Editorial

Analysis of lung asbestos content

The invention of the analytical electron microscope (a scanning or transmission microscope equipped with an energy or wavelength dispersive x ray spectrometer, or both) has permitted detailed, fibre by fibre, evaluation of the asbestos content of human lung. Over the past 10 to 15 years a substantial number of reports have appeared in which various correlations of some properties of asbestos such as fibre concentration, size, distribution, and disease patterns have been proposed. Analyses of individual cases have also been used in some instances as evidence concerning both asbestos aetiology and specific pathological diagnoses in medico legal cases.

What are the limitations of this type of analysis? One of the basic problems that has emerged as more and more laboratories have reported data is the wide discrepancy in absolute fibre concentrations between laboratories, even when analysing the same sample.[1] The exact reasons for this are unclear, although differences in tissue preparation methods, counting rules, and type of microscope probably have major roles.

The fact that interlaboratory values vary widely, however, does not invalidate the basic method. In a formal study in which seven laboratories counted the same samples, all reported the "high" samples as high and the "low" samples as low.[1] Also, remarkably good correlations were found between exposures determined by air sampling and fibre burdens determined by analytical electron microscopy.[2-4] Futher, patterns from laboratory to laboratory between fibre burden and specific disease type are quite reproducible. All of these findings provide support for the fundamental *intra*laboratory accuracy of this type of analysis.

What the problems with interlaboratory differences do indicate is that a single value from a particular laboratory is, in itself, meaningless. Each laboratory must generate its own set of standards including background population ranges for dealing with individual cases. For examining series of cases, some sort of case-control protocol may be preferable. And to make sense of the relation of fibre burden and disease, one must look for systematic variations in fibre parameters from disease to disease among different laboratories.

One of the surprising observations to emerge from analysis of lung asbestos content is that, compared with amphiboles, chrysotile is retained poorly in lung tissue. The reason for this phenomenon is argued,[5] but what this process means in practice is that substantial chrysotile exposure may be missed if fibre analysis is the only way of determining exposure (history helps a lot, of course!).

To some extent tremolite, which contaminates most chrysotile ores, and which, like all amphiboles, readily accumulates in the lung, can serve as a measure of the missing chrysotile. This subterfuge works well in chrysotile miners,[6 7] in whom the tremolite content of the lung usually greatly exceeds the chrysotile content, and in chrysotile textile workers,[2 3] another group in whom the chrysotile used appears to contain some reasonably consistent amount of tremolite. In other end users of chrysotile products, however, the amount of tremolite seems to be variable[6] and tremolite concentration may not provide a guide to past exposure.

Measurements of fibre size can be helpful in this regard. Exposure to commercial chrysotile products leads to the inhalation of long fibres[8] whereas the numerous fibres present in urban air are very short. We found that the presence of chrysotile or tremolite fibres longer than 8 μm was highly specific for occupational chrysotile exposure.[6] Conversely, an analysis that shows only very short chrysotile or tremolite and no commercial amphibole (amosite or crocidolite) is strongly suggestive of either background ambient air exposure or contamination of the specimen from chrysotile in air or water during preparation.

Some have chosen to view the problems with chrysotile retention as a reason to reject totally the usefulness of mineral analysis for investigating the relation between specific fibre types and disease.[9] But to me the conclusion to be drawn is simply that fibre analysis, like any technique, has methodological limitations, and that to obtain useful results, considerable care must be exercised in the selection of worker groups for evaluation; if this is done correctly, then consistent correlations emerge (see later).

Despite these limitations, analysis of lung asbestos content has led to some interesting findings. Firstly, is the realisation that everyone in the population carries quite a substantial burden of asbestos fibres in their lungs, a burden derived from both indoor and outdoor ambient air.[6 10 11] Absolute numbers vary, as usual, from laboratory to laboratory; in our hands the upper 95th percentile for the general population of

Vancouver is around 1 000 000 fibres of chrysotile, 1 000 000 fibres of tremolite, and 10 000 fibres of amosite plus crocidolite per g lung tissue.[6] Assuming an average pair of dried normal lungs weighs 40 g, this translates to upper limits of 40 000 000 fibres each of chrysotile and tremolite and 400 000 fibres of amosite or crocidolite, numerically rather substantial values. Yet despite this fibre burden no epidemiological evidence exists to suggest that the general population suffers from any type of asbestos related disease.

A similar conclusion arises from examination of the lungs of long term residents of the chrysotile mining townships in eastern Quebec. Studies from two different laboratories[12-14] have shown that persons living in the townships but never employed in the mining and milling industry none the less carry a five to 10-fold greater burden of chrysotile (and tremolite in some areas) than typical urban dwellers in North America. This burden is derived from ambient air contaminated by chrysotile mining activities and extensive chrysotile and tremolite in local soil and rocks; the ambient concentrations of chrysotile are several hundredfold greater than those seen in urban air or asbestos containing buildings.[15] But again epidemiological investigations have failed to find asbestos related disease in those who live in the townships but were never employed in the industry.[16] Thus clearly there is a burden of asbestos fibres that can be tolerated without the development of disease, and, at least for chrysotile and tremolite, this burden is considerably higher than most city dwellers in North America would ever carry. This point appears to be lost on those who advocate wholesale removal of chrysotile asbestos from public buildings.

