

**The quantitative risks of mesothelioma and lung cancer
in relation to asbestos exposure
– a comparison of risk models based on asbestos exposed cohorts**

Introduction and aims

1. In 2000, we published quantitative risk estimates for lung cancer and mesothelioma in relation to asbestos exposure based on statistical models fitted to data extracted from published studies of asbestos exposed cohorts¹. Risks were quantified separately for chrysotile, amosite and crocidolite using data derived from studies of cohorts involving exposure exclusively or predominantly to these single asbestos types. Mesothelioma and lung cancer risks in relation to amphibole (amosite and crocidolite) exposure were found to be substantially higher than those in relation to chrysotile. Crocidolite was found to pose the highest mesothelioma risk – which, at the exposure levels typical of occupational cohorts (average cohort exposures typically 10-1000 f/ml.yr), was about 500 times that due to chrysotile. For lung cancer the risk differential was lower but still substantial – the risk being between 10 and 50 times greater for both amphibole types than chrysotile.

2. More recently, in work commissioned by the United States Environmental Protection Agency (EPA), Berman and Crump also produced quantitative risk estimates separately for amphibole and chrysotile asbestos using data available from existing cohort studies². Despite different methodology the results were broadly consistent with those from our analyses – that is, risks from amphibole exposure were substantially higher than those from chrysotile – particularly in the case of mesothelioma. This is not surprising given that the relatively small number of cohorts reporting quantitative exposure estimates for exposures to single types of asbestos resulted in both analyses being based on largely the same source data. The fact that a small number of cohorts were not common to both analyses was due to the availability of studies when the work was carried out and the data required for applying the different methodologies used.

3. These risk models are potentially useful in estimating risks in relation to asbestos exposure scenarios not typical of the original occupational cohorts. In particular, most interest is likely to be in estimating the risks at substantially lower exposures. In order to help inform considerations of how reliable these models are likely to be for estimating risk at these levels, it is of interest to compare risk estimates based on each of the models across a range of cumulative exposures. This paper presents such a comparison as well as a discussion of a number of issues which relate to the application of these models in general – and which may be particularly relevant when considering low level exposures.

Summary of the risk models

Hodgson and Darnton (HD) models

4. In our analysis (referred to as “HD” from now on), we used cohort-level summary data to fit models for mesothelioma mortality (as a proportion of expected total mortality in order to allow for differing follow up times) and proportional excess lung cancer mortality in relation to cumulative asbestos exposure, taking into account the fibre types for the exposures within each cohort. At the time of analysis 20 cohorts were available with necessary information published to allow construction of the summary measures of mortality and cohort average cumulative asbestos exposures (see Appendix 1). In 10 of these cohorts, exposures were to single types of asbestos (3 cohorts with exclusively crocidolite exposures, 2 with amosite and 5 with chrysotile), the remainder involved mixed exposures. We also studied the relationship between pleural and peritoneal mesothelioma risk for cohorts with exposures to single amphibole asbestos types where quantitative exposure information was unavailable.

5. Our analyses led to risk models for mesothelioma (with separate terms for the pleural and peritoneal mesothelioma risk) and relative risk models for lung cancer in relation to cumulative asbestos exposure which are non-linear in form (see Appendix 2). They describe mesothelioma and lung cancer risk in terms of cumulative asbestos exposure and fibre type. To allow for the effects of age of first exposure, risk measures for mesothelioma for individual cohorts were adjusted for exposure starting at age 30 (the average for all cohorts) before fitting, and adjustment factors for the risk for exposures starting at younger or older ages were developed from the HEI mesothelioma model³. The models assume that the cumulative exposures are accrued over relatively short exposure durations – typical durations within cohorts being about 5 years.

