Proceedings of an International Expert Meeting on

New Advances in Radiology and

Screening of Asbestos-Related Diseases

9–11 February 2000
Espoo, Finland

Organizer
Finnish Institute of Occupational Health

Edited by
Antti Tossavainen
Suvi Lehtinen
Matti Huuskonen
Jorma Rantanen

People and Work • Research Reports 36

Finnish Institute of Occupational Health
Helsinki 2000

Asbestos and lung cancer: a selective up-date to *The Helsinki Criteria* for individual attribution

D.W. Henderson[1], *J. Leigh*[2]

[1]Department of Anatomical Pathology, The Flinders University and Flinders Medical Centre, Adelaide, Australia

[2]Research Unit, National Occupational Health & Safety Commission, Sydney, and Department of Public Health and Community Medicine, University of Sydney, Australia

Introduction

At a meeting held in Helsinki in January 1997, a group of 19 authorities from 8 nations that do not produce asbestos formulated a set of criteria for the diagnosis of asbestos-related diseases and their attribution to asbestos. Published later in the same year, in the *Scandinavian Journal of Work, Environment and Health* (1), the criteria for the attribution of lung cancer to asbestos have proven to be the most controversial outcome of the meeting – as anticipated by the participants and organizers.

In most published studies, there is a direct and linear relationship between the relative risk of lung cancer and cumulative exposure to asbestos, including chrysotile and the amphiboles, expressed as:

$$RR = 1 + K*E$$

where RR is the relative risk of lung cancer, E represents cumulative asbestos exposure, expressed as fibres/ml-years (fibre-years), and K is the industry-specific slope of the relationship (RR for the increase per 1 fibre-year of exposure) for lung cancer. The value of K varies across cohorts (e.g. 0.001–0.0005 in miners and for friction products manufacture, to 0.03–0.05 in cohorts of asbestos textile and insulation workers), whereas cohorts with mixed exposures usually have intermediate values (2, 3). Positive estimates for K have been obtained in all studies, but some are based on a small number of cases or deaths (2). Lung cancer risk does not appear to correlate with the types of asbestos (2). Some authorities suggest an 'average' value of K = 0.01 independent of fibre type, corresponding to an increase of 1% of the risk of lung cancer for every fibre-year of exposure (2). The figure of 4% mentioned in *The Helsinki Criteria* is intermediate between the K values of 0.03–0.05 for textile and insulation workers. As reported in different studies (e.g. see 4 and 5), the interactive effect in combination with tobacco smoke ranges from less than additive to supramultiplicative, but the model for insulation workers approximates a multiplicative effect (6, 7). If the multistage model of carcinogenesis holds, and asbestos and smoking act at different stages, then a multiplicative relationship follows (8).

The additive increase in RR for 25 fibre/ml-years exposure has been estimated at 1.5 for amosite factory workers (9); de Klerk et al (10) put the multiplicative increase in RR at

1.25 per $\log_e$ fibre-year – i.e. for 25 fibre-years the RR is 4; the additive increase in RR for 25 fibre-years would be about 1.25 (de Klerk, personal communication). In an earlier paper on the Wittenoom cohort, the multiplicative increase in RR per $\log_e$ fibre-year was estimated at 1.4 – i.e. exposure of 25 fibre-years would give an RR of 4.5 (11).

The Helsinki Criteria

For the individual case, *The Helsinki Criteria* set exposure estimates or correlates sufficient to increase the lung cancer RR to 2.0 or more, with an attributable fraction of > (2-1)/2 = 0.5, equating to a probability of causation of 50% – the civil standard of proof (4, 5). In the case of some occupational lung cancers, a relative risk of 1.1 (rather than 2) has been accepted as indication of a material contribution to causation rather than "the cause of" by civil courts (12, 13).

The Helsinki Criteria do not require the presence of asbestosis for attribution of lung cancer to asbestos, and instead focus upon cumulative exposure to asbestos as assessed clinically (e.g. estimated cumulative exposure) or pathologically (e.g. asbestos bodies or uncoated fibre concentrations within lung tissue).

"Because of the high incidence of lung cancer in the general population, it is not possible to prove in precise deterministic terms that asbestos is the causative factor for an *individual* patient, even when asbestosis is present. However, attribution of causation requires *reasonable* medical certainty on a probability basis that the agent (asbestos) has caused or contributed materially to the disease. The likelihood that asbestos exposure has made a substantial contribution increases when the exposure increases. Cumulative exposure, on a probability basis, should thus be considered the main criterion for the attribution of a substantial contribution by asbestos to lung cancer risk. For example, relative risk is roughly doubled for cohorts exposed to asbestos fibres at a cumulative exposure of 25 fibre-years or with an equivalent occupational history, at which level asbestosis may or may not be present or detectable."

