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 10 000 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 15 316 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.

545 in 1994, thereby surpassing the number of mesotheliomas ($n=350$ in 1992 and $n=495$ in 1994). For 1999, some 776 cases of lung + laryngeal cancer were classified as asbestos-related in comparison to 617 mesotheliomas. This ratio (1.26:1) corresponds to the proportions of excess lung cancer cases and mesotheliomas observed in cohort studies (see Table 1).[36,238]

Further data on the German system of dose estimation have been reported[239] for 3498 male lung cancer cases in comparison to 3541 population controls, in a pooled analysis based on two sub-studies[240,241] (see also Jöckel *et al.*[242]). A detailed smoking and occupational history was obtained by a personal standardised interview where asbestos exposure was assessed on the basis of 17 job-specific supplementary questionnaires in a semi-automated fashion. Ever exposure to asbestos after adjustment for smoking was associated with an OR_{LCA} of 1.41 (95%CI = 1.24–1.60), and a clear dose-response relationship with an OR_{LCA} of 1.79 (95%CI = 1.39–2.30) was found for >2500 days of exposure. For a sub-sample of 301 cases and 313 controls, estimates of fibre-years of exposure based on the convention of the *Berufsgenossenschaften*[215] were performed by two experts. In a logistic regression model adjusted for smoking and stratified for age and origin of the patients, the OR_{LCA} was associated with log (fibre-years + 1); 25 fibre-years corresponded to an OR_{LCA} of 1.99 (95%CI = 1.20–3.30). In a two-phase case-referent study, Pohlabeln *et al.*[243] derived results 'consistent with a doubling of the lung cancer risk with 25 fibreyears asbestos exposure'.

In an analysis of two German case-referent studies, Hauptmann *et al.*[89] found that the OR_{LCA} was 1.8 (95%CI = 1.2–2.7) for subjects who had worked for 3–7 years in a job with potential exposure to asbestos, and was 2.4 (95%CI = 1.7–3.4) for those who worked in similar jobs for ≥8 years, in comparison to never-exposed subjects.

ASBESTOS FIBRE CONCENTRATIONS IN LUNG TISSUE, ESTIMATED CUMULATIVE EXPOSURE, AND THE RISK OF LUNG CANCER

In The Helsinki Criteria,[102] the following lung tissue concentrations were delineated to identify workers with a high probability of exposure to asbestos in the workplace:

(a) >1000 ABs/g dry lung (equivalent to >100 ABs/g wet lung);
(b) >100 000 amphibole fibres >5 μm in length/g dry lung;
(c) >1 000 000 amphibole fibres >1 μm in length/g dry lung;
(d) >1 AB/mL BAL fluid.

Each laboratory should establish its own reference values, and the median values of those exposed occupationally should be substantially above the reference values. Besides other criteria (discussed also in The Helsinki Criteria), a lung fibre count exceeding this background range should be sufficient for probabilistic attribution of mesothelioma to asbestos exposure.

The basis for these concentrations of ABs and asbestos and amphibole fibres is tabulated in a review by Tossavainen,[17] for lung tissue samples and BAL fluid from the general population or from patients not exposed in the workplace. Different fibre definitions, different measuring methods and different statistical parameters complicate comparison of these data. In Fig. 2A–C (data for BAL fluid not shown), the data are presented as the percentage of measurements below a certain concentration value according to the following rules:

(i) Geometric mean and median values: <50%
(ii) Arithmetic mean values: <70%
(iii) Upper limit of the range: <100%

If several of these parameters were given for a series of measurements, they are presented side by side.

With the exception of two series of mesothelioma patients, the median values of the concentrations of short and long amphibole fibres and ABs ranged below the limit values given by The Helsinki Criteria. In most of the studies, less than 20% of the measured values exceed these limits. An increased percentage of counts exceeding the limits is observed for short amphibole fibres among Australian and, probably, Japanese patients. For ABs, an increased percentage is observed for one of the French and the Belgian series, as well as for Canadian patients living near the Quebec mines.

In a German mesothelioma case-referent study, 15% of 66 hospital referents who underwent lung resections mainly for lung cancer exceeded the limit value for long amphibole fibres (length >5 μm), in comparison to about 70% of the cases.[244,245] The same percentages of measurements above the delimiting value were obtained for short fibres (length >1 μm). AB counts were also available for 147 referents and 66 cases: the limit value of 100 ABs/g wet lung (≅1000 ABs/g dry) was exceeded for 18% of the referents in comparison to 73% of the cases, and this percentage for referents diminished to 8.7% when evaluation was restricted to 69 unexposed referents.

In a mesothelioma case-referent study on patients from Yorkshire,[246] the concentration of total amphibole fibres longer than 0.5 μm was measured. Twenty-two per cent of 122 referents exceeded the limit value in comparison to 80% of 147 cases; when evaluation is restricted to referents not exposed occupationally to asbestos according to the judgement of surviving relatives ($n=61$; Table 4 in Howel *et al.*[246]), the percentage is slightly less than 20% (Fig. 1 in Howel *et al.*[246]). For controls and workers from the textile factory in South Carolina, fibres were counted at a magnification of ×20 000 without specification of a minimum fibre length.[86] Among 31 controls, the delimiting value for amphibole fibres >1 μm in length was exceeded for 9.7% of the tremolite counts, 6.4% of the anthophyllite counts and 12.9% of the amosite and crocidolite counts. It may be assumed that some of these counts were obtained from the same patients.

In a study of 33 patients from Texas with no history of occupational exposure to asbestos, Dodson *et al.*[247,248] found that all had no more than 20 ABs/g wet lung and 26 had no detectable ABs; chrysotile was undetectable in 19 cases, and 10 of the 33 had no asbestos fibres within the detection limits of the study (the total uncoated asbestos fibre burden was in the range of 0–290 000 fibres/g dry, for fibres >0.5 μm with an aspect ratio of ≥3:1). Although amosite and crocidolite fibres were found occasionally,

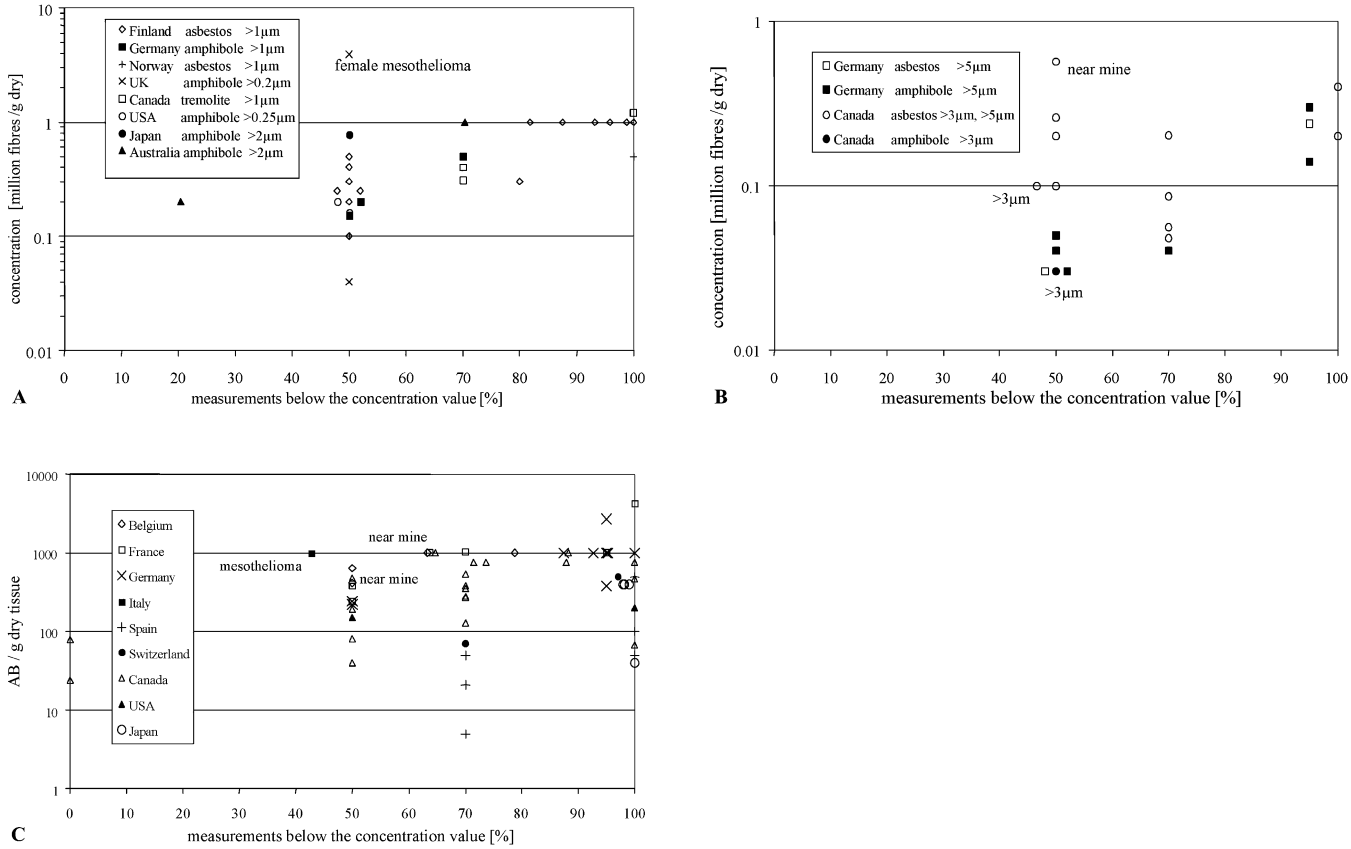

Fig. 2 (A) Amphibole fibres longer than a minimum value of 0.2–2 µm in lung tissue samples from the general population or from patients not exposed at the workplace.[17] Measurements from Finland and Norway represent asbestos fibres but because of scanning electron microscopy (SEM) was used at a magnification of ×5000, predominantly amphibole fibres were registered. In the German measurements, fibres originally were counted if they were longer than 0.3 µm but with the magnification (×10 000) of this study, only very few fibres shorter than 1 µm were recorded. (B) Asbestos and amphibole fibres longer than a minimum value of 3–5 µm in lung tissue samples from the general population or from patients not exposed in the workplace.[17] (C) Asbestos bodies in lung tissue samples from the general population or from patients not exposed in the workplace.[17].

they were few in number: anthophyllite (12 of 33 cases) was almost as likely.

It is also notable that in mesothelioma case-referent studies,[86,245,249–251] increased ORs are found at fibre concentrations immediately above the delimiting values for occupational exposure given in The Helsinki Criteria. In comparison to a reference group for whom the tissue concentration was less than 50 000 fibres/g dry lung, Rödelsperger *et al.*[245] found that the OR for mesothelioma (OR_{MESO}) increased in an almost linear fashion according to the relationship:

$$OR_{MESO} = \frac{\text{Concentration of amphibole fibres longer than 5 µm/g dry lung}}{\text{25 000 fibres/g dry lung}}$$

In this study, a significantly increased OR_{MESO} of 4.5 (95%CI = 1.1 − 17.9) was observed, even at the low fibre concentration range between 100 000 and 200 000 fibres longer than 5 µm/g dry lung.

Roggli and Sanders[111] studied 234 cases of lung cancer with some history of asbestos exposure, but with no quantitation of exposure as fibre-years. For 70 patients with asbestosis they recorded a median total asbestos fibre concentration of 2.53 million fibres/g dry for fibres 5 µm in length or more (converted from wet weight figures), which included a median count of 2.53 million commercial amphiboles (crocidolite/amosite) and 220 000 non-commercial amphiboles, and a median count of 270 000 ABs/g dry; although this AB count is well above (18 times) the upper limit of 5000 − 15 000 ABs specified in The Helsinki Criteria, the uncoated fibre count is roughly comparable to the figure of 2 million in The Criteria. The Helsinki figure of 5 million fibres/g dry (for fibres >1 µm in length) also bears comparison to the geometric mean fibre concentration of 2.5 million fibres/g dry for Western Australian asbestosis cases whose exposure occurred other than at Wittenoom.[158,159] The number of ABs in The Helsinki Criteria is about 23 times above the upper limit of the range of AB concentrations, and the uncoated fibre count is almost 79 times above the upper limit for the range of uncoated total fibres and crocidolite/amosite fibres, reported for the control group in Roggli and Sanders[111] (220 ABs/g dry and 25 400 fibres/g dry, respectively).

In 1994, Karjalainen *et al.*[109] reported a case-referent study that examined the relationship between lung fibre burden and the risk of lung cancer based on 113 surgically treated lung cancer patients in comparison to 297 autopsy referents from the Finnish population. Lung tissue fibre analysis was carried out for fibres longer than 1 µm by scanning electron microscopy (SEM) at a magnification of ×5000 and included mainly amphibole fibres. In comparison to a reference group with a tissue concentration of

less than 1 million fibres/g dry, the OR_{LCA} increased to 1.7 for concentrations in the range 1.0–4.99 million fibres/g dry and to 5.3 for concentrations of 5.0 million or more fibres/g dry. Karjalainen *et al.*[109] stated that when two cases of asbestosis and seven cases of minor 'histological fibrosis compatible with asbestosis' were excluded, an elevated OR_{LCA} was still associated with asbestos fibre concentrations of 5.0 million or more fibres/g dry lung (age-adjusted $OR_{LCA} = 2.8$; 95%CI = 0.9–8.7; $P = 0.07$) and for asbestos fibre counts in the range 1.0–4.99 million fibres/g dry ($OR_{LCA} = 1.5$; 95%CI = 0.8–2.9; $P = 0.19$). One criticism directed at this study is that the results fail to achieve significance in terms of P values, thereby proving that 'significance' lies only with the cases of fibrosis.[115] This objection overlooks the fact that the limit $P \leq 0.05$ is an arbitrary statistical convention and that reality lacks sharp boundaries of this type: what is important in this study is the trend from a low to a higher OR_{LCA} with transition from an intermediate fibre count (1.0–4.99 million) to the higher value (≥ 5.0 million). If one excludes the nine cases of fibrosis and assumes that seven were in the high fibre group (≥ 5.0 million fibres/g dry) and two were in the intermediate fibre group (1.0–4.99 million fibres/g dry),** one can calculate the crude lung cancer ORs to be 2.85 and 1.8, respectively, as consistent as possible with the age-adjusted ORs of 2.8 and 1.5 in the original paper; trend testing then yields χ^2_1 (trend) = 7.2 ($P < 0.01$). In addition, it is possible from the published data to recalculate the OR for adenocarcinoma only, after exclusion of all cases with any fibrosis: assuming that all were in the high fibre group, the OR is still significantly elevated for a count > 1.0 million compared with < 1.0 million ($OR_{LCA} = 2.65$; 95%CI = 1.11–6.26; $P < 0.001$).[1]

Much steeper dose–response relationships were obtained from mesothelioma case-referent studies;[86,245,249–251] e.g., Rödelsperger *et al.*[245] calculate the mesothelioma OR to be about 100 when patients with a burden of 2.5 million amphibole fibres/g dry (for fibres longer than 5 μm) are compared with the reference group.

