A meta-analysis of the relation between cumulative exposure to asbestos and relative risk of lung cancer

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Abstract

Objectives—To obtain summary measures of the relation between cumulative exposure to asbestos and relative risk of lung cancer from published studies of exposed cohorts, and to explore the sources of heterogeneity in the dose-response coefficient with data available in these publications.

Methods—15 cohorts in which the dose-response relation between cumulative exposure to asbestos and relative risk of lung cancer has been reported were identified. Linear dose-response models were applied, with intercepts either specific to the cohort or constrained by a random effects model; and with slopes specific to the cohort, constrained to be identical between cohorts (fixed effect), or constrained by a random effects model. Maximum likelihood techniques were used for the fitting procedures and to investigate sources of heterogeneity in the cohort specific dose-response relations.

Results—Estimates of the study specific dose-response coefficient ($k_{i,1}$) ranged from zero to 42×10^{-3} ml/fibre-year (ml/f-y). Under the fixed effect model, a maximum likelihood estimate of the summary measure of the coefficient ($\hat{\kappa}_1$) equal to 0.42×10^{-3} (95% confidence interval (95% CI) 0.22 to 0.69×10^{-3}) ml/f-y was obtained. Under the random effects model, implemented because there was substantial heterogeneity in the estimates of $k_{i,1}$ and the zero dose intercepts (A_i), a maximum likelihood estimate of $\hat{\kappa}_1$ equal to 2.6×10^{-3} (95% CI 0.65 to 7.4×10^{-3}) ml/f-y, and a maximum likelihood estimate of $\hat{A}$ equal to 1.36 (95% CI 1.05 to 1.76) were found. Industry category, dose measurements, tobacco habits, and standardisation procedures were identified as sources of heterogeneity.

Conclusions—The appropriate summary measure of the relation between cumulative exposure to asbestos and relative risk of lung cancer depends on the context in which the measure will be applied and the prior beliefs of those applying the measure. In most situations, the summary measure of effect obtained under the random effects model is recommended. Under this model, potency, $\hat{\kappa}_1$, is fourfold lower than that calculated by the United States Occupational Safety and Health Administration.

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Occupational exposure to asbestiform fibres causes lung cancer.¹ The relation between extent of exposure and risk of lung cancer influences (a) regulatory activity,² (b) estimates of risk from low level exposures to asbestos,³ and (c) prediction of the impact of exposures on public health—such as lung cancer mortality among exposed workers in asbestos industries.⁴ Overviews of the dose-response relation conducted to date have been semiquantitative and have not been examined in the light of updates of the cohort studies upon which they rely. We present a quantitative meta-analysis of the relation between cumulative exposure to asbestos and relative risk of lung cancer. We discuss potential sources of heterogeneity in the relation that was evident in the studies.

Methods

We identified published studies by reviewing an existing overview of the dose-response relation,⁵ searching the Medline database from 1966 to December 1995, and by searching citations in the studies found by the first two methods. Any study reporting a measure of the relative risk for lung cancer associated with a quantitative measure of cumulative exposure was eligible for the meta-analysis. No such studies were intentionally excluded. Most studies identified, and all studies included in the meta-analysis, were retrospective cohort studies of mortality due to lung cancer. The diseases encompassed by the term lung cancer differed in the different studies. We abstracted and report, when available, the international classification of diseases (ICD) codes included under the definition of lung cancer in each study. We also extracted from each study the cohort entrance requirements; number, sex, and race of people studied; amount of person-time accumulated, noting exclusions; type of asbestos industry and of asbestos fibre; method of estimating cumulative exposure; characteristics of the referent population; method of ascertaining vital status and of classifying causes of death; number of total lung cancer deaths observed; number of observed and expected lung cancer deaths, and the corresponding standardised mortality ratio (SMR), within cumulative exposure strata; and any information on tobacco use by the cohort.

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Cumulative exposure strata were usually defined by a range, often with an open end for the highest exposure stratum—for example, ≥ 100 fibre-year/ml (f-y/ml). We assigned fixed exposures to these ranges as the midpoint of the range, unless a mean or median was reported. For open ended categories, we assigned a fixed exposure by repeating the pattern found at lower exposures. We calculated 95% confidence intervals (95% CIs) about the SMR for each cumulative exposure with an approximation to a Poisson distribution.⁶ For each study reporting SMRs for more than one cumulative exposure category, we fitted the following dose-response model:

$$E_{ij} = A_i (1 + k_{i,j} d_{ij}) e_{ij} \quad k_{i,j} \geq 0$$

where E_{ij} is the number of deaths from lung cancers expected under the model in study i at dose j , A_i is the fitted intercept corresponding to the relative risk of lung cancer among the cohort at zero exposure, $k_{i,j}$ (a measure of potency) is the coefficient relating cumulative exposure to asbestos to relative risk of lung cancer in study i under the linear dose-response model,⁷ d_{ij} is the dose of asbestos assigned to cumulative exposure category j of study i , and e_{ij} is the population based expected number of deaths from lung cancer. The number of observed deaths from lung cancer in study i at dose j , which we denote O_{ij} , was assumed to be a Poisson random variable with expectation E_{ij} . To obtain estimates of A_i and $k_{i,j}$, we maximised the likelihood ($\mathcal{L}_i$) for each study:

$$\mathcal{L}_i = \prod_j \left(\frac{E_{ij}^{O_{ij}}}{O_{ij}!} e^{-E_{ij}} \right)$$

We estimated the 95% CI about each $k_{i,j}$ with the profile likelihood method.

We obtained a maximum likelihood summary measure of the dose-response coefficient ($\hat{\kappa}_i$) by substituting $\hat{\kappa}_i$ for each $k_{i,j}$ and maximising the sum of the $\ln \mathcal{L}_i$ with respect to $\hat{\kappa}_i$ and A_i , constraining i to the subset of studies chosen to represent unique cohorts. This con-

straint was necessary because some cohorts have been studied more than once. A 95% CI about $\hat{\kappa}_i$ was obtained by the profile likelihood method. The likelihood method weights each study by its precision.

We found substantial heterogeneity of the A_i and $k_{i,j}$, so the fixed effect summary estimate of the dose-response coefficient and its 95% CI may be inappropriate. We then calculated a random effects summary estimate of the dose-response coefficient by assuming that the A_i and $k_{i,j}$ derive from log normal distributions. Restating the likelihood under the random effects model, we have:

$$\mathcal{L} = \prod_i \left(\int_{-\infty}^{\infty} \frac{dz_i}{\Sigma \sqrt{2\pi}} \exp \left(-\frac{(z_i - \xi)^2}{2\Sigma^2} \right) \times \right. \\ \left. \int_{-\infty}^{\infty} \frac{dw_i}{\sigma \sqrt{2\pi}} \exp \left(-\frac{(w_i - \phi)^2}{2\sigma^2} \right) \times \right. \\ \left. \prod_j \frac{(e^{w_i} e_{ij} (1 + e^{z_i} d_{ij}))^{O_{ij}} \exp(-e^{w_i} e_{ij} (1 + e^{z_i} d_{ij}))}{O_{ij}!} \right)$$

where z_i is $\ln(k_{i,j})$, ξ is $\ln(\hat{\kappa}_i)$, and $z - \xi$ is normally distributed with SD Σ ; and w_i is $\ln(A_i)$, ϕ is $\ln(\hat{A}_i)$, and $w - \phi$ is normally distributed with SD σ .

We tested various hypotheses on sources of heterogeneity in estimates of $k_{i,j}$ under the model with likelihood techniques.

