

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.

Received 8 June, accepted 1 September 2004

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 Samet¹² 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. Axelsson²³ has estimated that more than a quarter of all

lung cancer cases in Sweden are related to occupational exposures and similar proportions have been reported for Finland,²⁴ Norway²⁵ 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 fraction²⁹ 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 lung¹¹ 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, Raffin *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. Tossavainen¹⁷ 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) document⁷ 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}

Year	United Kingdom*			Germany†		
	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 <i>et al.</i> 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 1998/99⁴⁵ (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 1995⁴⁸—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 Italy⁵² 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 Barroetavena⁵⁶ 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 Barroetavena⁵⁶ 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 asbestosis⁵⁷ (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 Tossavainen⁶⁰ 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 authors⁶⁰ 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 exposure⁶² (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/m³).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–Darnton⁷³ 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 Darnton⁷³ 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 authors⁷³ 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 chrysotile⁷⁰ 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 authors⁸⁰ 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.

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, Lee¹⁵ 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) Lee⁹³ 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 effect¹⁶).

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

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.

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 Stevens⁹⁷ 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

TABLE 3 Age-adjusted ORs for lung cancer in 'current' cigarette smokers¹⁰⁰

	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.

associated with tobacco smoking are squamous and small cell carcinomas, with a somewhat weaker association for adenocarcinoma.^{14,99,100} Accordingly, Zang and Wynder¹⁰⁰ 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).

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 *RR*s 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 smoking¹—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 Boffetta¹⁴ discussed three studies with information on this issue: they concluded that the data in one study⁹⁹ pointed to an approximately multiplicative ($\sim M$) effect for squamous cell carcinoma, an additive (A) effect for adenocarcinoma, and an $\sim A$ relationship for small cell carcinoma; in the second study¹⁰⁶ '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 Sanders¹¹¹ 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. Baker¹¹⁶ 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-Cremer¹¹⁷ 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 authors¹¹⁹ 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 Isenberg¹²¹ and Hillerdal¹²² 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 Sanders¹¹¹ 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, Nordmann³ 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 Mannino¹⁴¹ 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 Bezuidenhout¹⁴³ (lung cancer and the presence or absence of histological asbestosis and its grade at autopsy among South African amphibole miners), and Hughes and Weill¹³⁶ (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 Bezuidenhout¹⁴³ 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 Weill¹³⁶ 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, Finkelstein¹⁵¹ found an increase in the RR_{LCA} in the absence of radiographic asbestosis. These studies have also attracted criticism: e.g., the Finkelstein¹⁵¹ 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 Taylor¹⁵² 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, Weiss¹⁵⁵ 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. Weiss¹⁵⁵ cited one study¹⁵⁷ 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). Weiss¹⁵⁵ 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 study¹⁵⁷ 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. Weiss¹⁵⁵ 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 $1 \mu\text{m/g}$ 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 $1 \mu\text{m/g}$ 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 Dufresne¹⁶⁰).

- (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 Darnton⁷³ 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

exposures, asbestos-exposed cohorts are divisible into two subclasses—one subclass with asbestosis and an increased RR_{LCA} , and a second subclass without asbestosis for which $RR_{LCA} = 1.0$ —so that the high RR_{LCA} in the first subclass is diluted when mixed with the second, while maintaining dose-response linearity across the whole cohort, because of dose-response linearity for asbestosis.

However, in their investigation of the South Carolina (Charleston) asbestos textile workers, Dement *et al.*⁷⁸ found an SMR of 2.59 and a standardised risk ratio (SRR) of 2.63 for white males (95%CI=1.20–5.75) at exposures as low as the range of 2.7–6.8 fibres/mL-years (for white males, the SMR and SRR were 1.96 and 2.03, respectively, for exposures in the range 6.8–27.4 fibre-years; for the same group, the SMR and SRR were 3.08 and 2.95 at 27.4–109.5 fibre-years, and 8.33 and 6.60, respectively, when the exposure was >109.5 fibre-years). The estimated cumulative exposure of 2.7–6.8 fibres/mL-years was below the level at which Green *et al.*,⁸⁶ in an autopsy study on the same cohort, found histological asbestosis; in addition, the predicted fibrosis score at 2.7–6.8 fibre-years would be in the range for the reference group. These findings indicate that for this cohort an increase in the lung cancer rate occurred at cumulative exposures insufficient for induction of histological asbestosis, so that this observation constitutes a falsification factor for the fibrosis→cancer hypothesis.^{29,59,162,163} (See also later discussion of the studies reported by Gustavsson *et al.*^{94,164} and Carel *et al.*,¹⁶⁵ which also recorded elevated RRs/SMRs for lung cancer at estimated cumulative exposures that were insufficient to induce asbestosis.)

Case and Dufresne¹⁶⁰ have argued that the fibrosis→cancer hypothesis ventures into the realm of ‘mechanistic speculation’ beyond existing evidence, and they also observed that the clinical diagnosis of asbestosis can be arbitrary and not consistently reproducible. In this respect, it is known that chest radiographs may fail to detect asbestosis in some individuals with histologically proven asbestosis,^{6,131,134} so that the sensitivity of conventional chest X-rays for the detection of asbestosis is about 80–85% or less, depending upon the grade of the disease, and abnormalities suggestive of asbestosis have been found by high-resolution CT scans in up to about 30–35% of asbestos-exposed workers with normal chest radiographs.¹⁵⁸ In addition, although pleural abnormalities such as plaques may point to a radiological diagnosis of asbestosis, the interstitial opacities lack specificity by themselves and cannot be distinguished with certainty from other forms of interstitial disease,^{65,131,134,158} so that the diagnosis of asbestosis may be arbitrary on occasions,¹⁶⁰ and Case and Dufresne¹⁶⁰ refer to ‘an excess of idiopathic diffuse pulmonary fibrosis’ among cases of lung cancer without asbestosis. Pleural plaques are also liable to over-diagnosis in plain chest radiographs unless strict criteria are used for their diagnosis, when they are liable to under-diagnosis.¹³¹ In a review of approaches to compensation for occupational diseases, Piekarski *et al.*⁵⁷ point out that medical criteria appear to be applied ‘arbitrarily and inconsistently’ for compensation, including claims for asbestosis: for one series of patients who filed claims for non-malignant asbestos diseases during the 1980s

in Washington, the likelihood of claim acceptance was unrelated to the severity of the radiographic abnormalities.

