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CHRYSOTILE, TREMOLITE AND CARCINOGENICITY

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Abstract—It has been suspected for many years that amphibole fibres in the tremolite series, a low level contaminant of chrysotile asbestos, may contribute disproportionately to the incidence of mesothelioma and perhaps other exposure-related cancers. A cohort of some 11 000 Quebec chrysotile workers, 80% of whom have now died, provided the opportunity to examine this hypothesis further. 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 four times higher in the former than in the latter. Odds ratios for work in the central mines were raised substantially and significantly for mesothelioma and lung cancer, but not for the gastric, intestinal or laryngeal cancer sites. In the peripheral mines, there was little or no evidence of increased risk for any of the 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 substantiated. That the explanation may lie in the greater biopersistence of amphibole fibres than chrysotile is important in framing policies for the use and control of asbestos and is directly relevant to the selection of man-made mineral fibre substitutes. © 1997 British Occupational Hygiene Society. Published by Elsevier Science Ltd.

INTRODUCTION

Since the observation by Dr Chris Wagner 40 years ago of malignant mesothelial tumours in crocidolite miners and millers and their family contacts, but rarely in miners of chrysotile or amosite, the history of asbestos-related research has been dominated by efforts to assess the relative carcinogenicity of the main mineral fibre types (see McDonald and McDonald, 1996). While this aim was largely achieved for chrysotile in an extensive and continuing research program in the mines and mills of Quebec, and by numerous cohort studies of factory workers exposed to chrysotile only, until quite recently there had been no comparable data for crocidolite or amosite. Meanwhile, confusion was created by the inevitable difficulty of interpreting findings in workers usually exposed to amphibole–chrysotile mixtures in manufacturing and product use; this in turn gave rise to much bitter controversy. There were those investigators (the 'chrysophiles') who believed the evidence to show a major difference between the relatively low carcinogenicity of chrysotile and the much higher risk, particularly of mesothelioma, usually associated with amphibole exposure; others (the 'chrysophobes') concluded from much the same

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evidence that all types of asbestos were equally dangerous. These arguments seem likely to continue (for example see Smith and Wright, 1996).

During the past 20 years the suspicion has grown, at least among the chrysophiles, that the frequent contamination of chrysotile deposits by amphibole fibres in the tremolite series may contribute disproportionately to the carcinogenic effects of occupational exposure. Beginning in the 1970s, newly applied techniques for lung burden analysis revealed the unexpected finding that despite the overwhelming exposure of Quebec miners and millers to chrysotile, tremolite was usually the predominating fibre present at death (Pooley, 1976; Rowlands *et al.*, 1982). Wagner *et al.* (1982) reported that the carcinogenicity of tremolite in experimental animals was similar to that of the other fibrous amphiboles and in a study by Churg *et al.* (1984) of six cases of mesothelioma in Quebec mine workers tremolite was reported as the predominating fibre type. The fibrogenic and carcinogenic potential of fibrous tremolite was confirmed a few years later by both mortality and radiographic studies of American vermiculite miners and millers exposed to tremolite, but to no other type of asbestos. The risk of mesothelioma, lung cancer and pulmonary fibrosis among these men was many times higher than that experienced by Quebec chrysotile workers (Amandus *et al.*, 1988; Armstrong *et al.*, 1988). Later, carefully controlled case–referent studies of deaths from mesothelioma across Canada, with detailed lung burden analyses, showed that while tremolite was indeed the dominant fibre in cases from the Quebec mining area its aetiological contribution to cases elsewhere was probably fairly similar to that of amosite and of crocidolite (McDonald *et al.*, 1989).

Given that chrysotile and tremolite tend to occur together it has not been easy to assess separately their effects on mortality. Even in our Quebec mortality cohort, until recently the number of mesothelioma and lung cancer deaths was not large enough for a sufficiently detailed study. However, the most recent update of deaths in the cohort to the end of 1992 (see Liddell *et al.*, 1997) identified a much larger number of such cases among the 8000 deaths from all causes. From this total, 38 deaths were considered due to mesothelioma and it was estimated that some 65 deaths from lung cancer were in excess. Also important was the growing evidence that neither the risk of these two diseases nor the level of tremolite contamination was equally distributed across the Quebec mining region, both being higher at Thetford Mines than at Asbestos (McDonald *et al.*, 1994).