Berman and Crump (BC) models

6. In the analysis by Berman and Crump (referred to as “BC”), a common risk model for lung cancer and a second model for mesothelioma was fitted separately to dose-response data within cohorts. For mesothelioma, 12 cohorts were available with suitable data to enable model fitting; for lung cancer 18 cohorts had suitable data (Appendix 1). In order to determine what values of the model coefficients should be used for risk estimation in generalised exposure scenarios, an attempt was made to explain the substantial variation in the coefficients from the individual model fits by accounting for the type of asbestos and likely size distribution of fibres in the various exposure settings. The motivation for this methodology was the development of an exposure metric which counts only long thin fibres (>10 µm long, < 0.4 µm wide) via Transmission Electron Microscopy (TEM) and thus relates more closely to biological activity than the more usual exposure metric which counts “regulated fibres” (those >5 µm long, aspect ratio >3:1) via Phase Contrast Microscopy (PCM).

7. The BC analyses employed the HEI model in which mesothelioma risk is proportional to the exposure concentration multiplied by time since first

exposure raised to the power of three. In the BC lung cancer model, the excess relative risk is simply proportional to the cumulative asbestos exposure. Lifetime risks based on these models are thus of a linear form. Potency coefficients for amphibole and chrysotile exposures are given for both the recommended exposure metric (which counts only long thin fibres) and the Phase Contrast Microscopy Equivalent (PCME) metric.

8. The HD model coefficients are dependent to some extent on judgements about the interpretation of certain cohorts. In particular, the cohort of chrysotile textile manufacturing workers in South Carolina showed a large excess of lung cancer with relatively low exposures. This observation is problematic since other cohorts with lower risks but higher exposures then seem to imply a negative relationship between risk and chrysotile exposure. We concluded that the results of the chrysotile cohorts alone don't provide a sufficient basis for determining the exposure-response shape for lung cancer. Instead, we based the chrysotile shape on the amphibole results, scaling the level of risk downwards in line with the observed risk at the average exposure level of chrysotile cohorts. Berman and Crump conclude that the high observed lung cancer risk in the Carolina cohort is explicable in terms of the likely distribution of fibre sizes in the exposures in this particular industrial setting.

Comparison of the models

Methods

9. In order to illustrate the broad similarities and differences in the predictions of the HD and BC models, a comparison of lifetime risk estimates for mesothelioma and lung cancer are presented in Tables 1 and 2 below for a range of cumulative exposures based on the format of Table 11 of our original paper.

10. Lifetime risk estimates based on the HD models were calculated using the methodology set out in our original paper. Corresponding risk estimated based on the BC models were calculated according to the methodology set out in Appendix E of their report using British all cause mortality and lung cancer mortality data. The relevant PCME potency coefficients provided in Table 7-17 of the Berman and Crump report were used rather than coefficients for the model for the modified exposure index. In each scenario presented, exposures are assumed to be accrued over a five year period starting at age 30.

11. Our original presentation in Table 11 only included estimated lifetime risks of 1 per 100,000 or greater, since lifetime risks below this are equivalent to annual risks below 1 per million which are usually regarded as insignificant. This resulted in exposures of 0.005 f/ml.yr being the lowest considered, and this approach is repeated here. Where risk estimates below 1 per 100,000 are presented (by virtue of other risk estimates for same exposure being above 1 per 100,000) they are shown as "<1" in the tables. For each exposure scenario, the ratio of the HD to BC risk estimate is given. Since the HD analyses led to separate mesothelioma models for crocidolite and amosite

exposures, the mid point of these two risk estimates was used to calculate the ratio for amphibole exposure. HD risk estimates are based on our “best” model with uncertainty ranges based on the “minimum” and “maximum” alternative models shown in brackets.

Table 1: Estimated lifetime risk of mesothelioma and lung cancer per 100,000 in relation to chrysotile asbestos by model (HD or BC) and cumulative exposure.