In assessing the significance of asbestos lung fibre burdens for attribution of lung cancer, it should be emphasised that the 'controls' for case-referent studies represent individuals without the disease in question, sampled randomly and independently of exposure.[29,31] This is a critical necessity for the validity of a case-referent study. Thus, the 'control' group will generally comprise both exposed and unexposed individuals. In using data from 'control' groups in case-referent studies for assessing likely lung fibre levels in the unexposed in comparison to those exposed, only data from the unexposed fraction of the 'controls' should be used.

Estimates of cumulative exposure as fibre-years apply equally to all types and mixtures of asbestos. In contrast, fibre analysis of lung tissue applies mainly to amphiboles because of the lower biopersistence of chrysotile in lung tissue.[54,252,253] Therefore, the concentrations of asbestos and amphibole fibres that correspond to 25 fibre-years of exposure are largely dependent on the proportion of amphiboles in the relevant asbestos-containing materials. From historical national data on the consumption of the different types of asbestos and the known composition of various products (e.g., asbestos-cement products), there is abundant evidence that chrysotile comprised about 94–95% or more of asbestos consumption, and amphiboles about 5% or less.[54,254,255] However, in some industries—e.g., workers at the Nottingham gas mask factory[256] and the Wittenoom crocidolite miners/millers in Western Australia[257]—the exposures involved a far higher proportion of amphiboles (notably crocidolite for both of these industries, so that exposure at Wittenoom unaffected by other exposures was to virtually 100% crocidolite). It follows that for these workers, much higher tissue concentrations of amphibole fibres are equivalent to an exposure of 25 fibre-years than for those exposed to a small percentage of amphibole fibres during their lives.

Table 6 gives summary estimates of lung tissue concentrations of amphibole fibres and ABs that may be related to a cumulative exposure of 25 fibre-years. As expected, the concentrations increase according to the percentage of the amphibole used, so that the smallest amount is encountered among 38 workers from the South Carolina textile plant.[86]

In the South Carolina textile industry, chrysotile contaminated with less than 1% tremolite was the only type of asbestos processed as raw material, besides a small amount of crocidolite yarn. The concentrations of asbestos fibres of all lengths (without a specified minimum length) per gram dry lung were compared with individual fibre-years, which were available for the same patients from an extensive industrial hygiene survey.[260] Roughly 40 million asbestos fibres/g dry lung correspond to an exposure of 25 fibre-years, but this result is influenced by a high number of small chrysotile fibres; nevertheless, the quantity of amphibole fibres may be estimated to be 4.5 million fibres/g dry lung using geometrical mean values given for the single types of asbestos (Table 3 in Green *et al.*[86]). Figure 3 in this paper represents the relationship between tremolite as the main type of amphibole fibre and estimated fibre-years of exposure, and shows concordance with The Helsinki Criteria.

Somewhat greater amounts of amphiboles may be expected for the cases and controls in Rödelsperger *et al.*[194,244] and for the cohort reported by Albin *et al.*[258,259] However, Rödelsperger[244] reported that: 'A relationship is demonstrated between asbestos fibre dose estimated from the interview and concentration of amphibole fibres from lung tissue analysis. From this a dose of 25 fibre-years corresponds to an amphibole fibre concentration of 2 fibres/μg' (in other words, 2 million amphibole fibres/g dry lung for fibres longer than 5 μm; abstract and p. 307).

In Rödelsperger's study on mesothelioma patients,[244] 25 fibre-years and the count of 2 million uncoated fibres/g dry lung corresponded roughly to an AB count of 15 000/g dry lung given in The Helsinki Criteria (see also Thimpont and De Vuyst[233]); for obvious reasons, these values could not be derived for the control patients.

By far the largest amount of amphibole is expected for 90 crocidolite miners/millers from Wittenoom. A strong correlation between analysis of the lung burden and the estimate of fibre-years was observed.[257,261] For these workers, concentrations of 21 000 ABs/g wet lung and

**Based upon an assumption that the clinical asbestosis cases were in the heaviest exposure group and that the mild histological fibrosis cases were in the intermediate exposure group.

TABLE 6 Concentrations of amphibole fibres and ABs from fibre analysis of lung tissue, relative to an estimated exposure of 25 fibre-years from occupational histories

		Exposure			Concentration related to 25 fibre-years		
Study	Patients	Type of asbestos	Fibre-years estimate by (ref)	Lung tissue fibre analysis	Million f/g dry	ABs/g wet	Remarks
258	Swedish asbestos cement factory: 76 workers	More than 85% chrysotile; up to 4% crocidolite until 1966; up to 17% amosite before 1956	259	TEM; fibres of all lengths	Asbestos: 189 Amphibole: 55 Asbestos: 96 Amphibole: 9		Seven mesothelioma cases, from median values Sixty-nine other workers, from median values
86	South Carolina asbestos textile factory: 54 workers	Chrysotile with $<1\%$ tremolite; very little crocidolite (difference in consumption $>4000{:}1$)	260	TEM; fibres of all lengths	Asbestos: 40 Amphibole: 4.5		See Fig. 1; from geometrical mean values of Table 3 in original, the ratio of amphibole to all asbestos fibres is $\sim 9{:}1$
244 194	Germany: 66 mesothelioma cases; 66 and 147* controls respectively with lung resection	Mixed, according to consumption of $\sim 94\%$ chrysotile in Germany	194	TEM; fibres $>5\,\mu m$ in length	Amphibole: 2	1500	Sixty-six cases and 66 (147*) controls: comparison of different types by regression analysis
261	Wittenoom: 32 miners/millers	Almost 100% crocidolite	262	LM		4400	
257	Wittenoom: 90 miners/millers	Almost 100% crocidolite	262	TEM; length $>0.4\,\mu m$	Crocidolite: 220	21	From geometrical mean values, Fig. 1 in original. The AWARD Criteria specify a count of 100 million crocidolite fibres longer than $1\,\mu m$ to correspond to 25 fibres/mL-yr.[225]

ABs, asbestos bodies; Ref, reference; TEM, transmission electron microscopy.
*ABs only counted by light microscopy, per gram wet lung.

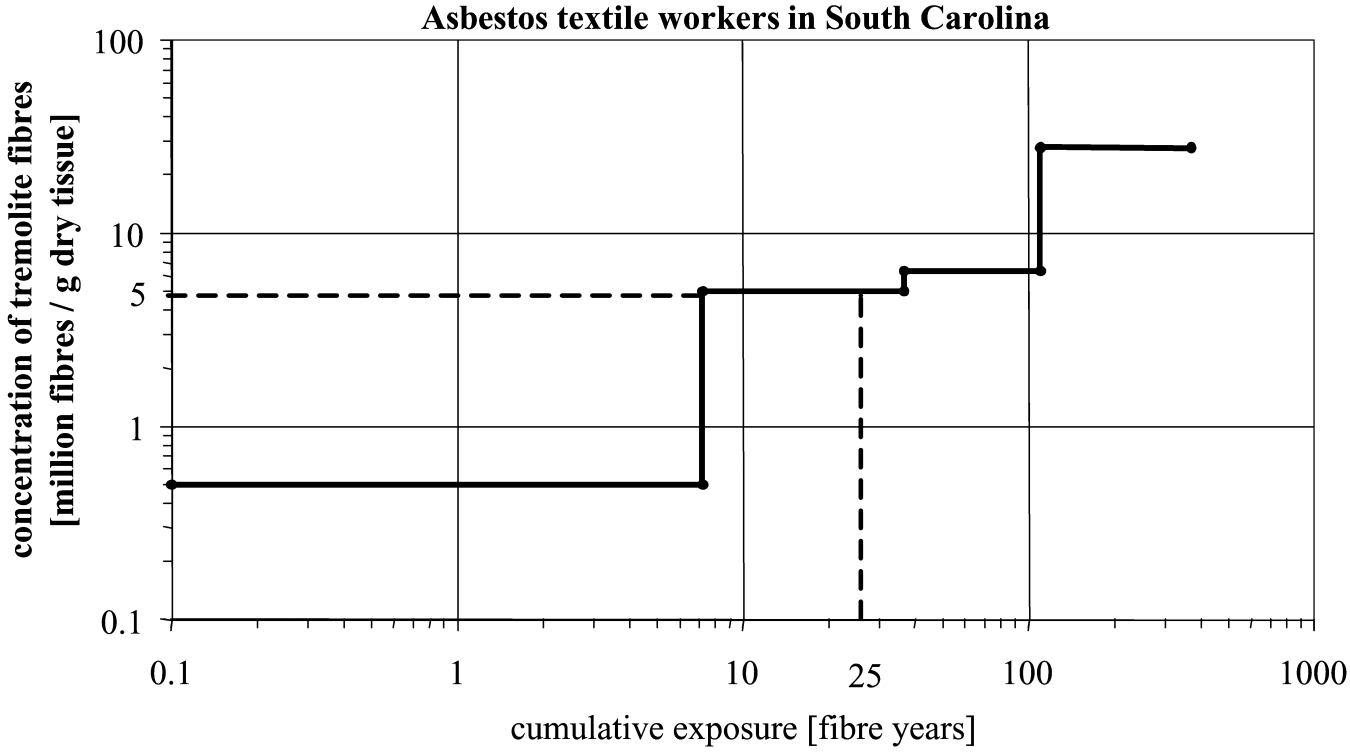

Fig. 3 Relationship between the concentration of tremolite fibres in the lung tissue and the estimate of the fibre-years for 39 textile workers from the cohort from South Carolina, after Table 5 in Green *et al.*[86].

220 million crocidolite fibres longer than 0.4 μm/g dry lung (~100 million fibres longer than 1.0 μm)[225] correspond to an exposure of 25 fibre-years. These concentrations are respectively 20- and 45-fold greater than the AB and fibre concentrations specified by The Helsinki Criteria. They support the proposition that the percentage of amphiboles used in the workplace is crucial if the concentration of asbestos fibres in the lung tissue forms the basis for estimation of fibre-years of cumulative exposure.

LUNG CANCER AND THE CLASTOGENICITY AND MUTAGENICITY OF ASBESTOS

Detailed discussion of the molecular and genetic aberrations inducible by asbestos in experimental animals and cultured cell lines lies outside the scope of this review (see references 1, 96, 167, 263–266). However, asbestos is known to be genotoxic and clastogenic, with the capacity to induce DNA strand breaks, anaphase-telophase abnormalities and sister chromatid exchanges in cell lines *in vitro*—where fibrosis cannot be implicated—and free radicals generated from the surface of asbestos fibres or macrophages are implicated in these aberrations. Both crocidolite and chrysotile have been shown to disturb cell division, producing binucleated cells, which may lead to aneuploidy or polyploidy.[267] Asbestos fibres can also induce oncogene expression—such as *c-fos* and *c-jun* proto-oncogenes—in cultured rodent mesothelial cells.[268] Asbestos-related adenocarcinoma of lung is also associated with *p53* and *k-ras* mutations.[96,265,269–272]

In a study of 84 male patients with a histological diagnosis of adenocarcinoma of lung, Nelson *et al.*[272] found a higher prevalence of *k-ras* mutations in those with a history of asbestos exposure than in those without, after adjustment for age and pack-years smoked, and that the estimated intensity of exposure was greater for the patients with *k-ras* mutations than those without. There was no detectable association with the duration of exposure, but the time since first exposure was associated with mutation status; in addition, the association was not dependent on radiographic evidence of asbestos-related disease. Nelson *et al.*[272] concluded that their data were suggestive of an increased likelihood of *k-ras* codon 12 mutations as a consequence of asbestos exposure and that 'this process occurs independently of the induction of interstitial fibrosis'.

Wang *et al.*[273] have also reported that chrysotile and cigarette smoke in solution act synergistically to produce DNA damage in a dose-dependent fashion and to activate *c-ras* in human embryo lung cells as assessed by *p21* expression. Jung *et al.*[274] found that amosite and cigarette smoke each produced an increase in DNA strand breaks and necrosis in rat bronchiolar epithelial cells *in vivo,* both alone and in additive fashion when in combination.

Using a papillomavirus-immortalised human bronchial epithelial cell line, Hei *et al.*[275] found that a single 7-day treatment of the cells with chrysotile induced stepwise transformation, with altered growth kinetics, resistance to terminal differentiation and anchorage-independent growth, to produce progressive tumorigenic growth in nude mice.[276] Hei *et al.*[277] also found that treatment of the same cell line with α-particles to simulate the effects of radon, induced a similar pattern of apparent neoplastic transformation in the same cell line. The same group of researchers[278] had shown earlier that chrysotile is

mutagenic for cultured mammalian cells—with the production of large deletions—and comparable with the mutagenicity of γ-rays.

The fragile histidine triad (FHIT) tumour suppressor gene located at 3p14.2[279–283] appears to represent a site of genomic fragility relevant to carcinogenesis: FHIT protein is expressed in most non-neoplastic tissues, and the highest levels of expression occur in epithelial cells. FHIT appears to be subject to deletion or loss of heterozygosity (LOH) by cigarette smoke and asbestos.[279,280,282,283] Diminished expression of FHIT has been recorded in up to 80% of cigarette smoke-associated lung cancers,[279] and in both asbestos-associated lung cancers (~69%) and non-exposed cases (~59%) in one study,[282] and in ~54% of mesotheliomas[283] (Pylkkänen *et al.*[283] suggest that LOH affecting FHIT can be concealed by normal cells present in mesotheliomas). Genomic instability affecting FHIT has also been identified in cases of idiopathic pulmonary fibrosis.[284]

GENETIC SUSCEPTIBILITY TO LUNG CANCER

It is well known that genetic factors play a major causal role in the genesis of some cancers, notably those related to mutations in tumour suppressor genes or DNA repair genes, with high penetrance of the mutated gene(s):[285,286] such cancers include gastrointestinal cancers among families with familial adenomatous polyposis (APC gene), and cancers related to mutations affecting DNA repair genes, such as hereditary non-polyposis colon cancer (HNPCC) and xeroderma pigmentosum (XP[A-D] genes),[286] and it has been estimated that genetic abnormalities of this type may account for about 1–4% of all cancers.[286,287]

It is also known that in some circumstances there is an interplay between genetic predisposition to cancer and environmental factors.[286,288] One classical example is xeroderma pigmentosum (XP), where the mutated DNA repair genes XP(A-D) produce extreme susceptibility (>1000-fold above 'normal'[289]) to skin cancers (basal and squamous cell carcinomas and melanoma),[286] because of an impaired capacity to repair DNA damage induced in the skin by ultraviolet radiation in sunlight; management of patients with XP includes isolating them from sunlight to minimise the DNA damage and hence to reduce the otherwise virtually certain risk of skin cancer.