Results

We identified 15 cohorts in which the dose-response relation between cumulative exposure to asbestos and relative risk of lung cancer has been reported in 22 publications. The table contains a summary of each publication, including its $k_{i,j}$, A_i , and the 95% CI about $k_{i,j}$. Figure 1 shows the distribution of the individual $k_{i,j}$ plotted against the inverse normal of its rank, and fig 2 shows the distribution of the individual A_i plotted against the inverse normal

Figure 1 Distribution of maximum likelihood estimates of $k_{i,j}$ observed in 21 studies and 95% CIs about $k_{i,j}$. The lower bound on the CI about studies with error bars overlapping the abscissa equals 0. The maximum likelihood estimate for studies with no square marker equals 0. Two studies, in which only one dose group was reported, are not depicted. The shape of the distribution indicates that the $k_{i,j}$ is approximately log normally distributed.

Figure 2 Distribution of maximum likelihood estimates of A_i observed in 21 studies. Two studies, in which only one dose group was reported, are not depicted. The shape of the distribution indicates that the A_i are approximately log normally distributed.

Summary of 23 investigations of the relation between cumulative exposure to asbestos and relative risk of lung cancer in 15 cohorts (the number in the first column indicates the cohorts and the letter indicates published studies of the cohort; cohort 1 was split into two, described under 1b and 1c)

1a Weill *et al* (1979).⁸ 5645 men employed for at least one month between 1942 (first plant) or 1920 (second plant) and 1 January, 1955 at two asbestos cement building plants in New Orleans, Louisiana that used primarily chrysotile but also crocidolite, amosite, and silica. 51 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in Social Security Administration records, were observed in 154 527 person-years of follow up accumulated to 31 December 1974. Expected lung cancer deaths (ICD-8 160-163) estimated from age, sex, race, and calendar year US rates. Cumulative exposure based on workplace air measurements beginning in 1950 and work histories including exposures only within 20 years of onset. Tobacco habits not available. $k_1 = 4.7 \times 10^{-3}$ (95% CI = 1.5 to 11×10^{-3}) ml/f-y. $A = 0.69$.

Range in study (mppcf-y)	Value used in meta-analysis (f-y/ml)‡	Lung cancer O/E	SMR	95% CI*
≤ 10	7	19/24.7	0.77	(0.46 to 1.20)
11-50	42	8/11.4	0.70	(0.30 to 1.38)
51-100	105	1/3.8	0.26	(0.003 to 1.46)
101-200	210	9/3.1	2.90	(1.32 to 5.51)
> 200	560	14/6.2	2.26	(1.23 to 3.79)

1b †Hughes *et al* (1987).⁹ 2565 men employed for at least one month between 1942 and 1 January 1970 at the first asbestos cement building materials plant in New Orleans, Louisiana that used primarily chrysotile but also crocidolite, amosite, and silica. 48 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in local state, and federal records, were observed in an unreported number of total person-years of follow up accumulated to 31 December 1982 or age 80. Expected lung cancer deaths (ICD-8 162-163) estimated from age, sex, race, and calendar year Louisiana rates. Cumulative exposure based on workplace air measurements beginning in 1952 and work histories. Person-years were contributed to the cumulative exposure category attained 10 years previously. In 1969, 52% of workers were current smokers, 25% were ex-smokers, and 23% were never smokers. 55% of US men were current smokers in 1969 according to the authors. $k_1 = 0.66 \times 10^{-3}$ (95% CI = 0 to 9.9×10^{-3}) ml/f-y. $A = 0.93$.

Range in study (mppcf-y)	Value used in meta-analysis (f-y/ml)‡	Lung cancer O/E	SMR	95% CI*
< 6	5.6	3/2.9	1.04	(0.21 to 3.02)
6-24	18.2	9/8.0	1.12	(0.51 to 2.14)
25-49	49	2/3.7	0.55	(0.06 to 1.95)
50-99	103.6	3/3.8	0.78	(0.16 to 2.31)
≥ 100	256.2	5/4.1	1.23	(0.39 to 2.85)

1c †Hughes *et al* (1987).⁹ 4366 men employed for at least one month between 1937 and 1 January 1970 at the second asbestos cement building materials plant in New Orleans, Louisiana that used primarily chrysotile, some crocidolite, and silica. 107 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in local state and federal records, were observed in an unreported number of total person-years of follow up accumulated to 31 December 1982 or age 80. Expected lung cancer deaths (ICD-8 162-163) estimated from age, sex, race, and calendar year Louisiana rates. Cumulative exposure based on workplace air measurements beginning in 1950 and work histories. Person-years were contributed to the cumulative exposure category attained 10 years previously. In 1969, 49% of workers were current smokers, 26% were ex-smokers, and 25% were never smokers. 55% of US men were current smokers in 1969 according to the authors. $k_1 = 5.2 \times 10^{-3}$ (95% CI = 0.38 to 14×10^{-3}) ml/f-y. $A = 1.17$.

Range in study (mppcf-y)	Value used in meta-analysis (f-y/ml)‡	Lung cancer O/E	SMR	95% CI*
< 6	4.2	20/18.9	1.06	(0.65 to 1.63)
6-24	16.8	19/14.5	1.31	(0.79 to 2.05)
25-49	50.4	12/6.0	2.00	(1.03 to 3.49)
50-99	99.4	10/5.5	1.81	(0.87 to 3.34)
≥ 100	229.6	12/5.2	2.31	(1.19 to 4.03)

2a †Finkelstein (1984).¹⁰ 535 men employed for at least one year between 1948 and 1 January 1960 at an asbestos cement building materials plant in Ontario, Canada that used chrysotile, crocidolite, and silica. 26 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in local and national records, were observed in 6328 person-years of follow up accumulated to 31 December 1977. Expected lung cancer rates (ICD-8 162) estimated from age and sex specific Ontario rates, 1970 to 1974, with only person-time more than 20 years after the onset of exposure contributing. Cumulative exposure based on personal and ambient workplace air measurements beginning in 1949 and work histories up to 18 years. Exposures longer than 18 years generally contributed less than 10% of the total. Person-years were contributed to the cumulative exposure category attained 10 years previously. 16 of 17 lung cancer cases queried were current or ex-smokers. $k_1 = 6.9 \times 10^{-3}$ (95% CI = 0 to 250×10^{-3}) ml/f-y. $A = 3.46$.

Range in study (f-y/ml)	Value used in meta-analysis (f-y/ml)‡	Lung cancers	Relative rate	95% CI*
≤ 30	15	3	2.31	(0.46 to 6.75)
30.1-75	52.5	6	6.15	(2.25 to 13.39)
75.1-105	90	5	12.07	(3.89 to 28.16)
105.1-150	127.5	5	9.00	(2.9 to 21.0)
> 150	165	2	2.69	(0.3 to 9.71)

of its rank. Figure 1 justifies the use of a log normal distribution for k_1 in the random effects model. Figure 2 shows that a log normal distribution is appropriate for the A_i in the random effects model, as does the log normal distribution of SMRs for lung cancer found in 88 unexposed cohorts.³⁰ We considered using these unexposed cohorts to provide a prior estimate of the distribution of the A_i , but discovered that the distribution obtained from the asbestos cohorts differed significantly ($P = 0.002$).

Under the fixed effect model, from the 15 cohorts, we obtained a maximum likelihood estimate of k_1 equal to 0.42×10^{-3} (95% CI 0.22 to 0.69×10^{-3}) ml/f-y. Under the random effects model, implemented because we found substantial heterogeneity in the estimates of k_{1i} and A_i , we found a maximum likelihood estimate of k_1 equal to 2.6×10^{-3} (95% CI 0.65 to 7.4×10^{-3}) ml/f-y and a maximum likelihood estimate of A equal to 1.36 (95% CI 1.05 to 1.76). Our estimates of k_{1i} ranged from 0 ml/f-y^{11 13 20} to 42×10^{-3} ml/f-y.¹⁶ The dose-response model could not be fitted to two of the studies^{12 25} because only one cumulative exposure category was reported. Given the substantial range of the k_{1i} s, we thought it imperative to measure possible causes for the heterogeneity found.

