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MESOTHELIOMA IN QUEBEC CHRYSOTILE MINERS AND MILLERS: EPIDEMIOLOGY AND AETIOLOGY

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Abstract—In a cohort of some 11 000 men born 1891–1920 and employed in the Quebec chrysotile production industry, including a small asbestos products factory, of 9780 men who survived into 1936, 8009 are known to have died before 1993, 38 probably from mesothelioma—33 in miners and millers and five in factory workers. Among the 5041 miners and millers at Thetford Mines, there had been 4125 deaths from all causes, including 25 (0.61%) from mesothelioma, a rate of 33.7 per 100 000 subject-years; the corresponding figures for the 4031 men at Asbestos were eight out of 3331 (0.24%, or 13.2 per 100 000 subject-years). At the factory in Asbestos, where all 708 employees were potentially exposed to crocidolite and/or amosite, there were 553 deaths, of which five (0.90%) were due to mesothelioma; the rate of 46.2 per 100 000 subject-years was 3.5 times higher than among the local miners and millers. Six of the 33 cases in miners and millers were in men employed from 2 to 5 years and who might have been exposed to asbestos elsewhere, otherwise, the 22 cases at Thetford were in men employed 20 years or more and the five at Asbestos for at least 30 years. The cases at Thetford were more common in miners than in millers, whereas those at Asbestos were all in millers. Within Thetford Mines, case-referent analyses showed a substantially increased risk associated with years of employment in a circumscribed group of five mines (Area A), but not in a peripherally distributed group of ten mines (Area B); nor was the risk related to years employed at Asbestos, either at the mine and mill or at the factory. There was no indication that risks were affected by the level of dust exposure. A similar pattern in the prevalence of pleural calcification had been observed at Thetford Mines in the 1970s. These geographical differences, both within the Thetford region and between it and Asbestos, suggest that the explanation is mineralogical. Lung tissue analyses showed that the concentration of tremolite fibres was much higher in Area A than in Area B, a finding compatible with geological knowledge of the region. These findings, probably related to the far greater biopersistence of amphibole fibres than chrysotile, have important implications in the control of asbestos related disease and for wider aspects of fibre toxicology © 1997 British Occupational Hygiene Society. Published by Elsevier Science Ltd

INTRODUCTION

In 1966, a cohort of some 11 000 men, born 1891 through 1920 and employed for one month or more in the mining and milling of chrysotile in the Eastern Townships of Quebec, or in a small asbestos products factory, was registered for study. After exclusion of men lost to view, almost all after very short employment before 1935, the cohort consisted of 9780 men: 4175 registered in the main complex of mines and

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mills, under one ownership for many years, in the area of Thetford Mines, where production started in 1878; 866 in six smaller mines in the same region, the largest (with 358 men in the cohort) set up a few years later, but the rest much more recently, the latest in 1965; 4031 men in the mine and mill opened in 1882 in a town called Asbestos; and 708 in the asbestos products factory there, which was owned by the same mining company.

Analyses of mortality have been published at intervals since 1971, the most recent on deaths to 1992 (Liddell *et al.*, 1997). At this point, a total of 8009 men were known to have died, including 38 probably from mesothelioma. With three quarters of the cohort dead and the youngest survivor aged 72, an almost complete picture of mortality from this disease can now be seen.

Although brief references have been made to the occurrence of mesothelioma in all our reports on the cohort since the first (McDonald *et al.*, 1971), no previous attempt has been made at a comprehensive description. Initially there were very few cases; later, when the number had grown to a dozen or so their classification by place of employment and exposure remained difficult to explain. Now, with more knowledge of the widely differing opportunities for exposure of the cohort to amphibole fibres—commercial and naturally occurring—a clearer and more interpretable pattern has emerged. The body of this paper is arranged in three main sections, first a full description of the cases, second an analysis of exposure-response and third an examination of the question of fibrous tremolite in the aetiology of mesothelioma.

The rate of mortality from this disease was much higher for the factory in Asbestos than for the other employees in that town, but our main objective relates to miners and millers there and at Thetford Mines.

