Risk estimates for silicosis: comparison of animal and human studies

CL Tran, BG Miller and CA Soutar
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Estimates of human risks of occupational exposures to chemicals based on the results of animal studies conventionally apply simple scaling and safety (uncertainty) factors to the no-observed-adverse-effect level (NOAEL) in animals to estimate acceptable occupational exposure limits in humans.

We have conducted a risk assessment for lung fibrosis from inhaled crystalline silica that follows the traditional approach of extrapolation from animal studies, and we compare this result with observed human risks based on epidemiological studies.

To our knowledge animal inhalation studies of crystalline silica, that use a sufficient range of exposures to estimate NOAEL directly, have not been performed, so we have applied bio-mathematical modelling to the available animal data to estimate the NOAEL for inflammation. The resulting estimate for the rat is 0.1mg.m$^{-3}$.

Conventional scaling and extrapolation methods recommended by the US EPA have then been applied to estimate a human acceptable average exposure limit. This resulted in an estimate of about 0.001mg.m$^{-3}$.

The risk estimates were compared with human risk estimates for fibrosis based on epidemiological data. These comprised ACGIH summary conclusions on the risk estimates provided by epidemiological studies, and the risks demonstrated by one epidemiological study with unusually detailed exposure information.

The average exposure limits implied by the risk estimates from the epidemiological studies ranged from 0.01mg.m$^{-3}$ to about 0.05mg.m$^{-3}$, some 9 to 45 times higher than the limits derived from the animal studies.

The conventional uncertainty factors applied in the animal-based risk estimates may be over-precautionary. Extension of the biomathematical model to extrapolate from animals to humans would provide a sounder basis for extrapolation than the present uncertainty factors.
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1. INTRODUCTION

Estimates of human risks of occupational exposures to chemicals based on the results of animal studies conventionally apply simple scaling and safety (uncertainty) factors to the no-observed-adverse-effect level (NOAEL) in animals to estimate acceptable occupational exposure limits (AOEL) in humans.

It will be informative on the validity of these standard procedures to compare the resulting AOEL with information on human risks in practice.

We have conducted a risk assessment for lung fibrosis from inhaled crystalline silica that follows the traditional approach of extrapolation from animal studies, and we compare this result with observed human risks based on epidemiological studies.

To our knowledge animal inhalation studies of crystalline silica, that use a sufficient range of exposures to estimate a NOAEL directly, have not been performed, so we have applied biophysical modelling to the available animal data to estimate the animal NOAEL for inflammation and fibrosis. Conventional scaling and extrapolation factors recommended by the US EPA are then applied to estimate a human AOEL. The resulting risk estimates are compared with human risk estimates for fibrosis based on epidemiological data. These comprised ACGIH summary conclusions on the risk estimates provided by epidemiological studies, and the risks demonstrated by one epidemiological study with unusually detailed exposure information.
2. METHODS

2.1 ANIMAL STUDIES

The experimental data were from inhalation experiments with Crystalline Silica (Minu-Sil 5, MMAD=1.62 μm (gsd=0.12; high=1.86, low=1.47), Porter et al., 2000). Male Fischer 344 rats were exposed at 15 mg.m\(^{-3}\) for up to 84 days. Groups of 8 rats were sacrificed at 28, 56 and 84 days during exposure. For each exposure group, a corresponding group of 8 rats were left to recover for 36 days before sacrifice. The following assays were measured at each of these time-points:

- Lavageable lung burden,
- Non-lavageable lung burden,
- Lymph node burden,
- Differential cell count from the Bronchio-Alveolar Lavaged (BAL) fluid:
  - Number of Alveolar Macrophages (AM),
  - Number of Neutrophils (PMN).

These experimental data were used to estimate some model parameters. Later, a second and third dataset were used to validate the model predictions. They are from:

1. Another short-term inhalation experiment with the same type of Minu-Sil-5. Groups of 6 rats were exposed at 15 mg.m\(^{-3}\) for up to 161 days (Porter et al., 2001). Sacrifice time points were at 1, 7, 14, 28, 56, 112 and 161 days. The following assays were measured:
   - Total burden (lung plus lymph node burden),
   - Number of PMN cells,
   - Number of AM cells,
   - Hydroxyproline level (mg/lung) at 28, 56, 112 and 161 days respectively.

2. A chronic 2-year study with Crystalline Silica (MMAD=1.4 μm, gsd=1.8, DQ-12 quartz; Muhle et al., 1989) at 0.75 mg.m\(^{-3}\). The data consist of lung and lymph node burden for up to 2 years and one time point for 1.5 month after 2 years exposure.

2.2 THE BIOMATHEMATICAL MODEL

The biomathematical model includes three main model components; exposure-dose, impairment of macrophage function and inflammation (the precursor of fibrosis).

The exposure/dose model

An earlier model describing the exposure-dose-response for Crystalline Silica was developed (Tran et al., 1992). However, that model was deemed to be over parameterised. In the current study, the exposure-dose model is an extended version of that described by Kuempel et al., 1999. This model was tested against human data (Tran and Buchanan, 2000). The extension, an alveolar compartment representing the silica burden in alveolar macrophages, is necessary because silica is known to impair alveolar macrophage function (Adamson and Bowden, 1992). This brings the current model closer to an earlier model developed for ‘Low Toxicity’ dusts (Tran et al., 1999a; Tran et al., 1999b).

The model consists of four compartments;

- \(X_1\): The silica burden (mg) lying free in the alveolar region;
- \(X_2\): The silica burden (mg) within alveolar macrophages in the alveolar region.
- $X_1$ = The silica burden (mg) in the interstitium,
- $X_4$ = The silica burden (mg) in the lymph nodes.

Figure 1 illustrates the model.

Mathematically, the exposure-dose model is described by a set of differential equations describing the rates of change of dust burden in each compartment and rates of transition between compartments, as follows:

$X_1$, the free silica burden in the alveolar region; the rate of change is governed by the rate of deposition (Dose in mg) of the inhaled silica, the rate of phagocytosis (r mg/day) of this burden into the alveolar macrophage compartment ($X_2$), the rate of interstitialisation ($k_i$ in mg/day) of free silica through the alveolar walls into the interstitial region ($X_3$), and the decay rate ($k_d$ in mg/day) representing release back into free status ($X_1$) from the alveolar macrophages as they decay.

$X_2$, the silica burden in the alveolar macrophages; the rate of change is governed by the rate (r) of phagocytosis by alveolar macrophages, the rate ($k_c$ in mg/day) of clearance by alveolar macrophages upwards in the bronchial tree, and the rate ($k_d$) of release back into free status ($X_1$) from the alveolar macrophages as they decay.
$X_3$, the burden in the interstitial region; the rate of change is governed by the rate of interstitialisation ($k_i$) of free silica from the alveolar compartment ($X_1$) through the alveolar walls into the interstitial region ($X_3$), and the translocation rate ($k_t$ in mg/day) of transition through the lymphatics to the lymph nodes ($X_4$).