Cumulative exposure (f/ml.yr)	Mesothelioma			Lung cancer		
	HD	BC	HD/BC	HD	BC	HD/BC
10	25 (5-70)	10	2.7	30 (15-250)	100	0.3
1	5 (1-20)	1	4.8	2 (<1-25)	10	0.1
0.1	1 (<1-5)	<1	8.4	<1 (<1-5)	1	0.1
0.01	<1 (<1-1)	<1	15	<1	<1	0.03
0.005	<1 (<1-1)	<1	18	<1	<1	0.03

Table 2: Estimated lifetime risk of mesothelioma and lung cancer per 100,000 in relation to amphibole asbestos by model (HD or BC) and cumulative exposure.

Cumulative exposure (f/ml.yr)	Mesothelioma			Lung cancer		
	HD	BC	HD/BC*	HD	BC	HD/BC
10	croc: 4000 (2500-6000); amos: 550 (150-1500)	3000	0.7	1500 (800-2500)	300	6
1	croc: 650 (250-1500); amos: 90 (15-300)	300	1.3	85 (20-250)	30	3
0.1	croc: 100 (25-350); amos: 15 (2-75)	30	2.2	5 (1-25)	3	1.5
0.01	croc: 20 (2-85); amos: 3 (<1-20)	3	4	<1 (<1-3)	<1	0.8
0.005	croc: 10 (1-55); amos: 2 (<1-15)	1	5	<1 (<1-1)	<1	0.6

*Ratio for amphibole based on the average of HD amosite and crocidolite estimates.

Overall comparison

12. There are some important similarities between the risk estimates based on the HD and BC models. Both predict that risks due to amphibole exposure are substantially higher than those due to chrysotile – particularly in the case of mesothelioma. In addition the BC estimates lie consistently within the uncertainty ranges of the HD models. However, given the substantial degree of uncertainty reflected in these ranges, this fact still allows some considerable differences to remain. In particular, over the range of exposures presented, the BC models predict a larger differential in mesothelioma risk for amphibole vs chrysotile exposure (300:1) than the HD models (approximately 150:1 for crocidolite vs chrysotile for exposures between 0.1 and 10 f/ml.yr). Conversely, the BC models predict a smaller differential in lung cancer risk for the fibre types (3:1) compared with the HD models (50:1).

Chrysotile exposure (Table 1)

13. The largest differences between the HD and BC estimates are for mesothelioma and lung cancer in relation to chrysotile exposure, with estimates diverging as exposures reduce – the largest differences being restricted to the range of exposures for which estimated risks are “insignificant” (below 1 per 100,000). For mesothelioma in relation to chrysotile, the BC model predicts that the risk is insignificant below about 1 f/ml.yr, whereas the HD model predicts that this occurs at exposures around an order of magnitude lower (0.1 f/ml.yr), though with substantial uncertainty. In fact Berman and Crump note that their results could be consistent statistically with there being zero risk of mesothelioma in relation to chrysotile. In contrast, for lung cancer in relation to chrysotile exposure, the BC model predicts substantially higher risks than the HD model. Based on the HD models, the case for a threshold (zero, or at least very low risk) becomes strongly arguable at about 0.1 f/ml.yr.

Amphibole exposure (Table 2)

14. There is broad agreement between mesothelioma risk estimates based on the combined BC amphibole model and separate HD models for crocidolite and amosite. At higher exposures the predictions of the BC model are closer to the HD crocidolite model. At lower exposures the BC model predicts fewer deaths than both the HD crocidolite and amosite models with the risk predicted to be insignificant below 0.005 f/ml.yr. For lung cancer in relation to amphibole exposure there is better agreement between the HD and BC estimates at lower exposures, both predicting that the risk becomes insignificant below about 0.01 f/ml.yr.

Discussion

15. Though there is a broad level of agreement between the HD and BC risk estimates, the differences described above reflect the considerable inherent uncertainties in the models themselves – largely due to limitations in the exposure measurements available in historic studies – and their different mathematical forms.