Delineation of the genetic component for cancers related to multiple gene variants of low penetrance poses far greater difficulties than for high-penetrance single-gene disorders, and familial aggregation of some cancers is complicated by the fact, that apart from some shared genes, family members frequently share environmental factors, including diet, lifestyle, recreations and occupations.

Although lung cancer risk is highly dependent on environmental factors such as cigarette smoke (and less commonly asbestos and other occupational/environmental factors), it is a truism that that only a minority of tobacco smokers ever develop lung cancer during their lifetimes (about one in $10^{[287,290]}$), and only a minority of those exposed to asbestos ever develops lung cancer. Chance alone might be invoked as the explanation for cancer/not-cancer—for example the 'correct' combination of mutational events may not occur at all or in the 'correct' order, or a mutational event may be lethal to the cell—however, there is evolving evidence for modulation of cancer risk by genetic susceptibility/resistance (G_S and G_R) factors.[287,290–295]

In studies based on the Swedish Family-Cancer Database,[296–298]†† the 'proportion of cancer susceptibility, accounted for by genetic effects' was estimated at 14%[285] and later at 8%[299] for lung cancer, with shared and childhood environmental components of 9 and 4%, respectively, and 79% for non-shared environmental factors.[299] A further study on the same database gave an estimated familial population attributable fraction (PAF) of ~3% for lung cancer, with a familial percentage proportion of ~6% (defined as the percentage of affected offspring with affected parents).[300] A further study on the Swedish Database also yielded a higher familial risk for large cell carcinoma and adenocarcinoma of lung (SIRs = 2.29 and 2.18, respectively) than for other histological types (small cell carcinoma = 1.74 and squamous cell carcinoma = 1.78).[296]

Apart from gatekeeper genes such as *p53* and *k-ras*, a number of studies have focused on polymorphisms for caretaker genes[301]—for example, those encoding the cytochrome p450 superfamily,[288,302,303] such as CYP1A1,[302,303] as well as *N*-acetyltransferase, glutathione *S*-transferase M1 (GSTM1), microsomal epoxide hydrolase (*m*EH)[290,304] NAD(P)H:quinone oxidoreductase ($^{609}C \rightarrow T$ polymorphism)[290,305] and myeloperoxidase (MPO)[306]—which are involved in the activation or detoxification of carcinogens,[290,307] and on DNA repair genes[290,308] (about 130 DNA repair genes have been recorded, divisible into base excision repair, nucleotide excision repair and mismatch repair genes).[309] For example, in relation to DNA repair genes it has also been reported that polymorphisms affecting exons 10 and 23 of XPD modulate risks for lung cancer among never-smokers, so that the presence of one or two variant alleles was associated with an OR_{LCA} of 2.6 for exon 10 (95%CI = 1.1–6.5) and 3.2 for exon 23 (95%CI = 1.3–8.0);[289] in addition, current or recent smokers had higher aromatic DNA adduct levels than former/never smokers, and the same study[289] found that subjects with exon 10 AA and exon 23 CC had significantly higher aromatic DNA adduct levels than subjects with any other genotype, with an increased risk of lung cancer.

In all probability, many potential G_S/G_R genes have yet to be identified,[290] and analysis of the interplay between multiple G_S and G_R genes and environmental carcinogens constitutes a problem of great complexity; nonetheless, it seems likely that 'everyone may have a unique combination of polymorphic traits that modify genetic susceptibility and response to ... carcinogens',[290] especially for multifactorial diseases such as lung cancer.[290] To simplify matters, the following discussion concentrates mainly on the MPO gene.

MPO is a lysosomal enzyme found in both neutrophils

††The largest database of its type in the World, the Swedish Family-Cancer Database contains data on people born in Sweden after 1931, including their parents; by 2002, the Database comprised information on 10.2 million individuals across 3.2 million families, with data on more than 1 million tumours.[296–298]

and macrophages, and it catalyses the reaction between H_2O_2 and Cl^-, generating hypochlorous acid (HOCl)[310] and other reactive oxygen species (ROS); MPO is involved in the metabolism of several DNA-damaging intermediary factors that include tobacco smoke mutagens, and MPO appears to contribute to lung carcinogenesis by activation of procarcinogens such as benzo[*a*]pyrene intermediates, 4-aminobiphenyl and arylamines.[311] The MPO gene is localised to the long arm of chromosome 17 and comprises 11 introns and 12 exons.

Multiple investigations have evaluated the potential protective effect of the variant A allele for MPO in comparison to the wild-type genotype G/G ($^{-463}$MPO G→A) on the risk of lung cancer.[311–321] Although two studies[316,319] did not detect any significant association between the A allele in comparison to G/G, most found that the A allele was associated with up to a 70% reduced RR_{LCA}/OR_{LCA} at equivalent levels of smoking; in one study[314] the reduced risk was confined to the homozygous AA polymorphism and not to the heterozygous G/A form, but others detected a reduced risk for G/A,[311,313,317,318,320] and one[315] reported the findings as the risk for G/A + A/A only. Most studies reported the protective effect of the A allele in terms of RR_{LCA}/OR_{LCA} relative to G/G, but Lu *et al.*[321] and Schabath *et al.*[322] reported their results as an increased OR_{LCA} for G/G relative to G/A + A/A. The proportions of G/G versus G/A and A/A appear not to differ greatly from lung cancer cases in comparison to controls: across all studies cited above,[311–321] G/G was found in 62% of controls versus 65% of cases; for G/A and A/A for controls versus cases, the percentage proportions were 33 vs 31% and 5 vs 4%; when the two studies that found no effect of MPO polymorphisms on lung cancer risk[316,319] are removed, the proportions for controls versus cases become 61 vs 68% for G/G, 29 vs 33% for G/A and 3 vs 6% for A/A.

Evidence for a component of genetic susceptibility for asbestos-related mesothelioma[323–325] and for lung cancer is much less extensive than the evidence for cigarette smoke-related lung cancer. Nonetheless, this notion has biological plausibility,[326] and is supported by the following observations: (i) only a minority of asbestos-exposed individuals, even those exposed heavily to crocidolite, develop mesothelioma during their lifetimes[327,328] (see preceding discussion); (ii) familial clusters of asbestos-associated mesothelioma are well documented;[329–341] (iii) one study[323] found that patients with mesothelioma have a greater frequency of non-mesothelioma cancers among their parents than non-mesothelioma cases; and (iv) genomic variants have been described in mesothelioma, such as inactivating mutations of the neurofibromatosis type 2 (NF2) gene[342] and simian virus 40 (SV40) transcripts incorporated into the genome (although the evidence for a contributory causal role of SV40 in the development of asbestos-related mesothelioma remains unproven[343,344]).

So far as we are aware, there are only two reports on G_S/G_R for asbestos-associated lung cancer, relative to polymorphisms for the GSTM1[345] and MPO genes.[322] Stucker *et al.*[345] found no evidence that the risk of lung cancer after asbestos exposure differed according to the GSTM1 genotype, although this study had 'low statistical power'.[345] Conversely, in a molecular case-referent study, Schabath *et al.*[322] found that subjects with self-reported asbestos exposure and with the MPO genotype G/G had an OR_{LCA} of 1.72 for asbestos exposure compared with no exposure after controlling for age, gender and smoking, whereas subjects with a G/A + A/A genotype had a lower OR_{LCA} of 0.89. Subjects with G/G had an OR_{LCA} of 1.69 for ≥45 pack-years of smoking (heavy) compared with <45 (light), whereas the OR_{LCA} for those with G/A + A/A was <1.0. For GG, the joint effect of asbestos and heavy smoking in comparison to no asbestos and light smoking was 2.19, and the analogous OR_{LCA} for G/A + A/A was 1.18.

Given the emerging evidence on G_S/G_R for lung cancer, for both cigarette smoke and (to a far lesser extent) asbestos, and taking into account the complexity of the multiple genes and polymorphisms implicated so far, it seems that individuals comprising any population will vary in their susceptibility to (and risk from) these carcinogens. Therefore, one can deduce that the risk derived as an average or mean across entire cohorts/populations will tend to underestimate the risk for those with a G_S profile (RR_{GS}) and to overestimate risk for those with G_R (RR_{GR}). It also follows that those with the disease in question are more likely to have G_S for that disease and therefore to be at greater risk than either: (i) those who are resistant (G_R); or (ii) the average/mean risk (i.e., $RR_{GS} > [RR_{GS} + RR_{GR}]/2$), even if the variation in risk from the mean is only very small.

Assessing the significance of interaction between genetic and environmental factors in disease causation involves a new type of epidemiological study, the case-only study,[345,346] in which departure from a purely multiplicative model of joint effect can be assessed by computing the case-only OR (OR_{C-O}), derived for cases with and without the susceptibility gene and with and without exposure from a 2 × 2 table; if OR_{CS} represents the OR among control subjects related to exposure and susceptibility genotype, then:

$$OR_{C-O} = [OR_{GE}/(OR_E \cdot OR_G)] \cdot OR_{CS}$$

where OR_{GE}, OR_G and OR_E are conventional case–control ORs for combined genetic susceptibility plus exposure, genetic susceptibility, and exposure separately.[346] Because the genotype and the exposure are generally independent variables in the source population from which the cases arise, the expected value of OR_{CS} is unity; if the joint effect is more than multiplicative, OR_{C-O} is greater than 1.0, and it is less than 1.0 if the joint effect is less than multiplicative.[346] Applied to the data in Table III of Schabath *et al.*[322] (asbestos and genotype), the above analysis gives an OR_{C-O} of 0.96, indicating near-multiplicativity.

If such findings[322] are validated in other analogous investigations, they would suggest that the asbestos-related lung cancer risk derived as an average across groups might be revised upwards for those with a susceptibility genotype, so that cumulative exposures lower than the average (e.g., <25 fibres/mL-years) could be accepted as imposing an OR ≥2.0, and the risk would be correspondingly revised downward for those with a genetic resistance profile, with the requirement for a greater cumulative exposure to impose the same risk. We consider that this approach to carcinogenesis by environmental factors in general has a sound theoretical and, to a lesser extent,

empirical basis, and we expect that molecular epidemiological studies that address these issues will lead to further refinement of approaches to causation by cigarette smoke, asbestos, and other environmental carcinogens. Nonetheless, we consider that at present it is not possible to apply existing data on G_S/G_R for the attribution of lung cancer to asbestos in the individual patient, or to modify existing cumulative exposure approaches to causation, because of: (i) contradictory and inadequate G_S/G_R data, even for single gene polymorphisms; (ii) uncertainties surrounding G_S/G_R profile effects overall; (iii) inadequate data on net G_S/G_R interactivity with asbestos; and, as a consequence, (iv) unquantifiability of any such effects. We also emphasise that these theorisings do not detract from the critical role of the exogenous carcinogens in causation of the disease:[287] in the absence of the carcinogen, it would be less likely that genetic susceptibility (G_S/no-exposure) would be expressed as a particular cancer at the time of occurrence of the cancer, than for a G_S/exposure situation (in other words, the carcinogens produce an increment in risk above 'background' G_S).

We emphasise that although 'traditional' epidemiology has been highly effective for the detection and quantitation of the net or average causal effects of various carcinogens across populations or groups as reflected in cohort or case-referent studies, it becomes less precise for the quantitation of causal effects when applied to assessment of causation in an individual, because of the following factors among many others:

1. Differential exposures to the carcinogen within the cohort or within the cases group for case-referent studies (unless the exposure estimates are individualised or stratified for different patterns of work and exposure). (See discussion of the study by Carel *et al.*,[165] p. 529.)

2. Changes over time in exposures and smoking habits across the cohort/group unless the parameters of exposure/smoking are evaluated longitudinally over time.

3. Differential clearance of asbestos fibres from bronchopulmonary tissues, related to differences in the proportions of asbestos fibre types for mixed asbestos exposures and fibre dimensions, and the efficacy of host clearance mechanisms as influenced by a variety of factors that include innate and acquired differences in the capacity for fibre clearance.

4. Differential genetic susceptibility to the carcinogen(s).

In general, these factors will tend to depress unquantifiably the slope of the dose–response line in comparison to the real effects for those who have asbestos-associated lung cancer, and thereby underestimate probability of causation.

EXPOSURE ASSESSMENT: NATIONAL APPROACHES AND FUTURE DIRECTIONS

The cumulative exposure standard of 25 fibre-years or more for lung cancer attribution is also applied in Denmark, and equivalent job histories elsewhere in Scandinavia, with no requirement for asbestosis.[1] Occupational histories similar to those delineated by The Helsinki Criteria[102] also form the basis for attribution in France and Belgium.[49,233] In Australia, the courts have ruled in favour of the cumulative exposure model as a basis for attribution, and similar criteria were also endorsed by the AWARD Workshop.[225,235]

Because decision-making on compensation now appears to favour The Helsinki Criteria approach, construction of databases such as those described by Burdorf and Swuste[228] or *Faserjahre*[64] will be essential for equitable compensation of lung cancer due to asbestos, when evidence of quantified exposure must be based on history.[2] The approach in The Netherlands is more qualitative than the German system, with probabilistic assessments of the likelihood of different exposure levels. Without such systems, boards and tribunals will continue to spend inordinate time evaluating uncertainties over past exposures and conflicting opinions from expert witnesses. The aim of databased systems of these types is to create a matrix that defines asbestos exposure by industry, occupation and time. In association with each value, one can then assign a level of confidence ranging from:

1. Direct measurement.
2. Interpolated measurement.
3. Measurement in a similar facility.
4. Interpolation from a similar facility.
5. Consensus estimate.
6. Estimate for which no consensus can be reached.

