Rat- and Human-based Risk Estimates of Lung Cancer from Occupational Exposure to Poorly-Soluble Particles: A Quantitative Evaluation

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Abstract. In risk assessment there is a need for quantitative evaluation of the capability of animal models to predict disease risks in humans. In this paper, we compare the rat- and human-based excess risk estimates for lung cancer from working lifetime exposures to inhaled poorly-soluble particles. The particles evaluated include those for which long-term dose-response data are available in both species, i.e., coal dust, carbon black, titanium dioxide, silica, and diesel exhaust particulate. The excess risk estimates derived from the rat data were generally lower than those derived from the human studies, and none of the rat- and human-based risk estimates were significantly different (all p-values > 0.05). Residual uncertainty in whether the rat-based risk estimates would over- or under-predict the true excess risks of lung cancer from inhaled poorly-soluble particles in humans is due in part to the low power of the available human studies, limited particle size exposure data for humans, and ambiguity about the best animal models and extrapolation methods.

1. Introduction

Quantitative risk assessment (QRA) requires dose-response data to evaluate the relationship between exposure to a toxicant and the probability of developing an adverse health effect. When epidemiological exposure-response data are available (e.g., from an occupational cohort), risk estimates can be obtained directly from humans. However, human exposure-response data can be inadequate for QRA (e.g., insufficient exposure data or follow-up time). The goal of risk assessment is to determine the probability of disease or injury so that risk management intervention measures can be taken to prevent adverse effects in humans. QRA often relies on data from laboratory animals to estimate disease risks in humans.

Chronic inhalation studies in rats exposed to poorly-soluble particles have shown significantly elevated lung tumor response, while studies in mice and hamsters have not [1-3]. Occupational exposures to some respirable, poorly-soluble particles have been associated with elevated lung cancer in some studies, including carbon black [4,5]; diesel exhaust particulate [6-8]; and titanium dioxide [9], although generally without evidence of an exposure-response relationship; no association with particle exposure and lung cancer was found in other studies of titanium dioxide [10], carbon black...
Significant exposure-response relationships have been reported for crystalline silica in several studies [15, 16] including a pooled analysis of six cohorts [17], but not in a recent U.K. study with lower exposures [18]. Because epidemiology studies typically do not have sufficient power to detect disease risk (e.g., lung cancer) at levels of concern to regulatory agencies (e.g., 1/1000), negative studies generally cannot be used to rule out such risks [19]. Thus, experimental studies in animals are often used to determine dose-response relationships and estimate risk in humans.

There is some debate about the extent to which rodent data may be useful for predicting human lung cancer risk of inhaled poorly soluble particles, particularly in regards to the role of particle overload of lung clearance and inflammation and cell proliferation processes in the rat lung tumor response [20-23]. These evaluations have largely been qualitative, and quantitative dose-response data in both animals and humans are needed.

In this study, we quantitatively compare working lifetime excess risk estimates of lung cancer derived from both rat and human dose-response data of respirable poorly-soluble particles including coal dust, carbon black, titanium dioxide, silica, and diesel exhaust particulate. These comparisons provide a quantitative evaluation of the relevance of the rat model of particle-induced lung cancer for risk assessment in humans.

2. Methods
Comparison of the animal and human-based excess risk estimates included several steps, including: estimate working lifetime excess risk of lung cancer in humans; predict the retained particle lung burden in humans; estimate the rat-equivalent lung burden; compute the excess risk in rats at that lung burden; and finally compare the human- and rat-based excess risks (Figure 1).

![Figure 1](image-url)
Excess risk (ER), or exposure-attributable risk, is defined here as the increased probability of an adverse response at a given dose compared to that in unexposed individuals:

\[ \text{ER(dose)} = P(\text{dose}) - P(0) \]  

(1)

where \( P(\text{dose}) \) and \( P(0) \) represent the probability of tumor response at a given dose or zero dose, respectively. Dose was expressed as either cumulative exposure to airborne particles (human studies) or the retained lung burden as particle mass or particle surface area at the end of exposure (rat studies).

The methods shown in Figure 1 were performed for each of the particle types investigated in this study (i.e., coal dust, carbon black, titanium dioxide, and crystalline silica). The models used at each step are described in Sections 2.1 and 2.2.