$X_4$, the burden in the lymph nodes; the rate of change is governed by the rate of translocation ($k_t$) from the interstitial compartment ($X_3$) to the lymph nodes.

The mathematical expression of the model is:

$$
\begin{align*}
\frac{dX_1}{dt} &= Dose - r.X_1 - k_i.X_1 + k_d.X_2 \\
\frac{dX_2}{dt} &= r.X_1 - k_i.X_2 - k_d.X_2 \\
\frac{dX_3}{dt} &= k_i.X_1 - k_t.X_3 \\
\frac{dX_4}{dt} &= k_t.X_3
\end{align*}
$$

(1)

Note that, with the onset of inflammation, neutrophils will also be present in the alveolar region. These cells were known to be phagocytosing particles (Donaldson et al., 1988). However, neutrophils live less than a day, and once dead, they are quickly taken up by macrophages. Therefore, macrophages are the main cells for ingesting and removing silica particles, and to keep the modelling simple, a compartment representing the silica burden inside neutrophils is not included.

*Dose* is the deposited dose of silica and is calculated as a function of the airborne mass silica concentration (conc, mg.m$^{-3}$), deposited fraction (FD), volume of air inhaled (VI, litres/minute), number of days exposed per week (DE), number of hours exposed per day (HE), with a conversion factor into units of m$^3$ per day (CONV);

$$
Dose = FD \cdot conc \cdot VI \cdot DE \cdot HE \cdot CONV
$$

(2)

**Impairment of macrophage function**

The phagocytosis ($r$) and clearance ($k_t$) of silica particles by alveolar macrophages are unimpaired as long as the silica burden inside alveolar macrophages ($X_2$) remains below a critical level ($m_{crit}$). Once $m_{crit}$ is reached, clearance quickly becomes impaired and an inflammatory reaction is activated. This impairment ($F$) is expressed as a function of the amount of the difference between the alveolar macrophage burden ($X_2$) and the critical burden ($m_{crit}$), divided by the difference between the critical burden and the maximum lung burden $m_{max}$. This function was used to model the impairment of clearance in the earlier model (Kuempel et al., 1999). Mathematically the impairment is expressed by;

$$
F = \begin{cases} 
1 & \text{for } X_2 \leq m_{crit} \\
\frac{X_2 - m_{crit}}{m_{max} - m_{crit}} & \text{else} \\
\end{cases}
$$

(3)
\( m_{\text{max}} \) is the maximum level of silica burden such that when \( X_2 = m_{\text{max}} \), the impairment \( F \) will be \( e^B \) (i.e. determined by \( B \)). \( B \) and \( G \) are parameters governing the speed of the impairment.

The impairment is assumed to affect the clearance of silica particles by alveolar macrophages and the rate of release of silica from decaying alveolar macrophages back to the alveolar surface (Tran et al, 1999). Mathematically, the parameters \( k_t \) and \( k_d \) are made to be dependent on \( m_{\text{crit}} \) by writing \( k_t \) and \( k_d \) as \( F.k_t \) and \( F.k_d \).

### 2.3 INFLAMMATION MODEL

The criterion for inflammation is the recruitment of polymorphonuclear cells (PMN) to the affected area of the alveolar surface. This occurs when free silica particles come into contact with alveolar epithelial cells and become interstitialised. This inflammatory reaction is in accordance with the results of ‘low toxicity’ dusts (Tran et al, 2000). However, a second source of PMN recruitment comes from activated alveolar macrophages once the critical burden \( m_{\text{crit}} \) is reached. This second inflammatory reaction is due to the direct effect of silica particles on alveolar macrophages. The PMN recruitment rate is modelled as a function of the interstitialisation rate \( k_i \), the impairment of macrophage function \( F \) and the disappearance rate \( (k_3) \) of PMNs present, or:

\[
\frac{dPMN}{dt} = k_1.k_t.X_1 + k_2.(1 - F).X_2 - k_3.PMN \quad (4)
\]

The first term on the right hand side of eqn (4) represents the first source of PMN recruitment which is proportional to the interstitialisation rate (\( k_1 \) being the constant of proportionality). The second term is the second source of PMN recruitment. This is dependent on the burden of silica inside alveolar macrophages and is switched on when \( m_{\text{crit}} \) is reached. The third term is the disappearance rate of PMNs (being taken up by AMs after undergoing apoptosis/necrosis).

\( k_1 \) constant of proportionality (in units of number of PMNs per mg of silica),
\( k_2 \) first order kinetics parameter (in units of number of PMNs per mg of silica per day),
\( k_3 \) disappearance rate of PMNs (in units of day\(^{-1}\)).

Interestingly from the data the alveolar macrophage population did not appear to change during and after exposure in comparison to the control population. Thus, the rate of change of this population is zero;

\[
\frac{dAM}{dt} = 0 \quad (5)
\]

### 2.4 METHOD FOR MODEL CALIBRATION

The model may appear to be over-parameterised at a first glance. However, the majority of the parameters have been derived from earlier studies (Tran et al, 2000; Kuempel et al, 1999). The strategy for model calibration is to estimate only the parameters suspected of being dependent on the specific properties of silica particles.

**Fixed Parameters**

The fixed model parameters, derived from earlier models, and their values are given in Table 1 overleaf.
Table 1. The fixed parameters of the exposure-response model

<table>
<thead>
<tr>
<th>Parameters related to Dose</th>
<th>Parameters</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>FD (deposited fraction)</td>
<td></td>
<td>0.06</td>
<td>Unitless</td>
</tr>
<tr>
<td>Conc (airborne respirable dust)</td>
<td></td>
<td>15</td>
<td>mg.m(^{-3})</td>
</tr>
<tr>
<td>VI (volume of air inhaled)</td>
<td></td>
<td>0.18</td>
<td>litre/min</td>
</tr>
<tr>
<td>DE (days exposed)</td>
<td></td>
<td>0.714</td>
<td>Days</td>
</tr>
<tr>
<td>HE (hours exposed)</td>
<td></td>
<td>6</td>
<td>hrs/day</td>
</tr>
<tr>
<td>CONV (conversion factor)</td>
<td></td>
<td>0.06</td>
<td>Unitless</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters related to the exposure-dose model</th>
</tr>
</thead>
<tbody>
<tr>
<td>r (phagocytosis rate)</td>
</tr>
<tr>
<td>(k_d) (macrophage decay rate)</td>
</tr>
<tr>
<td>(k_t) (bronchial clearance rate)</td>
</tr>
<tr>
<td>Value</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>4.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters related to the impairment function (F)</th>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td></td>
<td>6.9</td>
<td>Unitless</td>
</tr>
<tr>
<td>(G)</td>
<td></td>
<td>0.7</td>
<td>Unitless</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters related to the dose-response model</th>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>(k_3) (PMN decay rate)</td>
<td>k_3</td>
<td>0.01</td>
<td>day(^{-1})</td>
</tr>
</tbody>
</table>

Parameters to be estimated

There are five parameters, specific to silica, that have to be estimated. They are:

i) \(k_i\) the interstitialisation rate,

ii) \(k_l\) the translocation rate to the lymph nodes,

iii) \(m_{\text{crit}}\) the critical lung burden of silica.

iv) \(k_1\) the parameter relating to the first source of PMN recruitment,

v) \(k_2\) the first order kinetics related to the second source of PMN recruitment.