Of the 38 deaths from mesothelioma in the cohort, 33 were in miners and millers—25 from Thetford Mines and 8 from Asbestos, and the remaining 5 were in an associated asbestos products factory. Thetford Mines offered the best opportunity for study, partly because of the higher levels of tremolite thought to prevail there than at Asbestos but mainly because the industry at Thetford originally comprised 21 mining companies, some located centrally and the others at varying distances peripherally. Six of the 21 companies were small and independent; the remaining 15 had been amalgamated many years ago into a large complex where 80% of the cohort in the Thetford area had been employed.

In a preliminary study, (see McDonald and McDonald, 1995), the work histories of the 22 cases of mesothelioma in men who had been employed by the largest company at Thetford Mines were compared in detail with similar data for a large series of comparable referents. The total number of years worked by the case series

in the clearly definable group of five centrally located mines (area A) was six times greater than in 10 mines located peripherally (area B), whereas the ratio for the referent series was 1.5. That this difference might be related to the distribution of fibrous tremolite in the ore body was supported by observations made by Sébastien *et al.* (1989) of mineral fibres in lung tissue from 83 cohort members who had worked in the same mines and died from causes other than mesothelioma. In that investigation, the geometric mean concentration of mineral fibres 5 μm or more in length was for tremolite four times higher in area A than in area B, a difference of very high statistical significance ($p = 0.0002$), whereas for chrysotile it was lower in A than in B.

Although this preliminary study thus provided evidence of a strong geographical correlation between the distribution of tremolite and the incidence of mesothelioma, the question of risk in relation to duration and intensity of exposure in the two areas was not addressed, and in retrospect it was felt that the referent series had not been matched sufficiently closely. The present paper describes a study designed to test the question of risk not only for mesothelioma but also for lung cancer and other malignant diseases potentially associated with chrysotile exposure.

MATERIALS AND METHODS

Cases

The cohort of 10 918 men born 1891–1920 who had worked for a month or more in the chrysotile mines and mills of Quebec, included over 4000 employed by the largest company in the region of Thetford Mines (Liddell *et al.*, 1997). Of these more than 80% had died by the end of 1992, giving the following numbers of cancer deaths for the current analysis: mesothelioma 22 (as before), lung 266, larynx 16, stomach 99, colon and rectum 79.

Referents

For each death in the five categories of malignant disease, referents were selected from men who had survived the case, closely matched individually for year of birth and age at first recorded employment in the industry. Ten referents were sought for each mesothelioma, four for each laryngeal cancer and one for each cancer of lung, stomach, colon or rectum. In three cases of mesothelioma only six, five and three adequately matched referents could be found. A total of nine cases (mesothelioma, one; lung cancer, four; laryngeal cancer, one; colon and rectum cancer, three) had to be eliminated from the analysis, usually because either the case himself or his only referent had had frequent changes of employment between areas A and B which had not been recorded. The number of cases analysed is shown in Table 1.

Analysis

From the detailed work histories for each subject, periods of employment in central (area A) or peripheral (area B) mines were calculated. Periods of service within 10 years of death of the case were excluded for all cases and referents; these exclusions were made to reduce dilution by periods of exposure generally believed to be aetiologically unimportant. For the mesothelioma cases and referents, the periods

Table 1. Odds ratios from conditional logistic regression analyses of matched case-referent sets of selected malignant disease deaths at Thetford Mines

Cause of death	No. of matched sets analysed	Central mines (Area A) OR*	Central mines (Area A) (90% confidence interval)	Peripheral mines (Area B) OR*	Peripheral mines (Area B) (90% confidence interval)	Likelihood ratio comparing areas
Mesothelioma	21	2.55	(1.52–4.27)	1.11	(0.47–2.62)	4.50
Lung cancer	262	1.98	(1.53–2.57)	1.09	(0.78–1.51)	8.25
Laryngeal cancer	15	0.48	(0.15–1.56)	1.16	(0.38–3.55)	1.20
Stomach cancer	99	1.36	(0.86–2.16)	0.99	(0.56–1.75)	0.71
Colo-rectal cancer	76	1.18	(0.73–1.91)	0.85	(0.42–1.73)	0.48

*Based on 20 yr employment in central or peripheral mines derived as (odds ratio associated with one year of employment)[20].

were adjusted for the length of the working week, as fully described by Liddell *et al.* (1997). This was not done for the other cancers because the considerable amount of work required did not appear to be justified. Cases and referents were compared for years of employment in areas A and B by conditional logistic regression, and odds ratios were calculated with 90% confidence intervals.