THE CASES

Ascertainment

The total of 38 cases was arrived at by investigating: all deaths in which the term mesothelioma was mentioned on the death certificate; deaths coded since 1978 to ICD* 163; and by ongoing ascertainment of malignant mesothelioma through all Canadian pathologists, 1966–1984. In addition, data from recent studies by Quebec investigators with special interest in mesothelioma, notably Bégin *et al.* (1992) and Case *et al.* (1997), were used. Included are deaths where in our opinion, after review of all accessible clinical and pathological sources of information, the cause was a primary malignant mesothelial tumour, more likely than not. The diagnosis was confirmed by full autopsy in 27 cases, but in eight of these the pathologist expressed an element of doubt. In the 11 cases without autopsy, the diagnosis was based on clinical evidence plus biopsy taken at open surgery, except one (TM1) diagnosed in 1956 by a needle biopsy only.

After review of all the available evidence, an admittedly subjective assessment of the diagnosis being correct was high in 19, moderate in 14, and low (though more likely than not) in five. Of the 38 cases, only 18 had been coded on the death

International Classification of Diseases, Ninth Revision.

certificate to ICD 163 and the rest to a variety of other diagnostic codes. In all cases the disease was pleural but in one (TM11) the peritoneum was also invaded.

Electron microscopic analyses of dried lung tissue have been made in all but six of the 27 cases of mesothelioma for which there was an autopsy. All the information which we have on the 38 cases is summarised in Table 1.

Trends

In the first report on mortality, to November 1966, there were three deaths ascribed to mesothelioma in a total of 2413 (0.12%) and in the last, to 1992, the proportion had become 38 in 8009 (0.47%). The pattern of increasing mortality is seen below:

	Before 1950	1950–1974	1975–1984	1985–1992
Total deaths	857	3405	2208	1539
Mesothelioma	0	6	15	17
Proportional mortality	0	0.18%	0.68%	1.10%

This trend undoubtedly reflects the long latent period for this tumour—and possibly also some increase in diagnostic awareness.

Latency

The time from first employment to death for the 38 cases ranged from 21 to 60 years (mean 47 years).

Employment

After exclusion of men lost, almost all before 1935, the net entry and total deaths of men first employed in the mines and mills of Thetford were 5041 and 4125, of which 25 (0.61%) were from mesothelioma, and for the mine and mill at Asbestos 4031 and 3331 of which eight (0.24%) were due to mesothelioma; the corresponding figures for the factory in Asbestos were 708 and 553 of which five (0.90%) were from this cause.

It can be seen in Table 1 that of the 38 cases, eight were employed for only 2–5 years, whereas duration of employment in the remaining 30 cases ranged from 20 to 49 years, with very similar average periods in the three groups (Thetford Mines 35 years, Asbestos 36 years, factory 33 years). This raises the question of whether the eight cases with short employment were caused by exposure to asbestos elsewhere. However, of the two cases in the factory, one was in a man (F1) known to have worked for 3 years during the carding of pure crocidolite for military gas mask filters (McDonald and McDonald, 1978) and whose dried lung at autopsy contained 3.96 crocidolite fibres per μg, and the other was in a man (F3) who worked over the same period, but without autopsy or lung burden analysis. Of the six cases among miners and millers, the diagnostic probability was high in one (A7), moderate but with autopsy in four (TM21, TM25, A1 and A4) and moderate without autopsy in one (TM9). These six cases were in men who had spent almost all their working lives outside the Quebec mining industry, and in four (TM21, TM25, A4 and A7) it is conceivable that their other known employment entailed asbestos exposure. The scanty information which we have about their work outside the mining industry is summarised below, with ages in parenthesis; also shown are the three available results of lung burden analysis in fibres per μg.