Finally, the fibrosis→cancer hypothesis cannot account easily for the observation that asbestosis affects distal lung tissue, whereas the anatomical distribution of lung cancer among asbestos workers does not differ significantly from lung cancers among the general population, with localisation to the larger airways for a high proportion of cases^{1,125,126,160} (see preceding discussion on elevated concentrations of asbestos fibres, including both amosite and chrysotile fibres, in the airway tissues as opposed to parenchymal asbestos fibre concentrations, in smokers versus non-smokers⁹⁷). Paris *et al.*¹⁶⁶ also recorded a significant and independent association between high-grade intra-epithelial bronchial mucosal lesions (severe dysplasia/carcinoma *in situ*) and the duration of exposure to asbestos (as well as an association with active smoking status, synchronous invasive cancer, and exposure to other occupational carcinogens).

As is evident from the preceding discussion, the fibrosis→cancer hypothesis invokes a specific and invariable causal mechanism for lung cancer induction by asbestos, despite incomplete knowledge of the precise mechanics of the process. There is increasing evidence that the capacity of asbestos to induce oxidative damage to DNA is an important mechanism for asbestos-mediated carcinogenesis and for fibrosis;^{167–169} there is a well-recognised dose-response effect for both asbestos-related cancers and fibrosis, but there is no proven sequential or obligatory mechanistic linkage between fibrosis and carcinogenesis.^{96,167} This issue has been summarised by Nelson *et al.*:¹⁶⁷ ‘Both fibrosis of the lung and cancer of the lung are dose-related occurrences ... consequently ... [the] majority of cancers will occur in those people who have the highest exposure ... [and who] ... will be most likely to have asbestosis, regardless of whether the process that produces lung cancer has anything to do with fibrosis. ... Only if the biologic process that gives rise to fibrosis itself also directly induces genetic changes important for the production of lung cancer (or creates conditions that enhance the likelihood of these mutations in relevant cells) can it be *necessary* for interstitial lung disease to be present for asbestos to cause lung cancer. ... [Little] direct evidence that this occurs has been presented to date. Thus, it can be said that ... there is no direct evidence that there is any necessity for asbestosis to be present for a lung cancer to be caused by [asbestos]’ (p.478; italics in the original).

CUMULATIVE EXPOSURE TO ASBESTOS AND THE RISK OF LUNG CANCER: THE CUMULATIVE EXPOSURE MODEL

The cumulative exposure hypothesis for lung cancer induction by asbestos is not new and was endorsed by the Ontario Royal Commission in 1984,¹⁷⁰ before publication of the three pivotal studies^{136,142,143} in favour of the fibrosis→cancer hypothesis discussed in the preceding section of this chapter (1987–1991). Even earlier, in its 1982 Report to Parliament, the Industrial Injuries Advisory Council for the United Kingdom¹⁷¹ reached the following conclusions:¹⁷² ‘33. We are clear

from the evidence we have received that occupational exposure to asbestos may cause lung cancer in the absence of overt asbestosis. The evidence provides no information about the frequency with which this may happen, except that it is likely to be low. We are also clear that, although among such cases tobacco smoking is likely to be a more important causal factor than the asbestos exposure, the risk of workers developing lung cancer is [asbestos] dose-related, regardless of smoking habits'.

Multiple subsequent studies and reviews have also supported the cumulative exposure model,^{1,2,36,73,90,158,160,173–176} with no clearly delineated threshold.^{73,94,164,165,176} The problem with the cumulative exposure model is to derive indices of asbestos exposure appropriate for probabilistic attribution in the individual.

In most epidemiological studies, a direct linear relationship has been demonstrated between RR_{LCA} and cumulative exposure to asbestos,^{8,46,62,72} including chrysotile and the amphiboles, expressed as:

$$RR_{LCA} = 1 + K_L \cdot E$$

where E is cumulative asbestos exposure, expressed as fibres/mL-years (fibre-years), and K_L is the industry-specific slope of the relationship expressed as the increase in the excess risk ($RR_{LCA}-1.0$) per one fibre-year of exposure. In this respect, a 1991 consensus paper³⁶ reviewed five government-sponsored reports that described 15 cohort studies, and it was accepted that RR_{LCA} is proportional to cumulative exposure. The value of K_L varies across cohorts: i.e., from 0.0001–0.002 (0.01–0.2% per fibre-year) in miners and for friction products manufacture, to 0.003–0.09 (0.3–9% per fibre-year) in cohorts of asbestos-cement,^{177,178} asbestos textile,^{179,180} and insulation workers^{181,182} (Fig. 1).¹⁸³

Positive estimates for K_L have been obtained in most studies, but some are based on a small number of cases or deaths,⁸ and some authorities have suggested an average value of $K_L=0.01$ independent of fibre type—after exclusion of chrysotile miners because of their substantially lower RR_{LCA} per unit exposure—corresponding to an increase of 1% in RR_{LCA} for each fibre-year of exposure.⁸ The figure of 4% per fibre-year mentioned in The Helsinki Criteria¹⁰² lies near the mid-point of the K_L value range of 0.003–0.09 for textile, insulation and asbestos-cement workers, corresponding to the most frequent patterns of exposure across industrialised nations.^{9,54,62}

The additive increase in RR_{LCA} for 25 fibre-years of exposure has been estimated at 1.5 for amosite factory workers.¹⁸⁴ For the Wittenoom cohort of crocidolite miners/millers, the RR_{LCA} is 1.8 at 25 fibre-years and 2.0 at 35 fibre-years,¹⁸⁵ suggesting a greater proportional carcinogenic effect of asbestos at low exposures than at higher exposures (see following discussion). In 1995, Rödelsperger and Woitowitz¹⁸⁶ reviewed estimated dose-response relationships for lung cancer and mesothelioma in humans and in animal models, and they calculated the cumulative exposures for white South African amphibole miners: 'An average cumulative exposure of 15.2 fibre years for amosite miners and 9.83 fibre-years for crocidolite miners can be obtained from the discussion in Sluis-Cremer *et al.* (1992). Despite the fact that this

