M). However, since there were very few non-smokers within the M category, it was necessary to repeat the analyses without excluding subjects with less reliable exposure information and after grouping the M and F category lungs. The latter grouping was also necessary since there was evidence that residual variation was greater within the less diseased categories compared to those with PMF (Figure 1.2). This grouping resulted in data for 15 non-smokers and 15 ex-smokers to be compared to 136 current smokers.

Table 1.4 shows the estimated coefficients (intercept and slope terms) of the exposure-dose relationship by last known smoking status. Among subjects with least evidence of disease, retained dose relative to cumulative exposure was estimated to be greater among those who were life-long non-smokers than among ex-smokers (greater by ×1.5) or current smokers (greater by ×2.5), although the differences among the slope parameters were not statistically significant (P=0.14). The same was true among subjects with evidence of PMF, although among these subjects, the principal difference in retained dose relative to cumulative exposure was between non- and ex-smokers compared to current smokers.

Adjusting for cumulative exposure, there was no evidence of a decrease in lung burdens with increasing time since last exposure that would indicate that significant post-exposure dust clearance had occurred. In fact, adjusted for cumulative exposure, the coefficient for time since last exposure was estimated to have a positive sign, indicating higher burdens at greater elapsed time, among both the least diseased (M+F) and most diseased (PMF) categories.

1.4.4 Lymph nodes

Figure 1.3 shows a scatter plot of lymph node and lung burdens at autopsy among all 120 subjects for whom lymph node burdens were available. The figure also includes a cubic spline smoother, using 3 d.f., which indicates that after lymph node burdens initially increase linearly with lung burdens, for lung burdens greater than approximately 30 g, lymph burdens tend to stabilise. The general trend is similar even when the two subjects with highest lung burdens (> 70 g) are excluded. However, while the spline smoother highlights the general trend of this relationship, there is also a large variation in individual lymph node burdens around this trend. In part, the assumption of constant dry weight of lymph nodes across subjects will have contributed to this variation. The general trend appears to be similar within the PMF and F pathology categories, although it is not possible to discern whether this is also true of the M category since the lung burdens among these subjects are all among the lowest, and in the main, lower than 10 g.

1.4.5 Relationships with disease

The relationship between exposure and dose with pathology at autopsy was explored using logistic regression. Both retained burden and cumulative exposure were statistically significant predictors of PMF status (P<0.001), however, the improvement in model deviance was greater for retained burden (deviance=75.1, 1d.f.) than for cumulative exposure (deviance=13.1, 1 d.f.). This indicated that retained burden was a more powerful variable for discriminating between subjects with and without PMF. This can be seen more clearly in Figure 1.4 which shows smoothed kernel density functions of the proportions within each pathology category in relation to retained lung burden (4(a)) and cumulative dust exposure (4(b)). This shows that, for retained burdens less than 10g, M and F categories are most prevalent, and as burdens approach zero, PMF cases are virtually absent. However, as burden increase above 20 g, there is a clear excess of those in category PMF compared to category F categories, with virtually no category M subjects. A significant proportion, approximately 30%, remain as F cases at the highest lung burdens.

The distinction between categories is less marked when plotted on the cumulative exposure scale. At the lowest exposures there is less of a difference in the relative proportions of the three categories, with a significant proportion of PMF cases even as exposure approached zero (approximately 20%). As exposure increases, the increase in proportion of PMF subjects is less marked than for retained burden, and there is no clear separation in relative proportions of the F and PMF categories.

After fitting a linear term for burden, smoking status (P=0.05), but not rank (P=0.26), was a statistically significant predictor of PMF. The smoking effect was principally due to a higher odds of PMF among ex-smokers relative to either non-smokers (OR=2.4) or current smokers (OR=1.7). This effect remained as a significant explanatory variable for prediction of subjects in either categories F or PMF relative to category M.

1.5 DISCUSSION

In this study, interpretation of the results has to be take account of the fact that the sample of coal miners necessarily over-represent miners at PFR collieries with chronic lung disease, principally CWP, due to inhaled coal mine dust. However, since the true extent of lung disease could not be known prior to autopsy, it is valid to explore the extent to which differences in pathology are related to exposure, dose and other relevant factors. Also, it is valid to explore the relationship between exposure and retained dose among miners who, on autopsy, revealed minimal evidence of lung disease.

There was little difference in burdens, split by pathology category, among the lower rank coals (B-D). However, burdens among those with PMF mining the highest rank coal were noticeably higher relative to the lower rank coals. This could reflect increased accumulation of this type of coal in the lungs of miners with PMF or suggest that the non-coal component of the dust, which is lower in high rank coal, has an important role in the development of PMF. The most important non-coal component with implications for lung health is silica. It has been shown however that the toxic effect of pure quartz is masked when it is inhaled as a small component of a mixed dust (Ross *et al*, 1962; Le Bouffant *et al*, 1982; Davis *et al*, 1991). Among the current study subjects the estimated proportion of silica exposure was generally lower than 10% and, for the majority, lower than 6% (Figure 1.5), although these lifetime average proportions could conceal fluctuations at higher time resolutions.

Comparing the exposure-dose relationships across subjects with different pathology at autopsy showed that, for a given cumulative exposure, there was a clear trend of increasing retained burdens from those with soft macules (M) to those with fibrotic nodules (F) and, in turn to those with PMF.

The time course of the extent and magnitude of fibrotic nodules cannot to determined from autopsy data alone. Therefore, it is difficult to deduce with certainty whether those with the highest burdens were more likely to develop PMF or, whether those who developed PMF subsequently accumulated burden at a greater rate than those without PMF, or whether both of these occurred. Assuming a linear relationship and non-zero intercept (at zero exposure), there was no strong evidence, across the study group as a whole, that the increase in retained lung burden per unit of cumulative exposure was greater among those in pathology group PMF at autopsy compared to the less fibrotic categories. However, inclusion of a non-zero intercept term was necessary and significant for the two most fibrotic categories and this is consistent with those with the highest burdens at all levels of cumulative exposure being most likely to develop fibrotic nodules. An intercept term may also be the product of the attenuation, or flattening, of the regression line due to random errors in the exposure variable. However, no significant intercept was noted within the least fibrotic category (M), when the effect of coal rank had been removed. Since there is no reason to suspect that exposure estimates would be subject to a greater degree of measurement error within the most fibrotic categories, this suggests that an attenuation effect has not been a significant factor in the occurrence of the non-zero intercept within the most fibrotic categories.

There was no evidence, given the large variability in retained burdens at any given cumulative exposure, that retained burden was anything other than linearly related to cumulative exposure.

There was no evidence of post-exposure clearance of dust from the lung, which was consistent with the findings of Kuempel *et al* (1997). However, all subjects showed evidence of the onset of fibrosis at autopsy and this may have led to the general impairment of the normal lung clearance mechanisms.

The vast majority of subjects in the study sample were known to have been smokers during their working lifetime. Those known to be ex-smokers prior to death were more likely to have PMF than non-smokers or current smokers suggesting those with a higher likelihood of external indications of lung disease (e.g. via radiographs, spirometry) may have given up smoking. There was weak evidence that non-smokers accumulated dust in the lung at a higher rate than smokers, among those both with and without PMF. A similar relationship was also found by Kuempel *et al* (1997), who suggested that the deposited dose in the alveoli was lower in smokers due to enhanced mucus secretion and cough clearance in smokers.

The relationship between disease status and lung burden at autopsy suggests that progression from the soft macules (M) occurs at burdens lower than 10g. However, due to the roughly constant proportion of cases of small fibrotic lesions (F), the results suggest that some subjects progressed relatively quickly to large fibrotic lesions (PMF) while others remained in category F.

A clear nonlinear trend was observed in the relationship between lymph node and lung burdens at autopsy suggesting that lymph burdens increased with lung burdens to a limit of, on average, 3 g. At lung burdens higher than the lowest level corresponding to the onset of this lymph node limit value, i.e. approximately 20 g, subjects were most likely to be diagnosed as PMF, with a significant minority diagnosed as having small fibrotic lesions (F), but virtually none diagnosed with only soft macules (M). This supports a role for the lymph nodes, once heavily burdened, in the onset of fibrosis as proposed by Seaton and Cherrie (1998). Almost all subjects showing only soft macules (M) had lung burdens lower than 10g in the region where lymph node burdens were approximately linearly related to lung burdens.

Table 1.1 Distribution of age at death among autopsy study subjects

Age group	**Subjects**	
	n	**%**
-49	8	*2*
50-59	51	*12*
60-69	175	*41*
70-79	175	*41*
80-	14	*3*
Total	423	*100*

Table 1.2 Summary of retained lung and lymph node burdens at autopsy. Lymph burdens are based on an assumed dry weight of 25 g

Statistic	**lung burden (g) n=423**		**Lymph burden (g) n=120**	
	dust	**quartz**	**Dust**	**quartz**
Min	0.7	0.0	0.4	0.0
Q1	6.3	0.3	1.5	0.2
Median	11.2	0.6	2.2	0.4
Q3	18.7	1.1	2.9	0.5
Max	78.0	5.6	5.0	1.2

Q1=25th percentile, Q3=75th percentile

Table 1.3 Interaction between pathology category and coal rank showing adjusted mean lung burdens (g), for cumulative dust exposure = 256 g.h.m^{-3}, and estimated linear coefficient for cumulative dust exposure (g per g.h.m^{-3}).

