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REVIEW

After Helsinki: a multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997–2004

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Summary

Despite an extensive literature, the relationship between asbestos exposure and lung cancer remains the subject of controversy, related to the fact that most asbestos-associated lung cancers occur in those who are also cigarette smokers: because smoking represents the strongest identifiable lung cancer risk factor among many others, and lung cancer is not uncommon across industrialised societies, analysis of the combined (synergistic) effects of smoking and asbestos on lung cancer risk is a more complex exercise than the relationship between asbestos inhalation and mesothelioma. As a follow-on from previous reviews of prevailing evidence,[1,2] this review critically evaluates more recent studies on this relationship—concentrating on those published between 1997 and 2004—including lung cancer to mesothelioma ratios, the interactive effects of cigarette smoke and asbestos in combination, and the cumulative exposure model for lung cancer induction as set forth in The Helsinki Criteria and The AWARD Criteria (as opposed to the asbestosis→cancer model), together with discussion of differential genetic susceptibility/resistance factors for lung carcinogenesis by both cigarette smoke and asbestos. The authors conclude that: (i) the prevailing evidence strongly supports the cumulative exposure model; (ii) the criteria for probabilistic attribution of lung cancer to mixed asbestos exposures as a consequence of the production and end-use of asbestos-containing products such as insulation and asbestos-cement building materials—as embodied in The Helsinki and AWARD Criteria—conform to, and are further consolidated by, the new evidence discussed in this review; (iii) different attribution criteria (e.g., greater cumulative exposures) are appropriate for chrysotile mining/milling and perhaps for other chrysotile-only exposures, such as friction products manufacture, than for amphibole-only exposures or mixed asbestos exposures; and (iv) emerging evidence on genetic susceptibility/resistance factors for lung cancer risk as a consequence of cigarette smoking, and potentially also asbestos exposure, suggests that genotypic variation may represent an additional confounding factor potentially affecting the strength of association and hence the probability of causal contribution in the individual subject, but at present there is insufficient evidence to draw any meaningful conclusions concerning variation in asbestos-mediated lung cancer risk relative to such resistance/susceptibility factors.

Key words: Lung cancer, adenocarcinoma, cigarette smoke, asbestos, asbestosis, cumulative exposure, amphibole, chrysotile, epidemiology, relative risk, odds ratio, attributable fraction, causation, attribution, criteria, genetic susceptibility.

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We are too much accustomed to attribute to a single cause that which is the product of several, and the majority of our controversies come from that. (Justus Liebig, 1803–1873)

INTRODUCTION AND GENERAL COMMENTS ON ASBESTOS-RELATED LUNG CANCER

Reports of lung cancer among asbestos workers predated the recognition of mesothelioma as an asbestos-induced cancer (1935–1955 versus 1960),[3–5] but analysis of the relationship between asbestos and lung cancer has always been more problematical,[6] for several reasons:

1. Asbestos is the only identifiable cause for the majority of mesotheliomas: the relationship is highly specific, and mesothelioma incidence is widely considered to be an index of societies' past usage of asbestos.[7–9] In particular, there is no evidence that tobacco smoke contributes to mesothelioma induction, whereas cigarette smoke constitutes the greatest risk factor for lung cancer,[10–13] and most asbestos-influenced lung cancers are the outcome of dual exposure to asbestos and tobacco smoke,[14–16] so that the asbestos–lung cancer nexus has less specificity than asbestos–mesothelioma.

It has been estimated that about 4–12% or more of lung cancers are related to occupational exposure to asbestos.[17–22] In a review of the epidemiology of lung cancer, Alberg and Samet[12] claim that about 90% of lung cancers are related to smoking, 9–15% to occupational exposures, 10% to radon, and perhaps 1–2% to air pollution. Axelson[23] has estimated that more than a quarter of all

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lung cancer cases in Sweden are related to occupational exposures and similar proportions have been reported for Finland,[24] Norway[25] and Denmark.[26] Because two or more causal factors are implicated in many cases and the combined effects of those factors may be more than additive, the sum of the attributable fractions (AFs) in the exposed (AF_Es) related to each factor may exceed 1.0 (100%).[12,27–29] (AF_E can be defined as the proportion of exposed cases attributable to the risk factor,[30] is synonymous with the rate fraction[29] and 'can be interpreted as the proportion of disease cases over a specified time that would be prevented following elimination of the exposures, assuming the exposures are causal';[28] AF_E is given by the relative risk [RR] minus one, divided by the RR: [RR–1]/RR, usually converted to a percentage.)* As stated by Rockhill *et al.*:[28] '... it is possible, albeit counterintuitive, that a set of individual [AF_Es] will sum to more than 1.0 .... The population [AF] does not address probability of causation for a specific case of disease, nor does its estimation enable epidemiologists to discriminate between those cases caused by, and those not caused by, the risk factors under consideration' (see also references 27, 29, 34 and 35). Accordingly, there is no inconsistency in assigning an AF_E of 87.5% for cigarette smoke imparting a RR of 8.0 in a patient with adenocarcinoma of lung[11] and 75% for asbestos if the subject also sustained asbestos exposure sufficient to give a RR of 4.0.

The ratio of excess lung cancers to mesotheliomas across cohorts of asbestos workers has been variously estimated at about 0.5:1 to >30:1,[36–38] and a ratio of 2:1 is widely cited.[21,37,39–41] For example, in a study of Danish asbestos-cement workers, Raffn *et al.*[42] found a standardised incidence rate (SIR) of 1.80 for lung cancer among asbestos-cement workers (observed = 162; expected = 89.81); the observed versus expected cases for pleural mesothelioma for the same cohort were 10 and 1.83; from these figures, one can calculate the excess lung cancer to mesothelioma ratio to be 8.8:1. In a study of cigarette filter makers, Talcott *et al.*[43] observed 11 lung cancers versus 0.7 expected and five mesotheliomas versus 0.01 expected, so that the excess lung cancer to mesothelioma ratio was 2:1. As a consequence of a general diminution of asbestos exposures over the years and changing smoking habits, the ratio seems likely to decline to about ≤1:1, when the difference in the slope of the dose-response line between asbestos-related lung cancer and mesothelioma is taken into account[7,9,44] (see later discussion).