To estimate i, ii and iii we use the data from the lavageable lung burden, the non-lavageable lung burden and the lymph node burden. To estimate iv and v we shall use the PMN data.

Method for Parameter Estimation

The model is written in the language of MATLAB (MathWork\(^c\)). Subroutines from the MATLAB libraries (the toolboxes) were used to combine the numerical integration of the system of differential equations with non-linear least squares method for parameter estimation. Appropriate confidence intervals were also calculated.

The strategy is firstly to estimate the parameters related to the exposure-dose model (1, 2 and 3), then estimate the parameters related to the dose-response model (4 and 5). In all cases, the mean values of the data are used in the parameter estimation process. The routines used were: \(\text{ode45}\) for solving the model numerically, \(\text{nonlinfit}\) for non-linear least squares and \(\text{nlpredci}\) plus \(\text{nlparci}\) for the parameter confidence interval estimations.
3. RESULTS

Table 2 shows the results of the parameter estimation process. Figure 2 shows the model predictions and the experimental data.

**Table 2.** Estimates for $k_i$, $k_l$, $m_{crit}$, $k_1$ and $k_2$ and their corresponding confidence intervals

<table>
<thead>
<tr>
<th></th>
<th>$k_i$ Interstitialisation</th>
<th>$k_l$ Translocation</th>
<th>$m_{crit}$ Critical lung burden</th>
<th>$k_1$ 1st order kinetics parameter</th>
<th>$k_2$ PMN number/mg silica</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower 95pc Estimate</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0234</td>
<td>2.5780</td>
<td>0.2134</td>
</tr>
<tr>
<td>Estimate</td>
<td>2.1910</td>
<td>0.0042</td>
<td>0.2079</td>
<td>9.4072</td>
<td>0.3423</td>
</tr>
<tr>
<td>Upper 95 pc Estimate</td>
<td>4.7642</td>
<td>0.0196</td>
<td>0.3925</td>
<td>16.2365</td>
<td>0.4711</td>
</tr>
</tbody>
</table>

**Figure 2.** Model predictions (lines) and experimental data (circles at end of inhalation, squares after recovery) for (a) Lavageable lung burden; (b) Non-Lavageable lung burden; (c) Lymph node burden and (d) Number of Neutrophils in the BAL fluid. Inhalations were for 28, 56 and 84 days, with subsequent recovery periods.
From Figure 2, it is clear that a very good fit of the model to the data (including both the exposure and post-exposure period) was achieved. As expected for a toxic dust, the critical threshold burden for silica is low (0.208 mg), the interstitialisation and PMN recruitment rate are higher than the values found in the model for low-toxicity dusts (Tran et al., 2003).

All the model parameters are now identified. The model was further validated using two independent datasets. The results of the validation exercise are presented in the Appendix.

3.1 NO OBSERVED ADVERSE EFFECT LEVEL (NOAEL)

The adverse effect considered in this paper is inflammation as represented by the number of PMN in the BAL fluid. The working criterion for a ‘no adverse effect level’ used in this exercise is the concentration level such that ‘the PMN response is lower than the average of control level minus twice the standard error as found in the second inhalation experiment described in page 2. From these data, this level was calculated as $1.28 \times 10^6$ (with $2 \times ste = 1.8 \times 10^6$).

In this section, the extrapolation exercise is taken one step further. Using the results from a separate chronic animal experiment with DQ12 Quartz (Muhle et al., 1989) as starting point, the model is used to simulate the exposure-dose-response relationship at concentration levels lower than the target level in the experiment, 0.75 mg m$^{-3}$. Starting at a concentration level of 0.5mg.m$^{-3}$ and reducing the concentration at a step of 0.1 a time until 0.1 mg.m$^{-3}$. The concentration level that satisfies the definition of no adverse effect (no inflammation), described above, is 0.1 mg.m$^{-3}$. This approach was used to predict an NOAEL at the low dose region where there are no data available. Corresponding simulations of the exposure-dose-response are shown in Figure 3 overleaf.
Figure 3. Extrapolations to lower concentration levels to derive a safe level for the average rat. The bold curves correspond to 0.1 mg.m$^{-3}$; others are 0.2, 0.3, 0.4 and 0.5 mg.m$^{-3}$ (note that in 3c, the curve for 0.2 is bold and lies above that for 0.1); (a) Lung burden; (b) Lymph node burden; (c) PMN level

3.2 APPLICATION OF SAFETY (UNCERTAINTY) FACTORS

In a draft document the US EPA (1994) recommend an approach for deriving a safe limit for humans, from animal studies. This involves a reduction of the animal-based NOAEL by three uncertainty factors:

- A rat/human dosimetric adjustment
- A factor for intrahuman variability;
- A factor for interspecies toxicodynamic differences that is to be judged according to the substance and the known mechanisms of tissue damage.

We have applied

- A factor of 3 for toxicodynamic differences as normally applied when dosimetric adjustments have been applied (Haber et al., 2000).
- A factor of 10 for dosimetric adjustment. This is based on the observations that macrophage-mediated clearance of insoluble particles in rats under the normal (non-inflammatory) condition is about 10 times faster than humans (Bailey et al., 1982, 1985; Miller, 2000). We recognise that a tenfold difference in clearance does not necessarily translate directly into a tenfold difference in dose, but consider that an, at
least tenfold, uncertainty factor is suitably precautionary for this highly toxic substance.

On this basis for Crystalline Silica, a reduction by a total factor of 90 is applied to the predicted rat NOAEL of 0.1 mg.m$^{-3}$, resulting in an exposure level of 0.0011 mg.m$^{-3}$ for humans.

### 3.3 HUMAN RISKS FROM EPIDEMIOLOGICAL STUDIES

**ACGIH**

The ACGIH draft document of 2004: “Silica, crystalline: α-quartz and cristobalite”, proposes a TLV-TWA of 0.025 mg/m$^3$. This recommendation is based on a review of a number of occupational studies of the relationship between crystalline silica exposure and the development of fibrotic change, or silicosis; and on studies of lung cancer and its relationship with existing silicosis and with exposure.