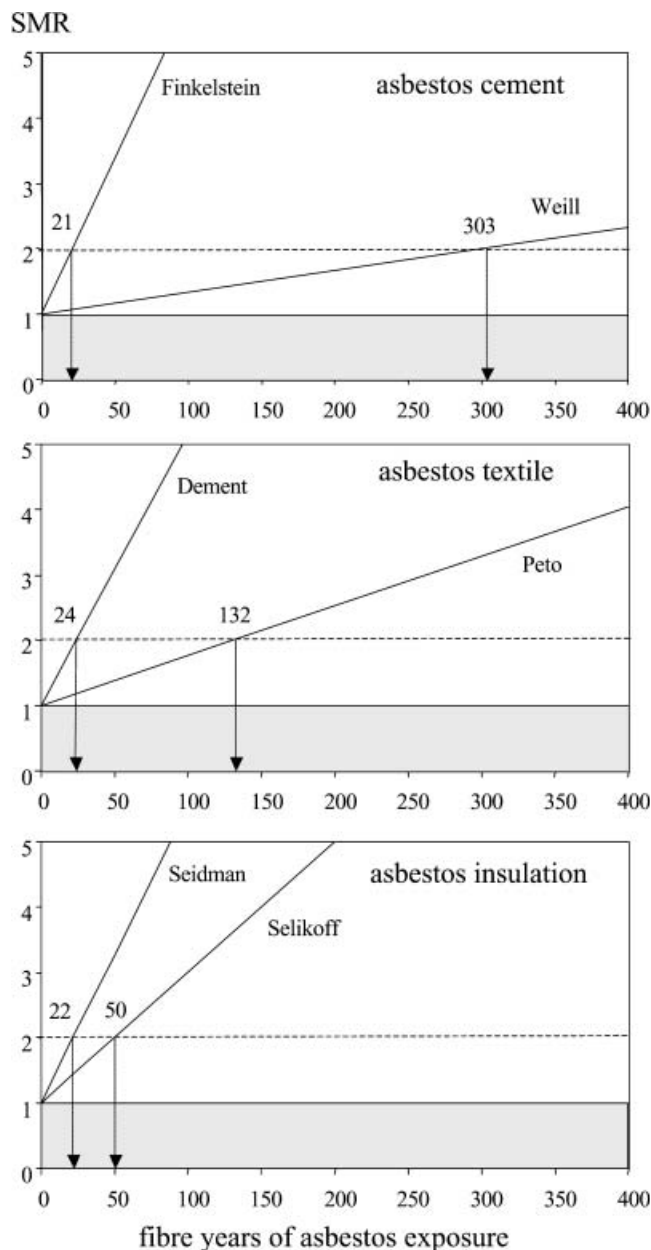


Fig. 1 Dose-response relationship expressed as SMR for lung cancer related to cumulative asbestos exposure measured as fibre-years for cohorts of asbestos textile, asbestos cement and asbestos insulation workers.¹⁸³ Fibre-years of exposure that may be related to a 2-fold risk of lung cancer (SMR = 2.0) range between 20 fibre-years ($K_L=5.0\%$ per fibre-year) and 300 fibre-years ($K_L=0.033\%$ per fibre year).

estimated exposure is very low, the SMR for lung cancer altogether increased to 1.72 (95% confidence interval CI=1.32–2.21); for amosite miners the SMR amounted to 1.38 (90%CI=0.97–1.91) and for crocidolite miners to 2.03 (90%CI=1.43–2.80)', thereby suggesting that the RR or SMR for lung cancer may reach 2.0 with cumulative exposures less than 25 fibre-years.

The linear model implies that RR_{LCA} is proportional to fibre-years of exposure and does not depend on: (i) age at the commencement of exposure; (ii) time since cessation of exposure; and (iii) smoking habits.⁷² From pooled evaluation of several studies, there appears to be a

somewhat higher risk for non-smokers¹⁸⁷ (see preceding discussion in Introduction). There is also some evidence that the risk may fall after cessation of exposure,⁸⁹ and short-term workers may have a disproportionately high risk, despite low exposure estimates.^{36,188,189} By use of the linear no-threshold model and extrapolation from high exposures to low-level exposure, Goldberg⁷² estimates that about 30 excess cases of lung cancer could be expected among 10 000 men exposed at 0.1 fibre/mL from age 20 to 65 years, and about 16 additional cases among the same number of women.

The linearity of the dose-response effect has been questioned,⁷³ and there are some data to suggest that the slope of the dose-response line may be steeper at low exposures than at high exposures.^{94,164,190} In a case-referent study on 1042 lung cancer cases and 2364 referents in Sweden, Gustavsson *et al.*¹⁶⁴ found that asbestos produced an unexpectedly high lung cancer risk at low exposures (Table 4), and dose-response analysis found a 14% increase in lung cancer risk per fibre/mL-year of exposure.

In a further analysis that addressed the interactive effect of asbestos and tobacco smoke, Gustavsson *et al.*¹⁹⁰ reported that after adjustments for age, year of inclusion, radon exposure and environmental air pollution, the RR_{LCA} was 3.4 at asbestos exposures >0.9 fibre/mL-year among non-smokers, whereas the RR_{LCA} was 21.7 for current smokers with no identifiable exposure and 29.2 for current smokers with asbestos exposures in excess of 0.9 fibre/mL-year. The interactive effect at these low exposures approximated an additive model and the increase in risk per fibre/mL-year was 'higher than that predicted by linear extrapolation from highly exposed cohorts, especially among non-smokers'.¹⁹⁰

Gustavsson *et al.*⁹⁴ later reported a further population-based case-referent analysis of lung cancer risk among men in Stockholm for the period 1985–1990 relative to low-dose occupational exposure to asbestos (mainly chrysotile and mainly end-use exposures). This study involved 1038 cases and 2359 referents, with adjustments for other occupational exposures and environmental pollutants, including radon, as in the preceding paper.¹⁶⁴ Assessment of smoking took into account smoking status, including ex-smokers and life-long non-smokers, the amount smoked, and potential misclassification of smoking habits. Asbestos exposure was assessed from the airborne fibre measurements (see following paragraph), taking into account changes in asbestos levels over 'calendar periods',

and cumulative exposures were estimated with blinding for the case/referent status of the individuals, as in the preceding publication.¹⁶⁴ Twenty per cent of the cases and 14.4% of the referents had been exposed to asbestos for at least 1 year and the cumulative exposures were low, ranging from zero (background) to a maximum of 20.4 fibres/mL-years. Gustavsson *et al.*⁹⁴ found that lung cancer risk increased with cumulative exposure according to an almost linear relationship, with a joint effect with smoking that lay between additivity and multiplicativity at the low-dose exposures estimated for this study. The calculated risk at a cumulative dose of 4.0 fibres/mL-years was 1.90 (95%CI=1.32–2.74), and was 5.38 among never-smokers and 1.55 for current smokers. The authors⁹⁴ claimed that this study appeared to have reasonable precision up to about 5.0 fibre-years but gave no information on higher cumulative exposures. The RR_{LCA} for those who smoked >30 cigarettes per day was 50 times higher than the risk for never-smokers.

