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 Dufresne[160] 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 Dufresne[160] 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-smokers[97]). 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 Kingdom[171] 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 paper[36] 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 Criteria[102] 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 Woitowitz[186] 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

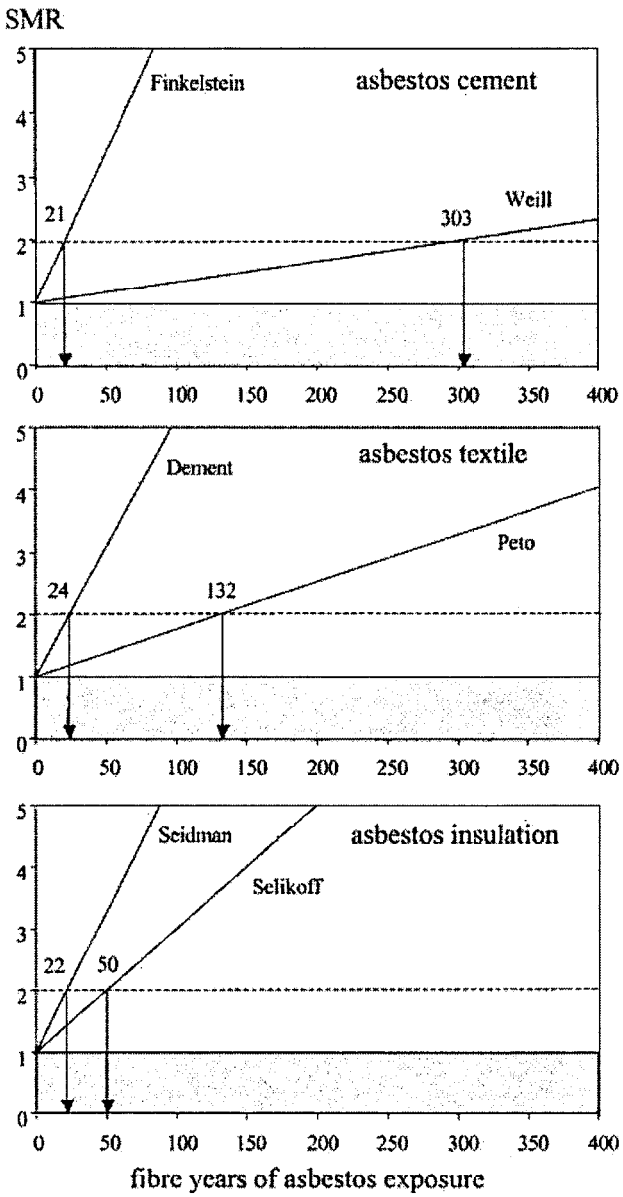

Fig. 1 Dose-response relationship expressed as SMR for lung cancer related to cumulative asbestos exposure measured as fibre-years for cohorts of asbestos textile, asbestos cement and asbestos insulation workers.[183] Fibre-years of exposure that may be related to a 2-fold risk of lung cancer (SMR = 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-smokers[187] (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, Goldberg[72] 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 authors[94] 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, Sweden[164]

Asbestos exposure (fibres/mL-years)	Mean cumulative exposure in class (fibres/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 Stayner[196] 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 Study[18] 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 study[203] involved a complex assessment that included measurements of fibre concentrations for fibres longer than 5 μm 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

	Univariate analysis		Multivariate analysis*	
Marker/job	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·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 Wittenoom 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 authors[209] 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 Sanden[209] 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 1993[212] 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 Darnton[73] 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 review[73] 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 Greenland[29] 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 paper[73] 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, generalisability[29] 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 Criteria[102] 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.

or

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 (>5 μm 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] Greenland[34] 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 factor[221] or one component of sufficient cause.[29]

amphibole fibres >1 μm in length/g dry; this tissue count of ABs is also roughly equivalent to 5–15 ABs/mL of bronchoalveolar lavage (BAL) fluid. The Criteria also recommend that when the AB concentration is <10 000/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 fiber 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 thickening[45] (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] Browne[223] and Churg[135] 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 Swuste[228] 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-Cremer[117] also recorded 'slight' asbestosis associated with cumulative exposures to amphibole asbestos estimated to have been as little as 2–5 fibres/mL-years (although Browne[230] 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 Swuste[228] 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] Thimpont and De Vuyst[233] also found that concentrations of ABs >5000/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 Criteria[102] and is emphasised by The AWARD Criteria[225]—because of the low biopersistence of chrysotile fibres in lung tissue.[226,227]

and identifiable ABs in histological sections.[233] In a series of 924 cases of lung cancer, Mollo *et al.*[52] diagnosed asbestosis by histological examination in 54 of 116 (46.6%) 'surgical' cases with an AB concentration >1000 ABs/g dry lung.

In a case-referent study on AB concentrations in autopsy lung tissue with allowance for smoking, Mollo *et al.*[234] found a 4-fold increase in the RR for pulmonary adenocarcinoma at a lower cut-off count of 1000 ABs/g dry lung. In a stratified analysis from multiple comparisons, the RR was 5.59 for all lung cancers versus referents and 17.75 for adenocarcinomas versus referents (i.e., RR ~4 for 1000–9999 ABs/g dry lung, with evidence of a dose–response effect, with higher RRs for counts in excess of 10000 ABs/g dry). This study did not detect an association between asbestos exposure and lung cancer phenotypes other than adenocarcinoma.