In practice, when there are no direct measurements of airborne fibre levels in a particular workplace, as is often the case in nations such as Australia, experts often express estimated cumulative exposure as a low/high range in fibre-years, based on: (i) the number and duration of work shifts which together comprise about 20% of calendar time; and (ii) published low and high values for airborne fibre concentrations generated by the same or similar types of work in other workplaces, and with derivation of a likely mean estimate.

On the basis of prevailing evidence, the cumulative exposure model for lung cancer induction by asbestos appears to conform to modern approaches to assessment of causality,[29,59,221,326,347,348] with coherence of data across multiple different types of investigation that include dose-response data from epidemiological studies and case-referent studies based on lung tissue fibre measurements; the evidence also encompasses a variety of pathological observations that include the separate and combined clastogenic and mutagenic effects of asbestos and tobacco smoke on cell lines *in vitro* and on bronchiolar epithelium *in vivo*. In terms of generalisability,[29] the cumulative exposure model appears to have explanatory-predictive value: after the 25 fibres/mL-year standard was introduced in Germany—where attribution is primarily an administrative exercise, so that decision-making is less likely to be skewed than by adversarial court-based systems of compensation—the excess lung cancer to mesothelioma ratio has shown close agreement with the same ratio obtained from multiple epidemiological investigations.

Finally, we emphasise that estimates of cumulative exposure (25 fibre-years or an equivalent job history) set forth in The Helsinki Criteria are applicable to amphibole and asbestos textile exposures and, we believe, mixed exposures (notably exposures to asbestos-cement and insulation materials that contained chrysotile and amphiboles);

they are not applicable to the Quebec chrysotile miners/millers and they may not be appropriate for friction products manufacture or some other chrysotile-only exposures, or perhaps mixed exposures where the composition (i.e. the proportions of airborne fibre types) is known with precision (virtually never the case for end-use exposures). The fibre concentrations in lung tissue refer primarily to the amphibole content related to mixed exposures; for amphibole-only exposures, higher concentrations are required, and asbestos fibre measurements in lung tissue are unsuitable in general for estimates of cumulative exposure to chrysotile only. In the future, a lower cumulative asbestos exposure than say 25 fibres/mL-years or an equivalent occupational history may be acceptable for attribution of lung cancer to asbestos among those with an identifiable genetic susceptibility profile for lung cancer, and a higher cumulative asbestos exposure would be required to impose the same lung cancer risk among those with an identifiable genotype that confers a measure of protection against the carcinogenic effects of asbestos. Use of the upper 95th percentile confidence interval for assessment of risk for some cancers[27] arguably goes some way towards addressing differences in risk related to a variety of factors including differential G_S/G_R, in terms of probabilistic approaches to the causation of disease in the individual; use of the mean, based on average exposures with no individualisation of exposure estimates or consideration of innate susceptibility/resistance factors, does not.

ACKNOWLEDGEMENTS We are grateful to Dr Per Gustavsson of Stockholm for his comments on the Swedish case-referent analyses,[94,164,190] and to Dr Xifeng Wu of the MD Anderson Cancer Center, Houston, USA, for information on myeloperoxidase polymorphism as a risk factor for lung cancer.[311,315,322]

POTENTIAL CONFLICT-OF-INTEREST STATEMENT DWH and JL have prepared reports on asbestos exposure and lung cancer for the Courts in Australia, notably the Dust Diseases Tribunal (DDT) in New South Wales (and in the United Kingdom for DWH and the USA for JL), and have given courtroom testimony on this issue. No equivalent issues were identified for KR and H-JW. None of the authors has any affiliation with the Asbestos Industry or any non-professional group that lobbies for or against the Industry.

Address for correspondence: Professor D.W. Henderson, Department of Anatomical Pathology, Flinders Medical Centre, Bedford Park, SA 5042, Australia. E-mail: Douglas.Henderson@flinders.edu.au

References

1. Henderson DW, de Klerk NH, Hammar SP, *et al*. Asbestos and lung cancer: is it attributable to asbestosis, or to asbestos fiber burden? In: Corrin B, editor. *Pathology of Lung Tumours*. New York: Churchill Livingstone, 1997; 83–118.
2. Henderson DW, Leigh J. Asbestos and lung cancer: a selective up-date to The Helsinki Criteria for individual attribution. *People and Work Research Reports 36*. Helsinki: Finnish Institute for Occupational Health, 2000; 3–18.
3. Nordmann M. Der berufskrebs der asbestarbeiter. *Z Krebsforsch* 1938; 47: 288–302.
4. Doll R. Mortality from lung cancer in asbestos workers. *Br J Ind Med* 1955; 12: 81–6.
5. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. *Br J Ind Med* 1960; 17: 260–71.
6. Australasian Faculty of Occupational Medicine (AFOM) Working Party on Occupational Cancer. *Occupational Cancer: A Guide to Prevention, Assessment and Investigation*. Sydney: AFOM, The Royal Australasian College of Physicians, 2003.
7. Hutchings S, Jones J, Hodgson J. Asbestos-related diseases. In: Drever F, editor. *Occupational Health Decennial Supplement No 10*. London: Office of Population Censuses (OPCS), Health & Safety Executive (HSE), 1995; 136–52.
8. Boffetta P. Health effects of asbestos exposure in humans: a quantitative assessment. *Med Lav* 1998; 89: 471–80.
9. Peto J, Decarli A, La Vecchia C, *et al*. The European mesothelioma epidemic. *Br J Cancer* 1999; 79: 666–72.
10. Doll R, Peto R, Wheatley K, *et al*. Mortality in relation to smoking: 40 years' observations on male British doctors. *Br Med J* 1994; 309: 901–11.
11. Simonato L, Agudo A, Ahrens W, *et al*. Lung cancer and cigarette smoking in Europe: an update of risk estimates and an assessment of inter-country heterogeneity. *Int J Cancer* 2001; 91: 876–87.
12. Alberg AJ, Samet JM. Epidemiology of lung cancer. *Chest* 2003; 123 (Suppl.): 21S–49S.
13. Multiple authors. Lung cancer. In: Stuart BW, Kleihues P, editors. *World Cancer Report*. Lyon: International Agency for Research on Cancer (IARC), 2003: 182–7.
14. Vainio H, Boffetta P. Mechanisms of the combined effect of asbestos and smoking in the etiology of lung cancer. *Scand J Work Environ Health* 1994; 20: 235–42.
15. Lee PN. Relation between exposure to asbestos and smoking jointly and the risk of lung cancer. *Occup Environ Med* 2001; 58: 145–53.
16. Liddell FD. The interaction of asbestos and smoking in lung cancer. *Ann Occup Hyg* 2001; 45: 341–56.
17. Tossavainen A. Asbestos, asbestosis and cancer: exposure criteria for clinical diagnosis. *People and Work Research Reports 14*. Helsinki: Finnish Institute of Occupational Health, 1997; 8–27.
18. Van Loon AJ, Kant IJ, Swaen GM, *et al*. Occupational exposure to carcinogens and risk of lung cancer: results from The Netherlands cohort study. *Occup Environ Med* 1997; 54: 817–24.
19. Multiple authors. *Environmental Health Criteria 211: Health Effects of Interactions between Tobacco Use and Exposure to Other Agents*. Geneva: World Health Organization, 1999.
20. Howie RM. An important source of error in asbestos-related lung cancer estimates. *Ann Occup Hyg* 2000; 44: 484–7.
21. Mándi A, Posgay M, Vadász P, *et al*. Role of occupational asbestos exposure in Hungarian lung cancer patients. *Int Arch Occup Environ Health* 2000; 73: 555–60.
22. Rödelsperger K, Mándi A, Tossavainen A, *et al*. Inorganic fibres in the lung tissue of Hungarian and German lung cancer patients. *Int Arch Occup Environ Health* 2000; 74: 133–8.
23. Axelson O. Alternative for estimating the burden of lung cancer from occupational exposures: some calculations based on data from Swedish men. *Scand J Work Environ Health* 2002; 28: 58–63.
24. Nurminen M, Karjalainen A. Epidemiologic estimate of the proportion of fatalities related to occupational factors in Finland (erratum in *Scand J Work Eniron Health* 2001; 27: 295). *Scand J Work Environ Health* 2001; 27: 161–213.
25. Kjuus H, Langard S, Skjaerven R. A case-referent study of lung cancer, occupational exposures and smoking III: etiologic fraction of occupational exposures. *Scand J Work Environ Health* 1986; 12: 210–5.
26. Kvale G, Bjelke E, Heuch I. Occupational exposure and lung cancer risk. *Int J Cancer* 1986; 37: 185–93.
27. Armstrong B, Theriault G. Compensating lung cancer patients occupationally exposed to coal tar pitch volatiles. *Occup Environ Med* 1996; 53: 160–7.
28. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 1998; 88: 15–9.
29. Rothman KJ, Greenland S*Modern Epidemiology*. 2nd ed. Philadelphia: Lippincott-Raven, 1998.
30. Armitage P, Berry G, Matthews JNS. *Statistical Methods in Medical Research*. 4th ed. Oxford: Blackwell, 2002.
31. Dos Santos Silva I. *Cancer Epidemiology: Principles and Methods*. Lyon: IARC, 1999.
32. Kirkwood BR, Sterne JAC. *Essential Medical Statistics*. 2nd ed. Oxford: Blackwell; 2003.
33. Gigerenzer G. *Reckoning with Risk: Learning to Live with Uncertainty*. London: Allen Lane, 2002. (Published in the USA as