Specifically, *The Criteria* include the following:

- The presence of asbestosis (e.g. asbestosis diagnosed clinically, radiologically – including high-resolution CT – or histologically);

  or

- A count of 5,000 to 15,000 asbestos bodies (ABs) or more per gram dry lung tissue, which is about equivalent to an uncoated fibre burden of 2 million amphibole fibres (> 5 micrometers in length) per gram dry lung tissue, or 5 million amphibole fibres > 1 micrometer in length per gram dry lung; this tissue count of ABs is also roughly equivalent to 5 to 15 ABs per ml of broncho-alveolar lavage fluid (e.g. see 14 and 15).

  The Criteria also recommend that when the AB concentration is < 10,000 per gram dry lung, the count be supplemented by an uncoated fibre burden analysis using electron microscopy.

These fibre counts relate only to the amphibole types of asbestos. *The Criteria* state that chrysotile does not accumulate within lung tissue to the same extent as the amphiboles, because of faster clearance rates; therefore, occupational histories (fibre-years of exposure) are considered probably to represent a better indicator of lung cancer risk from chrysotile than fibre burden analysis.

or

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

Clinical cases of asbestosis can be encountered at this level of exposure (16): e.g. Churg (17) indicates that the dose required for the development of asbestosis is in the range 25–100 fibre-years; in an autopsy study on South Carolina asbestos textile workers exposed to Canadian chrysotile, Green et al. (18) reported that asbestosis was usually present at 20 or more fibre-years of exposure, and a few cases were encountered at estimated cumulative exposures of 10–20 fibre-years. Rödelsperger (15) reported that an estimated cumulative exposure of 25 fibre-years correlates with the uncoated asbestos fibre concentrations given above (see also 19, discussed below):

"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/microgram" (abstract and p. 307). (I.e. 2 million amphibole fibres per gram dry lung for fibres 5 micrometers in length or more; in Rödelsperger's study on mesothelioma patients (15), 25 fibre-years and the count of 2,000,000 uncoated fibres per gram dry lung corresponded roughly to an AB count of 1,500 per gram wet lung; for obvious reasons, these values could not be derived for the control patients).

or

• An occupational history* of one year of heavy exposure to asbestos (e.g. manufacture of asbestos products, asbestos spraying, insulation work with asbestos materials, demolition of old buildings) or 5–10 years of moderate exposure (e.g. construction or shipbuilding). *The Criteria* go on to state that a 2-fold risk of lung cancer can be reached with exposures lasting < 1 year if the exposure is of extremely high intensity. Again, the basis for this criterion derives from correlative studies whereby estimated cumulative dose is calculated from the work history (e.g. types of work carried out, and their frequency and duration) or correlation of the occupational history with asbestos fibre concentrations in lung tissue.

(*Occupational history is the only means whereby latency can be assessed.)

and

• A minimum lag-time of 10 years.

Asbestos body and asbestos fibre content of lung tissue and lung cancer risk

In a study on the asbestos body (AB) and fibre content in resected lung tissue from 477 consecutive patients with lung cancer, de Vuyst et al. (20) found that a count of 5,000 or more ABs per gram dry lung correlated with "significant occupational" cumulative exposure; the figure of 5,000 ABs or more was considered to be about equivalent to 5,000,000 f/g dry lung. Thimpont and de Vuyst (19) also found that concentrations of ABs > 5,000/g dry lung do not occur in non-exposed control subjects and are always indicative of occupational exposure; about 50% of patients with > 5,000 ABs/g dry lung tissue have low-grade fibrotic lesions affecting small airways and the interstitium, and identifiable ABs in histological sections.

Lung cancer is now accepted in Belgium as an asbestos-related disorder if *one* of the following *major* criteria is present:

1. Asbestosis or bilateral diffuse pleural thickening.

2. Cumulative exposure $\geq$ 25 fibre-years.

3. AB concentrations in lung tissue or in BAL respectively $\geq$ 5000/g dry lung or 5/ml BAL.

4. A duration of at least 10 years' work in a limited list of jobs.

5. A minimum lag-time of 10 years.

Thimpont and de Vuyst (19) also referred to a series of *minor* criteria (insufficient by themselves for attribution): (i) pleural plaques; (ii) unilateral diffuse pleural thickening; and (iii) bronchiolar and peribronchiolar fibrosis without detectable ABs in lung tissue.

