The Quantitative Risks of Mesothelioma and Lung Cancer in Relation to Asbestos Exposure

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Mortality reports on asbestos exposed cohorts which gave information on exposure levels from which (as a minimum) a cohort average cumulative exposure could be estimated were reviewed. At exposure levels seen in occupational cohorts it is concluded that the exposure specific risk of mesothelioma from the three principal commercial asbestos types is broadly in the ratio 1:100:500 for chrysotile, amosite and crocidolite respectively. For lung cancer the conclusions are less clear cut. Cohorts exposed only to crocidolite or amosite record similar exposure specific risk levels (around 5% excess lung cancer per f/ml.yr); but chrysotile exposed cohorts show a less consistent picture, with a clear discrepancy between the mortality experience of a cohort of chrysotile textile workers in Carolina and the Quebec miners cohort. Taking account of the excess risk recorded by cohorts with mixed fibre exposures (generally<1%), the Carolina experience looks uptypically high. It is suggested that a best estimate lung cancer risk for chrysotile alone would be 0.1%, with a highest reasonable estimate of 0.5%. The risk differential between chrysotile and the two amphibole fibres for lung cancer is thus between 1:10 and 1:50.

Examination of the inter-study dose response relationship for the amphibole fibres suggests a non-linear relationship for all three cancer endpoints (pleural and peritoneal mesotheliomas, and lung cancer). The peritoneal mesothelioma risk is proportional to the square of cumulative exposure, lung cancer risk lies between a linear and square relationship and pleural mesothelioma seems to rise less than linearly with cumulative dose. Although these non-linear relationships provide a best fit to the data, statistical and other uncertainties mean that a linear relationship remains arguable for pleural and lung tumours (but not for peritoneal tumours).

Based on these considerations, and a discussion of the associated uncertainties, a series of quantified risk summary statements for different levels of cumulative exposure are presented. Crown Copyright © 2000 Published by Elsevier Science Ltd on behalf of British Occupational Hygiene Society. All rights reserved

Keywords: asbestos; amphibole hypothesis; exposure-response; lung cancer; mesothelioma; quantified risk assessment

INTRODUCTION

There has been much debate on the relative hazardousness of the three main asbestos types: crocidolite, amosite and chrysotile (commonly known as blue, brown and white asbestos respectively), but no systematic attempt to quantify the differences. Existing published quantitative risk assessments have mostly not distinguished between the fibre types, and none

has produced quantified estimates of the risk from amphiboles (a collective mineralogical term covering crocidolite and amosite). A review commissioned by the HSE in the 1980s from Professors Richard Doll and Julian Peto (1985) gave estimates for chrysotile alone; more recently a review by the Health Effects Institute (1991) produced estimates for an unspecified mixture of fibre types. An INSERM review (1996) also ignored differences in fibre type, and drew heavily on the HEI review.

The studies included in this review were selected by reviewing the material referenced in the Doll and Peto, HEI and INSERM reports and identifying all cohort mortality reports for which quantified data on

exposure was available either as an average for the cohort as a whole, or for individual subgroups. Seventeen such cohorts were identified (Albin *et al.*, 1990a; de Klerk *et al.*, 1994; Dement *et al.*, 1994; Enterline *et al.*, 1987; Finkelstein, 1984; Hughes *et al.*, 1987; Liddell *et al.*, 1997; McDonald *et al.*, 1983b, 1984; Neuberger and Kundi, 1990; Newhouse and Sullivan, 1989; Peto *et al.*, 1985; Piolatto *et al.*, 1990; Seidman *et al.*, 1986; Seidman and Selikoff, 1990; Sluis-Cremer *et al.*, 1992; Talcott *et al.*, 1989). Three of the selected cohorts have been split into sub-cohorts which have been separately treated in this review: the South African crocidolite and amosite mining cohorts have been treated separately; the New Orleans asbestos cement cohort has been split into the two separate plants covered, since the mix of fibres used in the two plants was different; and the Carolina textile cohort has been split by sex, since the results for men and women were rather different. The cohorts have been referred to by their geographical location except for cohorts 3 (Enterline *et al.*, 1987) and 17 (Newhouse and Sullivan, 1989) which are identified by a company name, and cohort 15 (Albin *et al.*, 1990a) where the name of the principal author on the cohort has been used.

Information extracted

Information was extracted from the identified reports on the following:

- The number of deaths in the cohort from all causes and from lung cancer, and the corresponding SMRs;
- Dose specific lung cancer SMRs (or rates), where available;
- The number of mesothelioma deaths in the cohort (for pleural and peritoneal mesothelioma separately);
- The rates of mesothelioma by categories of time since first exposure;
- The process/type of work being carried out;
- Cohort recruitment period and duration of follow up;
- Average age at first exposure, when available;
- The type(s) of asbestos fibre used in the process;
- The average fibre levels for the entire cohort and the average employment duration for workers in the cohort, or simply the average cumulative exposure for the entire cohort;
- Information about the smoking habits of the workers in the cohort where available;
- The sex of the workers.

Some general issues on the summary of outcome and exposure measures are discussed below. A more detailed discussion on some of these points is given in Appendix A, and the extracted data is shown in full in Tables 12 and 13.

Excess lung cancer measure

Excess overall lung cancer mortality has been expressed as a percentage excess of expected lung cancer mortality per unit of cumulative exposure.

$$R_L = 100(O_L - E_L)/(E_L.X)$$

Where O_L and E_L are the numbers of observed and expected lung cancers, respectively and X is cohort mean exposure. This estimate of the lung cancer risk is described as the 'cohort average' estimate. 95% confidence limits for the cohort average estimate R_L have been calculated assuming a Poisson distribution for O_L.

Mesothelioma measure

Mesothelioma mortality was expressed as a per cent of expected mortality from all causes (adjusted to an age of first exposure of 30) per unit of cumulative exposure.

$$R_M = 100O_M/(E_{Adj}X)$$

Where O_M is the number of mesothelioma deaths, E_{Adj} the total expected deaths from all causes adjusted to an age of first exposure of 30, and X the mean cumulative exposure. (See Appendix A for a discussion of this measure, and the calculation of E_{Adj}). When the expected all causes mortality was not available, the denominator was taken to be the total observed deaths less the total of asbestos-related deaths (mesothelioma, asbestosis and any excess lung cancer deaths). A 95% confidence interval for R_M was calculated assuming a Poisson distribution for O_M.

Treatment of 'best evidence' cause of death data

In some studies causes of death have been assigned in two ways, one based purely on data given on the death certificates (DC), the other using other data (e.g. autopsy reports) to establish a 'best evidence' (BE) cause of death. For lung cancer this review has generally used the DC data, since this preserves comparability with the reference rates, and with the majority of other studies. For mesothelioma however, the BE data has been used, since reference rates are inappropriate, and most studies use some sort of best evidence judgement to identify mesotheliomas.

It might be thought that where reference rates are derived from DC data (as in the SMR analyses in this report) the observed deaths on a DC basis should always be used. The argument is not as clear cut as it seems. The coding of death certificates is subject to a range of errors, and the net error in the count of deaths coded to lung cancer on national death certificates will be determined by the balance of these errors across the whole population. One of these errors is the tendency of pleural mesothelioma deaths to be coded to lung cancer. In the population as a whole,

this error is very small, but in an asbestos exposed cohort it may have a substantial effect. Leaving the miscoded mesotheliomas in the lung cancer count will overstate the true lung cancer SMR. Excluding them will in theory understate it, but only to the small extent that this error affects the population as a whole. The best available approximation to a true estimate of the risk is therefore to exclude the miscoded mesotheliomas, and this has been done for this review.

Derivation of cohort mean exposure estimates

Mean exposure for cohorts was calculated in different ways, depending on the available information. When data was given for separate exposure groups, the cohort mean was calculated by weighting the individual group means by the expected deaths from lung cancer in the group. On the assumption that excess risk is proportional to cumulative exposure, this weighting preserves the same proportionality when the results from subgroups with different exposures are aggregated, it is therefore the optimal statistical measure of aggregate exposure.

Where mean exposure values for individual dose categories were not given, the midpoints were used. The top exposure category was usually given as an open interval (e.g. exposures>100 f/ml.yr): in these cases a value was chosen based on a view of the highest likely exposure and the distribution of individuals across all exposure categories. It was assumed that where the highest category contains a relatively small proportion of the population, the category mean will be a smaller multiple of the lower band than otherwise.

For cohorts where results for exposure specific subgroups were not given, the cohort mean was either given directly (cohorts 4, 13 and 15); derived from information given on the distribution of individual doses (cohorts 1 and 7), or on the exposure of internal controls (cohort 17), or by multiplying a mean exposure level by mean exposure duration (cohorts 8 and 14).

Exposure estimates given in particle counts were converted to counts of 'regulated fibres' (fibres with an aspect ratio greater than 3:1, and length>=5 microns), using conversion factors calculated by the report authors where possible. The most commonly used conversion was 1 mppcf (million particles per cubic foot)=3 f/ml (fibres per millilitre), and this was the value adopted for the Johns Manville cohort, where a conversion was not given. For the Massachusetts cohort, where the fibre involved was crocidolite (rather than chrysotile as in the other cohorts with particle counts), an independent expert hygienist was asked for an assessment (see Appendix B).

The exposure estimates for Wittenoom have been questioned by Rogers (1990) who has suggested—having re-examined some of the original samples using modern light and electron microscopy—that the levels may have been underestimated by up to a factor of 10. Details of this reassessed data were to be published, but these have not so far appeared in print. It is therefore difficult to know whether to make an adjustment to the published estimates, and if so by how much. Similar comments may of course apply to other cohorts and introducing a correction might then distort rather than correct the overall picture. de Klerk and colleagues, developing estimates of environmental risk at Wittenoom (1992) use a factor of 4 without detailed discussion. The effect of using this adjusted exposure level is examined as a variant of the main analyses.

Exposure-specific risk estimates

It is generally assumed that the most reliable guide to dose-specific risk is provided by exposure analyses using estimates of individual exposure. This is clearly the case when these individual exposure values can be accurately determined. However this assumption is very much not the case in the studies in this review. Not only are there the inevitable problems of extrapolating earlier exposures on the basis of more recent measurements; there are also problems of converting the most usual historic measurements (in terms of particle counts) to the more relevant measure of fibre counts. Direct fibre counting only became generally used in the 1970s.

In these circumstances it is at least arguable that global assessments of average exposure, set against overall mortality outcomes, should be preferred. Exposure–response regressions with inaccurate individual exposure assignments will produce a slope estimate biased downwards. Use of an overall assessment will also minimise the error introduced by conversion from particle counts to fibres, since these average conversion factors will represent a more accurate conversion for the totality of exposure than for a particular individual.

However, the arguments are not all one way. Overall mortality outcomes can only be assessed against some outside reference—usually the regional or national population—and this may not represent a true baseline level for the exposed population in question. Assessment of an internal exposure response gives some check on this issue. A complete absence of exposure response must cast some doubt on any overall excess being counted as a measure of risk (the Albin and Connecticut cohorts are examples of this).

Cohort-level risk measures were chosen for this review both because these allow a wider range of data to be assessed than if attention is restricted to internal exposure response analyses and since (as argued above) cohort-level exposure estimates are likely to be more accurate than individual exposures.

Smoking

The evidence on the joint effect of smoking and asbestos exposure on lung cancer has been reviewed

recently (Vainio and Bofetta, 1994) who conclude that the overall evidence indicates an interaction in the multiplicative region. This implies that the relative risk of lung cancer due to asbestos exposure will be the same for smokers and non-smokers alike. Thus SMRs for lung cancer based on a reference population with the same smoking habits as the cohort members should only reflect the effect on mortality due to asbestos exposure. An earlier review by Berry *et al.* (1985) estimated that the effect of asbestos exposure was about 1.8 times greater in non-smokers than in smokers (though with confidence limits which did not exclude a simple multiplicative interaction). If this is the case the observed effect of asbestos on lung cancer rates will be greater in populations with lower smoking prevalence. However, given the relative lung cancer risks typical of smoking (about 15-fold) and asbestos exposure (about 2-fold) together with the generally high prevalence of smoking in the observed populations, the scope for bias—if there is indeed a differential effect of the scale suggested—is limited. In either case, a problem arises when the smoking habits of the cohort members differ from those of the reference population, which is the case for some of the cohorts reviewed. For this reason, any information about smoking given in the studies was summarised. The amount of information given was very variable, and could be categorised as follows:

1. No information given, (Ferodo, US Insulators, Paterson, South Africa, Johns Manville, Albin).
2. The percentage of the cohort that smoked, usually based on a cross sectional survey conducted in a particular year, (Connecticut, Balangero, Quebec, Pennsylvania, Rochdale, Wittenoom).
3. Comparison of the prevalence of smoking in the cohort and the reference population, (New Orleans, Massachusetts, Carolina).
4. Estimation of the effect of any differences in prevalence—for example calculation of smoker adjusted lung cancer SMRs, (Vocklabruck)
5. Data on prevalence of smoking within exposure categories—but with no external comparison (Ontario).

Most studies fell within the first two of the above categories. In these cases only subjective judgements could be made by the authors about the smoking habits of the cohort members. Also, cross sectional studies were often based on a small proportion of the cohort and may not be very representative. For most studies which addressed the issue the authors concluded that there was no major difference in smoking prevalence or that the slight differences in prevalence were not likely to change the expected number of lung cancer deaths in a substantial way. Of the studies where comparative smoking data were given, the Vocklabruck cohort showed the largest difference in cohort smoking habits and those of the general popu-lation, and this was the only study where an explicit adjustment for smoking was made. Unadjusted data was used for all other studies.

Fibre type and industry process

For the purpose of summarising the information given in the studies, each cohort was given a fibre type classification of 1, 2 or 3 letters according to the type of fibre used, with the letters y, a and o representing chrysotile, amosite and crocidolite exposures respectively. For example:

'yao'   means all three commercial asbestos types were used in the cohort
'yo'   means chrysotile and crocidolite were used
'a'   means only amosite was used

The order of the letters indicates the relative importance of the fibres used. Very small quantities of fibre were ignored in some cohorts (Carolina, New Orleans plant 1, Connecticut), the reasoning for this in each case is set out in Appendix A (Table 14). In a similar way, for display in tabular and graphical data summaries, industry process was coded as follows.

M   Mines
C   Cement
T   Textiles
I   Insulation Products
F   Friction Products
L   Lagging and work with insulation
O   Other

Meta-analytic issues

The aim of a meta-analysis is to identify where evidence from different studies is discrepant; ideally, to explain the reasons for the discrepancies; and where data from different studies are coherent to combine them into a common summary which will be more precise and soundly based than the estimate from any single study. For this review the coherence of estimates of R_L and R_M from different studies has been assessed in a Poisson regression framework, fitting a common value of the parameter of interest across a group of studies and testing the residual deviance between the observed and predicted numbers of events (mesothelioma or lung cancer deaths) in the studies in the group. Confidence limits around the group estimates were calculated by profile likelihood methods. Confidence limits are not shown for the means of groups which show very significant heterogeneity, since such limits have no ready interpretation. Indeed, in this situation it is not clear that the mean itself has any natural meaning. Faced with clearly discrepant data, purely statistical criteria cannot be used to decide on a 'correct' summary or compromise estimate.

The statistical analyses in this report only take account of the statistical variability of the mortality

outcomes. The statistical variability in expected mortality levels and cohort average exposures are ignored. This means that calculated confidence intervals will be narrower and statistical distinctions sharper than they would be if these variabilities were known and allowed for. This needs to be borne in mind in the interpretation of these analyses.

RESULTS

Overview

Figure 1 shows a graphical comparison of the mesothelioma and lung cancer risk coefficients. In order to plot zero values (which convert to minus infinity on the log scale), convenient nominal positive values smaller than any real non-zero value in the (relevant) data have been used. These are in the range 0.001–0.002 for R_L and between 0.0001 and 0.0003 for R_M. The three panels of Fig. 1 display the same data, with each cohort represented by its cohort code, fibre type and process. Cohorts which did not show a statistically significant excess of lung cancer (R_L) are shown in brackets.

Both risk measures cover about three orders of magnitude. For the bulk of the data risk estimates for lung cancer and mesothelioma are strongly correlated with R_L, very roughly equal to 100 R_M. This heterogeneity seems more readily explicable in terms of fibre type than process. For example there are mining and asbestos cement cohorts at both extremes of the risk scale, while all the amphibole cohorts are at the high risk end of the scale. But there are not really enough examples within each category statistically to draw definitive conclusions of this type.

Total mesothelioma

The summarised data for total (pleural and peritoneal) mesothelioma mortality are shown in Table 1 and Fig. 2. The estimates of R_M for crocidolite cohorts are closely grouped around an average value of 0.51. Similarly, the two amosite cohorts show results statistically consistent with their average of 0.10. The results from mixed fibre cohorts cover a wide range from a value close to that seen for the crocidolite cohorts (R_M=0.59 for Ontario) to values nearly three orders of magnitude lower, close to those seen in the chrysotile mining cohorts. The test for heterogeneity is very clearly significant ($P<0.001$). The ranking of mixed cohorts by mesothelioma risk does not appear to correspond either to process or fibre mix.