2.1. Human data

Epidemiological studies were selected which had quantitative estimates of cumulative exposure to respirable particles and lung cancer mortality rates. Studies with clear evidence of confounding exposures were excluded, but no additional criteria for study quality were imposed. These studies include: crystalline silica [15, 16, 18]; coal dust [14]; carbon black [4] and titanium dioxide [9, 10]. For silica, the pooled analysis [Steenland et al. 2001] was not used here due to more complicated methods required to estimate excess risks; and the three most recent individual studies were selected, one of which [15] was included in the pooled analysis. In addition, studies of diesel exhaust particulate studies evaluated in Stayner et al. [6] are illustrated separately.

The lifetime excess risks of lung cancer were estimated using Poisson regression models and lifetable analyses that account for competing causes of death, in U.S. males up to age 85 after a 45-year working lifetime [24]. A linear relative rate model was used to fit the data for crystalline silica [15, 16, 18], coal dust [14], carbon black [4], and one of the titanium dioxide studies [9]. In fitting this model to the Brown and Rushton study [18], which reported results as categorical relative risks, correlations were not accounted for in the categories. All models were fit by iteratively re-weighted least squares. Goodness of fit (\( p > 0.05 \)) was evaluated for each model, except in Fryzek et al. [10], since the coefficient for that model was provided by personal communication (Fryzek to NIOSH in 2004). The linear relative rate model was of the form:

\[ \text{RR}(X) = 1 + \beta \times X \]  

(2)

A log-linear relative rate model was used to fit the data in the other titanium dioxide study [10], since that study reported relative risks based on this model form:

\[ \text{RR}(X) = \exp(\beta \times X) \]  

(3)

where \( \text{RR}(X) \) is the relative rate in the exposed population; \( \beta \) is the coefficient for cumulative exposure; and \( X \) is the cumulative exposure to airborne particles (mg/m\(^3\) x years) (respirable size fraction, except Fryzek et al. [10], which used total particulate).

Excess risks were estimated at the airborne mean concentrations (8-hour time-weighted average) that are equivalent to the cohort mean or median cumulative exposures reported in each epidemiology study, averaged over a 45-year working lifetime. For example, a cohort mean cumulative exposure of 64 mg/m\(^3\) x yr [14] averaged over 45 years is equivalent to an airborne mean concentration of 1.4 mg/m\(^3\). Similarly, a mean concentration of 0.83 mg/m\(^3\) is estimated from a 45-year exposure at 37.5 mg/m\(^3\) x yr (the midpoint of the middle cumulative exposure group for all-plants) [4]. In Boffetta et al. [9], a mean concentration of 0.044 mg/m\(^3\) is estimated from a 45-year exposure at 1.98 mg/m\(^3\) x yr (the cohort median cumulative exposure). Insufficient information was available in Fryzek et al. [10] to estimate a mean concentration, and the excess risk was estimated at the mean concentration from Boffetta et al. [9].
The 15-year lag model for cumulative exposure was used in Fryzek et al. [10]. Cumulative exposure group midpoints were used to fit the linear relative rate models in the other studies, and for Boffetta et al. [9], a value of 78.1 mg/m$^3$ × yr was assumed for the highest category.

A human lung dosimetry model (multiple-path particle deposition model, or MPPD) [25] was used to estimate the retained particle lung burdens after 45-years of exposure at these mean concentrations (assuming 8 hrs/day, 5 days/wk, 50 wks/yr). The Yeh-Schum deposition model within MPPD was selected, along with the default model parameters, except for the following, which represent occupational exposures: breathing frequency (17.5 breaths/min) [26] and tidal volume (1143 ml, to yield a minute volume of 20 L/min) [26]. In addition, breathing scenario was assumed to be oronasal-normal augmenter, and the inhalability adjustment was selected. Particle sizes and input parameter values are provided in Appendix A.

2.2. Rat data

Chronic inhalation studies in rats were selected on the same types of particles as those in the epidemiological studies. The rat studies included: coal dust [27, 28]; carbon black [3, 29], titanium dioxide [3, 30, 31]; and crystalline silica [31]. The dose-response data analyzed include the retained lung burden after two years of inhalation exposure and the lung tumor proportion, excluding squamous cell keratinizing cystic tumors (which have been considered a noncancerous lesion in rats [32]). The particle mass lung dose was used for coal dust, carbon black, and silica. For titanium dioxide, data were available in both fine and ultrafine particle sizes, so the mass lung doses of titanium dioxide were converted to particle surface area doses (using specific surface area) in order to utilize the data available for both particle sizes.

