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Commentary

Epidemiology of Malignant Mesothelioma—An Outline

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In the 1960s and 1970s, well designed case-referent studies put beyond doubt that exposure to airborne asbestos fibres was a cause of malignant mesothelioma. Some 35 cohort mortality studies in a large variety of industries during the 20-year period, 1974–1994, showed a wide range of outcomes, but in general that the risk was higher in exposures which included amphiboles rather than chrysotile alone. Real progress began, however, with discoveries along several lines: the link between pleural changes and mineralogy, the concept and importance of biopersistence, the developments in counting and typing mineral fibres in lung tissue, and data on amphibole mining in South Africa and Australia for comparison with that on chrysotile in Canada and Italy. This led to the recognition of the potential contamination in North America of chrysotile with tremolite. A survey in Canada in 1980–1988 and other surveys demonstrated that crocidolite, amosite, and tremolite could explain almost all cases of mesothelioma. Effective confirmation of this was finally achieved with data on vermiculite miners in Libby, Montana, in the years 1983–1999, where exposure was to tremolite–actinolite and/or other amphibole fibres alone.

Keywords: asbestos; Canada; chrysotile; Libby; mesothelioma; Quebec; tremolite

INTRODUCTION

The first clear evidence of a causal link between asbestos exposure and primary malignant tumours of the mesothelium was the observation by Wagner *et al.* (1960) of 33 cases of pleural mesothelioma in the Northwest Cape Province of South Africa, 28 in persons who had lived close to the crocidolite mines, mostly as children. Confirmation was provided by eight case–control studies published in 1965–1975, based on a total of 657 cases, predominantly male, exposed to asbestos mainly in shipyards, heating trades, insulation, and factory work (see Table 1) (McDonald and McDonald, 2005). Relative risks ranged from 2.3 to 7.0. An important early event was the 1964 conference in New York on the Biological Effects of Asbestos, at which several confirmatory findings were reported; notably, a study by the Selikoff group of 632 men employed on insulation work in 1942 of whom, by 1964, 307 had died, 10 from mesothelioma—4 pleural and 6 peritoneal (Hammond *et al.*, 1965). At the end of the conference, a Working Group of the International Union against Cancer (UICC) made a series of recommendations, with emphasis on the need for studies of a single asbestos fibre type in countries where asbestos was mined and milled. Initially, this approach was taken only in the extensive chrysotile mines and mills of Quebec and in the similar but smaller industry of northern Italy. It was some 20 years before any comparable research was undertaken in the amphibole mining industries of South Africa and Australia. As a result, inevitable confusion was caused by the many cohort studies in secondary manufacturing and processing industries, in most of which both chrysotile and amphibole types of fibre were used.

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Table 1. Early case–control studies of mesothelioma giving definite or probable occupational exposure to asbestos[a]

Author group (year)	Place	Years diagnosed	Cases/ controls	Male (%)	Occupationally exposed (%)	Relative risk
Elmes *et al.* (1965)	Belfast	1950–1964	42/42	95	76	3.6
Newhouse and Thompson (1965)	London	1917–1964	76/76	49	41	3.9
McEwen *et al.* (1970)	Scotland	1950–1967	80/80	91	58	4.2
McDonald *et al.* (1970)	Canada	1960–1968	165/165	65	21	7.0
Rubino *et al.* (1972)	Piedmont	1960–1970	50/50	64	12	6.0
Ashcroft (1973)	Tyneside	1948–1967	27/56	88	93	2.3
Hain *et al.* (1974)	Hamburg	1958–1968	150/150	71	58	6.3
Zielhuis *et al.* (1975)	The Netherlands	1969–1971	67/67	94	72	4.0

[a]Based on Table 1 in McDonald and McDonald (1996).

RISK IN THE SECONDARY INDUSTRIES

In the 20-year period, 1974–1994, some 35 cohort studies were published based on asbestos exposure in manufacture or application in nine categories of industry. These were summarized in a detailed analysis presented by McDonald and McDonald (2005). Chrysotile only was used in 10 cohorts in four industries and amphibole only in 7 cohorts in two industries. In the chrysotile-only group, the proportional mortality rate (PMR) per thousand for mesothelioma in the four industrial categories was 2.5, 3.3, 3.9, and 5.6. In the amphibole-only group, the PMRs in the two different industrial categories were both 23.1. In the remaining 18 cohorts, both chrysotile and amphibole were used in five industrial categories, with PMRs ranging from 14.8 to 60.2. Since exposures were not defined qualitatively or quantitatively, these findings are difficult to interpret.