Based on a multiplicative model for the interaction between asbestos and smoking (see later discussion), one can also calculate that differences exist between men and women in the excess lung cancer to mesothelioma ratio, because of different smoking habits, as illustrated by the following example. Let us suppose that a cohort has an asbestos-related RR of lung cancer (RR_{LCA}) of 5.0, and the individual lifetime risk of mesothelioma is 5.0% for both men and women; the expected risk of lung cancer as a consequence of different smoking habits is 1% for women and 3% for men; the excess lung cancer rate is (5–1)% = 4% for women and (15–3)% = 12% for men, so that the excess lung cancer to mesothelioma ratio is 0.8:1 for women and 2.4:1 for men. In addition, the excess lung cancer to mesothelioma ratio is substantially greater for chrysotile-only exposures than for amphibole or mixed exposures.[36]

Peto *et al.*[9] have predicted about 190 000 mesothelioma deaths across six nations in Western Europe (Britain, France, Germany, Italy, The Netherlands and Switzerland) over the 35-year period from about 1999. If a lung cancer:mesothelioma ratio of 1:1 holds, about 190 000 asbestos-related lung cancers can also be predicted, and the figure would rise to 380 000 asbestos-associated lung cancers at a ratio of 2:1. Tossavainen[17] estimates that about 20 000 asbestos-related lung cancers and 10 000 mesotheliomas occur each year across North America, Australia, and seven nations in Western Europe and Scandinavia (combined population ~800 million).

According to Howie,[37] the number of officially registered deaths from asbestos-induced diseases in the United Kingdom for the years 1929–1996 included 17 999 mesotheliomas (M = 15 298; F = 2701) and 1878 lung cancers, a lung cancer to mesothelioma ratio of about 0.1:1, and this ratio was maintained with minor variation over the years 1988–2000 in figures published by the Health and Safety Commission (HSC)[44,45] (Table 1).

However, an Office of Population Censuses (OPCS)/ Health and Safety Executive (HSE) document[7] published in 1995 reported that asbestos exposure caused about equal numbers of excess deaths from lung cancer (~200; 749 observed; 549 expected) and mesothelioma (183) for the period 1968–1991, a ratio of 1.09:1. In a study of cancer mortality among about 5100 asbestos factory workers in east London followed for over 30 years since first exposure,[46] the excess lung cancer to mesothelioma ratio was 1.55:1 (Table 1).

In its 1999 and 2001 reports on *Health and Safety Statistics*,[44,45] the HSC in the United Kingdom stated that: '... There is no clinical feature by which lung cancers caused by asbestos can be definitively distinguished from cases in which asbestos has not been involved, and therefore many of these cases may not be recognized as asbestos related by the sufferers or by their doctors...' (reference 45; p. 86); and '... There is evidence that these figures [UK disablement benefit awards for asbestos-related lung cancer] substantially underestimate the true extent of the disease. In heavily exposed populations there have typically been at least as many, sometimes up to five times as many, excess lung cancers as there have been mesotheliomas. The ratio depends on a range of factors ... so one cannot be too precise about the overall ratio. A reasonable rule of thumb would be to allow for one or two extra lung cancers for each mesothelioma ...' (reference 44; p. 101).

There is also evidence that asbestos-related lung cancers were under-recognised in France before introduction of a compensation standard based on 10 or more years

*There has been great confusion in the epidemiological literature over AF, rate fraction, excess fraction and aetiological fraction (see references 28–32 for further discussion of these concepts). Although the expression 'relative risk' is in widespread use, it is worth emphasising that RR does not deal with hypothetical risk, but instead is derived from observed numbers of cases in the exposed, relative to a control group: 'rate ratio' is arguably preferable, but 'relative risk' is well entrenched; for a remarkably lucid discussion of the confusion that can sometimes arise from dealing with RRs, see Gigerenzer.[33]

TABLE 1 Cases of asbestos-related lung cancers (LCAs) in the United Kingdom, 1988–2000, as assessed by Special Medical Boards,[44,45] in comparison to compensated cases in Germany, 1986–1999, and excess lung cancer to mesothelioma ratios from two other reports[7,46]

	United Kingdom*			Germany†		
Year	Asbestos-related LCAs	Meso	Ratio lung cancer to meso	Asbestos-related LCAs (including laryngeal CAs since 1997) (BK4104)	Meso (BK4105)	Ratio respiratory tract cancer to meso (BK4104÷BK4105)
1986				38	172	0.22:1
1987				53	198	0.27:1
1988	59	479	0.12:1	100	228	0.44:1
1989	54	441	0.12:1	125	273	0.46:1
1990	58	462	0.13:1	129	296	0.44:1
1991	55	519	0.11:1	171	315	0.54:1
1992	54	551	0.10:1	223	350	0.64:1
1993	72	608	0.12:1	388	416	0.93:1
1994	77	583	0.13:1	545	495	1.10:1
1995	55	685	0.08:1	648	503	1.29:1
1996	51	642	0.08:1	726	535	1.36:1
1997	26	553	0.05:1	672	534	1.26:1
1998	42	590	0.07:1	723	575	1.26:1
1999	38	620	0.06:1	776	617	1.26:1
2000	42	652	0.06:1	697‡	670‡	1.04:1
1995–2000	254	3742	0.07:1	4242	3434	1.24:1
Excess lung cancer to mesothelioma ratio (OPCS/HSE, 1995[7]; see also reference 20).						1.09:1
Excess lung cancer to mesothelioma ratio: Berry *et al.*;[46] about 5100 asbestos factory workers in east London; 232 lung cancer deaths observed; 77 expected; standardised mortality ratio (O/E)=3.01 (95%CI=2.6–3.4); 100 mesothelioma deaths (52 pleural; 48 peritoneal).						1.55:1