	Rank							
Category	**A**		**B**		**C**		**D**	
	adjusted mean	**Coeff. (SE)**	**adjusted mean**	**coeff. (SE)**	**adjusted mean**	**Coeff. (SE)**	**adjusted mean**	**coeff. (SE)**
M	7.8	0.021 (0.015)	7.2	0.013 (0.022)	14.2	0.048 (0.021)	9.4	0.037 (0.020)
F	13.0	0.031 (0.011)	13.2	0.048 (0.016)	10.4	0.006 (0.016)	12.6	0.014 (0.010)
PMF	25.3	0.022 (0.008)	16.9	0.031 (0.015)	18.4	0.027 (0.012)	16.1	0.020 (0.013)

Table 1.4 Exposure-dose relationships by last known smoking status showing estimated coefficients for intercepts and linear cumulative exposure terms (g.h.m^{-3}). Standard errors are in parenthesis

	smoking status		
	Never	**ex-**	**current**
M and F subjects :			
n	15	15	136
intercept	-0.83 (4.55)	2.26 (3.78)	4.66 (1.35)
coefficient	0.061 (0.020)	0.041 (0.013)	0.024 (0.005)
PMF subjects :			
n	7	17	79
intercept	5.50 (7.26)	7.98 (4.15)	12.13 (2.34)
coefficient	0.048 (0.027)	0.044 (0.012)	0.018 (0.008)

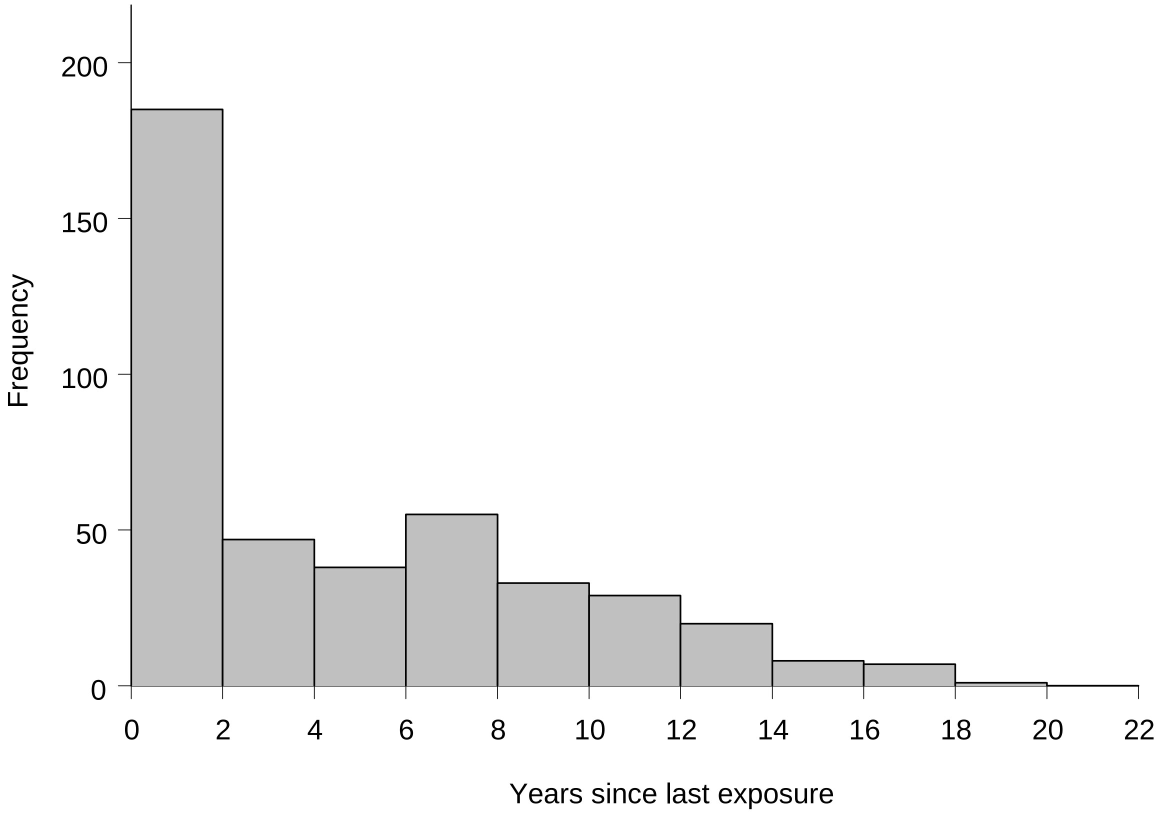

Figure 1.1 Histogram of estimated years since last exposure to death, assuming retiral at age 65

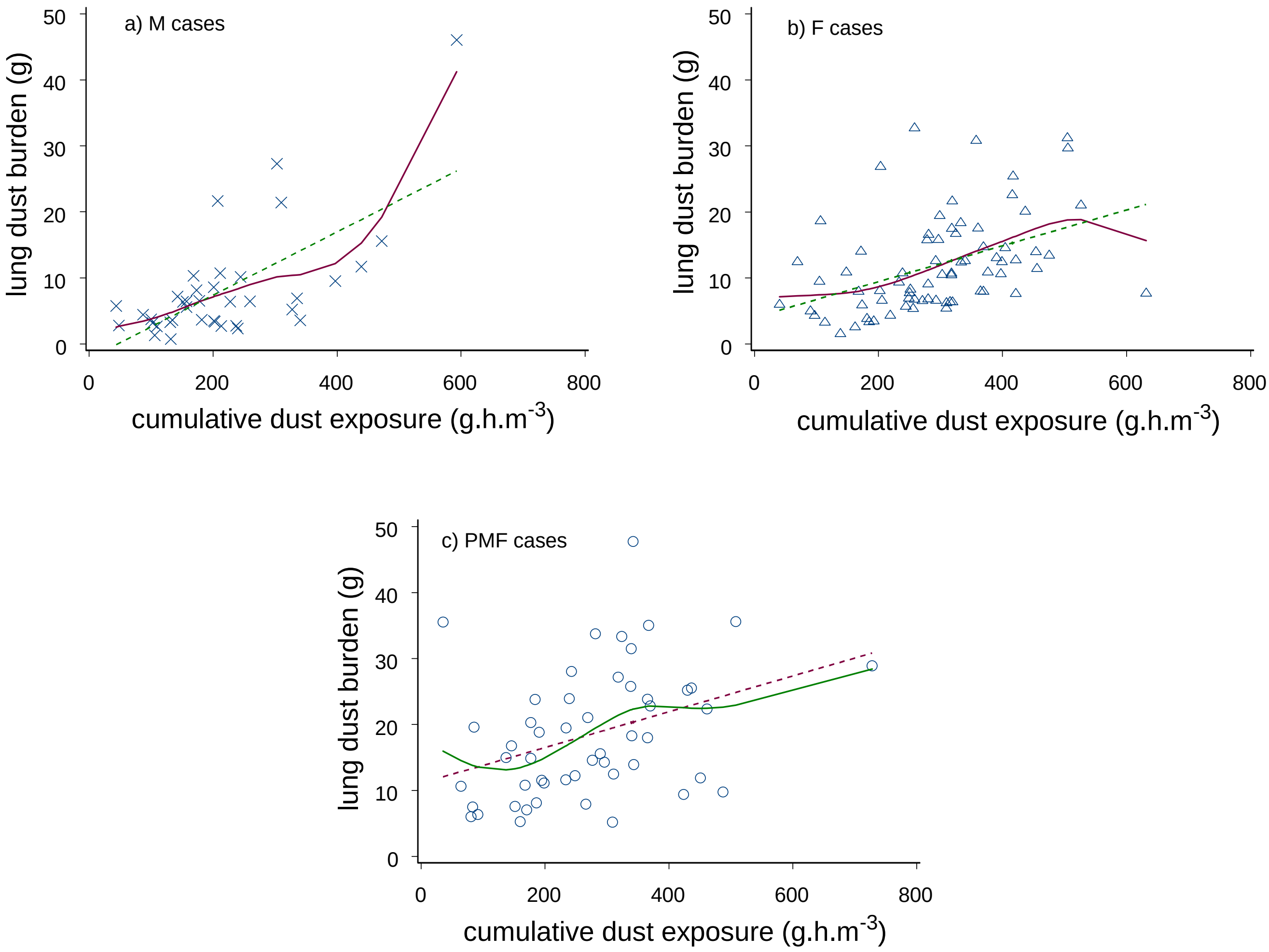

Figure 1.2 Lung burdens at autopsy against cumulative exposure by disease status among subset with reliable exposures (n=162), showing both linear (-----) and cubic spline (——) fits

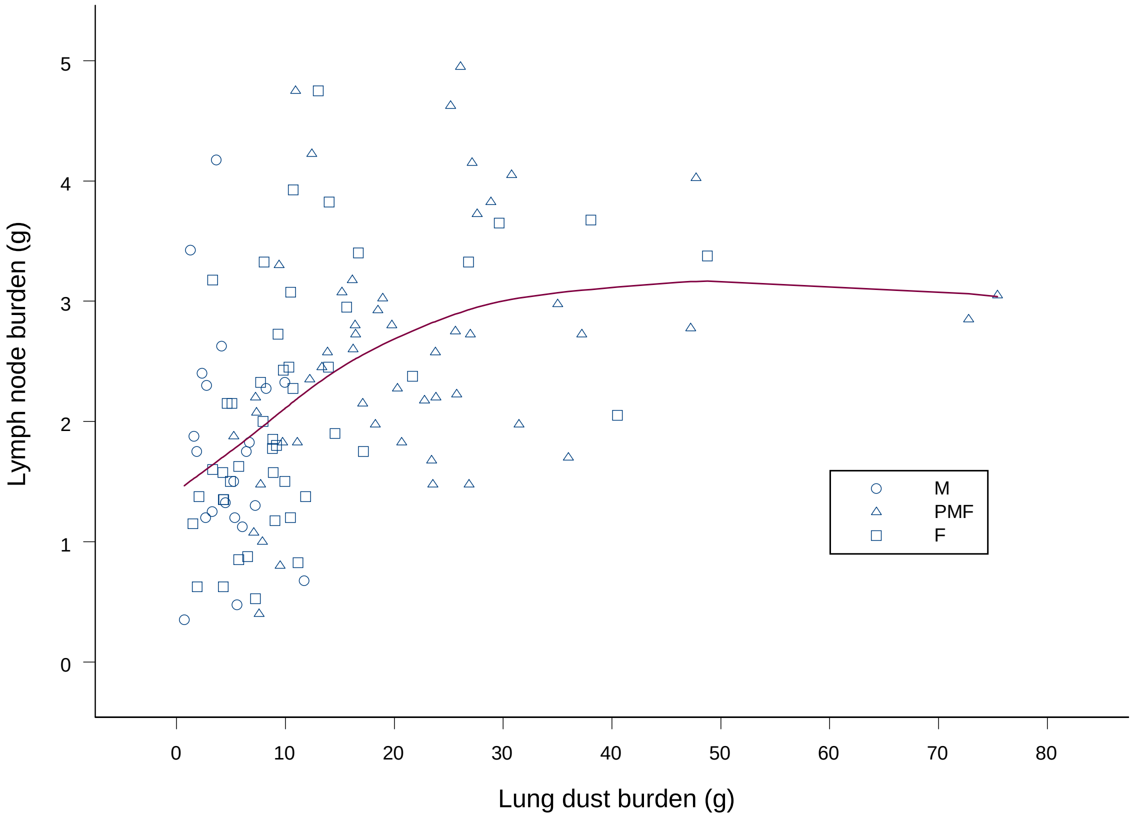

Figure 1.3 Relationship between lymph node burdens and lung burdens showing cubic spline fit