Three geographical surveys with case-referent analysis were more informative. A detailed review and analysis published in 1977 of all 4539 known cases based on reports from 22 countries (McDonald and McDonald, 1977) identified work with insulation materials in shipyards as by far the most common occupation. In 1980, the findings from ascertainment through all 7400 pathologists in the USA and Canada of all fatal mesothelial tumours gave a total of 668 cases, 1960–1975 (McDonald and McDonald, 1980). Occupational histories were obtained from most of the cases and from matched controls. Relative risks were 46.0 for insulation work, 6.1 for asbestos production and manufacture, and 4.4 for other heating trades. Specimens of lung tissue were obtained from 99 of the 172 autopsied case–control pairs and analysed by electron microscopy. Amosite fibres were found in 26 male cases and 8 controls and crocidolite in 15 cases and 5 controls. Equal quantities of chrysotile were found in cases and controls overall (McDonald *et al.*, 1982).

More recently, a survey was conducted in the UK of all reported cases of mesothelioma diagnosed in 1990–1996, in persons born 1943 or later. These criteria were chosen to ensure that these persons would have been employed at a time when the importation of crocidolite in the UK, but not amosite, had essentially ceased. Of these eligible cases, 140 (126 men and 14 women) were finally selected for study of detailed work histories and lung tissue samples taken at autopsy for lung fibre analysis. Of the 37 industrial occupations analysed, odds ratios were significantly raised in 8 of them—5 in the construction trades and the other 3 in shipbuilding, cement products, and non-metal mineral products (McDonald *et al.*, 2001b). It was estimated that crocidolite and amosite fibres (especially amosite) could account for 80–90% of cases; tremolite fibres were rarely found (McDonald *et al.*, 2001a).

LUNG-RETAINED FIBRE ANALYSES

The introduction in the 1970s of techniques for counting and typing mineral fibres in lung tissue allowed for greater specificity in exposure estimation in epidemiological studies, but not one that proved easy to achieve. Results from eight case-referent studies in six different countries are shown in Table 2 (McDonald and McDonald, 2005). They all show a substantial increase in odds ratios for amphibole fibres and little or none for chrysotile. These findings, however, apply only to the situation at time of death and cannot exclude the possibility of a role for chrysotile at an earlier stage. Much therefore depends on whether biopersistence is a quality on which aetiological potency depends; this in turn may be related to exposure intensity.

BIOPERSISTENCE

Though not yet completely understood, asbestos fibre types have been shown to vary considerably

Table 2. Analyses of mineral fibres in lung tissue from mesothelioma cases and controls

Author group (year)	Country	Cases	Controls	Odds ratio for amphibole fibres[a]	Evidence on chrysotile
Jones *et al.* (1980)	UK	86 cases notified by coroners and pathologists, 1976	56 cases (lung cancer 27, cerebrovascular disease 29, matched for age, sex, and place	7.4	Chrysotile present in two of four cases without amphiboles
McDonald *et al.* (1982)	Canada and USA	99 cases from survey of pathologists	Secondary lung cancer; matched for age, sex, date, and hospital	3.8	In pairs where amphibole content was $<10^6$ f g^{-1} closely similar distributions of chrysotile
Mowe *et al.* (1985)	Norway	14 cases, county cancer registry, 1970–1979	28 cases excluding malignant and chronic pulmonary disease matched for age, sex, year, and residence	8.5 (based on all types of amphibole fibre)	Fibre type not identified
Gaudichet *et al.* (1988)	France	20 cases from Nantes district, 1980–1982	20 each of adenocarcinoma and squamous carcinoma, secondary lung cancer and cardiovascular disease, matched for age, sex, and hospital	Amphibole fibre concentration two to three times higher than in controls	Similar concentration in cases and controls
McDonald *et al.* (1989)	Canada	78 cases from survey of pathologists, 1980–1984	Non-malignant non-respiratory disease, matched for age, sex, date, hospital, and type of sample	6.6 for fibres $\geq$8 μm in length	Low-level risk in univariate analysis and none in multivariate analysis
Rogers *et al.* (1991)	Australia	221 cases from national surveillance, 1980–1985	359 tissue samples from a hospital in Sydney excluding NMRD and abdominal cancer; unmatched	16.6 for fibres $\geq$10 μm in length	7 of 25 cases and 3 of 31 controls without amphibole fibres had $\geq 10^5$ f g^{-1} chrysotile
Rödelsperger *et al.* (1999)	Germany	66 cases from five German cities	66 cases undergoing lung re-section mainly for lung cancer, matched for age, sex, and region	4.5 for fibres $\geq$15 μ in clear linear dose–response	No increase in odds ratio
McDonald *et al.* (2001a)	UK	69 male cases aged $\leq$50 years at diagnosis	57 cases of accidental or sudden death of similar age, sex, and region	Related linearly to concentrations: 0.1–0.9 μg, 8.8 (1.8–43.5); 1.0–9.9 μg, 59.9 (9.0–40.0)	No significant increase in odds ratio