If the exposure estimate for Wittenoom is increased by a factor of 4, the summary value of R_M falls to 0.15, and the consistency of the three crocidolite values is completely lost ($P<0.001$).

Three of the six chrysotile cohorts had no observed mesothelioma deaths. The rates in the two chrysotile mining cohorts are similar at around 0.0015, while the
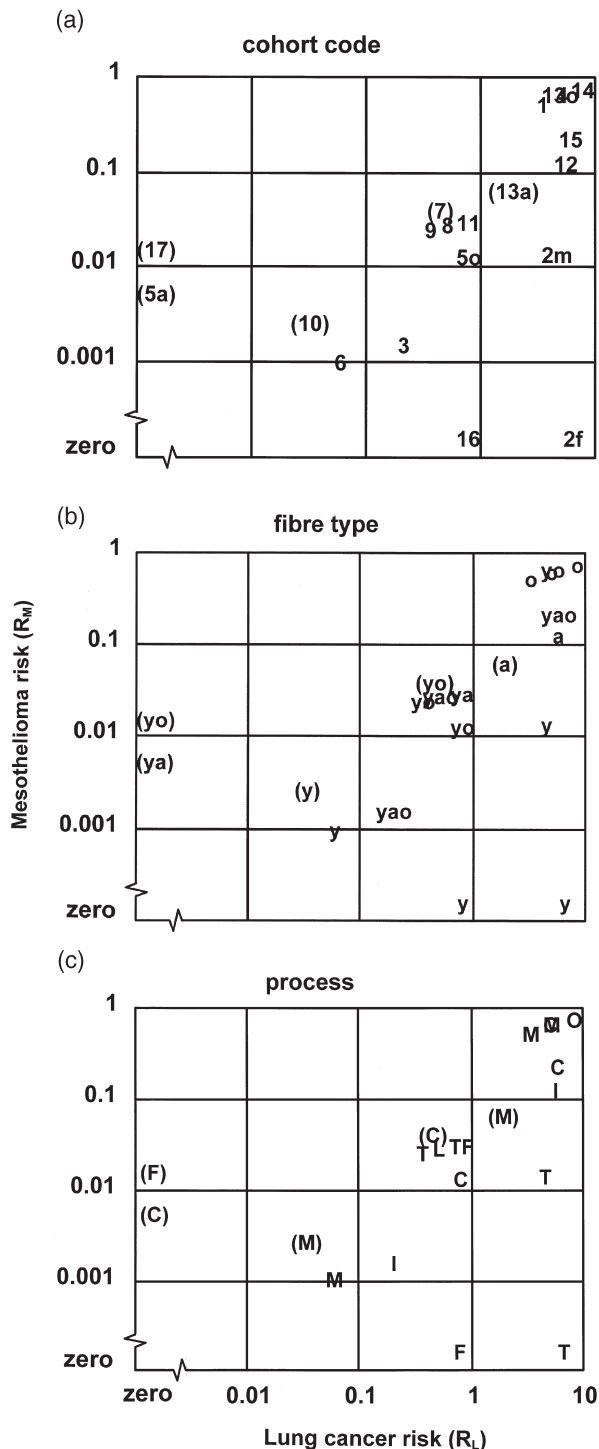

Fig. 1. Comparison of exposure-specific risks of mesothelioma and lung cancer (% per f/ml.yr), with cohorts labelled by cohort code, fibre type and process. [Note: the two coincident cohorts in the top right of the chart are Ontario (4, yo, C) and SA crocidolite mines (13o, o, M). Symbols in brackets indicate a non-significant lung cancer excess].

Table 1. Summary of mesothelioma mortality data and exposure-specific risk estimates

Cohort number	Cohort name	Process	Fibre	Mesothelioma deaths – Total number	Number peritoneal	Total expected mortality	Adjustment factor for age first exposed	Average cumulative exposure (f/ml.yr)	Mesothelioma risk expressed as percentage total expected mortality per f/ml.yr (R_M) – Unadjusted	Adjusted for age at first exposure	95%CI	P-value for heterogeneity
14	Massachusetts	O	o	5	3	8.3	0.74	120	0.50	0.68	(0.22,1.6)	
1	Wittenoom	M	o	72	10	601.8	1.08	23	0.52	0.48	(0.38,0.60)	
13o	SA crocidolite mines	M	o	20	2	223.2[a]	0.93	16.4	0.55	0.59	(0.36,0.91)	
	Total – Crocidolite			97	15					0.51	(0.41,0.61)	0.6
12	Paterson	I	a	17	9	355.9	0.63	65	0.073	0.12	(0.068,0.19)	
13a	SA amosite mines	M	a	4	1	305.7[a]	0.93	23.6	0.056	0.060	(0.016,0.015)	
	Total – amosite cohorts			**21**	**10**					**0.10**	**(0.062,0.15)**	**0.2**
4	Ontario	C	yo	17	8	62.2	0.77	60	0.46	0.59	(0.34,0.9)	
15	Albin	C	yao	13	0	493.3	1	13	0.2	0.2	(0.11,0.35)	
7	Vocklabruck	C	yo	5	1	530.2	1.05	25	0.038	0.036	(0.012,0.084)	
8	US/Canada insulators	L	yao	453	282	3170.6	1.09	500	0.029	0.026	(0.024,0.029)	
11	Pennsylvania	TF	ya	14	4	821.1	1.08	60	0.029	0.027	(0.014,0.044)	
9	Rochdale	T	yo	10	0	602.5	1	74	0.022	0.022	(0.011,0.041)	
17	Ferodo	F	yo	13	0	2646.3	1	35	0.014	0.014	(0.0075,0.024)	
5o	New Orleans (plant 2,yo)	C	yo	3	0	217[b]	1.26	93	0.015	0.012	(0.0024,0.034)	
5a	New Orleans (plant 1)	C	ya	1	0	294.5	0.85	79	0.004	0.005	(0.0001,0.028)	
3	Johns Manville retirees	I	yao	8	2	762.5	1	750	0.001	0.001	(0.0005,0.0028)	
	Pooled chrysotile estimates									**0.021**		*P<0.001*
2m	Carolina (men)	T	y	1	1	410.1	1.34	28	0.017	0.013	(0.0016,0.047)	
10	Balangero	M	y	2	0	225.4	1.2	300	0.003	0.0025	(0.0003,0.009)	
6	Quebec	M	y	33	0	5912.7	1	600	0.001	0.0009	(0.0006,0.0013)	
2f	Carolina (women)	T	y	0	-	299.2	1.34	26	0	0	(0,0.035)	
5y	New Orleans (plant 2, y)	C	y	0	-	397.1[b]	1.26	22	0	0	(0,0.033)	
16	Connecticut	F	y	0	-	550.7	0.93	46	0	0	(0,0.016)	
	Total			**37**	**0**					**0.0010**	**(0.0007,0.0014)**	**0.11**
	– excluding Carolina men			**35**	**0**					**0.0010**	**(0.0007,0.0013)**	**0.69**
	– excluding mines			**70**	**0**					**0.0033**	**(0.0006,0.010)**	**0.14**

[a] Reduced by a factor of 0.67 to exclude expected deaths less than 10 yr from first exposure (see Appendix C).
[b] Expected all cause mortality in plant 2 partitioned in proportion to share of expected lung cancer.
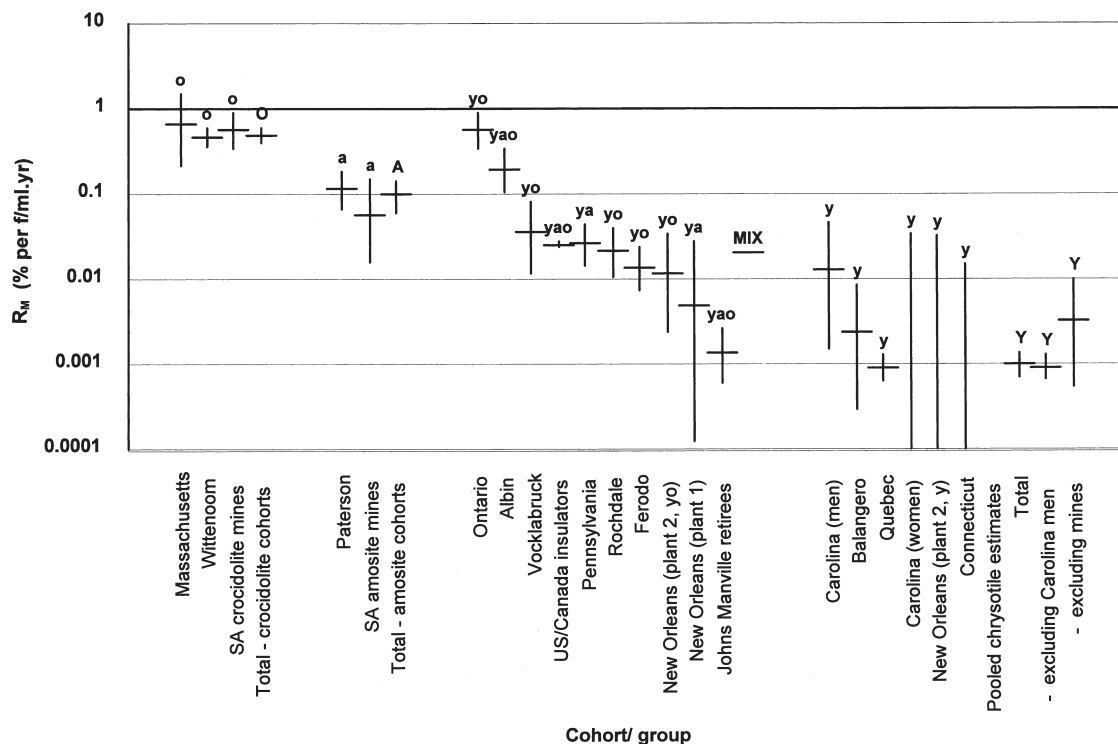
Fig. 2. Exposure-specific mesothelioma mortality (R_M) by cohort and fibre type groupings, showing 95% confidence intervals. Group means labelled in capitals. Confidence intervals not shown for groups with very significant heterogeneity.

two cases seen in among men in the Carolina cohort produce an estimate, with wide confidence limits, of 0.013—about an order of magnitude higher than for the mines cohorts. The very wide confidence limits for the three cohorts where no cases were observed are statistically consistent with either end of this range. Indeed there is no significant heterogeneity between R_M estimates in the chrysotile group, although the total shows some tendency to heterogeneity (P=0.11). If the mines cohorts are excluded, the central combined estimate of R_M increases to 0.0033, but with wide confidence limits (0.0006–0.01) and with a similar level of heterogeneity (P=0.14). With the Carolina men excluded, the remaining data are coherent (P for heterogeneity=0.69), and the mean estimate of R_M is 0.001 (95% CI 0.0007 to 0.0013) No summary estimate of R_M has been calculated for the mixed fibre cohorts, since these are so clearly statistically heterogeneous. This heterogeneity is plausibly explicable by variations in the mix of fibres encountered. The estimates from the pure fibre cohorts suggest a difference in potency approaching two orders of magnitude between chrysotile and amosite, and a further five-fold difference between amosite and crocidolite. If these gross differences are even approximately correct, quite small variations in the fibre mix in the cohorts exposed to several fibre types could have important effects on the mesothelioma risk in the cohort. This would have the consequence that the generally measured fibre levels would

be an unreliable estimate of the true risk status. This will be particularly true where the history of usage of different fibre types has varied over time.

Lung cancer

The summary data for lung cancer is shown in Table 2 and Fig. 3. The pure fibre groupings are less coherent for R_L than for R_M, although the general picture is similar, with higher values for the amphibole cohorts, lower values for most of the chrysotile cohorts and intermediate values for the mixed exposure groups. The Carolina cohort is the one clear exception to this pattern. The mean estimate for the three crocidolite cohorts is 4.2% per f/ml.yr (95% CI 2.8–5.8). The two amosite cohorts give somewhat different results, and despite the wide confidence limits on the South African data they are not statistically consistent (P=0.022). Their joint mean is 5.2% per f/ml.yr (95% CI 4.0–6.5). The five amphibole cohorts taken together are also not a statistically consistent group (P=0.027), with a joint mean of 4.8% per f/ml.yr (95% CI 3.9–5.8). The heterogeneity is mainly due to the SA amosite cohort, and if this is set aside the remaining four amphibole cohorts are just statistically consistent (P=0.072) with a joint mean of 5.1% per f/ml.yr (95% CI 4.1–6.2). If the exposure estimate for Wittenoom is increased by a factor of 4, the summary value of R_L falls to 2 for the combined amphibole cohorts and to 1.1 for the three crocidolite

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Table 2. Summary of lung cancer mortality data and exposure-specific risk estimates

| Cohort number	Cohort name	Process	Fibre	Lung cancer deaths					Average cumulative exposure (f/ml.yr)	Lung cancer risk (% expected lung cancer per f/ml.yr) R_L (95% CI)		P-value for heterogeneity
				Observed	Expected	SMR	Excess	% Excess				
14	Massachusetts	O	o	8	0.6	13.1	7.4	1210	120	10	(3.9,21)	
13o	SA crocidolite mines	M	o	19	10.2	1.86	8.8	85.5	16.4	5.2	(0.71,12)	
1	Wittenoom	M	o	87	48.7	1.79	38.3	78.6	23	3.4	(1.9,5.2)	
	Total – crocidolite cohorts									**4.2**	**(2.8,5.8)**	**0.090**
	All amphibole cohorts									**4.8**	**(3.9,5.8)**	**0.027**
	ex. SA amosite									**5.1**	**(4.1,6.2)**	**0.072**
12	Paterson	I	a	98	20.5	4.78	77.5	378	65	5.8	(4.4,0.7.4)	
13a	SA amosite mines	M	a	21	14.5	1.45	6.5	44.8	23.6	1.9	(−0.44,5.1)	
	Total – amosite cohorts									5.2	(4.0,6.5)	0.022
15	Albin	C	yao	35	19.4	1.8	15.6	80	13	6.2	(−0.77,21)	
4	Ontario	C	yo	22	5.3	4.14	16.7	314	60	5.2	(2.7,8.8)	
5o	New Orleans (plant 2, yo)	C	yo	31	17.7	1.75	13.3	75.1	93	0.81	(0.21,1.6)	
11	Pennsylvania	TF	ya	50	33.8	1.48	16.2	47.9	60	0.8	(0.16,1.6)	
8	US/Canada insulators	L	yao	934	256.8	3.64	677	264	500	0.53	(0.48,0.58)	
7	Vocklabruck	C	yo	47	42.2	1.11	4.8	11.4	25	0.45	(−0.72,1.9)	
9	Rochdale	T	yo	56	37.1	1.51	18.9	51	138	0.37	(0.10,0.70)	
3	Johns Manville retirees	I	yao	73	28.4	2.57	44.6	157	750	0.21	(0.14,0.30)	
5a	New Orleans (plant 1)	C	ya	21	22.5	0.93	−1.5	−6.7	79	0	(−0.53,0.54)	
17	Ferodo	F	yo	241	242.5	0.99	−1.5	−0.6	35	0	(−0.36,0.36)	
	All mixed									**0.47**		**P<0.001**
	Mixed excl. Ontario, Insulators and JM									**0.32**	**(0.16,0.50)**	**0.056**
2f	Carolina (women)	T	y	38	13.8	2.75	24.2	175	26	6.7	(3.6,11)	
2m	Carolina (men)	T	y	74	32.2	2.3	41.8	130	28	4.6	(2.9,6.7)	
5y	New Orleans (plant 2, y)	C	y	42	32.4	1.3	9.6	29.6	22	1.3	(−0.29,3.4)	
16	Connecticut	F	y	49	35.8	1.37	13.2	36.9	46	0.80	(0.029,1.8)	
6	Quebec	M	y	587	431.6	1.36	155	36	600	0.06	(0.042,0.079)	
10	Balengeno	M	y	19	17.3	1.1	1.7	9.8	300	0.03	(−0.11,0.24)	
	All pure chrysotile									**0.062**		**P<0.001**
	Pure chrysotile excluding mines									**2.3**		**0.0013**
	Pure chrysotile excluding mines									**0.060**	**(0.043,0.079)**	**0.91**
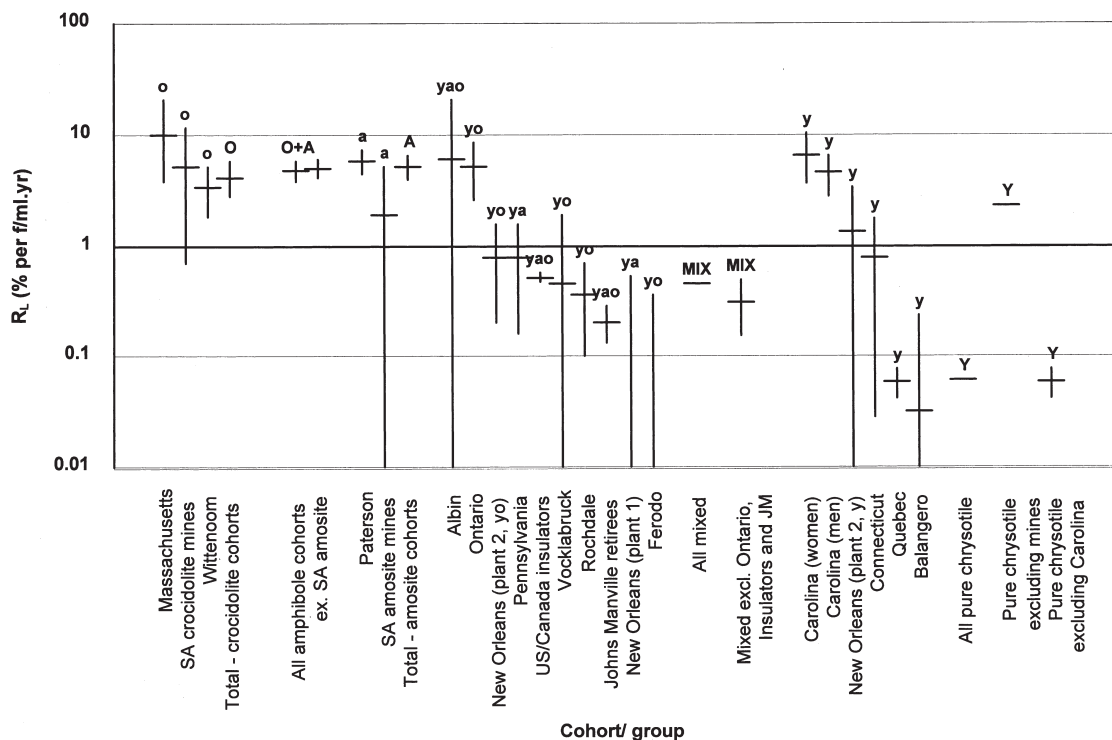
Fig. 3. Exposure-specific excess lung cancer mortality (R_L) by cohort and fibre type groupings, showing 95% confidence intervals. Group means labelled in capitals. Confidence intervals not shown for groups with very significant heterogeneity.

cohorts, but both groupings now show very significant heterogeneity ($P<0.001$).