Meso, mesothelioma; CI, confidence interval.
*For the UK, asbestos-related lung cancers comprise only cases of primary carcinoma of lung with either asbestosis or pleural thickening; until April 1997, only cases of bilateral pleural thickening were accepted; thereafter, unilateral pleural thickening was also allowed. The UK figures are from the Health and Safety Commission Report, Health and Safety Statistics 1998/99[45] (Tables A2.5 and A2.6), and from Table 2.1 in the equivalent report for 2000/2001.[44] The OPCS/HSE survey seems to have been more encompassing for asbestos products manufacture and insulation than for other patterns of exposure.[7]
†The figures for Germany are from Giesen and Zerlett.[47] The figures since 1995 include cases from the former East Germany so far as they conform to the West German regulations in existence. From 1993, the mesotheliomas include pericardial mesotheliomas. Asbestos-related lung cancers include those fulfilling the criterion of 25 fibres/mL-years of exposure, introduced in 1992. See also Baur and Czuppon,[48] where the 1995 asbestos-associated lung cancer to mesothelioma ratios are 2.16:1 for reported cases, 1.29:1 for 'recognised' cases and 1.29:1 for cases compensated for the first time. Since 1997, the numbers of lung cancer cases include laryngeal carcinomas related to 25 fibres/mL-years or more exposure to asbestos, by an extension to the existing German lung cancer category BK4104.[48] On this basis, the number of laryngeal carcinomas attributed to asbestos is small—15 cases of laryngeal carcinoma were 'recognised' in 1995[48]—and would have only a slight effect on the lung cancer to mesothelioma ratio: e.g., if there were 25 cases of laryngeal cancer attributed to asbestos for 1999, the excess lung cancer to mesothelioma ratio would be 1.22:1. See also pre-1997 lung cancer to mesothelioma ratios. Consideration of asbestos and cancer of the larynx lies outside the scope of this chapter.
‡German data for 2000 represent a personal communication to H-JW.

of occupational exposure.[49–51] Similar under-recognition occurs in Italy[52] and Japan.[53]

Lung cancers also appear to be under-represented among asbestos-related diseases compensated in New South Wales (NSW) in Australia. For example, the 1998 Report of the NSW Dust Diseases Board lists the following disablement determinations among 2338 claims during 1997–1998: 96 mesotheliomas in comparison to nine 'asbestos induced carcinomas of the lung', a lung cancer:mesothelioma ratio of 0.09:1.[2] Predictions for asbestos-related disorders in Australia (population in 2003 ~20 million) include about 18 000 cases of mesothelioma for the period 1945–2020, and about 30 000–40 000 cases of lung cancer.[54,55]

In 1992, Teschke and Barroetavena[56] reported that for the years 1980–1989, about 0.15 to 0.76% of incident cases of lung cancer were compensated as an occupational disorder across British Columbia, Saskatchewan and Ontario in Canada. In comparison, the estimated population-attributable risk percentage (PAR%) for lung cancer attributable to occupational factors was 3–17% across the same three provinces, and asbestos was the agent listed for 36% of the lung cancer claims. Teschke and Barroetavena[56] concluded that accepted claims for lung cancer were lower by a factor of four or more than the lowest PAR% estimates from epidemiological studies in the US and Britain, so that lung cancer in Canada was under-compensated, mainly because of under-recognition and under-reporting to compensation boards. There is also evidence of inconsistency in the diagnosis of other asbestos-related disorders such as asbestosis[57] (see later discussion).

After introduction of the 25 fibres/mL-year standard in 1992 for compensation of asbestos-related lung cancer in Germany, the lung cancer (plus laryngeal cancer since 1997) to mesothelioma ratio rose to 1.24:1 for the period 1995–2000 (see Table 1 and later discussion).

2. Because most asbestos-related lung cancers are attributable to the combined effects of asbestos and tobacco smoke, it becomes necessary to allow for cigarette smoking in a comparable reference population not exposed to asbestos in order to estimate the (excess) number of asbestos-attributable lung cancers.[38,58] Moreover, lung

cancer is prevalent across industrialised societies, so that evaluation of a small increase in lung cancer incidence or risk poses greater statistical difficulties than detection of a hitherto rare cancer such as mesothelioma.[54] Cohort or case-referent studies on the relationship are most persuasive when they demonstrate a dose-response effect.[59]

3. Many studies have weak statistical power to detect small increases in the RR_{LCA} because they deal with small populations. For example, Nurminen and Tossavainen[60] calculated the RR for pleural plaque-associated lung cancer in the general population to be as low as 1.1, and detection of this RR_{LCA} at a level of statistical significance would require a population sample of about 300 000, taking into account the prevalence of plaques and lung cancer among men with unlikely and probable asbestos exposure. These authors[60] drew attention to a study carried out by Partanen *et al.*,[61] where the cohort had generally low levels of environmental exposure: not all subjects with plaques had been exposed to asbestos and not all pleural abnormalities represented asbestos-related plaques. There were 28 lung cancers among 604 subjects with plaques, in comparison to 25 lung cancers among 604 referents, some of whom might have been exposed to asbestos ($RR_{LCA}=1.1$; 95% confidence interval [CI] = 0.6–1.8). Had the study focused on a subpopulation with definite or probable asbestos exposure, a sample size calculation with the same statistics and estimates would produce the following result: at the 0.05 level and power 80%, the sizes of asbestos-exposed and non-exposed groups would need to be 538 + 538 to detect a RR_{LCA} of 2, or 175 + 175 for a RR_{LCA} of 3. In this respect, a low risk in a small cohort may nonetheless translate into a substantial body of disease when spread over a large population: as one example, a RR of 1.1 representing an increase in risk of 10% for a common disease such as lung cancer may amount to a substantial burden of morbidity and mortality when spread across a population of, say, 1 million or 10 million.[54] In other words, a small increase in the incidence of a common disease affecting a large population may produce greater absolute numbers than a higher frequency of another disease affecting a smaller population.[54]

4. Analysis of the dose-response relationship for lung cancer—and other asbestos-induced disorders—is complicated by heterogeneity between cohorts for the dose–response relationship (see later discussion), and by uncertainties over exposure data.[38,62,63] Early estimates of cumulative exposure—when exposures for past cohorts were generally greater than for similar regulated industries in more recent times[62,64]—were based on measurements of airborne dust concentrations as millions of particles per cubic foot (mppcf) in comparison to later measurements as fibres per mL (fibres/mL; f/mL) for fibres longer than 5 μm, now widely accepted as the most suitable parameter of exposure[62] (the expression 'WHO fibres' is sometimes applied to fibres of this type, as defined by a length > 5 μm and an aspect ratio ≥3:1). In order to translate mppcf to fibres/mL, conversion factors ranging from 1.4 to 3.0 to 6.0 have been used for different studies.[62,63,65] Some studies have also used mass/gravimetric measurements (mg/m^3).[66] Uncertainties also beset other facets of exposure for some cohorts, such as the type of asbestos,[67,68] and fibre dimensions, such as the length and diameter distributions.[69] For example, besides the asbestiform varieties of tremolite and actinolite (which release long, thin fibres composed of fibrils), non-asbestiform varieties also occur,[70] which release only cleavage fragments that fulfil the definition of WHO fibres, while their size distribution does not differ from other minerals.[71]