Table 1. The 38 deaths from malignant mesothelioma

No. (ICD)	Autopsy Yes/No	Diagnostic probability	Year of birth	Year first employed	Year of death	Start to death (years)	Years employed (gross)	Years employed (excluding 20 years prior to death) in mine	Years employed (excluding 20 years prior to death) in mill	Lung fibre analysis (fibres per μg) Chrysotile	Tremolite	Crocidolite	Amosite
Thetford Mines													
TM1 162	No	low	1916	1935	1956	21	20	1					
TM2 212	No	moderate	1904	1919	1964	45	44	24					
TM3 212	Yes	moderate	1894	1937	1967	30	25	10					
TM4 215	Yes	high	1910	1928	1972	44	38	8	16*	8.4	32.7	0	0
TM5 420	Yes	high	1907	1920	1975	55	20		20	0.2	82.1	0	0
TM6 163	Yes	high	1911	1923	1975	52	43	10	10	9.4	238.8	0	0
TM7 163.0	Yes	high	1912	1926	1976	50	48	15	15*	11.2	13.1	0	0
TM8 228	No	moderate	1898	1928	1977	49	36	6	21*				
TM9 163.9	No	moderate	1909	1923	1979	56	2		2				
TM10 163.9	Yes	high	1915	1937	1983	46	42	26		4.0	40.0	0	0
TM11 199.1	Yes	moderate	1917	1935	1983	48	40		28	170.0	2040.0	0	0
TM12 162.9	Yes	high	1917	1929	1984	55	38	job history lost		15.0	112.0		
TM13 163.9	No	low	1914	1931	1985	54	33	33					
TM14 571.2	Yes	moderate	1916	1947	1985	38	34	7	11	32.1	100.6	0	0
TM15 163.9	Yes	high	1908	1937	1985	48	36		28*	45.0	243.0	0	0
TM16 163.9	No	low	1907	1940	1985	45	32	5	20				
TM17 199.1	Yes	high	1915	1942	1986	44	38	22	2	54.0	256.0	0	0
TM18 163.5	Yes	high	1918	1937	1987	50	45	30		17.6	433.7	0	0
TM19 163.9	No	low	1917	1937	1987	50	45	30					
TM20 163.9	Yes	high	1910	1928	1988	60	47	39		81.0	1190.0	0	0
TM21 162.9	Yes	moderate	1917	1939	1988	49	5	5					
TM22 163.9	No	moderate	1912	1954	1990	36	23	16					
TM23 199.1	Yes	high	1904	1935	1991	56	31	31		56.4	1051.6	0	0
TM24 199.1	Yes	high	1918	1935	1991	56	31	7	18*	2.5	12.6	0	0
TM25 163.9	Yes	moderate	1918	1938	1991	53	2		2	1.6	0.6	0	0

Asbestos													
A1 163	Yes	moderate	1902	1918	1966	48	3	1	2	11.1	8.9	0	0
A2 212	Yes	high	1910	1936	1967	31	30		11[a]				
A3 162.9	Yes	high	1917	1935	1980	45	45		25[a]	19.9	34.2	14.7	0
A4 163.9	Yes	moderate	1919	1936	1980	44	2	2					
A5 162.9	Yes	high	1919	1936	1983	47	37		27[a]	12.0	13.6	7.0	0.7
A6 163.9	Yes	high	1918	1944	1984	40	38		13[a]				
A7 410	Yes	high	1909	1936	1985	49	3	1	3[a]	0	0	0.7	0
A8 163.9	Yes	high	1915	1937	1987	50	39		30	5.8	57.6	2.0	1.5
Factory													
F1 162.1	Yes	moderate	1918	1940	1977	37	3			7.6	0	4.0	0
F2 163.0	No	moderate	1901	1922	1978	56	23	1	2				
F3 162.9	No	low	1919	1940	1978	38	5						
F4 163.9	No	moderate	1910	1926	1985	59	49						
F5 199	Yes	high	1920	1948	1986	38	28			0.6	2.2	10.1	1.0

[a] Tradesman

TM9	baker (16–38); hotelier (38–70)	
TM21	watchman (27–70)	
TM25	welder (22–27); salesman (28–65)	chrysotile 1.6; tremolite 0.6
A1	barber (20–60)	chrysotile 11.1, tremolite 8.9
A4	army (25–29); truck mechanic (29–61)	
A7	mining engineer (20–27); professor of engineering (30–65)	crocidolite 0.7

The concentration of tremolite fibres in the lungs of the barber (A1) was perhaps related to the quality of talc used in his work.

Excluding the factory workers, 9072 miners and millers of chrysotile at Thetford Mines and Asbestos were traced of whom 7456 (82%) have died, 33 from suspected mesothelioma (PMR 0.44%). No case was identified in some 4000 men employed less than 2 years (McDonald *et al.*, 1994) and it is possible that the six cases in men employed from 2 to 5 years were attributable to some other source of asbestos exposure. The 27 remaining cases were in men employed in the mines or mills for between 20 and 48 years; whereas all but three of the 22 from Thetford Mines had worked at some time as miners, none of the five at Asbestos had done so. Of the eight cases of men at Thetford or Asbestos who had never worked in mining, five had been employed mainly as tradesmen, for example, as mechanics, electricians, or carpenters.