TOBACCO HABITS

The prevalence of tobacco use among asbestos workers in different cohorts, compared with their standard populations, provides a likely source of heterogeneity in the dose-response coefficient. To evaluate this source, we allowed the intercept of the dose-response curve to differ from 1.0. We then fitted a model that forced the effect of asbestos exposure to multiply the intercept. Positive interaction between occupational exposure to asbestos and tobacco use would cause higher values for k_{1i} to be found in studies in which the deviation between tobacco use in the cohort and the standard population is greatest. This required an assumption that the deviation of the intercept from 1.0 was constant across all dose groups. None the less, we expected some residual heterogeneity due to variation in relative tobacco habits. This expectation arose because cumulative tobacco use probably correlates with cumulative

Figure 3 Fraction total mortality v k_{1i} at different stages of follow up in four cohorts.

- 2b Finkelstein (1938).¹¹ 339 men employed for at least nine years hired before 1960 at an asbestos cement building materials plant in Ontario, Canada that used chrysotile, crocidolite, and silica. 20 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status, were observed in 2902 person-years of follow up accumulated to 31 October 1980. Expected lung cancer rates (ICD-8 162) estimated from age and sex specific Ontario rates, 1970-4, with only person-time 20 to 33 years after the onset of exposure contributing. Cumulative exposure based on personal and ambient workplace air measurements beginning in 1949 and work histories up to 18 years. Exposures longer than 18 years generally contributed less than 10% of the total. 16 of 17 lung cancer cases queried were current or ex-smokers. $k_i = 0$ (95% CI = 0 to 17×10^{-3}) ml/f-y. $A = 12.6$.

Range in study (f-y/ml)	Value used in meta-analysis (f-y/ml)†	Lung cancers	Relative rate	95% CI*
8-69	44	5	8.5	(2.7 to 19.8)
69-121	92	7	16.3	(6.5 to 33.6)
122-420	180	6	7.4	(2.7 to 16.4)

- 3 †Ohlson and Hogstedt (1985).¹² 1176 men employed for more than three months between 1943 and 1976 at an asbestos cement products plant in Sweden that used predominantly chrysotile, but also crocidolite and amosite. 11 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status, were observed in 26 931 person-years of follow up accumulated until age 79 from 1951 to 1982. Expected lung cancer deaths estimated from age, sex, and calendar year specific Swedish rates from 1951 to 1982. Cumulative exposure based on ambient workplace air measurements beginning in 1950s and work histories. 40% Of workers participating in a voluntary health survey in 1980 were smokers, 24% never smokers, and 36% ex-smokers. The investigators say this distribution is close to the national average. Dose-response model does not fit individual study because there was only one exposure group.

Range in study (f-y/ml)	Value used in meta-analysis (f-y/ml)†	Lung cancer O/E	SMR	95% CI*
Median = 10	10	11/9	1.23	(0.61 to 2.19)

- 4 †Neuberger and Kundi (1990).¹³ 2816 people employed for at least three years between 1950 and 1981 at an asbestos cement products factory in Vöcklabruck, Austria that used primarily chrysotile, but also crocidolite. 49 Lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in national records, were observed in 51 218 person-years of follow up accumulated to the end of 1987. Expected lung cancer deaths (ICD-9 162) estimated from age, sex, and calendar year specific Upper Austrian rates. Cumulative exposure based on workplace air measurements beginning in 1950 and personal air samplers after 1975, both in combination with work histories. Lung cancer SMRs were 1.26 (95% CI 0.83 to 1.95) for ≤ 25 f-y/ml and 0.96 (95% CI 0.64 to 1.43) for > 25 f-y/ml after adjustment for smoking history. $k_i = 0$ (95% CI = 0 to 22×10^{-3}) ml/f-y. $A = 2.1$.

Range in study (f-y/ml)	Value used in meta-analysis (f-y/ml)†	Lung cancer O/E	SMR	95% CI*
≤ 25	12.5	25/12.8	1.95	(1.17 to 3.74)
> 25	37.5	24/15.04	1.60	(1.01 to 2.96)

- 5a †Dement *et al* (1994).¹⁴ 1247 white men employed for at least one month between 1 January 1940 and 31 December 1965 at an asbestos textile plant in Charleston, South Carolina that used chrysotile, and a negligible amount of crocidolite. 74 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in national records, were observed in 44 131 person-years of follow up accumulated from 1 January, 1940 to 31 December 1990. Expected lung cancer deaths (ICD-9 162) estimated from age, sex, and calendar year specific US rates. Cumulative exposure based on workplace air measurements and work histories. 52.4% were current smokers, 22.3% were ex-smokers, and 25.3% were non-smokers, based on samples of the cohort. The prevalence of smokers among white men in the US population was 51.5% according to the authors. $k_i = 24 \times 10^{-3}$ (95% CI = 11 to 48×10^{-3}) ml/f-y. $A = 1.32$.

Range in study (f-y/ml)	Value used in meta-analysis (f-y/ml)†	Lung cancer O/E	SMR	95% CI*
< 2.7	1.35	11/12.3	0.89	(0.45 to 1.60)
2.7-6.8	4.75	15/5.8	2.59	(1.45 to 4.27)
6.8-27.4	17.1	10/5.1	1.96	(0.94 to 3.61)
27.4-109.5	68.45	16/5.2	3.08	(1.76 to 5.00)
> 109.5	215.4	20/2.4	8.33	(5.09 to 12.87)

- 5b Dement *et al* (1983).¹⁵ 1261 white men employed for at least one month between 1 January 1940 and 31 December 1965 at an asbestos textile plant in Charleston, South Carolina that used chrysotile, and a negligible amount of crocidolite. 35 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in state and national records, were observed in 33 141 person-years follow up accumulated from 1 January 1940 to 31 December 1975. Expected lung cancer (ICD-7 162-163) estimated from age, sex, race, and calendar year specific US rates. Cumulative exposure based on workplace air measurements and work histories. 52.4% were current smokers, 22.3% were past smokers, and 25.3% were non-smokers, based on samples of the cohort. The prevalence of smokers among white men in the US population in 1965 was 51.5%, of ex-smokers 22.1%, and of non-smokers 26.4%, according to the authors. $k_i = 28 \times 10^{-3}$ (95% CI = 8.4 to 90×10^{-3}) ml/f-y. $A = 1.56$.

Range in study (f-y/ml)	Value used in meta-analysis (f-y/ml)†	Lung cancer O/E	SMR	95% CI*
< 2.7	1.4	5/3.58	1.40	(0.42 to 3.07)
2.7-27.4	15.1	9/3.23	2.79	(1.27 to 5.29)
27.4-109.5	68.5	7/1.99	3.52	(1.41 to 7.25)
109.5-274	191.8	10/0.91	10.99	(5.26 to 20.21)
> 274	411	2/0.11	18.18	(2.04 to 65.64)

asbestos exposure and because occupational exposure to asbestos and tobacco use interact positively to cause lung cancer.³¹ A correlation between cumulative asbestos exposure and cumulative tobacco use would cause higher relative risks of lung cancer to be found in groups with a higher dose of asbestos, regardless of the effect of asbestos exposure (and therefore higher $k_{i,i}$) to be found in the studies of workers with higher cumulative asbestos exposures. To investigate the extent of the first source of heterogeneity, we plotted the A_i versus $k_{i,i}$. We found no correlation, suggesting that $k_{i,i}$ is unrelated to the extent of the deviation between tobacco use in the cohort and in the standard population. To investigate the influence of the second source of heterogeneity, we plotted the maximum dose studied in each cohort versus the cohort's $k_{i,i}$ and found the opposite of the expected correlation. The $\ln(k_{i,i})$ were negatively correlated with maximum dose ($P = 0.001$, $r^2 = 0.50$). We discuss this finding further in the section on dose measurement as a source of residual heterogeneity.