Calculated Risks: How to Know when Numbers Deceive You. New York: Simon & Schuster, 2002.).
34. Greenland S. Relation of probability of causation to relative risk and doubling dose: a methodologic error that has become a social problem. *Am J Public Health* 1999; 89: 1166–9.
35. Bryant AH, Reinert A. Epidemiology in the legal arena and the search for truth. *Am J Epidemiol* 2001; 154 (Suppl.): S27–35.
36. Health Effects Institute—Asbestos Research (HEI-AR). *Asbestos in Public and Commercial Buildings: A Literature Review and Synthesis of Current Knowledge*. Cambridge, MA: HEI-AR; 1991.
37. Howie R. Asbestos-induced deaths in the United Kingdom. In: Peters GA, Peters BJ, editors. *Sourcebook on Asbestos Diseases.* Vol. 19. Charlottesville: Lexis, 1999; 219–38.
38. Camus M. Do risk assessments justify banning chrysotile or not? *Can Mineral* 2001 (Spec Publ 5): 227–38.
39. Barroetavena MC, Teschke K, Bates DV. Unrecognized asbestos-induced disease. *Am J Ind Med* 1996; 29: 183–5.
40. Tulchinsky TH, Ginsberg GM, Iscovich J, *et al*. Cancer in ex-asbestos cement workers in Israel, 1953–1992. *Am J Ind Med* 1999; 35: 1–8.
41. Ulvestad B, Kjaerheim K, Martinsen JI, *et al*. Cancer incidence among workers in the asbestos-cement producing industry in Norway. *Scand J Work Environ Health* 2002; 28: 411–7.
42. Raffn E, Lynge E, Juel K, Korsgaard B. Incidence of cancer and mortality among employees in the asbestos cement industry in Denmark. *Br J Ind Med* 1989; 46: 90–6.
43. Talcott JA, Thurber WA, Kantor AF, *et al*. Asbestos-associated diseases in a cohort of cigarette-filter workers. *New Engl J Med* 1989; 321: 1220–3.
44. Health and Safety Commission (HSC). *Health and Safety Statistics 2000/01*. London: HSE Books, 2001.
45. HSC. *Health and Safety Statistics 1998/99*. London: HSE Books, 1999.
46. Berry G, Newhouse ML, Wagner JC. Mortality from all cancers of asbestos factory workers in east London 1933–80. *Occup Environ Med* 2000; 57: 782–5.
47. Giesen T, Zerlett G. *Berufskrankheiten und medizinischer Arbeitsschutz: ergänzbare Ausgabe mit Rechtsvorschriften, Merkblättern, Statistiken und Hinweisen zu Paragraph 9 Abs. 2 SGB VII*. Stuttgart: Kohlhammer-Losebl-Ausg, 2000; 23.
48. Baur X, Czuppon AB. Regulation and compensation of asbestos diseases in Germany. In: Peters GA, Peters BJ, editors. *Sourcebook on Asbestos Diseases*. Vol. 15. Charlottesville: Lexis, 1997; 405–19.
49. Hindry M. Asbestos-related disease compensation in France. In: Peters GA, Peters BJ, editors. *Sourcebook on Asbestos Diseases*. Vol. 16. Charlottesville: Lexis, 1997; 423–48.
50. Legrand Cattan K, Chouaid C, Monnet I, *et al*. Evaluation of occupational exposures in lung cancer (French.). *Rev Mal Respir* 2000; 17: 957–62.
51. De Lamberterie G, Maitre A, Goux S, *et al*. How do we reduce the under-reporting of occupational primary lung cancer (French.). *Rev Mal Respir* 2002; 19: 190–5.
52. Mollo F, Magnani C, Bo P, *et al*. The attribution of lung cancers to asbestos exposure: a pathologic study of 924 unselected cases. *Am J Clin Pathol* 2002; 117: 90–5.
53. Kishimoto T, Ohnishi K, Saito Y. Clinical study of asbestos-related lung cancer. *Industrial Health* 2003; 41: 94–100.
54. World Trade Organization (WTO) Disputes Settlement and Appellate Body Reports WT/DS135. *European Communities—Measures Concerning Asbestos and Asbestos-containing Products*. Geneva: WTO, 2000. http//:www.wto.org (accessed May 2004).
55. Leigh J, Driscoll T. Malignant mesothelioma in Australia 1945–2002. *Int J Occup Environ Health* 2003; 9: 206–17.
56. Teschke K, Barroetavena MC. Occupational cancer in Canada: what do we know? *Can Med Assoc J* 1992; 147: 1501–7.
57. Piekarski C, Jennison EA, Parker JE. Workers' compensation for occupational lung disease: German–US parallels. In: Banks DE, Parker JE, editors. *Occupational Lung Disease: An International Perspective*. London: Chapman & Hall Medical, 1998: 83–93.
58. Langer AM. Health experience of some US and Canadian workers exposed to asbestos: foundation for risk assessment. *Can Mineral* 2001; (Spec Publ 5): 9–20.
59. Stolley PD, Lasky T. *Investigating Disease Patterns: The Science of Epidemiology*. New York: Scientific American, 1998.
60. Nurminen M, Tossavainen A. Is there an association between pleural plaques and lung cancer without asbestosis? *Scand J Work Environ Health* 1994; 20: 62–4.
61. Partanen T, Nurminen M, Zitting A, *et al*. Localized pleural plaques and lung cancer. *Am J Ind Med* 1992; 22: 185–92.
62. Multiple authors. *Environmental Health Criteria 203: Chrysotile Asbestos*. Geneva: World Health Organization, 1998.
63. Egilman D, Fehnel C, Bohme SR. Exposing the 'myth' of ABC, 'Anything But Chrysotile': a critique of the Canadian asbestos mining industry and McGill University chrysotile studies. *Am J Ind Med* 2003; 44: 540–57.
64. BK-report *Faserjahre. Berufsgenossenschaftliche Hinweise zur Ermittlung der kumulativen Asbestfaserstaub-Dosis am Arbeitsplatz (Faserjahre) und Bearbeitungshinweise zur Berufskrankheit Nr 4104 BKV (Lungenkrebs)*. Abridged English Version: Report on Occupational Diseases 'Fibre Years' 1/1997. Sankt-Augustin: Schriftenreihe des Hauptverbandes der gewerblichen Berufsgenossenschaften, 1997.
65. Churg A. Nonneoplastic diseases caused by asbestos. In: Churg A, Green FHY, editors. *Pathology of Occupational Lung Disease*. New York: Igaku-Shoin; 1988: 213–77.
66. Tossavainen A. Health and exposure surveillance of Siberian asbestos miners: a joint Finnish–American–Russian project. *People and Work Research Reports 19*. Helsinki: Finnish Institute of Occupational Health, 1998; 89–91.
67. Smith AH, Wright CC. Chrysotile asbestos is the main cause of pleural mesothelioma. *Am J Ind Med* 1996; 30: 252–66.
68. Stayner LT, Dankovic DA, Lemen RA. Occupational exposure to chrysotile asbestos and cancer risk: a review of the amphibole hypothesis. *Am J Public Health* 1996; 86: 179–86.
69. Schneider T, Skotte J. Fiber exposure reassessed with the new indices. *Environ Res* 1990; 51: 108–16.
70. Williams-Jones AE, Normand C, Clark JR, *et al*. Controls of amphibole formation in chrysotile deposits: evidence from the Jeffrey Mine, Asbestos, Quebec. *Can Mineral* 2001; (Spec Publ 5): 89–104.
71. Rödelsperger K, Brückel B, Turowski S, *et al*. Actinolite/tremolite and other inorganic fibres from a gabbro quarry. Proceedings of the 9th International Inhalation Symposium, Hanover, Germany, June 2003. *Effects of Air Contaminants on the Respiratory Tract—Interpretations from Molecules to Meta-Analysis*. Hanover: INIS Monographs, 2003.
72. Goldberg M. Asbestos and risk of cancer: exposure-effect relationships for occupationally exposed populations (French.). *Rev Mal Respir* 1999; 16: 1278–85.
73. Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann Occup Hyg* 2000; 44: 565–601.
74. Liddell FD, McDonald AD, McDonald JC. Dust exposure and lung cancer in Quebec chrysotile miners and millers. *Ann Occup Hyg* 1998; 42: 7–20.
75. McDonald AD, Case BW, Churg A, *et al*. Mesothelioma in Quebec chrysotile miners and millers: epidemiology and aetiology. *Ann Occup Hyg* 1997; 41: 707–19.
76. McDonald JC. Unfinished business: the asbestos textiles mystery (Editorial). *Ann Occup Hyg* 1998; 42: 3–5.
77. Brown DP, Dement JM, Okun A. Mortality patterns among female and male chrysotile asbestos textile workers. *J Occup Med* 1994; 36: 882–8.
78. Dement JM, Brown DP, Okun A. Follow-up study of chrysotile asbestos textile workers: cohort mortality and case-control analyses. *Am J Ind Med* 1994; 26: 431–47.
79. Dement JM, Brown DP. Lung cancer mortality among asbestos textile workers: a review and update. *Ann Occup Hyg* 1994; 38: 525–32, 412.
80. Case BW, Dufresne A, McDonald AD, McDonald JC. Asbestos fiber type and length in lungs of chrysotile textile and production workers: fibers longer than 18 μm. *Inhal Toxicol* 2000; 12 (Suppl. 3): 411–8.
81. Yano E, Wang Z-M, Wang X-R, *et al*. Cancer mortality among workers exposed to amphibole-free chrysotile. *Am J Epidemiol* 2001; 154: 538–43.
82. Cai SX, Zhang CH, Zhang X, Morinaga K. Epidemiology of occupational asbestos-related diseases in China. *Ind Health* 2001; 39: 75–83.
83. Tossavainen A, Kovalevsky E, Vanhala E, Tuomi T. Pulmonary mineral fibers after occupational and environmental exposure to asbestos in the Russian chrysotile industry. *Am J Ind Med* 2000; 37: 327–33.
84. Tossavainen A, Kotilainen M, Takahashi K, *et al*. Amphibole fibres in Chinese chrysotile asbestos. *Ann Occup Hyg* 2001; 45: 145–52.

85. Sebastien P, McDonald JC, McDonald AD, *et al*. Respiratory cancer in chrysotile textile and mining industries: exposure inferences from lung analysis. *Br J Ind Med* 1989; 46: 180–7.
86. Green FH, Harley R, Vallyathan V, *et al*. Exposure and mineralogical correlates of pulmonary fibrosis in chrysotile asbestos workers. *Occup Environ Med* 1997; 54: 549–59.
87. Luce D, Bugel I, Goldberg P, *et al*. Environmental exposure to tremolite and respiratory cancer in New Caledonia: a case-control study. *Am J Epidemiol* 2000; 151: 259–65.
88. Menvielle G, Luce D, Fevotte J, *et al*. Occupational exposures and lung cancer in New Caledonia. *Occup Environ Med* 2003; 60: 584–9.
89. Hauptmann M, Pohlabeln H, Lubin JH, *et al*. The exposure-time-response relationship between occupational asbestos exposure and lung cancer in two German case-control studies. *Am J Ind Med* 2002; 41: 89–97.
90. Gong MN, Christiani DC. Lung cancer. In: Hendrick DJ, Burge PS, Beckett WS, Churg A, editors. *Occupational Disorders of the Lung: Recognition, Management, and Prevention*. London: Saunders, 2002; 305–26.
91. Liddell FD, Armstrong BG. The combination of effects on lung cancer of cigarette smoking and exposure in Quebec chrysotile miners and millers. *Ann Occup Hyg* 2002; 46: 5–13.
92. Liddell FD. Joint action of smoking and asbestos exposure on lung cancer. *Occup Environ Med* 2002; 59: 494–5; discussion 5–6.
93. Lee PN. Joint action of smoking and asbestos exposure on lung cancer (Reply). *Occup Environ Med* 2002; 59: 495–6.
94. Gustavsson P, Nyberg F, Pershagen G, *et al*. Low-dose exposure to asbestos and lung cancer: dose-response relations and interaction with smoking in a population-based case-referent study in Stockholm, Sweden. *Am J Epidemiol* 2002; 155: 1016–22.
95. Erren TC, Jacobsen M, Piekarski C. Synergy between asbestos and smoking on lung cancer risks. *Epidemiology* 1999; 10: 405–11.
96. Nelson HH, Kelsey KT. The molecular epidemiology of asbestos and tobacco in lung cancer. *Oncogene* 2002; 21: 7284–8.
97. Churg A, Stevens B. Enhanced retention of asbestos fibers in the airways of human smokers. *Am J Respir Crit Care Med* 1995; 151: 1409–13.
98. Bach PB, Kattan MW, Thornquist MD, *et al*. Variations in lung cancer risk among smokers. *J Natl Cancer Inst* 2003; 95: 470–8.
99. Vena JE, Byers TE, Cookfair D, Swanson M. Occupation and lung cancer risk: an analysis by histologic subtypes. *Cancer* 1985; 56: 910–7.
100. Zang EA, Wynder EL. Cumulative tar exposure: a new index for estimating lung cancer risk among cigarette smokers. *Cancer* 1992; 70: 69–76.
101. Hammar SP. Common neoplasms. In: Dail DH, Hammar SP, editors. *Pulmonary Pathology*. 2nd ed. New York: Springer, 1994; 1123–278.
102. Multiple authors. Consensus report: asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution. *Scand J Work Environ Health* 1997; 23: 311–6.
103. Chase GR, Kotin P, Crump K, Mitchell RS. Evaluation for compensation of asbestos-exposed individuals II: apportionment of risks for lung cancer and mesothelioma. *J Occup Med* 1985; 27: 189–98.
104. Langård S. Partitioning of causal weights of work and environment related diseases based on epidemiologic results (Norwegian.). *Nor J Epidemiol* 1997; 4: 26–31.
105. Leigh J, Berry G, de Klerk NH, Henderson DW. Asbestos-related lung cancer: apportionment of causation and damages to asbestos and tobacco smoke. In: Peters GA, Peters BJ, editors. *Sourcebook on Asbestos Diseases*. Vol. 13. Charlottesville: Michie, 1996; 141–66.
106. Mollo F, Bellis D, Delsedime L, *et al*. Autopsy indicators of exposure to asbestos and lung cancer. In: Riboli E, Delendi M, editors. *Autopsy in Epidemiology and Medical Research*. Lyon: IARC, 1991: 141–7.
107. Husgafvel-Pursiainen K, Hackman P, Ridenpää M, *et al*. K-*ras* mutations in hunan adenocarcinoma of the lung: association with smoking and occupational exposure to asbestos. *Int J Cancer* 1993; 53: 250–6.
108. Karjalainen A. *Occupational Asbestos Exposure, Pulmonary Fiber Burden and Lung Cancer in the Finnish Population*. (Thesis.) Helsinki: University of Helsinki, 1994.
109. Karjalainen A, Anttila S, Vanhala E, Vainio H. Asbestos exposure and the risk of lung cancer in a general urban population. *Scand J Work Environ Health* 1994; 20: 243–50.
110. Raffn E, Lynge E, Korsgaard B. Incidence of lung cancer by histological type among asbestos cement workers in Denmark. *Br J Ind Med* 1993; 50: 85–9.
111. Roggli VL, Sanders LL. Asbestos content of lung tissue and carcinoma of the lung: a clinicopathologic correlation and mineral fiber analysis of 234 cases. *Ann Occup Hyg* 2000; 44: 109–17.
112. Colby TV, Koss MN, Travis WD. *Tumors of the Lower Respiratory Tract*. Washington, DC: Armed Forces Institute of Pathology/ American Registry of Pathology, 1995.
113. de Klerk NH, Musk AW, Eccles JL, *et al*. Exposure to crocidolite and the incidence of different histological types of lung cancer. *Occup Environ Med* 1996; 53: 157–9.
114. Churg A. Neoplastic asbestos-induced diseases. In: Churg A, Green FHY, editors. *Pathology of Occupational Lung Disease*. New York: Igaku-Shoin, 1988; 279–325.
115. Churg A. Neoplastic asbestos-induced disease. In: Churg A, Green FHY, editors. *Pathology of Occupational Lung Disease*. 2nd edn. Baltimore: Williams & Wilkins, 1998: 339–91.
116. Baker JE. *Lung Cancer Incidence Amongst Previous Employees of an Asbestos Mine in Relationship to Crocidolite Exposure and Tobacco Smoking*. (Thesis.) Perth: Department of Medicine, University of Western Australia, 1985.
117. Sluis-Cremer GK. Asbestos disease at low exposures after long residence times. *Ann NY Acad Sci* 1991; 643: 182–93.
118. Menegozzo M, Belli S, Borriero S, *et al*. Mortality study of a cohort of insulation workers (Italian.). *Epidemiol Prev* 2002; 26: 71–5.
119. Nicholson WJ, Perkel G, Selikoff IJ, Seidman H. Cancer from occupational asbestos exposure projections 1980–2000. In: Peto R, Schneiderman M, editors. *Quantification of Occupational Cancer*. New York: Cold Spring Harbor Laboratory, 1981; 87–111.
120. Coviello V, Carbonara M, Bisceglia L, *et al*. Mortality in a cohort of asbestos cement workers in Bari (Italian.). *Epidemiol Prev* 2002; 26: 65–70.
121. Warnock ML, Isenberg W. Asbestos burden and the pathology of lung cancer. *Chest* 1986; 89: 20–6.
122. Hillerdal G. Pleural plaques and risk for bronchial carcinoma and mesothelioma: a prospective study. *Chest* 1994; 105: 144–50.
123. Greenberg SD, Roggli VL. Carcinoma of the lung. In: Roggli VL, Greenberg SD, Pratt PC, editors. *Pathology of Asbestos-Associated Diseases*. Boston: Little Brown, 1992: 189–210.
124. Hammar SP, Dodson RF. Asbestos. In: Dail DH, Hammar SP, editors. *Pulmonary Pathology*. 2nd ed. New York: Springer, 1994: 901–83.
125. Roggli VL, Hammar SP, Pratt PC, *et al*. Does asbestos or asbestosis cause carcinoma of the lung? *Am J Ind Med* 1994; 26: 835–8.
126. Paris C, Benichou J, Saunier F, *et al*. Smoking status, occupational asbestos exposure and bronchial location of lung cancer. *Lung Cancer* 2003; 40: 17–24.
127. Huuskonen M. Clinical features, mortality and survival of patients with asbestosis. *Scand J Work Environ Health* 1978; 4: 265–74.
128. Auerbach O, Garfinkel L, Parks VR, *et al*. Histologic type of lung cancer and asbestos exposure. *Cancer* 1984; 54: 3017–21.
129. Johansson L, Albin M, Jakobsson K, Mikoczy Z. Histological type of lung carcinoma in asbestos cement workers and matched controls. *Br J Ind Med* 1992; 49: 626–30.
130. Lee BW, Wain JC, Kelsey KT, *et al*. Association of cigarette smoking and asbestos exposure with location and histology of lung cancer. *Am J Respir Crit Care Med* 1998; 157: 748–55.
131. Hillerdal G, Henderson DW. Asbestos, asbestosis, pleural plaques and lung cancer. *Scand J Work Environ Health* 1997; 23: 93–103.
132. Koskinen K, Pukkala E, Martikainen R, *et al*. Different measures of asbestos exposure in estimating risk of lung cancer and mesothelioma among construction workers. *J Occup Environ Med* 2002; 44: 1190–6.
133. Oksa P, Klockars M, Karjalainen A, *et al*. Progression of asbestosis predicts lung cancer. *Chest* 1998; 113: 1517–21.
134. Roggli VL, Pratt PC. Asbestosis. In: Roggli VL, Greenberg SD, Pratt PC, editors. *Pathology of Asbestos-Associated Diseases*. Boston: Little Brown, 1992; 77–108.
135. Churg A. Nonneoplastic disease caused by asbestos. In: Churg A, Green FHY, editors. *Pathology of Occupational Lung Disease*. 2nd ed. Baltimore: Williams & Wilkins, 1998; 277–338.
136. Hughes JM, Weill H. Asbestosis as a precursor of asbestos related lung cancer: results of a prospective mortality study. *Br J Ind Med* 1991; 48: 229–33.
137. Jones RN, Hughes JM, Weill H. Asbestos exposure, asbestosis, and asbestos-attributable lung cancer. *Thorax* 1996; 51 (Suppl. 2): S9–15.
138. Cagle PT. Criteria for attributing lung cancer to asbestos exposure (Editorial.) *Am J Clin Pathol* 2002; 117: 9–15.