Lung tissue analyses

Of the 27 cases of mesothelioma for which there was an autopsy, electron microscopic analyses of dried lung tissue have been made in 19 miners and millers, including five from Asbestos, and two factory workers (Churg *et al.*, 1993; Case *et al.*, 1997); detailed results are in Table 1. Given the possible effects of selection, small numbers, the inevitable uncertainty of diagnosis and the absence of controls or denominators, questions of risk and causation cannot be addressed; nevertheless, the findings, summarised in Table 2, are informative. It is fairly clear that tremolite fibres predominated in the lungs of miners and millers who died of mesothelioma, especially in Thetford Mines, although these men were exposed overwhelmingly to chrysotile; however, in the two factory workers and in three of the five miners and millers from Asbestos there were substantial concentrations of crocidolite.

Mortality rates

Liddell *et al.* (1997), presented in their table 9 mesothelioma death rates per 100 000 subject-years, 1945–1992, for miners and millers, after age 55, by place of

Table 2. Asbestos fibre concentrations in lungs at autopsy from 21 mesothelioma cases (fibres per μg: geometric means[a])

Place of employment	No. of cases	Chrysotile	Tremolite	Crocidolite	Amosite
Mines and mills					
Thetford Mines	14	12.8	104.1	[b]	[b]
Asbestos	5	4.3	7.5	1.7	0.3
Factory					
Asbestos	2	2.1	0.5	6.4	0.3

[a]In calculating geometric means, a zero count has been replaced by half the detectable limit.
[b]All counts were zero, that is below the detectable limit.

employment and according to exposure accumulated by age 55. There was little evidence that risk was related to cumulative exposure, and so it is not unreasonable to quote rates on the same bases but regardless of the degree of exposure: after exclusion of the one death at age 40 (TM1), they were as follows:

	Number of mesothelioma deaths	Subject-years (000s)	Rate (per 100 000 subject years)
Thetford Mines:			
main complex and the oldest of the smaller mines	23	65.14	35.3
the five smallest mines	1	6.01	16.6
Asbestos			
mine and mill	8	60.64	13.2
factory	5	10.84	46.2

There are two main reasons for the low rate for the five smallest mines: the employees within the cohort were considerably younger than elsewhere, that is, few of them had been born before 1900; and the mines had started so recently that there were inadequate periods of latency. The other rates are reasonably comparable. It can be seen that the rate for miners and millers was over 2.5 times higher at Thetford Mines (excluding the smallest mines) than at Asbestos ($P \approx 0.015$), and the rate for the factory was 3.5 times that for mine and mill in Asbestos ($P \approx 0.02$).

EXPOSURE-RESPONSE

To examine exposure–response relationships within place of employment, we sought ten referents for each case except the three from the smaller mines in the Thetford region (TM12, TM21 and TM22). The selection criteria were that, relative to the case, the referent must have had a similar date of birth and survived to a greater age, and must have started work at the same place of employment, that is either at the main complex in Thetford Mines or at the mine and mill in Asbestos or in the factory there, and at a similar age. For most of the cases, more than ten men met these criteria, and a random selection was made. However, for four cases (TM3, TM23, TM6 and F4), we could find only six, five, three and two referents, respectively. There were thus 326 referents in all for the 35 cases.

For these 361 subjects we calculated eight measures of exposure as follows: net service (years, adjusted for work-week*, and excluding gaps in employment); years (adjusted) worked in each of six dust categories defined† in terms of million particles per cubic foot (mpcf); and accumulated dust exposure (mpcf × years). For a case, the calculations were carried out up to 10 years before death; for a referent, they were carried out up to 10 years before he reached the age at which the relevant case died.

Conditional logistic regression analysis by means of the EGRET package (Statistics and Epidemiology Research Corporation, 1989), and assuming multiplicative relative risks, provided likelihood ratio (LR) statistics which are given in Table 3; those in the last line of this table were obtained after pooling years in

*The working week had been of 60–72 h before 1938, 48 h 1938–1949, and 40 h thereafter; see Liddell *et al.* (1997) for details of adjustments.

†Definitions are not given because of the completely negative findings: see Table 3.