Among the mixed cohorts, two stand out with particularly high values (Ontario and Albin). Both are asbestos cement cohorts, and both also had high levels of mesothelioma mortality. The values for R_L for these two cohorts are both more than six times the level of the next highest observation.

The heterogeneity among the mixed fibre cohorts is driven principally by three of them: Ontario, US/Canada Insulators and the Johns Manville retirees. Other reviewers (Doll and Peto, 1985; Hughes and Weill, 1986), have remarked on the unusually high risk estimate implied by the Ontario cohort and have suggested that the exposure estimates for this group may have been underestimated. Another potential contribution to the high risk of lung cancer in this cohort is exposure to silica: 8 out of 26 workers with post mortem examinations showed signs of silicosis (Finkelstein and Vingilis, 1984). There are clearly considerable uncertainties in the estimation of average exposures for the US/Canada Insulators cohort, since this is averaged over a very large cohort with no doubt very variable exposure experiences and over a long time period. The size of this group means that the value adopted for it will determine statistically the average risk in this group. The study of retirees from the Johns Manville asbestos products company is unusual in basing its estimates exclusively on follow-up of retired individuals

from the age of 65. There is no obvious theoretical reason why this should produce a seriously biased estimate of risk, though asbestos related mortality at ages below 65 will be missed. This cohort has been followed up almost to extinction, and if the impact of asbestos exposure on mortality eventually declines after the cessation of exposure, then cohorts with near complete lifetime follow up will tend to show rather lower excess mortalities than those where survivors form a substantial proportion of the cohort. In addition, the Johns Manville cohort was one where the authors had not suggested a conversion factor from particles to fibres, and this review has used the most commonly used value of 3 f/ml=1 mppcf. If this conversion implies higher exposure than in fact took place (the recent review by Lash et al. (1997), used a value of 1.4 borrowed from the New Orleans cohort), then the risk coefficient implied here would be too low. If these three cohorts are excluded from the group the remaining eight are just statistically consistent ($P=0.056$), and their joint mean is 0.32 (95% CI 0.16–0.50).

The six chrysotile cohorts fall into two groups: the two Carolina cohorts give values around 6% per f/ml.yr; the other four, including the two mines cohorts and dominated by the large Quebec cohort, are consistent with a joint R_L estimate of 0.06% per f/ml.yr (95% CI 0.043–0.079). The Connecticut and New Orleans (chrysotile only) cohorts give central estimates of R_L substantially above this value, (0.80

and 1.3 respectively) but both confidence intervals are very wide. Even if the mines cohorts are excluded there is still very clear statistical inconsistency between the Carolina results and those from Connecticut and New Orleans (P=0.0013). The Carolina results are also out of line with the two other (mixed fibre) textile cohorts—Rochdale and Pennsylvania—whose 95% confidence intervals for R_L have no overlap with those for Carolina.

RISK ASSESSMENT AT MODERATE AND HIGHER CUMULATIVE EXPOSURES

Mesothelioma

The quantified risk for mesothelioma at the kinds of cumulative exposure levels recorded in the reviewed cohorts—say, from 10 f/ml.yr upwards—presents a reasonably coherent picture, with values of R_M, in round figures, of 0.5, 0.1 and 0.001 (at most 0.003) for crocidolite, amosite and chrysotile respectively (see Fig. 2).

Lung cancer

It is more difficult to come to a clear view of the quantified risks of lung cancer, because of the inconsistency of the results especially for the chrysotile cohorts (see Fig. 3). The amphibole estimates are reasonably consistent. In round figures the estimates fall in the range 2–10% per f/ml.yr. The mean for the crocidolite group is rather lower (4.2) than that for the amosite group (5.2), though their confidence limits overlap substantially. The mean risk for all amphibole cohorts is 4.8% per f/ml.yr (95%CI 3.9–5.8), but with some evidence of heterogeneity (P=0.027). If the SA amosite cohort data are set aside, the remaining data are reasonably consistent (P=0.072), and the mean estimate becomes 5.1 (95%CI 4.1–6.2). In round figures, a value of 5% per f/ml.yr would represent a reasonable risk estimate for both amphibole fibre types.

The pure chrysotile cohorts produce estimates of R_L spanning two orders of magnitude, from a value of 6.7 for the Carolina women to 0.03 for Balengero mine. How should this very wide range of R_L estimates be interpreted? As far as evidence from 'pure' exposure goes there are only two strongly informative cohorts: Quebec and Carolina. The differences between these two has been studied and discussed extensively but, finally, inconclusively. The hypothesis that mineral oil used to suppress dust in the Carolina plant may have contributed to the lung cancer excess has been addressed by an internal case-control analysis of this factor reported by Dement et al. (1994) and Dement (1991)). The most recent report (Dement et al., 1994), shows that the odds ratios for different cumulative asbestos exposure categories are essentially unchanged by the addition of a variable representing subjects' typical level of exposure to

mineral oil (slight, moderate, high). The coefficients for these categories in the joint model were not reported, but were as follows, expressed as odds ratios relative to 'slight' exposure:

Mineral oil exposure	Odds ratio	95% Confidence interval
Moderate	1.12	0.57–2.21
High	1.47	0.8–2.75

(Dement, personal communication)

Although these ORs are not statistically significant (and do not form a statistically significant trend), there is some suggestion that mineral oil may have a role in enhancing the asbestos effect, particularly since all the effect of exposure *duration* is absorbed in the asbestos measure (workers were assigned to oil exposure categories according to the assessed oil exposure level at which they had spent the longest *proportion* of their employment in the plant). Early results from this case control study showed a cross tabulation of cases and controls by asbestos exposure and mineral oil category (Dement, 1991), without formal modelling. Crude odds ratios on this data suggest that the asbestos response is progressively steeper with increasing mineral oil category. If mineral oil does have an enhancing effect, the anomalous increase in estimated exposure specific lung cancer risk for men in the Rochdale cohort first exposed after 1950 could be explained, since dust suppression using mineral oil was introduced from that date (Peto et al., 1985). The regression slope estimate of R_L for the men first exposed after 1950 is 1.3 (95%CI 0.37–2.6), three times the value for men first exposed between 1930 and 1950.

The plausible suggestion that the longer fibre used in textile processes are responsible seems to be contradicted by the comparative analyses of lung fibre burdens in Quebec and Carolina cohorts reported by Sébastien et al. (1989). They found that the proportionate distribution of fibres by length was very similar in Quebec and Carolina lungs. Nevertheless, the notion that the longer fibres used in textile processes do represent a higher risk, is consistent with experimental evidence that longer fibres are more carcinogenic (Meldrum, 1996; Stanton et al., 1981; Miller et al., 1999). Green et al. (1997) have shown that the mean length and aspect ratio of chrysotile fibres in the lungs of Carolina workers are greater than in a local population control series; and than in the lungs of workers from the Albin cohort (Albin et al., 1990a,b).

Both studies on the lung content of Carolina workers have found amphibole (crocidolite or amosite) fibres in an appreciable proportion of them, though at much lower levels than for chrysotile and its associated tremolite. Sébastien et al. (1989 report that amphibole fibres at concentrations >0.1 f/μg (fibres >5 microns long) were only found in the lungs of work-

ers hired before 1940, which conflicts with the period of known use of crocidolite yarn (in very small quantities—see Appendix A) in the plant after 1950. This raises the possibility that some amphibole formed part of the exposure mix in this cohort in an early period. Green *et al.* (1997) show that the levels of amphibole are higher in Carolina workers than in local controls (2-fold difference in geometric mean, $P=0.031$) but much less strikingly than for chrysotile (5-fold, $P<0.0001$) or tremolite (14-fold, $P<0.0001$). They also report that amphibole at levels >1.0 f/μg (all fibre lengths) were found in only one of the ten lung cancer cases for whom this datum was available. This last observation limits the extent to which amphibole exposure—perhaps unrecognised—might play a role in this cohort. Whatever mechanism is in play does not appear to apply—to the same extent, at least— to the other two textile cohorts reviewed. As already pointed out, the Pennsylvania and Rochdale cohorts (with mixed fibre exposures) both give substantially lower estimates of R_L.

If it is accepted that some such feature of the processing in the Carolina cohort has genuinely produced a much higher risk than seen in other chrysotile cohorts the question can be asked how typical these features are of the bulk of applications? Looked at in the wider context of cohorts with mixed fibre exposure, the R_L value for Carolina looks untypically high. Setting aside the possibility that amphibole presents a higher risk of lung cancer, the observations of R_L from mixed fibre cohorts can be taken as informative of the R_L level for chrysotile. This suggests that in typical applications (including other textile processes) R_L for chrysotile is generally lower than the value derived from the Carolina cohort. The median R_L for the 16 cohorts with some chrysotile exposure is 0.5, compared to 4.5 for Carolina men and 6.7 for Carolina women. All but two of the mixed fibre cohorts give an R_L estimate less than 1, and of the two exceptions one (Albin) has a confidence limit including zero, and the other (Ontario) shows features suggestive of significant exposure to crocidolite (see below, Fig. 4 and related text).

To the extent that amphibole fibres make a disproportionate contribution to the lung cancer risk in the mixed exposure cohorts—and the evidence presented here suggests that they do—the typical risk of lung cancer from chrysotile exposure would be even lower. In most circumstances a value of 0.5% per f/ml.yr should probably be regarded as an upper limit to the lung cancer risk from pure (commercial) chrysotile. The mean R_L estimate for mixed fibre cohorts excluding the three with particular interpretational difficulties is 0.32% per f/ml.yr with an upper 95% confidence limit of 0.50.

It should be noted that a value of 0.5% per f/ml.yr is not as far out of line with the Carolina observations as it might seem. The 'cohort average' risk estimate from this cohort (6.7 for women, 4.7 for men) prob-
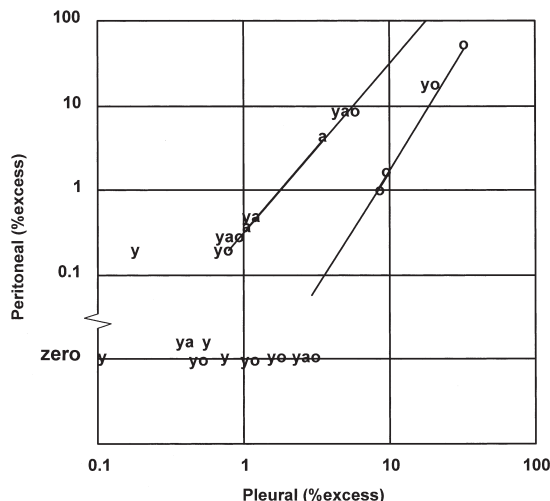

Fig. 4. Comparison of excess mortality from pleural and peritoneal mesothelioma, showing fibre type.

ably overestimates the risk, which from internal analysis is 1 for women and 3 for men (Dement *et al.*, 1994, p. 439). The exposure response regressions on this cohort give an intercept close to zero excess risk at zero dose, and there is thus no reason to suspect serious error in the reference rates (with consequential doubts about interpreting the slope). There is also the possibility of inaccuracies in the conversion of particle counts to fibre counts. One early report on this cohort (McDonald *et al.*, 1983a) suggested that the average conversion factor should be about 6 f/ml to 1 mppcf. If this were true, the risk per f/ml.yr would be halved.

A 'best estimate' of the lung cancer risk would be lower than 0.5% per f/ml.yr. Noting that the mean risk of the mixed fibre cohorts (excluding the three mentioned above) is 0.32% per f/ml.yr, and that the amphibole risk is over 10 times higher, it is possible that virtually all the observed risk could be explained by rather less than 10% of amphibole in the mixed exposures. However there is no direct evidence on which an estimate of the risk of 'pure' chrysotile could be based. Apart from the Balangero cohort, all the chrysotile evidence considered here effectively relates to Canadian chrysotile, since this was the dominant source of fibre for the other chrysotile cohorts. The risk of 'commercial' chrysotile as estimated from the mining cohorts is 0.06% per f/ml.yr. Given that the processing of chrysotile may produce some additional risk, the best estimate should be set higher than the mines level, say at 0.1% per f/ml.yr. The overall risk, of a mixture of 96% chrysotile with a risk of 0.1, and 4% amphibole with a risk of 5.1 would be 0.3% per f/ml.yr.

EXTRAPOLATION TO LOW EXPOSURES

All these cohort observations reflect the effect of exposure to high levels of asbestos. The main interest

in quantitative risk assessment in current conditions is to apply this evidence to the estimation of the risks associated with exposure levels 100–1000 times lower. The standard assumption is that, other things being equal, the risk will be proportional to dose; but this is more a cautious default assumption than anything more soundly based. To quote from the HEI review: "The assumption of dose-linearity for low-dose assessment purposes is thus a widely accepted and scientifically reasonable compromise rather than an established scientific principle of carcinogenesis".

However, if the true relationship between exposure and response was not linear, the impact on low dose extrapolations could be dramatic. There is some indication in the present data suggesting a non-linear exposure response, particularly for peritoneal mesothelioma, and the next sections examine this question.

Relationship of pleural and peritoneal mesothelioma

Figure 4 plots the percentage excess mortality from peritoneal mesothelioma against that from pleural mesothelioma. Cohorts with no mesothelioma cases of either kind are excluded. Cohorts with no peritoneal mesotheliomas are plotted on the peritoneal scale on or close to the 0.01 ordinate. The positioning of the cohort points strongly suggests a pattern of two alignments, one defined by the pure crocidolite cohorts, the other by the two pure amosite cohorts. Four mixed exposure cohorts lie very close to the amosite line: the US/Canada Insulators, New Orleans plant 1, the Johns Manville retirees and the Albin cohorts. All but the last of these clearly had amosite as the main amphibole fibre. The point representing the Ontario cohort lies very close to the crocidolite line, suggesting perhaps that the anomalous results from this cohort may be explained by underestimated exposure to crocidolite.

The position of the (male) Carolina cohort seems somewhat anomalous. The single peritoneal mesothelioma in this group is the only one in a cohort without material amphibole exposure, and the equality between pleural and peritoneal numbers (one of each) is only otherwise seen in cohorts with much higher levels of mesothelioma (and substantial amphibole exposure). The possibility of unrecognised amphibole exposure again suggests itself, but too much should not be read into this single peritoneal case. It is clear that the three fibre types produce different mesothelioma responses overall. The question of differential responses by mesothelioma site can really only be addressed for the amphibole fibres.

This relationship does not depend on quantified exposure data, and if it is real it should be reproduced in other cohorts with predominant amphibole exposure. The most informative cohorts will be those with crocidolite or amosite exposure, but not both. A Medline search identified eight such cohorts. The relevant data are summarised in Table 3, and a plot of the percent excess mortalities from these cohorts (and the pure fibre quantified cohorts) is shown in Fig. 5.

There is still an apparent separation between crocidolite and amosite cohorts, though the segregation is now less clear cut (as might be expected given the small numbers often involved). There is, of course considerable statistical uncertainty in both of these variables, and a simple regression (in which uncertainty about '*x*' values is ignored) would be misleading. Table 4 summarises the results of regressions in which the fit is optimised in both variables simultaneously (fit being measured by deviance, assuming Poisson variation for the numbers of mesotheliomas at each site).