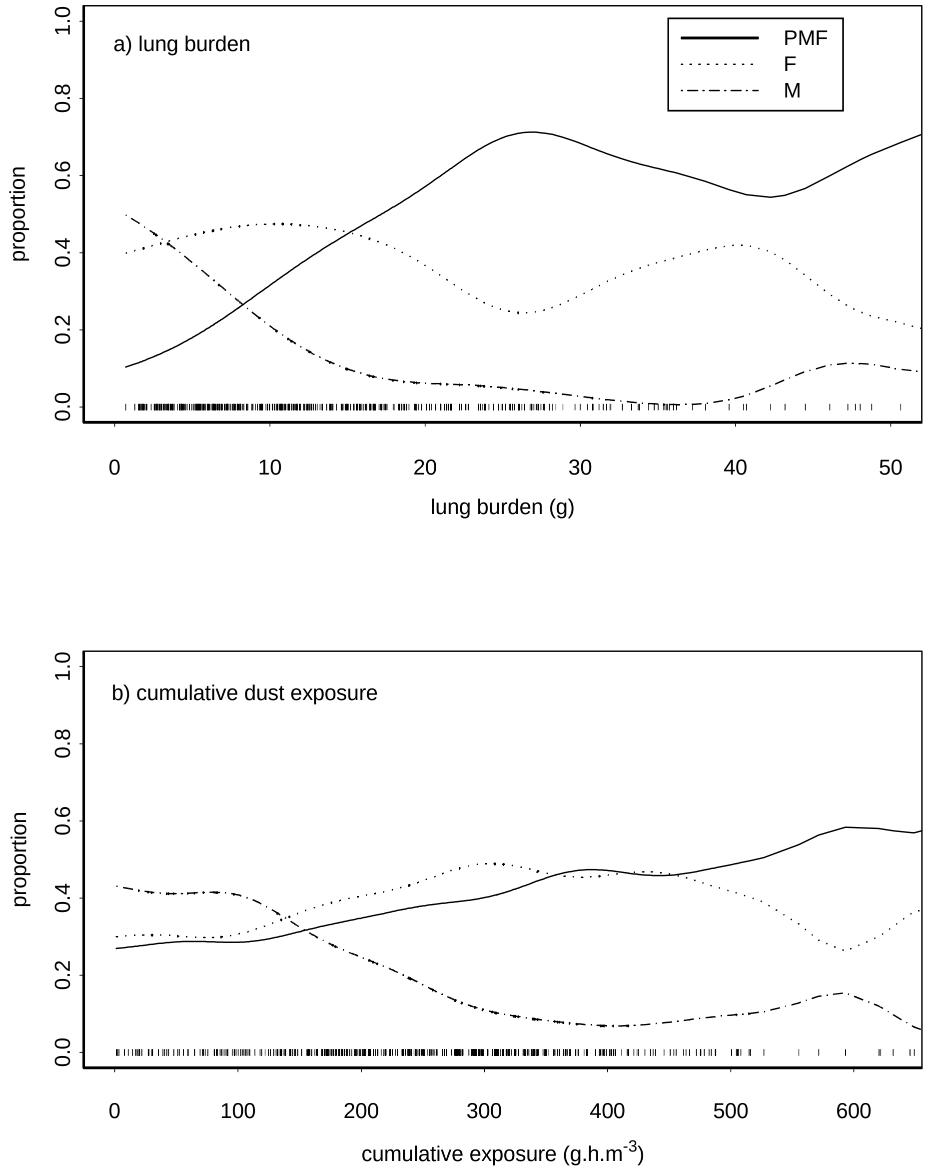

Figure 1.4 Smoothed prevalence of disease status by a) lung burden and b), cumulative exposure. Distributions of burdens and exposure among study group as shown as vertical lines along horizontal axis.

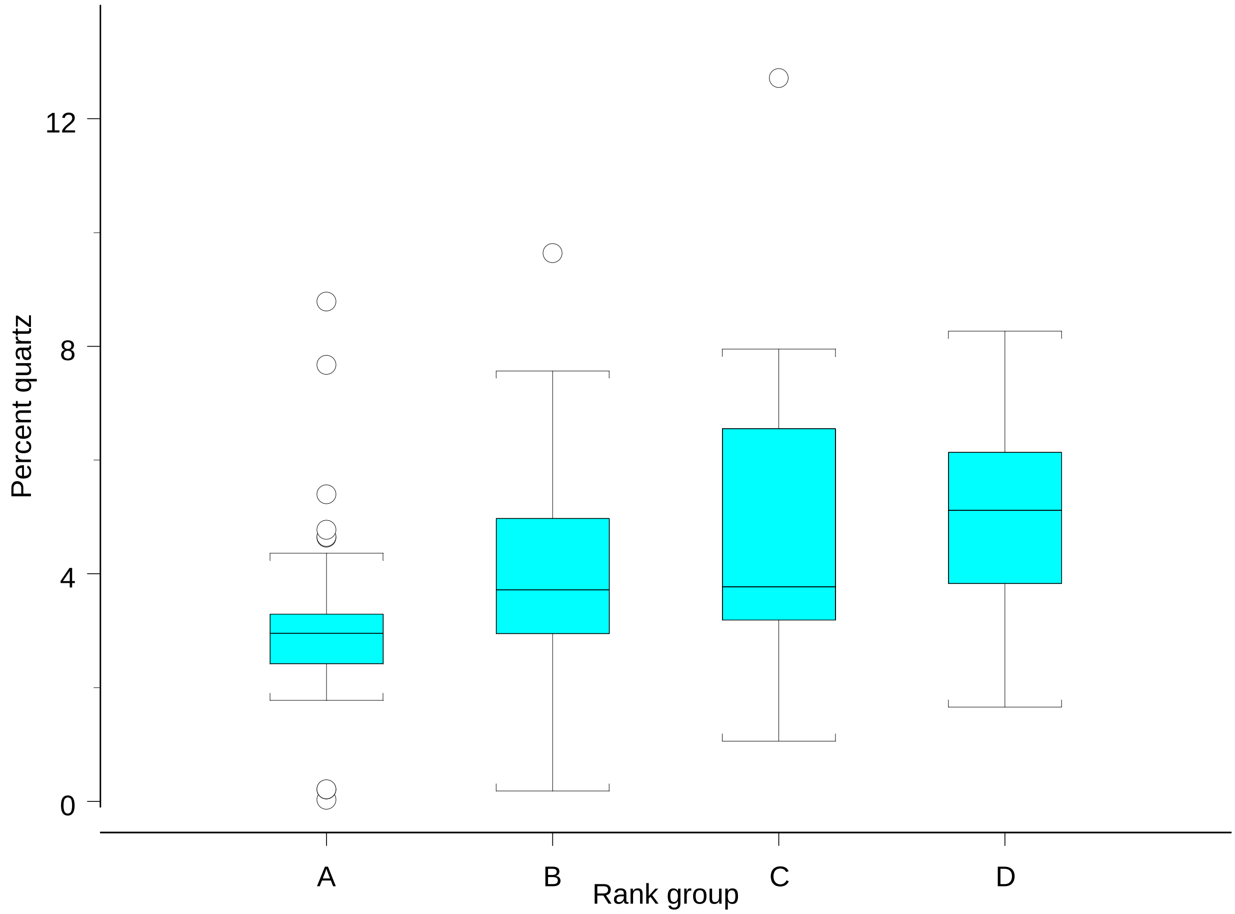

Figure 1.5 Box plots of estimated quartz fraction of cumulative total dust exposure of miners by coal rank

2. EVALUATION AND EXTENSION OF A HUMAN LUNG MODEL AND ESTIMATION OF MODEL PARAMETERS

2.1 AIM

The aim of this study is to investigate exposure-dose relationships in humans with working lifetime exposures to respirable particulates, by using a bio-mathematical exposure-dose model to predict lung and lymph node dust burdens in coalminers with long-term exposure to respirable dust. The bio-mathematical model was developed by Kuempel *et al.* (1999). The model parameters were estimated from data available in the US, consisting of exposure histories and lung dust burden data in an autopsy study of US coalminers.

Specifically, the objectives of this study are

(a) to test for validation of the bio-mathematical model (Kuempel *et al*., 1999). This is done by testing its consistency with autopsy and exposure data of UK miners held at the Institute of Occupational Medicine;
(b) to evaluate the relevance in humans of the overloading of particle clearance in the lungs, as observed in animal studies, using this model and the UK dataset,
(c) to use the current model and the UK dataset to describe the kinetics of retention and clearance of the quartz fraction of the total dust in the lungs.

Meeting these objectives will allow us to stimulate and support development of knowledge of the adverse health effects of exposure to respirable particles and to advance the fields of risk assessment methodology, pulmonary toxicology and occupational health.

2.2 METHOD

2.2.1 Testing for validation of the US model

The US model was originally developed with the 'Overload' hypothesis observed in animal studies where pulmonary clearance of insoluble particles was shown to be impaired at high lung burdens (Morrow, 1988; Miller, 2000; Tran *et al*., 1999a,b).

The Model

Briefly, the model is described by 3 compartments: the alveolar region (X_1), the interstitium (X_2) and the lymph nodes (X_3). The rate of dust accumulation in each compartment is described by a differential equation.

Mathematically, the model is described as:

$$\begin{aligned}\frac{dX_1}{dt} &= Dose - K_t.X_1 - K_i.X_2 \\ \frac{dX_2}{dt} &= K_i.X_1 - K_{\ln}.X_2 \\ \frac{dX_3}{dt} &= K_{\ln}.X_2\end{aligned} \qquad (2.1)$$

where dX_i/dt is the rate of dust accumulating in compartment i (mg/day).