[a]Based on Table 17.3 in McDonald and McDonald (2005).

in the speed with which they are cleared from the lung (Sébastien *et al.*, 1987; McDonald, 1994). With amphiboles, clearance is slow, and if exposure continues, the concentration builds up, with increasing probability of adverse effects. Chrysotile, in contrast, has much lower biopersistence and is rapidly cleared from the lung. These characteristics thus offer a possible mechanism for the observed higher mesothelioma risks associated with amphibole exposure. Certainly, the early work by Wagner *et al.* (1974) on chrysotile and amosite and that in the 1980s by Sébastien *et al.* (1987) on chrysotile and amphiboles (see Figure 1) support this view. It is important nevertheless to recognize that mechanisms do not necessarily imply or explain causation. It is of note that tests of persistence are currently used for screening in the development of new man-made mineral fibres.

THE TREMOLITE FACTOR

When the extensive programme of epidemiological research in the asbestos production industry of Quebec began in the 1960s, it was believed that we were dealing with exposure to chrysotile only. It was soon evident, however, that pleural thickening

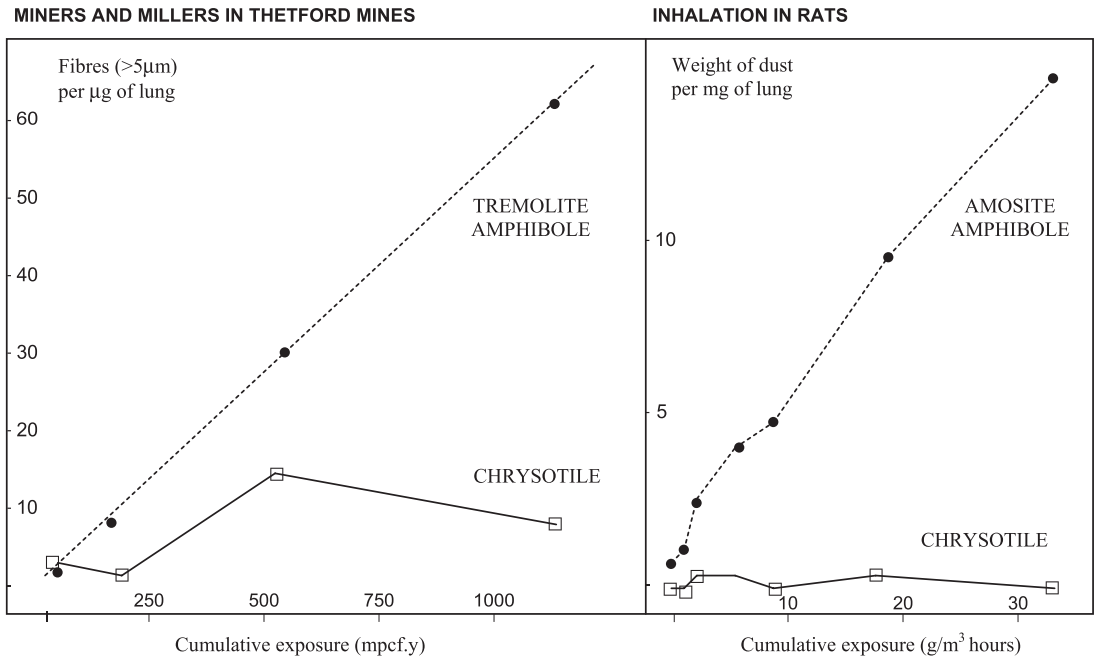


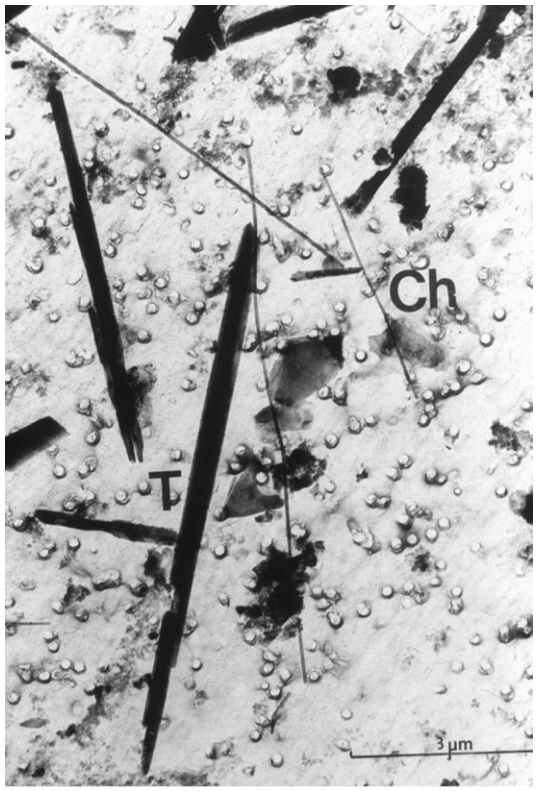
Fig. 1. Human and experimental data on the relationships between cumulative exposure to asbestos dust and lung retention (based on Sébastien *et al.*, 1987).

and calcification were very much more frequent in Thetford than in Asbestos. Detailed analyses by Gibbs in 1972 and 1979 (Gibbs 1972, 1979) showed that calcification and other pleural changes were much more prevalent in some mines than others, suggesting that minerals other than chrysotile could well be responsible. There followed electron microscopic studies by Pooley (1976) and Rowlands *et al.* (1982), which both showed that tremolite fibres were present in surprisingly similar concentrations to chrysotile in the lungs of Thetford employees (see Figure 2) (McDonald and McDonald, 2005) and later that this was two to three times more common in the Thetford region than in Asbestos. In the 1980s, Patrick Sébastien undertook the lung tissue analysis of 78 mesothelioma cases and matched controls in Canada, 1980 through 1984 (McDonald *et al.