Mineral analysis has also played a useful part in defining the types and degree of fibre burden that are associated with specific diseases in occupationally exposed populations[3 4 10-14 17 19-23] (see [11] and [19] for more detailed citations). This is a complex problem because most working populations have been exposed to both chrysotile and amphiboles, but the different biological properties of these two types of fibre make it critical to examine them separately to discern disease fibre burden relations. Indeed, one of the unexpected findings from mineral analysis has

been the extent to which "chrysotile" factory workers and also man made mineral fibre factory workers have had exposure to amosite or crocidolite.[3 19 21 24] Given the appreciably greater carcinogenicity of amphiboles in regard to mesothelioma and their suspected greater pathogenicity in regard to other diseases,[25] this type of contamination is a serious confounder, particularly when such exposures have been used to propose standards for occupational exposure to chrysotile.[22]

An important question that has been answered by mineral analysis is whether chrysotile asbestos actually causes mesothelioma in human subjects. Analyses of lung tissue from the small number of Quebec miners and millers who develop mesothelioma have shown high concentrations of chrysotile and tremolite with background concentrations of amosite and crocidolite,[23] thus indicating unequivocally that chrysotile (that is, chrysotile plus its tremolite contaminant) can cause mesothelioma, but also indicating that very high fibre loads are required. Such analyses have additionally suggested that the tremolite rather than the chrysotile might be the actual aetiological agent of mesothelioma, but this issue is unresolved.[23 25]

Despite problems of co-exposures, it has been possible to use populations such as chrysotile miners and millers or textile workers to determine a disease fibre burden relation for chrysotile and tremolite, and similarly, to use workers with heavy amphibole exposure (ignoring for the purposes of analysis the chrysotile, which is usually present in small amounts) to obtain the same information for amosite and crocidolite.[3 4 10 14 17-19 23] As shown in the table these two different types of fibre have distinct disease dose-responses. The fact that, in those with exposure to chrysotile, mesothelioma only appears at levels sufficient to also produce asbestosis should reinforce the lack of danger from low level environmental or occupational chrysotile exposure.

A futher conclusion starting to emerge from fibre burden studies is the dominant role of commercial amphibole in producing disease. As is evident in the table, the presence of heavy exposure to amphibole shifts the fibre burden-asbestosis-mesothelioma relation. What is not apparent from the above but is

Table *Approximate mean fibre burdens by disease and fibre type*

Increasing fibre burden					→
Amphibole exposure	General < population	Pleural < plaques	Mesothelioma < <		Asbestosis
Chrysotile exposure	General < population; urban areas	General < population; mining townships	Chrysotile miner < without disease	Pleural < < plaques	Asbestosis or mesothelioma

Amphibole indicates amosite or crocidolite; chrysotile indicates chrysotile plus tremolite.
Specific diseases such as mesothelioma refer to fibre burdens in workers with occupational exposure.
Symbol < indicates the number of orders of magnitude difference in mean burden.

equally important is that, for any given condition, disease appears at a considerably lower amphibole than chrysotile burden; in our laboratory this difference is about one order of magnitude in mean or median fibre burden. Detailed comparisons have also shown that amphibole is more fibrogenic, fibre for fibre, than chrysotile.[26] These observations lend support to the idea that chrysotile is less pathogenic than the amphiboles.

Most published studies in this area have confined themselves to the question of fibre concentration and little information is available about the effects of fibre size or distribution in human subjects. It is clear that persons in the general population tend to have much shorter chrysotile and tremolite fibres than those with occupational exposure,[6] a finding consistent with the lack of asbestos induced disease in the general population. McDonald *et al*,[27] using a case-control design, suggested that the relative risk of mesothelioma could be explained on the basis of the long (>8 μm) fibre content of the lung and that inclusion of shorter fibres did not appear to improve risk estimates, an observation consistent with conventional wisdom on effects of fibre size. The paucity of mesotheliomas in chrysotile miners and millers may also reflect the relatively short tremolite that such workers inhale.[6] But some of the published data on the effects of fibre size do not correspond at all with experimental data—for example, we found negative rather than positive correlations between local fibrosis (asbestosis) grade and local mean fibre length for amosite, tremolite, and chrysotile in humans.[26]

The effects of distribution are obscure. Studies examining distribution have either shown no consistent patterns or patterns diametrically opposite to experimental and theoretical predictions (see [28] [29] for more details). Does the failure to match theory with fact indicate that fibres redistribute within the lung after inhalation? Certainly, evidence exists that this occurs in animals.[30] What is the effect of structural variations from person to person on fibre distribution? Several groups[31-33] have suggested that lung structure, including lung size and airway size, may determine who does or does not develop inhaled dust disease. Correlations of fibre size and distribution patterns with underlying lung structure and disease patterns deserve further investigation.

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Examples of common forms of references are:

1 International Steering Committee of Medical Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1979;1:532–5.

2 Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosino-phil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976;294:687–90.

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