The rat dose-response data were fit with a multistage model, using the benchmark dose software (BMDS) [33]:

$$P(D) = 1 - \exp(-Q_0 - Q_1*D - Q_2*D^2)$$

where $P(D)$ is the probability of lung tumors at a given dose; $Q_0$ is the coefficient for the background tumor rate; $Q_1$ and $Q_2$ are the coefficients for dose; and $D$ is dose (particle mass or surface area lung burden). Multistage models have been used for many years in cancer risk assessment. A 2nd-degree polynomial model form was used to allow for nonlinearity in the dose-response curve while not over-fitting the data, and the coefficients were restricted to be nonnegative. Male and female rat data were generally combined, except for carbon black, where only the female rat data were used [3, 29] due to the heterogeneity in the data from the lack of an exposure-related increase in lung tumors in male rats [29]. Model fits to the dose-response data were considered adequate at $p$-values > 0.05 (goodness of fit test).

The rat-based excess risks associated with the doses of interest from the human studies were estimated by linear extrapolation below the 10% BMD (estimated by the multistage model; target BMD was derived from the slope of the line from 10% BMD to zero). Dose was normalized between humans and rats based on the ratio of alveolar lung surface area [34] – using the values of 102.2 and 0.4 m$^2$, respectively [35]. An assumption of the interspecies dose extrapolation is that equal responses will occur at an equivalent lung dose [36, 37], either the total mg or m$^2$ of particles/g lung. A two-year inhalation exposure in the chronic studies in rats and a 45-year working lifetime in humans were assumed to be equivalent durations of exposure relative to an average lifetime in each species.

2.3. Comparison of rat and human excess risk estimates

The rat- and human-based maximum likelihood estimate (MLE) of excess risk and the 95% upper confidence limit (95% UCL) were computed using the models for cumulative exposure reported in the epidemiology studies and in rats at the equivalent lung burdens (Sections 2.1 and 2.2). The rat- and human-based excess risk estimates were quantitatively compared using a statistical test of the hypothesis that the animal and human-based excess risks are equal. The test statistic is the difference
in these risk estimates divided by the standard error of the difference. P-values are based on the standard normal distribution.

Excess risk estimates for diesel exhaust particulate, based on the rat and human studies reported in Stayner et al. [6], are provided here in graphical form. These estimates are expressed as unit cancer risk, which is defined as the excess risk of lung cancer after 45-yr occupational exposure to 1 μg/m³ of diesel exhaust particulate.

3. Results

All multistage models provided adequate fit to the rat dose-response data (p-values 0.3 – 1.0; goodness of fit test). For carbon black, the initial models including male and female rat data from Nikula et al. [29] did not provide adequate fit (p-values 0.01 – 0.02); and models applied to the male rat data alone did not converge due to the lack of a positive dose-response relationship. Models applied to the female rat data from Nikula et al. [29] and Heinrich et al. [3] (which used female rats only) provided adequate fit (p-values 0.3-0.8). All human models evaluated provided adequate fit (p-values >0.05).

The rat- and human-based excess risk estimates are provided in Table 1 for the poorly-soluble, low toxicity particles (coal mine dust, carbon black, and titanium dioxide) and in Table 2 for respirable crystalline silica. Statistical comparison of these rat- and human-based excess risk estimates show that none of the excess risk estimates based on rat or human data is significantly different (all p-values > 0.05).

Regarding the magnitude of the excess risk estimates, the rat-based MLEs were clearly higher than the human-based estimate for coal dust (which was negative); however, the rat-based estimates (MLEs and 95% UCLs) did not exceed the 95% UCL from the human study (Table 1). For carbon black, the rat-based excess risk estimates exceeded those from the human study, but the differences were not statistically significant. For titanium dioxide, the rat-based excess risk estimates (MLE and 95% UCL) were lower than the 95% UCL of the human studies, although the MLE from Fryzek et al. [10] was negative. For crystalline silica, the rat-based MLEs and 95% UCLs were very similar in magnitude to the human-based estimates MLEs and 95% UCLs from all three epidemiological studies, except for the negative MLE from Brown and Rushton [18] (Table 2).