Two studies of one cohort reported dose-response information stratified by smoking status.^{28,29} Fitting the dose-response model to each smoking stratum,²⁹ we found $A_{\text{non-smokers}} = 0.19$ and $k_{i,\text{non-smokers}} = 4 \times 10^{-3}$ ml/f-y; $A_{\text{moderate smokers}} = 1.16$ and $k_{i,\text{moderate smokers}} = 0.7 \times 10^{-3}$ ml/f-y; and $A_{\text{heavy smokers}} = 2.11$ and $k_{i,\text{heavy smokers}} = 0.8 \times 10^{-3}$ ml/f-y. A test of the hypothesis of uniform k_i yielded $P = 0.12$ and a uniform estimate of k_i in all smoker groups of 0.8×10^{-3} ml/f-y. Given the small number of lung cancers found among non-smokers, the test for homogeneity should not be considered particularly powerful. Pooling the observed and expected lung cancers across smoker strata within dose groups, and then implementing the dose-response model—that is, reaggregating the data into the form that they are usually reported—yielded $A_{\text{pooled}} = 0.96$ and $k_{\text{pooled}} = 0.9 \times 10^{-3}$ ml/f-y. Analyses of the first study of the cohort²⁸ yielded similar results. These data provide weak evidence that the dose-response coefficient is larger among non-smokers than among smokers and that the opposite is true for the intercept term. The pooled estimates of $k_{i,i}$ and A_i may depend, therefore, on the tobacco habits of the cohorts. The variability of tobacco habits in the cohorts included in the meta-analysis, compared with their respective standard populations, should be considered to be a source of heterogeneity.

INDUSTRY AND FIBRE TYPE

The United States Occupational Safety and Health Administration (OSHA)² postulated that the potency of asbestos exposure to cause lung cancer, measured on a relative scale, depends on the type of occupational exposure and type of asbestos fibre at issue. The notion is that mining and milling entails exposure to the least refined asbestos fibres, so is associated with the lowest potency per unit of cumulative exposure. Industries such as manufacturers of cement products that use asbestos of interme-

- 5c McDonald *et al* (1983).¹⁶ 2543 men employed for at least one month between 1938 and 1958 at an asbestos textile plant in Charleston, South Carolina that used chrysotile, and a negligible amount of crocidolite. 66 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in local and national records, were observed in an unreported number of person-years of follow up accumulated from 1 January 1938 to 31 December 1977. Expected lung cancer deaths (ICD-7 160-164) estimated from age, sex, race, and calendar year specific South Carolina rates. Cumulative exposure based on workplace air measurements and work histories. A lag time of 10 years before death or 1977 was imposed in determining exposure and only deaths 20 or more years after first employment were included. Cite Dement *et al* (1983)¹⁵ for smoking habits. $k_1 = 42 \times 10^{-3}$ (95% CI = 15 to 120×10^{-3}) ml/f-y. $A = 1.09$.

Range in study (mppcf-y)	Value used in meta-analysis (f-y/ml)	Lung cancer O/E	SMR	95% CI*
< 10	7	31/21.66	1.43	(0.97 to 2.03)
10- < 20	21	5/2.74	1.83	(0.59 to 4.26)
20- < 40	42	8/2.63	3.04	(1.31 to 5.99)
40- < 80	84	7/1.67	4.20	(1.68 to 8.64)
≥ 80	168	8/0.77	10.32	(4.47 to 20.47)

- 6 †Peto *et al* (1985).¹⁷ 3211 men first employed between 1933 and 1974 at an asbestos textile factory in Rochdale, England that used principally chrysotile, but also crocidolite. 132 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in company and national records, were observed in an unreported number of person-years of follow up accumulated over an unstated period. Expected lung cancer deaths were estimated from age, sex, and calendar year specific rates for England and Wales. Cumulative exposure based on workplace air measurements and work histories. A lag time of 5 years was imposed in determining exposure and only deaths 20 or more years after first employment were included. No information on tobacco habits. $k_1 = 4.1 \times 10^{-3}$ (95% CI = 0.8 to 9.8×10^{-3}) ml/f-y. $A = 1.10$.

Range in study (py/ml)	Value used in meta-analysis (f-y/ml)	Lung cancer O/E	SMR	95% CI*
< 1000	6.0	34/29.53	1.15	(0.80 to 1.61)
1000-2000	40.3	8/7.66	1.04	(0.45 to 2.06)
2000-3000	71.7	11/6.60	1.67	(0.83 to 2.98)
3000-4000	99.3	6/5.66	1.06	(0.39 to 2.31)
4000-5000	130.0	10/4.29	2.33	(1.12 to 4.29)
≥ 5000	258.8	24/10.83	2.22	(1.42 to 3.30)

- 7 †McDonald *et al* (1982).¹⁸ 4137 men first employed between 1937 and 1 January 1959 for at least one calendar month at an asbestos textile factory in Pennsylvania that used principally chrysotile, but also crocidolite and amosite. 70 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in local and national records, were observed in an unreported number of person-years of follow up accumulated to 31 December 1977. Expected lung cancer deaths (ICD-7 162-164) were estimated from age, sex, and calendar year specific rates for Pennsylvania. Cumulative exposure based on workplace air measurements beginning in 1956 and work histories. A lag time of 10 years was imposed in determining exposure and only deaths 20 or more years after first employment were included. Nine of 36 workers first employed between 1910 and 1919 had never smoked. $k_1 = 36 \times 10^{-3}$ (95% CI = 13 to 110×10^{-3}) ml/f-y. $A = 0.53$.

Range in study (mppcf-y)	Value used in meta-analysis (f-y/ml)	Lung cancer O/E	SMR	95% CI*
< 10	7	21/31.4	0.67	(0.41 to 1.02)
10- < 20	21	5/6.0	0.84	(0.27 to 1.94)
20- < 40	42	10/6.41	1.56	(0.75 to 2.87)
40- < 80	84	6/3.75	1.60	(0.58 to 3.48)
≥ 80	168	11/2.64	4.16	(2.08 to 7.46)

- 8 †Henderson and Enterline (1979).¹⁹ 1075 men age ≥ 65 who retired between 1941 and 1967 from an asbestos products manufacturing factory in the United States that used chrysotile, crocidolite, and amosite. 63 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in Social Security Administration records, were observed in an unreported number of person-years of follow up accumulated through 31 December 1973. Expected lung cancer deaths (ICD-7 162-163) were estimated from white male rates for the United States. Cumulative exposure based on workplace air measurements and work histories. No history of tobacco use reported. $k_1 = 2.5 \times 10^{-3}$ (95% CI = 0.6 to 8.4×10^{-3}) ml/f-y. $A = 1.46$.