The review highlights occupational settings with high exposures can express high risks for silicosis, although (as has often been remarked) the risks are not uniformly related to exposure, and suggest that silica in some industries is much less actively toxic than in others.

Regarding the ACGIH proposal, the draft states “It is the concern about fibrosis (silicosis) resulting from silica exposures, and the association of fibrosis with lung cancer, that leads to this recommendation”. The recommendation does not appear to be derived from the quoted exposure-response relationships for silicosis. Rather, the review notes that “several epidemiological studies of workers protected at the 0.05 mg.m$^{-3}$ level have not shown a change in longevity or lung function”, but that a significant increase in mortality risk for lung cancer has been identified at average exposure levels greater than 0.046 mg.m$^{-3}$. The committee applied a safety factor of two to this value, to arrive at the TLV-TWA of 0.025 mg.m$^{-3}$. Thus it appears that the recommendation has in fact been based principally on indirect measures of silicosis, and on the lung cancer risk.

This implies that ACGIH considered that the human NOAEL average exposure for silicosis is 0.05 mg.m$^{-3}$, and for lung cancer is 0.046 mg.m$^{-3}$. Note that strict daily observance of a TLV will result in average exposures well below the TLV value (see later).

**Estimates from Scottish Coalworkers**

ACGIH chose to downplay the importance of the IOM work on silica exposures in the Scottish coalworkers (most recent report Buchanan et al, 2003). This was based on earlier and less detailed reports than have since become available, and their judgment might now be different. Nevertheless, the current ACGIH draft states that our results may be “misleading since exposure concentrations for some workers were at times very high, exceeding 10 mg.m$^{-3}$ quartz, recruiting efforts could not eliminate possible biases and the presence of coal dust may have modified tissue responses to quartz”.

In answer to these criticisms, we would make the following points:

- while the exposures for some workers were very high, only some of the workers received high silica exposures, and many received quite low exposures to respirable silica, because they did not work on the seam where the geological problems arose;
• since we fitted various non-linear functions of exposure, the responses of those with the highest exposures is irrelevant for the present purposes, where we are interested in responses at low exposures;
• while the response rate was far from perfect (but fairly respectable for a study of ex-workers in an extinct industry), we have no reason to expect that this will have biased the exposure-response function;
• the response seen was very typical of exposure to crystalline silica, both in its radiological appearance and in the fact that it progressed after cessation of exposure;
• the whole incident arose against a background of very low pneumoconiosis incidence in the Scottish coalfields;
• the PFR study, of which the Scottish study was a part, had extremely detailed job-specific measurements of respirable dust and quartz concentrations, and linked these to detailed records of individuals’ jobs, to create a much more detailed and better characterized set of cumulative exposures than are available in most occupational studies.

We therefore feel that the Scottish data are stronger than suggested by the ACGIH document; and we note that this study is the only one to report detailed model fits to a higher grade of silicosis (2/1+). (We add that the estimates we derive here are from a model from the peer-reviewed paper of Buchanan et al (2003), which differed somewhat from those in the original report of 2001, and considerably from earlier reports using less intensive statistical analyses; in particular, they differ from those quoted by the ACGIH document. These recent estimates have been highly influential in the deliberations of the UK HSE on regulating silica exposure.)

Table 3 overleaf summarises some predictions of risk from the logistic regression equations derived from the Scottish data (Buchanan et al, 2003).
Table 3. Predictions of risk for selected exposure scenarios, based on the study of Scottish coal workers

<table>
<thead>
<tr>
<th>Exposure conc. (mg.m(^{-3}))</th>
<th>Follow-up</th>
<th>Exposure (mg.yrs.m(^{-3}))</th>
<th>Response grade</th>
<th>Estimated risk</th>
<th>Difference from risk at zero exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>15 yrs + 15 post-exp</td>
<td>1.5</td>
<td>2/1+</td>
<td>2.48%</td>
<td>1.69%</td>
</tr>
<tr>
<td>0.03</td>
<td>15 yrs + 15 post-exp</td>
<td>0.45</td>
<td>2/1+</td>
<td>1.12%</td>
<td>0.33%</td>
</tr>
<tr>
<td>0.025</td>
<td>15 yrs + 15 post-exp</td>
<td>0.375</td>
<td>2/1+</td>
<td>1.06%</td>
<td>0.27%</td>
</tr>
<tr>
<td>0.01</td>
<td>15 yrs + 15 post-exp</td>
<td>0.15</td>
<td>2/1+</td>
<td>0.89%</td>
<td>0.1%</td>
</tr>
<tr>
<td>0.0</td>
<td>15 yrs + 15 post-exp</td>
<td>0</td>
<td>2/1+</td>
<td>0.79%</td>
<td>0</td>
</tr>
</tbody>
</table>

The predictions quoted from the study of Buchanan et al (2003), for the risks of reaching grade 2/1+, are based on the logistic regression equation

\[
\ln\left(\frac{p}{1-p}\right) = -4.83 + 0.771 \times CE
\]  

(5)

where \(p\) is the probability (risk) of having opacities of grade 2/1+ around 15 years after cessation of exposure, and \(CE\) is the cumulative exposure to respirable silica in the preceding years. This version of the equation assumes that no exposure takes place in concentrations above 2 mg/m\(^3\). (The coefficient of \(CE\) differs from that in Buchanan et al (2005), to allow for the change of units of exposure from g.h.m\(^{-2}\) to the more common mg.y.m\(^{-3}\)).

We see that, even with a zero exposure, the fitted equation predicts a risk of less than 0.8%. This may be partly due to the descriptive and non-diagnostic nature of the ILO classification scheme under which the radiographs were interpreted, and to possible misattribution of exposures.

For 15 years’ exposure to a concentration of 0.1 mg/m\(^3\) of respirable silica, the IOM equation predicts a risk of almost 2.5%. Such a risk would be unacceptable, and clearly limits should be set so as to avoid such exposures. The ACGIH draft document recommends a TLV-TWA of 0.025 mg/m\(^3\) (stated limit for lung cancer risk) and refers to an implied limit for silicosis of 0.046 mg/m\(^3\).

In a workplace correctly controlled to a TLV such as 0.025 mg.m\(^{-3}\), we might expect that the mean exposure would be considerably lower than this, perhaps around 0.01 mg.m\(^{-3}\). At that level, the IOM equation predicts a risk of 0.89%, and this is increased over the unexposed baseline by only 0.1 percentage points of risk, or 1 in 1000. In a workplace where individuals are exposed on average at the proposed TLV-TWA, risk is predicted as 1.06%, which is an increase over baseline of 0.27 percentage points, i.e. less than 3 in 1000.