For diesel exhaust particulate, the rat- and human-based excess risk estimates for lung cancer are shown in Figure 2. Unit cancer risks are shown (i.e., mean concentration of 1 μg/m³ diesel exhaust particulate over a 45-yr occupational exposure). The rat 95% UCL are not shown because they are not sufficiently different from the MLEs to be discernable on this log scale. Figure 2 shows that, in general, the rat studies underpredict the excess risks based on the human studies.
Table 1. Comparison of human- and rat-based excess risk estimates of lung cancer following 45-year working lifetime exposure by particle type and mean concentration.

| Particle type and human study | Mean concentration (mg/m³)ᵃ | MLE (95% UCL) Human | Ratᵇ | Comparison of human & rat excess risks (p-value) |
|------------------------------|-------------------------------|---------------------|------|-----------------------------------------------|
| Coal mine dust               | 1.4                          | -2.5 x 10⁻³ (6.6 x 10⁻³) | 4.1 x 10⁻³ (1.0 x 10⁻²) | 0.3                                           |
| Attfield and Kuempel [14]    |                               |                     |      |                                               |
| Carbon black                 | 0.83                          | 5.6 x 10⁻³ (1.1 x 10⁻²) | 1.4 x 10⁻² (2.0 x 10⁻²) | 0.09                                          |
| Sorahan et al. [4]           |                               |                     |      |                                               |
| Titanium dioxide             | 0.044                         | -9.4 x 10⁻⁴ (6.8 x 10⁻⁴) | 7.0 x 10⁻⁵ (8.2 x 10⁻⁵) | 0.2                                           |
| Fryzek et al. [10]           |                               |                     |      |                                               |
| Titanium dioxide             | 0.044                         | 4.4 x 10⁻⁴ (7.1 x 10⁻⁴) | 7.0 x 10⁻⁵ (8.2 x 10⁻⁵) | 0.1                                           |
| Boffetta et al. [9]          |                               |                     |      |                                               |

Abbreviations: Maximum likelihood estimate (MLE); 95% upper confidence limit (95% UCL).
ᵃ Estimated from the cohort mean or median cumulative exposure averaged over 45 years of exposure.
b Rat data from: coal dust [27, 28]; carbon black [3, 29] (female rats); titanium dioxide [3, 30, 31].

Table 2. Comparison of human- and rat-based excess risk estimates of lung cancer following 45-year working lifetime exposure to respirable crystalline silica.

| Human study                | Mean concentration (mg/m³)ᵃ | MLE (95% UCL) Human | Ratᵇ | Comparison of human & rat excess risks (p-value) |
|----------------------------|-------------------------------|---------------------|------|-----------------------------------------------|
| Rice et al. [15]           | 0.162                         | 3.8 x 10⁻² (8.0 x 10⁻²) | 3.7 x 10⁻² (6.5 x 10⁻²) | 1.0                                           |
| Attfield and Costello [16] | 0.047                         | 1.3 x 10⁻² (2.0 x 10⁻²) | 1.1 x 10⁻² (1.9 x 10⁻²) | 0.8                                           |
| Brown and Rushton [18]     | 0.025                         | -7.8 x 10⁻⁴ (1.0 x 10⁻²) | 5.7 x 10⁻³ (1.0 x 10⁻²) | 0.3                                           |

Abbreviations: Maximum likelihood estimate (MLE); 95% upper confidence limit (95% UCL).
ᵃ Estimated from the cohort mean cumulative exposure averaged over 45 years of exposure: 7.3 mg/m³ x yr [15]; 2.2 mg/m³ x yr [16]; 1.12 mg/m³ x yr [18].
b Rat data from Muhle et al. [31].
Figure 2. Diesel exhaust particulate and lung cancer: comparison of rat- and human-based excess risk estimates across studies (estimates from Stayner et al. [6]). Maximum likelihood estimates are shown for both rat and human studies; 95% upper confidence limits are shown for the human studies.

4. Discussion

The findings of the epidemiological studies have been mixed with regard to elevated lung cancer and occupational exposure to poorly-soluble particles. All of the studies with cumulative exposure data have been included in this study, whether or not a relationship between particle exposure and lung cancer was observed. In contrast, each of the rat studies found statistically-significant elevations in lung tumors after chronic inhalation exposure to coal dust, carbon black, titanium dioxide, diesel exhaust particulate, or silica.

It may be hypothesized that if the rat is not a reasonable model of particle-elicited lung cancer, e.g., due to a rat-specific oversensitive lung response to particle overload, then the rat-based risk estimates may exceed those based on the human data. If so, then risk estimates based on the rat dose-response data may over-predict the unknown, true excess risks of particle-elicited lung cancer in humans.