In a case-control study on AB concentrations in autopsy lung tissue with allowance for smoking, Mollo et al. (21) found a 4-fold increase in the RR for adenocarcinoma at a lower cut-off count of 1,000 ABs/g dry lung. In a stratified analysis from multiple comparisons, the RR was 5.59 for all cancers vs. controls and 17.75 for adenocarcinomas vs. controls (i.e. RR about 4 for 1,000–9,999 ABs per gram dry lung, with evidence of a dose-response effect, with higher RRs for counts > 10,000).

In 1995, Rödelsperger and Woitowitz (22) reviewed estimated dose-response relationships for lung cancer and mesothelioma in humans and in animal models, and they calculated the cumulative exposures for white South African amphibole miners:

"An average cumulative exposure of 15.2 fibre-years for amosite miners and 9.83 fibre-years for crocidolite miners can be obtained from the discussion in Sluis-Cremer et al (1992). Despite the fact that this estimated exposure is very low, the SMR [standardized mortality ratio] for lung cancer altogether increased to 1.72 (95% confidence interval CI = 1.32–2.21); for amosite miners the SMR amounted to 1.38 (90% CI = 0.97–1.91) and for crocidolite miners to 2.03 (90% C1 = 1.43–2.80)",

thereby suggesting that the RR or SMR for lung cancer may reach 2.00 with exposures < 25 fibre-years.

Exposure assessment

The cumulative exposure standard of 25 fibre-years or more is also applied in Germany (23) and Denmark, and job histories elsewhere in Scandinavia (asbestosis not required). Occupational histories also form the basis for attribution in France, as reviewed recently by Hindry (24).

In Australia, the New South Wales (NSW) Dust Diseases Tribunal and the Worker's Compensation Court have ruled repeatedly in favour of *The Helsinki Criteria* as basis for attribution, and in 1999 *The Criteria* were under consideration as a National Standard (25).

Because legal decisions now appear to favour a *Helsinki Criteria* approach, construction of databases such as described by Burdorf and Swuste (26) or *Faserjahre* (BK Report 1/97) will be essential for equitable compensation of lung cancer due to asbestos, when evidence of quantified exposure must be based on history.

The German system is based partly on a quantified exposure of 25 fibre-years, derived from a standardized work history and reference to a database of some 27,000 measurements covering a broad range of jobs, industries and time periods. This is, in turn, based on actual measurements and expert opinions.

The 90th percentile for a given job/industry is taken or a conventional value defined. The Dutch system uses a more qualitative approach with probabilistic assessments of the likelihood of different exposure levels. Without such systems, Boards and Tribunals will continue to spend inordinate time considering differing opinions of expert witnesses in determining past exposures. The aim of this system is to create a matrix that defines asbestos exposure by time, occupation and industry.

In association with each value, there will be assigned 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 could be reached.

Chest X-ray status for asbestosis and the risk of lung cancer

In a chest X-ray study on lung cancer in the Wittenoom cohort, de Klerk et al. (10) found an increase in the RR of lung cancer with increasing cumulative exposure to asbestos, in the absence of radiographic asbestosis, but the presence of asbestosis had an adjuvant effect on risk. In a study of asbestos-cement workers in Ontario, based on chest X-rays, Finkelstein (27) also found an increase in the RR of lung cancer in the absence of radiographic asbestosis (although this study has been criticized because no relationship to smoking was identified – apparently due to misclassification of smoking habits for some patients – and there was no "significant" dose-response effect).

7

Epidemiological studies and meta-analyses

Between 1993 and 1999, multiple epidemiological studies have reported on lung cancer risk in individuals exposed to asbestos. The Netherlands cohort study (28) found the RR to be 2.49 overall, with a value of 1.59 for low exposures, 0.96 for intermediate exposures, and 3.49 for high exposures (exposures divided into tertiles; in this study, the tertiles do not correspond to cumulative doses, but to probabilities of exposure); the RRs adjusted for age and other occupational factors were 1.82 [low], 1.29 [intermediate] and 2.72 [high]).

In 1997, Steenland and Stayner (29) summarized 24 epidemiological studies on lung cancer, published between 1979 and 1994. Across these studies, lung cancer SMRs varied from 0.9 to 5.0, with a mean value of about 2. An exposure-response relationship was demonstrated in 15 of these studies, with no such relationship in 4, and there was no information in 5. Van Loon et al. (28), in their report on The Netherlands cohort study, also referred to five studies on asbestos and lung cancer with RR estimates that varied from 2.0 to 4.1, among which only one reported a non-significant positive association between cumulative exposure to asbestos and risk of lung cancer.