16. The exposure metric based on Phase Contrast Microscopy (PCM) is likely to be limited for two main reasons. Firstly, there is the issue of how closely the measurements taken or estimated in the various studies actually relate to personal exposures. For the cohort studies underlying the HD and BC analyses, construction of exposure histories may have involved use of measurements taken at the plant, process or job-task level, extrapolation of earlier exposures on the basis of more recent measurements, and the conversion of historic measurements in the form of particle counts into fibre counts. Secondly, there is the issue of how well exposures as measured by PCM relate to biologically relevant doses. The proportion of fibres counted within PCM measurements which actually constitute a hazard may vary considerably between measurements – particularly across different industrial settings where distributions of sizes and shapes of fibres are known to have varied.

17. Exposure-response regressions with inaccurate individual exposure assignments, or where the exposure metric itself is a relatively poor measure of dose, will produce a slope estimate biased downwards. This led us to suggest that models based on global assessments of average exposure and overall mortality outcomes may be preferable to those based on within-cohort dose-response relationships. The inclusion of a parameter in the BC lung cancer model to allow for the fact that occupational cohorts may have different background lung cancer mortality rates than the control populations (for example, where smoking habits differ) will affect the gradient of the slopes in some of the individual fits of the model to cohort-level data. Berman and Crump also concluded that the substantial variation in fitted slopes (for both mesothelioma and lung cancer) is largely a result of the fact that the PCM metric is not an adequate measure of the relevant dose. This led them to develop an exposure metric more closely associated with biological activity, in which only long thin fibres are counted. Assessments of risk for exposures measured via PCM using either the HD models or the BC PCME (Phase Contrast Microscopy Equivalent) models with no adjustment for fibre size will inevitably comprise a substantial degree of uncertainty – even at levels of cumulative exposure typical of the original cohorts.

18. The mathematical form of the models also has an effect on the comparisons described above. The HD models are non-linear whereas the BC models are linear. For example, in the HD mesothelioma model for amphibole exposure, the mesothelioma risk has two components: one for pleural and the other for peritoneal mesothelioma. The pleural mesothelioma component dominates other than at the highest exposures and this is proportional to cumulative exposure raised to a power less than 1 (See Appendix 2). The resulting risk estimates are therefore higher than those predicted by a linear model (where cumulative exposure has an exponent of 1 and with the same proportionality coefficient) at exposures below 1 f/ml.yr, and this effect becomes more pronounced moving down the exposure scale. The effects of the non-linearity in the HD models are evident in the comparisons in Tables 1 and 2 and account for the fact that the HD/BC ratios shown are non-constant, despite all models passing through the origin. For example, for mesothelioma in relation to amphibole exposures, at 10 f/ml.yr the HD/BC ratio is 0.7 compared with 4 at 0.01 f/ml.yr. In other words, though the models are broadly in line at higher exposures, the HD model predicts substantially higher risks than the BC model at lower exposures.

19. The range of cumulative exposures in the original cohort studies was approximately 10-1000 f/ml.yr (though some of the exposure categories in the cohort-level dose-response data used in the BC analyses were below 10 f/ml.yr.) Most of the cumulative exposures shown in Tables 1 and 2 are well below this range. Although we have suggested there is evidence for non-linear dose-response models for both mesothelioma and lung cancer, it is not possible to determine whether these relationships hold at the lowest exposure levels. In the absence of any clear evidence to prefer non-linear models at these levels – and given the substantial uncertainties in models based on the PCM exposure metric – the versions of the linear BC models optimised for

use with the modified exposure metric based on TEM are likely to provide a more adequate basis for estimating risks at the lowest exposure levels.