The purpose of this study was to quantitatively and statistically compare the rat- and human-based excess risk estimates of lung cancer for working lifetime exposures to each of these particle types. This analysis provides comparisons to assess whether the rat-based risk estimates over- or under-predict the human lung cancer risk from exposure to poorly-soluble particles of various types. These findings may be relevant to other poorly-soluble particles for which dose-response data are available in rats but not humans.

4.1. Quantitative evaluation

This analysis showed statistically consistent excess risk estimates based on the rat and human studies. That is, there were no statistically significant differences in the rat- and human based estimates of lung cancer excess risk from long-term exposure to poorly-soluble respirable particles (all p values > 0.05).

Among the poorly-soluble low toxicity particles, the rat-based MLE estimates for coal dust and titanium dioxide were lower than the human 95% UCL, even when the human study did not show an association between particle exposure and lung cancer. For carbon black, the rat-based MLE estimate
was higher than the human 95% UCL, although not significantly. In the coal miner study [14], a potential exists for bias in the exposures associated with the SMRs including for lung cancer. Since the cumulative exposure data were available only until the start of follow-up, the cumulative exposure assigned to each miner is biased downward, and for the younger miners with shorter tenures at start of follow-up, the relative bias could be substantial. For this reason, possible bias in the excess risk estimates from the human study (Table 1) cannot be dismissed, which could also influence the comparison with the rat data.

For crystalline silica, the rat- and human-based excess risk estimates (MLEs and 95% UCLs) were remarkably similar. Although only one chronic inhalation study in rats exposed to respirable crystalline silica was available (and only a linear model was possible due to the limited data), the epidemiological studies were based on three different occupational cohorts. Unlike other poorly-soluble particles with low inherent toxicity, crystalline silica is cytotoxic, and significant exposure-response relationships have been observed in the rat [31] and human studies [16, 17]. Brown and Rushton [18] did not observe a positive exposure-response relationship, which may be due to the low exposure concentrations and durations.

For diesel exhaust particulate, the rat-based excess risk estimates generally under-predicted those based on the human studies. While the rat dose-response relationships to diesel exhaust particulate and carbon black appear to be similar [3, 29], it may be that the human excess risk estimates include additional risk due to the carcinogenic activity of the adsorbed poly-aromatic hydrocarbons on the diesel exhaust particulate, or that other unmeasured factors in the humans studies increases their apparent exposure-attributable risk.

4.2. Study limitations
These rat- and human-based excess risk comparisons are limited to exposures that are consistent with the human studies. Because the models used to describe human excess risk based on the human data differ from the models based on the rat data, it is possible that some comparisons could yield nonsignificant differences over one range of exposures and significant differences over another range for a given set of data. However, the practical implication of this limitation may be modest for comparisons of risk estimates at the exposures reported in the human studies.

Another limitation of this analysis is the relatively low power of the epidemiological studies. Human studies with large variability in the excess risk estimates may be consistent with a wide range of possible risk estimates, and even a non-significant exposure coefficient could be consistent with a positive exposure-response relationship in studies with large imprecision [19]. Thus, although this analysis showed that the rat- and human-based excess risk estimates are statistically consistent, the large variability in the human excess risk estimates may result in low power to detect a true difference in the animal- and human-based risk estimates.

The animal data were also relatively sparse due to relatively few dose groups (which were nonetheless typical of chronic bioassays); the data for silica and coal dust were limited to one and two dose groups, respectively, in addition to controls. Thus, while the standard errors of the human-based excess risk estimates are typically larger than those from the animal studies (by approximately an order of magnitude), the standard errors are similar for the rat- and human-based risk estimates for silica and coal dust. More dose-response data in both animals and humans would be needed to reduce the uncertainty in these excess risk comparisons.

There is uncertainty in what model would best describe the rat dose-response relationship for particle lung burden and tumor response. The rat-based excess risk estimates were based on multistage stage model with linear extrapolation below the 10% BMD. The dose-response relationships in the range of the data are clearly nonlinear for the poorly-soluble particles with low inherent toxicity (e.g., titanium dioxide and carbon black). Models and methods that account for low-dose curvature in the rat data (e.g., other BMD models or Bayesian model averaging of those models [38]) may provide different rat-based excess risk estimates, which may be lower. However, since the rat-based estimates from the multistage model were generally below the human-based risk estimates.
(and none was significantly different), it is unlikely that these other models would alter the overall findings.