The accuracy of retrospective assessment of asbestos exposure is a major inherent problem with case-referent studies of this type,^{191–194} especially when the exposures are low. Under-estimation of exposures equally for cases and referents will lead to over-estimation of effects in terms of the RR or OR for lung cancer at a particular calculated exposure level, whereas the converse holds true for equivalent over-estimation of exposures (analogous comments also apply to cohort studies). For such case-referent studies, the estimates of probability, frequency and intensity of exposure are often based not on specific individuals, but on specific combinations of occupations and industries, with the potential for introduction of an uncertainty factor into the findings (see following discussion, including the section on meta-analysis). In this respect, 6.8% of the cases and 3.6% of the referents for the Gustavsson *et al.*¹⁶⁴ study had estimated exposures of 1.5 fibres/mL-years or more, whereas Rödelsperger *et al.*¹⁹⁴ found that 21 of 125 population controls (16.8%) had exposures in excess of 1.5 fibres/mL-years; in a case-referent study from Norway reported in 1986,²⁵ 25% of the cases and 10% of the referents had been moderately to heavily exposed to asbestos during their working careers. In a screening program in Finland, however, Huuskonen *et al.*¹⁹⁵ found that about 4% of the entire population had some work-related exposure to asbestos, and ~1% had considerable to high exposures. The exposure estimates in the studies reported by Gustavsson *et al.*^{94,164,190} were based on a large survey of asbestos exposures in Swedish

TABLE 4 Relative risk of lung cancer by quartiles of cumulative asbestos exposure for Stockholm County, Sweden¹⁶⁴

Asbestos exposure (fibre/mL-years)	Mean cumulative exposure in class (fibre/mL-years)	Number of cases	Number of referents	RR crude (95%CI)	RR adjusted #1* (95%CI)	RR adjusted #2† (95%CI)
None	0	833	2024	1.0	1.0	1.0
>0–0.50	0.29	42	84	1.20 (0.82–1.76)	1.25 (0.81–1.92)	1.23 (0.80–1.89)
0.51–0.88	0.70	34	81	1.01 (0.67–1.53)	0.96 (0.61–1.51)	0.89 (0.56–1.41)
0.89–1.49	1.16	62	90	1.65 (1.18–2.30)	1.59 (1.09–2.32)	1.48 (1.01–2.17)
≥1.5	4.03	71	85	2.05 (1.48–2.84)	1.83 (1.27–2.65)	1.68 (1.15–2.46)

Modified from Table 4 in Gustavsson *et al.*¹⁶⁴

CI, confidence interval.

*#1, adjusted for age, selection year, smoking, residential radon levels, and environmental exposure to nitrogen dioxide.

†#2, RRs were in addition adjusted for occupational exposure to diesel exhausts and combustion products.

workplaces in 1969–1973, involving 2400 samples at 35 workplaces and was considered representative of 70–75% of the asbestos imported into Sweden at that time;⁹⁴ airborne fibre levels were measured by the membrane filter method and phase-contrast light microscopy according to criteria specified by the American Conference of Governmental Industrial Hygienists (ACGIH) in 1973.⁹⁴

Between 1993 and 2003, multiple epidemiological studies reported on lung cancer risk in individuals exposed to asbestos. In 1997, Steenland and Stayner¹⁹⁶ summarised 24 epidemiological studies on lung cancer published between 1979 and 1994, in which lung cancer SMRs varied from 0.9 to 5.0. An exposure-response relationship was demonstrated in 15 studies, with no such relationship in four, and there was no information in five. Van Loon *et al.*,¹⁸ in their report on The Netherlands Cohort Study also referred to five studies on asbestos and lung cancer, with RR_{LCA} estimates that varied from 2.0 to 4.1, among which only one reported a non-significant positive association between cumulative exposure to asbestos and RR_{LCA} . The Netherlands Cohort Study¹⁸ found the RR_{LCA} to be 2.49 overall, with a value of 1.59 for low exposures, 0.96 for intermediate exposures, and 3.49 for high exposures; the exposures were divided into tertiles that did not correspond to cumulative doses, but to probabilities of exposure: the RRs adjusted for age and other occupational factors were 1.82 (low), 1.29 (intermediate) and 2.72 (high).

In a study across 13 nations of pulp/paper industry workers, 36% of whom had some asbestos exposure, Carel *et al.*¹⁶⁵ did not detect any increment in the risk of lung cancer in comparison to age-specific and period-specific national mortality rates (a slight deficit in overall and neoplasm-related mortality was observed); however, on internal analysis, there was a trend in mortality for both lung cancer and pleural cancer, weighted for individual probability of asbestos exposure and its duration. Accordingly, the lung cancer SMR was 1.44 for exposures amounting to ≥ 0.78 fibres/mL-years in comparison to ≤ 0.01 fibres/mL-years (95%CI=0.85–2.45); for pleural cancer at the same compared levels of exposure, the SMR was 2.43 (95%CI=0.43–13.63).

Szeszenia-Dabrowska *et al.*¹⁹⁷ found a statistically significant increased SMR for lung cancer among subjects with asbestosis and cumulative asbestos exposures of >25 fibres/mL-years. In a study from Spain, Badorrey *et al.*¹⁹⁸ found that the OR_{LCA} was related to both smoking ($OR=10.10$; 95%CI=3.5–29.13) and occupational exposure to asbestos ($OR=2.8$ after adjustment for smoking; 95%CI=1.0–7.84), but this investigation did not quantify the asbestos exposures.

Among 3057 asbestos-cement factory workers in Israel during the period 1953–1992 (where the asbestos comprised 90% chrysotile and 10% crocidolite), and employed for an average of 3.4 years, Tulchinsky *et al.*⁴⁰ found a non-significant lung cancer SIR of 135 (95%CI=85–185), but the SIR was >200 for workers employed for about ≥ 13 years (Fig. 1 in the original); this study was affected by low statistical power related to the small number of lung cancers detected (34) and the short follow-up interval, and the authors commented that ‘we can expect the numbers to rise [in coming years] as the full impact of

earlier exposures take their toll...’.[‡] Ulvestad *et al.*⁴¹ reported a lung cancer SIR of 3.1 among workers involved in asbestos-cement manufacture in Norway (95%CI=2.1–4.3), but again this study did not quantify the exposures and it did not detect a dose-response effect.

In a study of 13 354 unionised carpenters in New Jersey, Dement *et al.*²⁰¹ recorded an SIR of 1.52 for cancers of the respiratory system, and for carpenters in the union for >30 years the lung cancer SIR was 4.56.