Estimating risks for exposures at the current control limit

20. The Control of Asbestos Regulations 2006 have a single control limit for all types of asbestos of 0.1 f/ml. The control limit is a maximum concentration of asbestos fibres in the air (averaged over a continuous 4 hour period) that must not be exceeded. Clearly this means that exposures at the control limit could lead to a wide variety of cumulative exposures (and therefore risk estimates) depending on the duration of exposure. The extent of the extrapolation of the risk models required to estimate risk at the control limit therefore depends on exposure duration. Table 3 illustrates the kind of exposure durations which would lead to the cumulative exposures considered in Tables 1 and 2 for various exposure scenarios if the concentration of exposure was the level of the current control limit. For example, in order for those exposed for half of their working hours to achieve a cumulative exposure of 0.1 f/ml.yr exposure at the control limit would need to take place for 2 years. All exposure durations are calculated in relation to working time, taken as 8 hours per day, 5 days per week and 48 weeks per year. Continuous exposure is taken to be twice working time exposure.

Table 3: Exposure durations for five exposure scenarios in order to produce cumulative exposures considered in Table 1 if the exposure concentration was 0.1 f/ml

Cumulative exposure (f/ml.yr)	Exposure scenario				
	Continuous	Working time	Half working time	1 hour per work day	1 hour per work week
10	50 years	> lifetime	> lifetime	> lifetime	> lifetime
1	5 years	10 years	20 years	80 years	> lifetime
0.1	6 months	1 year	2 years	8 years	40 years
0.01	2.5 weeks	5 weeks	10 weeks	38 weeks	4 years
0.005	6 days	2.5 weeks	5 weeks	19 weeks	2 years

21. Table 3 shows that exposures at the control limit, even if they took place for a lifetime, would result in cumulative exposures below 10 f/ml.yr (the bottom of the range of average cumulative exposures in the original cohort studies.) More plausible exposure scenarios at the control limit – for example, 1 hour per work day – would have to be repeated for over a decade in order for the cumulative exposure to be within an order of magnitude of this.

Further considerations for extrapolation to low exposures

Effect of age and exposure duration

22. The risks presented in Tables 1 and 2 are for exposures accrued over relatively short periods of time (5-years) during working hours and at working age (exposures starting at age 30). However, where the focus is on estimating risks from low-level exposures, some scenarios may entail extended exposure periods starting from earlier ages. A given cumulative exposure accrued over periods much longer than 5 years will give rise to

lower mesothelioma risks than those shown in Tables 1 and 2. This is because a substantial portion of the exposure will occur at older ages and therefore contribute less risk than if all the exposure occurred earlier in life. However, this effect may be outweighed if exposures start at younger ages. For example, the HD risk estimate for a cumulative exposure of 10 f/ml year to amosite is 550 per 100,000 (uncertainty range 150 to 1500). However, the risk estimate for the same cumulative exposure accrued over 30 years starting at age 30 is 300 per 100,000 (uncertainty range 70 to 750) – and if the exposure was accrued over 30 years starting at age 20 the risk estimate is 600 per 100,000 (uncertainty range 150 to 1500).

23. Adjustment factors for the effect of age exposure started on the mesothelioma risk estimates were provided in Table 9 of our original paper based on the HEI risk model. Under the assumption that the mesothelioma risk continues to increase for about 60 years after the start of a given brief (approximately 5-year) exposure period, we previously suggested that exposures starting at ages below 20 would not result in any further increase in risk. However, this does not take account of the fact that for exposures starting at very young ages substantially more individuals will survive to ages at which mesothelioma is most likely to be expressed (typically about 40 years from first exposure). Thus Table 4 below presents adjustment factors for the mesothelioma risk including start ages for exposure down to birth. While there is evidence that the mesothelioma risk does not continue to increase at very long follow-up times, if it did, the impact could be substantial for exposures starting at the youngest ages. As an illustration of the potential impact this would have on risk for exposures starting below age 20, Table 4 also shows adjustment factors for mesothelioma risk truncated at 80 years from the start of exposure.

Table 4: Adjustment factors to convert estimates of mesothelioma mortality due to asbestos exposure starting at age 30 to other exposure start ages for assuming risk persists for 60 and 80 years after the start of exposure.