In addition, the risk estimates may vary depending on the choice of lung dosimetry model and parameter values. For example, predicted human mean lung burdens associated with occupational exposures varied by several-fold [39] between the ICRP [26] clearance model (used in the MPPD model [25]) and those developed by Kuempel et al. [40] and Tran and Buchanan [41] based on coal miner data. The values selected to normalize lung burden between rat and human can also influence the risk estimates (e.g., lung mass or lung surface area), including whether the mean or distribution of these values is considered.

4.3. Qualitative evaluation
Although the mechanisms of particle-induced lung disease have not been fully elucidated, the rat and human lung responses to some poorly-soluble particles (e.g., coal dust and silica) appear to be qualitatively similar in many of the key steps for which there are data [23, 42, 43]. In humans, workers in dusty jobs had elevated pulmonary inflammation markers [44, 45], and in coal miners a relationship between dust exposure, pulmonary inflammation, and fibrosis was observed [46]. Although not linked to particle exposure, individuals with chronic pulmonary inflammation and epithelial cell proliferation due to idiopathic pulmonary fibrosis have an increased risk of lung cancer [47].

Semi-quantitative comparisons of the lung responses in rats and humans to several types of particles (diesel exhaust, coal dust, silica, or talc) indicate both similarities and differences — including similar regions of particle retention in the lungs but at different proportions [48], and greater fibrotic response in humans but greater inflammation and epithelial hyperplasia responses in rats [49]. Mice and hamsters have been shown to have lower lung tumor response and to give false negatives in bioassays for some particulates that have been classified by IARC as human carcinogens (limited or sufficient evidence), including crystalline and diesel exhaust [2].

Lung clearance of particles is slower in humans than in rats, by approximately an order of magnitude [26, 50], and some humans in dusty jobs (e.g., coal miners) have exposures and lung burdens that would be considered overloaded in rats [51]. Thus, the doses that cause overloading in rats may be relevant to estimating disease risk in workers with high dust exposures. However, the lack of exposure-related elevation in lung cancer rates in coal miners raises questions about whether the rat model would overpredict disease risk in humans.

Comparison of the lung doses of rats and humans shows that although the mean lung burdens have been relatively high in coal miners historically (approximately 10-20 mg/g lung) [40, 41], these lung burdens are several times lower than the mean lung burdens associated with the excess lung tumors in rats. For example, in rats chronically exposed to coal mine dust, a lung burden of 57 mg/g was associated with 11% lung tumors (vs. 0% in unexposed controls) [27]. In rats exposed to fine TiO₂, lung burdens up to 55 mg/g were not associated with lung tumors, and lung tumors were elevated only in rats with lung burdens greater than 200 mg/g (approximately 16% in male and female rats, excluding keratinizing cystic tumors) [30]. Thus, as seen in rat studies, doses that cause overloading may not be high enough to cause lung cancer. However, particle size and surface reactivity are also important, and smaller mass doses of ultrafine particles (e.g., TiO₂) or cytotoxic particles (e.g., quartz) are associated with elevated lung tumor response in rats [3, 31].

5. Conclusions
The rat- and human-based excess risk estimates of lung cancer from long-term exposure to poorly-soluble respirable particles are statistically consistent based on available data. Residual uncertainty in whether the rat-based risk estimates would over- or under-predict the true excess risks of lung cancer in humans is due in part to the low power of the available human studies, limited particle size exposure data for humans, and ambiguity about the best animal models and extrapolation methods.
Disclaimer: The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