Fitting a single line through all the data produces a line with a slope (on the log–log scale) of 1.2, but the overall fit is unsatisfactory ($P<0.001$). Allowing the two fibres to have separate fits makes a very significant improvement to the fit ($P<0.001$), and both fits have steeper slopes (2.3 for crocidolite and 3.1 for amosite — not shown in table). These slopes are not very precisely determined, and constraining them to be equal does not materially degrade the fit ($P=0.75$). The central estimate for this common slope is 2.4.

This model provides a very close statistical fit to all but two of the cohorts. The two exceptions are the gas mask cohorts in Canada (McDonald and McDonald, 1978) and in Leyland (Acheson *et al*., 1982), which contribute 6.1 and 4.5 respectively to the total deviance. Possible reasons for these cohorts to be untypical can be identified. The Leyland cohort was not ascertained from employment records, but from occupational details recorded on the wartime population register compiled in September 1939. If the numbers directly involved with gas mask assembly have been over estimated the percentage excess mortalities will be proportionately under estimated. If, for example, only 2/3rds of the identified women were in fact exposed, the expected mortality denominator would fall to around 120, and the residual falls from 6.1 to 4.3—still an outlier, but materially less extreme ($P=0.038$ instead of 0.014). The overall excess mortality from mesothelioma recorded in the Leyland cohort is much lower than in the Nottingham cohort engaged on the same process: 2.7% at Leyland and 16.5% at Nottingham, again suggesting the possibility of underestimation (eg by dilution of the exposed population), perhaps substantial.

The assessment of mesothelioma in the Canadian gas mask cohort was particularly exhaustive, involving review of pathological data for all cancer cases. Three of the six peritoneal cases were only identified after this review. If the number of peritoneal mesotheliomas is reduced by three, the residual for this cohort falls from 4.5 ($P=0.034$) to 2.0 ($P=0.16$).

However these are post-hoc rationalisations, and it is not clear whether it is better to remove these cohorts from the model or not. Despite the large

Table 3. Additional data on pleural and peritoneal mesothelioma from cohorts with predominant exposure to crocidolite or amosite (but not both), and without reported quantified cumulative exposures

Cohort		Process	Fibre	Sex	Expected all cause morality	Pleural		Peritoneal	
No.	Reference					No.	% Excess mortality	No.	% Excess mortality
18	Jones *et al.* (1996)		o	f	400[a]	53	13	14	3.5
19	Acheson *et al.* (1982) (Leyland group)	Gas masks	o	f	185	3	1.6	2	1.1
20	McDonald and McDonald (1978)		oy	mf	41[a]	3	7.3	6	14.6
21	Hilt *et al.* (1981)	O	o	m	5[b]	1	20	1	20
22	Levin *et al.* (1998)	I	a	m	133.6	4	3	2	1.5
23	Parolari *et al.* (1987)	I	a	mf	115.1	2	1.7	1	0.87
24	Finkelstein (1989)	I	a	m	1.89			2	106
25	Acheson *et al.* (1984)	I	ay	m	298.8	4	1.3	1	0.33

[a]Estimated as observed deaths less asbestos related deaths.
[b]Estimated assuming 25% mortality from age 31 to 68.
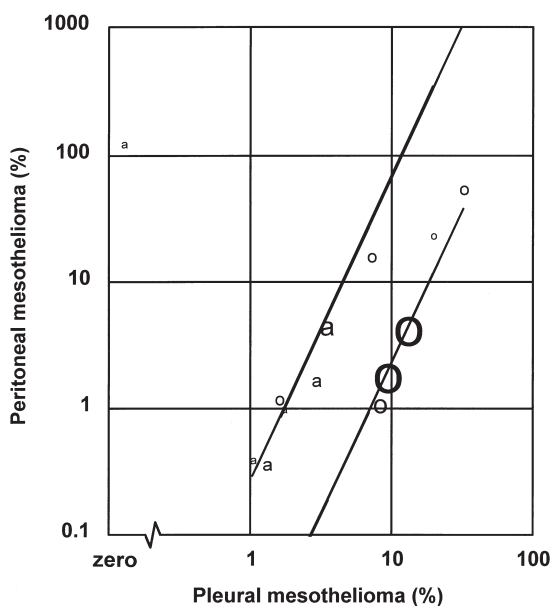

Fig. 5. Joint distribution of excess mortality from pleural and peritoneal mesothelioma, showing fibre type. [Note: Label size (area) roughly proportion to total mesothelioma numbers in each cohort].

residuals for these two cohorts, the overall residual deviance for the inclusive data (model 2) indicates a satisfactory fit (*P*=0.22). If the two outliers are removed, the separate fibre model fits the data almost exactly, and the slopes for the two fibres are very similar (model 3) and higher (around 3.2) than the 2.4 for the fit including them. In either case the single line model is rejected in favour of separate fits to the two fibre types, with similar slopes. The peritoneal rate is proportional to at least the square—perhaps as much as the cube—of the pleural rate.

The form of the relationship is unusual and somewhat surprising, since both outcomes reflect the effect of the same carcinogenic insult to the same type of tissue. If true, it is presumably related to the dynamics controlling the distribution of asbestos fibres around the body. Note that this relationship does not depend on the cumulative exposure, and is therefore not subject to the uncertainties attached to exposure estimation. Whatever its physical/biological explanation, these observations imply that at least one of these outcomes has a non-linear relationship with exposure.

Pleural mesothelioma and cumulative exposure

To examine this question more closely, Fig. 6 shows a plot of excess mortality from pleural mesothelioma against cumulative exposure with cohorts represented by their fibre type code. Figure 7 shows a similar plot for peritoneal mesothelioma. The points for the pure amphibole cohorts show a clear pattern of alignment, with the slopes for pleural mesothelioma less than 1 and those for peritoneal mesothelioma greater than 1.

Table 5 summarises the results of Poisson regression fits to the relationship between percentage excess mortality from pleural cancer and cumulative exposure, and the observed data points and selected regression lines are shown in Fig. 6. The relationship is modelled as linear on a log scale for each variable, and therefore has the form $P_{pl} = A_{pl}X^r$ where P_{pl} is the percent excess mortality from pleural cancer, X is cumulative exposure and A_{pl} and r are regression parameters. The corresponding predicted number of pleural cancers for a given cohort is $A_{pl}X^rE_{Adj}/100$ (where E_{Adj} is expected all cause deaths adjusted to an age at exposure of 30). The parameters were estimated by minimising the residual deviance between the observed and predicted numbers of pleural cancer for each (pure fibre) cohort.

It is clear that a wide range of slopes (*r*) are statistically consistent with the data. With independent fits to each fibre type the slopes are 0.62, 1.2 and 0.72 for crocidolite, amosite and chrysotile respectively.

Table 4. Joint Poisson regression (structure model) of relationship between pleural and peritoneal mesotheliomas (%peritoneal=A.%pleural[b])

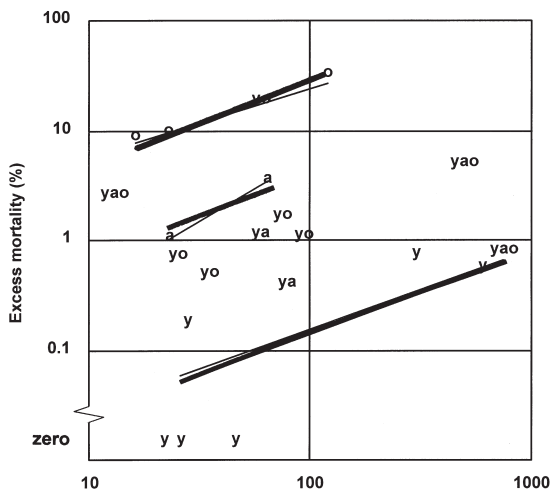| Model	A	b	Residual deviance	Degrees of freedom	P
1. All data	0.21	1.2	31.6	11	<0.001
2. By fibre, common slope					
o	0.0089	2.4	12.0	6	0.06
a	0.26	2.4	1.1	5	0.95
Overall			13.1	10	0.22
3. Fit excluding Leyland and Canadian gas mask data					
By fibre					
o	0.00074	3.3	0.1	3	0.98
a	0.17	3.1	1.0	4	0.91
Overall			1.1	7	0.99

Fig. 6. Excess mortality from pleural mesothelioma against cumulative exposure, showing fibre type. Regression lines fitted to pure fibre cohort. Bold lines indicate fits with slope constrained to be common across fibre types, narrow lines are unconstrained fits.

(The fit for amosite is of course completely determined since there are only two observations.) The total residual deviance is 3.93. Moving to a model in which the three slopes are constrained to be equal, the residual deviance increases marginally to 4.53, an increase of 0.6 with a corresponding increase of 2 degrees of freedom (*df*), clearly not a statistically significant change in overall fit (*P*=0.74), nor for any individual fibre type. The best fitting common slope is 0.75. Using deviance differences to construct a 95% confidence limits for the common slope gives estimated upper and lower limits of 0.27 and 1.3.

Peritoneal mesothelioma and cumulative exposure

Figure 7 and Table 6 show similar regression analyses for peritoneal cancer. Again the crocidolite and amosite points align themselves on two parallel lines. The small numbers of observed events means that the statistical uncertainties are quite wide. There
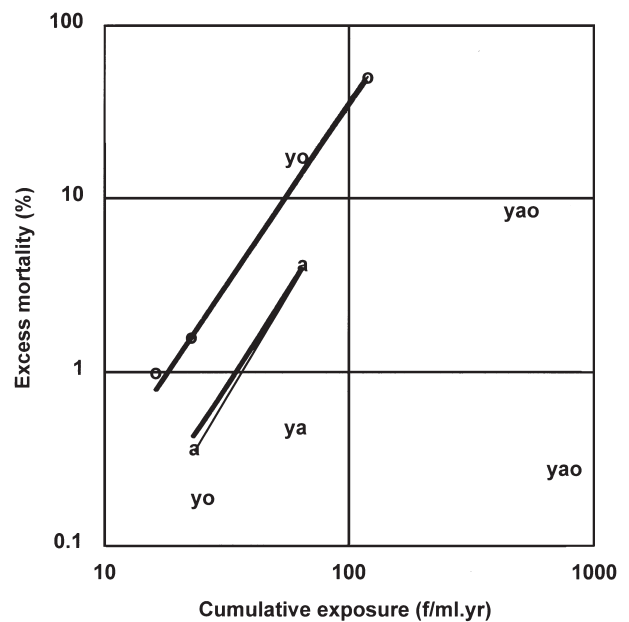

Fig. 7. Excess mortality from peritoneal mesothelioma against cumulative exposure, showing fibre type. Regression lines fitted to pure fibre cohorts. Bold lines indicate fits with slope constrained to be common across fibre types, narrow lines are unconstrained fits (the slopes are identical for crocidolite).

is very little difference between the slopes (*t*) for the two fibres, and the best common slope is 2.1, with a deviance based 95% confidence interval from 1.2 to 2.9.

The single peritoneal mesothelioma among the Carolina men, together with zero cases in the other chrysotile cohorts generates a negative value of *t*. If a common slope is imposed over all three fibres the best estimate is 1.6, but with significant heterogeneity (*P*=0.0025—data not shown). Only the amphibole cohorts have enough data to draw valid conclusions on peritoneal mesotheliomas.

The comparison of pleural and peritoneal slopes independent of exposure levels suggested a ratio of slopes between 2.4 and 3.2. If the ratio of the esti-

Table 5. Possion regression of pleural cancer against cumulative exposure by fibre type

Fit/fibre type	A_{pl}	r	95% CI for r	Residual deviance	Degrees of freedom	P
1. Independent fits						
o	1.4	0.62	(−0.54, 1.43)	0.25	1	0.62
a	0.02	1.2	(−0.32, 3.5)		0	
y	0.0057	0.72	(0.17, 1.79)	3.68	4	0.45
Overall				3.93	5	0.56
2. Best common slope						
o	0.93			0.36	2	0.84
a	0.13	0.75	(0.27,1.3)	0.49	1	0.48
y	0.0047			3.68	6	0.72
Overall				4.53	7	0.72
3. Common slope, amphiboles only						
o	0.88			0.39	2	0.82
a	0.120	0.77	(−0.069, 1.62)	0.44	1	0.51
Overall				0.83	2	0.66

Table 6. Possion regression of peritoneal cancer against cumulative exposure by fibre type

Fit/fibre type	A_{pr}	t	95% CI for t	Residual deviance	Degrees of freedom	P
1. Independent fits						
o	0.0022	2.1	(0.93, 2.9)	0.10	1	0.75
a	0.00018	2.4	(0.41,6.4)			
y	1.4	−1.7	(−22, 0.91)	2.60	4	0.63
Overall				2.70	5	0.75
2. Common slope, amphiboles only						
o	0.0022			0.10	2	0.95
		2.1	(1.2,2.9)		1	0.76
a	0.0006			0.09	2	0.91
Overall				0.19		

mates of the peritoneal and pleural slopes is constrained to be 2.4, the best fit pleural and peritoneal slopes are : 0.86 (95%CI 0.51–1.15) and 2.1 (95%CI 1.2–3.6). If ratio of slopes is constrained to be 3.2, the estimated values are $r=0.67$ (95%CI 0.40–0.90) and $t=2.1$ (95%CI 1.3–2.9).

Support for a convex ($r<1$) increase of pleural mesothelioma risk with exposure can be found in the detailed dose-specific analyses of the Wittenoom mesotheliomas by Berry (1991). Most of these cases (62 of 72) were pleural. Figure 8 plots the constant terms in the four exposure categories of Berry's analysis against their mean cumulative exposure. The slope is very close to 0.5. In addition, Coggon et al. (1995), concluded from a comparison of the ranking of occupations by mortality from pleural and peritoneal cancers and from asbestosis that "a more plausible explanation [of the different rankings] is that the exposure response relations for mesothelioma and asbestosis are non-linear, with the risk of pleural mesothelioma rising relatively more steeply at low exposures, but less steeply at high exposures".

A non-linear relationship between exposure and the rates of pleural and peritoneal mesothelioma means that the percent excess mortality per f/ml.yr (R_M) will
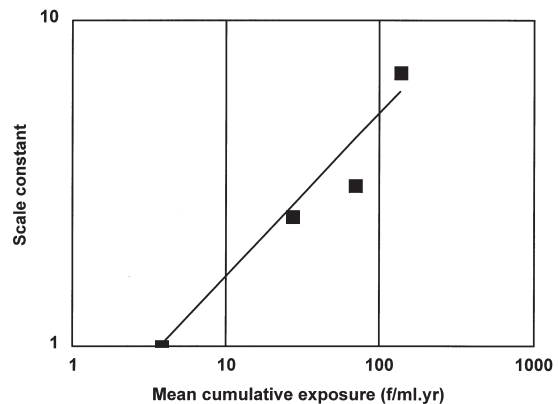
Fig. 8. Scaling constant in the four exposure groups of Berry (1991) analysis of the Wittenoom crocidolite cohort, plotted against the mean cumulative exposure in each group. The plotted line is proportional to the square root of cumulative exposure.

not provide a consistent summary of the effect for mesothelioma at the two sites considered individually. Each additional unit of exposure will add—progressively—less risk for pleural tumours, and more for peritoneal tumours. The point at which the absol-

(a) amphibole and mixed cohorts, fit to amphibole data

(b) chrysotile and mixed cohorts, fits to chrysotile

Fig. 9. Percent excess lung cancer by cumulative exposure, showing fibre type, with regression lines fitted to pure fibre cohorts (A: combined amphibole data, (1) slope free, (2) slope fixed=1; Y: chrysotile data, (1) all data, slope free (2) excl. Carolina, slope free, (3) excl. Carolina, slope fixed=1).
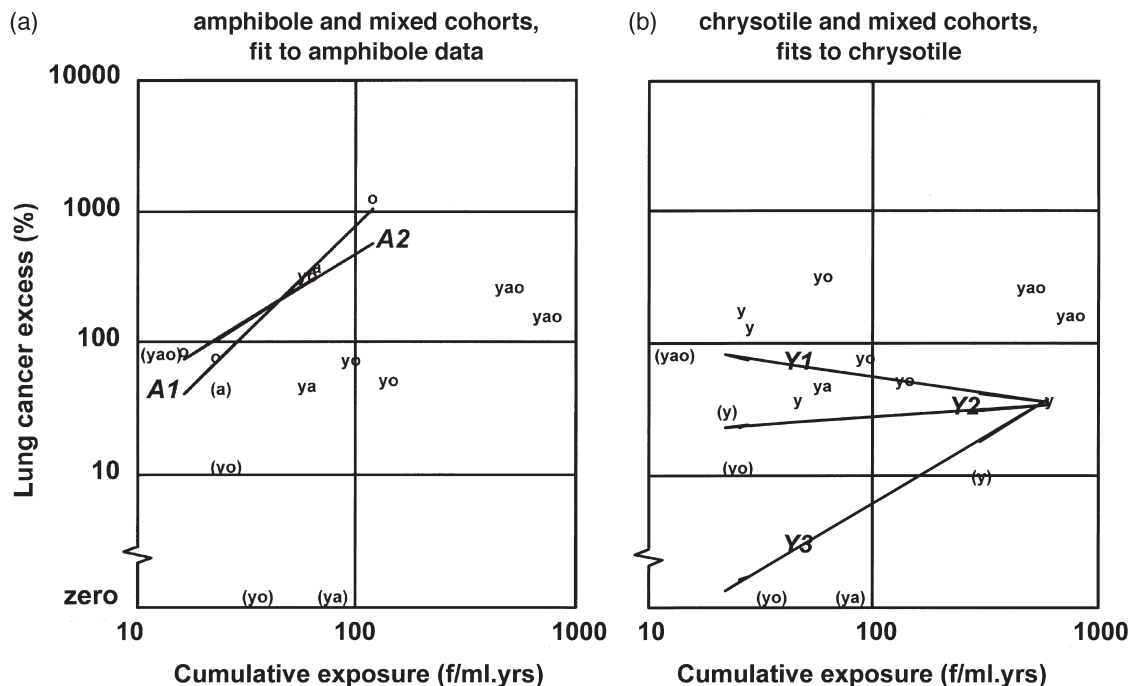
ute risks for tumours at the two sites are predicted to be equal is around 90f/ml.yr for crocidolite, around 55f/ml.yr for amosite. Below these values pleural tumours are more common, and at higher levels peritoneal tumours dominate. It happens that across the scale of cumulative exposure values in the reviewed cohorts (from about 10 to nearly 1000 f/ml.yr), the relationship between exposure and total mesothelioma risk is not far from linear, so the summary index R_M does provide a reasonable index of the overall mesothelioma risk over this range.