There have been some attempts to carry out meta-analysis of published studies on quantitative dose-related lung cancer risk with asbestos exposure. The study of Lash et al. (30) illustrates the difficulty of this exercise when very heterogeneous studies are considered. The limitations of this type of study have been pointed out in reviews by Blettner et al. (31) and Ioannidis et al. (32). Accordingly, Blettner et al. (31) state that "... Meta-analyses from published data are in general insufficient to calculate a pooled estimate since published estimates are based on heterogeneous populations, different study designs and mainly different statistical models [abstract] ... Meta-analyses using published data are, therefore, restricted and seldom useful to produce a valid quantitative estimate or to investigate exposure relations such as dose-response (p. 8)...". It is possible that pooled data studies may give more valid answers, but in the asbestos-lung cancer field, industry differences may preclude this. (In a meta-analysis of 69 asbestos-exposed occupational cohorts, Goodman et al. (33) identified "... meta-SMRs of 163 and 148 (for lung cancer) with and without latency, with significant heterogeneity of results...".)

The summary estimate obtained from a random-effects model recommended by Lash et al. (30) has no population-specific interpretation; instead it represents the mean of a distribution that generates effects. Unlike a standardized rate ratio, it does not correspond to an average effect in a population.

Random-effects summaries give proportionally greater weight to small studies than do fixed-effects summaries. As a consequence, random-effects summaries will be more heavily affected by biases that more strongly affect small studies.

Lobar distribution of lung cancer, lung cancer in asbestosis versus diffuse interstitial fibrosis, and the South Carolina asbestos textile cohort

Lee et al. (34) addressed the lobar distribution of lung cancer in asbestos-exposed individuals and found that the tumours were predominantly located in the upper lobe (i.e.

they did not find the reversal of the upper lobe to lower lobe ratio reported in some other studies).

Churg (35) refers to a study in Japan by Nagai et al. (36) which identified lung cancer in 38% of patients with diffuse interstitial fibrosis (DIF) who were smokers, and in 11% of the same group who were non-smokers; the figure of 38% is roughly comparable to the high frequency of lung cancer development in asbestosis (e.g. see 5). Nonetheless, analysis of the paper by Nagai et al. (36) reveals some unusual data that call this figure into doubt: e.g. 88% of the tumours were peripheral in distribution and the diagnosis in 27 out of 31 cases was established by transbronchial biopsy of lung (in limited samples of this type, there is a problem in distinguishing between reactive broncho-alveolar epithelial proliferation that is an almost invariable accompaniment of DIF, from genuine lung cancer; in other words, the technique by which the diagnosis of cancer was made casts doubt on the figure).

From an analysis of death certificates in the United States, Wells and Mannino (37) found a 5% rate of association between DIF and lung cancer, in comparison to 27% for asbestosis and lung cancer.

Lung cancer rates in patients with progressive vs. non-progressive asbestosis might be claimed as evidence in favour of the fibrosis-cancer nexus. For example, Oksa et al. (38) identified 11 lung cancers in 24 patients with progressive asbestosis (46%; SIR = 37), in comparison to 5 of 54 non-progressors (9%; SIR = 4.3). At this stage, it should be emphasized that progression or severity of disease such as asbestosis is not the same as the presence or absence of the disorder (asbestosis); because the paper did not address a group of patients with comparable exposures in the absence of asbestosis, it does not by itself contribute information to the question of whether asbestosis is an obligate precursor for the cancer, or not.

In addition, the classical studies carried out by Dement et al. (39, 40) on South Carolina asbestos textile workers are worth mention (e.g. see 39); this cohort worked with Canadian chrysotile, and is known to have up to 30–50-fold higher K value than the Quebec chrysotile miners and millers − a difference that remains unexplained (41). Dement et al. (39) found an SMR of 2.59 and a standardized risk ratio of 2.63 (95% CI, 1.20–5.75) at 2.7–6.8 fibre-years of exposure, for white males. This estimated cumulative exposure is below the level at which Green et al. (18) − in an autopsy study based on the same cohort − found histologic asbestosis.

More recently, Case and Dufresne (42) have revisited the study reported in 1989 by Sébastien et al. (43) on the fibre content of lung tissue from the South Carolina textile workers in comparison to the Quebec (Thetford) miners/millers, concentrating on fibres > 18 micrometers in length; Case and Dufresne (42) reported that a significant amount of amosite/crocidolite fibres was found in the textile workers' lungs, with the implication that these commercial amphiboles, as opposed to chrysotile, might explain the difference in the K values for the two cohorts (there were only slight differences in fibre length, so that exposure to long fibres cannot explain the K differences). Green et al. (18) also reported a fibre burden study on the South Carolina textile workers, with a comparable control group: the textile workers had a higher lung content of chrysotile in comparison to the controls (geometric mean = 33,450,000 vs. 6,710,000 f/g dry lung), with a higher content of tremolite (3,560,000 vs. 260,000); the asbestos workers also

had a slightly elevated mean amosite/crocidolite content of 470,000 fibres vs. 210,000 for the controls.