139. Aubry MC, Myers JL, Douglas WW, *et al*. Primary pulmonary carcinoma in patients with idiopathic pulmonary fibrosis. *Mayo Clin Proc* 2002; 77: 763–70.
140. Nagai A, Chiyotani A, Nakadate T, Konno K. Lung cancer in patients with idiopathic pulmonary fibrosis. *Tohoku J Exp Med* 1992; 167: 231–7.
141. Wells C, Mannino DM. Pulmonary fibrosis and lung cancer in the United States: analysis of the multiple cause of death mortality data, 1979 through 1991. *South Med J* 1996; 89: 505–10.
142. Kipen HM, Lilis R, Suzuki Y, *et al*. Pulmonary fibrosis in asbestos insulation workers with lung cancer: a radiological and histopathological evaluation. *Br J Ind Med* 1987; 44: 96–100.
143. Sluis-Cremer GK, Bezuidenhout BN. Relation between asbestosis and bronchial cancer in amphibole asbestos miners. *Br J Ind Med* 1989; 46: 537–40.
144. Rudd RM. Pulmonary fibrosis in asbestos insulation workers with lung cancer (Letter.) *Br J Ind Med* 1987; 44: 428–9.
145. Weiss W. Pulmonary fibrosis in asbestos insulation workers with lung cancer (Letter.) *Br J Ind Med* 1989; 46: 430.
146. Suzuki Y, Kipen H, Lilis R, Selikoff IJ. Pulmonary fibrosis in asbestos insulation workers with lung cancer (Reply.) *Br J Ind Med* 1987; 44: 719–20.
147. Sluis-Cremer GK, Bezuidenhout BN. Relation between asbestosis and bronchial cancer in amphibole asbestos miners (Reply.) *Br J Ind Med* 1990; 47: 215–6.
148. Rudd RM. Relation between asbestosis and bronchial cancer in amphibole asbestos miners (Letter.) *Br J Ind Med* 1990; 47: 215.
149. Wilkinson P, Hansell DM, Janssens J, *et al*. Is lung cancer associated with asbestos exposure without small opacities on the chest radiograph? *Lancet* 1995; 345: 1074–8.
150. de Klerk NH, Musk AW, Glancy JJ, *et al*. Crocidolite, radiographic asbestosis and subsequent lung cancer. *Ann Occup Hyg* 1997; 41 (Suppl. 1): 134–6.
151. Finkelstein MM. Radiographic asbestosis is not a prerequisite for asbestos-associated lung cancer in Ontario asbestos-cement workers. *Am J Ind Med* 1997; 32: 341–8.
152. McDonald C, Newman Taylor A. Asbestos: a risk too far? (Reply.) *Lancet* 1995; 346: 306.
153. Browne K. Asbestos: a risk too far? (Letter.) *Lancet* 1995; 346: 305–6.
154. Weill H, Hughes JM, Jones RN. Asbestos: a risk too far? (Letter.) *Lancet* 1995; 346: 304; discussion 6.
155. Weiss W. Asbestosis: a marker for the increased risk of lung cancer among workers exposed to asbestos (erratum in Chest 1999; 115: 1485). *Chest* 1999; 115: 536–49.
156. Banks DE, Wang ML, Parker JE. Asbestos exposure, asbestosis, and lung cancer (Editorial, comment.) *Chest* 1999; 115: 320–2.
157. Newhouse ML, Berry G, Wagner JC. Mortality of factory workers in east London 1933–80. *Br J Ind Med* 1985; 42: 4–11.
158. Henderson DW, Roggli VL, Shilkin KB, *et al*. Is asbestosis an obligate precursor for asbestos-induced lung cancer? In: Peters GA, Peters BJ, editors. *Sourcebook on Asbestos Diseases*. Vol. 11. Charlottesville: Michie, 1995; 97–168.
159. Williams VM, de Klerk NH, Musk AW, *et al*. Measurement of lung tissue content of asbestos (an example from Western Australia). In: Peters GA, Peters BJ, editors. *Sourcebook on Asbestos Diseases*. Vol. 15. Charlottesville: Lexis, 1997; 17–46.
160. Case BW, Dufresne A. Asbestos, asbestosis, and lung cancer: observations in Quebec chrysotile workers. *Environ Health Perspect* 1997; 105 (Suppl. 5): 1113–9.
161. Anonymous. *Full public report: Chrysotile Asbestos—Priority Existing Chemical no. 9*. National Industrial Chemicals Notification and Assessment Scheme (NICNAS). National Occupational Health and Safety Commission (NOHSC). Sydney: Commonwealth of Australia; 1999.
162. Popper K. *The Logic of Scientific Discovery*. London: Routledge Classics, 1959/2002. (Originally published as *Logic der Forschung*. Vienna: Verlag von Julius Springer, 1935.).
163. Popper K. *Conjectures and Refutations: The Growth of Scientific Knowledge*. London: Routledge Classics, 1963/2002.
164. Gustavsson P, Jakobsson R, Nyberg F, *et al*. Occupational exposure and lung cancer risk: a population-based case-referent study in Sweden. *Am J Epidemiol* 2000; 152: 32–40.
165. Carel R, Boffetta P, Kauppinen T, *et al*. Exposure to asbestos and lung and pleural cancer mortality among pulp and paper industry workers. *J Occup Environ Med* 2002; 44: 579–84.
166. Paris C, Benichou J, Bota S, *et al*. Occupational and nonoccupational factors associated with high grade bronchial pre-invasive lesions. *Eur Respir J* 2003; 21: 332–41.
167. Nelson HH, Wang X, Kelsey KT. Lung carcinogenesis: molecular and cellular mechanisms. In: Banks DE, Parker JE, editors. *Occupational Lung Disease: An International Perspective*. London: Chapman & Hall, 1998: 467–98.
168. Kamp DW, Weitzman SA. The molecular basis of asbestos induced lung injury. *Thorax* 1999; 54: 638–52.
169. Manning CB, Vallyathan V, Mossman BT. Diseases caused by asbestos: mechanisms of injury and disease development. *Int Immunopharmacol* 2002; 2: 191–200.
170. Dupres JS, Mustard JF, Uffen RJ. *Report of the Royal Commission on Matters of Health and Safety Arising from the Use of Asbestos in Ontario.* Vols 1, 2. Toronto: Ontario Ministry of Government Services, 1984.
171. Industrial Injuries Advisory Council. *Asbestos-related Diseases Without Asbestosis: Report by the Industrial Injuries Advisory Council in Accordance with Section 141 of the Social Security Act 1975 on the Question Whether Asbestos-Related Diseases Without Asbestosis Should Be Prescribed Under The Act*. Presented to Parliament, November 1982. London: HMSO, 1982.
172. Britton M. Compensation for asbestos-related diseases—the UK model. *Respir Med* 1989; 83: 95–102.
173. Egilman D, Reinert A. Lung cancer and asbestos exposure: asbestosis is not necessary. *Am J Ind Med* 1996; 30: 398–406.
174. Begin R. Asbestos exposure and pleuropulmonary cancer (French.). *Rev Mal Respir* 1998; 15: 723–30.
175. Billings CG, Howard P. Asbestos exposure, lung cancer and asbestosis. *Monaldi Arch Chest Dis* 2000; 55: 151–6.
176. Guidotti TL. Apportionment in asbestos-related disease for purposes of compensation. *Industrial Health* 2002; 40: 295–311.
177. Finkelstein MM. Mortality among long-term employees of an Ontario asbestos-cement factory. *Br J Ind Med* 1983; 40: 138–44.
178. Weill H, Hughes J, Waggenspack C. Influence of dose and fiber type on respiratory malignancy risk in asbestos cement manufacturing. *Am Rev Respir Dis* 1979; 120: 345–54.
179. Dement JM, Harris RL, Jr, Symons MJ, Shy C. Estimates of dose–response for respiratory cancer among chrysotile asbestos textile workers. *Ann Occup Hyg* 1982; 26: 869–87.
180. Peto J. Lung Cancer Mortality in Relation to Measured Dust Levels in an Asbestos Textile Factory. Lyon: IARC 1980; 30: 829–36.
181. Seidman H, Selikoff IJ, Hammond EC. Short-term asbestos work exposure and long-term observation. *Ann NY Acad Sci* 1979; 330: 61–89.
182. Selikoff IJ, Hammond EC, Seidman H. Mortality experience of insulation workers in the United States and Canada, 1943–1976. *Ann NY Acad Sci* 1979; 330: 91–116.
183. Occupational Safety and Health Administration (OSHA). *Occupational Exposure to Asbestos, Tremolite, Anthophyllite, and Actinolite: Final Rules*. Cincinatti: OSHA, 1986.
184. Seidman H, Selikoff IJ, Gelb SK. Mortality experience of amosite asbestos factory workers: dose-response relationships 5 to 40 years after onset of short-term work exposure. *Am J Ind Med* 1986; 10: 479–514.
185. de Klerk NH, Musk AW, Armstrong BK, Hobbs MST. Smoking, exposure to crocidolite, and the incidence of lung cancer and asbestosis. *Br J Ind Med* 1991; 48: 412–7.
186. Rödelsperger K, Woitowitz HJ. Airborne fibre concentrations and lung burden compared to the tumour response in rats and humans exposed to asbestos. *Ann Occup Hyg* 1995; 39: 715–25.
187. Berry G, Newhouse ML, Antonis P. Combined effects of asbestos and smoking on mortality from lung cancer and mesothelioma in factory workers. *Br J Ind Med* 1985; 42: 12–8.
188. Doll R, Peto J. *Effects on Health of Exposure to Asbestos.* London: Health and Safety Commission, HMSO; 1985.
189. Lash TL, Crouch EA, Green LC. A meta-analysis of the relation between cumulative exposure to asbestos and relative risk of lung cancer. *Occup Environ Med* 1997; 54: 254–63.
190. Gustavsson P, Nyberg F, Pershagen G, *et al*. Asbestos, diesel exhaust and interaction with smoking in a population-based case-referent study of lung cancer in Sweden. In: *International Commission on Occupational Health (ICOH 2000)*. Singapore, August 2000; FP50: 354.
191. Benke G, Malcolm S, Forbes A, Salzberg M. Retrospective

