Carcinogenicity of fibrous tremolite in workplace and general environments

Corbett McDonald MD

National Heart & Lung Institute, Imperial College School of Medicine,
Dovehouse Street, London SW3 6LY, UK

Summary of paper to be presented at EPA Asbestos Health Effects Conference, Oakland, California on May 24, 2001

Background

The McGill programme of epidemiological research in Quebec chrysotile miners and millers, initiated in 1965, was conducted largely in the belief that exposure in that industry was to chrysotile only. While investigating the uneven distribution of pleural changes among workers in the various mines and mills, Gibbs was probably the first to suggest, in 1979, that the explanation might lie with minerals other than chrysotile. Some years earlier, however, when Pooley and Rowlands *et al.* examined by electron microscopy lung tissue taken at autopsy from former miners and millers, chrysotile and tremolite fibres had been seen in surprisingly similar concentrations. These observations raised the question of the extent to which the fibrogenic and carcinogenic consequences of exposure were attributable to tremolite, chrysotile or both.

The fact that tremolite fibres may penetrate the airways more deeply than chrysotile, and are certainly more persistent in lung tissue, has little epidemiological significance unless there is also evidence of their greater pathogenicity. That this is so was shown in the 1980s by a McGill study of a small cohort of 406 vermiculite miners and millers in Libby, Montana where, among 165 deaths, there was a substantial excess of lung cancer, NMRD, and four deaths ascribed to mesothelioma. At the same time, a radiographic survey of current and retired Libby mine workers found a close correlation between prevalence of small opacities and cumulative exposure (f/ml.y). A further observation of potential importance, made by Sébastien *et al.*, was that the concentration of asbestos bodies in sputum was as good or better a predictor of radiographic changes as cumulative exposure estimated from environmental measurements. Mortality and radiographic studies undertaken by NIOSH in parallel, but on slightly different study groups, resulted in very similar findings to our own. It was uncertain, however, whether the fibres to which these workers were exposed, although classified mineralogically as in the tremolite series, were necessarily the same biologically as those found in association with Quebec chrysotile.

Tremolite contamination of chrysotile

In the cohort of some 11,000 male Quebec miners and millers, almost 10,000 of whom were alive in 1930, 38 cases of mesothelioma were identified among over 8000 deaths before 1993. Of these, five were from a small asbestos products factory where commercial amphiboles were also used and the remaining 33 were in miners and millers: 25 from mines in the Thetford Mines region and eight from the large mine at Asbestos. There was reason to believe that the proportion of tremolite in the chrysotile was some three times higher in the former than the latter, but it was not then known whether the distribution of tremolite was responsible for this apparent difference in risk.

To resolve the question, an analysis was made of deaths from mesothelioma (21), cancers of the lung (262), larynx (15), stomach (99), and colon and rectum (76) in men employed by the largest company in Thetford Mines, with closely matched referents. Risks were estimated by logistic regression for these five cancers in two groups of mines – five mines located centrally and ten mines located peripherally; tremolite contamination had been demonstrated to be some three times higher in the former than in the latter. Odds ratios for work in the central mines were found to be raised substantially and significantly for mesothelioma and lung cancer, but not for the gastric, intestinal or laryngeal cancers. In the peripheral mines, or indeed in Asbestos, Quebec, there was little or no evidence of increased risk for any of these five cancers. The hypothesis that, because of the difference in distribution of fibrous tremolite, cancer risks in the central area would be greater than in the periphery, was thus confirmed, implying that this might well be due to their far greater biopersistence.

Biopersistence and the amphibole hypothesis

Use of a single commercial term, asbestos, to cover at least five fibrous silicate minerals, each with quite different physical, chemical and biological properties, has done much to inhibit proper consideration of their individual health effects. Whereas it has been consistently evident from cohort studies of Quebec miners and millers since the early 1970s that chrysotile rarely caused mesothelioma and, except at very high levels of exposure, was not a major cause of lung cancer, comparable information on miners and millers of crocidolite and amosite was not available until 20 years later. Meanwhile, thanks to the fact that occupational exposures were usually to chrysotile amphibole mixtures, the field became confused and subject to considerable controversy about what has become known as the amphibole hypothesis.