In the Green et al. (18) study, the lung cancer cases on which fibre burden analysis was carried out were not representative of the cohort as a whole (e.g. autopsies were carried out on only about 10% of all deaths in the cohort, and the mean lifetime cumulative exposure for the 10 lung cancer cases was 94.6 fibre-years in comparison to 67 fibre-years for male lung cancer cases across the whole cohort (18, 39)). There are even greater concerns about the representativeness and comparability of the cases on which fibre burden analysis was carried out by Sébastien et al. (43) and, therefore, Case et al. (42) (i.e. no more than 5.56% of the South Carolina lung cancers studied; > 10 years difference in the mean age at death; substantial over-representation of asbestos-related disorders in the Thetford autopsies (42%) in comparison to the cohort as a whole (7%); median interval of 20 years after cessation of exposure for the textile workers vs. 8 years for the miners/millers; and differences in estimated exposures, especially when fibre clearance is taken into account). In addition, the total amphibole content (amosite/crocidolite + tremolite) was significantly higher in the miners/millers. Finally, the difference in the amosite/crocidolite content seems too small to account for the K difference.

The Weiss review

In 1999, Weiss (44) reviewed multiple cohort studies on the relationship between asbestosis exposure and lung cancer, and supported the view that excess lung cancer risk occurs only among those cohorts where asbestosis also occurs. He concluded that "asbestosis is a much better predictor of excess lung cancer risk than measures of exposure and serves as a marker for attributable cases." However, this review was the subject of critical comment by Banks et al. (45) in the same issue of the Journal.

In addition, the following comments on the Weiss review (44) can be adduced:

- This review specifically excludes case-control studies, autopsy investigations, and fibre burden analyses, and it confines itself largely to the English-language literature.

- The review is confined to studies and reports published up to January 1997 only.

- For Weiss' review of the Hillerdal study on patients with pleural plaques (46), Banks et al. (45) point out that Weiss' calculated RR for workers aged 40–69 years appears to be in error, because age was mistaken for years from first exposure.

- The Weiss review also contains data that undermine its own conclusions. For example, Table 4 (Lung cancer specific mortality ratios among Quebec miners and millers by chest radiograph status) records an SMR of 3.11 for workers with radiological small opacities (an X-ray marker for asbestosis; 95% CI 2.14–4.39). However, the SMR was also elevated at 3.30 (95% CI 2.32–4.62) in workers with radiographic abnormalities other than small opacities; Banks et al. (45) point out that 11 out of 37 in this category had a "large opacity" (not feature of asbestosis), so that the SMR for

lung cancer was increased among those with radiological abnormalities other than asbestosis.

• In Table 10 (Association between cumulative asbestosis mortality rate and cumulative excess lung cancer mortality rate in one study), the excess lung cancer death rate was 8.48 among 884 workers with light/moderate exposure lasting ≤ 2 years (likely to be insufficient to produce asbestosis, so that the asbestosis death rate in the same Table was zero); the figure of 8.48 was based on an observed number of 24 vs. an expected number of lung cancer deaths of 16.5, with an SMR of 1.45 (95% CI 0.93–2.16). However, if one assumes that the excess lung cancer death rate = 0 when there is no asbestos exposure (zero exposure, zero effect; SMR = 1.0), and notes that the excess lung cancer death rate is 19.49 among those with light/moderate exposure lasting > 2 years (when the asbestosis death rate = 3.61), then it appears that a trend to an increase in lung cancer SMR is evident even at light/moderate exposure ≤ 2 years (no asbestosis), and χ^2_1 (trend) = 163.9.

• Even if one sets aside, for the moment, all of these criticisms of the Weiss review and others outlined by Banks et al. (45), a fundamental problem remains. Weiss argues that increased death rates or risks of lung cancer occur in cohorts where asbestosis also occurs. But this does not mean – and one should not jump to the conclusion – that the asbestosis and lung cancer must occur in the same individual. All the data indicate is that lung cancer death rates are raised in cohorts where asbestosis occurs in some individuals. This observation is equally explicable by a dose-response effect for both asbestosis and lung cancer whereby they are not pathogenetically linked.