Dose = *Fractional-deposition x Volume-inhaled x Concentration*, is the deposited dose in the alveolar region (mg/day). *Fractional-deposition* is the percentage of inhaled dust that reaches the alveolar region. *Volume-inhaled* is the volume of air inhaled (m^3) either by nose or mouth-beathing; *Concentration* is the airborne concentration (mg/m^3).

Ks are rate parameters (day^{-1}). K_i is the interstitialisation rate, K_{ln} is the dust translocation rate to the lymph nodes and K_t is the pulmonary clearance rate of dust.

As observed in animal experiments, pulmonary clearance becomes impaired at high lung burden. So, the clearance rate K_t is dependent on the lung burden, X_1.

If X_1 is less than the minimum critical burden, X_{min} then

$$K_t = K_{\ln_0}$$

Otherwise,

$$K_t = K_{t_0}.e^{-B.\left(\frac{X_1 - X_{\min}}{X_{\max} - X_{\min}}\right)^C} \quad (2.2)$$

where X_{max} is the lung burden such that K_t declines by 50 percent of its original value (K_{t0}).

Similarly, K_{ln} increases with high interstitialised burden (X_2).

$$K_{\ln} = K_{\ln_0}.e^{B_i.X_2} \quad (2.3)$$

where B and C are parameters governing the extent of impairment of clearance and B_i relates the increase in the rate of translocation rate to the interstitialised lung burden X_2 and K_{ln0} is the original value.

The model came with three scenarios, each with a different parameter set describing a different hypothesis (or scenario) regarding the extent of the overloading of clearance mechanisms (Table 1.2). Specifically, the hypotheses were: (1) 'Severe Overload' when 90 percent of the clearance rate became impaired, (2) 'Moderate Overload' with 50 percent impairment of clearance and (3)'No Overload with high sequestration'. The last hypothesis described a scenario in which alveolar clearance is effective but the amount of dust in the alveolar region is small in proportion to the amount retained in the interstitial region at exposures experienced by these miners.

The UK dataset

To meet objectives (a) and (b), the UK data were organised so that exposure histories of each UK coalminer can be readily read into the kinetics model.

The UK data consists of 527 men who had both lung burden and exposure data. Actual whole lung weights were measured and therefore were better estimates of actual lung burdens (whereas the lung weights in the US data were estimated as a constant standard weight for a 'reference man'. Data was extracted from the PFR studies for exposure to dust and to quartz. An extrapolation was made of additional exposure beyond that recorded to whichever was earlier of death or assumed retirement at age 65. There were 5 men for whom we could not establish a date of death or birth and consequently they could not have any extrapolated exposure. Lymph burden data was available for 120 of the remaining men. However, dry weight of lymph was not available and this was assumed to be 25g as in the US studies. A file was created of the collated data on lung burden, lymph burden (if available), exposures and date and cause of death. Implausibility or inconsistency of the data on exposures resulted in a further 8 men being excluded from the study, leaving 514 men for whom analysis was carried out.

The model was used, together with the data, to simulate the different hypotheses regarding the retention and clearance of coalmine dusts in the lungs of each these coalminers. The simulated end-of-life lung and lymph node burdens were compared to observed burdens available for these coalminers.

Statistics

Appropriate 'goodnesss-of-fit' (GOF) statistics were calculated from the predicted and observed values for lung and lymph node burdens.

The two GOF statistics used to evaluate the model's power of prediction are the mean squared error (mse) and bias. They are defined as

$$mse = \frac{1}{N}\sum_{j=1}^{N}(predicted_j - observed_j)^2 \qquad (2.4)$$

$$bias = \frac{1}{N}\sum_{j=1}^{N}(predicted_j - observed_j) \qquad (2.5)$$

for observations 1...*N*.

Using the mse has advantages as it can be broken down into bias and variance components:

$$mse = \frac{1}{N}\sum_{j=1}^{N}(D_j - \bar{D})^2 + \bar{D}^2 = \text{error variance + bias}^2 \qquad (2.6)$$

where D_j = prediction error = $predicted_j$ – $observed_j$ and $\bar{D}$ is the mean of D.

The hypothesis (parameter set) yielding the least mean square error was selected as the 'best' model describing the retention and clearance of dusts in coalminers' lungs.

2.2.2 Model extension

To meet objective (c), appropriate numerical optimisation methods were required. This was necessary because kinetics parameters for the retention and clearance of quartz (and the non-quartz fraction) were not available in the US study (Kuempel *et al*, 1999) and also because there was an interest in comparing the parameters, estimated using these new algorithms and based on the UK dataset, with the original US parameter sets.

Fixed Parameters

To avoid over-parameterisation, we have to restrict the number of parameters to be estimated to two parameters since we only have two data points (lung and lymph node burden at autopsy) per miner. The two parameters we are most interested in are the clearance rate K_t and translocation rate to the lymph nodes K_{ln}. The factors affecting the deposited dose (i.e. deposition fraction, breathing rate) are kept fixed for all miners in the current study but will be investigated in future studies. The fractional deposition is for particles with Mass Median Aerodynamic Diameter (MMAD) of 0.5 μm. The human subject is assumed to be caucasian with a height of 1.76 metre, involved in heavy manual work, with mouth breathing (IRCP, 1994). The volume inhaled is for a 8-hr shift.

Furthermore, since the lung burden can not be separated into 2 sub-components, alveolar and interstitial burden, it is difficult to estimate the interstitialisation rate K_i. Therefore, this parameter is also kept fixed in this study. Other parameters to be kept fixed are X_{min} and X_{max}, they are scaled up from results in animal experiments (Muhle *et al*, 1990).

Table 2.1 summarises the parameters kept constant in this study

Table 2.1 The factors affecting the deposition and clearance of respirable particles in the human avleolar region.

Fractional Deposition	0.12
Volume Inhaled (m^3/hr)	1.69
K_i (day^{-1})	3×10^{-4}
X_{min} (mg)	105
X_{max} (mg)	10500

A routine written in MATLAB script was developed to estimate K_t and K_{ln} for each individual miner. This routine involves solving the system of differential equations describing the retention and clearance of coalmine dusts in the human lungs (Kuempel *et al*, 1999) for each individual miner and selecting the best fit parameters to the data for this individual using an optimisation routine which minimised

$$total\_mse = (predicted_{lung} - observed_{lung})^2 + (predicted_{lymph} - observed_{lymph})^2 \qquad (2.7)$$

A detailed description of the numerical routines is given in Kuempel *et al*, (in press).

The dataset for all 514 miners was divided into 2 subsets (a and b) by a random selection process that included evenly dividing the lymph node data available, resulting in 2 datasets each consisting of 257 miners (of which data for lymph node burden were available for 60 miners in each group). The former was used for parameter estimation and the latter to test the model for validation.

Our aim was

Model Calibration

- to estimate the relevant model parameters for each individual miner,
- derive average parameters from the distribution of the parameters,

Model validation

- predict the lung and lymph node burden of each miner from the 'model validation' sub-group.

For the estimation of the rate of dust translocation to the lymph nodes (K_{ln}), the parameter estimation process was restricted to data where lymph node burden data are available, i.e. the 60 miners of subset (a) and the 60 miners of subset (b).

This method was applied for the quartz and the non-quartz fraction of the total dust.

2.3 RESULTS

2.3.1 Model validation

To validate the US model with UK data, lung and lymph node burden as well as individual exposure histories for 514 UK coalminers were used. For a given hypothesis (scenario), a simulation of a life-time lung retention and clearance for a given exposure history for each coalminer was made and the final lung and lymph node burdens predicted.

For each hypothesis, the factors affecting the deposition of (human) respirable coalmine dusts were kept constant. This choice was made, in both the US and UK studies, so as to keep the number of parameters estimated to the acceptable minimum, and also because the interest in the current study was to assess the extent of variation in the clearance rate and the translocation rate to the lymph nodes.

The kinetics parameters consisted of two types: Those which govern the translocation of dusts in different pulmonary compartments and those used to quantify the extent of overload. Parameters pertaining to each category and each hypothesis are summarised in Table 2.2.

Table 2.2 The hypotheses and their corresponding parameter sets.

		Hypothesis 1	Hypothesis 2	Hypothesis 3
	B	2.3	0.7	$1x10^{-4}$
Overload	C	1.0	1.0	1.0
Parameters	B_1	$1x10^{-9}$	$1x10^{-9}$	$1x10^{-9}$
	X_{min} (mg)	105	105	105
	X_{max} (mg)	10500	10500	10500
	K_t	$1x10^{-3}$	$1x10^{-3}$	$1x10^{-3}$
Kinetics	K_i	$3x10^{-4}$	$3x10^{-4}$	$4.7x10^{-4}$
Parameters	K_{ln}	$1x10^{-5}$	$1x10^{-5}$	$1x10^{-5}$

The value for K_t (= $1x10^{-3}$ day^{-1} approximately) was taken from Bailey, 1985. This study gave a half-time of the effective clearance rate for normal humans at approximately 693 days. Values of K_i and K_{ln} were estimated by the US studies (Kuempel *et al.*,1997).

The results for the three simulations (based on the 3 hypotheses) are shown in Table 2.3 and Figure 2.1. Each simulation was for lung burden in 514 miners, and for lymph node burden in the subset of 120 miners with this data. The results summarised in Table 2.3 give the mean squared error (mse) and the squared bias ($bias^2$) calculated from the model predictions and observed data for lung and lymph node burden.

Table 2.3 The mean squared error and $bias^2$ calculated for each hypothesis underlying the model.