Table 3. Likelihood ratio (LR) statistics, with degrees of freedom in brackets

	Thetford Mines	Asbestos	
	Main complex	Mine and mill	Factory
Net service (adjusted years)	7.94 (1) $P=0.005$	0.04 (1) $P=0.85$	0.00 (1) $P=0.99$
Accumulated dust exposure (mpcf x years)	0.13 (1) $P=0.72$	0.30 (1) $P=0.58$	0.16 (1) $P=0.69$
Years (adjusted) worked in different dust categories	0.79 (2) $P=0.68$	0.54 (3) $P=0.91$	Did not converge

adjacent dust categories, to avoid purported protective effects, and thus reducing the degrees of freedom. The LR statistics can be referred to the χ^2 distribution with the stated degrees of freedom and the corresponding approximate P values are included in the table; all but one lie between 0.58 and 0.99, implying minuscule effects. However, that for net service at the main Thetford complex is of undoubted statistical significance: the corresponding odds ratio relating to 20 years service is 2.31, with 90% confidence limits of 1.35 and 3.93.

The opportunity was taken to compare risks among cases and referents at the main complex in Thetford Mines in non- and ex-smokers with those of cigarette smokers: the LR statistic with 1 degree of freedom was only 0.13 ($P \approx 0.91$), about as close as it is possible to get to 'proving a negative'.

THE TREMOLITE HYPOTHESIS

Background

When this cohort was set up in response to international requests for study of the effects on human health of exposure to pure chrysotile and other asbestos fibre types, no serious thought was given to the possibility that the Quebec ore body might contain mineral fibres other than chrysotile. Nor was it thought that the known use of crocidolite in the small products factory in Asbestos was of any scientific importance, even given the possibility of unrecorded movement of workers between it and the mines and mills. Soon, however, evidence that the situation was not so simple began to unfold.

First, it was found that in our initial large scale morbidity surveys of current and past workers, there were qualitative and quantitative differences in exposure-response between Thetford Mines and Asbestos, assessed radiographically (Rossiter *et al.*, 1972). Parenchymal changes were more frequent and more systematically related to estimates of cumulative dust exposure in Thetford Mines than in Asbestos. Pleural changes showed even bigger differences in that calcification was common in Thetford, but very seldom seen in Asbestos. As the chrysotile seemed reasonably similar in the two areas, some other geological explanation seemed probable, at least for the pleural changes. The results of a special study of pleural calcification among workers in Thetford Mines by Gibbs (1979) supported this view. These changes were more common among miners than millers and much more common in men who had worked in a localised central group of mines than in other

mines located peripherally. Gibbs concluded that the cause might be related to some mineral closely associated with chrysotile, possibly mica, talc or brünnerite.

A few years later studies of lung tissue at autopsy from miners and millers in the Thetford area revealed the unexpected finding that, despite overwhelming exposure to chrysotile, amphibole fibres in the tremolite series were present in similar or greater concentration (Pooley, 1976; Rowlands *et al.*, 1982; Churg *et al.*, 1984). This led to speculation as to the relative importance of chrysotile and tremolite fibres in the causation of human disease. Indications that this was no academic question were shown by cohort mortality and radiographic studies of vermiculite miners and millers in Montana exposed to contamination by amphibole fibres in the tremolite series but to no other type of asbestos (Amandus *et al.*, 1988; Armstrong *et al.*, 1988). In terms of radiographic changes and mortality from lung cancer and mesothelioma the results of fibrous tremolite exposure were on a par with crocidolite and thus might explain much of the disease observed in chrysotile miners and millers.

Geographical distributions

By the end of 1988, 33 deaths from mesothelioma had been identified in the cohort, sufficient to show that the risk of this disease was two to three times higher in miners and millers from Thetford Mines than from Asbestos and perhaps higher still in factory workers (McDonald *et al.*, 1994). A small number of lung tissue samples taken at autopsy from ex-employees in the 1980s showed that fibrous tremolite was present in both regions but that the level of exposure may have been about three times higher in Thetford.

By the end of 1992, the total number of cases had grown to 38, all but five in miners and millers, 25 from Thetford Mines and eight from Asbestos. A detailed analysis of work histories showed that the cases from Thetford were predominantly men who had been employed in a localised area of five central mines (Area A) rather than in ten mines located peripherally (Area B) (McDonald and McDonald, 1995). Lung burden analyses made some years earlier by Sébastien *et al.* (1989) subsequently indicated that concentrations of tremolite fibres, but not of chrysotile, were some four times higher in Area A than Area B. Moreover, the mines in Area A were the same as those identified by Gibbs (1979) as carrying the highest risk of pleural calcification. A recent re-analysis of representative samples of fibres from the study by Sébastien *et al.* (1989) showed no important difference in dimensions or elemental composition of either chrysotile or tremolite between the two areas.