Range in study (mppcf-y)	Value used in meta-analysis (f-y/ml)**	Lung cancer O/E	SMR	95% CI*
< 125	86.8	19/9.6	1.98	(1.19 to 3.09)
125-249	254.8	9/5.0	1.80	(0.82 to 3.42)
250-499	492.8	19/5.8	3.28	(1.97 to 5.12)
500-749	848.4	9/2.0	4.50	(2.05 to 8.54)
≥ 750	1366.4	7/0.9	7.78	(3.12 to 16.03)

diate refinement are associated with intermediate potency. Industries that use the most refined asbestos—the asbestos most enriched in long thin fibres—are associated with the highest potency. As for fibre type, it has been postulated that chrysotile asbestos is least potent and other forms more potent. We investigated these potential sources of heterogeneity by categorising each cohort by industry type (mining and milling, cement and cement products, or manufacturing and textile products) and by fibre type (predominantly chrysotile, chrysotile mixed with other, or other).

Under the fixed effect model, we found that these industry categories were a significant source of heterogeneity ($P < 0.001$). The fixed effect dose-response coefficient for the mining and milling cohorts was $\hat{\kappa}_{i,mm} = 0.3 \times 10^{-3}$ (95% CI 0.01 to 0.5×10^{-3}) ml/f-y, for the cement products cohorts it was $\hat{\kappa}_{i,cm} = 3.4 \times 10^{-3}$ (95% CI 0.1 to 8.8×10^{-3}) ml/f-y, and for the manufacturing and textile cohorts it was $\hat{\kappa}_{i,man} = 7.7 \times 10^{-3}$ (95% CI 4.7 to 12×10^{-3}) ml/f-y. Addition of a variable representing a uniform multiplicative modification to the industry specific dose-response coefficients for cohorts exposed to predominantly chrysotile fibres added no significant information ($P = 0.58$), suggesting that after accounting for industry type, fibre type added no significant heterogeneity. Ignoring the industry specificity, the uniform multiplicative modification to the overall $\hat{\kappa}_i$ under the fixed effect model for cohorts exposed to predominantly chrysotile fibre equaled 0.05 (95% CI 0.02 to 0.14) with $\hat{\kappa}_i = 5.4 \times 10^{-3}$ (95% CI 2.5 to 11×10^{-3}) ml/f-y.

Under the random effects model, applied to each of the three subsets of cohorts, we found insufficient evidence that industry category was a significant source of heterogeneity ($P = 0.58$). The maximum likelihood estimates of the industry specific dose-response coefficients under the random effects model were similar to those estimated under the fixed effect model. The uniform multiplicative modification to the overall $\hat{\kappa}_i$ under the random effects model for cohorts exposed to predominantly chrysotile fibre equaled 0.19 (95% CI 0.02 to 1.6) with $\hat{\kappa}_i = 7.9 \times 10^{-3}$ (95% CI 1.2 to 43×10^{-3}) ml/f-y. Fibre type, even independent of industry type, did not contribute significantly to the heterogeneity under the random effects model.

The disparity in the strength of the evidence supporting the hypothesis of industry specific dose-response coefficients under the fixed and random effects models probably arises from the treatment of the intercept terms. Under the fixed effect model, the A_i are fitted to their maximum likelihood value conditional on the dose-response coefficient, whether it be the summary or industry specific measure. The strength of the evidence supporting industry specific dose-response coefficients under the fixed effect model reflects both the goodness of fit of the dose-response and the additional freedom of fitting the intercept terms conditional on three, rather than

9 †McDonald *et al* (1984).²⁰ 3513 men employed for one month before 1 January 1959, and who had a social security number, at an asbestos friction products manufacturing factory in Connecticut that used chrysotile nearly exclusively. 89 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status in Social Security Administration records, were observed in an unreported number of person-years of follow up accumulated to 31 December 1977. Expected lung cancer deaths (ICD-7 162-164) were estimated from age, sex, race, and calendar year specific rates for Connecticut. Cumulative exposure based on workplace air measurements and work histories. Only deaths 20 years or more years after first employment were included. No history of tobacco use reported. $k_i = 0$ (95% CI = 0 to 3×10^{-3}) ml/f-y. $A = 1.6$.

Range in study (mppcf-y)	Value used in meta-analysis (f-y/ml)	Lung cancer O/E	SMR	95% CI*
< 10	7	55/32.9	1.67	(1.26 to 2.18)
10- < 20	21	6/5.9	1.02	(0.37 to 2.21)
20- < 40	42	5/4.7	1.05	(0.34 to 2.48)
40- < 80	84	6/3.7	1.63	(0.59 to 3.53)
≥ 80	168	1/1.8	0.55	(0.01 to 3.09)

10a Seidman *et al* (1979).²¹ 820 white men employed for between less than one month and 13 years beginning in June 1941 to December 1945 and ending in November 1954 at an asbestos insulation factory in Paterson, New Jersey that used amosite nearly exclusively. 83 lung cancer deaths, ascertained by coding of death certificates, were observed in an unreported number of person-years of follow up accumulated to the end of 1977. Expected lung cancer deaths (ICD-6 to ICD-8) were estimated from age, sex, race, and calendar year specific rates for New Jersey. Cumulative exposure based on duration of work and fibre concentrations observed in similar industries (Nicholson, 1983).⁵ Only deaths five or more years after first employment were included. No history of tobacco use reported. $k_i = 12 \times 10^{-3}$ (95% CI = 4.6 to 27×10^{-3}) ml/f-y. $A = 2.80$.

Range in study	Value used in meta-analysis (f-y/ml)††	Lung cancer O/E‡‡	SMR	95% CI*
< 1 month	1.4	3/1.46	2.06	(0.41 to 6.00)
1 month	3.15	5/1.84	2.72	(0.88 to 6.34)
2 months	5.95	6/2.26	2.66	(0.97 to 5.78)
3-5 months	10.15	8/3.35	2.39	(1.03 to 4.71)
6-11 months	20.65	12/5.05	4.75	(1.23 to 4.15)
1 year	44.8	155/2.44	6.15	(3.44 to 10.14)
≥ 2 years	166.95	34/4.30	7.91	(5.47 to 11.05)

10b †Seidman *et al* (1986).²² 820 white men employed for between less than one month and 13 years beginning in June 1941 to December 1945 and ending in November 1954 at an asbestos insulation factory in Paterson, New Jersey that used amosite nearly exclusively. 102 lung cancer deaths, ascertained by coding of death certificates, were observed in an unreported number of person-years of follow up accumulated to 31 December 1982. Expected lung cancer deaths (ICD-6 to ICD-9) were estimated from age, sex, race, and calendar year specific rates for New Jersey. Cumulative exposure based on duration of work and fibre concentrations observed in similar industries (Nicholson, 1983).⁵ Only deaths five or more years after first employment were included. No history of tobacco use reported. $k_i = 8.8 \times 10^{-3}$ (95% CI = 3.4 to 18×10^{-3}) ml/f-y. $A = 3.33$.

Range in study (f-y/ml)	Value used in meta-analysis (f-y/ml)	Lung cancer O/E	SMR	95% CI*
< 6.0	3	14/5.31	2.64	(1.44 to 4.42)
6.0-11.9	9	12/2.89	4.15	(2.14 to 7.25)
12.0-24.9	18.5	15/3.39	4.42	(2.47 to 7.30)
25.0-49.9	37.5	12/2.78	4.32	(2.23 to 7.54)
50.0-99.9	75	17/2.38	7.14	(4.16 to 11.44)
100.0-149.9	125	9/1.49	6.04	(2.76 to 11.47)
150.0-249.9	200	12/1.32	9.09	(4.69 to 15.88)
≥ 250.0	325	11/0.94	11.70	(5.83 to 20.94)

11a McDonald *et al* (1986).²³ 406 men employed for at least one year before 1 January 1963 at a vermiculite mine in Montana, at which the ore contained tremolite asbestos. 23 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status with family, local, and Social Security Administration records, were observed in an unreported number of person-years of follow up accumulated to 1 July 1983. Expected lung cancer deaths (ICD-8 160-163) were estimated from age and calendar year specific rates for US white men. Cumulative exposure based on workplace air measurements and work histories. No history of tobacco use reported. $k_i = 1.1 \times 10^{-3}$ (95% CI = 0 to 4.7×10^{-3}) ml/f-y. $A = 2.32$.