*, 1989). The results of this study indicated that long (>8 μm) amphibole fibres could have explained most cases of mesothelioma (attributable to asbestos) and other inorganic fibres, including chrysotile, very few. Fibrous tremolite was probably responsible for most cases in the Quebec mining region and for an unknown proportion elsewhere.

THE LIBBY ENIGMA

Clear evidence of carcinogenic potency from what was initially believed to be fibrous tremolite was obtained in studies of miners and millers in the relatively small vermiculite production plant in Libby, Montana (McDonald *et al.*, 1986). Vermiculite ore containing 4–6% tremolite was fed into the Libby mill, and initially it was thought that dust exposure of the workers had a similar composition. However, detailed analyses in the workplace by Patrick Sébastien indicated that the situation was more complex and that the airborne fibres were probably a mixture of different types of asbestiform and massive amphiboles. Whether or not this had always been the situation remains unknown, but the enigma remained. In addition to a study of chest radiographs in current and past employees, a small cohort of 406 miners and millers was followed for deaths first to 1983 and later to the end of 1998. Mortality by cause at both these dates (McDonald *et al.*, 2004) is shown in Table 3, reaching a level of risk on a par with that of crocidolite. Total deaths to the end of 1998 were as follows: lung cancer 44 (SMR 2.40), non-malignant respiratory diseases (NMRDs) 51 (SMR 3.09), all causes 285 (SMR 1.27); included among the total were 12 deaths attributed to mesothelioma (PMR 4.21%) (see Table 3). Adjusted linear relative risks (per 100 f ml^{-1} $year^{-1}$), estimated by Poisson regression, were as follows: lung cancer [0.36, 95% confidence interval (CI) 0.03–1.20], NMRD (0.38, 95% CI 0.12–0.96), and all causes

(0.14, 95% CI 0.05–0.26). The 12 deaths from mesothelioma, though with a typical latency range of 22–47 years (median 35.5 years), showed a limited relationship to estimated exposure.



(Photomicrograph kindly provided by Dr Patrick Sébastien)

Fig. 2. Chrysotile (Ch) and tremolite (T) fibres in lung tissue of a Quebec asbestos miner at autopsy.