Geological evidence

The potential importance of geographical differences in the distribution of tremolite warrants some consideration of the geology of the region, well described by Riordon (1957). Among the amphiboles, tremolite was rarely mentioned nor its form, whether fibrous or not. The chrysotile in Area A tends to be less harsh than in Area B. Differences between mines were examined in a search for the aetiology of pleural calcification by Gibbs (1972). He noted that the distribution by mine of more than 150 mineral/rock types, indicated that rarely did a specific mineral occur in Area A which was not also found in Area B.

A key factor in tremolite occurrence may be the frequency and nature of what have been termed 'acid/syenitic/aplitic/felspathic' dykes. In Area A, these numerous acid dykes occur as irregular shapes, often at shear zones in the serpentinised rock. According to Cooke (1937) the freshest dykes consisted mainly of oligoclase feldspar altered through kaolinisation to 'needles of tremolite, actinolite and colourless pyroxene'. Later, Riordon (1957) noted that serpentinised peridotite near contact points with acid dykes was converted to talc and tremolite. While tremolite had been noted to occur at the margins of dykes in Area B, the pattern in Area A would probably result in tremolite, some in fibrous form, being mined with the ore. The mineral assemblages associated with tremolite in commercial chrysotile samples (Addison and Davies, 1990) are not dissimilar from those predicted for Area A if tremolite were derived from 'acid' intrusive alteration. This adds credence to acidic dykes being the main factor in the higher exposure of workers in Area A to tremolite.

The hypothesis tested

Following the preliminary report by McDonald and McDonald (1995), a formal test of the hypothesis that the risk of mesothelioma was higher in the mines with substantial tremolite contamination was made as follows. The detailed work histories of all cases and referents at the main complex in Thetford Mines were re-examined and for every man each period of employment was classified as in the central or the peripheral area. One case (TM15) and six referents had to be eliminated because of frequent unrecorded moves between Areas A and B; also eliminated were the 10 referents of case TM15 and another because his work record could not be found. For the remaining 21 cases and 187 referents, periods of service (calendar years, without adjustment for work week) were calculated: for cases, up to 10 years before death; for referents, to the corresponding age of the relevant case. Of the 208 subjects, 104 (class C) had been employed only in the central mines and a further 69 (class P) only in peripheral mines, while 35 (class M) had had jobs in both areas. The EGRET package was again used to carry out conditional logistic regression analysis. The analyses reported in the first column of Table 3 were repeated: the results were almost identical, indicating that the exclusions had had virtually no effect. The introduction of class (C, M or P) as a factor into the analyses indicated lower risks for men in class P than for the other men. After pooling classes C and M, the LR statistic for the improvement in the fit of net service, with a single degree of freedom, was 6.33 ($P \approx 0.01$). From the corresponding odds ratios in Table 4, it is clear that service in the central area led to definite risks of mesothelioma. However, the odds ratio for class P is rather unstable, as shown by

Table 4. Odds ratios (with 90% confidence limits) at the main complex in Thetford Mines

	Some or all years in central area[a]	All years in peripheral area[b]
Net service (20 adjusted years)	2.50 (1.49–4.20)	0.80 (0.27–2.38)
Accumulated dust exposure (300 mpcf×years)	1.28 (0.94–1.75)	0.32 (0.06–1.76)

[a]Classes C and M.
[b]Class P.

the very wide confidence intervals, and as the point estimate is well below unity it is quite unrealistic. The slight indication that the risk in the central area was related to cumulative exposure is almost certainly a statistical artefact arising out of the negative tendency in the peripheral area (the difference between areas being associated with a 'significant' LR statistic). One of the reasons that the estimates for class P are so unreliable is that it contained only three cases (TM1, TM3 and TM14).

A further analysis was carried out of net service in the two areas: it showed the odds ratio in relation to 20 years work in the central area to be 2.55 (90% confidence interval 1.52–4.27), a finding of high statistical significance compared to an odds ratio of 1.11 (with very wide confidence interval, 0.47–2.62, and hence negligible significance: $P \approx 0.84$) in the peripheral area; see also McDonald and McDonald (1997). These odds ratios and those in Table 4 in relation to net service are entirely compatible with that of 2.31 quoted above under Exposure–Response, particularly in the light of methodological differences.