Range in study (f-y/ml)	Value used in meta-analysis (f-y/ml)	Lung cancer O/E	SMR	95% CI*
0- < 25	12.5	7/3.43	2.04	(0.82 to 4.21)
25- < 200	112.5	5/2.54	1.97	(0.63 to 4.59)
200- < 500	350	7/0.93	7.53	(3.02 to 15.51)
≥ 500	2000	4/0.72	5.58	(1.49 to 14.22)

one, dose-response coefficients. Under the random effects model, the A_i are assumed to derive from a distribution of intercepts. We allowed the distribution to be fitted to each industry, thus providing the greatest power to detect differences in dose-response. None the less, constraining the intercept term to an industry specific distribution significantly reduced the strength of the evidence supporting the notion of industry specific dose-response coefficients. We conclude that industry type is a source of heterogeneity in these cohorts, but that the importance of its contribution to the heterogeneity of the dose-response coefficients is overstated under the fixed effect model.

DOSE MEASURE

Equivalent dose measures assigned to cumulative exposure categories in different cohorts likely reflect vastly different actual cumulative doses. We expect that differences in methods of measuring fibre concentrations and assigning cumulative exposures across studies introduce an important source of heterogeneity in dose-response coefficients. We explain with three lines of evidence. Firstly, for most cumulative exposure categories we assigned the midpoint of the range as the dose to be used in the dose-response analysis. For four cohorts^{19,9,17} we used the mean cumulative exposure because it had been provided for each cumulative exposure category. Reanalysing these studies based on the midpoints rather than the means, we obtained ratios of $k_{i,\text{mean}}/k_{i,\text{midpoint}}$ of 1.0, 0.6, 0.7, and 1.5, respectively. Thus, substituting the midpoint for the mean, as we were forced to do for most cohorts, can artificially inflate or deflate the dose-response coefficient and must contribute to its heterogeneity. Secondly, some studies reported cumulative exposure categories in units other than f-y/ml. For those studies, we converted from the stated units to f-y/ml with the following conversion factors: f-y/ml = $1.4 \times \text{mppcf-y}$ (million particles per cubic foot-year) for the cement and manufacturing industries⁵; f-y/ml = $3 \times \text{mppcf-y}$ for the mining and milling industries³; and f-y/ml = $1/35 \times \text{py/ml}$ (particles per millilitre-year) for the textile industry.¹⁷ We parameterised these three conversion factors and maximised the likelihood under the fixed effect model with respect to k_i , A_i , and the conversion parameters. We obtained estimates of the conversion factors equal to f-y/ml = $0.6 \times \text{mppcf-y}$ for the cement and manufacturing industry; f-y/ml = $0.07 \times \text{mppcf-y}$ for the mining and milling industry; and f-y/ml = $\text{ppcf-y}/80$ for the textile industry. We cannot distinguish the extent to which the disparity between the published conversion factors and these maximum likelihood estimates depend on industry specific differences in fibre potency versus heterogeneity in estimating cumulative exposures between studies. We suspect that both factors play some part. Thirdly, we noted above a significant correlation between $k_{i,\text{mean}}$ and the maximum cumulative exposure studied. This correlation provides the strongest evi-

- 11b †Amandus and Wheeler (1987).²⁴ 575 men employed before 1970 for at least one year at a vermiculite mine in Montana, at which the ore contained tremolite asbestos. 20 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status with family, local, and Social Security Administration records, were observed in 13 502 person-years of follow up accumulated to 31 December 1981. Expected lung cancer deaths (ICD-8 162-163) were estimated from age and calendar year specific rates for US white men. Cumulative exposure based on workplace air measurements and work histories. No history of tobacco use reported. $k_1 = 4.5 \times 10^{-3}$ (95% CI = 0.7 to 21×10^{-3}) ml/f-y. A = 1.12.

Range in study (f-y/ml)	Value used in meta-analysis (f-y/ml)	Lung cancer O/E	SMR	95% CI*
< 50	25	6/4.0	1.51	(0.55 to 3.26)
50-99	75	2/1.4	1.46	(0.16 to 5.16)
100-399	250	2/1.9	1.06	(0.12 to 3.80)
> 399	750	10/1.7	5.76	(2.82 to 10.82)

- 12 †Armstrong *et al* (1988).²⁵ 6506 men employed between 1943 and 1967 at a crocidolite mine in Western Australia. 91 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status with local and national records, were observed in 95 264 person-years of follow up accumulated to 31 December 1980. Expected lung cancer deaths (ICD-9) were estimated from age, sex, and calendar year specific rates for Western Australia. Cumulative exposure based on workplace air measurements and work histories. No history of tobacco use reported. Dose-response model does not fit individual study because there was only one exposure group.

Range in study (f-y/ml)	Value used in meta-analysis (f-y/ml)	Lung cancer O/E	SMR	95% CI
55.8% of workers < 10	28.8 =	91/34.5	2.64	(2.15 to 3.24)
29.1% 10-100	(0.558 × 5+ 0.291 × 55+ 0.047 × 150)/			
4.7% > 100	(0.558 + 0.291 + 0.047)			
10.4% unknown				

- 13 †Piolatto *et al* (1990).²⁶ 1058 men employed for at least one year between 1946 and 1987 at a chrysotile mine in Balengero, Italy. 22 lung cancer deaths, ascertained by coding of death certificates obtained after checking vital status with population registries, were observed in 27 010 person-years of follow up accumulated to 31 December 1987. Expected lung cancer deaths were estimated from age, sex, and calendar year specific rates for Italy. Cumulative exposure based on workplace air measurements and work histories, lagged one year. Deaths and person-years beyond age 80 were excluded. No history of tobacco use reported. $k_1 = 0.2 \times 10^{-3}$ (95% CI = 0 to 2.9×10^{-3}) ml/f-y. A = 1.01.

Range in study (f-y/ml)	Value used in meta-analysis (f-y/ml)	Lung cancer O/E	SMR	95% CI
< 100	50	4/5.1	0.8	(0.21 to 2.01)
100-400	250	8/6.1	1.3	(0.56 to 2.58)
> 400	1000	10/8.7	1.1	(0.55 to 2.11)

- 14a Liddell *et al* (1977).²⁷ 10 951 men born between 1891 and 1920 and employed for at least one month before November 1966 at either of two chrysotile mines in Quebec, Canada. 214 lung or trachea cancer deaths (ICD-7) were observed in an unreported number of person-years of follow up accumulated to 31 December 1973. Expected lung cancer deaths were estimated from age, sex, and calendar year specific rates for Quebec. Cumulative exposure based on workplace air measurements and work histories. Person-time and deaths before 20 years after first employment were excluded. History of tobacco use known for a large portion of the cohort. $k_1 = 0.5 \times 10^{-3}$ (95% CI = 0.2 to 0.9×10^{-3}) ml/f-y. A = 0.76.

Range in study (mppcf-y)	Value used in meta-analysis (f-y/ml)	Lung cancer O/E	SMR	95% CI
< 3	4.5	28/31.93	0.88	(0.58 to 1.27)
3- < 10	19.5	11/19.09	0.58	(0.29 to 1.03)
10- < 30	60	17/18.76	0.91	(0.53 to 1.45)
30- < 100	195	37/40.08	0.92	(0.65 to 1.27)
100- < 300	600	34/45.02	0.76	(0.52 to 1.06)
300- < 600	1350	43/31.04	1.39	(1.00 to 1.87)
≥ 600	3900	28/12.13	2.31	(1.51 to 3.29)

dence that equivalent cumulative exposures reported for different cohorts represent different effective doses.