3.4 COMPARISON OF LIMITS

Table 4 overleaf sets out a comparison of some average exposure limits implied by these risk estimates.
Table 4. Comparison of risk estimates.

<table>
<thead>
<tr>
<th>ACGIH conclusions from epidemiological studies</th>
<th>Average exposures to Crystalline Silica (0.05 mg.m$^{-3}$), and the ACGIH TLV</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOAEL for silicosis (implied)</td>
<td>0.05 mg.m$^{-3}$</td>
</tr>
<tr>
<td>NOAEL for Lung cancer</td>
<td>0.046 mg.m$^{-3}$</td>
</tr>
<tr>
<td>Risk estimates from Scottish coalminers study (Silicosis Category 2 or greater)</td>
<td></td>
</tr>
<tr>
<td>Risk 27/1000</td>
<td>0.025 mg.m$^{-3}$</td>
</tr>
<tr>
<td>Risk 1/1000</td>
<td>0.01mg.m$^{-3}$</td>
</tr>
<tr>
<td>Human NOAEL estimated from animal studies (this paper)</td>
<td>0.0011mg.m$^{-3}$</td>
</tr>
<tr>
<td>ACGIH recommended TLV</td>
<td>0.025 mg.m$^{-3}$</td>
</tr>
</tbody>
</table>

It can be seen from Table 4 that the average exposure limit based on extrapolation from the animal studies is some 9 to 45 times lower than those based on estimates from epidemiological studies.
4. DISCUSSION

In this paper, we aimed to compare estimates of NOAEL for crystalline silica using two different methods.

The first approach used data from animal experiments. Since available animal data does not directly provide information on no-effect levels, we adopted a relatively new approach of estimating the rat internal dose threshold for crystalline silica (MIN-U-SIL 5) by means of a bio-mathematical model. From this we derived the rat NOAEL. Conventional extrapolation or uncertainty factors (US EPA, 1994; Haber et al., 2000; ECETOC, 2003) were then applied to this estimate, to account for possible interspecies toxicokinetic differences, dosimetric adjustments and differences in human susceptibility (it is possible to adapt the model to extrapolate directly to humans, as we describe later, but this we have not included at present).

The second approach derived the NOAEL using available human data from epidemiological studies. For this we compared with the draft ACGIH conclusions on epidemiological studies, and also with the results of an epidemiological study that benefited from uniquely detailed exposure measurements.

In this discussion we compare the risk estimates from epidemiological and from animal studies.

Estimates from animal studies

Crystalline silica is a known toxic dust. In animal models, it can cause an inflammatory reaction at very low internal mass dose in comparison to low-toxicity particles (Donaldson and Borm, 1998). Chronic inflammation in rats caused by exposure to silica dust does not subside with the cessation of exposure and can lead to cancer (Muhle et al., 1989). In our current approach we chose inflammation as the adverse effect to be prevented. The NOAEL is defined as the highest level of concentration of silica, in a chronic 2-year inhalation exposure for rats, such that the resulting inflammation is not above the background level. Due to lack of data at the low dose spectrum, the threshold internal dose can only be estimated from a mathematical model describing the exposure-dose-response relationship. Thus, much depends on the nature of the model.

Our approach allows for the estimation of the threshold dose and the derivation of the NOAEL within a single, consistent framework. The results can be integrated subsequently with established procedures for extrapolation to humans (US EPA, 1994). In this study, we applied factors to extrapolate the animal-based NOAEL to humans and a further factor for intra-human variations to derive the human equivalent NOAEL.

An alternative method is to construct a human model of exposure-dose-response and deduce the corresponding NOAEL. This approach will involve the scaling of the model parameters, currently based on animal data, to their human counterparts using allometric scaling with appropriate human values used whenever such values can be obtained. The uncertainty and variability in the human model predictions will have to be investigated using Monte Carlo simulations. We have carried out a similar study for low-toxicity particles (Tran et al., 2003), this method could also be used to investigate exposure-dose-response with respect to silica.

The abundance and the quality of the data available to test the model are one of the key strengths of our animal-based approach. The first dataset was used to estimate key model parameters and covered both the exposure and post-exposure period. Particularly, the dataset includes both the lavageable and unlavageable dose which is necessary for estimating the
interstitialisation rate of silica. This type of animal data is often not available. More data were also available to validate the model. This also enabled further development of the model to include a threshold for fibrosis. This, less validated, feature referred to higher doses than used to estimate the threshold for inflammation defined as the relevant adverse effect, so our conclusions are based only on well-validated parts of the model.

The model used has been applied to coalmine and low-toxicity dusts (Kuempel et al, 1999). It describes plausible mechanisms occurring in the lung following inhalation of particles. Specifically, it describes the well observed clearance mechanisms by alveolar macrophages; the cessation of clearance and the initiation of inflammation; and the translocation of silica particles to the lymph nodes. While the structure of the model remains the same over the range of particles which the model has been tested on, the actual values of the model parameters change according to the dust types. For silica, the threshold dose is much smaller, in mass terms, comparing to low-toxicity particles while the interstitialisation rate is higher, reflecting the potency of silica.

During the process of modelling, we extended the model to take account of the formation of fibrosis. This extension does not invalidate the prediction on inflammation. However, it associates the formation of fibrosis with a second wave of inflammatory reaction and a rise in the level of alveolar macrophages found in the bronchio-alveolar fluid, indicative of damage to macrophages.

The identification of a second threshold dose associated with fibrosis is still in need of validation by further experimentation. However, it is worth noting that clearance ceases once the first threshold is reached. If exposure continues, it will become difficult to avoid reaching this second threshold. Furthermore, even before reaching this, inflammation (as measured by the number of PMN cells in the BAL fluid), was already high. This was the reason for us to choose the first threshold and the associated exposure level as the NOAEL.

Our current approach of applying uncertainty factors for extrapolating the rat NOAEL to humans follows that of the US EPA (1994) and Haber et al (2000). Here the uncertainty factor is allocated a value of 300, including an allowance for dosimetric differences. This is an area, our results suggest, which will benefit from further investigation.

It is also important to note that in estimating human no or low-effects exposures from the results of animal studies, well recognized and continually developing methods of extrapolation or uncertainty factors are applied to take account of some fundamental differences between animal studies and the human experience. For inhaled silica, the main differences are:

- The differences between rats and humans in lifespan and exposure duration. Silicosis in humans rarely becomes apparent in less than 3-5 years (unless the silica concentrations are exceptionally high), and may take decades to become apparent. The duration of the rat experiment we quote was only 84 days. In the Buchanan et al human study the exposures were experienced during a period of 15 years., plus 15 years follow-up, with lengthier periods in some of the ACGIH quoted studies.
- The measures of risk are not the same; the animal risks are based on average values of measured effects and process rates, while the human risks are based on the numbers of individuals affected.
- The rat experiments were based on relatively homogeneous inbred populations. The exposed humans were genetically diverse.
• Only 24 animals were included in the main rat experiment (plus so many more in the experiments used for validation, parameter generations etc). The human study populations are numbered in hundreds or thousands.