Asbestos-attributable lung cancer remains under-recognized

Although higher percentage figures are given for some countries, it has been estimated that about 3–5% of lung cancers can be related to asbestos. However, there seems to be little doubt that the role of asbestos as a contributory factor for many lung cancers goes unnoticed. The 1998 Report of the NSW Dust Diseases Board (DDB) is of interest in relation to the proportions of lung cancer cases relative to mesotheliomas: the Medical Authority considered 2,338 claims during 1997–98 (2,665 in 1996–97), with the following certifications:

1. The 238 certificates of disablement for 1997–98 included 96 mesotheliomas (97 in 1996–97) in comparison to 9 asbestos-induced carcinomas of the lung (10).

2. The 138 certificates for deaths (1997–98) included 104 mesotheliomas (101) vs. 14 lung cancers (13).

Some 1,509 workers were "certified to have not contracted a dust disease ...". In other words, the mesothelioma:lung cancer ratio was almost 10–11:1 (disablement) or 7.5–8:1 (death). These ratios stand in contrast to – and are the reverse of – those reported in epidemiological studies for other nations, where there are estimated to be about 1–10 asbestos-related lung cancers for every mesothelioma. There are a number of possible explanations for this apparent discrepancy of about two orders of magnitude:

1. The ratios reported elsewhere are incorrect and the NSW DDB figure is accurate.

2. The ratios reported elsewhere are correct and so is the NSW DDB ratio. In this case there must be something peculiar about the aetiology of lung cancer in NSW, but we are not aware of any evidence that this is so.

3. Both ratios are incorrect.

4. The NSW DDB ratio embodies an under-estimate of the number of lung cancers relative to mesotheliomas: this might be explicable by lung cancer patients not seeking compensation – i.e. they never came to the attention of the DDB – or, alternatively, by rejection of their claims, or both. It would be of interest to ascertain the numbers of lung cancers in the 1,509 claims that were rejected for 1997–98.

Some problems encountered with application of *The Helsinki Criteria*

In practice, there are cases where there is a disparity between the asbestos body vs. the uncoated fibre concentration in lung tissue, so that one or the other conforms to *The Criteria*, whereas the other does not. Alternatively, the count is occasionally high in one lobe of the lung and within normal values at another site. (According to Thimpont and de Vuyst (19), only one of the Belgian criteria need be satisfied.)

Again, *The Criteria* do not provide clear guidelines on how to handle a case where the amphibole concentration in lung tissue is elevated but does not reach the threshold figure, whereas there is an additional burden of chrysotile fibres – e.g. 3 million amphibole fibres > 1 micrometer in length per gram dry lung tissue, together with 3 million chrysotile fibres. Taking into account the lack of convincing evidence for a difference in carcinogenic potency between the amphiboles and chrysotile for lung cancer, can one simply add the chrysotile and amphibole content together, or is it better to base attribution on estimated cumulative exposures?

How does one resolve the issue if there are conflicting estimates of cumulative doses of asbestos, or if the occupational histories are too fragmentary for methodical assessment? For example, we have seen one case where one occupational hygienist assessed cumulative exposure at up to 90 fibre-years, but another came up with a figure of < 1 fibre-year. With a difference of this magnitude, the assumptions underlying each exposure estimate require critical re-evaluation (e.g. interpolation of data from a similar facility), because one or other estimate will not withstand scrutiny; when the estimates are closer but one fulfils *The Criteria* and the other does not, this introduces a diminished confidence level.

Screening for lung cancer in asbestos-exposed cohorts

In a recent review, Mulshine (47) gives a useful summary of trends in screening for lung cancer in order to improve therapeutic outcomes. Evaluation of screening programs is usually carried out on groups with an extremely high risk of lung cancer – e.g. males ≥ 45 years of age who are heavy cigarette smokers or cigarette-smoking tin miners in Yunnan, China, exposed also to arsenic and radon (48, 49). Cigarette smokers among

asbestos-exposed cohorts represent another group suitable for the evaluation of screening programmes.

Screening is based on the observation that surgical resection appears to be curative in a high proportion (up to 70%) of small stage I lung cancers and that thin-section or spiral CT can detect non-calcified lung nodules as small as ≤ 5 mm in diameter (e.g. see 50 and 51).

In the past, screening programmes have usually involved:

• Serial (e.g. annual) chest radiographs; *and/or*

• Serial sputum cytology examinations.

Using these modalities, some studies have returned disappointing results, presumably because of lack of sensitivity of the diagnostic techniques. However, others have been more encouraging. Midori et al. (52) found significantly increased lung cancer incidence and mortality in a radiation-exposed group screened biennially by plain X-ray compared to a non-screened but exposed group, but a lower mortality/incidence in the screened group, suggesting a benefit of earlier detection on outcome. This was a large study (1,799 screened; 8,735 not screened) and had been carried out since 1958. In another study from Japan, Okamoto and Tanaka (53) found that CT scanning was more cost-effective than plain X-ray screening: even though CT costs are higher they are more than balanced by the increased benefits of early detection. Encouraging results have also been reported by Sone et al. (54) in Japan, and in the Early Lung Cancer Action Project (ELCAP) in the US (50, 55).