DURATION VERSUS CONCENTRATION OF EXPOSURE

We considered the possibility that short exposure to high concentrations might confer different relative risk of lung cancer than long exposure to low concentrations, although both would entail similar cumulative exposures. Were this the case, then different patterns of exposure in different cohorts would contribute to heterogeneity. To test the hypothesis, we fitted the fixed effect model to the mean duration of exposure and mean concentration of exposure data provided in one study²⁸ and to the midpoint exposure and midpoint concentration data provided in a second.⁸ We added to the relative risk model coefficients applied only to the concentration term and only to the duration term, while retaining the coefficient (k_1) applied to the product of the two. For both studies, the additional coefficients added no significant information to the relative risk model ($P = 0.42^{28}$ and $P = 0.43^8$). We conclude that, within the cumulative dose ranges found in the studies at issue, the product of concentration and duration of exposure adequately measured dose. Thus, variation in patterns of exposure within cohorts is unlikely to be an important source of heterogeneity in the dose-response coefficient.

COHORT AGE

McDonald *et al*²⁹ argue that when comparing occupational cohorts, one must take account of "the stage reached in their evolution and the level of mortality observed." We tested for the stage of evolution as a source of heterogeneity by plotting the $k_{1,i}$ measured at different stages of follow up in four cohorts versus the fraction of the cohort that had died at that stage of follow up (fig 3). We noted that for all four cohorts, the $k_{1,i}$ was lowest for the latest follow up. This pattern may reflect declining relative risk due to increasing rates of lung cancer among the standard populations as the cohort ages. We noted no consistent pattern across cohorts in the relation of $k_{1,i}$ to the total mortality fraction, either in the four cohorts shown or in all cohorts (not shown). We conclude that the total mortality fraction is not an important source of heterogeneity of $k_{1,i}$. Our decision to include the latest follow up from each cohort, to maximise precision, may slightly bias the summary estimates of k_1 toward the null.

CALENDAR PERIOD OF EXPOSURE

We considered the possibility that the calendar period of exposure of different cohorts might contribute to the heterogeneity of their $k_{1,i}$. For each cohort, we plotted its $k_{1,i}$ versus the date of first employment, date of last employment, and difference between date of last follow up and date of last employment. We discerned no patterns in any of these plots, so consider the calendar period of exposure to be a negligible source of heterogeneity.

- 14b McDonald *et al* (1980).²⁸ 10 939 men born between 1891 and 1920 and employed for at least one month before November 1966 at either of two chrysotile mines in Quebec, Canada. 250 lung cancer deaths (ICD-7 162-164) ascertained by coding of death certificates obtained after checking vital status, were observed in an unreported number of person-years of follow up accumulated to 31 December 1975. Expected lung cancer deaths were estimated from age, sex, and calendar year specific rates for Quebec. Cumulative exposure based on workplace air measurements and work histories. Person-time and deaths before 20 years after first employment were excluded. History of tobacco use known for a large portion of the cohort, stratified by cumulative exposure. $k_i = 0.5 \times 10^{-3}$ (95% CI = 0.2 to 0.8×10^{-3}) ml/f-y. $A = 0.96$.

Range in study (y, mppcf)	Value used in meta-analysis (f-y/ml)§§	Lung cancer O/E	SMR	95% CI
< 1,y 2-6 mppcf	1.6	19/16.2	1.17	(0.71 to 1.83)
< 1,4.3	5.2	12/13.2	0.91	(0.47 to 1.59)
< 1,14.4	17.3	9/10.2	0.88	(0.40 to 1.68)
< 1,78.0	117	7/8.8	0.80	(0.32 to 1.64)
1- < 5,2.5	9.8	5/7.6	0.66	(0.21 to 1.54)
1- < 5,6.2	40.9	13/13.7	0.95	(0.50 to 1.62)
1- < 5,2.3-6	177	6/7.32	0.82	(0.30 to 1.78)
1- < 5,8.2-6	693.8	5/6.4	0.78	(0.25 to 1.82)
5- < 20,2.5	48	13/9.2	1.41	(0.75 to 2.42)
5- < 20,5.6	174.7	14/11.5	1.22	(0.67 to 2.04)
5- < 20,17.0	535.5	7/8.4	0.83	(0.33 to 1.72)
5- < 20,62.3	2112.0	16/7.4	2.17	(1.24 to 3.51)
≥ 20,4.2	313.7	28/23.1	1.21	(0.81 to 1.75)
≥ 20,9.4	784.0	20/18.55	1.08	(0.66 to 1.67)
≥ 20,19.2	1647.4	24/10.9	2.20	(1.41 to 3.28)
≥ 20,46.8	4324.3	32/12.1	2.65	(1.81 to 3.73)

- 14c McDonald *et al* (1993).²⁹ 10 925 men born between 1891 and 1920 and employed for at least one month before November 1966 at either of two chrysotile mines in Quebec, Canada. 321 lung cancer deaths (ICD-8 or 9 162), ascertained by coding of death certificates obtained after checking vital status, were observed in an unreported number of person-years of follow up accumulated to 31 December 1989. Expected lung cancer deaths were estimated from age, sex, and calendar year specific rates for Quebec. Cumulative exposure based on workplace air measurements and work histories accumulated to the age of 55. History of tobacco use known for a large portion of the cohort, stratified by cumulative exposure. $k_i = 0.2 \times 10^{-3}$ (95% CI = 0.1 to 0.4×10^{-3}) ml/f-y. $A = 1.22$.

Range in study (mppcf-y)	Value used in meta-analysis (f-y/ml)	Lung cancer O/E	SMR	95% CI
< 3	4.5	36/31.4	1.14	(0.80 to 1.58)
3- < 10	19.5	40/25.3	1.58	(1.13 to 2.15)
10- < 30	60	33/31.3	1.05	(0.73 to 1.48)
30- < 60	135	39/24.4	1.60	(1.14 to 2.19)
60- < 100	240	30/22.8	1.32	(0.89 to 1.88)
100- < 200	450	32/28.3	1.13	(0.77 to 1.60)
200- < 300	750	20/17.3	1.15	(0.71 to 1.78)
300- < 400	1050	16/10.7	1.50	(0.86 to 2.44)
400- < 1000	2100	42/25.4	1.65	(1.19 to 2.23)
≥ 1000	4200	22/7.2	3.04	(1.90 to 4.60)

*95% CI calculated by an approximation to the Poisson⁶ for our study, not by the original investigators.

†Represents the cohort in the calculation of the summary measures.

‡Unless otherwise noted, cumulative exposures assigned to ranges were calculated as the mid-point of the range, with application of a conversion factor of 3 f-y/ml per mppcf-y for mining and milling cohorts and 1.4 f-y/ml per mppcf-y for all other cohorts.⁵ Values were assigned to open ended ranges by repeating the pattern observed at lower exposures.

§Assigned as the mean cumulative exposure reported by the authors, multiplied by 1.4 f-y/ml per mppcf-y.

¶Assigned the mean cumulative exposure reported by the authors.

||Assigned the mean cumulative exposure reported by the authors, multiplied by 1/35 f-y/ml per py/ml.¹⁷

**Assigned the mean cumulative exposure reported by the authors, multiplied by 1.4 f-y/ml per mppcf-y.

††Assigned the values reported in another review.⁵

‡‡As reported in another review.⁵

§§Assigned the product of average duration of exposure and average exposure concentration reported by the authors, multiplied by 3 f-y/ml per mppcf-y.