ASBESTOS FIBRE TYPES AND LUNG CANCER

The greater carcinogenicity of the amphiboles for the mesothelium in comparison to chrysotile appears not to extend so clearly to the induction of lung cancer.[68,72,73] The Hodgson–Darnton[73] review found that commercial amphiboles are more potent than chrysotile for lung cancer induction, and that amosite and crocidolite are about equipotent (see later discussion). Although chrysotile is implicated in one of the lowest rates of asbestos-associated lung cancer, in Quebec chrysotile miners and millers (although the associated fibrous tremolite has been invoked as the factor responsible for lung cancer induction in this cohort,[74] as for mesothelioma[75,76]), it is also associated with one of the highest, in South Carolina asbestos textile workers who used Quebec chrysotile.[77–79]

The reasons for this 30-fold or greater difference in lung cancer risk remain unexplained.[63,76] The use of potentially carcinogenic mineral oils or co-existent exposure to amphiboles for workers in the South Carolina (Charleston) industry, and differences in fibre length, have all been invoked to account for this differential, but none has provided a clear explanation;[54,62,76,79,80] for example, two nested case-referent studies on the Charleston cohort found that the relationship between lung cancer risk and chrysotile exposure was virtually unaffected by exposure to mineral oils.[62] Hodgson and Darnton[73] argue in support of some adjuvant carcinogenic effect from mineral oils, but the data cited from the Charleston cohort seem inadequate to explain the huge differential in cancer risk; even so, these authors[73] suggest that the dose-response effect for the Charleston textile cohort is 'untypically high', and they emphasise the greater carcinogenic potency of the amphiboles than chrysotile for lung cancer induction as well as for mesothelioma.

Subsequently, Yano *et al.*[81] reported a 25-year longitudinal cohort study on male asbestos workers exposed to chrysotile in Chongqin, China; the factory used only Sichuanese chrysotile that was claimed to be virtually amphibole-free (<0.001% tremolite; below the detection limit of the assays). Airborne fibre concentrations in the raw materials section and the textile section of the factory were 7.6 and 4.5 fibres/mL, respectively, and the workers were employed for an average of 24.6 years. This study found no increase in the risk of lung cancer at low exposures for office workers and asbestos-cement work ($RR_{LCA}=1.0$), but the RR_{LCA} was 3.6 (95%CI = 0.7–17.5) for intermediate exposures that included maintenance work, and it was 8.1 (95%CI = 1.8–36.1) for high exposures related to textile work and the use of raw material (see also reference 82). Nonetheless, despite claims that chrysotile samples from China (and Russian chrysotile) represent virtually 'pure chrysotile' on the basis that some studies

were unable to demonstrate the presence of amphiboles on X-ray micro-analysis (electron probe analysis) of the chrysotile,[81] subsequent investigations reported by Tossavainen *et al.*[83,84] using acid-alkali digestion of the bulk samples of chrysotile[70] or from analysis of the lung tissue asbestos fibre types have demonstrated that tremolite or anthophyllite is in fact present in both Russian and Chinese chrysotile (including chrysotile from the two Sichuanese mines that apparently supplied the factory studied by Yano *et al.*[81]). There is probably no such thing as 'pure' chrysotile.

Case *et al.*[54,80] have revisited the study reported in 1989 by Sebastien *et al.*[85] on the fibre content of lung tissue from the South Carolina textile workers in comparison to the Quebec (Thetford) miners/millers, focusing on fibres longer than 18 μm. These authors[80] found only marginal differences in mean fibre length for amosite, crocidolite and tremolite:[54,80] the mean length of tremolite fibres was 21.7 μm for the Quebec miners/millers versus 21.9 μm for the Charleston textile workers. Therefore, the great inequality in the lung cancer rate cannot be explained by skewed exposure to longer fibres in the Charleston textile workers, unless there is a specific and precise 'critical length' for fibre-mediated carcinogenesis for lung cancer,[80] which is highly unlikely. Case *et al.*[80] reported a somewhat higher content of amosite/crocidolite fibres in the textile workers' lungs (Table 2), but the total amphibole content (amosite/crocidolite + tremolite) was significantly higher in the miners/millers, and the difference in the amosite/crocidolite content seems far too small to account for the large difference in the slope of the dose–response line (K_L).

Green *et al.*[86] also reported a fibre burden study on the South Carolina textile cohort, with a comparable control group: the textile workers had a higher lung content of chrysotile in comparison to the controls (geometric mean = 33 450 000 vs 6 710 000 fibres/g dry lung), with a higher content of tremolite (3 560 000 vs 260 000 fibres/g dry lung); the textile workers also had a slightly elevated mean amosite/crocidolite content of 470 000 fibres/g vs 210 000 for the controls.

The cases on which fibre burden analysis was carried out in the studies reported by Green *et al.*,[86] Sebastien *et al.*[85] and Case *et al.*[54,80] were not representative of the cohorts whence they came and were not comparable with each other: e.g., as discussed in detail elsewhere,[54] only a small proportion of the cohorts came to autopsy, with over-representation of asbestos-related disorders in comparison to the cohort as a whole, and there were also differences in the mean age at death, estimated cumulative exposures, and the interval following cessation of exposure.

Tremolite appears to be no less potent than amosite and crocidolite for lung cancer induction: as one example, Luce *et al.*[87] reported that Melanesian women in New Caledonia who prepared and applied a whitewash known as *pö*—which consisted of 'virtually pure tremolite' and was in use from about 1930 until the end of the 1960s—have a lung cancer odds ratio (OR_{LCA}) of 4.89 (95%CI = 1.13–21.2), and the OR_{LCA} for smokers was 9.26 (95%CI = 1.72–49.7); no increase in the OR_{LCA} was found among Melanesian men, probably because of lower exposures. In a subsequent study from New Caledonia, Menvielle *et al.*[88] found an OR_{LCA} of 3.3 (95%CI = 2.4–4.5) for women with ever exposure to *pö*, and 1.7 (95%CI = 0.6–5.0) for women with ever exposure to field dust (which in some regions is known to contain tremolite), with a trend to a dose–response effect; increased ORs for lung cancer were also found in men with analogous exposures.