assessment of occupational exposure to chemicals in community-based studies: validity and repeatability of industrial hygiene panel ratings. *Int J Epidemiol* 1997; 26: 635–42.
192. Siemiatycki J, Fritschi L, Nadon L, Gérin M. Reliability of an expert rating procedure for retrospective assessment of occupational exposures in community-based case-control studies. *Am J Ind Med* 1997; 31: 280–86.
193. Siemiatycki J, Boffetta P. Invited commentary: is it possible to investigate the quantitative relation between asbestos and mesothelioma in a community-based study? *Am J Epidemiol* 1998; 148: 143–7.
194. Rödelsperger K, Jöckel K-H, Pohlabein H, *et al*. Asbestos and man-made vitreous fibres as risk factors for diffuse malignant mesothelioma: results from a German hospital-based case-control study. *Am J Ind Med* 2001; 39: 262–75.
195. Huuskonen MS, Koskinen K, Tossavainen A, *et al*. Finnish Institute of Occupational Health Asbestos Program 1987–1992. *Am J Ind Med* 1995; 28: 123–42.
196. Steenland K, Stayner L. Silica, asbestos, man-made mineral fibers, and cancer. *Cancer Causes Control* 1997; 8: 491–503.
197. Szeszenia-Dabrowska N, Urszula W, Szymczak W, Strzelecka A. Mortality study of workers compensated for asbestosis in Poland, 1970–1997. *Int J Occup Med Environ Health* 2002; 15: 267–78.
198. Badorrey MI, Monsó E, Teixidó A, *et al*. Frequency and risk of bronchopulmonary neoplasia related to asbestos (Spanish.). *Med Clin (Barc)* 2001; 117: 1–6.
199. Howie RM. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure (Letter). *Ann Occup Hyg* 2001; 45: 335–6, discussion 6–8.
200. Sun J, Shibata E, Hisanaga N, *et al*. A cohort mortality study of construction workers. *Am J Ind Med* 1997; 32: 35–41.
201. Dement J, Pompeii L, Lipkus IM, Samsa GP. Cancer incidence among union carpenters in New Jersey. *J Occup Environ Med* 2003; 45: 1059–67.
202. Benhamou S, Benhamou E, Flamant R. Occupational risk factors of lung cancer in a French case-control study. *Br J Ind Med* 1988; 45: 231–3.
203. Camus M, Siemiatycki J, Meek B. Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. *New Engl J Med* 1998; 338: 1565–71.
204. Scherbakov SV, Dommin SG, Kashansky SV. Dust levels in workplace air of the mines and mills of Uralasbest Company. *People and Work Research Reports 19*. Helsinki: Finnish Institute of Occupational Health, 1998; 104–8.
205. Dunnigan J. Concentrations of asbestos fibres in the general environment resulting from the use of modern, high-density chrysotile-asbestos-based products. *Can Mineral* 2001; (Spec Publ 5): 115–8.
206. Camus M, Siemiatycki J. Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer (Reply). *New Engl J Med* 1998; 339: 1001–2.
207. Finkelstein MM. Mortality among employees of an Ontario asbestos-cement factory. *Am Rev Respir Dis* 1984; 129: 754–61.
208. Goodman M, Morgan RW, Ray R, *et al*. Cancer in asbestos-exposed occupational cohorts: a meta-analysis. *Cancer Causes Control* 1999; 10: 453–65.
209. Sanden A, Jarvholm B, Larsson S, Thiringer G. The risk of lung cancer and mesothelioma after cessation of asbestos exposure: a prospective cohort study of shipyard workers. *Eur Respir J* 1992; 5: 281–5.
210. Sandén A, Näslund P-E, Järvholm B. Mortality in lung and gastrointestinal cancer among shipyard workers. *Int Arch Occup Environ Health* 1985; 55: 277–83.
211. Danielsen TE, Langard S, Andersen A. Incidence of cancer among welders and other shipyard workers with information on previous work history. *J Occup Environ Med* 2000; 42: 101–9.
212. Fletcher AC, Engholm G, Englund A. The risk of lung cancer from asbestos among Swedish construction workers: self-reported exposure and a job matrix compared. *Int J Epidemiol* 1993; 22: S29–S35.
213. Sackett DL. Bias in analytic research. *J Chron Dis* 1979; 32: 51–63.
214. Stephenson JM, Babiker A. Overview of study design in clinical epidemiology. *Sex Transm Infect* 2000; 76: 244–7.
215. BK-Report *Faserjahre. Bearbeitungshinweise zur Berufskrankheit Nr 4104*. Sankt Augustin: Hauptverband der gewerblichen Berufsgenossenschaften (HVBG), 1994.
216. Paddle GM. Metaanalysis as an epidemiological tool and its application to studies of chromium. *Regul Toxicol Pharmacol* 1997; 26: S42–50.
217. Ioannidis J, Schmid CH, Lau J. Meta-analysis approaches for epidemiologic research on asbestos. In: Peters GA, Peters BJ, editors. *Sourcebook on Asbestos Diseases.* Vol. 18. Charlottesville: Lexis, 1998; 93–116.
218. Blettner M, Sauerbrei W, Schlehofer B, *et al*. Traditional reviews, meta-analyses and pooled analyses in epidemiology. *Int J Epidemiol* 1999; 28: 1–9.
219. Stroup DF, Berlin JA, Morton SC, *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *J Am Med Assoc* 2000; 283: 2008–12.
220. Mustacchi P. Lung cancer latency and asbestos liability. *J Legal Med* 1996; 17: 277–300.
221. Karhausen LR. Causation: the elusive grail of epidemiology. *Med Health Care Philos* 2000; 3: 59–67.
222. Smith KA, Sykes LJ, McGavin CR. Diffuse pleural fibrosis—an unreliable indicator of heavy asbestos exposure? *Scand J Work Environ Health* 2003; 29: 60–3.
223. Browne K. A threshold for asbestos-related lung cancer. *Br J Ind Med* 1986; 43: 556–8.
224. Fischer M, Gunther S, Muller KM. Fibre-years, pulmonary asbestos burden and asbestosis. *Int J Hyg Environ Health* 2002; 205: 245–8.
225. Multiple authors. The diagnosis and attribution of asbestos related diseases in an Australian context: Adelaide Workshop on Asbestos Related Diseases. *J Occup Health Safety Aust NZ* 2002; 18: 443–52.
226. Henderson DW. Commentary regarding the article by Fischer *et al.*: fibre years, pulmonary asbestos burden and asbestosis. Int J Hyg Environ Health 205, 245–248 (2002). *Int J Hyg Environ Health* 2003; 206: 249–50.
227. Rödelsperger K, Woitowitz H-J. Commentary regarding the article by Fischer *et al.*: fibre years, pulmonary asbestos burden and asbestosis. Int J Hyg Environ Health 205, 245–248 (2002). *Int J Hyg Environ Health* 2003; 206: 245–7.
228. Burdorf A, Swuste P. An expert system for the evaluation of historical asbestos exposure as diagnostic criterion in asbestos-related diseases. *Ann Occup Hyg* 1999; 43: 57–66.
229. Dement JM, Harris RL, Jr, Symons MJ, Shy CM. Exposures and mortality among chrysotile asbestos workers. Part II: mortality. *Am J Ind Med* 1983; 4: 421–33.
230. Browne K. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure (Letter.). *Ann Occup Hyg* 2001; 45: 327–9, discussion 36–8.
231. Rödelsperger K, Schneider J, Woitowitz H-J. Umwelt- und Innenraumgefährdung durch Asbestfaserstaub ausserhalb des Arbeitsplatzes. *Gefahrstoffe Reinh Luft* 1996; 56: 117–26.
232. De Vuyst P, Missouni A, Van Muylen A, *et al*. Systematic asbestos bodies counting in lung specimens resected for lung cancer. *Eur Respir J* 1997; 10 (Suppl. 25): 19s.
233. Thimpont J, De Vuyst P. Occupational asbestos-related diseases in Belgium (epidemiological data and compensation criteria). In: Peters GA, Peters BJ, editors. *Sourcebook on Asbestos Diseases.* Vol. 17. Charlottesville: Lexis, 1998; 311–28.
234. Mollo F, Pira E, Piolatto G, *et al*. Lung adenocarcinoma and indicators of asbestos exposure. *Int J Cancer* 1995; 60: 289–93.
235. Henderson DW, Jones ML, de Klerk N, *et al*. The diagnosis and attribution of asbestos-related diseases in an Australian context: report of the Adelaide workshop on asbestos-related diseases. *Int J Occup Environ Health* 2004; 10: 40–6.
236. Bundesgesetzblatt. Zweite Verordnung zur Änderung der Berufskrankheitenverordnung vom 18.12.1992; Nr 59: 2343–4.
237. Bundesarbeitsblatt. *Merkblatt zu Nr 4104 Lungenkrebs.* 1/1994.
238. McDonald JC, McDonald AD. Mesothelioma as an index of asbestos impact. In: Schneiderman M, Peto R, editors. *Quantification of Occupational Cancer Banbury Report No 9*. New York: Cold Spring Harbor Laboratory Press, 1981; 73–85.
239. Jöckel K-H, Brüske-Hohlfeld I, Wichmann HEH. Lungenkrebsrisiko durch berufliche Exposition. In: Wichmann HE, Jöckel K-H, Robta BPH, editors. *Forschritte in der Epidemiologie*. Landsberg: Ecomed, 1998.
240. Wichmann HE, Jöckel K-H, Molik B. Luftverunreinigung und Lungenkrebsrisiko—Ergebnisse einer Pilotstudie. *Bericht des Umweltbundesamtes 7/91.* Berlin: Erich-Schmidt-Verlag, 1991.
241. Jöckel K-H, Ahrens W, Wichmann HE, *et al*. Occupational and

environmental hazards associated with lung cancer. *Int J Epidemiol* 1992; 21: 202–13.
242. Jöckel KH, Ahrens W, Jahn I, *et al*. Occupational risk factors for lung cancer: a case-control study in West Germany. *Int J Epidemiol* 1998; 27: 549–60.
243. Pohlabeln H, Wild P, Schill W, *et al*. Asbestos fibreyears and lung cancer: a two phase case-control study with expert exposure assessment. *Occup Environ Med* 2002; 59: 410–4.
244. Rödelsperger K. *Anorganische Fasern im menschlichen Lungengewebe. Lungenstaubfaseranalytik zur Epidemiologie der Risikofaktoren des diffusen malignen Mesothelioms (DMM)*. (Inorganic fibres in human lung tissue. Epidemiology of the risk factors for diffuse malignant mesothelioma (DMM) based on lung dust fibre analysis.) Berlin: Bundesanstalt für Arbeitsmedizin, 1996.
245. Rödelsperger K, Woitowitz HJ, Bruckel B, *et al*. Dose–response relationship between amphibole fiber lung burden and mesothelioma. *Cancer Detect Prev* 1999; 23: 183–93.
246. Howel D, Gibbs A, Arblaster L, *et al*. Mineral fibre analysis and routes of exposure to asbestos in the development of mesothelioma in an English region. *Occup Environ Med* 1999; 56: 51–8.
247. Dodson RF, Williams MG, Huang J, Bruce JR. Tissue burden of asbestos in nonoccupationally exposed individuals from east Texas. *Am J Ind Med* 1999; 35: 281–6.
248. Dodson RF. Asbestos tissue burden of the general population. In: Peters GA, Peters BJ, editors. *Sourcebook on Asbestos Diseases.* Vol. 20. Charlottesville: Lexis, 1999; 1–23.
249. McDonald JC, Armstrong B, Case B, *et al*. Mesothelioma and asbestos fiber type: evidence from lung tissue analyses. *Cancer* 1989; 63: 1544–7.
250. Rogers AJ, Leigh J, Berry G, *et al*. Relationship between lung asbestos fiber type and concentration and relative risk of mesothelioma: a case-control study. *Cancer* 1991; 67: 1912–20.
251. Tuomi T, Huuskonen MS, Virtamo M, *et al*. Relative risk of mesothelioma associated with different levels of exposure to asbestos. *Scand J Work Environ Health* 1991; 17: 404–8.
252. Churg A. Deposition and clearance of chrysotile asbestos. *Ann Occup Hyg* 1994; 38: 625–33, 424–5.
253. Churg A, Wright JL. Persistence of natural mineral fibers in human lungs: an overview. *Environ Health Perspect* 1994; 102 (Suppl. 5): 229–33.
254. Rösler JA, Woitowitz HJ. Recent data on cancer due to asbestos in Germany. *Med Lav* 1995; 86: 440–8.
255. Jarvholm B, Englund A, Albin M. Pleural mesothelioma in Sweden: an analysis of the incidence according to the use of asbestos. *Occup Environ Med* 1999; 56: 110–3.
256. Jones JSP, Roberts GH, Pooley FD, *et al*. The pathology and mineral content of lungs in cases of mesothelioma in the United Kingdom in 1976. In: Wagner JC, editor. *Biological Effects of Mineral Fibres*. Lyon: IARC, 1980; 187–99.
257. de Klerk NH, Musk AW, Williams V, *et al*. Comparison of measures of exposure to asbestos in former crocidolite workers from Wittenoom Gorge, W. Australia. *Am J Ind Med* 1996; 30: 579–87.
258. Albin M, Jakobsson K, Attewell R, *et al*. Mortality and cancer morbidity in cohorts of asbestos cement workers and referents. *Br J Ind Med* 1990; 47: 602–10.
259. Albin M, Johansson L, Pooley FD, *et al*. Mineral fibres, fibrosis, and asbestos bodies in lung tissue from deceased asbestos cement workers. *Br J Ind Med* 1990; 47: 767–74.
260. Dement JM, Harris RL, Jr, Symons MJ, Shy CM. Exposures and mortality among chrysotile asbestos workers. Part I: exposure estimates. *Am J Ind Med* 1983; 4: 399–419.
261. Williams V, de Klerk NH, Whitaker D, *et al*. Asbestos bodies in lung tissue following exposure to crocidolite. *Am J Ind Med* 1995; 28: 489–95.
262. Armstrong BK, de Klerk NH, Musk AW, Hobbs MST. Mortality in miners and millers of crocidolite in Western Australia. *Br J Ind Med* 1988; 45: 5–13.
263. Both K, Henderson DW, Turner DR. Asbestos-induced aberrations and mutations in cells. In: Peters GA, Peters BJ, editors. *Sourcebook on Asbestos Diseases.* Vol. 10. Salem: Butterworths Legal Publishers, 1994; 1–55.
264. Schiffmann D, Rahman Q. Chromosomal changes induced by asbestos fibers: an overview. In: Peters GA, Peters BJ, editors. *Sourcebook on Asbestos Diseases.* Vol. 14. Charlottesville: Lexis, 1997; 41–59.
265. Liu B. Mutations of the p53 gene in asbestos-related cancer. In: Peters GA, Peters BJ, editors. *Sourcebook on Asbestos Diseases*. Vol. 20. Charlottesville: Lexis, 1999; 145–58.
266. Rahman Q, Dopp E, Schiffmann D. Genotoxic effects of asbestos fibers. In: Peters GA, Peters BJ, editors. *Sourcebook on Asbestos Diseases.* Vol. 21. Charlottesville: Lexis, 2000; 223–42.
267. Pelin K, Kivipensas P, Linnainmaa K. Effects of asbestos and man-made vitreous fibers on cell division in cultured human mesothelial cells in comparison to rodent cells. *Environ Mol Mutagen* 1995; 25: 118–25.
268. Janssen Y, Marsh J, Quinlan T, *et al*. Activation of early cellular responses by asbestos: Induction of *c-FOS* and *c-JUN* protooncogene expression in rat pleural mesothelial cells. In: Davis JMG, Jaurand M-C, editors. *Cellular and Molecular Effects of Mineral and Synthetic Dusts and Fibres.* NATO ASI Series, H85. Berlin: Springer, 1994; 205–13.
269. Vainio H, Husgafvel-Pursiainen K, Anttila S, *et al*. Interaction between smoking and asbestos in human lung: role of K-ras mutations. *Environ Health Perspect* 1993; 101 (Suppl. 3): 189–92.
270. Liu BC, Fu DC, Miao Q, *et al*. p53 gene mutations in asbestos associated cancers. *Biomed Environ Sci* 1998; 11: 226–32.
271. Husgafvel-Pursiainen K, Karjalainen A, Kannio A, *et al*. Lung cancer and past occupational exposure to asbestos: role of p53 and K-ras mutations. *Am J Respir Cell Mol Biol* 1999; 20: 667–74.
272. Nelson HH, Christiani DC, Wiencke JK, *et al*. K-ras mutation and occupational asbestos exposure in lung adenocarcinoma: asbestos-related cancer without asbestosis. *Cancer Res* 1999; 59: 4570–3.
273. Wang Q, Fan J, Wang H, Liu S. DNA damage and activation of c-ras in human embryo lung cells exposed to chrysotile and cigarette smoking solution. *J Environ Pathol Toxicol Oncol* 2000; 19: 13–9.
274. Jung M, Davis WP, Taatjes DJ, *et al*. Asbestos and cigarette smoke cause increased DNA strand breaks and necrosis in bronchiolar epithelial cells in vivo. *Free Radic Biol Med* 2000; 28: 1295–9.
275. Hei TK, Wu LJ, Piao CQ. Malignant transformation of immortalized human bronchial epithelial cells by asbestos fibers. *Environ Health Perspect* 1997; 105 (Suppl. 5): 1085–8.
276. Hei TK, Xu A, Louie D, Zhao Y. Genotoxicity versus carcinogenicity: implications from fiber toxicity studies. *Inhal Toxicol* 2000; 12 (Suppl. 3): 141–7.
277. Hei TK, Piao CQ, Willey JC, *et al*. Malignant transformation of human bronchial epithelial cells by radon-simulated alpha-particles. *Carcinogenesis* 1994; 15: 431–7.
278. Hei TK, Piao CQ, He ZY, *et al*. Chrysotile fiber is a strong mutagen in mammalian cells. *Cancer Res* 1992; 52: 6305–9.
279. Sozzi G, Sard L, De Gregorio L, *et al*. Association between cigarette smoking and FHIT gene alterations in lung cancer. *Cancer Res* 1997; 57: 2121–3.
280. Nelson HH, Wiencke JK, Gunn L, *et al*. Chromosome 3p14 alterations in lung cancer: evidence that FHIT exon deletion is a target of tobacco carcinogens and asbestos. *Cancer Res* 1998; 58: 1804–7.
281. Croce CM, Sozzi G, Huebner K. Role of FHIT in human cancer. *J Clin Oncol* 1999; 17: 1618–24.
282. Pylkkänen L, Wolff H, Stjernvall T, *et al*. Reduced Fhit protein expression and loss of heterozygosity at *FHIT* gene in tumours from smoking and asbestos-exposed lung cancer patients. *Int J Oncol* 2002; 20: 285–90.
283. Pylkkänen L, Wolff H, Stjernvall T, *et al*. Reduced Fhit protein protein expression in human malignant mesothelioma. *Virchows Arch* 2004; 444: 43–8.
284. Demopoulos K, Arvanitis DA, Vassilakis DA, *et al*. MYCL1, FHIT, SPARC, p16(INK4) and TP53 genes associated to lung cancer in idiopathic pulmonary fibrosis. *J Cell Mol Med* 2002; 6: 215–22.
285. Hemminki K, Lonnstedt I, Vaittinen P, Lichtenstein P. Estimation of genetic and environmental components in colorectal and lung cancer and melanoma. *Genet Epidemiol* 2001; 20: 107–16.
286. Multiple authors. Genetic susceptibility. In: Stewart BW, Kleihues P, editors. *World Cancer Report*. Lyon: IARC, 2003; 71–5.
287. Miller YE, Fain P. Genetic susceptibility to lung cancer. *Semin Respir Crit Care Med: Genet Pulmon Dis* 2003; 24: 197–204.
288. Benhamou S, Bonaiti-Pellie C. Susceptibility to bronchial cancer: an example of genetic-environmental interaction (French.). *Ann Biol Clin* 1995; 53: 507–13.
289. Hou SM, Falt S, Angelini S, *et al*. The XPD variant alleles are associated with increased aromatic DNA adduct level and lung cancer risk. *Carcinogenesis* 2002; 23: 599–603.
290. Kiyohara C, Otsu A, Shirakawa T, *et al*. Genetic polymorphisms and lung cancer susceptibility: a review. *Lung Cancer* 2002; 37: 241–56.