Lung cancer

If pleural and peritoneal mesothelioma have a non-linear relationship with asbestos exposure, the question arises as to whether the relationship for lung cancer is linear. Figure 9 shows a plot of percent excess lung cancer against cumulative exposure and Table 7 summarises regression results for lung cancer by cumulative exposure. There is no significant difference between the regressions for crocidolite and amosite points, so these are treated together. Using all the data, independent fits for amphibole fibres gives a concave relationship ($r=1.6$), and for chrysotile a negative slope ($r=-0.25$). These are clearly inconsistent with each other, and both depart very significantly from linearity ($P<0.001$).

The negative slope for chrysotile depends entirely on the Carolina data, and if this is removed the slope is just positive ($r=0.039$) with a CI that just includes 1. Clearly the data for chrysotile-only cohorts do not provide a coherent basis for direct estimation of the exposure–response slope, and some appeal to the evidence provided by cohorts with mixed exposure is necessary (as in the discussion of Table 2 and Fig. 3).

The concave slope for amphibole cohorts is largely dependant on the two extreme points, the Massachusetts and SA amosite cohorts. The lung cancer excess in the SA amosite cohort is quite small and statisti-

Table 7. Poisson regression of lung cancer against cumulative exposure by fibre type

Fit/fibre type	A_L	r	95% CI for r	Residual deviance	Degrees of freedom	P
Combined amphibole						
	0.49	1.6	(1.1, 2.1)	2.35	3	0.50
…excluding Massachusetts and SA amosite:						
	1.1	1.4	(0.89, 2.0)	0.83	1	0.36
Chrysotile …excluding Carolina	195	−0.27	(−0.44, −0.07)	19.8	4	<0.001
	27.5	0.030	(−0.26, 1.1)	0.91	2	0.63

cally unstable, and the exposure estimate for the Massachusetts cohort is based on fairly slender evidence. If these two cohorts are removed the best fit slope becomes 1.4, with a confidence interval that includes 1.

The Massachusetts cohort with its very high levels of excess mortality, and as cohort with the highest estimated mean exposure to crocidolite, has an important—though not determining—impact on the estimates. It is unfortunate that the exposure estimates are somewhat speculative (see Appendix B). At the same time it should be noted that in relation to a prior expectation of a linear dose response the effects of this observation on the pleural and lung cancer estimates are opposite: the pleural slope is flattened and the lung slope is steepened. This does not of course prove that the exposure estimate is correct, but if it is materially in error then either the pleural or the lung slope is even further from linear than suggested by the present analyses.

DEVELOPMENT OF NON-LINEAR RISK ESTIMATES

Mesothelioma

The data in Tables 5 and 6 and Figs. 6 and 7 suggest the following model with separate components for pleural and peritoneal tumours:

$$P_{\mathrm{M}} = A_{\mathrm{pl}}X^r + A_{\mathrm{pr}}X^t$$

where P_{M} is the percent excess mortality, r and t are the pleural and peritoneal slopes of the exposure response on a log–log scale, A_{pl} and A_{pr} are constants of proportionality for the pleural and peritoneal elements of the risk respectively, and X is cumulative exposure in f/ml.yr.

If the information about the ratio of r and t from the non-quantified cohorts is ignored, the best fit values using all the data are $r=0.75$ and $t=2.1$. Without the chrysotile data, the estimate of r is essentially the same (0.77). Analysis of the ratio t/r including the non-quantified cohorts (Table 4) indicates values for this ratio around 2.4 with all the data, around 3.2 excluding the two outlying cohorts. If a simultaneous fit is made to the full data with the ratio of pleural and peritoneal slopes fixed at 2.4, the resulting estimates (using only the amphibole data) are $r=0.86$ and $t=2.1$. If the ratio of slopes is constrained to be 3.2, the estimated values are $r=0.67$ and $t=2.1$.

There is little to choose between values of r from 0.67 to 0.86. We will use a slope of 0.75 as our best estimate for r. The estimates for t are less variable, and in any case have no bearing on risk estimates at low levels. We will take $t=2.1$ as the best estimate.

How wide a margin of uncertainty should be allowed on these slopes? On purely statistical criteria, values of r between 0.4 and 1.2 could be chosen. However a slope as low as 0.4 seems unlikely on physical grounds. Berry's analysis of Wittenoom data

using individual doses implies a slope of about 0.5, but the uncertainties of individual dose assignment are likely to have biased this estimate downwards. The argument above suggests that the lower end of range should be set at 0.67 or lower. We will take 0.6 to represent the lower end of the plausible slope range.

There are quite strong *a priori* reasons for using a slope of 1. It is the value that all previous risk estimations have used, and represents a natural assumption (effect is proportional to cause) in the absence of evidence to the contrary. A linear relationship is also (in most models) consistent with the data. We therefore take $r=1$ as the upper end of the slope range. Different slopes imply different best fit values for A_{pl} and A_{pr}. These estimates and their 95% confidence intervals for the three fibre types are shown in Table 8.

Effects of exposure duration and age at first exposure

This formulation does not take duration of exposure or age at first exposure into account. The HEI (and similar) risk models (see Appendix A) imply that for equivalent cumulative exposures, short exposure times produce larger risks than long exposure times, (in other words 10 f/ml for 1 yr is worse than 1 f/ml for 10 yr); and that exposure at younger ages will produce higher excess mortality rates. All the amphibole cohorts considered here had short exposures (averaging about 2 yr). The suggested risk model for amphiboles is therefore appropriate for short exposures, but will overstate the risk from extended exposure periods. The chrysotile coefficients are effectively determined by the Quebec cohort, where the average exposure durations were quite long (averaging about 10 yr). A given cumulative exposure accrued over 2 yr (starting at age 30) produces about 40% more deaths as the same exposure accrued over 10 yr. For general risk assessment purposes, where short exposures are more likely to be at issue, the chrysotile coefficient should be increased by a factor of 1.4. Reductions in the exposure accrual time below 2 yr have very little impact on the risk.

The risk estimates summarised above apply to exposure starting at age 30. Table 9 shows adjustment factors derived from the HEI model to convert risk estimates for an age at exposure of 30 to other exposure ages.

Predicted effects at very long follow up

It can reasonably be questioned whether a given asbestos exposure will continue to generate a constant excess mesothelioma mortality beyond 40 or 50 yr follow up. The evidence from cohorts with long follow up is that the incidence eventually falls. In the Paterson cohort a significant fall is seen for follow up beyond 35 yr. In the US/Canada insulators there

Table 8. Estimated coefficients[a] with 95% confidence intervals for constants in the risk prediction equation for P_M at three levels of the slope coefficient r

Slope/Fibre	A_{pl}	95% CI	A_{pr}	95% CI
Best estimate slope (r=0.75, t=2.1)				
Crocidolite	**0.94**[a]	(0.71,1.2)	0.0022	(0.0011,0.0039)
Amosite	**0.13**[b]	(0.060,0.25)	0.0006	(0.00025,0.0012)
Chrysotile	**0.0047**[a]	(0.0030,0.0069)		
High slope (r=1, t=2.5)				
Crocidolite	0.43	(**0.33**[b],0.54)	0.00053	(0.00029,0.00087)
Amosite	0.052	(**0.022**[b],0.099)	0.00012	(0.000049,0.00024)
Chrysotile	0.000970	(**0.00064**[b],0.0014)		
Low slope (r=0.6, t=1.7)				
Crocidolite	1.5	(1.1,**1.9**[c])	0.0083	(0.0043,0.014)
Amosite	0.24	(0.11,**0.44**[c])	0.003	(0.0013,0.0058)
Chrysotile	0.012	(0.0078,**0.018**[c])		

[a]Coefficients used for risk extrapolation at low doses shown in bold:
[a]best estimate, [b]lowest arguable, [c]highest arguable (see Table 11). Numbers of peritoneal mesotheliomas at low doses are negligible. For short exposure, chrysotile coefficients should be multiplied by 1.4.

Table 9. Adjustment factors to convert estimates of mesothelioma mortality due to asbestos exposure starting at age 30 to other exposure start ages

Age	20	25	35	40
Factor	2.1	1.5	0.6	0.4

Table 10. Estimated coefficients with 95% confidence intervals for constants in the risk prediction equation for P_L for chosen levels of the slope coefficient r

Fibre/model		A_L	95% CI
Amphibole			
	Linear (r-1)	4.8	—[a]
	Best (r=1.3)	1.6	(1.2, 1.9)
	Steepest (r=1.6)	0.49	(0.37,0.62)
Chrysotile[b]			
	Best (r=1.3)	0.028	—[b]
Cautious model-max of:			
	Linear (r=1)	0.5	—[b]
	Steepest (r=1.6)	0.039	—[b]

[a]A linear model is not strictly statistically consistent with the observed data. The line with A_L=4.8 is the single best fit.
[b]Non-statistical uncertainties dominate choice of chrysotile models, 95% confidence intervals cannot be properly calculated. See text for discussion.

is a fall beyond 50 yr. Qualitatively it seems clear that the risk does not increase indefinitely, but there is insufficient evidence on very long follow up to fix the risk profile in this period. A rough and ready way of limiting the predicted risk at very long follow up periods is to truncate the predictions at some age. The Doll and Peto and HEI reports both truncated their predictions at age 80, and we will follow this convention. It is likely that this would still overstate the risk from exposure at ages below 20, and truncation of the predicted effect at 60 yr follow up might then be appropriate.

Lung cancer

The data in Table 7 and Fig. 9 suggest that the relation between lung cancer and cumulative exposure may be concave—i.e. that the excess lung cancer risk is proportional to a power greater than 1 of cumulative exposure. Statistically the range of powers consistent with all the amphibole data is from 1.1 to 2.1. Without the two extreme cohorts the range becomes 0.89–2.0 with a central estimate of 1.4. No previous analysis of the epidemiological data has suggested a concave relationship, though experimental data for a wide range of carcinogens (Hoel and Portier, 1995) suggest they may be quite common. Across the range of exposures in a single study, and given the uncertainties in individual exposure estimation, a moderate degree of non-linearity will be difficult to detect.

The reasonably arguable values for r fall in the interval 1 to 2: a degree on conservatism and some doubts about the two extreme cohorts lead us to prefer the lower end of this interval. We will take r=1 (a linear relationship) and r=1.6 to represent the flattest and steepest slopes for risk assessment, and the mid point of this range (r=1.3) as our best estimate assumption.

The estimates and 95% confidence limits for the constant term A_L in a model for lung cancer $P_L = A_L X^r$ with r=1 (linear) 1.3, and 1.6 based on amphibole data are shown in Table 10. As already discussed, the inconsistencies in the pure chrysotile data rule out a direct estimate of the exposure–response slope based on this data. The dominant uncertainties for chrysotile are the reasons for the observed differences in exposure-specific lung cancer risk, rather than the statistical uncertainties in estimating this risk level. This uncertainty is already reflected in the five-fold difference between our 'best' and 'cautious' estimates of R_L (0.1 and 0.5 respectively). In the absence of a better approach we will assume

the same range of possible slopes for the chrysotile lung cancer relationship as for the amphiboles, and determine the scaling constant by fixing the predicted excess mortality at the median exposure for chrysotile cohorts (70 f/ml.yr) to 0.1% for the best estimate and 0.5% for the cautious estimate. The resulting values are shown in Table 10.

The pattern of excess lung cancer—broadly constant relative excess from 10 to 40 (perhaps more) years from exposure (see Appendix A) implies that for exposure starts between 20 and 40 yr of age there is very little difference in the predicted risk. There may be some decline for very long follow up, but the rate of decline is unknown. As for mesothelioma we address this possibility approximately by truncating the predicted excess at age 80.

IS THERE A THRESHOLD?

Another question with important implications for risk at low levels of exposure is whether there is a threshold for cancer initiation by asbestos. The HSE's recent *Review of fibre toxicology* (Meldrum, 1996), presents arguments mainly on a toxicological basis for believing that there may be a threshold for asbestos induced lung cancer. The argument is essentially based on a view of the carcinogenic process induced by asbestos as being an extension of the chronic inflammatory processes producing fibrosis. It is widely agreed that heavy doses of chrysotile are required to produce lung fibrosis. And some evidence has been derived from the New Orleans cohort suggesting a threshold dose of about 30 f/ml.yr for radiological fibrosis (Weill, 1994). Analysis of necropsy material from the Carolina cohort also shows a distinct step increase in fibrosis score for cumulative exposures around 20–30 f/ml.yr (Green *et al*., 1997). This does not apply to amphibole exposure: radiological fibrosis which progressed after the cessation of exposure has been documented (Sluis-Cremer, 1991), in South African amphibole miners under medical surveillance and with cumulative doses less than 5 f/ml.yr. This suggests that if a threshold applies to the lung cancer effect of amphibole asbestos, it is very low. The adoption of a slightly concave exposure response slope entails a moderately threshold-like behaviour.

Several lines of argument also suggest that any threshold for mesothelioma is at a very low level. Some cohorts (Neuberger and Kundi, 1990; Newhouse and Sullivan, 1989; McDonald and McDonald, 1978; Thomas *et al*., 1982; Rossiter and Coles, 1980), have produced mesotheliomas in conditions where no excess lung cancer was seen. Occupational PMRs for British men suggest that the range of jobs for which mesothelioma rates are above background levels is very wide (Hutchings *et al*., 1995; Hodgson *et al*., 1997). Also the proportion of mesothelioma cases in population studies for whom no likely source of

asbestos exposure can be identified is often quite high. All these observations suggest that relatively brief exposures may carry a low, but non-zero, risk of causing mesothelioma.

Some authors (Ilgren and Browne, 1991; Liddell, 1993) have argued for a mesothelioma threshold, or threshold-like behaviour of the dose–response. Such arguments are fraught with statistical and logical difficulties. The attempt (Ilgren and Browne, 1991) to deduce a 'threshold' by identifying the lowest estimated dose received by any observed case is a logical nonsense. Furthermore, the existence of zero cases in a dose category (human or animal) should not be automatically interpeted as zero risk. Direct statistical confirmation of a threshold from human data is virtually impossible. One would need accurate assessment of very low doses across a large population with long term follow up. Case-control studies with lung content measures of exposure (McDonald *et al*., 1989; Rödelsperger *et al*., 1999; Rogers *et al*., 1991) do not suggest any threshold, or downward inflexion of the dose response at the lower end of their exposure scales. Some of the animal data cited by Ilgren and Browne are suggestive of a threshold— particularly that from intra-pleural and intra-peritoneal injection—but it is not clear how this would translate into a estimated human effect threshold for exposure by inhalation. Taking this evidence together we do not believe there is a good case for assuming any threshold for mesothelioma risk.

QUANTIFIED RISK ASSESSMENT

Under current conditions, the main interest in the health risks of asbestos relates to exposure circumstances well outside the range for which we have direct observations. The statements we can make about risk therefore incorporate two kinds of uncertainty. First there is the usual statistical uncertainty of inferring underlying risk from observations in particular groups. This kind of uncertainty depends essentially on the number of events (in this case cancer deaths) observed. The uncertainty can therefore—given some assumptions—be quantified: the more observed events, the less the statistical uncertainty. Statistical uncertainty is expressed as a confidence interval (a range of values with—conventionally—a 95% probability of covering the true value).

The second kind of uncertainty relates to the question whether the relationship between exposure and outcome seen in the observed range continues to hold outside that range. This kind of uncertainty cannot be quantified statistically. Qualitatively one can reasonably argue that the agreement will be better for exposures close to the observed range, but with increasing distance from the observed range our confidence that we know what to expect decreases. For example, previous assessments of cancer risk from asbestos have all assumed that the effect is linear.

This review has presented evidence suggesting that this may not be the case. Uncertainty about the slopes of exposure–response lines has an increasing impact with increasing distance from the observed range. Also the strength of qualitative arguments such as those advanced in the HSE review (Meldrum, 1996), in favour of a threshold for the lung cancer effect increase as exposure falls.