References
[1] Driscoll KE 1996 Particle overload in the rat lung and lung cancer, implications for human risk assessment eds JL Mauderly and RJ McCunney (Washington, DC: Taylor and Francis) pp 139-53
[2] Mauderly JL 1997 Environ. Health. Perspect. 105(Suppl 5) 1337–46
[3] Heinrich U, Fuhr R, Rittinghausen S, Creutzenberg O, Bellmann B, Koch W and Levsen K 1995 Inhal. Toxicol. 7(4) 533–556
[4] Sorahan T and Harrington JM 2007 Am. J. Ind. Med. 50(8) 555-64
[5] Wellmann J, Weiland SK, Neiteler G, Klein G and Straif K 2006 Occup. Environ. Med. 63(8) 513-21
[6] Stayner L, Dankovic D, Smith R and Steenland K 1998 Am. J. Ind. Med. 34(3) 207-19
[7] Steenland K, Deddens J and Stayner L 1998 Am. J. Ind. Med. 34(3) 220–28
[8] Garshick E, Laden F, Hart JE, Rosner B, Smith TJ, Dockery DW and Speizer FE 2004 Environ. Health. Perspect. 112(15):1539–43
[9] Boffetta P, Soutar A, Cherrie JW, Granath F, Andersen A, Anttila A, Blettner M, Gaborieau V, Klug SJ, Langard S, et al. 2004 Cancer Causes Control 15 697–706
[10] Fryzek JP, Chadda B, Marano D, White K, Schweitzer S, McLaughlin JK and Blot WJ 2003 J. Occup. Environ. Med. 45 400–9
[11] Dell LD, Mundt KA, Luippold RS, Nunes AP, Cohen L, Burch MT, Heidenreich MJ and Bachand AM 2006 J. Occup. Environ. Med. 48(12) 1219-29
[12] Miller BG and Jacobsen M 1985 Br. J. Indus. Med. 42(11) 723-33
[13] Morfield P, Lampert K, Ziegler H, Stegmaier C, Dhom G and Piekarski C 1997 Appl. Occup. Environ. Hyg. 12(12) 909-14
[14] Attfield MD and Kuempel ED 2008 Am. J. Ind. Med. 51(4) 231-45
[15] Rice FL, Park R, Stayner L, Smith R, Gilbert S and Checkoway H 2001 Occup. Environ. Med. 58(1) 38-45
[16] Attfield MD and Costello J 2004 Am. J. Indus. Med. 45(2) 129-38
[17] Steenland K, Mannetje A, Boffetta P, Stayner L, Attfield M, Chen J, Dosemeci M, DeKlerk N, Hnizdo E, Koskela R, et al. 2001 Cancer Causes Control 12(9) 773-84
[18] Brown TP and Rushton L 2005 Occup. Environ. Med. 62(7) 446-52
[19] Stayner LT and Smith RJ 1993 Epidemiol. Prev. 14(53) 32-9
[20] Watson AY and Valberg PA 1996 Particle overload in the rat lung and lung cancer, implications for human risk assessment eds JL Mauderly and RJ McCunney (Washington, DC: Taylor and Francis) pp 227–57
[21] ILSI 2000 Inhal. Toxicol. 12(1-2) 1-17
[22] Hext PM, Tomenson JA and Thompson P 2005 Ann. Occup. Hyg. 49(6) 461-72
[23] Baan RA 2007 Inhal. Toxicol. 19(Suppl. 1) 213-28
[24] BEIR IV 1998 Health risks of radon and other internally deposited alpha-emitters (Washington, DC: National Academy Press) pp 131-36
[25] CIIT and RIVM 2006 Multiple-path particle dosimetry model (MPPD V 2.0, 2002-2006) (Research Triangle Park, NC: Centers for Health Research and The Netherlands: National Institute for Public Health and the Environment).
[26] ICRP 1994 Human respiratory tract model for radiological protection (Annals of the ICRP Publication No. 66) ed H Smith (Tarrytown, New York: International Commission on Radiological Protection)
[27] Martin JC, Dániel H and LeBouffant L 1977 Inhaled particles part I (Oxford, UK: Pergamon Press) 361–70
[28] Lewis TR, Morrow PE, McClellan RO, Raabe OG, Kennedy GL, Schwetz BA, Goehl TJ,
[29] Roycroft JH and Chhabra RS 1989 Toxicol. Appl. Pharmacol. 99(3) 377–83

[30] Lee KP, Trochimowicz HJ and Reinhardt CF 1985 Toxicol. Appl. Pharmacol. 79 179–92

[31] Nikula KJ, Snipes MB, Barr EB, Griffith WC, Henderson RF and Mauderly JL 1995 Fundam. Appl. Toxicol. 25 80–94

[32] Lee KP, Trochimowicz HJ and Reinhardt CF 1985 Toxicol. Appl. Pharmacol. 79 179–92

[33] Muhle H, Bellmann B, Creutzenberg O, Dasenbrock C, Ernst H, Kilpper R, MacKenzie JC, Morrow P, Mohr U, Takenaka S, Merkelstein R 1991 Fund. Appl. Toxicol. 17 280–99

[34] Boorman GA, Brockman M, Carlton WW, Davis JMG, Dungworth DL, Hahn FF, Mohr U, Reichhelm H-BR, Turusov VS, Wagner BM 1996 Toxicol. Pathol. 24 564–72

[35] US EPA 2003 Benchmark dose software, version 1.3.2 (Washington, DC: US Environmental Protection Agency, National Center for Environmental Assessment)

[36] US EPA 2005 Guidelines for carcinogen risk assessment (Washington, DC: US Environmental Protection Agency, Risk Assessment Forum) EPA/630/P-03/001F