TABLE 2 Lung tissue asbestos fibre burdens for South Carolina chrysotile textile workers versus Quebec chrysotile miners/millers, for fibres longer than 18 μm

Type of fibre (geometric mean values, as millions of fibres/g dry lung)	South Carolina textile workers	Quebec miners/millers
Chrysotile	0.054	0.231
Tremolite	0.027	0.325
Amosite/crocidolite	0.037	0.024
Total amphiboles (tremolite + amosite/crocidolite)	0.053	0.294

Modified from references 54, 80; total amphibole content as given in Table 2 in reference 80.

INTERACTION BETWEEN CIGARETTE SMOKE AND ASBESTOS IN THE CAUSATION OF LUNG CANCER

Cigarette smoke and asbestos are considered by most authorities to have a joint synergistic effect for lung cancer induction, and both are complex carcinogens that can affect multiple steps in the multistage process of carcinogenesis.[14] The composite effect may range from less than additive to supramultiplicative, but the effect among insulation workers and as derived from case-referent studies approximates a multiplicative model, which has been accepted by many authorities[13,14,16,89,90] for about the last 30 years.

In a meta-analysis of 31 datasets across 23 epidemiological studies, Lee[15] argued that the joint relation between smoking and asbestos exposure for lung cancer risk was 'much better described by a multiplicative than by an additive model ... [and] ... the fit to the multiplicative model is generally good ...'. In contrast, others[16,91] argue that the information from case-referent studies in support of a multiplicative relationship is 'essentially unreliable' (see later discussion), and that the 'multiplicative hypothesis is not generally satisfactory',[92] although 'the additive hypothesis is not generally applicable either'.[91] (For the cohort of Quebec miners and millers, the data best fitted an additive model.[91]) Lee[93] responded that the existing data 'do not clearly reject the simple multiplicative relation', although more complex models might fit the data better: the interactive effect may not conform to any simple hypothesis,[91] and the model that best fits most situations might be supra-additive but submultiplicative.[94] In either a multiplicative or a submultiplicative model, the combined effect of cigarette smoke and asbestos involves an interactive effect whereby the joint effect is greater than the sum of the two separate effects (in an additive model, there is no interactive effect[16]).

Erren *et al.*[95] explored the strength of the synergy

between asbestos and tobacco smoke according to three indices: (i) the synergy index (S), defined as the ratio of the combined effects to the sum of the separate effects of asbestos and smoking; (ii) the relative excess risk due to the interaction (RERI); and (iii) the attributable proportion (AP) of risk due to the interaction, defined as the fraction of total lung cancer risk among those exposed to both asbestos and tobacco smoke and which is attributable to the combined effects of these two factors, as opposed to their separate effects. Across the 12 epidemiological studies reviewed, *S* varied from 1.2 to 5.3 (with a weighted summary value of 1.64–1.66) and RERI from 0.88 to 38.22 (the figure for the Wittenoom cohort was 4.89); AP varied from 0.16 to 0.67. Erren *et al.*[95] estimated that the excess lung cancer risk from simultaneous exposures to asbestos and tobacco smoke was higher than the sum of the two separate risks by a factor of 1.64, and that among smokers also exposed to asbestos, about 33% of lung cancers were attributable to the interactive effect of the two carcinogens as opposed to their separate effects and other 'background' factors.

According to Liddell,[16] one consequence of departure from a multiplicative model is that the RR_{LCA} from asbestos exposure is 'about twice as high in non-smokers [than] in smokers'.

At least four mechanisms have been proposed as potential explanations for the synergy between cigarette smoke and asbestos:[1] (i) tobacco smoke may facilitate penetration of asbestos fibres into bronchial walls; (ii) carcinogens in cigarette smoke such as benzo[*a*]pyrene may be adsorbed onto asbestos fibres (e.g., crocidolite or chrysotile), with subsequent delivery of the carcinogens into cells at high concentration;[96] (iii) tobacco smoke may interfere with the clearance of asbestos from the lungs, and Churg and Stevens[97] recorded elevated concentrations of asbestos fibres in the airway tissues of smokers in comparison to non-smokers, for both amosite (~6-fold) and chrysotile (~50-fold), especially for short fibres (in comparison, parenchymal amosite fibre concentrations were comparable in the smoker and non-smoker groups); and (iv) free fatty acids in tobacco may translocate iron into cell membranes, with enhancement of cell sensitivity to oxidants such as active oxygen species.

SMOKING, ASBESTOS AND LUNG CANCER PHENOTYPE

Most epidemiological studies on smoking and lung cancer do not distinguish between the four major histological types and instead they derive a generic risk across all phenotypes (for example, reference 10).† However, it has long been known that the histological types most strongly associated with tobacco smoking are squamous and small cell carcinomas, with a somewhat weaker association for adenocarcinoma.[14,99,100] Accordingly, Zang and Wynder[100] found a steep near-linear dose-response relationship between cigarette smoking and lung cancer, but the ORs were 3- to 5-fold greater for squamous, small cell and large cell carcinomas than for adenocarcinoma (Table 3).

TABLE 3 Age-adjusted ORs for lung cancer in 'current' cigarette smokers[100]

	Squamous, small cell and large cell carcinoma*	Adenocarcinoma†
Pack-years		
01–19	4.9	4.6
20–39	22.8	6.1
40–49	33.7	9.1
≥50	60.9	13.0
Cigarettes per day		
01–10	14.4	3.9
11–20	22.3	6.0
21–40	41.4	10.3
≥41	74.0	15.8

Modified from Tables 2 and 3 in Zang and Wynder;[100] designated in the reference as Kreyberg Type I* and Type II† carcinomas; data for cumulative tar exposure, women and ex-smokers not shown.

In a later and larger pooled analysis of 10 case-referent studies across six European nations, Simonato *et al.*[11] also found that the OR was substantially greater for squamous + small cell carcinoma in men (OR ~58 in current smokers) than for adenocarcinoma (OR = 8.0 in current smokers), with a generic risk of ~24 across all histological types (with extensive data on the generic OR_{LCA} according to the amounts smoked [pack-years and number of cigarettes per day], duration of smoking and the effect of cessation on risk, but not quantified for the different histological types). A similar differential in RR_{LCA} is set forth in graphic form in the 2003 *World Cancer Report*[13] for different histological types (Figs 5.5 and 5.6 in the original).