All the above implies that simply to present a table of risk estimates—or even risk ranges—for different cumulative exposures cannot capture the changing balance of the different kinds of uncertainty. Table 11 gives a verbal assessment of risk at a range of representative cumulative exposures. No estimates have been given for lifetime risks lower than 1 in 100 000, and this level is referred to as 'insignificant'. A lifetime risk of 1 in 100 000 corresponds to an annual risk well below 1 in a million, which HSE has suggested (Health and Safety Executive, 1999) as a "guideline for the boundary between the broadly acceptable and tolerable regions [of fatal risk to an individual]." It is also well below the level at which it is suggested that mesothelioma would occur in the absence of asbestos exposure: a clear majority of the very few mesotheliomas that would occur at this level would not be caused by asbestos.

Mesothelioma risks in the observed cohorts have been expressed as a percentage (P_M) of total expected mortality in order to standardise observations from different follow up configurations. To make predictions of risk this measure must be converted back into absolute terms, and this is done using the average male life table discussed in Appendix A. For exposures starting at age 30 the excess mortality estimate P_M is applied to the total expected mortality from age 40 to age 79 (allowing a 10 yr minimum latency, and truncating risk at age 80). The life table predicts that about 70% of survivors to age 30 will die between the ages of 40 and 80. Absolute risk estimates can therefore be derived from the P_M value for a given exposure by multiplying by a factor of 0.7. Lung cancer risks have been expressed as a percentage excess of expected lung cancer mortality. The major determinant of this underlying lung cancer risk is smoking—especially cigarette smoking—and the number of asbestos-related lung cancers will be affected by the prevalence of smoking in the exposed population. Currently (in 1997) about 9.5% of male deaths between the ages of 40 and 79 are due to lung cancer. For women the figure is 7%, reflecting differences in past smoking. Total survival to age 80 is lower in men than in women, and combining data for survival and proportionate mortality from lung cancer it can be predicted that for 1000 30-yr-old men 54 will die of lung cancer between the ages of 40 and 79. For women the number is 28. Thus for a population with the past smoking habits of British men aged 60+ (the ages at which most lung cancers occur), the lung cancer risk from asbestos exposure is given by $0.054 P_L$. For women with typical past smoking habits the figure would be $0.028 P_L$.

Table 11 makes statements about the lifetime risks of exposures accumulated over short (up to 5 yr) periods from age 30. The factors given in Table 10 can be used to apply the mesothelioma estimates to other ages at exposure. The lung cancer estimates are based on 1997 male lung cancer rates. They are not sensitive to age at exposure.

For the lung cancer risk due to chrysotile two principal figures are given: a best estimate and a cautious estimate. A risk estimate derived from the Carolina cohort is also given, with the qualification that this might be arguable in 'exceptional circumstances'. These exceptional circumstances cannot be defined with any certainty since the features of exposure at this plant responsible for the very high lung cancer risks there are not known. Exposure to textile grade (i.e. long fibre) chrysotile is presumably necessary, but does not seem to be sufficient, since other textile plants have recorded much lower exposure-specific risk (even with additional exposure to amphibole fibre). The spraying of the raw fibre with mineral oil (as a dust suppression measure) has been suggested as a possible explanation. This hypothesis seems to be supported by a case-control study of lung cancers at Carolina (though the relevant results have not been fully reported), and by observations from another asbestos textile plant (Rochdale), where men first employed after oil spraying was introduced had three times the exposure-specific risk of those first employed in earlier periods (though still lower than the Carolina risk).

The main uncertainties in this picture relate to the effects of chrysotile, particularly at low doses. The application of these estimates in the assessment of a particular risk situation will depend on the purposes of that particular assessment, and the extent to which a precautionary approach is appropriate.

DISCUSSION

There have been a number of papers (Cullen, 1998; Stayner *et al*., 1996; Nicholson and Landrigan, 1996; Smith and Wright, 1996), in the literature recently which directly or indirectly consider whether there are differences in potency between the fibre types as causes of mesothelioma and lung cancer. The claim that there are important differences is often described as 'the amphibole hypothesis'. In its strongest form this has been said to claim that pure chrysotile (i.e. without any associated tremolite fibre) would present little or no carcinogenic risk. At the other extreme, it has been argued (Smith and Wright, 1996), that there is virtually no difference between the risks presented by the different fibre types. Most commentators (e.g. Doll and Peto, 1985; Hughes and Weill, 1986; Health Effects Institute, 1991) have considered that the amphibole fibre types are more dangerous, parti-

Table 11. Summary statements of the quantitative cancer risks from asbestos exposure at different levels of cumulative exposure[a,b,c,d]

Fibre	Mesothelioma	Lung cancer
Risk summaries for cumulative exposures between 10 and 100 f/ml.yrs		
Crocidolite	Best estimate about 400 deaths per 100 000 exposed for each f/ml.yr of cumulative exposure. Up to 2-fold uncertainty.	Rising from about 150 (range 100 to 250) excess lung cancer deaths per 100 000 exposed for each f/ml yr of cumulative exposure at 10 f/ml.yrs to 350 (range 250 to 550) at 100 f/ml.yrs.
Amosite	Best estimate about 65 deaths per 100 000 exposed for each f/ml.yr of cumulative exposure. 2-fold to 4-fold uncertainty.	Best estimate about 5 excess lung cancer deaths per 100 000 exposed for each f/ml yr of cumulative exposure. Cautious estimate 30. In exceptional circumstances (see note c) it is arguable that an estimate of 100 might be justified.
Chrysotile	Best estimate about 2 deaths per 100 000 exposed for each f/ml.yr of cumulative exposure. Up to 3-fold uncertainty.	
Risk summaries for cumulative exposures of 1 f/ml.yrs		
Crocidolite	Best estimate about 650 deaths per 100 000 exposed. Highest arguable estimate 1500, lowest 250.	Best estimate about 85 (range 20 to 250) excess lung cancer deaths per 100 000 exposed.
Amosite	Best estimate about 90 deaths per 100 000 exposed. Highest arguable estimate 300, lowest 15.	Best estimate about 2 excess lung cancer deaths per 100 000 exposed. Cautious estimate 30 per 100 000. In exceptional circumstances (see note c) it is arguable that an estimate of 100 per 100 000 might be justified. The case for a threshold—ie zero, or at least very low risk—is arguable.
Chrysotile	Best estimate about 5 deaths per 100 000 exposed. Highest arguable estimate 20, lowest 1.	
Risk summaries for cumulative exposures of 0.1 f/ml.yrs		
Crocidolite	Best estimate about 100 deaths per 100 000 exposed. Highest arguable estimate 350, lowest 25.	Best estimate about 4 (range <1 to 25) excess lung cancer deaths per 100 000 exposed.
Amosite	Best estimate about 15 deaths per 100 000 exposed. Highest arguable estimate 80, lowest 2.	Excess lung cancer deaths probably insignificant. Cautious estimate 3 per 100 000. In exceptional circumstances (see note c) it is arguable that an estimate of 10 per 100 000 might be justified. The case for a threshold—ie zero, or at least very low risk—is strongly arguable.
Chrysotile	Risk probably insignificant, highest arguable estimate 4 deaths per 100 000 exposed.	
Risk summaries for cumulative exposures of 0.01 f/ml.yrs		
Crocidolite	Best estimate about 20 deaths per 100 000 exposed. Highest arguable estimate 100, lowest 2.	Risk is probably insignificant (range <1 to 3 excess lung cancer deaths per 100 000 exposed). Mesothelioma is now the dominant risk, so precise estimation of the lung cancer risk is not critical.
Amosite	Best estimate about 3 death per 100 000 exposed. Highest arguable estimate 20, lowest insignificant.	Risk of excess lung cancer very probably insignificant except in exceptional circumstances (see note c) when it is arguable that an estimate of 1 death per 100 000 might be justified. The case for a threshold—ie zero, or at least very low risk—is strongly arguable.
Chrysotile	Risk probably insignificant, highest arguable estimate 1 deaths per 100 000 exposed.	

(Continued on next page)

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Table 11. (*continued*)

Fibre	Mesothelioma	Lung cancer
Risk summaries for cumulative exposures of 0.005 f/ml.yr and lower		
	At these levels only mesothelioma need be considered. The absolute risk is low—, but quantitative uncertainties are very considerable.	
Crocidolite	Best estimate about 10 deaths per 100 000 exposed. Highest arguable estimate 55, lowest. Best estimate falls to insignificant level at 0.0002 f/ml.yr, and highest arguable risk becomes insignificant at 6×10^{-6} f/ml.yr	Insignificant, possibly zero
Amosite	Best estimate about 2 deaths per 100 000 exposed highest arguable lifetime risk 15, falling to <1 (ie. insignificant) at 7×10^{-5} f/ml.yr	
Chrysotile	Insignificant	Insignificant, very possibly zero

[a]Exposure assumed to be accumulated over short—up to 5 yr periods starting at age 30. For exposure at other ages adjust the predicted mesothelioma figures using the factors in Table 9. Estimates for longer periods of exposure can be approximated by making separate estimates for successive 5-year periods and adding the resulting risks (this will slightly overestimate risk). Estimates have been rounded to nearest 5 in second significant digit (or to one significant digit when less than 10).

[b]The lung cancer risk is based on British male mortality in 1997 when 9.5% of male deaths at ages 40–79 were due to lung cancer. This represents an average for a population with a past pattern of smoking similar to that of older British men. In 1996 23% of men aged 60+ had never (or only occassionally) smoked, and 25% were current smokers. For lifetime smokers the lung cancer risk will be about double the stated levels, for non-smokers about a sixth (if the interaction with asbestos is multiplicative) or about a third if the relative risk is higher than in non-smokers as suggested by Berry *et al.* (1985).

[c]The lung cancer risk arguable in 'exceptional circumstances' is derived from the Carolina cohort using a value of R_L of 2.19 taken from the analysis of Stayner *et al.* It should only be considered where there is simultaneous exposure to textile grade (i.e. long fibre) chrysotile and mineral oil or some analogous co-exposure.

[d]The simple pro rata formulae proposed in this table do not take account of the impact of competing causes of mortality. The impact will be trivial so long as the predicted asbestos related mortality is low, and limited for predicted (individual cause) mortality below about 30 percent. Above this level the individual asbestos related diseases (including asbestosis, which is not covered by this analysis) will reduce each other's observed impact. In this situation all that can usefully be predicted is that total asbestos related mortality will be very high indeed.

culary for mesothelioma, but some (Cullen, 1998; Stayner *et al*., 1996) have regarded the extent of these differences as unimportant, particularly since chrysotile has been overwhelmingly the most commonly used fibre.

The interpretation of the whole body of evidence depends importantly on the interpretation of results from cohorts with predominantly chrysotile exposure together with a minority contribution—usually a few per cent—from amphiboles. As long as the difference in potency is not extreme these cohorts can be reasonably interpreted as indicating the risk of chrysotile exposure. But if the differences in potency are very substantial this is no longer the case. Furthermore, in this situation an additional source of error in the estimation of exposure will be introduced, since the measured exposure (mainly of chrysotile) will often be a poor proxy for the relevant exposure.

The data in this review suggest that order of magnitude differences in potency may indeed apply for mesothelioma, and probably also for lung cancer. The main reason this review differs from earlier similar reviews is in its use of the information from the amphibole mining cohorts in South Africa and Australia. The publication of mortality results from the South African mines seems to have gone almost unnoticed. The Australian cohort has been the subject of a series of publications with varying analytical approaches and varying results. One of these analyses gave a lung cancer risk from the cohort of around 1% per fibre/ml.yr, and this is the value that has been most usually quoted, but this is probably an underestimate due to incomplete follow up at older ages. This review is also the only one to have exploited the (admittedly uncertain) quantitative exposure information in the Massachusetts cohort.

Implications of the non-linear exposure response for mesothelioma

A non-linear relationship between the rates of pleural and peritoneal mesothelioma is more readily explicable if the cancer risk is proportional to some function of the concentration of fibres in the target tissue, rather than the simple number burden.

If concentration rather than number burden is the relevant parameter, then the possibility of a threshold type relationship becomes much more plausible, since if the effect depends on fibres acting together, there must presumably be some point at which individual fibres are simply too far apart to exert any joint effect. Of course, if the mechanisms of distribution of fibres within the lung and pleura are such that fibres tend to be delivered preferentially to particular areas—and there is evidence that this is the case in the pleura (Boutin *et al*., 1996)—the effective threshold level may be very low. In any case such a threshold is unlikely to be a sharp cut-off. Random variations in the distribution of fibres in particular lungs, and dif-

ferences in individual susceptibility will mean that the exposure response curve simply starts to descend more steeply from some point on the cumulative exposure scale.

Also, fibre concentration is the more plausible exposure metric for the production of fibrosis, so this interpretation is consistent with the link suggested by the HSE fibre review (and by other authors) between the two processes. It should be noted that the suggestion is not that tumours arise directly from fibrosis, but that both are products of an underlying inflammatory process.

If fibre concentration in tissue is the key risk measure, the extreme sensitivity in animal experiments to intra-peritoneal and intra-tracheal instillation of massive fibre doses is also readily explicable.

Combined with the knowledge of the much greater solubility of chrysotile in the lung, this may also explain why asbestos related diseases have only been clearly seen with heavy chrysotile exposures. If exposures are heavy and sustained a sufficient concentration of fibre in the lung may be maintained to trigger both fibrosis and malignancy. The extreme rarity of peritoneal mesothelioma in cohorts exposed to chrysotile alone may also be explained. If the route by which asbestos reaches the peritoneum is from the pleural cavity, it may well be that chrysotile fibres do not survive long enough in body tissues to make the journey in sufficient numbers.

Chrysotile and asbestos related malignancy

Smith and Wright (1996), showed a ranking of 25 cohort studies by proportional mortality from pleural mesothelioma and argued that since chrysotile was the primary exposure for two of the top 10 cohorts and present as part of the mix in six of them, and that the picture for crocidolite in terms of its presence in the mix was similar, while amosite was less evident than either of the other two fibre types, that chrysotile must therefore be similarly potent as a cause of pleural mesothelioma. What this argument ignores is any quantification of exposure. Without quantification it is very difficult to draw any conclusion about relative risk from a simple ranking by mesothelioma rate. In relation to the 25 cohorts identified in this review an equally pertinent observation might be that all of them involved exposure to one or other of the amphibole fibres. Smith and Wright also present arguments based on the relative levels of mortality from pleural mesothelioma and from excess lung cancer to suggest that there is only moderate difference between the potency of chrysotile and the amphibole fibres for causing mesothelioma—they suggest a factor of three or four. However this argument is based on the assumption that all fibre types are equally potent for lung cancer. If this review is correct in suggesting that this is not the case, these arguments are not valid.

Nicholson and Landrigan (1996), present similar

arguments based on the assumed equivalence of the fibre types to cause lung cancer. They also show an analysis of the mesothelioma mortality of a small subset of the US insulators study which shows that the pattern of deaths over time implies that members of this cohort were exposed to a pleural carcinogen before 1935. Since, reportedly, amosite was first used from around 1935, and prior to this date only chrysotile was used, some of these deaths must have been due to chrysotile. The authors do not mention the possible role of crocidolite, but if we accept that no amphibole fibre was used before 1935 by US insulation workers, these observations do show that some of the cases in this cohort must have been caused by exposure to chrysotile prior to 1935. These exposures will often have been heavy. In fact the contemporary US trade journal 'Asbestos' (published monthly from July 1919) makes it clear that both amosite and crocidolite were used in the US through the 1920s, though probably in limited quantities, since the US industry seems to have been resistant to their use on technical grounds, and chrysotile was the fibre of choice for most applications.

Stayner et al.'s review of the issues (1996), sets out similar arguments, and also points to the evidence that all three commercial fibre types have produced a similar level of lung tumours in animal inhalation experiments. This is the most problematic evidence to reconcile with the human evidence that amphibole fibres are substantially more potent lung carcinogens. However, the time periods needed to induce cancer in humans (yr) and in rats (months) are very different, and it is at least plausible that all fibres are equally potent in rats because none of them are materially cleared from the rat lung over the months needed to initiate a rat lung tumour. By contrast, in humans chrysotile (cleared in months) might have less effect than the amphibole fibres (cleared in years). A detailed elaboration of this argument has recently been published by Berry (1999). It may also be relevant that the animal experiments were made with exposure concentrations massively in excess of those represented in the human data. The differences in the human data summarised in this review seem reasonably clear (certainly in respect of mesothelioma), and are based on a range of independent data. In the end, if a choice has to be made between animal and human evidence as a basis for assessing human risk, adequate human data must be given priority.

Many of the arguments presented against the 'amphibole hypothesis' in connection with mesothelioma are variants on the basic theme that it is simply unbelievable that such a small component of the exposure could be responsible for the observed risk. If it is true that the mesothelioma risk is proportional to a less than unit power of exposure, then these arguments are correct in their basic perception that a disproportionate effect of the amphibole component was required to explain the data. Low levels of amphibole *do* have a disproportionate effect.

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Appendix A

EXTRACTED COHORT DATA

The details of extracted data is shown in Tables 12 and 13, with explanatory notes in Tables 14 and 15.