[37] Mercer RR, Russell ML, Roggli VL and Crapo JD 1994 Cell. Mol. Biol. 10 613-24

[38] Jarabek AM, Asgharian B and Miller FJ 2005 Inhal. Toxicol. 17(7-8) 317-34

[39] Kuempel ED, Tran CL, Castranova V and Bailer AJ 2006 Inhal. Toxicol. 18(10) 717-24

[40] Wheeeler MW and Bailer AJ 2007 Risk Anal. 27(3) 659-70

[41] Kuempel ED and Tran CL 2002 Ann. Occup. Hyg. 46(Suppl 1) 337–41

[42] Kuempel ED, O’Flaherty EJ, Stayner LT, Smith RJ, Green FHY and Vallyathan V 2001 Reg. Toxicol. Pharmacol. 34(1) 69-88

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

[44] Vallyathan V, Shi X and Castranova V 1998 Environ. Health Perspect. 106(suppl 5) 1151-55

[45] Castranova V 2000 Inhal. Toxicol. 3 7–14

[46] Rom WL 1991 Am. J. Indust. Med. 19 15–27

[47] Lapp NL and Castranova V 1993 Occup. Med. 8(1) 35–56

[48] Kuempel ED, Attfield MD, Vallyathan V, Lapp NL, Hale JM, Smith RJ and Castranova V 2003 J. Biosci. 28(1) 61-9

[49] Katabami M, Dosaka-Akita H, Honma K, Saitoh Y, Kimura K, Uchida Y, Mikami H, Ohsaki Y, Kawakami Y and Kikuchi K 2000 Am. J. Respir. Crit. Care Med. 162 295–300

[50] Nikula KJ, Vallyathan V, Green FH and Hahn FF 2001 Environ. Health Perspect. 109(4) 311-8.

[51] Green FH, Vallyathan V and Hahn FF 2007 Toxicol. Pathol. 35(1) 136-47

[52] Snipes MB 1996 Particle overload in the rat lung and lung cancer, implications for human risk assessment eds JL Mauderly and RJ McCunney (Washington, DC: Taylor and Francis) pp 91-109

[53] Freedman AP and Robinson SE 1988 Respirable dust in the mineral industries: health effects, characterization, and control eds RL Frantz and RV Ramani (University Park, PA: The Pennsylvania State University) pp 181-6

[54] Roller M and Pott F 2006 Ann. N.Y. Acad. Sci. 1076 266-80

[55] Vallyathan V, Schwagler D, Reasor M, Stettler L, Cleare J and Green FHY 1988 Ann. Occup. Hyg. 32(suppl 1) 279-89
Appendix A.

The particle parameters used in the lung dosimetry modeling, and the lung burden predictions in rats and humans are provided in Table A-1.

**Table A-1. Particle characteristics used in lung burden estimation.**

| Particle Type | Density (g/cm³) | MMAD (GSD) | Mean concentration (mg/m³) | Human lung burden (mg/lung) | Rat-equivalent lung burden (mg/lung) |
|---------------|----------------|------------|-----------------------------|----------------------------|-------------------------------------|
| Coal dust     | 1.5            | 3.4 (2)    | 1.4                         | 1,159                      | 4.5                                 |
| Carbon black  | 1.85           | 0.64 (2.06)| 0.83                        | 884                        | 3.4                                 |
| TiO₂ - F      | 4.25           | 1.6 (2)    | 0.044                       | 52                         | 0.20                                |
| SiO₂          | 2.5            | 3.5 (2)    | 0.16                        | 135                        | 0.53                                |

Abbreviations: TiO₂-F: titanium dioxide (fine); SiO₂: crystalline silica; MMAD: mass median aerodynamic diameter; GSD: geometric standard deviation.

* Reported by various internet sources and consistent with values in Roller and Pott [52].

* Reported in: Vallyathan et al. [53]: coal dust and SiO₂, MMAD; Heinrich et al. [3]: carbon black MMAD and GSD; Lee et al. [30]: TiO₂-F, MMAD. Assumed GSD of 2 for coal dust, TiO₂-F, and SiO₂, which is similar to values reported for the other particles.

* Mean concentration equivalent to the cohort mean or median cumulative exposure averaged over 45-year working lifetime (8 hr/d, 5 d/wk, 50 wk/yr).

* Normalized from human to rat by the ratio of lung surface areas (0.4 rat/102.2 human) [35].