291. Amos CI, Xu W, Spitz MR. Is there a genetic basis for lung cancer susceptibility? *Recent Results Cancer Res* 1999; 151: 3–12.
292. Spitz MR, Wei Q, Li G, Wu X. Genetic susceptibility to tobacco carcinogenesis. *Cancer Invest* 1999; 17: 645–59.
293. Brockmoller J, Cascorbi I, Henning S, *et al*. Molecular genetics of cancer susceptibility. *Pharmacology* 2000; 61: 212–27.
294. Stellman SD, Takezaki T, Wang L, *et al*. Smoking and lung cancer risk in American and Japanese men: an international case-control study. *Cancer Epidemiol Biomarkers Prev* 2001; 10: 1193–9.
295. Zhu Y, Spitz MR, Lei L, *et al*. A single nucleotide polymorphism in the matrix metalloproteinase-1 promoter enhances lung cancer susceptibility. *Cancer Res* 2001; 61: 7825–9.
296. Hemminki K, Li X. Familial risk of cancer by site and histopathology. *Int J Cancer* 2003; 103: 105–9.
297. Hemminki K, Li X. Time trends and occupational risk factors for pleural mesothelioma in Sweden. *J Occup Environ Med* 2003; 45: 456–61.
298. Hemminki K, Li X. Time trends and occupational risk factors for peritoneal mesothelioma in Sweden. *J Occup Environ Med* 2003; 45: 451–5.
299. Czene K, Lichtenstein P, Hemminki K. Environmental and heritable causes of cancer among 9.6 million individuals in the Swedish Family-Cancer Database. *Int J Cancer* 2002; 99: 260–6.
300. Hemminki K, Czene K. Attributable risks of familial cancer from the Family-Cancer Database. *Cancer Epidemiol Biomarkers Prev* 2002; 11: 1638–44.
301. Bouchardy C, Benhamou S, Jourenkova N, *et al*. Metabolic genetic polymorphisms and susceptibility to lung cancer. *Lung Cancer* 2001; 32: 109–12.
302. Le Marchand L, Guo C, Benhamou S, *et al*. Pooled analysis of the CYP1A1 exon 7 polymorphism and lung cancer (United States). *Cancer Causes Control* 2003; 14: 339–46.
303. Vineis P, Veglia F, Benhamou S, *et al*. CYP1A1 T3801 C polymorphism and lung cancer: a pooled analysis of 2451 cases and 3358 controls. *Int J Cancer* 2003; 104: 650–7.
304. Benhamou S, Reinikainen M, Bouchardy C, *et al*. Association between lung cancer and microsomal epoxide hydrolase genotypes. *Cancer Res* 1998; 58: 5291–3.
305. Chen HW, Lum A, Seifried A, *et al*. Association of the NAD(P)H:quinone oxidoreductase ^{609}C→T polymorphism with a decreased lung cancer risk. *Cancer Res* 1999; 59: 3045–8.
306. Williams JA. Single nucleotide polymorphisms, metabolic activation and environmental carcinogenesis: why molecular epidemiologists should think about enzyme expression. *Carcinogenesis* 2001; 22: 209–14.
307. Multiple authors. Carcinogen activation and DNA repair. In: Stewart BW, Kleihues P, editors. *World Cancer Report*. Lyon: IARC, 2003; 89–95.
308. Park JY, Lee SY, Jeon HS, *et al*. Polymorphism of the DNA repair gene XRCC1 and risk of primary lung cancer. *Cancer Epidemiol Biomarkers Prev* 2002; 11: 23–7.
309. Wood RD, Mitchell M, Sgouros J, Lindahl T. Human DNA repair genes. *Science* 2001; 291: 1284–9.
310. Masuda M, Suzuki T, Friesen MD, *et al*. Chlorination of guanosine and other nucleosides by hypochlorous acid and myeloperoxidase of activated human neutrophils: catalysis by nicotine and trimethylamine. *J Biol Chem* 2001; 276: 40486–96.
311. Schabath MB, Spitz MR, Hong WK, *et al*. A myeloperoxidase polymorphism associated with reduced risk of lung cancer. *Lung Cancer* 2002; 37: 35–40.
312. London SJ, Lehman TA, Taylor JA. Myeloperoxidase genetic polymorphism and lung cancer risk. *Cancer Res* 1997; 57: 5001–3.
313. Cascorbi I, Henning S, Brockmoller J, *et al*. Substantially reduced risk of cancer of the aerodigestive tract in subjects with variant -463A of the myeloperoxidase gene. *Cancer Res* 2000; 60: 644–9.
314. Le Marchand L, Seifried A, Lum A, Wilkens LR. Association of the myeloperoxidase -463G→A polymorphism with lung cancer risk. *Cancer Epidemiol Biomarkers Prev* 2000; 9: 181–4.
315. Schabath MB, Spitz MR, Zhang X, *et al*. Genetic variants of myeloperoxidase and lung cancer risk. *Carcinogenesis* 2000; 21: 1163–6.
316. Misra RR, Tangrea JA, Virtamo J, *et al*. Variation in the promoter region of the myeloperoxidase gene is not directly related to lung cancer risk among male smokers in Finland. *Cancer Lett* 2001; 164: 161–7.
317. Dally H, Gassner K, Jager B, *et al*. Myeloperoxidase (MPO) genotype and lung cancer histologic types: the MPO -463 A allele is associated with reduced risk for small cell lung cancer in smokers. *Int J Cancer* 2002; 102: 530–5.
318. Feyler A, Voho A, Bouchardy C, *et al*. Point: myeloperoxidase -463G→A polymorphism and lung cancer risk. *Cancer Epidemiol Biomarkers Prev* 2002; 11: 1550–4.
319. Xu LL, Liu G, Miller DP, *et al*. Counterpoint: the myeloperoxidase -463G→A polymorphism does not decrease lung cancer susceptibility in Caucasians [comment]. *Cancer Epidemiol Biomarkers Prev* 2002; 11: 1555–9.
320. Kantarci OH, Lesnick TG, Yang P, *et al*. Myeloperoxidase -463 (G→A) polymorphism associated with lower risk of lung cancer. *Mayo Clin Proc* 2002; 77: 17–22.
321. Lu W, Xing D, Qi J, *et al*. Genetic polymorphism in myeloperoxidase but not GSTM1 is associated with risk of lung squamous cell carcinoma in a Chinese population. *Int J Cancer* 2002; 102: 275–9.
322. Schabath MB, Spitz MR, Delclos GL, *et al*. Association between asbestos exposure, cigarette smoking, myeloperoxidase (MPO) genotypes, and lung cancer risk. *Am J Ind Med* 2002; 42: 29–37.
323. Huncharek M, Kelsey K, Muscat J, Christiani D. Parental cancer and genetic predisposition in malignant pleural mesothelioma: a case-control study. *Cancer Lett* 1996; 102: 205–8.
324. Ascoli V, Mecucci C, Knuutila S. Genetic susceptibility and familial malignant mesothelioma. *Lancet* 2001; 357: 1804.
325. Huncharek M. Non-asbestos related diffuse malignant mesothelioma. *Tumori* 2002; 88: 1–9.
326. Bradford Hill A. The environment and disease: association or causation? *Proc Royal Soc Med* 1965; 58: 295–300.
327. Leigh J, Hendrie L, Berry D. Malignant mesothelioma in Australia, 1945–2000. *J Occup Health Safety Aust NZ* 2001; 17: 453–70.
328. Health and Safety Executive (ESE). *Mesothelioma Occupation Statistics: Male and Female Deaths Aged 16–74 in Great Britain 1980–2000 (Excluding 1981)*. London: HSE, 2003. http://www.hse.gov.uk/statistics/causdis/occ8000.pdf (accessed May 2004).
329. Li FP, Lokich J, Lapey J, *et al*. Familial mesothelioma after intense asbestos exposure at home. *J Am Med Assoc* 1978; 240: 467.
330. Risberg B, Nickels J, Wågermark J. Familial clustering of malignant mesothelioma. *Cancer* 1980; 45: 2422–7.
331. Lynch HT, Katz D, Markvicka SE. Familial mesothelioma: review and family study. *Cancer Genet Cytogenet* 1985; 15: 25–35.
332. Krousel T, Garcas N, Rothschild H. Familial clustering of mesothelioma: a report on three affected persons in one family. *Am J Prev Med* 1986; 2: 186–8.
333. Munoz L, Guzman J, Ponce de Leon S, *et al*. Familial malignant pleural mesothelioma: report of 3 cases (Spanish.). *Rev Invest Clin* 1988; 40: 413–7.
334. Hammar SP, Bockus D, Remington F, *et al*. Familial mesothelioma: a report of two families. *Hum Pathol* 1989; 20: 107–12.
335. Otte KE, Sigsgaard TI, Kjaerulff J. Massive exposure to asbestos and malignant mesothelioma, familial accumulation (Danish.). *Ugeskr Laeger* 1990; 152: 3013–4.
336. Dawson A, Gibbs A, Browne K, *et al*. Familial mesothelioma: details of 17 cases with histopathologic findings and mineral analysis. *Cancer* 1992; 70: 1183–7.
337. Bianchi C, Brollo A, Zuch C. Asbestos-related familial mesothelioma. *Eur J Cancer Prev* 1993; 2: 247–50.
338. Ascoli V, Scalzo CC, Bruno C, *et al*. Familial pleural malignant mesothelioma: clustering in three sisters and one cousin. *Cancer Lett* 1998; 130: 203–7.
339. Hiyama J, Marukawa M, Shiota Y, *et al*. Two familial mesothelioma cases with high concentrations of soluble cytokeratin 19 fragment in pleural fluid. *Intern Med* 1998; 37: 407–10.
340. Dogan AU, Baris YI, Emri S, *et al*. Familial malignant mesothelioma. *Lancet* 2001; 358: 1813–4.
341. Saracci R, Simonato L. Familial malignant mesothelioma. *Lancet* 2001; 358: 1813.
342. Bianchi AB, Mitsunaga SI, Cheng JQ, *et al*. High frequency of inactivating mutations in the neurofibromatosis type 2 gene (NF2) in primary malignant mesotheliomas. *Proc Natl Acad Sci USA* 1995; 92: 10854–8.
343. Lee YCG, de Klerk NH, Henderson DW, Musk AW. Malignant mesothelioma. In: Hendrick DJ, Burge PS, Beckett WS, Churg A, editors. *Occupational Disorders of the Lung: Recognition, Management, and Prevention*. London: Saunders, 2002; 359–79.
344. Immunization Safety Review Committee. *Immunization Safety Review: SV40 Contamination of Polio Vaccine and Cancer*. Washington, DC: National Academies Press, 2003.
345. Stucker I, Boffetta P, Antilla S, *et al*. Lack of interaction between asbestos exposure and glutathione S-transferase M1 and T1

genotypes in lung carcinogenesis. *Cancer Epidemiol Biomarkers Prev* 2001; 10: 1253–8.
346. Khoury MJ. Genetic epidemiology. In: Rothman KJ, Greenland S, editors. *Modern Epidemiology*. 2nd ed. Philadelphia: Lippincott-Raven, 1998; 609–21.
347. Salmon WC. *Causality and Explanation*. New York: Oxford University Press, 1998.
348. Mandel DR. Judgment dissociation theory: an analysis of differences in causal, counterfactual, and covariational reasoning. *J Exp Psychol Gen* 2003; 132: 419–34.