SUMMARISING MORTALITY AND EXPOSURE MEASURES - THE CHOICE OF FOLLOW UP PERIOD IN RELATION TO EXPOSURE PERIOD

LUNG CANCER

For most of the studies considered in this review, mortality was reported for the period 20 or more years from first exposure. The reason for this is that it is assumed that this represents a period in which the effect of exposure will be fully expressed. Deaths observed in the period immediately following first exposure will be unaffected by that exposure, and the effect of exposure will become progressively more apparent as follow up time increases. Comparisons of observed and expected deaths that include periods immediately after first exposure will introduce some downward bias to the assessed risk level.

Evidence on the levels of excess in different periods after exposure suggests that between 10 or 20 and about 40 yr from exposure the lung cancer risk is reasonably stable. Beyond 40 or 45 yr follow up there may be some decline in risk, but the extent to which this may have diluted recorded lung cancer risk in these cohorts seems limited (for example, there is very little difference between the US/Canada insulators lung cancer SMR calculated over all follow up from 20 yr and one restricted to the period between 20 and 40 yr). No adjustment for differences in maximal follow up between cohorts has therefore been applied.

The impact of follow up less than 10 yr being included in the reported results, and the related problem of choosing an average exposure appropriate to the observed mortality needs to be considered. If observed and expected mortality from observations less than 10 yr from first exposure are uninformative of the possible effects of the exposure the inclusion of such observations in the reported results for a cohort, will dilute any actually occurring effect. Provided there is a reasonable amount of informative follow up on every cohort member this dilution effect can probably be ignored, since the observed and expected deaths generated from the early (uninformative) follow up will be outweighed for all individuals by their later observations. But if a high proportion of a cohort generates mainly uninformative follow up, reported overall results may be seriously distorted. This can happen if recruitment to a cohort continues to the end of follow up. Subjects starting within 10 yr of the end of follow up will contribute no informative mortality data.

Table 12. Summary of cohort data (part 1)[a]

Code	Name	Reference	Process	Fibre	Sex	Average age at first exposure	Typical follow up[b]	Predicted mortality for typical follow up from avg. age first exposed[c] — Proportion	Relative to age at first exposure of 30	Number of years latency	Obs	Exp	SMR	Mesothelioma deaths — Total number	% Excess mortality
1	Wittenoom	de Klerk et al. (1994)	M	o	m	29	35	0.24	1.08	10	719	601.8*	1.19	72*	12
2m	Carolina (men)	Dement et al. (1994)	T	y*	m	26	41	0.32	1.34	15	607	410.1	1.48	2	0.49
2f	Carolina (women)		T	y*	f	26	41	0.32	1.34	15	362	299.2	1.21	0	0
3	Johns Manville retirees	Enterline et al. (1987)	I	yao	m	37	65	1	1	age>65	944	762.5	1.24	8	1
4	Ontario	Finkelstein (1984)	C	yo	m	33	27	0.17	0.77	20	108	62.2	1.73	17	27
5a	New Orleans (plant 1)	Hughes et al. (1987)	C	ya*	m	32	35	0.3	0.85	20	259	294.5	0.88	1	0.34
5o	New Orleans (plant 2)		C	yo	m	27	38	0.27	1.26	20	603	614.1	0.98	3	0.49
6	Quebec	Liddell et al. (1997)	M	y	m	23	72	1	1	age>55	6587	5912.7*	1.11	33*	0.56
7	Vocklabruck	Neuberger and Kundi (1990)	C	yo	mf	24	65	0.95	1.05	20	540	530.2*	–	5	0.94
8	US/Canada insulators	Seidman and Selikoff (1990)	L	yao*	m	24	62	0.9	1.09	20	4626	3170.6	1.46	453	14
9	Rochdale	Peto et al. (1985)	T	yo*	m	30	42	0.45	1	20	727	602.5*	1.21	10	1.7
10	Balangero	Piolatto et al. (1990)	M	y	m	27	47	0.51	1.2	20	317	225.4	1.41	2	0.89
11	Pennsylvania	McDonald et al. (1983a,b)	TF	ya*	m	29	40	0.35	1.08	20	895	821.1	1.09	14	1.7
12	Paterson	Seidman et al. (1986)	I	a	m	37	40	0.6	0.63	5	593	355.9	1.67	17	4.8
13a	SA amosite mines	Sluis-Cremer et al. (1992)	M	a	m	31	40	0.4	0.93	0	648	456.3*	1.42	4	0.88
13o	SA crocidolite mines		M	o	m	31	40	0.4	0.93	0	423	333.1*	1.27	20	6
14	Massachusetts	Talcott et al. (1989)	O	o	m	34	37	0.4	0.74	0	28	8.3	3.37	5	60
15	Albin	Albin et al. (1990a,b)	C	yao*	m	30	62	0.98	1	20	592	493*	1.2	13	2.6
16	Connecticut	McDonald et al. (1984)	F	y*	m	31	40	0.41	0.93	20	557	550.7	1.01	0	0
17	Ferodo	Newhouse and Sullivan (1989)	F	yo*	mf	30	45	0.56	1	10	2577	2646.3	0.97	13	0.49

[a]Notes on starred entries in Table 14.
[b]Follow up duration which divides the observation field beyond the minimum latency into two equal areas.
[a]See text.

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Table 13. Summary of cohort data (part 2)[a]

Cohort code	Lung cancer deaths						Average cumulative average exposure (f/ml.yr)	Basis for average exposure estimate (see codes below[b])	Lung cancer risk expressed as % expected lung cancer per f/ml.yr			Mesothelioma risk expressed as		Estimated K_M in HEI model
	Observed	Diagnostic basis (see codes below[b])	Expected	SMR	Excess	% Excess			Cohort Average (R_L)	SMR regression slope	Regression slope internal	% Total expected mortality per f/ml.yr (R_M)		
												Unadjusted	Adjusted for age at first exposure	
1	87	DC	48.7	1.79	38.3	79	23*	ind	3.4	3.1*	0.7 to 5.4*	0.52	0.48	13.8
2m	74	DC	32.2	2.3	41.8	130	28	CatAv	4.6	3*	–	0.017	0.013	–
2f	38	DC	13.8	2.75	24.2	175	26	CatAv	6.7	1*	–	0	0	–
3	73	DC	28.4	2.57	44.6	157	750	CatAv	0.21	0.18	–	0.0014	0.0014	–
4	22	BE	5.3	4.14	16.7	314	60	text	5.2	–*	–	0.53	0.68	13
5a	21	DC	22.5	0.93	–1.5	–6.7	79	CatAv	0	0.03	–	0.0024	0.0028	–
5o	73	DC	50.1	1.46	22.9	46	47	CatAv	0.97	0.76	–	0.0069	0.0055	–
6	587*	DC	431.6	1.36	155.4	36	600	CatAv	0.060*	0.037*	0.012*	0.0009	0.0009	0.011
7	47*	DC	42.2	1.11	4.8	11	25*	ind	0.45	–	–	0.038	0.036	–
8	934*	BE	256.8	3.64	677.2	264	500	L*D	0.53	–	–	0.029	0.027	1.7
9	56*	DC	37.1	1.51	18.9	51	138*	CatAv	0.37	0.51	–	0.022	0.022	0.9
10	19	DC	17.3	1.1	1.7	10	300*	CatAv	0.03	–*	–	0.003	0.0025	–
11	50*	DC	33.8	1.48	16.2	48	60	CatAv	0.80	–*	–	0.029	0.027	–
12	98*	BE	20.5	4.78	77.5	378	65	CatAv	5.8	2.7*	–	0.073	0.117	3.0
13a	21*	DC	14.5*	1.45	6.5	45	23.6*	text	1.9	–	–	0.056	0.06	2.7
13o	19*	DC	10.2*	1.86	8.8	86	16.4*	text	5.2	–	–	0.55	0.59	34
14	8	DC	0.6	13.1	7.4	1210	120*	L*D	10	–	–	0.5	0.68	–
15	35	BE	19.4*	1.8	15.6	80	13	text	6.2	–	0	0.18	0.18	–
16	49	DC	35.8	1.37	13.2	37	46	CatAv	0.80	–*	0.058*	0	0	–
17	241*	DC	242.5	0.99	–1.5	–0.6	35*	con	0	–	–	0.014	0.014	–

[a]Notes on starred entries in Table 15.
[b]DC: Death certificate; BE: Best evidence; CatAv: Exposure category mid points weighted by expected mortality; ind: Mean of individual dose distribution (person weighted); L*D: Mean exposure level times mean exposure duration; text: Value given in text, assumed to be mean of individual dose distribution (person weighted); con: Mean exposure of controls matched to lung cancer cases.

Table 14. Explanatory notes on cohort data

Code	Name	General cohort notes	Fibre type	Obs	Exp	Mesothelioma mortality
1	Wittenoom					
2m	Carolina (men)		Very small amounts of crocidolite yarn were used, but raw crocidolite fibre was not processed. The quantity of crocidolite used was about 0.002% of the total			Deaths to age 65 (evidence of incomplete death ascertainment a older ages)
2f	Carolina (women)					
3	Johns Manville retirees					
4	Ontario	Production and maintenance workers only				
5a	New Orleans (plant 1)	Excl. men with <3 months employment	Mainly chrysotile, amosite used from early 1940s; crocidolite used occasionally from 1962 (too recent to affect observed mortality)			Two additional mesotheliomas at <20 yr latency. A further four occurred after end of formal follow up
5o	New Orleans (plant 2)	Excl. men with <6 months employment	Mainly chrysotile, crocidolite used in pipe production process			
6	Quebec					Excluding Asbestos factory, but including cases at ages <55 and the smaller Thetford mines Table 9 and text
7	Vocklabruck					Observed less 5 mesotheliomas and 4.8 excess lung cancers
8	US/Canada insulators		Nicholson and Landrigan (1996) estimate the exposure to have been 60% chrysotile and 40% amosite, based on published product compositions. Analyses of lung burden in lungs from 16 US insulation workers given by Langer and Nolan (1989) found amosite in all 16, chrysotile in half of them and crocidolite in three.			
9	Rochdale		Predominantly chrysotile, but from mid 1930s a consitent 5% or so was crocidolite.			Expected all cause deaths cannot be restricted to men with >1 yr employment excess mesothelioma - and mean exposure - therefore expressed for whole cohort
10	Balangero					
11	Pennsylvania		About 10% of the fibre processed was amosite. Very small amounts of crocidolite were also used, but little was handled as raw fibre			

(Continued on next page)

Table 14. (*continued*)

Cohort identification		General cohort notes	Fibre type	Deaths By All Causes		Mesothelioma mortality
Code	Name			Obs	Exp	
12	Paterson					
13a	SA amosite mines					Reported expected number reduced to estimate the number relating to 10+ yr from first exposure (details in Appendix C)
13c	SA crocidolite mines					
14	Massachusetts					
15	Albin	Expected number estimated from observed and all cause RR	Mainly chrysotile (>95%), with smaller amounts of crocidolite and amosite. Recent crocidolite use <1%, never > 3-4%. Up to 18% of amosite used briefly during the 1950s. It is not clear which amphibole should be seen as the most important - amosite because of the relatively high percentage used during a limited period or crocidolite because of its regular historic use at low levels.			
16	Connecticut	Data on men exposed<1 year excluded	Chrysotile was the only type of asbestos used until 1957 when some anthophyllite was added for some product lines. About 400 lbs of crocidolite was handled experimentally on a few occasions in the laboratory, but only between 1964 and 1972. Given the small scale and timing of this amphibole use, the cohort has been treated as chrysotile only			
17	Ferodo		Apart from two periods before 1944, when crocidolite asbestos was used on one particular contract, only chrysotle asbestos has been used.			

Table 15. Explanatory notes on cohort data[a]

Cohort code	Lung cancer mortality	Average cumulative exposure (f/ml y)	Lung cancer risk coefficient		Mesothelioma risk coefficient K_M in HEI model
			SMR regression slope	Regression Slope — internal	
1		From Berry (1995)	Coefficient for exposure group covering cohort mean in Berry (1991)	Inferred from analyses in Armstrong et al. (1989) and de Klerk et al. (1991)	From de Klerk et al. (1992)
2m		Table 5	Given in text of main reference; Stayner et al. (1997) give an overall estimate of 2.19		
2f					
3	Excl. 4 mesotheliomas	Table 2	Reported value of 0.56, conversion factor 3		
4	Excl. an estimated 4 mesotheliomas		Exposure specific rates inconsistent, wide range of slopes can be fitted.		
5a	Exluding 1 mesothelioma	Tables 8, 10 and 11			
5o					
6	Data for asbestos factory cannot be consistently excluded, but impact on risk estimate is minor	Table 8	Poisson regression (data in Table 8)	From Liddell et al. (1998) (Table 3)	Fitted value×33/38 to adjust for factory cases
7	Smoking adjusted data for 20+ yr latency from Neuberger and Kundi (1993)	Estimated from Fig. 4 in Neuberger and Kundi (1991)			
8	Excluding an estimated 42 mesotheliomas (half the difference between DC and BE mesothelioma numbers)	The range of exposure conditions likely to have been met by this group, and the long time period over which these exposures were accrued means that any estimate of the levels of exposure will be very approximate. Other reviews have adopted notional values of average exposure level as 15–30 f/ml and average exposure duration as 25 yr, implying a mean cumulative exposure around 500 f/ml.yr, this is likely to be very uncertain estimate.			
9	Excluding workers with <1 yr employment	Overall mean is 73 f/ml.yr (Table 16); mean exposure duration 7.9 yr (Table 7); thus mean level around 10 f/ml; half the man years contributed by short term men (Table 8); assuming exposures of 5 f/ml.yr for short term men implies exposure of 138 f/ml.yr for men with >1 yr exposure.			
10		From Table 3: the result is sensitive to the choice of mean dose in the highest category (which covers 30% of men). With the top dose mean set at 500 f/ml.yr the overall mean is 250, increasing to 400 if the top dose mean is set at 1000 f/ml.yr. A value of 300 has been adopted for this review.	Reported dose specific data has not been used here, since comparison of the man-years in the dose specific categories of Table 3 of Piolatto et al. (1990) with the number of men in each category strongly suggests that all the man-years of follow-up for men in each category has been assigned to the dose category they eventually achieve, the exposure response is thus biased downwards by an unknown amount.		

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Table 15. (continued)

Cohort code	Lung cancer mortality	Average cumulative exposure (f/ml y)	Lung cancer risk coefficient		Mesothelioma risk coefficient K_M in HEI model
			SMR regression slope	Regression Slope — internal	
11	Excluding three (McDonald, personal communication) mesotheliomas. Expected multiplied by reported by SMR for lowest exposure category (0.669)	Table 5			The dose categories of the three mesotheliomas coded as respiratory cancer not known, so an adjusted exposure-response cannot be fitted.
12	Excluding an estimated four mesotheliomas	Table XVI	Poisson regression (Table VI)		
13a 13o	Observed an expected reduced by the estimated expected numbers within 10 yr from first exposure (See Appendix C). Observed numbers also reduced by the estimated number of mesotheliomas coded to lung cancer (1 in 13a, 5 in 13o)	Reported means adjusted to reflect weighing of expected mortality >10 yr from first exposure (see Appendix C)			
14 15	Lung cancer taken to be respiratory cancer excluding pleural mesothliomas, RR interpreted as SMR	Burdett, personal communication (see Appendix B)			
16	Table 3				Mortality data were reported by cumulative exposure, but high mortality in short term workers makes interpretation of this data difficult. The highest respiratory cancer mortality is seen in the lowest exposure category. This remains the case if short term workers are excluded: low-dose men in all employment duration categories had high levels of respiratory cancer mortality (Table 8). The most likely explanation seems to be that exposures have been wrongly assigned at the individual level. The available job details generally only allowed worker histories to be described by department, rather than process. Because of this the exposure–response data is not used here.
17	Total observed lung cancer=lung and pleural cancers less pleural mesotheliomas	From Berry and Newhouse (1983) (mean exposure of lung cancer controls)			From Berry and Newhouse (1983) (case control, analysis)

aTables or figures referred to are those found in the main references listed in Table 12, unless otherwise specified.

DEFINITION OF AVERAGE EXPOSURE

The inclusion of large numbers of cohort members who contribute no informative follow up may also bias the average exposure. An appropriately weighted average exposure will give zero weight to individual exposures in this group. If only a simple mean is used, and if this late entrant group is large and has—as is likely—systematically lower exposures, the apparent cohort exposure will be too low in relation to the observed mortality, and the estimated risk per unit exposure will be exaggerated.

REVIEW OF COHORTS WITH POTENTIAL EFFECT DILUTION OR BIASSED EXPOSURE AVERAGES

The potential biases discussed in the preceding paragraphs will not apply where the reported mortality excludes observations before the tenth year of follow up (or a later year), and where the average exposure has been weighted by expected lung cancer mortality. This leaves the following cohorts as potentially affected: Wittenoom, Ontario, Vocklabruck, US/Canada insulators, Balangero, Paterson, SA mines, Massachusetts, Albin and Ferodo. Table 16 summarises the relevant data.

The possibility of dilution due to uninformative follow up needs to be considered for the SA mines and for the Massachusetts and Paterson cohorts. This can certainly be ignored for Massachusetts and Paterson cohorts, because of their combination of limited recruitment period with long follow up. It cannot be dismissed for the SA mines, and an adjustment will be developed below (Appendix C).