Age	0	5	10	15	20	25	30	35	40	45	50	55
Factor (at risk for 60 years)	2.8	2.7	2.6	2.4	2.1	1.5	1	0.6	0.4	0.3	0.2	0.1
Factor (at risk for 80 years)	6.6	5.2	4	3	2.1	1.5	1	0.6	0.4	0.3	0.2	0.1

24. In order to adjust the HD risk estimates for extended exposure periods (longer than 5 years) account has to be taken of the change in age across the exposure period and the fact that the underlying models are non-linear in cumulative dose. This can be achieved by partitioning the overall exposure duration into 5 year increments and considering the contribution of the dose accrued in each to the total risk, applying the appropriate age factors from Table 4.

Lifetime risks of spontaneous mesothelioma

25. There some evidence that a small number of so called “spontaneous” mesothelioma cases occur each year in the absence of any exposure^{4,5}. Together with any cases caused by naturally occurring deposits of asbestos

or other mineral fibres – though these are unlikely in Great Britain – these form a background level of mesothelioma which can be thought of as the number of cases that would have occurred in the absence of any industrial exploitation of asbestos. Any consideration of the risks resulting from low level asbestos exposure needs to be set against the context of this background risk.

26. Several lines of argument (including levels of mesothelioma mortality in industrialised countries before 1950 and rates among children) suggest that the annual background mesothelioma rate may be around 1-2 per million⁴. Under the assumption that the background rate is the same in both sexes, and that there is no difference in mesothelioma risk due to asbestos exposure between the sexes, the intercept of a straight line fitted on a plot of annual female deaths against annual male deaths may also be used to estimate the background. Applying this technique to the annual mortality data from the mesothelioma register for 1968-2004 suggests a background rate of around 1 per million per year in Great Britain, which is consistent with the rate suggested by McDonald and McDonald⁴. This is equivalent to about 30 incident cases each year in males and the same in females – that is, about 60 background cases per year overall. If the background mesothelioma rate and total level of mortality are broadly constant, the proportion of all deaths in a given year that are background mesotheliomas provides an estimate of the lifetime risk. This suggests a lifetime risk of a background mesothelioma of around 1 per 10,000 (ie 10 per 100,000).

References

1. Hodgson JT, Darnton A (2000). The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Annals of Occupational Hygiene* 44(8): 565-601
2. Berman DW, Crump K. Technical support document for a protocol to assess asbestos-related risk (Draft prepared for US Department of Transportation and US Environmental Protection Agency, 2004)
3. Health Effects Institute (1991). *Asbestos in Public and Commercial Buildings: A Literature Review and Synthesis of Current Knowledge*. Health Effects Institute – Asbestos Research, Cambridge, MA.
4. McDonald, J. & McDonald, A. (1994). Mesothelioma: is there a background? In *The mesothelial cell and mesothelioma*, Bignon, J. & Jaurand, M.-C. (eds) pp. 37-45. Marcel Dekker: New York, Basel, Hong Kong
5. Ilgren, E. & Wagner, J. (1991). Background incidence of mesothelioma: animal and human evidence. *Regulatory toxicology and pharmacology*, 13, 133-149