• The rat no-effect level was estimated as 2 SDs below the average level for non-exposed rats. No further margin was added in the human (Buchanan et al) estimate (ACGIH did add a margin, but estimated higher low-effect exposures)

• The measures of disease are not identical. The criterion used in rats was the earliest signs of inflammation, while in humans X-ray signs of fibrosis represent a more advanced stage of disease than inflammation.

• Interspecies toxico-dynamic differences between rats and humans.

Finally, it is worth stressing again that the way forward for calculating the NOAEL for humans is to construct a human-based model of exposure-dose-response relationship and use it to estimate the NOAEL following the same approach as we have done for the animal-based NOAEL. The approach using the uncertainty factors will always be criticized for being arbitrary. Modelling, while not perfect, will be transparent and rational and therefore easier to justify.

Estimates from human studies

In the context of human limit-setting, the strength of an epidemiology-based approach is that it relies on observational data on the effect of concern: extrapolation across species is not required, and between-subject variation is already present in the population studied. Thus, it is arguable that risk assessment should favour evidence from human epidemiological studies where available.

However, human data on silica also contain many sources of uncertainty. The assessment of fibrotic lesions on chest radiographs is a subjective technique, and subject to reader variation between and even within readers. Silicosis is a progressive damage process, and there is no clear diagnostic point past which disease is discriminated from absence of disease, except by arbitrary convention. As a result, different researchers have reported results at different degrees of radiological severity. The ability of silicosis to progress even in the absence of further exposure is another factor, since the manifestation of risk depends importantly on the length of time elapsed between exposure(s) and the taking of the radiographs.

Characterisation of exposure is another source of variation, and studies that have less detailed exposure measurements and work histories may have considerable misclassification in their exposure estimates. Even with good characterisation, there is the additional complication, now well-established, that equal exposures to crystalline silica can imply very different risks, depending on both the process making the silica respirable and the other minerals present in the respirable cloud.

We have looked at the survey of data sets that the ACGIH compiled, and also at our own data from one Scottish colliery. Our own work was published in the peer reviewed literature after the ACGIH review, and has already been highly influential on the deliberations of the UK’s HSE on regulating exposure to crystalline silica. This was partly because it arose from a study (the PFR) in which exposures were differentiated and measured at a level of detail greater than any of those considered by the ACGIH.

We have noted that the risk estimates from the different studies in the ACGIH review gave very different risk estimates; but that our work gave results that were consistent, in order of magnitude, with the studies with the highest risks. We therefore believe that, although the numbers of subjects in the PFR study were relatively small, the detail of their silica exposures
gives them unique value in deriving a silica exposure-response relationship, and we have chosen to emphasise the predictions from this relationship.

Our predictions suggest that exposure for 15 years to a mean respirable silica concentration of 0.01 mg.m\(^{-3}\) would increase the risk, after a further 15 years, of showing a radiological category of 2/1 or greater, by somewhere in the region of one per thousand. This increase is over a baseline prevalence at zero exposure (probably due to other conditions with similar radiographic appearance, or misattribution of exposures) of less than 0.8%. In a workforce properly controlled to a limit of 0.01mg.m\(^{-3}\), we would expect the mean exposure to be lower than the limit, and the excess risk correspondingly reduced.

**Comparisons of estimates**

In this study, we have brought together two approaches for estimating a safe average level for silica. The animal-based approach has yielded an estimate of 0.0011mg.m\(^{-3}\) while the epidemiology-based approach has yielded values some 9 to 45-folds higher. It appears that in the absence of epidemiological findings, the animal-based method may lead to over stringent control limit settings.

We describe above the uncertainties in both animal based estimates and the results of epidemiological studies. Nevertheless it is probable that in this case the uncertainty factors used to translate risks from animals to humans are over-precautionary.

The present modelling technique could readily be used, by inserting human-based parameters, to estimate the dosimetric and toxicokinetic differences between animals and humans, and to model the human risks. Investigation of the uncertainty factors appropriate for human intraspecies variation in susceptibility would require a different approach, examining what information is available on human variations in the most influential mechanisms.
5. ACKNOWLEDGEMENTS

We thank the Nickel Producers Environmental Association for support for this work.
6. REFERENCES


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APPENDIX I - MODEL VALIDATION

Experimental data

The data used to validate the model were from an inhalation experiment with the same silica type (Minu-Sil 5) as in the first experiment (Porter et al., 2001). Groups of 6 rats were exposed at 15 mg.m$^{-3}$ for up to 161 days. Sacrifice time points were at 1, 7, 14, 28, 56, 112 and 161.

The following assays were measured:

- Total burden (lung plus lymph node burden),
- Number of PMN cells,
- Number of AM cells,
- Hydroxyproline level (mg/lung) at 28, 56, 112 and 161 days respectively.

Note that the Hydroxyproline assay, reflecting the process of fibrosis, was not measured in the last experiment and therefore this process was not part of the current model in the main text. However, the model is now extended to include this assay.

The model was used to simulate the outcomes of this experiment. The results are shown in Figure A.1.

Hydroxyproline is the assay used to quantify the formation of fibrosis. In the absence of fibrosis, it is expected that:

$$\frac{dH}{dt} = 0 \quad \text{(A.1)}$$

and therefore $H = H_0$, where $H_0$ is the control level of Hydroxyproline.
Since the AM-mediated clearance became impaired at very low lung burden, the model predicted a linear build up of total lung burden. This appears to be confirmed by comparing the predicted total lung burden with the burden data of this experiment.

The model also predicted well the level of AMs and PMNs up to 112 days. Interestingly, for the PMN, AM assays, the model under-predicted significantly the last time point (116 days). For Hydroxyproline, the level appeared to increase from 112 days.

It is clear from Figure A.1 that the current model predicted inflammation well over the range of interest for this paper, but could not predict the formation of fibrosis. Fibrosis is associated with (i) an increase in inflammation (i.e. increased PMN recruitment); (ii) an increase in the AM population; and; (iii) the formation of fibrosis appeared to occur once a threshold is reached.