For 16 696 building construction workers in Finland during the period 1990–2000, Koskinen *et al.*¹³² found that the overall cancer risk was not significantly increased ($SIR=1.1$; 95%CI=0.9–1.2), but the RR_{LCA} was ~ 2 for those with radiographic evidence of asbestosis and ~ 3 for a high index of cumulative exposure, with evidence of a dose-response effect (Table 5); there was only a slight or non-significant increment in risk for pleural plaques alone (~ 1.3 on univariate analysis, with a 95%CI of 1.0–1.7, and on multivariate analysis a RR_{LCA} of 1.2, with a 95%CI of 0.9–1.6). The overall RRs for mesothelioma in this study were small in comparison to the indices of exposure, as was the smoking-related RR_{LCA} (3.74; 95%CI=3.21–4.29), explicable by the fact that reference groups comprised those with an asbestos exposure index (AEI) <20 for lung cancer and 0–39 for mesothelioma (Table 5), so that the risk for the reference groups did not correspond to ‘background’ risk for the general population. From the crude incidence data in this paper for lung cancer and mesothelioma in relation to the AEI, a standard test for linear trend can be carried out: χ^2_1 (trend)=48.7; $P<0.001$ (lung cancer) and 5.6; $P<0.025$ (mesothelioma).

Contradictory findings on the SMR for lung cancer associated with non-occupational exposure to Quebec chrysotile were reported by Camus *et al.*,²⁰³ who investigated 2242 deaths (1970–1989) among women aged ≥ 30 years in two chrysotile asbestos-mining areas. Average cumulative exposure was estimated at 25 fibre-years (range 5–125 fibre-years) with a lung cancer SMR of 0.99 (95%CI=0.78–1.25). Estimates of airborne fibre concentrations for the Camus study²⁰³ involved a complex assessment that included measurements of fibre concentrations for fibres longer than $5\mu m$ visible by light microscopy, with an estimated peak neighbourhood level of 1.0 fibre/mL or more for 1940–1954, and above 0.2 fibre/mL for the period of about 1905–1965. However, the estimates of airborne fibre concentrations seem high in comparison to data on environmental fibre levels related to the Zimbabwean and Russian chrysotile industries; i.e., less than 0.01 to 0.02 fibre/mL for the Shabani mine in Zimbabwe,⁶² and about 0.1 fibre/mL for Asbest City as converted from environmental gravimetric

[‡]Ideally, the follow up for prospective cohort studies should be to death of the entire cohort, to ensure that all cases of the disease under investigation (lung cancer or mesothelioma) are captured.¹⁹⁹ Uncertainties are introduced when the follow up is short and only a small proportion of the cohort has developed the disease or died;¹⁹⁹ for example, in the mortality study of construction workers reported by Sun *et al.*,²⁰⁰ there were 479 deaths among 12 107 workers followed over a 20-year period (4%). Mathematical predictions of future cases of the disease, based on time trends, do not entirely address this problem unless correlated with actual numbers over time, to ensure that the predictions are, in fact, supported by empirical data (to account for unanticipated variation in the time trends).

TABLE 5 RR_{LCA} among Finnish construction workers, adjusted for age and smoking according to univariate and multivariate log linear models,¹³² versus RR for mesothelioma

Marker/job	Univariate analysis		Multivariate analysis*	
	RR _{LCA}	95%CI	RR _{LCA}	95%CI
Lung cancer				
ILO fibrosis score				
< 1/0	1.0	Reference	1.0	Reference
≥ 1/0	2.0	1.4–3.0	1.9	1.3–2.7
Asbestos exposure index (AEI)†				
< 20	1.0	Reference	1.0	Reference
20–39	1.2	0.6–2.5	1.3	0.6–2.6
40–89	1.7	0.8–3.4	1.8	0.9–3.8
≥ 90	2.7	1.2–6.0	3.3	1.3–8.3
RR _{LCA} by type of work				
Technician	1.0	Reference	1.0	Reference
Carpenter	2.0	0.9–4.0	2.1	1.0–4.4
Electrician	1.8	0.7–4.7	2.2	0.8–5.8
Insulator	5.0	2.0–12.6	3.7	1.4–9.9
Painter	2.1	0.9–4.7	1.9	0.9–4.4
Plumber‡	2.4	1.1–5.3	1.5	0.6–3.9
Mesothelioma				
Asbestos exposure index (AEI)†				
0–39	1.0	Reference	1.0	Reference
40–89	1.9	0.7–5.1	1.9	0.7–5.2
≥ 90	10.1	3.4–30.1	10.5	3.5–31.3

Modified from Tables 4 and 5 in Koskinen *et al.*¹³²

RR_{LCA}, relative risk of lung cancer; CI, confidence interval; ILO, International Labor Organization.

*The multivariate analysis included the following variables: age; smoking (for lung cancer); pleural plaques; ILO fibrosis score (for lung cancer); and AEI. †The AEI was calculated by summation of the product of the duration in years and the weighting factors (WFs) for exposures sustained before and after introduction of asbestos regulations in Finland in 1976/1977: that is, $AEI = \sum WF \cdot \text{duration (year)}$.

As listed in Table 1 of the Koskinen paper,¹³² the WFs do not correspond to airborne fibre concentrations (fibres/mL), although they were based on industrial assessments; for example, the WFs for pipe and other insulation work pre-1977 are given as 10 and 2, respectively, and 2 and 1 thereafter.

‡In a case-referent study from France, Benhamou *et al.*²⁰² found a RR_{LCA} of 1.8 for plumbers and pipefitters ($P < 0.04$) after adjustment for cigarette smoking.

measurements.^{66,204} Airborne asbestos fibre concentrations in Quebec chrysotile mining towns were in the vicinity of 0.005 fibre/mL in 1984, about 0.08 fibre/mL in 1973–1974,⁶² and ≤ 0.016 fibre/mL for fibres longer than 5 μm during the period 1982–1996;²⁰⁵ unless there had been drastically higher environmental airborne fibre concentrations before 1973, it is difficult to see how a cumulative exposure of 25 fibre-years would come about.

When the low risk of lung cancer for the Quebec chrysotile miners/millers is taken into account, one would not expect any detectable increase in lung cancer SMR at the low end of the range of estimated non-occupational exposures among residents (i.e., 5 fibre-years);²⁰³ the authors of this study pointed out it had low statistical power to detect small risks, as conveyed by the wide confidence intervals.²⁰⁶

META-ANALYSES

There have been some attempts to carry out meta-analysis of published studies on quantitative dose-related lung cancer risk with asbestos exposure. The study of Lash *et al.*¹⁸⁹ illustrates the difficulty of this exercise when very heterogeneous studies are considered. These authors analysed 23 papers on 15 cohorts, including the Witte-noom crocidolite miners (Australia), the chrysotile miners from Italy and the vermiculite miners from Montana, where the ore was contaminated with tremolite. One problem concerns the conversion factors used to change

original mppcf measurements of airborne dust concentrations into fibres/mL.