Appendix 1

List of cohorts

HD study number	BC study number	Cohort	Reference
1	RM18	Wittenoom	de Klerk, N. H., Musk, A. W., Armstrong, B. K. and Hobbs, M. S. T. (1994) Diseases in miners and millers of crocidolite from Wittenoom, Western Australia: a further follow-up to December 1986. <i>Annals of Occupational Hygiene</i> 38(supp 1), 647-655.
2f, 2m	CT6	Carolina (women)	Dement, J. M., Brown, D. P. and Okun, A. (1994) Follow-up study of chrysotile asbestos textile workers: cohort mortality and case-control analyses. <i>American Journal of Industrial Medicine</i> 26, 431-447.
3	MF13	Johns Manville retirees	Enterline, P. E., Harley, J. and Henderson, V. (1987) Asbestos and cancer: a cohort followed up to death. <i>British Journal of Industrial Medicine</i> 44, 396-401.
4	MP8	Ontario	Finkelstein, M. M. (1984) Mortality among employees of an Ontario asbestos-cement factory. <i>American Review of Respiratory Disease</i> 129, 750-761.
5a, 5o, 5y	MP9, CP5	New Orleans	Hughes, J. M., Weill, H. and Hammad, Y. Y. (1987) Mortality of workers employed in two asbestos cement manufacturing plants. <i>British Journal of Industrial Medicine</i> 44, 161-174.
6	CM1, CM2	Quebec	Liddell, F. D. K., McDonald, A. D. and McDonald, J. C. (1997) The 1891-1920 cohort of Quebec chrysotile miners and millers: development from 1904 and mortality to 1992. <i>Annals of Occupational Hygiene</i> 41, 13-36.
7	Not included	Vocklabruck	Neuberger, M. and Kundi, M. (1990) Individual asbestos exposure: smoking and mortality-a cohort study into the asbestos cement industry. <i>British Journal of Industrial Medicine</i> 47, 615-620.
8	MI15	US/Canada insulators	Seidman, H. and Selikoff, I. J. (1990) Decline in death rates among asbestos insulation workers 1967-1986 associated with diminution of work exposure to asbestos. <i>Annals of New York Academy of Science</i> 609, 300-318.
9	MT17	Rochdale	Peto, J., Doll, R., Hermon, C., Binns, W., Clayton, R. and Goffe, T. (1985) Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. <i>Annals of Occupational Hygiene</i> 29, 305-335.
10	CM3	Balangero	Piolatto, G., Negri, E., La Vecchia, C., Pira, E., Decarli, A. and Peto, J. (1990) An update of cancer mortality among chrysotile asbestos miners in Balangero, northern Italy. <i>British Journal of Industrial Medicine</i> 47, 810-814.
11	MT16	Pennsylvania	McDonald, A. D., Fry, J. S., Woolley, A. J. and McDonald, J. (1983) Dust exposure and mortality in an American chrysotile textile plant. <i>British Journal of Industrial Medicine</i> 40, 361-367. McDonald, A. D., Fry, J. S., Woolley, A. J. and McDonald, J. C. (1983) Dust exposure and mortality in an American factory using chrysotile, amosite, and crocidolite in mainly textile manufacture. <i>British Journal of Industrial Medicine</i> 39, 368-374.
12	AI19	Paterson	Seidman, H., Selikoff, I. J. and Gelb, S. K. (1986) Mortality experience of amosite asbestos factory workers: dose- response relationships 5 to 40 years after onset of short-term work exposure. <i>American Journal of Industrial Medicine</i> 10, 479-514.
13a, 13o	Not included	SA mines	Sluis-Cremer, G. K., Liddell, F. D. K., Logan, W. P. D. and Bezuidenhout, B. N. (1992) The mortality of amphibole miners in South Africa, 1946-80. <i>British Journal of Industrial Medicine</i> 49, 566-575.
14	Not included	Massachusetts	Talcott, J. A., Thurber, W. A., Kantor, A. F., Gaensler, E. A., Danahy, J. F., Antman, K. A. and Li, F. P. (1989) Asbestos-associated diseases in a cohort of cigarette-filter workers. <i>New England Journal of Medicine</i> 321, 1220-1223.
15	MP10	Albin	Albin, M., Jacobson, K., Attawell, R., Johannson, L. and Wellinder, H. (1990a) Mortality and cancer morbidity in cohorts of asbestos cement workers and referents. <i>British Journal of Industrial Medicine</i> 47, 602-610. Albin, M., Johannson, L., Pooley, F. D., Jakobsson, K., Attawell, R. and Mitha, R. (1990b) Mineral fibres, fibrosis and asbestos products