Recent developments also indicate that the following techniques are worth investigation, including:

• Spiral CT examination of the thorax.

• The use of immunocytochemistry to detect biomarkers expressed early during the development of bronchogenic carcinoma. For example, one monoclonal antibody used for this purpose (703D4) recognizes a heterogeneous nuclear ribonucleoprotein (hnRNP) A2/B1 and in the Yunnan tin miners (48, 49) this monoclonal antibody was found to be two to three-fold more sensitive for the detection of early disease in comparison to standard chest radiographs and sputum cytology examinations. (Screening for antibodies to nuclear auto-antigens also offers promise for the early detection of mesothelioma: Robinson et al. [56] found 93% of mesothelioma cases had antibodies to TOP11 antigen and 14% had antibodies to U2AF.)

• Perhaps more promising is the detection of oncogenes – e.g. K-ras (57) – in sputum, BAL fluid, or blood.

Two problems remain:

1. It needs to be shown that the techniques employed will lead to improvement in clinical outcomes in the cancers detected by screening programmes and that they are applicable to other high-risk groups.

2. Although well defined groups of asbestos-exposed individuals are suitable for the evaluation of screening programmes, screening becomes more problematical for the far more numerous workers who are exposed at various points of asbestos end-use, because many such individuals do not identify themselves as asbestos workers and it is difficult to recruit them into screening programmes.

References

1. Multiple authors. Consensus report: asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution. Scand J Work Environ Health 1997;23:311–6.

2. Boffetta P. Health effects of asbestos exposure in humans: a quantitative assessment. Med Lav 1998;89:471–80.

3. Multiple authors. Environmental Health Criteria 203: Chrysotile Asbestos. International Programme on Chemical Safety (IPCS). Geneva: World Health Organization; 1998.

4. 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, eds. Sourcebook on Asbestos Diseases, vol 13. Charlottesville: Michie; 1996;13:141–66.

5. 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, ed. Pathology of Lung Tumors. New York: Churchill Livingstone; 1997:83–118.

6. 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.

7. Churg A. Asbestos, asbestosis, and lung cancer. Mod Pathol 1993;6:509–10.

8. Day NE, Brown CC. Multistage models and primary prevention of cancer. J Natl Cancer Inst 1980;64:977–89.

9. 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.

10. 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.

11. 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.

12. Armstrong B, Theriault G. Compensating lung cancer patients occupationally exposed to coal tar pitch volatiles. Occup Environ Med 1996;53:160–7.

13. Begin R. Asbestos exposure and pleuropulmonary cancer [Fr]. Rev Mal Respir 1998;15:723–30.

14 Karjalainen A, Piipari R, Mäntylä T, et al. Asbestos bodies in bronchoalveolar lavage in relation to asbestos bodies and asbestos fibres in lung parenchyma. Eur Respir J 1996;9:1000–5.

15 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]. Schriftenreihe des Bundesanstalt fur Arbeitsmedizin: Forschung Fb 01 HK 076. Berlin: Bundesanstalt fur Arbeitsmedizin; 1996.

16. Browne K. A threshold for asbestos-related lung cancer. Br J Ind Med 1986;43:556–8.

17. Churg A. Nonneoplastic disease caused by asbestos. In: Churg A, Green FHY, eds. Pathology of Occupational Lung Disease, 2nd edn. Baltimore: Williams & Wilkins; 1998:277–338.

18 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.

19. Thimpont J, De Vuyst P. Occupational asbestos-related diseases in Belgium (epidemiological data and compensation criteria). In: Peters GA, Peters BJ, eds. Sourcebook on Asbestos Diseases, vol 17. Charlottesville: Lexis; 1998;17:311–28.

20. 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.

21. Mollo F, Pira E, Piolatto G, et al. Lung adenocarcinoma and indicators of asbestos exposure. Int J Cancer 1995;60:289–93.

22. 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.

23. Baur X, Czuppon AB. Regulation and compensation of asbestos diseases in Germany. In: Peters GA, Peters BJ, eds. Sourcebook on Asbestos Diseases, vol 15. Charlottesville: Lexis; 1997;15:405–19.

24. Hindry M. Asbestos-related disease compensation in France. In: Peters GA, Peters BJ, eds. Sourcebook on Asbestos Diseases, vol 16. Charlottesville: Lexis; 1997;16:423–48.