AETIOLOGICAL CONCLUSIONS

In a letter to *Science* (McDonald and McDonald, 1995), it was reported that by 1992, 37 deaths in the Quebec cohort were from mesothelioma, and 24 of the 37 were in Thetford Mines. Using 10 matched controls for each case, it was immediately evident that man-years employment of the cases was concentrated in a localized area of five mines in central Thetford (Area A), compared with a much lower frequency in 10 mines (Area B) located peripherally. It was quickly recognized that essentially this same geographical pattern applied to the distribution of fibrous tremolite in lung tissue (as shown by Sébastien) and of pleural calcification (as shown by Gibbs). These various sets of information were necessarily obtained from the mine-specific records of the cohort and linked geographically to the location of each mining company, which alone could provide the information required. The resulting conclusion is that tremolite activity is located mainly in a contiguous group of five or six mines near the centre of Thetford Mines (Area A).

There followed in 1997 (McDonald *et al.*, 1997) a detailed review of mesothelioma in the Quebec cohort since its inception, first with the steps taken to validate the 33 reported cases. There was some doubt about 6 cases in men employed 2–5 years, whereas the remaining 27 were employed 20–48 years: 22 in Thetford Mines and 5 in Asbestos. Of 27 cases with an autopsy, electron microscopic analyses of lung tissue were made for 14 of the 22 from Thetford and all five from Asbestos. Tremolite fibres predominated in the lungs of men from Thetford, whereas substantial concentrations of crocidolite were found in three of the five from Asbestos.

Table 3. Mortality in Libby cohort of vermiculite miners exposed to fibrous tremolite (n = 406) (reference: US white males) (McDonald *et al.*, 2004)

		Deaths to July 1983		Deaths since July 1983 (to 1 January 1999)		Total	
	ICD9*	Observed	SMR	Observed	SMR	Observed	SMR
Respiratory cancers	160–165	23	2.45	21	2.35	44	2.40
All other cancers	140–159, 165–208, 230–239	20	1.09	19	1.29	39	1.18
NMRD	010–018, 460–519	21	2.55	30	3.63	51	3.09
Circulatory disease	390–459	65	0.87	39	1.11	104	0.95
External	800–998	23	1.87	3	1.03	26	1.71
All causes		165	1.17	120	1.43	285	1.27
(including mesothelioma)		4	(PMR = 2.4%)	8	(PMR = 6.7%)	12	(PMR = 4.2%)

*International Classification of Diseases, Ninth Revision.

The extent to which cases of mesothelioma were similar in place of employment and accumulated dust exposure to 10 closely matched referents (non-cases) was tested in two case-referent analyses. The first of these compared work in Thetford with mines outside Thetford; the second compared work in defined areas of central Thetford (Area A) with mines in Thetford but outside the defined central area (Area B). A statistically significant odds ratio of 2.55 (90% CI 1.52–4.27) was found in relation to 20 years' work in mines in the same vicinity as those identified by Gibbs (1979) as the cause of pleural calcification in the 1970s. Risk of mesothelioma was strongly related to time worked in the central area (Area A), but less to level of dust exposure, suggesting that exposure was intermittent and that tremolite concentrations in the working environment were poorly related—if at all—to prevailing dust levels. It does not follow that pleural calcification and mesothelioma have the same aetiology, though they must be closely linked. Non-fibrous tremolite would meet this requirement and has been suggested on this and other evidence (McDonald, 1997). While the results of these two case-referent analyses certainly support the tremolite hypothesis, the evidence is not specific. However, a degree of specificity is provided by Libby, with 12 deaths from mesothelioma in a cohort of only 406 vermiculite miners not exposed to any other as yet identified carcinogenic agent.

When Schepers (1965), a principal discussant at the New York Conference in 1964, posed the prophetic question 'and what about tremolite?', he received no answer, and it is still none too clear, as much depends on what is meant by 'tremolite'. Scheepers was undoubtedly referring to the rarely used fibrous amphibole of that name. Pooley (1976) and Rowlands *et al.* (1982) may have done the same, as did the proprietors of Libby and Enoree quarries (McDonald *et al.*, 1988). The same is true of Sébastien in his lung tissue analyses and in his reservations about exposures at Libby. In recent years, there has been increasing mineralogical and related biological research on tremolite, which may have epidemiological implications.

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