In addition, Lash *et al.*¹⁸⁹ introduced an intercept different from 1.0 as an indication of smoking habits different from the standard population. Because of the interaction with asbestos, this deviation, ranging from 0.53 to 3.46, was believed to be relevant across all dose groups. As a consequence, the three steepest dose-response lines^{78,184,207} were depressed by factors of 1.32, 3.46 and 3.33, respectively, whereas the linear dose-response relationship in the earlier reviews began with an SMR of 1.0 for an exposure of zero fibre-year. This approach was justified by the uncertain estimate for short-term exposures resulting from the most dangerous jobs and by the extraordinarily high risk for short-term workers.^{183,188} From single studies included in the Lash meta-analysis,¹⁸⁹ the increase in lung cancer risk per fibre-year extends to $K_L = 4.6\%$. Across the meta-analysis, K_L is reduced to 0.042% per fibre-year for a fixed-effects model, required if there is only one dose-response relationship disturbed only by random error. Alternatively, the random-effects model yields $K_L = 0.26\%$ per fibre-year.

It is possible that pooled data studies may give more valid answers than meta-analyses of the type carried out by Lash *et al.*¹⁸⁹ but in the asbestos-lung cancer field, industry differences may preclude this. The summary estimate obtained from a random-effects model recommended by Lash *et al.*¹⁸⁹ has no population-specific interpretation: instead, it represents the mean of a distribution that generates effects. Unlike a standardised

rate ratio (SRR), it does not correspond to an average effect in a population. Random-effects summaries give proportionally greater weight to small studies than do fixed-effects summaries. As a consequence, random-effects summaries will be more heavily affected by biases that more strongly affect small studies.²

In another meta-analysis of 69 asbestos-exposed cohorts, Goodman *et al.*²⁰⁸ derived meta-SMRs of 163 and 148 for lung cancer with and without latency, and with significant heterogeneity of results. This heterogeneity of lung cancer risk involves at least two factors: variation between industries and variation in the patterns and levels of exposure; the latter may account for different results obtained for the same type of industry and also for some of the variation between different industries. For example, in a study from Swedish shipyard workers, Sanden *et al.*²⁰⁹ did not find any increase in the risk of lung cancer 7–15 years after exposure to asbestos had ceased; these authors²⁰⁹ referred to six other studies that showed an increase in the RR_{LCA} of 1.4–2.2, and an earlier study by Sanden *et al.*²¹⁰ in 1985 was in agreement with those findings; Sanden *et al.*²⁰⁹ also referred to two other investigations where the RR_{LCA} was 1.2. In the 1992 Sanden²⁰⁹ study, asbestos had been used in relatively small amounts (30–35 tons per year) between 1950 and 1972, when the use of asbestos ceased; moreover, the insulation jobs ‘were carried out by subcontractors not included’ in the study, so that the shipyard workers appear to have sustained low exposures, mainly to chrysotile, although some ‘could have been indirectly exposed [bystander exposure] to crocidolite in ... four naval ships’. Another study by Danielsen *et al.*²¹¹ on cancer among welders and other shipyard workers did not find an increased prevalence of lung cancer, but this study appears to have focused mainly upon smoking and fumes among welders and other workers, and it included office personnel. Moreover, in this study, most of the work that involved handling of asbestos was carried out after 1960 by ‘external firms ... [although] ... most production workers employed at the yard before approximately 1975 may occasionally have been exposed to asbestos fibers’. In their meta-analysis of multiple studies on lung cancer among asbestos workers, which showed heterogeneity in lung cancer risk, Goodman *et al.*²⁰⁸ emphasised that: ‘It appears that no epidemiologic study can be considered truly representative of the entire asbestos-exposed population; however, some studies may be representative of the specific occupational groups that comprise their cohorts. It is clear that, when evaluating asbestos contribution in individual lung cancer cases, one has to consider epidemiologic literature in its totality. The risk of developing lung cancer in construction workers with low levels of exposure to asbestos cannot be equated to that in an insulator from the Selikoff cohort. The cohort of Swedish construction workers studied by Fletcher *et al.* in 1993²¹² represented a very mixed group, with over 60% of its members having no or only bystander asbestos exposure’.

In the meta-analysis carried out by Goodman *et al.*,²⁰⁸ the percentage of deaths from mesothelioma was used as an imprecise surrogate for cumulative exposure levels, and for 19 cohorts where the percentage of deaths due to mesothelioma was >2.4%, the meta-SMR was 255: these 19 cohorts included crocidolite miners and millers in

Australia and other amphibole miners, railroad car construction workers, asbestos textile workers, asbestos-cement production, electrochemical plant workers, gas-mask factory workers, shipyard workers, asbestos sprayers, insulation workers and German ‘asbestos workers’ not further specified.

In an extensive analysis of 17 cohort studies, Hodgson and Darnton⁷³ derived estimates for the increase in lung cancer risk per fibre/mL-year of exposure of 4.2% for crocidolite and 5.2% for amosite, with a joint mean of 4.8%, and with a range of 3.4–10% for crocidolite and 1.9–5.8% for amosite; the increase in the risk of lung cancer for ‘pure’ chrysotile exposure was about 6% per fibre/mL-year for the South Carolina textile cohort. The figure for four other chrysotile cohorts, including two cohorts of miners dominated by the Quebec miners, was 0.06% (with a range of 0.03–6.7%); the summary estimate was 0.062%. Cohorts with mixed exposures showed substantial heterogeneity in the increase in risk, with a range of 0–6.2% and a summary estimate of 0.47% per fibre/mL-year for all mixed exposures. Although individualised estimates of exposure are acknowledged to be the most reliable guide to dose-specific risk,^{73,194} this was ‘very much not the case’ for the cohort studies reviewed by Hodgson and Darnton,⁷³ and the review focused upon cohort average cumulative exposures. Some cohort studies, notably the Quebec miners/millers, the South Carolina textile workers and the Rochdale textile workers, are based on detailed and stratified exposure estimates,¹⁸⁸ derived from a large number of airborne fibre measurements at different work sites; although early measurements of airborne fibre levels were in the form of particle counts or mass concentrations, correlative studies were carried out to equate these counts to modern fibre counts based on phase-contrast microscopy. Therefore, one approach to meta-analysis of this type is to concentrate on single cohort studies with rigorous exposure estimates,¹⁸⁸ including stratified exposures within the cohort, with internal comparisons (see preceding discussion of the study by Carel *et al.*¹⁶⁵). Comparison of the cohort with an external reference group such as the national population can introduce a bias from factors such as smoking status, social status and the methods whereby the information was obtained.