	Hypothesis 1 'Severe Overload'	Hypothesis 2 'Moderate Overload'	Hypothesis 3 'No Overload'
Lung burden (n=514)			
mse	559.3	130.9	123.6
$bias^2$	82.91	0.225	1.040
Lymph node burden (n=120)			
mse	4.36	1.91	1.66

$bias^2$	0.04	0.42	0.18

Table 2.4 Summary statistics of the Residuals (Obs-Pred) of each hypothesis

	Hypothesis 1	**Hypothesis 2**	**Hypothesis 3**
Lung burden (n=514)			
Minimum	-103.61	-42.65	-33.82
Mean	-9.10	0.47	-1.02
Maximum	46.27	57.88	55.16
Lymph node burden (n=120)			
Minimum	-9.41	-2.88	-2.60
Mean	-0.21	0.65	0.42
Maximum	4.01	3.95	3.70

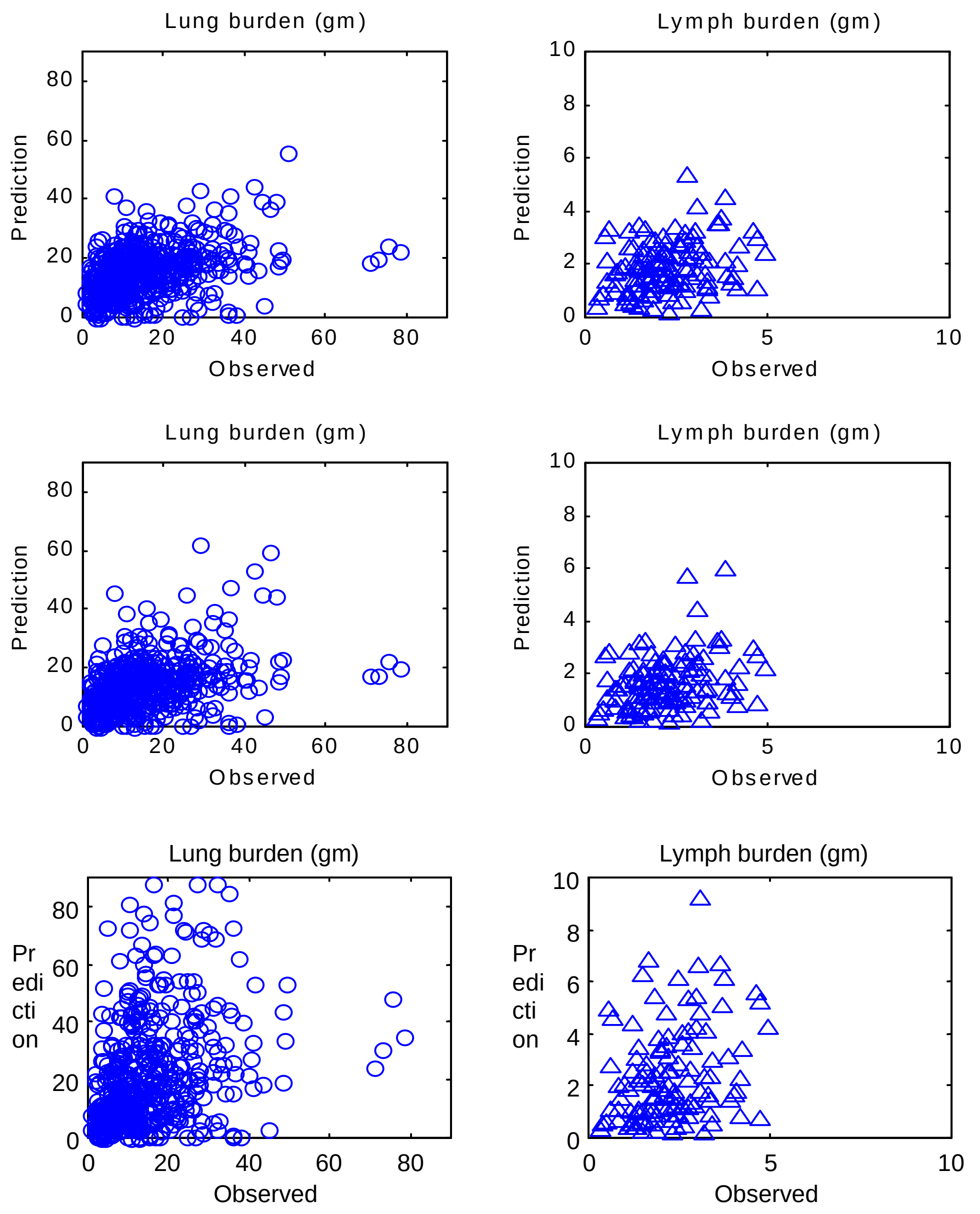

Figure 2.1 Model predictions and Observed data for lung and lymph node burdens for the three hypotheses (top to bottom). (1) 'No Overload'; (2) 'Moderate (50pc) Overload'; (3) 'Severe (90pc) Percent Overload'.

The assessment of the power of prediction of each of the hypotheses, summary statistics of the residuals (i.e. difference between observed and predicted) were also calculated. The results are given in Table 2.4.

The model representing the 'no overload and high interstitialisation' hypothesis (hypothesis 3) gave the lowest mean square error for lung and lymph node burden and therefore, according to this criterion provided the 'best predictions'. However, the model with hypothesis 2 ('50 percent overload') gave mean square error values which are comparable and a smaller bias for lung burden.

The model for the hypothesis 1 ('90% overload') gave the worst predictions when compared to UK data. Thus, our findings with the UK data have confirmed the early findings when the same hypotheses were tested with the US data (Kuempel *et al*, 1999).

Figure 2.2 (a) shows the plot of the residuals (Observed –Predicted) for lung burden against cumulative exposure. A locally-weighted regression smoother (LOESS) was fitted to capture the underlying trend of the relationship between the residual lung burdens and cumulative exposure. From Figure 2.2(a),

Further assessments of the model representing hypothesis 3 showed that

(i) the model slightly under-predicted the lung burden of miners with low cumulative dust exposure and (ii) over- predicted the lung burden of miners with high cumulative dust exposure.

Figure 2.2(b) shows the underlying trend of the lymph node burden and cumulative exposure.

From Figure 2.2(b),

(iii) the model under-predicted the lymph burden of most miners. The residual (Observed-Predicted) decreased with increasing cumulative exposure but, for the miners with cumulative exposure > 400 $gm.h.m^{-3}$, the model over predicted the lymph node burdens.

Furthermore, from Figure 2.3 (a) and (c),

(iv) the model over-predicted the lung burden of miners of pathology categories 'M' and 'F';

(v) the model under-predicted the lymph node burden of miners for all three pathological category. However, the average residual decreased as the category changes from 'M' to 'F' to 'PMF'. The model fits best on average for 'PMF' men in both lung and lymph node burdens.

From figure 2.3 (b) and (d),

(vi) the model over-predicted miner's lung burden across all different coal ranks, although the average residual lung burden are small for coal rank 1 and 5 and practically zero for coal rank 6;

(vii) the model under predicted lymph node burden for all coal ranks except coal rank 4 when it slightly over predicted the lymph node burden.

We have also restricted the comparisons of the model predictions (lung and lymph node burden) of a subset of 201 miners with more reliable exposure data. The model predictions of lung and lymph node burden for this subset were the same as in (i) and (ii).

The findings (i), (ii), (iv) and (vi) were similar to the results obtained with the model predictions and the US data (Kuempel *et al.*, 1999).

The model representing hypothesis 3 ('No Overload') was therefore chosen as the model which best represented the retention and clearance of coalmine dusts for both US and UK datasets.

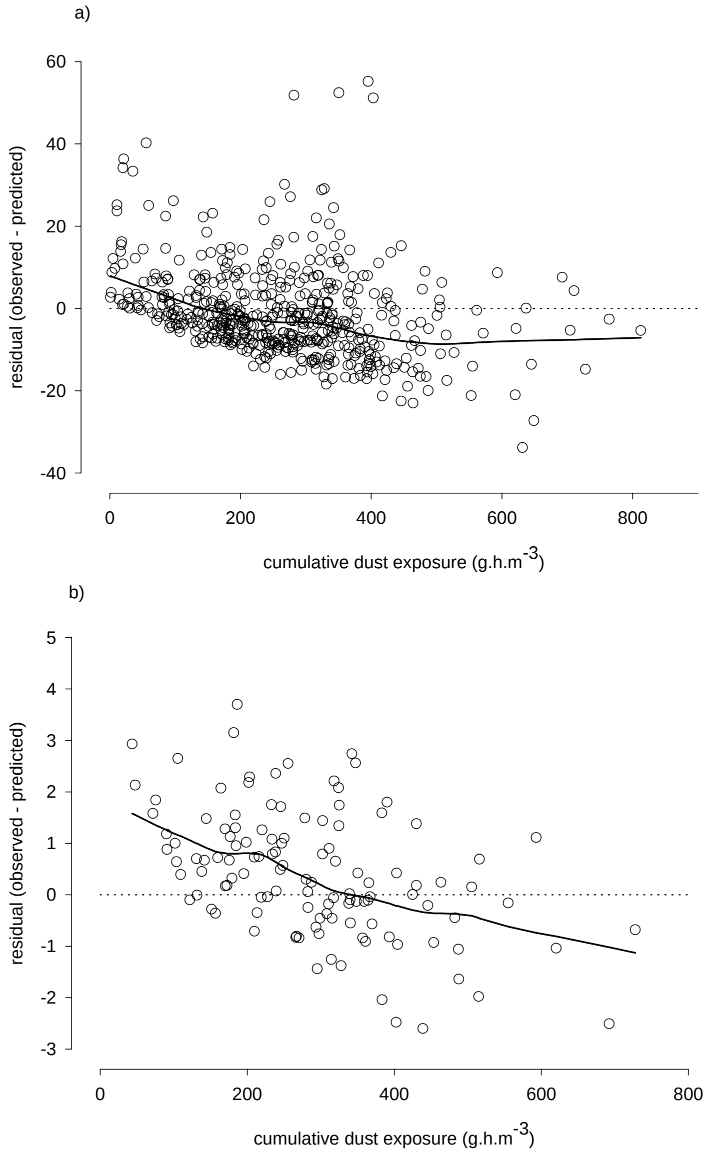

Figure 2.2 (a) The residual lung burdens (Observed-Predicted) and cumulative exposure. (b) The residual lymph node burdens and cumulative exposure