The possibility that a simple mean of individual exposures (the available figure) will be a poor proxy for the desired average weighted by expected lung cancer mortality needs to be considered for all the cohorts listed in Table 16. For all but one there are reasons (summarised individually below) for believing that the available figure is an acceptable proxy.

- For **Wittenoom**, the measure of excess mortality used has been truncated at subjects' 65th birthdays. The effect of this is broadly to equalise the follow up durations (and therefore the expected mortality weights) of different first exposure groups.
- The recruitment period of the **Ontario** cohort is relatively short, and no mention is made of major variations in exposure conditions.
- Only 18% of the **Vocklabruck** cohort started their exposure after 1969: described as 'the decisive year in improving the dust situation'.
- The basis for the 'mean' exposure in the **US/Canadian insulators** cohort (drawn from previous reviews) is very uncertain. It is not based on averaging known or estimated individual exposures. It is plausible that conditions may not have changed greatly over the relevant period (up to 1966).
- The narrow range of first exposure dates for the **Massachusetts** cohort implies limited scope for changes in average levels, and the long minimum follow up also means that even if there were such changes, the weighting applied to early and late entrants would be similar.
- Comparison of the most recent follow up report on the **Balangero** mine cohort with a previous report (recruitment to 1965, follow up to 1975), suggests that only a relatively small proportion of the latest cohort were first exposed after 1965; though it is not entirely clear how the two cohorts relate to each other, and the minimum employment qualification time was more restrictive (1 yr) for the later report than for the earlier (1 month), so the comparison is not straightforward. There was reportedly little change in exposure conditions between 1946 and 1960. Some downward bias in the derived exposure average is possible, but the extent of this is difficult to quantify. Even on an unadjusted basis, the derived risk per unit exposure for this cohort is one of the lowest seen.

Table 16. Recruitment and follow up configurations for cohorts with potential effect dilution or biassed exposure averages

Cohort	Numbers of years latency	Recruitment		follow up		Maximum follow up (yr)	Follow up on latest entrants (yr)
		From	To	From	To		
Wittenoom	10	1943	1966	1943	1986	44	20
Ontario	20	1948	1959	1948	1977	30	18
Vocklabruck	20	1907	1979	1950	1990	84	11
US/Canada insulators	20	1907	1966	1967	1986	80	20
Balangero	20	1930	1986	1946	1987	58	1
Paterson	5	1941	1945	1941	1982	42	37
SA mines	0	1925	1980	1946	1980	56	0
Massachusetts	0	1951	1953	1953	1988	38	35
Albin	20	1907	1977	1927	1986	80	9
Ferodo	10	1920	1977	1942	1979	60	2

- For the **Albin** cohort, major exposure changes started to apply only from the late 1960s, the last 10 yr of 70 yr of intake. The scope for bias is therefore limited.
- The average exposure used for the **Ferodo** cohort is that of controls matched to lung cancer cases. It is therefore—indirectly—weighted in the appropriate way.

The one exception is the **SA mines** cohort. The report on this cohort shows that a large proportion of the cohort (amosite and crocidolite workers combined) were first exposed less than 10 yr from the end of follow up. Illustrative exposure data is also shown which implies that these workers were exposed to levels 4–6 times lower than those which applied before about 1950. Some adjustment to the reported individual mean exposure is therefore indicated.

This adjustment, and the related adjustment to exclude observed and expected mortality arising from uninformative follow up are described in detail in Appendix C. Briefly, we conclude that both the observed excess lung cancer and the associated cumulative exposure should be adjusted upwards, the exposure by rather more than the mortality excess. The implied dose specific risk is reduced by about a quarter.

SUMMARY MEASURES FOR MESOTHELIOMA

Mesothelioma incidence rate rises very steeply with time since exposure, and this complicates the choice of a summary measure that will be properly comparable across cohorts. Comparisons between cohorts with different follow up times (or different mixes of follow up times) should be adjusted to allow for the impact of those differences on the observed mesothelioma mortality. One solution is to fit a statistical model. The following formulation was used in the HEI report, and is fairly typical:

$$r = K_M \cdot L \cdot [\{t-10\}^3 - \{t-10-D\}^3]$$

where L is exposure level expressed in f/ml, D is exposure duration in yr and the contents of the curly brackets {} are set to zero if<0.

However not all cohorts have the data needed to fit the HEI (or similar) models. A pragmatic way of making an equivalent adjustment is to express observed mesothelioma numbers as a percentage of expected mortality from all causes, since this too is a measure which increases steeply with follow up time.

The expected mortality from all causes has one drawback as a denominator for mesothelioma risk: it is dependent on age at first exposure. This would not be a serious problem if the mean age at first exposure was similar in different cohorts, but this is not the

case. For those cohorts for which the mean age at first exposure is given or can be estimated, it ranges from 23 for Quebec to 37 for Paterson, with a mean across cohorts of about 30. We have therefore standardised the expected all cause mortality figure given for each cohort to an assumed mean age at first exposure of 30. The amount of adjustment applied has been calculated using the following formula:

$$E_{Adj} = E_A M_{30}/M_a$$

Where E_{Adj} is the adjusted expected all cause mortality to be used as denominator for the observed mesothelioma mortality; a is the mean age at first exposure for the cohort in question; E_A is the actual expected all cause mortality from the person years in which the mesotheliomas arose; M_{30} and M_a are proportional expected all cause mortality estimates for the 'typical' follow up duration for the cohort (the follow up duration that divides the observation field beyond the minimum latency into two equal areas) from ages 30 and a respectively. The schedule of all cause death rates used to calculate M_{30} and M_a, was rate=$\exp(-9.61+.0936a)$—where a is age in yr—which provides a close fit to male all cause mortality in Australia, Austria, USA and Great Britain (using data taken from the mid 1970s). The fit is less good for South African and for Swedish death rates, but the adjustment depends on the ratio (M_{30}/M_a) of expected deaths in different—and quite wide—age ranges, a measure that is not sensitive to the precise underlying life table. So for convenience the same life table approximation was used for all cohorts. For the two cohorts where mean age at first exposure was not available (Rochdale and Albin), a mean age of 30 was assumed.

A similar argument to that set out above in relation to the effect of uninformative follow up on recorded lung cancer mortality in the SA mines cohorts also applies to the excess mortality from mesothelioma. All the recorded mesotheliomas in these cohorts occurred more than 10 yr from first exposure. An estimate of the expected all cause mortality arising from follow up less than 10 yr from first exposure has been subtracted from the reported total expected all cause mortality, and this adjusted figure used as the denominator for excess mesothelioma mortality in these cohorts. Details of this calculation are given in Appendix C.

COMPARISON OF COHORT AVERAGE RISK MEASURES WITH ALTERNATIVES BASED ON INTERNAL COMPARISONS

For reasons explained in the main report, this review has taken cohort level measures of exposure and outcome as the basic units of observation. In the next two sections these cohort-level measures are compared to the corresponding internal analyses for those cohorts where both are available.

COMPARISON OF RISK MEASURES—MESOTHELIOMA

For cohorts where details of mesothelioma deaths and person years by time from first exposure were given, the HEI model fitted to these rates. The model was fitted using values for individual calendar years of time from first exposure aggregated to give the reported latency categories. Best fit was assessed by maximum likelihood methods assuming a Poisson distribution, and the resulting estimates of K_M are shown in Table 12.

Figure 10 compares the two alternative measures of mesothelioma risk: the HEI coefficient K_M and the percent excess mortality per f/ml.yr index R_M. There is good agreement between these measures. The most discrepant point relates to the Quebec cohort (code 6), though this is on either measure clearly the lowest value. It may be relevant that the HEI parameter K_M for the Quebec cohort was calculated using data based on age at death as a proxy for time since exposure, since this will have introduced additional inaccuracy. The HEI formula may be preferred for the purposes of risk projection, but the alternative measure seems to provide an equally valid summary of the relative levels of mesothelioma risk in these cohorts.

COMPARISON OF RISK MEASURES—LUNG CANCER

Where exposure response regressions were reported by authors, the regression slope has been noted: this provides the 'regression slope' estimate of the lung cancer risk. For cohorts where dose-specific SMR data had been reported, but no regression analysis was reported, a Poisson regression fit was calculated.

The association between the cohort average estimate of R_L with the regression slope estimate, for studies where both measures were available is shown in Fig. 11. There is a clear overall relationship, viewed across the whole risk scale. The discrepant points are those with substantial statistical uncertainty, either because they are based on small differences between observed and expected cases (5a—New Orleans, plant 1; and 17—Ferodo) or because of uncertainties deriving from the small size of the reference population (15—Albin).

The most discrepant point relates to the Albin cohort, which was analysed as an unmatched case-control study in relation to a control cohort of non-asbestos exposed industrial workers from the same area. The overall RR for respiratory cancer excluding mesothelioma was 1.8 (though with a wide confidence interval: 0.9–3.7) and the mean cumulative exposure was 13 f/ml.yr, giving a cohort average estimate of R_L of 6.2% per f/ml.yr (with an even wider confidence interval: −0.8–21). The value of the internal regression slope in relation to exposure is not reported, though we are told that it was not statistically significant ($P=0.5$). Inspection of the RRs for the three exposure categories implies that the slope would have been about 0.05. Whether this discrepancy reflects inaccuracy in the baseline, or in the exposure measurements (or a mix of these) is difficult to say. The high mesothelioma risk in this cohort tends to suggest that the cohort average measure is nearer the truth, but substantial uncertainty must remain.

A further discrepant point relates to women in the Carolina cohort (2f), where the regression implies $R_L=1$, while the cohort average gives $R_L=6.7$. The authors suggest that the low regression slope may reflect uncertainties in women's employment histories (which would tend to flatten the regression slope).

There is some tendency for the cohort average estimate to be larger than the corresponding regression
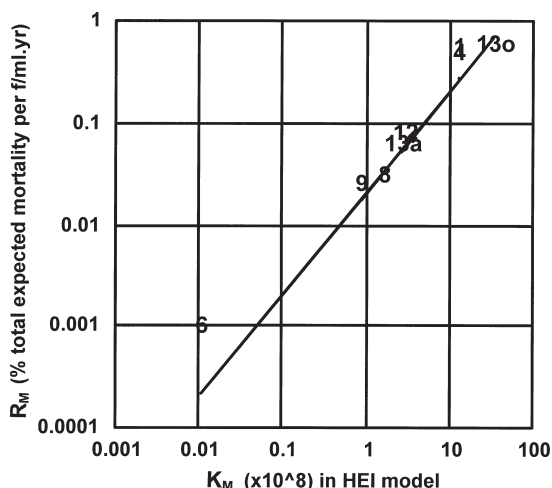

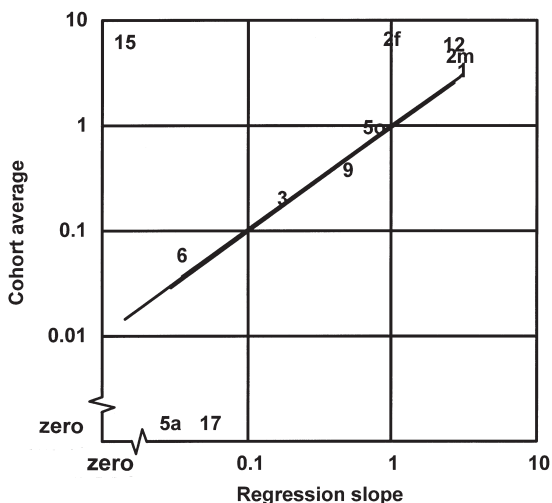Fig. 10. Comparison of alternative measures of mesothelioma mortality.

Fig. 11. Comparison of alternative measures of lung cancer mortality.

slope for those cohorts with clearly positive results. This might be predicted from the flattening of regression slopes by inaccuracies in exposure estimates. But it can also reflect inadequacies in baseline rates. For example, the two-fold difference between the cohort average and regression slope measures for the Quebec cohort reflects the SMR of about 1.3 seen in all the low dose subgroups, and which the authors interpret as non-asbestos related. Nevertheless, the broad agreement between the two measures across studies suggests that valid conclusions can be drawn from the cohort average measure.

ably present assuming some exhaust control on the bag opening, carding and mixing areas. Unfortunately no mention of the control system is made.

Also it is probably an average value that has been given for both the wet and dry methods as both were in use. It is probable given that the sampling locations are unknown that higher concentrations occurred in the dry areas: around 100 f/ml as measured by the current method.

Of course this is very approximate, but 100 f/ml looks to be a good maximum exposure with TWA of 60 f/ml.

Appendix B

FIBRE–PARTICLE CONVERSION FOR CROCIDOLITE CIGARETTE FILTER COHORT NOTE BY DR G. BURDETT

The measurements in 1952 which gave an average of 80 particles per ml, within the Massachusetts standard of 175 particles per ml, almost certainly refer to impinger measurements, which were frequently made for insurance company purposes.

The normal units are millions of particles per cubic foot (mppcf). As one cubic foot is equivalent to 28 316.8 ml the value of 80 particles per ml is equivalent to 2.265 mppcf and 175 particles per ml is equivalent to 5 mppcf.

Five mppcf was the threshold value in force from the 1930s to the 1960s (maybe even until 1972) when it was replaced by a membrane filter limit of 10 f/ml, which has been falling ever since.

As the units suggest, the method only counted particles using relatively low powered microscopy and would overlook many of the respirable fibres and is a very indirect measurement of the fibre level. It should also be remembered that impingers have poor capture efficiency below 1 μm.

It is also noted that cotton and acetate fibres were mixed, carded and deposited on crepe paper under dry conditions. This would suggest that fibres made up many of the particles but I have not referred to the patent to work out quantities used to estimate the fibre percentage.

My best guesstimate is that 30% of the particles were fibres but only about 10% of the fibres seen would be crocidolite (it is more dusty, but has very few >1 μm fibres compared to the other dusts).

This would mean about 3% of the count was crocidolite fibres or about 2.5 f/ml>1 μm wide. To convert to the current index we generally find one can assume only some 4% of the >5 μm long crocidolite fibres were visible as compared with the current index. This is equivalent to a concentration of about 60 crocidolite fibres per ml using a modern version of the membrane filter method.

This is several times higher than the better factories at this time but not too far away from what was prob-

Appendix C

DEVELOPMENT OF ADJUSTMENTS TO THE SOUTH AFRICAN MINES COHORT DATA

The starting point for the adjustment of the reported results from this cohort is the data given in Tables 1 and 2 of the published paper, which give illustrative data on exposure levels in different periods (Table 1) and a breakdown of the whole cohort by year of birth and date of first exposure (Table 2).

The average age at first exposure of the groups represented by the cells of Table 2 can be estimated using the mid points of the year of birth and year of first employment categories (1900 and 1935 were assumed for the earliest birth and employment categories respectively). Age specific all cause and lung cancer rates for white South African men in 1955, 1965 and 1975 were then used to calculate the distribution of expected lung cancer deaths by time since first exposure in each cell. The rates for 1955 were also used for the cells relating to first employment between 1941 and 1950, but the expected number was reduced by a factor of 0.64 to allow for the fact that cause specific follow up was only recorded from 1949.

The total expected lung cancers calculated in this way (39.3) agrees quite closely to the value reported in the paper (36.6) and the proportion of expected lung cancer deaths arising from follow up less than 10 yr from first exposure is 0.23. The reported observed and expected lung cancers in the two pure fibre subcohorts have therefore been reduced by 0.23 times the expected numbers given.

The data reported in Table 1 was used to estimate approximate relative exposure levels at ten year intervals from 1945. Taking 1945 as 1, the numbers used were 1, 0.6, 0.35, 0.25 for amosite; and 1, 0.5, 0.25, 0.15 for crocidolite. Exposures in the 1930s were assumed to be the same as in the 1940s. To derive an expected lung cancer weighting for this relative exposure pattern, the expected lung cancers in each birth-start cell from the 10th anniversary of first employment to the end of follow up in 1980 was calculated in a similar way to that described for the first 10 yr of follow up. The resulting distribution of

Table 17. Derivation of correction factor for reported mean exposure using assumed relative exposure and weighting factors by year of first employment in asbestos mines

Data item	Year of first employment					Mean weighted by	
	Before 1940	1941–50	1951–60	1961–70	1971–80	Persons	Expected lung cancer
Relative exposure							
Crocidolite	1	1	0.5	0.25	0.15	0.35	0.6
Amosite	1	1	0.6	0.35	0.25	0.44	0.68
Weighting factors						Totals	
Persons	62	404	2355	2408	2088	7317	
Expected lung cancers >10 yr from 1st exposure	1.68	6.75	17.59	4.36	0	30.38	

expected lung cancers in the five date of start groups is shown in Table 17.

Table 17 also shows the numbers of individuals in each group, and the assumed relative levels of exposure. Mean exposures are calculated using the two alternative weightings. The expected lung cancer weighted means are larger than the corresponding person weighted means by a factor of 1.71 for crocidolite and 1.55 for amosite. The reported mean exposures have been adjusted using these factors for use in this review.

Similar calculations for all cause deaths imply that the proportion of expected all cause deaths falling in the first 10 yr of follow up is 33%. The all cause mortality denominator for the observed mesotheliomas in the two subcohorts has therefore been reduced by a factor of 0.67.