The Hodgson–Darnton review⁷³ did not include case-referent studies such as those carried out in Germany where exposures were mixed and the data were individualised to a greater extent than virtually all other groups (see later discussion), or the study based on lung tissue fibre analysis reported by Karjalainen *et al.*^{108,109} In addition, because of the time of publication (2000), it could not address the dose-response estimates reported in 2000 and 2002 by Gustavsson *et al.*^{94,164,190} in case-referent analyses from Stockholm. Although the exposures across case-referent studies are very heterogeneous, we see no reason to exclude case-referent analyses from estimates of the general dose-response relationship between asbestos and lung cancer. Cohort studies are thought by some^{16,92,213,214} to have greater probative value than case-referent analyses, but these two methods of epidemiological investigation are comparable in many ways and suffer from similar weaknesses (e.g., each is critically dependent upon exposure estimates and a comparable control group).²¹³

Provided that recall bias can be addressed in addition, well-conducted case-referent studies are comparable in accuracy to cohort studies,²⁹ and they have an advantage in that they can address low-dose exposures^{94,164,190} and the end-use of asbestos-containing materials (e.g., in the building construction industry),⁶ in contrast to cohort studies. Therefore, case-referent analyses may be more representative of the overall risk of asbestos-related lung cancer for an industrialised society than cohort studies restricted to special industries.

As Rothman and Greenland²⁹ observed: 'Case-control research is in many ways emblematic of the modern synthesis of epidemiologic concepts. The methodology of case-control studies has a sound theoretical basis, and as a means of increasing measurement efficiency in epidemiology, it is an attractive option. Unfortunately, the case-control approach has often been misunderstood to be a second-rate substitute for follow-up [cohort] studies' (p. 5).

Therefore, one can argue that although the analysis in the Hodgson-Darnton paper⁷³ may have an internal average applicability for the 10 cohorts with mixed exposures included in the review, it does not necessarily have external validity; that is, generalisability²⁹ of the dose-response estimates to heterogeneous other groups represented by the multiple case-referent studies not included in the review and to the more general population exposed to asbestos mixtures at points of end-use (for which cohort studies are unrealistic). Application of the summary estimate of an increase in lung cancer risk of 0.47% per fibre/mL-year of exposure for all mixed exposures would create an anomaly with the observed lung cancer to mesothelioma ratio discussed already. This risk estimate would virtually eliminate asbestos-associated lung cancers without asbestosis from official recognition in Germany: among 301 German lung cancer patients (see later discussion), the exposure exceeded 8.4 fibre-years for 41 of the 301 cases and none appears to have had an exposure above 100 fibres/mL-years. Among 294 lung cancer and three mesothelioma patients from Hungary,²¹ 14 had estimated exposures in excess of 25 fibre-years (~5%; range 35–445 fibre-years);^{64,215} the highest estimates were obtained for exposures in an asbestos-cement factory where the three mesothelioma patients had worked (70, 128 and 445 fibre-years).

Critical reviews^{29,216–219} have pointed out the limitations of meta-analysis as a method for the assessment of dose-response relationships for occupational carcinogens; accordingly, Blettner *et al.*²¹⁸ state that: '... Meta-analyses from published data are in general insufficient to calculate a pooled estimate since published estimates are based on heterogeneous populations, different study designs and mainly different statistical models [abstract] ... Meta-analyses using published data are, therefore, restricted and seldom useful to produce a valid quantitative estimate or to investigate exposure relations such as dose-response ...' (p. 8).

THE HELSINKI CRITERIA

For the individual case, The Helsinki Criteria¹⁰² set exposure estimates or correlates at which the RR_{LCA} is at least doubled, with an attributable fraction (AF_E) of at least $(2-1)/2=0.5$, which is often considered to equate to a

probability of causation (POC) of 50%^{6,27,176} (but see preceding discussion of AF_{ES}).§

The Helsinki Criteria do not require the presence of asbestosis for attribution of lung cancer to asbestos, and instead focus upon cumulative exposure to asbestos as assessed clinically (e.g., estimates of cumulative exposure) or pathologically (e.g., asbestos bodies or uncoated fibre concentrations within lung tissue): 'Because of the high incidence of lung cancer in the general population, it is not possible to prove in precise deterministic terms that asbestos is the causative factor for an *individual* patient, even when asbestosis is present. However, attribution of causation requires *reasonable* medical certainty on a probability basis that the agent (asbestos) has caused or contributed materially to the disease. The likelihood that asbestos exposure has made a substantial contribution increases when the exposure increases. Cumulative exposure, on a probability basis, should thus be considered the main criterion for the attribution of a substantial contribution by asbestos to lung cancer risk. For example, relative risk is roughly doubled for cohorts exposed to asbestos fibers at a cumulative exposure of 25 fiber-years or with an equivalent occupational history, at which level asbestosis may or may not be present or detectable.'

Specifically, The Helsinki Criteria include the following:

1. The presence of asbestosis (e.g., asbestosis diagnosed clinically, radiologically—including high-resolution CT—or histologically). In this scheme, asbestosis has significance mainly as a surrogate for cumulative exposures comparable to the exposure indices set out below.
2. A count of 5000 to 15000 asbestos bodies (ABs) or more per gram dry lung tissue (/g dry), or an equivalent uncoated fibre burden of 2.0 million or more amphibole fibres (>5µm in length)/g dry, or 5.0 million or more

§Others consider that attribution of at least some occupational cancers to the postulated causal factor(s) can be based on $RRs < 2.0$.^{34,35} Greenland²⁴ argues that equating AF_E to POC involves a 'methodologic error' that tends to under-estimate POC because it does not take the time of occurrence of the disease into account ('accelerated occurrence'); differential genetic susceptibility/resistance to the carcinogenicity of either tobacco smoke or asbestos, or both, is another factor with the potential to affect AF_E and POC in the individual subject (see later discussion). Most cohort and case-referent studies either do not or cannot assess the time of occurrence of the disease relative to various levels of asbestos exposure and in comparison to no exposure, but in their studies on amosite factory workers, Seidman *et al.*^{181,184} found that the minimum latency interval decreased as cumulative exposure increased, so that the highest level of exposure (= 50 fibres/mL-years) was 'linked to the shortest observed latency'²²⁰ (10–14 years). Although they state that AF_E is equivalent to POC, Armstrong and Theriault refer to attribution for Ontario gold miners, based on the upper 95th percentile confidence interval for the exposure-response relationship, coinciding with a RR of about 1.4 and an AF_E of $0.4/1.4=29\%$; they also mention some other cases where the AF_E was <10%, 'apparently due to ... evaluating the probability that the exposure had contributed to rather than caused cancer'. This distinction between cause and causal contribution is artificial and, in a sense, nonsensical: because a low 'background' incidence of lung cancer (and also mesothelioma, as well as other cancers) exists in the absence of any identifiable exogenous causal factors, and because innate genetic susceptibility/resistance factors are thought to modulate the likelihood of the cancer in question, all known exogenous causal factors for lung cancer—such as tobacco smoke, asbestos, ionising radiation, certain heavy metals and so forth—represent causal-contributory factors by way of an incremental causal contribution above 'background', in that each represents a conditional probability factor²²¹ or one component of sufficient cause.²⁹