**Modelling for Fibrosis**

To overcome the limitation of the existing model, a modified model to describe the occurrence of fibrosis and its effects was subsequently introduced. The underlying hypothesis used to interpret the data was: At a second threshold ($m_{\text{cri2}}$), damages were inflicted on macrophages, resulting in an increase in the level of AMs and PMNs in the BAL fluid. Damaged AMs were also unable to phagocytose. This impairment of phagocytosis lead to increased interstitialisation of silica particles resulting in fibrosis.
Mathematically, equations (4), (5) and (A.1) were extended with the use of a second threshold impairment function $F_2$.

$$F_2 = \begin{cases} 1 & \text{for } X_2 \leq m_{\text{crit}_2} \\ \text{else} & \\ e^{-B \left( \frac{X_2 - m_{\text{crit}_2}}{m_{\text{max}} - m_{\text{crit}_2}} \right)^G} & \end{cases}$$

(A.2)

where $B$, $G$ and $m_{\text{max}}$ are given in the main text and $m_{\text{crit}_2} \geq m_{\text{crit}}$.

Equation (4) was extended as

$$\frac{dPMN}{dt} = k_1.k_4.X_i + k_2.(1 - F).X_2 + k_4.(1 - F_2).X_2 - k_5.PMN$$

(A.3)

Similarly for equation (5),

$$\frac{dAM}{dt} = k_6.AM_0 + k_6.(1 - F_2).X_2 - k_4.AM$$

(A.4)

and equation (A.1)

$$\frac{dH}{dt} = k_5.(1 - F_2).X_2$$

(A.5)

Finally, the phagocytosis rate, $r$, was made to be dependent on $F_2$, i.e.

$$r = r_0.F_2$$

(A.6)

where $r_0$ is the value of $r$ used in the original model.

**Results**

The re-modelling process introduced four extra parameters, namely, $m_{\text{crit}_2}$, $k_4$, $k_6$ and $k_5$. The parameters were estimated by the method described earlier,

**Table A.1** The parameter estimates and their upper and lower 95 pc confidence values

<table>
<thead>
<tr>
<th></th>
<th>$m_{\text{crit}_2}$ (mg)</th>
<th>$k_4$ (day$^{-1}$)</th>
<th>$k_5$ (day$^{-1}$)</th>
<th>$k_6$ (day$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower 95pc Estimate</td>
<td>1.848</td>
<td>1.158</td>
<td>0.012</td>
<td>0.373</td>
</tr>
<tr>
<td>Estimate</td>
<td>1.964</td>
<td>1.267</td>
<td>0.029</td>
<td>0.505</td>
</tr>
<tr>
<td>Upper 95pc Estimate</td>
<td>2.080</td>
<td>1.376</td>
<td>0.047</td>
<td>0.640</td>
</tr>
</tbody>
</table>

The extended-model predictions and the experimental data are shown in Figure A.2.
Further Validation

Using the parameters estimated using the ‘99 experiment data, the model was used to extrapolate to a low concentration situation. Data were available from a chronic 2-yr study with SiO$_2$ (MMAD=1.4 $\mu$m, gsd=1.8, DQ-12 quartz; Muhle et al, 1989) at 0.75 mg.m$^{-3}$. The data consist of lung and lymph node burden for up to 2 years and one time point for 1.5 month after 2 years exposure.

The procedure was to:

i.   Use the model to predict the Muhle experiment;

ii.   Change some parameters to make model to fit data if necessary.

Because of different particle size distribution, different silica type and different experimental conditions, it is expected that the deposition fraction and the translocation rate to the lymph nodes would be different.

The deposition fraction for the Minu-Sil 5 is 0.06. Using the data from Raabe et al (1977, 1988), the deposition fraction for the DQ-12 quartz was estimated to be 0.08 (see Figure A.3).
Figure A.3. Alveolar deposition fraction for particles inhaled by rats. Data from Raabe et al., 1977 (∆) and 1988 (∇).

Results

Figure A.4 shows the model simulations. The dotted lines represent the model simulations using the original parameters estimated earlier.

Figure A.4. Model predictions for a 2-yr chronic inhalation study with DQ-12 quartz at 0.75 mg.m$^{-3}$. (a) Lung burden; (b) Lymph node burden; (c) PMN level.
The solid lines are obtained using a value of deposition fraction $DF$ of 0.087 and a translocation rate $k_l$ of 0.0015 (day$^{-1}$). These values were obtained ‘by eye’, since the objective is to demonstrate the consistency in model predictions. The vertical line represents the end of the exposure period. The light solid lines are the simulations with $DF = 0.08$ and $k_l = 0.0042$ (the original value obtained earlier).

Note that the estimated value of $k_l$ is still within the 95 percent confidence interval of the estimated $k_l$ using the second experimental data.

The original model has predicted the onset of inflammation, in another experiment, accurately. However, it has failed in predicting the formation of fibrosis. This model was subsequently extended to include fibrosis and used to predict the outcome of a longer-term inhalation experiment at a lower concentration. The results of the prediction were qualitatively near to the observed data. Further data will be needed to test the prediction on fibrosis.
APPENDIX II - REPLY TO SELECTED COMMENTS FROM THE SPONSORS

- Could the large difference in OEL value between the animal and human data be due to: 1) a NOAEL (threshold, no risk) being calculated for the animal data while a value corresponding to $1/10^3$ excess risk was used for the human data?
  
  o Yes, in part, but the risk estimates are not exactly comparable anyway (see Discussion) and the nature of the data does not permit a reliable estimate of a $1/10^3$ excess risk in the rats. Relatively few animals (24) were used in the main experiment, so one can only be confident that the risk is less than 1 in 24. The human studies involved hundreds or thousands, and the risks at which we estimated exposure concentrations are very low (1 in 1000, much less than 1 in 24). It would be possible to calculate the exposures related to human risks of less than 1 in 24, but this would still not be directly comparable to the animal based risks.

- Could the animal data be used to calculate an exposure value at which the risk of inflammation is $1/10^3$; the endpoint of inflammation being considered for animals (more sensitive) and the presence of silicosis being considered for humans (less sensitive)?
  
  o In view of the above arguments, this approach would not yield a reliable estimate.

- Would the endpoint of fibrosis in animals be more comparable to silicosis in humans? If so, what would be the numerical difference between applying a threshold or a $1/10^3$ risk approach?
  
  o It is correct that in temporal order the inflammation starts before the fibrosis. However once the retained silica dose has reached the point of initiating inflammation, clearance has stopped, and the progression to fibrosis is inevitable. Thus, while the time course of inflammation and fibrosis are different, the associated silica doses are the same, given sufficient elapsed time. Furthermore, our rat model has been validated for the inflammation component, but not yet for the fibrosis component, so estimates based on the fibrosis part of the model would be less reliable.