CONCLUSION

Of the 38 deaths from mesothelioma in this cohort, 27 were in miners and millers with employment ranging from 20 to 48 years, and we conclude from the evidence presented that these 27 deaths can be attributed with reasonable certainty to occupational exposure in the Quebec chrysotile production industry. For the six further cases of men who worked in the mines and mills, employment was by contrast for only 2–4 years, and causation is more doubtful. This does not, however, affect our main conclusions; in particular, these cases were included in the analyses.

In the factory, where the mesothelioma mortality rate was over three times higher than in miners and millers at Asbestos, two of the five cases were also in men employed for less than 6 years, but they were present in the plant in the years 1940–[illegible] when crocidolite was being used in the manufacture of military gas mask filters and were known to have worked near the carding operation. We believe therefore that all five cases in factory workers should probably be attributed to work in the plant, where all employees were potentially exposed at some time to crocidolite and/or amosite, which could reasonably account for the greater risk. This finding, although undoubtedly important, is not relevant to the main concern of this report.

That concern is with the aetiology of the 33 cases in miners and millers, 25 at Thetford Mines in a total of 4125 deaths from all causes (PMR 0.61%), and eight at Asbestos among 3331 deaths (0.24%). Within Thetford Mines, there is clear evidence from case-referent analyses that the risk arising from employment in the localised area of central mines in the main complex (Area A) was much higher than in the peripherally located mines (Area B), where it was minuscule. A similar pattern of risk was documented for pleural calcification in the 1970s. As we have no reason to suspect that geographical variation in the character of chrysotile *per se* could account for these differences, the presence of other minerals in or near the ore body would appear to offer the best explanation. The only candidate capable of filling the role is fibrous tremolite, and there is considerable supporting evidence. Its pathogenicity and carcinogenicity have been amply demonstrated and lung burden analyses suggest that its geographical distribution in the mining region is closely related to the pattern of mesothelioma risk. Geological knowledge, so far as

it goes, is also compatible with this hypothesis. It does not follow that pleural calcification and mesothelioma have the same mineralogical cause, although the agents must be closely linked geologically. Indeed, there is no consistent correlation between the prevalence of pleural calcification and mesothelioma incidence in general populations or occupational groups (see McDonald, 1997).

The fact that the risk of mesothelioma was strongly related to years of service in the central area at Thetford, but hardly at all to accumulated dust exposure, suggests that employees were exposed to tremolite intermittently, probably at different intensities for periods of variable lengths and at irregular and fairly infrequent intervals, and that the concentrations of tremolite fibres in the working environment were only poorly—if at all—related to prevailing dust levels. This is entirely reasonable having regard for the local geology and the nature of the mining operations.

In Asbestos, Quebec, where amphiboles were used in the factory from time to time, there was not inconsiderable movement of labour between the factory and the mill, and, perhaps, mine, so that a substantial proportion of those registered as miners or millers will have worked in the factory, and of course *vice versa*. Further, some crocidolite was processed in the mill. It is not therefore surprising that crocidolite and to a lesser extent amosite fibres were found in the lungs of cases from both the factory and the mill; no such fibres were found in the lungs of the 14 autopsied cases at Thetford Mines. There must also have been some exposure to tremolite, although to nothing like the same extent as in the central area of Thetford Mines.

The tremolite hypothesis, if correct, has several important implications. First, it supports the widely but not universally held view that most, if not all, asbestos-related mesotheliomas are caused by amphibole fibres. This in turn points to fibre durability and biopersistence as critical factors in aetiology (McDonald, 1994), a point of even greater relevance in assessing the safety of man-made mineral fibres. Second, it implies that uncontaminated chrysotile carries very little risk of mesothelioma. In Asbestos, exposures were not to uncontaminated chrysotile, but also to some tremolite and crocidolite, yet among the miners and millers only five deaths from a total of over 3300 can be confidently attributed to their work.

At present day levels of dust control the mesothelioma risk must be vanishingly small. Even so, it remains desirable to minimise, perhaps by screening, the contamination of commercial chrysotile by amphibole fibres, however difficult this may be.

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REFERENCES

Addison, J. and Davies, L. S. T. (1990) Analyses of amphibole in chrysotile and other minerals. *Annals of Occupational Hygiene* **34**, 159–175.

Amandus, H. E., Armstrong, B. G., McDonald, A. D., McDonald, J. C., Sébastien, P. and Wheeler, R. (1988) Mortality of vermiculite miners exposed to tremolite. *Annals of Occupational Hygiene* **32**, 459–465.