THE AWARD CRITERIA

The AWARD (Adelaide Workshop on Asbestos-Related Diseases) Criteria[225,235] were formulated in October 2000 by a group of 15 Australasian experts in asbestos-related disorders—including epidemiologists, an industrial hygienist and a medical scientist, occupational and respiratory physicians, pathologists, and radiologists—to address the applicability of The Helsinki Criteria to Australasia. The AWARD Criteria basically endorsed The Helsinki Criteria as 'fair and reasonable' for the attribution of lung cancer to asbestos, with certain modifications for Australia:

1. Like The Helsinki Criteria, The AWARD Criteria also accept either clinical or histological asbestosis as a criterion for attribution of lung cancer to asbestos.

2. The AWARD document [225,235] acknowledged that the risks of lung cancer for the cohort of Quebec chrysotile miners/millers and for asbestos textile production (such as the South Carolina cohort) are not applicable to Australia, where the majority of asbestos exposures have been mixed amphibole-chrysotile exposures, or crocidolite-only exposure (the Wittenoom cohort).

3. The AWARD meeting also recognised that the counts of uncoated amphibole fibres in lung tissue as specified in The Helsinki Criteria apply to mixed amphibole-chrysotile exposures only. For amphibole-only exposures (such as 'virtually pure crocidolite exposure' for the Wittenoom cohort), higher lung tissue fibre counts are required to equate to 25 fibres/mL-years of exposure. For the Wittenoom cohort, about 220 million crocidolite fibres longer than 0.4 μm/g dry lung or, in the AWARD document itself,[225,235] a figure of at least 100 million crocidolite fibres longer than 1 μm/g dry lung are necessary to equate to 25 fibres/mL-years as an average or approximation.

In 2003, the Australasian Faculty of Occupational Medicine (AFOM) of The Royal Australasian College of Physicians addressed this issue independently of the AWARD group and commented that 'it is unlikely that consensus will be reached in the near future on whether asbestos exposure can cause lung cancer in the absence of asbestosis'.[6] However, 'if asbestosis is held not to be a precondition', the AFOM document[6] suggested that an asbestos-related doubling of risk for lung cancer occurs at about 21 fibre-years for amphibole-only and mixed exposures, at 1667 fibre-years for chrysotile mining, and at 43 fibre-years for 'pure chrysotile other than mining'.

CRITERIA FOR ATTRIBUTION OF LUNG CANCER TO ASBESTOS IN GERMANY

In the German prescription on occupational diseases (*Berufskrankheitenverordnung*), existing criteria for ascribing lung cancer to asbestos were supplemented in 1992 by an estimated cumulative workplace asbestos exposure of at least 25 fibre-years.[48,236] As shown in Fig. 1, a cumulative exposure of about 25 fibre-years was related to a 2-fold increased risk of lung cancer mortality in comparison to the general population, for the three areas of asbestos-cement, asbestos textile and asbestos insulation work,[177–182] representing the most important patterns of occupational exposure in Germany. The delimiting value of 25 fibre-years for compensation of lung cancer was obtained from the highest K_L for each of these three patterns of exposure,[177,181,229] because random errors in general would depress the slope of the dose-response line.[38,237]

Introduction of this new criterion was enabled by a convention on the magnitude of asbestos exposures at various workplaces, proposed by the German *Berufsgenossenschaften*.[64] For certain work situations, a catalogue of fibre concentrations corresponding to the 90th percentile (about twice the arithmetic mean value) of the measuring results was compiled,¶ based on 9974 fibre counts with the membrane filter method, 1600 konimeter counts and 15316 gravimetric measurements of the asbestos mass concentration.

These values are used throughout Germany to calculate cumulative workplace asbestos exposures relative to the delimiting value of 25 fibre-years. Following introduction of these regulations, the number of patients with compensated lung cancer increased from 223 in 1992 to

¶There have been some criticisms over use of the 90th percentile as opposed to the arithmetic mean (AM)—which corresponds roughly to the 70th percentile and not the 50th—with an argument that the German system tends to overestimate exposures (but see discussion in section 'Latency intervals between asbestos exposure and lung cancer'). The factor between the AM and the 90th percentile value is about 2 overall: it depends upon the geometric standard deviation (GS) of the logarithmic normal frequency distribution of the measured values. It is only 1.91 for GS=2, and it increases from 1.55 for GS=1.5 to 2.24 for GS=3. This difference is thought to be small in comparison to the uncertainties that surround exposure estimates based on historical measurements, related to conversion factors used to translate particle counts and mass measurements into fibre concentrations. In comparison, if the 50th percentile is used for GS=3, the figure would be only about half of the AM because it would not adequately consider high concentration values. It is also worth emphasising that the database for the BK-Report[64] does not deal with a random sample of workplace situations but a selection where there is routine supervision, and airborne fibre concentrations may be lower than in unsupervised workplaces elsewhere, although the airborne fibre concentrations were measured in the absence of protective measures such as dust extraction equipment. In such supervised workplaces, fibre concentrations in excess of the limit values are normally followed by measures to reduce exposures—the efficacy of those measures being evaluated by further measurements—so that action is taken to maintain exposures at levels lower than those expected for workplaces without such scrutiny.