The differences in opinion lie primarily in the interpretation of the epidemiological data. Cohorts exposed only to commercial chrysotile experienced far fewer deaths from mesothelioma and generally lower SMRs from lung cancer than those in which exposure had been to the commercial amphiboles or to products to which the amphiboles had been added. In summary, of 11,538 deaths in chrysotile cohorts, 44

were from mesothelioma and 267 were lung cancers in excess – proportional mortalities of 3.8 and 23.1 per thousand respectively. In amphibole-related cohorts, of 19,622 deaths, 590 deaths were from mesothelioma and 1042 lung cancers in excess – proportional mortalities of 30.1 and 53.1 per thousand. Although these differences in risk are large and consistent, others have drawn quite different conclusions.

At the heart of the controversy lies a fundamentally differing view of the importance of biopersistence in carcinogenesis. It is generally agreed that amphibole fibres are far more durable in lung tissue than chrysotile, and many see this as the explanation of what is observed in human studies. Within the same conceptual framework the results of controlled lung burden studies fit well, as do the current views of experimentalists on the role of biopersistence. On the other hand, those critical of the amphibole hypothesis see differences in fibre persistence as a reason for rejecting the results of lung burden studies, continuing instead to put more store on fibre dimensions.

Results now in press of a national case-referent study in the UK of 115 recent cases of mesothelioma in men aged ≤52 years at death, with lung fibre analysis in 69, do not support the view of the critics. Odds ratios were significantly raised in only 8 of 37 industrial occupations – carpenters, plumbers, electricians, insulators, unskilled construction workers and men employed in ship/boat building or the manufacture of cement and other asbestos products. Amphibole fibres were found in all but 6 of the 69 cases, in concentrations related linearly and highly significantly to adjusted odds ratios. The estimated proportion of cases attributable to amphiboles was 84%, including 7% to tremolite, often considered a marker for chrysotile.

Libby update

So far as the amphibole fibre, tremolite, is concerned, evidence for a high level of carcinogenicity, equivalent indeed to that of crocidolite, is strongly supported by a recent update of the Libby vermiculite mining cohort. Of the 406 men originally identified, 165 had died by July 1, 1983; the 241 survivors have now all been followed until January 1, 1999, among which there had been 120 deaths, all with certified cause. A comparison of SMRs in the two periods, against mortality rates, for US white males, is shown in Table 1. The results in the two periods are very similar, except that the total number of mesothelioma deaths (excluding three possible cases) had now reached 12 (PMR = 4.2%), and external causes (i.e. accidental death) are no longer in excess. Risks in relation to duration and intensity of exposure are now being analysed.

Table 1. Libby Cohort of vermiculite miners exposed to fibrous tremolite (n = 406)

	Deaths to July 1983		Deaths since July 1983*	
	n	*SMR*	*n*	*SMR*
Respiratory cancers	23	2.45	21	2.22
All other cancers	20	1.09	19	1.21
NMRD	21	2.55	30	3.35
Circulatory diseases	65	0.87	36	0.96
External	23	1.87	3	0.99
All causes	165	1.17	1.20	1.34
(incl. mesothelioma)	4 (PMR = 2.4%)		8 (PMR = 6.7%)	

to Jan 1, 1999

Synthesis

Further consideration of the research which has been reviewed suggests reasonable and probably reliable conclusions. Our findings at Libby, supported by the earlier studies of NIOSH, indicate that amphibole fibres in the tremolite series, in the absence of any other asbestos fibre types, are highly fibrogenic and carcinogenic for both lung and pleura. Results from the McGill and NIOSH studies in the 1980s estimated the excess risk of lung cancer to be about 1% per fibre year and of small radiographic opacities (≥1/0), at roughly 0.6% per fibre year. The excess mortality, all causes, in the Libby cohort to date, for whom the mean cumulative exposure is estimated at 145 f/ml.y, was 13.3%. Assuming linearity, and ignoring other possible factors, the estimated risk (all causes) is thus about 0.09% per f/ml.y. These levels of risk are probably sufficient to explain most if not all the adverse effects of exposure to commercial chrysotile.

The validity of all these estimates is put into question, however, by the fact that in both Thetford Mines and Libby, risks were related to duration of employment but not to average intensity of exposure. Having regard for the extremely uneven geological distribution of tremolite deposits in both these locations, it is not surprising that average exposure in terms of f/ml is virtually impossible to estimate. This limitation applies particularly to any attempt at assessing general environmental risks for inhabitants of regions where deposits of fibrous tremolite occur. In these circumstances, the further development and quantification of asbestos bodies in sputum may provide a useful approach.