HD study number	BC study number	Cohort	Reference
			in the lungs from deceased asbestos cement workers. British Journal of Industrial Medicine 47, 747-774.
16	CF4	Connecticut	McDonald, A. D., Fry, J. S., Woolley, A. J. and McDonald, J. C. (1984) Dust exposure and mortality in an American chrysotile asbestos friction products plant. British Journal of Industrial Medicine 46, 151-157.
17	MF7	Ferodo	Newhouse, M. L. and Sullivan, K. R. (1989) A mortality study of workers manufacturing friction materials: 1941-86. British Journal of Industrial Medicine 46, 176-179.
Not included	TM21	Libby	Amandus HE, Wheeler R et al (1987) The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part I. Exposure estimates. American Journal of Industrial Medicine 11:1-14
			Amandus HE, Wheeler R et al (1987) The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part II. Mortality. American Journal of Industrial Medicine 11:15-26
Not included	AI20	Tyler	Levin JL, McLarty JW et al (1998) Tyler asbestos workers: mortality experience in a cohort exposed to amosite. Occupational and Environmental Medicine. 55:155-160
Not included	MF11	Belgium cement	Lacquet LM, VanderLinden L et al (1980) Roentgenographic lung changes, asbestosis and mortality in a Belgian asbestos-cement factory. In Biological effects of mineral fibres, Wagner JC (ed.) IARC Sci Publ. pp. 783-793

Appendix 2

Summary of models

Hodgson and Darnton (HD)

Lung cancer:

$$P_L = A_L X^r$$

Where:

$P_L = 100 \times (O_L - E_L) / E_L$ = Percentage excess of expected lung cancer mortality

X = Cumulative asbestos exposure

A_L and r are fitted coefficients that depend on the type of asbestos (chrysotile or amphibole)

Coefficient values for “best” model (see HD Table 10):

Amphibole: $A_L=4.8$, $r=1.3$

Chrysotile: $A_L=0.028$, $r=1.3$

Mesothelioma:

$$P_M = A_{pl} X^r + A_{pr} X^t$$

Where:

$P_M = 100 \times O_M / E_{Adj}$ = Mesothelioma mortality as a percentage of expected mortality from all causes adjusted to an age of first exposure of 30

X = Cumulative asbestos exposure

A_{pl} and r are fitted coefficients for pleural mesothelioma which depend on the type of asbestos (chrysotile, amosite or crocidolite)

A_{pr} and t are corresponding fitted coefficients for peritoneal mesothelioma

Coefficient values for “best” model (see HD Table 8):

Crocidolite: $A_{pl}=0.94$, $r=0.75$, $A_{pr}=0.0022$, $t=2.1$

Amosite: $A_{pl}=0.13$, $r=0.75$, $A_{pr}=0.0006$, $t=2.1$

Chrysotile: $A_{pl}=0.0047$, $r=0.75$, $A_{pr}=0$

Berman and Crump (BC)

Lung cancer:

$$RR = \alpha(1 + K_L \times CE_{10})$$

Where:

RR = Relative risk of lung cancer mortality

K_L = Fitted lung cancer exposure-response coefficient

CE_{10} = Cumulative asbestos exposure disregarding the last 10 years

α = Fitted parameter to account for differential background lung cancer rates in cohort and reference population

Coefficient values for PCME summary model (See Table 7-17):

Amphibole: $K_L \times 100 = 0.47$, $\alpha = 1$

Chrysotile: $K_L \times 100 = 0.23$, $\alpha = 1$

Mesothelioma:

$$I_M = K_M \cdot f \cdot \left\{ (T - 10)^3 - [T - 10 - d]^3 \right\}$$

Where:

I_M = Mesothelioma mortality rate T years from onset of exposure

K_M = Dose-response proportionality constant

f = exposure concentration

d = exposure duration in years

And:

{...} set to zero for $T < 10$

[...] set to zero for $10 < T < 10 + d$

Coefficient values for PCME summary model (See Table 7-17):

Amphibole: $K_M \times 10^8 = 7.7$

Chrysotile: $K_M \times 10^8 = 0.025$