It is also well known that in comparison to continuing smokers, the smoke-related RR_{LCA} falls progressively following cessation of smoking after about 5 years,[10,13] although never quite reaching the baseline risk for a lifelong non-smoker[13,101] (for more detailed discussion, see references 10, 11, 13, 101). Graphic data in the *World Cancer Report*[13] also indicate that the fall off in the RR_{LCA} for adenocarcinoma following smoking cessation shows a trend similar to that for small cell lung carcinoma (SCLC), although the RRs for continuing smokers differ (~32 for SCLC versus ~11 for adenocarcinoma); the RR_{LCA} for adenocarcinoma at 16+ years after cessation (<2.0) is smaller. Although smoking and the histological type of lung cancer do not by themselves necessarily consolidate or detract from a causal contribution from asbestos—some systems of attribution such as The Helsinki Criteria[2,102] approach causation from the asbestos-related $RR/OR/AF_E$ alone, without consideration of smoking[1]—the histological type does affect the magnitude of the probable proportional causal contribution relative to the smoke-related contribution (that is, for the apportionment of the proportional causal contributions

†The study on variation in lung cancer risk reported by Bach *et al.*[98] mentioned that 77% of the cancers were non-small cell in type and 18% were small cell carcinomas, but the risk analyses did not distinguish between histological types. This study found an independent asbestos-associated RR_{LCA} of 1.24 (95%CI = 1.04–1.48; $P = 0.02$), based upon 'either radiologic evidence of asbestos exposure [not further specified: pleural plaques?] or a history of employment in a trade that put them at a high risk of asbestos exposure (primarily shipyard or construction workers)', with a 'minimum duration of 5 years in [that] trade'; the analysis did not include the 'type of asbestos exposed to [or] findings on chest X-ray ...'.

from smoking and asbestos exposure,[103–105] discussion of which lies outside the scope of this review).

Few studies have addressed the interactive effects between tobacco smoke and asbestos for causation of different histological types of lung cancer.[14] Vainio and Boffetta[14] discussed three studies with information on this issue: they concluded that the data in one study[99] pointed to an approximately multiplicative (~M) effect for squamous cell carcinoma, an additive (A) effect for adenocarcinoma, and an ~A relationship for small cell carcinoma; in the second study[106] 'there was no difference according to histological type in the interaction between exposure to asbestos and tobacco smoking', but the estimates were 'highly imprecise'; for the remaining study from Finland,[107] based on lung tissue fibre burdens, the findings suggested 'a stronger interaction ... closer to >M [supramultiplicative] than <A ... in the occurrence of adenocarcinoma than [for] squamous-cell carcinoma'.

Adenocarcinoma was the most common histological type of lung cancer in some studies on asbestos-exposed workers, and Karjalainen *et al.*[108,109] also found a higher asbestos-associated risk for adenocarcinoma than for squamous cell carcinoma, as did Raffn *et al.*[110] Roggli and Sanders[111] also found that adenocarcinomas predominated among 234 asbestos-associated lung cancers, for all three groups delineated—i.e., the asbestosis, plaque only, and no plaque/no asbestosis groups—with no significant difference in the distribution of the histological types of cancer between the three groups. (In this respect, adenocarcinoma is now also the most frequent histological type of lung cancer unrelated to asbestos.[112]) Among former workers from the Wittenoom crocidolite industry in Western Australia, all histological types except small cell carcinoma showed significant dose-response relationships to asbestos, the greatest for large cell carcinoma, followed by squamous carcinoma and adenocarcinoma.[113] From a survey of multiple studies in the literature, Churg[114,115] found that all four major histological types of lung cancer occur among asbestos-exposed subjects, in proportions little or no different from control cases.

LATENCY INTERVALS BETWEEN ASBESTOS EXPOSURE AND LUNG CANCER

Like mesothelioma, asbestos-related lung cancers are neoplasms of long latency. Baker[116] found that the number of crocidolite-associated lung cancers in Western Australia reached a peak <25 years after first exposure. For amphibole miners in South Africa, Sluis-Cremer[117] found a significant excess mortality from lung cancer in workers with exposures lasting 1–4 years, at 10–19 years after commencement of exposure. In a study of 893 insulation workers in Italy, Menegozzo *et al.*[118] found that excess lung cancer mortality was 'especially pronounced' at latency times longer than 10 years. For workers producing asbestos-containing insulation materials, of whom 77% were employed for <2 years, Nicholson *et al.*[119] observed a significantly elevated RR_{LCA} that occurred within 10 years and thereafter remained constant throughout the period of observation. Based on additional data for 17 800 US insulation workers, these authors[119] stated that the RR_{LCA} develops independently of age and pre-existing risk: an increased incidence was detectable earlier for workers first exposed in older age than for those exposed when young. In a cohort study of 417 asbestos-cement workers, Coviello *et al.*[120] found that the observed mortality from lung cancer diverged from the expected mortality at 30 years, with a peak at 35 years. Warnock and Isenberg[121] and Hillerdal[122] reported mean lag-times of about 35 and 44 years, respectively. Using pooled data from two German case-referent studies, Hauptmann *et al.*[89] calculated that the effect of an increment of asbestos exposure on the OR_{LCA} was greatest at 10–15 years after that exposure and then declined if exposure had ceased.

OTHER GENERAL AND CLINICOPATHOLOGICAL CHARACTERISTICS OF ASBESTOS-RELATED LUNG CANCER

Despite the uncertainties discussed in the preceding sections of this review, there is general agreement on many aspects of asbestos-related lung cancer:[1]

1. There seems to be no major difference in the proportion of peripheral versus central cancers in patients exposed to asbestos, in comparison to those who were not[114,115,123–125] (although the histological type of lung cancer is strongly associated with a central versus peripheral location). Paris *et al.*[126] found that there was a trend towards a peripheral location for lung cancers in long-term ex-smokers (i.e., cessation for ≥10 years) with asbestos exposure (59%) in comparison to those with no documented asbestos exposure (20%), but no significant differences were found in short-term ex-smokers (25 vs 24%) or current smokers (33 vs 26%).

2. A predominance of lower lobe carcinomas among asbestos-exposed workers has been recorded in several studies, with an upper lobe to lower lobe ratio that varied from 1:1.5 to 1:3.5,[1] whereas for most 'ordinary' lung cancers related to cigarette smoke, upper lobe tumours predominate in a ratio of up to 2:1 or more. Other investigators[127–129] found no difference in the lobar distribution of lung cancer in such workers, and Lee *et al.*[130] found that lung cancers in asbestos-exposed individuals were located most often in the upper lobe. Upper lobe cancers also outnumbered lower lobe tumours in a ratio of almost 3:1 in all three groups of patients (asbestosis; plaques without asbestosis; neither plaques nor asbestosis) studied by Roggli and Sanders.[111] In other words, there are no significant differences in either the phenotypic repertoire or the anatomical distribution of lung cancers related to asbestos versus those that are not.