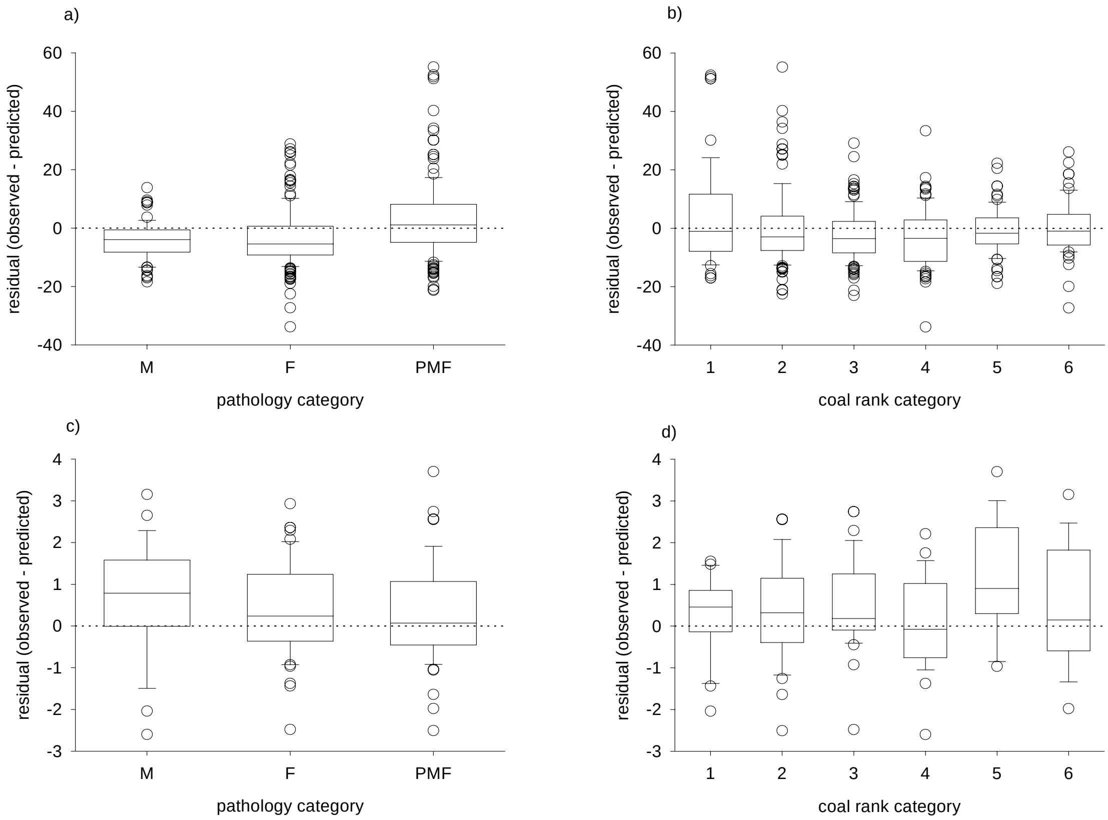

Figure 2.3 Boxplots of Residual lung burdens vs (a) pathology category; (b) coal rank category and of residual lymph node burdens vs (c) pathology category; (d) coal rank category

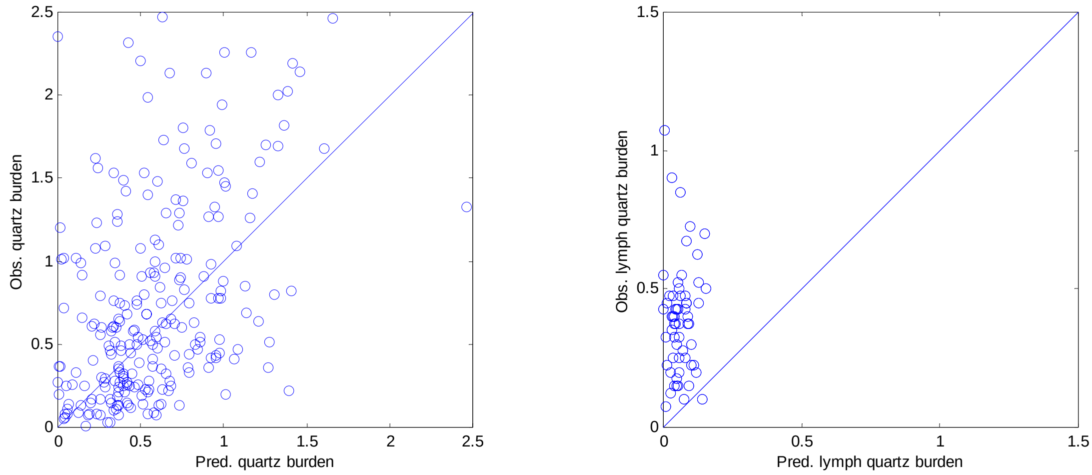

Figure 2.4 (a) Model predictions of quartz lung and (b) lymph node burden using the parameters of the third hypothesis compared with observed values

2.3.2 Model extension

The model representing 'no overload and high interstitialisation' was also used to predict the retention and clearance of quartz and the non-quartz fraction of the lung and lymph node burdens in coalminers. The toxicity of freshly cut quartz is well documented (Donaldson and Borm, 1998). However, the kinetics of the retention and clearance of quartz in humans are not known. Furthermore, there is variability in the extent of reported quartz toxicity. This may be due differences in the surface activity of quartz (Fubini *et al*, 1998). Thus, as a first step in our investigation, redicted the quartz lung and lymph node burden using the chosen model described above. The results are shown in Figure 2.4.

The model under-predicted the quartz lung burden generally and lymph node burden consistently and significantly, suggesting that the quartz fraction is preferentially retained (than the total dust) in the lung and lymph node. These findings were in accordance of the current understanding of quartz toxicity (Donaldson *et al*, 1988; Tran *et al*, 1994). However, the kinetics rates (K_t and K_{ln}) were still unknown for quartz. To estimate these parameters we used the method outlined in section 2.2

Results for quartz

Parameter estimation for each miner. Parameters K_t and K_{ln} were estimated for each miner. A perfect fit to lung and lymph node burden was often achieved with this sub-group of 120 miners. A distribution of K_t and K_{ln} were obtained and given in Figure 2.5(a,b). The goodness-of-fit for lung and lymph node burdens are shown in Figure 2.5 (c,d).

(Five miners were not included in the result because there was not enough dust from exposure to achieve the final level of burdens even if there is no clearance (i.e K_t was either less or equalled to 0)).

Derivation of average parameters for the sub-group with lymph node burden data. From Figure 2.5 (a and b), the distribution for K_t and K_{ln} are clearly skewed. The arithmetic and geometric means for K_t and K_{ln} were calculated and shown in Table 2.5.

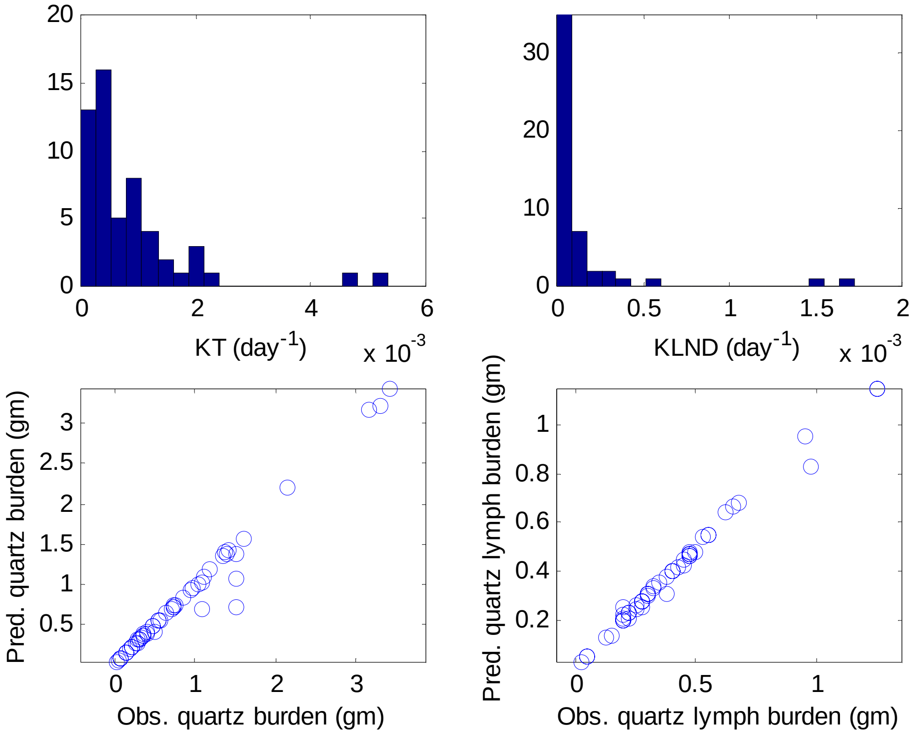

Figure 2.5 (a) Distribution of K_t. (b) distribution of K_{ln} for quartz. (c) Obs. *vs* Pred. for lung burden. (d) Obs. *vs* Pred. for lymph node burden

Table 2.5 The arithmetic and geometric mean of Kt and Kln for the quartz fraction

	Arithmetic mean	Geometric mean
K_t	8.3×10^{-4}	1.1×10^{-6}
K_{ln}	14.0×10^{-5}	5.8×10^{-5}

Note that K_{ln} is higher than the value originally assigned for total dust (1×10^{-5}).

Predictions of lung and lymph node burdens. The mean values of K_t and K_{ln} above was subsequently used to predict the lung and lymph node burdens in the 'model-validation' sub-group of 60 miners with lymph node burdens.

Figure 2.6 (a and b) shows the results of the predictions using the geometric mean of K_t and K_{ln}. The model tends to over-predict the lung and lymph node burden. However, the prediction of lung burden for individual miners is relatively better than the prediction of lymph node burden.