amphibole fibres $> 1 \mu\text{m}$ in length/g dry; this tissue count of ABs is also roughly equivalent to 5–15 ABs/mL of broncho-alveolar lavage (BAL) fluid. The Criteria also recommend that when the AB concentration is $< 10\,000/\text{g}$ dry, the count should be supplemented by an uncoated fibre burden analysis using electron microscopy. These uncoated fibre counts relate only to the amphibole types of asbestos (see later discussion). The Criteria state that chrysotile does not accumulate within lung tissue to the same extent as the amphiboles, because of faster clearance rates. Although one might presuppose that a substantially elevated concentration of chrysotile fibres in lung parenchyma is indicative of a relevant exposure because of faster clearance of chrysotile from lung tissue than the amphiboles, longitudinal splitting of the fibres as part of the clearance process will increase the number of fibres counted, so that it is difficult to assign significance to this observation.²² Therefore, occupational histories (fibre-years of exposure) are considered probably to represent a better indicator of lung cancer risk from chrysotile than fibre burden analysis.

or

3. Estimated cumulative exposure to asbestos of 25 fibre-years or more.

or

4. An occupational history, the only means whereby latency can be evaluated, of 1 year of heavy exposure to asbestos (e.g., manufacture of asbestos products, asbestos spraying, insulation work with asbestos materials, demolition of old buildings) or 5–10 years of moderate exposure (e.g., construction or shipbuilding). The Criteria go on to state that a 2-fold risk of lung cancer can be reached with exposures less than 1 year in duration if the exposure is of extremely high intensity (e.g., spraying of asbestos insulation materials).

and

5. A minimum lag-time of 10 years.

According to The Criteria, pleural plaques by themselves are inadequate for the probabilistic attribution of lung cancer to asbestos:¹⁰² 'Because pleural plaques may be associated with low levels of asbestos exposure, the attribution of lung cancer to asbestos exposure must be supported by [other parameters of exposure such as] an occupational history of substantial exposure or measures of asbestos fibre burden'.

However, because bilateral 'diffuse' pleural thickening is often associated with moderate to heavy exposures sufficient to induce asbestosis in some individuals, it is assigned significance similar to that of asbestosis for the purposes of attribution.¹⁰² In the United Kingdom, the requirement for 'bilateral' thickening was replaced in 1997 by 'unilateral' diffuse pleural thickening⁴⁵ (see Table 1). Nonetheless, Smith *et al.*²²² suggested that diffuse pleural fibrosis is an unreliable marker of heavy exposure.

ESTIMATES OF CUMULATIVE EXPOSURE AND THE HELSINKI CRITERIA

Cases of clinical asbestosis can be encountered at estimated cumulative exposures of 25 fibre-years.¹⁷⁰

Browne²²³ and Churg¹³⁵ indicate that the dose required for the development of asbestosis is in the range of 25–100 fibre-years. A study in China, based on chest X-rays for workers involved in asbestos products manufacture, found a 1% prevalence of grade I asbestosis, according to the Chinese system of grading, at a cumulative exposure level of 22 fibre-years.⁶² In an autopsy study on the South Carolina asbestos textile workers, Green *et al.*⁸⁶ reported that histological asbestosis was usually present with exposures above 20 fibre-years, and a few cases were encountered at estimated cumulative exposures of 10–20 fibre-years (histological examination is the most sensitive and specific means for the diagnosis of asbestosis). Fischer *et al.*²²⁴ reported that a requirement for ≥ 25 fibre-years of asbestos exposure for the diagnosis of asbestosis (including minimal histological asbestosis) would lead to under-recognition of 42% of asbestosis cases in the German Mesothelioma Register and false-positive diagnosis in 24%.||

The estimated cumulative dose of asbestos required for induction of asbestosis has diminished over the years. For example, Burdorf and Swuste²²⁸ refer to a lifetime risk of asbestosis of 2/1000 at 4.5 fibre-years and they draw attention to 'a few' asbestosis deaths at less than 5 fibre-years in the study reported by Dement *et al.*;²²⁹ in South Africa, Sluis-Cremer¹¹⁷ also recorded 'slight' asbestosis associated with cumulative exposures to amphibole asbestos estimated to have been as little as 2–5 fibres/mL-years (although Browne²³⁰ has criticised this finding because it did not represent an individualised estimate of exposure, but was instead derived from average airborne fibre concentrations). In their stepwise decision-tree approach to assessment of asbestosis, Burdorf and Swuste²²⁸ suggest that for any probability of exposure defined by industry, evidence of direct exposure at a level of 5.0 fibres/mL or more for more than 1 year is sufficient for 'ascertainment' of asbestosis (i.e., > 5.0 fibre-years). However, the occurrence of asbestosis following low exposures of this type raises the question of other unrecognised exposures to asbestos in the patients so affected, especially because elevated concentrations of amphiboles in lung tissue are observed occasionally in patients with minor exposures as evaluated from the occupational history.²³¹

In a study on the AB and fibre content in resected lung tissue from 477 consecutive patients with lung cancer, De Vuyst *et al.*²³² found that a count of ≥ 5000 ABs/g dry lung correlated with 'significant occupational' cumulative exposure; the figure of ≥ 5000 ABs was considered to be about equivalent to 5 million asbestos fibres/g dry and about 10 fibre-years of exposure.²³³ Thimpoint and De Vuyst²³³ also found that concentrations of ABs $> 5000/\text{g}$ dry lung did not occur in non-exposed control subjects and were always indicative of occupational exposure; about 50% of patients with > 5000 ABs/g dry had low-grade fibrotic lesions affecting small airways and the interstitium,

||Fischer *et al.*²²⁴ also found a poor correlation between fibre-year estimates of cumulative exposure versus lung tissue asbestos fibre counts, but this is explicable in part by their use of the total 'asbestos-fibre-concentration', with no distinction between chrysotile fibres and amphibole fibres—although this distinction is required by The Helsinki Criteria¹⁰² and is emphasised by The AWARD Criteria²²⁵—because of the low biopersistence of chrysotile fibres in lung tissue.^{226,227}