3. Asbestos-associated lung cancer incidence rates vary greatly from one occupational group to another (see later discussion).

4. For asbestos-exposed patients with pleural plaques as the only tissue marker of past exposure or whose estimated cumulative exposure is small, the increase in the RR_{LCA} may be small (<1.5) after allowance for other factors such as tobacco smoke.[122,131,132]

5. The RR_{LCA} in asbestos-exposed populations is greatest when asbestosis is present. Substantially higher RRs for

lung cancer are recorded for patients with progressive asbestosis than for those with clinically static asbestosis.[133] Allied to this observation, the RR_{LCA} appears to increase with the severity of the pulmonary fibrosis, and hence with the inhaled dose of asbestos, because the severity of asbestosis generally correlates with the fibre load in lung tissue.[134,135] In 2000, Roggli and Sanders[111] reported a study on the asbestos body (AB) and asbestos fibre content of lung tissue in 234 cases of lung cancer with 'some history of asbestos exposure'. They found the median AB and total asbestos fibre content for fibres 5 μm or longer, mainly commercial amphiboles and primarily amosite, to be >35 and 20 times higher, respectively, for 70 patients with histological asbestosis (Group I) than for 44 patients with pleural plaques as assessed at autopsy or thoracotomy in the absence of asbestosis (Group II), and 300 and 50 times higher than the AB/fibre content for 120 patients with neither plaques nor asbestosis (Group III), for whom the median AB/fibre content was about 28 and eight times greater, respectively, than the control group; the median AB and uncoated fibre counts for the plaque-only group (II) were about 245 and >23 times greater than the control group. In this study, like others, there was also overlap between Groups I–III in the counts of ABs and fibres.

ASBESTOSIS AND LUNG CANCER: THE FIBROSIS→CANCER HYPOTHESIS

From the time of the first anecdotal reports on the occurrence of lung cancer in patients with asbestosis, there has existed an assumption that the processes of asbestos-mediated fibrogenesis and carcinogenesis are closely interwoven,[131] leading to the postulate that the fibrosis is an obligate causal precursor for the cancer. In reviewing 1930s case reports on this association, Nordmann[3] suggested that the lung cancer has its origins in the bronchiolo-alveolar hyperplasia that accompanies late-stage asbestosis, as in other forms of diffuse interstitial fibrosis. In effect, the fibrosis→cancer hypothesis postulates that asbestos cannot induce lung cancer by itself, but only through an intermediary and obligatory step of interstitial fibrosis (i.e., asbestos→asbestosis→cancer);[115,136,137] basically this hypothesis postulates a specific and invariable causal mechanism.

Comprehensive discussion of the evidence for and against this proposition lies beyond the scope of this paper, but proponents of this hypothesis point *inter alia* to the occurrence of lung cancer in forms of diffuse interstitial fibrosis (DIF) other than asbestosis, such as usual interstitial pneumonia/fibrosing alveolitis and so-called scleroderma lung.[138,139] In a study from Japan, Nagai *et al.*[140] reported lung cancer in 38% of patients with DIF who were smokers and in 11% of the same group who were non-smokers. The figure of 38% is roughly comparable with the high frequency of lung cancer development in asbestosis.[1] Nonetheless, in this study, 88% of the tumours were peripheral in distribution and the diagnosis in 27 out of 31 cases was established by transbronchial biopsy of lung: in limited samples of this type, there is a problem in distinguishing between genuine lung cancer and the reactive bronchiolo-alveolar epithelial proliferation that is an almost invariable accompaniment of DIF. In contrast, Wells and Mannino[141] found a 5% rate of association between DIF and lung cancer in the US in comparison to 27% for asbestosis and lung cancer, as assessed from death certificates. In this respect, there is an extraordinary association between asbestosis and lung cancer, so that lung cancer occurs in about 25–45% of cases or more, and is now the leading cause of death among asbestotics.[1,115,133] Oksa *et al.*[133] identified 11 lung cancers in 24 patients with progressive asbestosis (46%; standardised incidence rate [SIR]=37), in comparison to five of 54 non-progressors (9%; SIR=4.3); however, this study did not address a group of patients with comparable exposures in the absence of asbestosis and does not contribute to the question of whether or not asbestosis is a necessary precursor for the cancer, as stated explicitly by the authors.[133]

Three cornerstones of the fibrosis→cancer hypothesis are the studies reported by Kipen *et al.*[142] (chest X-ray findings and histological evidence of asbestosis in insulation workers who died from lung cancer), Sluis-Cremer and Bezuidenhout[143] (lung cancer and the presence or absence of histological asbestosis and its grade at autopsy among South African amphibole miners), and Hughes and Weill[136] (lung cancer mortality and chest X-ray evidence of asbestosis among New Orleans asbestos-cement workers). The limitations of these studies have been discussed in detail elsewhere.[1] Here it is sufficient to point out that:

1. The study on insulation workers reported by Kipen *et al.*[142] involved problems of case selection—so that the asbestosis status by histology and radiology was unknown for 69% of the workers (312/450 deaths)—and also a problem with histological criteria for the diagnosis of asbestosis, with the potential for over-diagnosis:[144–146] histological evaluation was often carried out on the same side as the tumour, with the potential for confounding of interpretation by fibro-inflammatory changes secondary to the cancer; in addition, the diagnosis of asbestosis was made in 6% in the absence of detectable asbestos bodies.