- It is not clear from the information that is presented why 0.1 mg/m$^3$ was chosen as the animal NOAEL. On page 10, Figure 3, the response curves for different silica concentrations are not labeled, but Figures 3a and 3b show 5 curves, presumably corresponding to 0.1, 0.2, 0.3, 0.4, and 0.5 mg/m$^3$. The lowest 2 of the corresponding 5 curves for PMN on Figure 3c are more difficult to discern, but it appears that there is a flat curve close to zero (0.1 mg/m$^3$?). If this is the case, the bold curve would correspond to 0.2 mg/m$^3$ (and the animal NOAEL). Please help us clarify whether a higher NOAEL level could have been chosen.
  
  o The 0.2 mg.m$^3$ will be the first level to avoid inflammation (see Figure 3) while 0.1 mg.m$^3$ is a NOAEL according to the definition on page 10.

- It appears that the animal modelling reflects a lifetime exposure (approximately 2 years) and/or a lifetime risk. This would seem to be inconsistent with the human risks
which are associated with 15 years of exposure and 15 years post-exposure (less than lifetime exposure and lifetime risk). Should the animal exposure be adjusted to correspond to less than lifetime occupational exposure?

- We could extend the work to harmonise the two exposure scenarios. This would be likely to result in a relatively higher exposure level. However, this level will not correspond to the definition of a NOAEL defined here as a life-time exposure without a post-exposure period. It is also worth noting that if a life-time exposure does not result in an adverse effect then a shorter exposure period together with a post-exposure period is likely to produce the same results.

- In addition, typically the risk for workers is calculated over 40 years of occupational exposure. Why did you use 15 years? I believe that for pneumoconiosis there is some data to indicate that the risk due to high exposures for a short duration of time are greater than the risks due to long exposures at lower exposure levels, for equal cumulative exposures [mg/m$^3\times$years]. If this is true, would an occupational level based on shorter but higher exposures overestimate risks for longer but lower level exposures?

- The 15 year period corresponds to the timing of the observations in the Buchanan et al study. Our estimates are for the low exposure range. The expected time course of pneumoconiosis depends on the hazard. For mixed coal mine dust, it is accepted conventional wisdom that the best predictor of risk is cumulative exposure, regardless of the temporal pattern of the exposure. For silica, the situation is more complex. Exposure to higher concentrations increases riskiness, and fibrosis continues to develop after exposure ceases. So the answer to your last question is yes.

- The factor-of-10 dosimetric adjustment based on human-rat differences in macrophage-mediated clearance rates of insoluble particles may be overly aggressive. We are not aware of this kind of adjustment ever been made on risk assessments for particulates. Would you apply this adjustment to all water insoluble particles (e.g., nickel oxide, coal dust?). The "standard" deposition models, such as the US EPA RDDR model would suggest the use of a factor of ~2 based on deposition differences between the rat and the human lung (depending on the exact particle diameter, GSD). Given the importance of trying to reconcile the animal extrapolation estimates against human data, it would be appropriate to more carefully characterize the applicability of these factors to other substances besides silica.

- We applied 10 for intrahuman variability (see later), 3 for toxicodynamic differences, 10 for dosimetric adjustment, because of the slower macrophage clearance in humans. We believe this is justified by the evidence we quote.

- The estimated human risks from equation 5 do not correspond to those provided for non-zero exposures in Table 5. The equation gives estimates of 0.85%, 0.93%, 0.97%, and 1.53 % for 0.15, 0.375, 0.45, and 1.5 mg/m$^3\times$years, respectively. To obtain the risk estimates in Table 5, the slope coefficient for the log-odds response function should be approximately 0.782. Is there perhaps an upper confidence limit on the quoted slope coefficient (0.443) that is being used to provide the estimated risks in Table 5?
Thank you for spotting the mismatch. This was caused by the original exposures being in g.h.m$^{-3}$, but we quote here in the more commonly used units of mg.y.m$^{-3}$. So the coefficient should be rescaled as $0.443 \times 1.74 = 0.771$. The risks in the table are correctly calculated for the quoted exposures; it is the equation that has now been changed.

- In the case of the uncertainty factors, you used 10 for intraspecies variability. This would be fine for calculating ambient air levels as Haber did. In the case of workers a factor of 3 is often used in the EU (ECETOC, 2003) and 5 (Kalberlah and Schneider 1998 Quantification of extrapolation factors. Final report of the research project No. 11606113 of the Federal Environmental Agency. Schriftenreihe der Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Fb 797, Dormund/Berlin) because the workforce does not include the very young or very old.

  - Thanks for drawing our attention to these sources. We have now adopted the 3 factor recommended by ECETOC (2003), and this has reduced the difference between the animal and human estimates.

- The paper provides vastly different estimates of acceptable occupational exposure limits derived from human and animal data. Most of the difference is driven by the safety factors used in deriving the animal-based estimates. To make the paper more useful, the plausibility and basis for these factors needs to be more carefully examined and discussed to allow a better reconciliation and understanding of the differences between the animal and human estimates.

  - We agree it would be useful to review the further development of the use of safety factors since the US EPA (1994) document was published.

- For silica, the animal aerosols are in the respirable size range and the OEL for silica is a respirable OEL. Is it true that one would expect even more of a discrepancy between an animal derived OEL and an epidemiological study derived OELs if the OEL is defined in terms of ‘inhalable aerosol’?

  - Yes, one would expect differences due to the difference in the inhalable fraction between the two species, depending on the particle size distributions in practice.
Applying science for a better working environment

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Our beginnings

Our first major research programme began in the 1950s, on respiratory health problems in the coal mining industry. Major themes were quantification of airborne dust concentrations in different jobs, characterisation of types and constituents of the dusts, measurement of health effects, relationships between exposure and disease, and proposals for prevention. This research became an international benchmark for epidemiological studies of occupational health, and was the primary influence on dust standards in mines in the UK, US and other countries.

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Our current work spans many other industries including asbestos, MMMF, pesticides, chemicals, energy, telecoms, metals, textiles, construction, agriculture as well as the environment. While diseases of the respiratory tract remain a major interest, our scope now extends to many other health outcomes such as mortality, cardiovascular effects, cancer, back pain, upper-limb disorders, hearing loss, skin diseases, thermal stress and psychological stress. Related work includes the development and application of measurement and control systems, mathematical models and survey methods.

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Our work in these areas is conducted for a wide range of organisations in the UK, the EU, and the US, including Government departments, international agencies, industry associations, local authorities, charitable organisations, and industrial and commercial companies. The IOM is a World Health Organisation (WHO) collaborating centre and is an approved institute of the Universities of Edinburgh and Aberdeen, enjoying collaborative research links with NIOSH, IARC, and many other institutes throughout the world.

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We believe that our research findings should be publicly available and subject to the scrutiny of the international scientific community. We publish our findings in the peer reviewed scientific literature and through our own series of Research Reports.

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