25. Anonymous. Full public report: Chrysotile Asbestos – Priority Existing Chemical no. 9. National Industrial Chemicals Notification and Assessment Scheme (NIC-

NAS). National Occupational Health and Safety Commission (NOHSC). Sydney: Commonwealth of Australia, February 1999.

26. 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.

27. 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.

28. 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.

29. Steenland K, Stayner L. Silica, asbestos, man-made mineral fibers, and cancer. Cancer Causes Control 1997;8:491–503.

30. 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.

31. Blettner M, Sauerbrei W, Schlehofer B, et al. Traditional reviews, meta-analyses and pooled analyses in epidemiology. Int J Epidemiol 1999;28:1–9.

32. Ioannidis J, Schmid CH, Lau J. Meta-analysis approaches for epidemiologic research on asbestos. In: Peters GA, Peters BJ, eds. Sourcebook on Asbestos Diseases, vol 18. Charlottesville: Lexis; 1998;18:93–116.

33. Goodman M, Morgan RW, Ray R, et al. Cancer in asbestos-exposed occupational cohorts: a meta-analysis. Cancer Causes Control 1999;10:453–65.

34. 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.

35. Churg A. Neoplastic asbestos-induced disease. In: Churg A, Green FHY, eds. Pathology of Occupational Lung disease, 2nd edn. Baltimore: Williams & Wilkins; 1998:339–91.

36. Nagai A, Chiyotani A, Nakadate T, Konno K. Lung cancer in patients with idiopathic pulmonary fibrosis. Tohoku J Exp Med 1992;167:231–7.

37. 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.

38. Oksa P, Klockars M, Karjalainen A, et al. Progression of asbestosis predicts lung cancer. Chest 1998;113:1517–21.

39. 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.

40. Dement JM, Brown DP. Lung cancer mortality among asbestos textile workers: a review and update. Ann Occup Hyg 1994;38:525–32, 412.

41. McDonald JC. Unfinished business: the asbestos textiles mystery [editorial]. Ann Occup Hyg 1998;42:3–5.

42. Case BW, Dufresne A. Asbestos fibre type and length in lungs of chrysotile textile and production workers: a preliminary report. In: VIIth International Symposium on Inhaled Particles. Maastricht, October 1999.

43. 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;46:1807.

44. Weiss W. Asbestosis: a marker for the increased risk of lung cancer among workers exposed to asbestos. Chest 1999;115:536–49.

45. Banks DE, Wang ML, Parker JE. Asbestos exposure, asbestosis, and lung cancer [editorial; comment]. Chest 1999;115:320–2.

46. Hillerdal G. Pleural plaques and risk for bronchial carcinoma and mesothelioma: a prospective study. Chest 1994;105:144–50.

47. Mulshine JL. Reducing lung cancer risk: early detection. Chest 1999;116:493S–6S.

48. Qiao YL, Taylor PR, Yao SX, et al. Risk factors and early detection of lung cancer in a cohort of Chinese tin miners. Ann Epidemiol 1997;7:533–41.

49. Qiao YL, Tockman MS, Li L, et al. A case-cohort study of an early biomarker of lung cancer in a screening cohort of Yunnan tin miners in China. Cancer Epidemiol Biomarkers Prev1997;6:893–900.

50. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999;354:99–105.

51. Yankelevitz DF, Gupta R, Zhao B, Henschke CI. Small pulmonary nodules: evaluation with repeat CT – preliminary experience. Radiology 1999;212:561–6.

52. Midori S, Masazumi A, Shin-ichiro I, Hiroshi S. Evaluation on usefulness of lung cancer screening based on the cohort study. In: 21st Annual Conference of the International Association of Cancer Registries. Lisbon, October 1999:abstract, p 13.

53. Okamoto N, Tanaka T. Cost-effectiveness of lung cancer screening by CT in Japan. In: 21st Annual Conference of the International Association of Cancer Registries. Lisbon, October 1999:abstract, p 70.

54. Sone S, Takashima S, Li F, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. Lancet 1998;351:1242–5.

55. Henschke CI, Yankelevitz DF. Screening for lung cancer. J Thorac Imaging 2000;15:21–7.

56. Robinson C, Callow M, Stevenson S, Robinson BWS. Antigens associated with malignant mesothelioma. In: Congress on Peritoneal Repair and Adhesions, 5th Meeting, and International Mesothelioma Interest Group, 5th Meeting. Stoke Rochford, October 1999.

57. Scott FM, Modali R, Lehman TA, et al. High frequency of K-ras codon 12 mutations in bronchoalveolar lavage fluid of patients at high risk for second primary lung cancer. Clin Cancer Res 1997;3:479–82.