2. The autopsy-based study on South African amphibole miners reported by Sluis-Cremer and Bezuidenhout[143] also involved problems with case selection (399 autopsy cases analysed for whom compensation was sought,[147] out of 1165 deaths); in addition, when a logistic regression was carried out allowing for the grade of asbestosis, the authors acknowledged that years of exposure—the most accurately measurable parameter of cumulative exposure—accounted for most of the variation, although the grade of asbestosis remained a significant risk factor for bronchial cancer.[147,148]

3. The study on New Orleans asbestos-cement workers conducted by Hughes and Weill[136] was beset with a problem over statistical power; e.g., the power level for the sample of 420 to detect a lung cancer standardised mortality ratio (SMR) or RR_{LCA} of 1.5 would be about 40%, so that a true effect would be falsely found non-significant 60% of the time.[1]

In addition, other studies have been reported where there was evidence of an increased incidence or risk of lung cancer in the absence of radiographic evidence of

asbestosis. In an investigation of hospital patients, Wilkinson *et al.*[149] found that after adjustments for gender, age, smoking history and area of referral, the OR_{LCA} was 2.03 for 211 patients with a median ILO (International Labor Organization) chest radiograph score of $\geq 1/0$, whereas the OR_{LCA} was 1.56 in 738 patients with a score of $\leq 0/1$ (95%CI = 1.02–2.39). In a chest X-ray study on lung cancer in the Wittenoom cohort, de Klerk *et al.*[150] demonstrated an increase in RR_{LCA} with increasing cumulative exposure to asbestos, in the absence of radiographic asbestosis; the presence of asbestosis conferred an additional risk, but with a less steep slope for the dose-response line. In a chest radiograph-based study of asbestos-cement workers in Ontario, Finkelstein[151] found an increase in the RR_{LCA} in the absence of radiographic asbestosis. These studies have also attracted criticism: e.g., the Finkelstein[151] study failed to identify a relationship to smoking—apparently due to misclassification of smoking habits for some patients—and there was no 'significant' dose–response effect, whereas McDonald and Newman Taylor[152] answered the criticisms[153,154] directed at the study by Wilkinson *et al.*[149]

In a review of cohort studies that excluded case-referent studies, autopsy investigations and fibre burden analyses, Weiss[155] supported the view that excess lung cancer risk occurs only among those cohorts where asbestosis also occurs. He concluded that 'asbestosis is a much better predictor of excess lung cancer risk than measures of exposure and serves as a marker for attributable cases'. The subject of critical editorial comment by Banks *et al.*,[156] this review embodies several problems; for example:

1. The review pointed to an SMR of 3.11 for lung cancer among Quebec miners and millers with small opacities in chest radiographs, a marker for asbestosis. However, the SMR was also elevated at 3.30 (95%CI = 2.32–4.62) in workers with radiographic abnormalities other than small opacities; Banks *et al.*[156] point out that 11 out of the 37 in this category had a 'large opacity', not a feature of asbestosis, so that the SMR for lung cancer was apparently increased among those with radiological abnormalities other than asbestosis.

2. Weiss[155] cited one study[157] with data on the association between cumulative asbestosis and excess lung cancer mortality rates, which recorded an excess lung cancer death rate of 8.48 per 1000 among 884 workers with light/moderate exposure lasting ≤ 2 years, an exposure unlikely to be sufficient to induce clinical asbestosis, so that the asbestosis death rate was zero. The figure of 8.48/1000 was based on 24 lung cancer deaths observed minus 16.5 expected, which equates to 7.5/884 workers (SMR = 1.45; 95%CI = 0.93–2.16). Weiss[155] claimed that this '... small excess lung cancer death rate ... is not statistically significantly different from no excess ...'. However, if one theorises that the asbestos-attributable excess lung cancer death rate is zero when there is no asbestos exposure—a zero exposure, zero effect model—and notes that the excess lung cancer death rate in the same study[157] was 19.49/1000 among those with light/moderate exposure lasting > 2 years, when the asbestosis death rate was 3.61, then a trend to an increase in lung cancer SMR is evident even at light/moderate exposures of ≤ 2 years (no asbestosis): χ^2_1 (trend) = 163.9; $P \ll 0.005$.[2]

3. Weiss[155] argues that increased death rates or risks of lung cancer occur in cohorts where asbestosis also occurs. But this does not mean that asbestosis and lung cancer must occur *seriatim* in the same individual. All the data indicate is that lung cancer death rates are raised in cohorts where asbestosis occurs in some individuals (not necessarily those who develop lung cancer). This observation is equally explicable by a dose-response effect for both asbestosis and lung cancer without a direct fibrosis→cancer linkage.[156]

If it were to hold true, several conclusions and predictions flow from the fibrosis→cancer hypothesis: because the hypothesis postulates fibrosis as the linchpin in the pathogenesis of asbestos-associated lung cancer, it follows that:

(a) There can never be any increase in the RR_{LCA} when the exposure to asbestos is insufficient to induce asbestosis.

(b) No matter how heavy the asbestos exposure, lung cancer in an individual patient cannot be attributed to the exposure unless fibrosis (asbestosis) is also present as a precondition.Here one might draw attention to cases of lung cancer with clear evidence of heavy exposure to asbestos in the absence of detectable asbestosis. For example, in one case, the patient sustained heavy exposure to asbestos at an asbestos-cement factory and he later developed lung cancer; fibre burden analysis carried out on autopsy lung tissue revealed an amphibole count of about 40–108 million fibres longer than 1 μm/g dry lung in the lobes sampled (reference 158; Table 4–7), but there was no histological evidence of asbestosis; the geometric mean asbestos fibre count for the same laboratory among asbestosis patients whose exposure occurred other than at Wittenoom was ~2.5 million fibres longer than 1 μm/g dry lung.[158,159] According to the fibrosis→cancer hypothesis, lung cancers among the asbestosis patients would be attributable to asbestos, whereas this patient's exposure would not qualify, even though the fibre count on his lung tissue was up to about 40 times higher (see Case and Dufresne[160]).

(c) The hypothesis clearly presupposes a threshold effect. The possible existence of a threshold exposure to asbestos for lung cancer induction remains the subject of controversy and uncertainty, because there are few observational data on lung cancer risk for exposures at airborne fibre concentrations under 1.0 fibre/mL,[8,72] and no such threshold has been delineated.[8,62,73,161] Hodgson and Darnton[73] argue that if a threshold does apply to lung cancer induction by amphibole asbestos, 'it must be very low', whereas a threshold for chrysotile—'zero or at least very low risk'—is 'strongly arguable', and they calculate the excess risk of lung cancer to be insignificant at a cumulative chrysotile exposure of 0.01 fibres/mL-years (fibre-years), except in exceptional circumstances ('an estimate of 1 death per 100 000 might be justified').

(d) Explaining the dose-response relationship between cumulative asbestos exposure and the RR_{LCA} is a more complex exercise than in the cumulative exposure model discussed below, because the fibrosis→cancer hypothesis predicts that: (i) there is no dose–response effect at sub-asbestotic exposures, and (ii) at higher cumulative