STANDARDISED MORTALITY RATIOS AS MEASURES OF RELATIVE RISK

Rothman³² emphasises that comparisons of SMRs across exposure categories can be misleading because each SMR is standardised to a different population. Consider, for example, that the relative risk of lung cancer associated with asbestos exposure is positively correlated with age. Assume further that the highest cumulative exposure groups contain the oldest men. Under these assumptions, the SMRs in different cumulative exposure categories within a cohort might differ systematically and appear as a dose-response relation. The sys-

tematic variation would arise because of the different age structures of the subpopulations in each cumulative exposure category, no matter whether the exposure categories exerted any influence. The extent of the modification of $k_{i,i}$ might differ for each cohort, so could be an important source of heterogeneity. Two lines of evidence indicate otherwise. Firstly, Nicholson *et al*⁴ showed that, after accounting for duration of exposure to asbestos, age no longer affected the relative risk measure. The cumulative exposure categories within a study are essentially strata of durations of exposure. The potentially different underlying age structures should not substantially modify the SMRs. Secondly, one study¹⁴ presented both SMRs and standardised rate ratios (SRRs) (relative effect measures standardised to a single population). We applied the fixed effect model to both sets of measures. With the SMRs, we obtained maximum likelihood estimates of $A_i = 1.32$ and of $k_{i,i} = 24 \times 10^{-3}$ (95% CI = 11 to 48×10^{-3}) ml/f-y. With the SRRs, we obtained maximum likelihood estimates of $A_i = 1.49$ and of $k_{i,i} = 16 \times 10^{-3}$ (95% CI = 7 to 32×10^{-3}) ml/f-y. The rates standardised to the same population gave a slightly lower estimate of the dose-response coefficient. We see no reason that standardisation to a single population across cumulative exposure categories within each cohort would have an effect of the same size or in the same direction for all cohorts. Standardisation to different populations, as is the norm in the cohorts included in the meta-analysis, may be a source of heterogeneity.

MISCLASSIFICATION OF MESOTHELIOMA

Misclassification of mesothelioma as lung cancer may be a significant source of heterogeneity because mesothelioma occurs predominantly among the subcohorts with high cumulative exposure to non-chrysotile asbestos and a long latency period.²¹ Studies that include such subcohorts, if unduly influenced by misclassification of mesothelioma, should give the highest $k_{i,i}$. Recall, however, that we found both cohort age (a proxy for latency) and fibre type after controlling for industry type to be insubstantial sources of heterogeneity. Recall also that we found a negative correlation between the highest cumulative exposure category in a study and its $k_{i,i}$. These findings suggest that misclassification of mesothelioma as lung cancer is not a significant source of heterogeneity.

Discussion

Our analysis of this collection of occupational cohorts generated two summary measures, and one set of industry specific summary measures, of the relation between cumulative exposure to asbestos and relative risk of lung cancer. Under the fixed effect model, we found the measure of potency of asbestos to cause lung cancer, k_i , to be 0.42×10^{-3} (95% CI 0.22 to 0.69×10^{-3}) ml/f-y. Under the random effects model, we found that $k_i = 2.6 \times 10^{-3}$ (95% CI 0.65 to 7.4×10^{-3}) ml/f-y and $A = 1.36$ (95% CI 1.05 to 1.76). The

fixed effect dose-response coefficient for the mining and milling cohorts was $\hat{\kappa}_{i,mm} = 0.25 \times 10^{-3}$ (95% CI 0.01 to 0.45×10^{-3}) ml/f-y, for the cement products cohorts was $\hat{\kappa}_{i,cm} = 3.4$ (95% CI 0.1 to 8.8×10^{-3}) ml/f-y, and for the manufacturing and textile cohorts was $\hat{\kappa}_{i,man} = 7.7$ (95% CI 4.7 to 12×10^{-3}) ml/f-y.

Given the variety of choices, the reader might ask "which summary measure is right?" At this time, no unique correct answer exists. The choice depends on the beliefs and assumptions implicit in the context of the question. If the context requires an analysis in which each cohort measures the same dose-response relation, with only random error introduced, then the summary measure found under the fixed effect model should be chosen. If the context allows for a distribution of dose-response relations, and allows for the distribution to derive largely from unknown or unimportant (for the question) sources of heterogeneity, then the summary measure found under the random effects model should be chosen.

If the question assumes that industry type is an important source of heterogeneity in the dose-response relation and that the intercept term representing background risk of lung cancer compared with the standard population should not be constrained, then the industry specific summary measures under the fixed effect model should be chosen. The second assumption is as important as the first, because under the random effects model, which constrains the intercept term to a reasonable distributional form, the industry specific dose-response relations explained an insignificant fraction of the heterogeneity.

An earlier, semiquantitative review by Nicholson for OSHA⁵ of the relation between cumulative exposure to asbestos and relative risk of lung cancer gave a potency of $\hat{\kappa}_i = 10 \times 10^{-3}$ (range $3-30 \times 10^{-3}$) ml/f-y. The central tendency was selected as approximately the geometric mean of the individual $k_{i,j}$, and the range about the estimate derived primarily from consideration of uncertainties in the dose-measurements. The OSHA² adopted this estimate of $\hat{\kappa}_i$ in their 1986 rules. Our estimates for potency, $\hat{\kappa}_i$, are 24-fold lower than OSHA's under the fixed effect model and fourfold lower under the random effects model. Further, our 95% CIs exclude 10×10^{-3} ml/f-y under both models. Our study differs from the earlier review in the following respects. Firstly, we had available updates to many cohorts with additional cohort information that had not then been published. As shown above, updates have consistently yielded a lower estimate of $k_{i,j}$. Secondly, we allowed the intercept term to depart from a fixed value of 1.0 to allow for confounding, most likely by smoking, or the healthy worker effects. The earlier review, when calculating $k_{i,j}$ by regression methods, fixed the intercept at 1. Thirdly, we effectively weighted each measurement of relative risk within a cohort by the number of cases of lung cancer. The earlier review usually weighted all measurements of relative risk within a cohort equally. Fourthly,

we weighted each study by the number of cases of lung cancer in the study to obtain our summary measures of effect. The earlier review, by choosing the approximate geometric mean, weighted each study uniformly. Fifthly, we calculated a summary measure under both a fixed effect model and a random effects model. The earlier review, by virtue of choosing the geometric mean of the individual study $k_{i,j}$, is more analogous to a random effects model.

The issue of publication bias must, by convention, be considered. We do not deny the possibility that unpublished studies, or published studies unknown to us, exist that may alter these findings, possibly toward the null. Given the well accepted role of occupational exposure to asbestos in causing lung cancer, we find it unlikely that the 95% CI about our summary measures would overlap the null if these absent studies were to be included. Publication bias of this sort in meta-analyses is analogous to the problem of unknown confounders in aetiological research. The role of unknown confounders in aetiological research or of publication bias in meta-analyses can never be ruled out. The extent to which a given aetiological association is confounded by unknown causes, or to which a given meta-analytical result is influenced by publication bias, is a matter of individual judgment; it cannot be subjected to the scientific method.

A second sort of publication bias is of more concern to this meta-analysis. It may be that only cohorts that, in aggregate, show a positive relation between asbestos exposure and relative risk of lung cancer are subjected to further analysis and expenditure of resources by disaggregation into cumulative exposure categories. Such a practice would bias the results of this meta-analysis away from the null. It may also be that investigators, upon obtaining a null result, would choose to disaggregate the cohort into cumulative exposure categories in the hopes of finding effects in the highest exposure groups or a positive dose-response trend. Apparent examples of both possibilities exist in the publications upon which we based our report. We cannot assess the extent to which the two possibilities balance within the larger body of scientific literature.

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