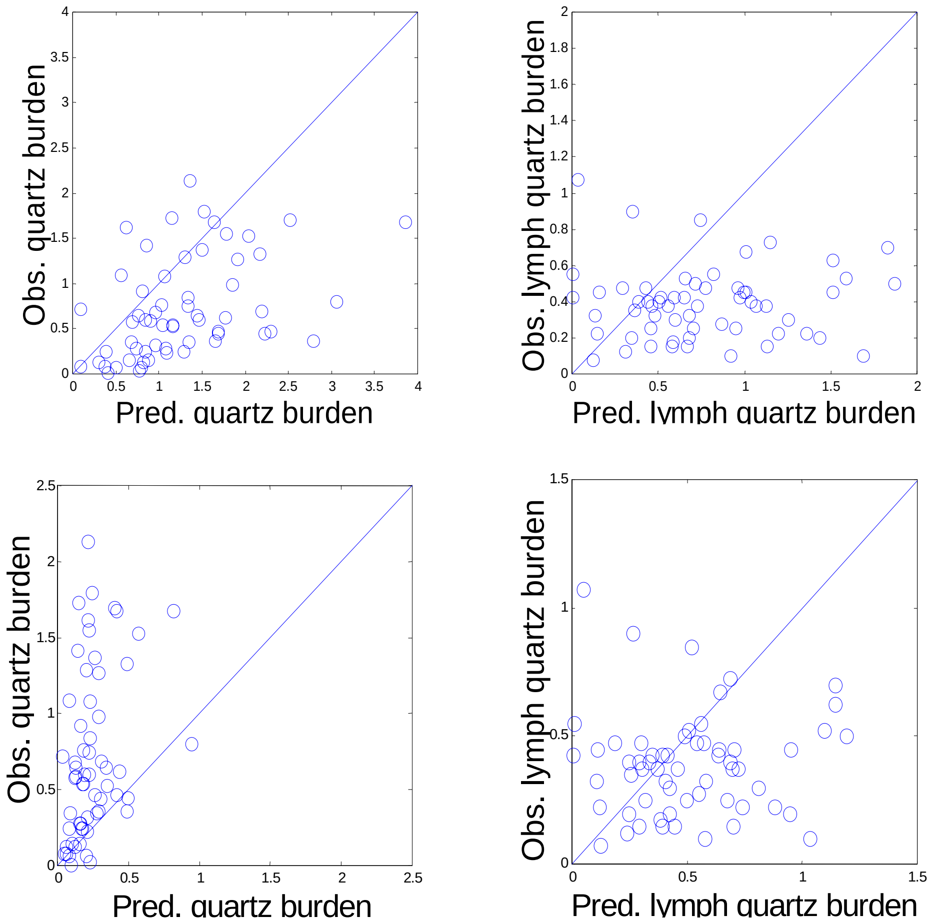

Figure 2.6 (a,b) Prediction of quartz burden in the lung and lymph node of individual miners using the geometric mean of K_t and K_{ln}; (c,d) Predictions using the arithmetic mean of K_t and K_{ln}

Figure 2.6 (c and d) shows the results of the predictions using the arithmetic mean for K_t and K_{ln}. The model tend to under-predict the lung and lymph node burdens for miners with over 0.2 gm of quartz burden. Generally, the prediction of lymph node burden are relatively better with the arithmetic mean than geometric mean.

Further predictions were also made for the whole dataset of 257 miners. Figure 2.7 (a,b) shows the results for quartz lung burdens when the arithmetic and geometric mean of K_t and K_{ln} were used.

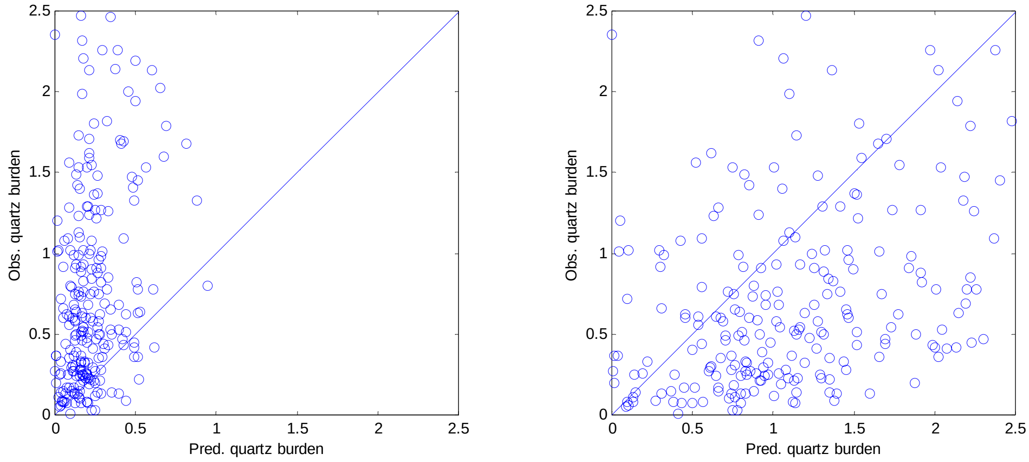

Figure 2.7 Prediction of quartz lung burden using (a) arithmetic mean of K_t, K_{ln} and (b) the geometric mean of K_t, K_{ln}. Note that the predictions of lymph node burden for all available data are shown in Figure 6

Table 2.6 The mse and bias for quartz lung and lymph node burden using the arithmetic and geometric mean for K_t and K_{ln}

	Arithmetic mean	Geometric mean
Lung burden		
Mse	1.13	0.95
Bias	-0.66	0.36
Lymph node burden		
Mse	0.13	0.38
Bias	0.11	0.37

Results for the non-quartz fraction

Derive parameters for each miner. We applied the same procedure to the non-quartz fraction. We obtained very similar distributions for K_t and K_{ln} to the results from Kuempel *et al*, (1999) (Figure 2.8a and b).

Derive average parameters for the sub-group. The arithmetic mean and geometric mean of K_t and K_{ln} are similar. (Table 2.7). This reflects the relative skewness in the distribution of K_{ln} as compared the distribution of K_t.

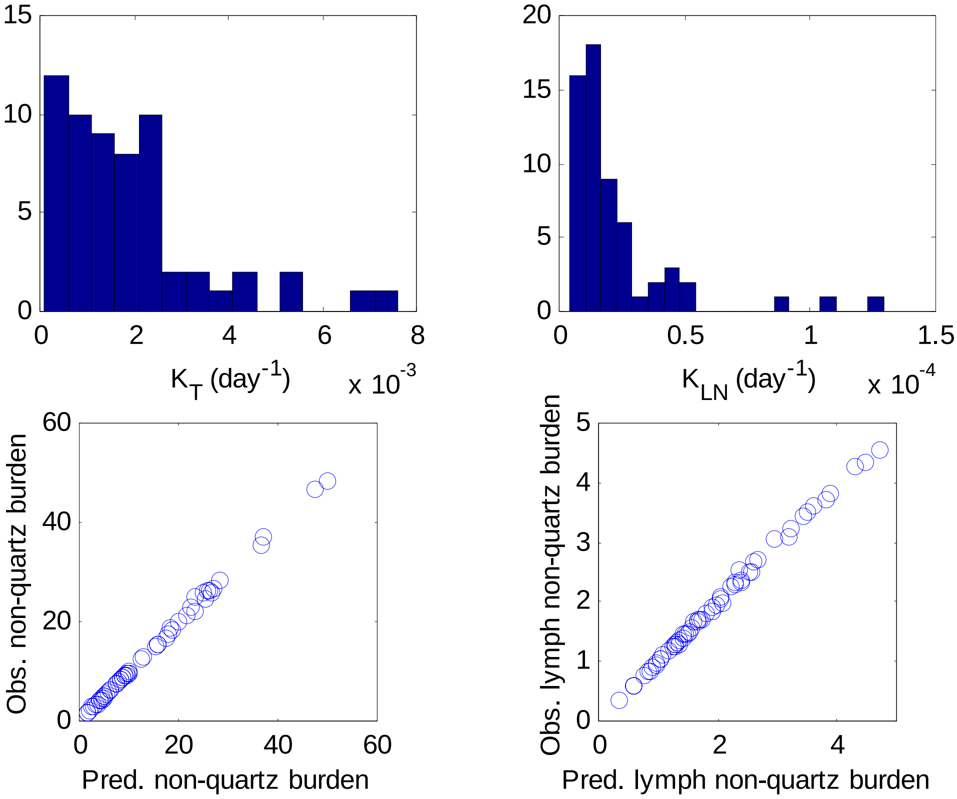

Figure 2.8 (a) Distribution of K_t and (b) K_{ln} for the non-quartz fraction. (c) Pred. vs Obs. for lung burden and (c) lymph node burden

Table 2.7 The arithmetic and geometric mean of K_t and K_{ln} for the non-quartz fraction for the calibration subset

	Arithmetic mean	**Geometric mean**
K_t	0.0019	0.0013
K_{ln}	0.22×10^{-4}	0.16×10^{-4}

Predictions of lung and lymph node burden. Using the geometric mean for K_t and K_{ln} , we predict the lung and lymph node burdens for the other sub-groups to validate the model (Figure 2.9 and 2.10).

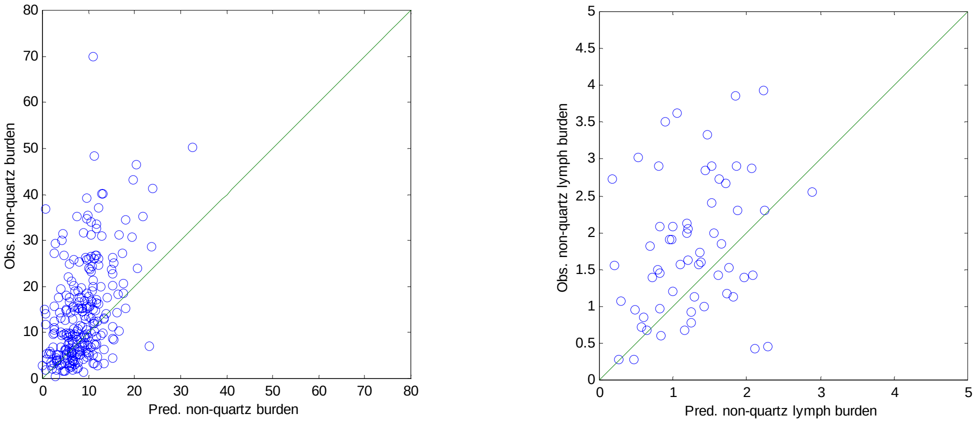

Figure 2.9 Model prediction of (a) lung burden and (b) lymph node burden for an independent subset of 257 miners with a subgroup of 60 miners with lymph node burden, using the arithmetic mean for K_t and K_{ln}