The results are summarised in Table 1, from which it can be seen that the odds ratios for mesothelioma and lung cancer were raised quite substantially in relation to work in the central mines (area A) but not for work in the peripheral mines (area B). The differences in risks between the two areas are reflected in likelihood ratios, also in Table 1, which can be referred to the χ^2 distribution with 1 degree of freedom, implying *p*-values of approximately 0.03 for mesothelioma and 0.004 for lung cancer; that the latter is much the lower is probably a reflection of the larger number of subjects. Table 1 also shows there was little relationship between the other cancers (laryngeal, stomach or colo-rectal) and work in either area.

That the main findings do not arise from greater intensity of exposure in area A than in area B is demonstrated by the time-weighted average levels of exposure of the referents during the same period, namely for mesothelioma referents 17.4 million particles per cubic foot (mpcf) in area A and 16.3 mpcf in area B, and for lung cancer referents 15.1 and 20.7 mpcf, respectively. As each average has a large standard error, all four can be considered quite similar.

DISCUSSION

Our studies of Quebec chrysotile miners and millers have consistently shown little evidence of a cancer risk except at very high levels of exposure and conclusively only for lung cancer and mesothelioma; it is important to note that the evidence presented in this paper on the role of tremolite also applied only to these two diseases. With the exception of a cohort of asbestos textile workers in Charleston, South Carolina, where a high risk of lung cancer but not of mesothelioma was observed (McDonald *et al.*, 1983a; Dement *et al.*, 1994), this has been the experience of the many other cohorts exposed to chrysotile only, in marked contrast to the far more serious effects of work with amphiboles (crocidolite and amosite) or chrysotile–amphibole mixtures (Hughes, 1991; McDonald and McDonald, 1996). Tremolite is also an amphibole and, although its fibres are seldom used commercially, it has been shown in the several studies mentioned earlier in this paper to share much the same carcinogenic potential for lung and pleura as crocidolite. Our findings are thus plausible and consistent with the view that amphibole fibres are considerably more hazardous than chrysotile in man.

If the incidence of mesothelioma and of lung cancer resulting from exposure to commercial chrysotile is mainly attributable to low but varying levels of tremolite fibres, effective steps are needed to minimise such contamination. In the meantime it must be accepted that for practical purposes chrysotile asbestos, as used commercially, may contain low but varying concentrations of fibrous tremolite. The extent to which this increases the potential carcinogenicity of the commercial product must be kept in proportion. As stated earlier our most recent findings indicate that the excess mortality from malignant disease in our cohort, some 80% of whom had then died, amounted to 38 deaths from mesothelioma and some 65

from lung cancer (Liddell *et al.*, 1997). These men, born 1891–1920, had worked through years of very high dust exposure yet with no discernible effect on mortality from lung cancer below an accumulated exposure of about 1000 (fibres/ml)×years and no case of mesothelioma among over 4000 men employed for less than 2 years. At present-day levels of exposure to commercial chrysotile, whether or not contaminated with tremolite, the risk must be vanishingly small. Full reports on mortality from mesothelioma and from lung cancer in the cohort, with emphasis on the estimation of risk in relation to quantitative and qualitative aspects of exposure, will be published shortly.

The discrepant risks of lung cancer in textile workers are not explained by our findings but tend to suggest that the factors responsible were specific to asbestos textile processes, not only in Charleston, South Carolina, but also in Mannheim, Pennsylvania (McDonald *et al.*, 1983b) and in Rochdale, England (Peto *et al.*, 1985), where important amounts of crocidolite were incorporated in the process. All three textile plants showed a similar high level of lung cancer risk, with few cases of mesothelioma in Charleston but many in both Mannheim and Rochdale.

The far greater durability in lung tissue of amphibole than chrysotile fibres underlines the importance of biopersistence in carcinogenicity and of avoiding this quality when selecting man-made fibres for industrial use.

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