Armstrong, B. G., McDonald, J. C., Sébastien, P., Althouse, R., Amandus, H. E. and Wheeler, R. (1988) Radiological changes in vermiculite workers exposed to tremolite. *Annals of Occupational Hygiene* 32, 469–473.

Bégin, R., Gauthier, J. J., Desmeules, M. and Ostiguy, G. (1992) Work related mesothelioma in Québec, 1967–1990. *American Journal of Industrial Medicine* 22, 531–542.

Case, B., Churg, A., Dufresne, A., Sébastien, P., McDonald, A. D. and McDonald, J. C. (1997) Lung fibre content for mesothelioma in the 1891–1920 birth cohort of Québec chrysotile workers: a descriptive study. *Annals of Occupational Hygiene* 41 (Supplement 1–*Inhaled Particles VIII*), 231–236.

Churg, A., DiPaoli, L., Kempe, B. and Stevens, B. (1984) Lung asbestos content in chrysotile workers with mesothelioma. *American Review of Respiratory Diseases* 130, 1042–1045.

Churg, A., Wright, J. L. and Vedal, S. (1993) Fiber burden and patterns of disease in chrysotile miners and millers. *American Review of Respiratory Diseases* 148, 25–31.

Cooke, H. C. (1937) Geological Survey Memoir 211. Thetford, Disraeli and half of the Warwick map-areas, Québec, Canada. Dept of Mines and Resources. Ottawa, King's Printer.

Gibbs, G. W. (1972) The epidemiology of pleural calcification. Ph.D. Thesis, McGill University.

Gibbs, G. W. (1979) Etiology of pleural calcification: a study of Québec asbestos miners and millers. *Archives of Environmental Health* 34, 76–82.

Liddell, F. D. K., McDonald, A. D. and McDonald, J. C. (1997) The 1891–1920 birth cohort of Québec chrysotile miners and millers: development from 1904 and mortality to 1992. *Annals of Occupational Hygiene* 41, 13–36.

McDonald, A. D., Liddell, F. D. K. and McDonald, J. C. (1994) Malignant mesothelioma in Québec chrysotile miners and millers: a preliminary report. DHHS (NIOSH) publication No. 94-112, pp. 225–228.

McDonald, A. D. and McDonald, J. C. (1978) Mesothelioma in persons exposed to crocidolite in gas mask manufacture. *Environmental Research* 17, 340–346.

McDonald, J. C. (1994) Epidemiological significance of mineral fibre persistence in human lung tissue. *Environmental Health Perspectives* 102, 221–224.

McDonald, J. C. (1997) Some observations on the epidemiology of benign pleural disease. *Indoor and Built Environment* 6, 96–99.

McDonald, J. C. and McDonald, A. D. (1995) Chrysotile, tremolite, and mesothelioma. *Science* 267, 775–776.

McDonald, J. C. and McDonald, A. D. (1997) Chrysotile, tremolite and carcinogenicity. *Annals of Occupational Hygiene* 41, 699–705.

McDonald, J. C., McDonald, A. D., Gibbs, G. W., Siemiatycki, J. and Rossiter, C. E. (1971) Mortality in the chrysotile asbestos mines and mills of Québec. *Archives of Environmental Health* 22, 677–686.

Pooley, F. D. (1976) An examination of the fibrous mineral content of asbestos in lung tissue from the Canadian chrysotile mining industry. *Environmental Research* 12, 281–298.

Riordon, P. H. (1957) The Asbestos belt of South Eastern Québec: the Asbestos deposits of Thetford Mines, Québec: the British Canadian Mine: Normandie and Vimy Ridge Mines. In *The Geology of Canadian Industrial Mineral Deposits: 6th Commonwealth Mining and Metallurgical Congress*, pp. 1–30.

Rossiter, C. E., Bristol, L. J., Cartier, P. H., Gilson, J. G., Grainger, T. R., Sluis-Cremer, G. K. and McDonald, J. C. (1972) Radiographic changes in chrysotile asbestos mine and mill workers of Quebec. *Archives of Environmental Health* 24, 388–400.

Rowlands, N., Gibbs, G. W. and McDonald, A. D. (1982) Asbestos fibres in the lungs of chrysotile miners and millers—a preliminary report. *Annals of Occupational Hygiene* 26, 411–415.

Sébastien, P., McDonald, J. C., McDonald, A. D., Case, B. and Harley, R. (1989) Respiratory cancer in chrysotile textile and mining industries: exposure inferences from lung analysis. *British Journal of Industrial Medicine* 46, 180–187.