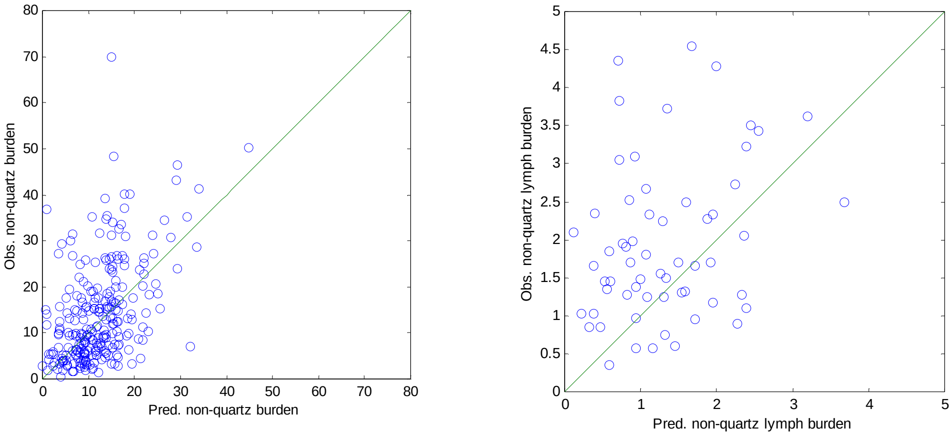

Figure 2.10 Model prediction of (a) lung burden and (b) lymph node burden for an independent subset of 60 miners with lymph node burden using the geometric mean for K_t and K_{ln}

Table 2.8 The mse and bias for the non-quartz lung and lymph node burden using the arithmetic and geometric mean for K_t and K_{ln} for the validation subset

	Arithmetic mean	Geometric mean
Lung burden		
Mse	120.82	96.13
Bias	-5.42	-1.76
Lymph node burden		
mse	2.20	2.21
bias	0.40	0.40

2.4 DISCUSSION

2.4.1 Model validation

The first objective of this study is to validate the model by Kuempel *et al* (2000), using data available in the UK. The validation criterion is based on the smallest mean square error (mse). Three models (hypotheses), with two representing different extents of overload (severe overload, moderate overload) and one representing the no overload but high interstitialisation hypothesis were tested. The model representing the no-overload in pulmonary clearance but high interstitialisation gave the smallest mse for both lung and lymph node burden. Originally, the same model gave also the smallest mse in the same test with the US data (Kuempel, 1997) therefore this model has been tested for validation with the UK data. The important finding here is that the models which attribute the retention of dust in the lungs of humans to some mechanisms of impairment of alveolar clearance, as observed in the rats, do not predict the end-of-life lung and lymph node burden as well as a model with an effective clearance and a high interstitialisation rate. This fundamental difference in the transfer kinetics of inhaled dust between different species has been observed in other studies (e.g Nikula *et al*, 2000). Our current results suggest that in extrapolating the data from inhalation studies with rodents to humans for risk assessment, interspecies differences in the kinetics of retention and clearance of inhaled particles must be taken into account. However, note that the UK data are not representative but over-represent the miners who had lung disease. Therefore, the poor predictions by the 'overload' models may also be because overload has already occurred (the model is unbiased for the 'PMF' men (Figure 2.3)).

The kinetics model (hypothesis 3) is based on one central (in terms of contributing to the total lung burden) and two peripheral compartments, namely the interstitial, alveolar and lymph node compartment. The alveolar compartment is non central because of the high interstitial rate removing dust away from the alveolar region to the interstititium, the interstitial compartment is consequently central because it sequestrates dust from the alveolar region and also because of the relatively slow translocation rate from the interstitium to the lymph node compartment. The input to the interstitial compartment is proportional to the deposited dose which, in turn, is proportional to the exposure concentration pattern, *C(t)* (Equation (2.1)). The amount of dust sequestrated in this compartment up to time *t* is simply the time integral (from the beginning of exposure) of the input and therefore is proportional to

$$\int_{t_0}^{t} C(s).ds \qquad (2.8)$$

where t_0 is the time corresponding to the beginning of exposure.

This integral is, however, the estimated cumulative exposure. Since the alveolar compartment was not central in this kinetics model, the lung burden is mainly represented by the interstitial compartment where dust is mainly sequestrated. Therefore, the model prediction of lung burden may be comparable to the regression based model in Chapter I.

In this study, other models, representing the extent of overload, were tested and rejected. The 'best' kinetics model was the model based on a sequestration hypothesis (attributed to the process of interstitialisation). In a sequestration model, dust simply accumulated and there is evidence that interstitialisation is prominent in higher primates (Nikula *et al*, 2000). Thus, the result suggests a tentative biological interpretation of the results from epidemiological studies.

The predictions from the chosen model were shown to under-predict the lung burdens of miners with low estimated cumulative exposure and over-predict those with high estimated cumulative exposure. One may speculate that this may be due to an under-estimation of the exposure concentration for those with low cumulative exposure and an over–estimation of those with high cumulative exposure. Alternatively, the predictions could be brought closer to of lung burden data if the clearance rate K_t could be lower for the low cumulative exposure miners and higher for those in the higher cumulative exposure group. However, this is unlikely since those in higher cumulative exposure are generally associated with lung disease and an impairment of alveolar clearance.

Examinations of the model predictions and coal rank showed no discerning trends. However, the model predictions are biased for miners with M and F and unbiased for those with PMF. This could be either because there is considerable uncertainty in the exposure history of the miners studied here or the relationship between dose and disease may involves other factors not considered in the current model.

2.4.2 Model extension

To explore further the possible factors which influence the relationship between exposure and dose, the extended model was used to investigate the kinetics of retention and clearance of the quartz and non-quartz fraction of coalmine dusts.

The quartz fraction

Unlike the kinetics of effective clearance in humans (Bailey *et al*, 1985), little is known on the retention and clearance of quartz in the human lungs. Animal experiments (e.g. Donaldson *et al*, 1988) have shown that quartz impaired lung clearance at very low lung burden. The cessation of particle clearance occurred together with inflammation and an increase in the rate of translocation to the lymph nodes.

Our results (Table 2.5) suggested that, for quartz, a lower clearance rate K_t and a higher translocation rate to the lymph node K_{ln} (than the rates for the non-quartz fraction, given in Table 2.7) should be used to describe the retention and clearance of the quartz fraction. This finding is consistent with the animal data on quartz.

To estimate K_t and K_{ln} for quartz, the method outlined by Kuempel *et al*, (in preparation) was used and the parameter pair was estimated for each miner. A distribution for K_t and K_{ln} was obtained (Figure 2.5).

Almost a perfect fit was obtained for both the lung burden and lymph node burden of 60 miners (with lymph node burden, Figure 2.6 (b) and (c)).

Summary statistics for K_t, whether based on the arithmetic or geometric mean of K_t, give an average value smaller than the original value for effective clearance (Table 2.5). Similarly, the average values for K_{ln} are higher than the originally assigned value for total dust (Table 2.5). (Note that the lower value of K_{ln} obtained using the geometric mean is compensated by the zero value of the clearance rate K_t). These findings appear to confirm our original expectation on the toxicity of quartz. The model used these average parameters to predict the lung and lymph node burdens of an independent set of 257 miners.

The predictions for lung burden using the arithmetic mean (for K_t and K_{ln}) gave a negative bias (i.e. the model under-predicted quartz lung burden) and the mse was higher than the mse obtained using the geometric means of K_t and K_{ln} for predictions. Note that the second method for prediction yielded a lower (positive) bias (Table 2.6). However, for lymph node burden, the first method (using arithmetic mean) gave a lower mse and bias as compared to the second method.

Therefore, the geometric mean of K_t and K_{ln} were chosen as the 'best' estimated values for the kinetics of retention and clearance of quartz in coalminer lungs.

Non-quartz fraction

The same method used for estimating the retention and clearance kinetics of quartz was also applied to the non-quartz fraction. Again, almost perfect individual fits were obtained for the non-quartz fraction of the lung and lymph node burden. A distribution of the values of K_t and K_{ln} were obtained (Figure 2.8). The distributions were similar to those obtained by Kuempel *et al,* (1997, 2000). The K_t and K_{ln} were averaged to obtain the arithmetic and geometric means (Table 2.7). Note that the values for the averages are generally close to the original values chosen by Kuempel *et al* (1997).

Since quartz only represents a small fraction of the total dust, it is not surprising that the non-quartz fraction has kinetics very close to those obtained originally using the total dust data. What is more interesting is that the geometric mean of K_t and K_{ln}, which gave the best prediction according to the criteria used in this study, were close to the original values estimated by Kuempel *et al* (1997).

2.5 CONCLUSIONS

In this study, a kinetics model with three alternative hypotheses describing the kinetics of retention and clearance of coalmine dust in humans was originally developed using data on coalminers' exposure history, lung burden at autopsy available in the US.

Using data available in the UK, with additional information on the quartz content and lymph node burden, a kinetics model describing the retention and clearance of coalmine dusts was tested for validation.

In order to validate this model, the relevance in humans of the overloading of particle clearance in the lungs, as observed in animal studies, was assessed using this model and available data. It was found that the model describing a peripheral alveolar compartment with an effective clearance, together with a major 'sequestration' compartment is the model best describing the retention and clearance of dusts in humans.

This model was subsequently extended to include the retention and clearance of quartz and the non-quartz fraction. It is found that the 'best' parameter set for quartz kinetics was estimated by the geometric mean of the clearance rate and the translocation rate to the lymph nodes. These parameters correspond to a hypothesis of impairment of clearance and a higher rate of translocation to the lymph nodes observed in animal studies.

The kinetics of the non-quartz fraction were found to be close to the original estimates by Kuempel *et al* (1997).

One major limitation of the current work is that it does not incorporate the range of variation seen in the lung and lymph node burden and reflected in the distributions of K_t and K_{ln}. Another limitation is that the exposure history of each individual miner and their breathing parameters were assumed fixed. To complete the current exercise, the same validation process described in this paper should be repeated with the kinetics parameters fixed and varying the deposited dose (or the parameters influencing the deposited dose). A sensitivity analysis on the model parameters would help to assess whether the range of variation seen in the data can be attributed to a single or group parameters.

Further model fitting to groups of miners, with 'P', 'M' and 'PMF' separately to assess possible differences in the kinetics parameters due to disease, is also important. Also, further investigation on the degree of bias in the model prediction could be done by fitting the model to the 'calibration' dataset (minimising the total mse) then predictions for the 'validation' dataset made and bias assessed.

Finally, a probability distribution fit on the distribution for K_t and K_{ln} followed by a Monte Carlo Simulation process may be the way forward as it incorporates the variations in the data in its predictions.

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