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Dust Exposure and Lung Cancer in Quebec Chrysotile Miners and Millers

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A large cohort of men born between 1891 and 1920 and employed for at least a month in the chrysotile producing industry of Quebec has been under study since 1966. These men were followed from first employment (the earliest in 1904) to 1992, by which time over 8000 had died, 657 from lung cancer. The current study is of 488 cases of lung cancer formerly employed at three places, *viz.* a major complex, here called Company 3, in the region of Thetford Mines (243 cases), the mine and mill in the town of Asbestos (206) and a small asbestos-products factory in the same town (39). For each case, four referents were sought by random selection from among survivors to a greater age, after matching on place of employment, age of starting work, smoking habit and date of birth. This process was highly successful, although six cases had less than four referents. For each man (the 488 cases with 1941 referents) and for each calendar year of employment, we obtained the fraction of the year worked at various levels of intensity, assessed in 13 'dust categories' of mpcf (million particles per cubic foot). We then calculated how many years each man spent at these various levels; these years, adjusted for the length of the working week (66 h until 1937; 48 h 1938–1949; and 40 h 1950–1985), were accumulated up to ten years before the death of the case. The men were classified according as they were non- or ex-smokers, or smokers, of cigarettes. For each man at Company 3 and one referent for each, his years of work in a central area of five mines and in a peripheral area of ten mines were differentiated; contamination of the chrysotile by fibrous tremolite was known to be much greater in the central than in the peripheral area. Case-referent comparisons, within place of employment, were made by conditional logistic regression. As anticipated from earlier subject–years analyses, lung cancer risks were found to be negligible for years worked in dust categories 1 and 2 (averaging 0.5 and 2 mpcf), regardless of place; as the upper limit of category 1 is considerably higher than permitted nowadays, the lung cancer risk from exposure to chrysotile at permitted levels can be taken as extremely small. Patterns of exposure-response for higher categories were irregular. At Company 3, some risks appeared elevated for years spent in the higher dust categories: 3–4, 5–7, 8–10 and 11–13, with averages around 9, 20, 36 and 92 mpcf, respectively. For categories 3–4 and 8–10, the odds ratios were high for some or all work in the central area, but minimal for years spent in the peripheral area only. Odds ratios were fairly low for cigarette smokers who worked in categories 5–7 and also for years spent in the highest categories (11–13). At the mine and mill in Asbestos, all risks were low except for years worked by non- and ex-smokers in categories 7–13 (ca. 40 mpcf). There were no increased risks at the factory. It was known from the subject–years analyses that most of the excess had occurred at Company 3, but it is now clear that for all practical purposes it was confined to the central area there, probably due largely to fibrous tremolite and in dust conditions of at least dust category 3. The average of this category was 7 mpcf or very roughly 24 fibres/ml, about two orders of magnitude higher than today's hygiene standards. © 1998 British Occupational Hygiene Society. Published by Elsevier Science Ltd.

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INTRODUCTION

Knowledge of the mortality experienced by chrysotile workers is largely derived from observations on one cohort, namely that which comprised all men born between 1891 and 1920 and employed for at least a month in the Quebec chrysotile producing industry. These 10,918 men were followed from first employment (the earliest in 1904) to 1992 and no further tracing is planned. Reports of mortality to several points in time, *viz.* 1966, 1969, 1973, 1975 and 1988, were published between 1971 and 1993, followed by a comprehensive review of the development of the mortality investigation from its inception (Liddell *et al.*. 1997). This presaged exhaustive reports on mesothelioma and lung cancer: the former is now in press (McDonald *et al.*, 1997); this is the latter.

Between 1 January 1950 and 31 May 1992, a period for which the expected numbers of deaths could be calculated on the basis of Quebec male mortality, 646 deaths due to lung cancer were recorded in the cohort and the standardized mortality ratio (SMR) was 1.37 (Liddell *et al.*, 1997 Table 6). The same table gave the numbers of deaths (with SMRs in brackets) by place of employment* as follows: 'Company 3' in Thetford Mines 280 (1.45); the mine and mill in Asbestos 253 (1.29); the small asbestos products factory also in Asbestos 49 (1.34); and the other six companies near Thetford Mines 64 (1.45). Well over half of the total excess of lung cancer deaths appeared to be due to smoking and the extent of lung cancer mortality attributable to asbestos exposure was estimated as 60–65 deaths. Taking account also of dust exposure, the attributable excesses by place of employment can be approximated, from the material in Tables 7 and 8 of Liddell *et al.* (1997), as close to 40 at Company 3, as near 18 at the mine and mill in Asbestos and as one at the factory there, with very few elsewhere, i.e. at the six small companies 4–9. It was thus necessary to consider each place of employment separately; and a further reason for separate consideration was that the patterns of dust exposure were quite different (see Appendix).

In view of the importance of smoking in the aetiology of lung cancer, this factor had to be taken into account. Use was made of the information on smoking habit that had been obtained in 1970 for almost everyone in the cohort alive at that time. Lung cancer mortality rates for Quebec males, 1950–1992, which had been utilised in the subject–years analysis of the cohort (Liddell *et al.*, 1997), exhibited marked age–period–cohort effects (Alderson, 1976); one illustration is that the equivalent average death rate per 100,000 population aged 50–84 increased 18-fold between 1950–54 and 1990–92, from 24.7 to 464.7. Clearly, this could not be ignored.

Another factor to be considered was contamination by fibrous tremolite which preliminary investigation (McDonald and McDonald, 1995) had suggested as important in the aetiology of mesothelioma. In the area of Thetford Mines, there were 15 geographically dispersed mines and mills falling into two clearly definable groups: five in a circumscribed *central* area and ten located in a *peripheral* area. Lung burden analysis (Sébastien *et al.*, 1989) of 58 members of the cohort in the central area and 25 in the peripheral area had shown that the geometric mean concentration of tremolite fibres 5 μm or more in length was 3.8 times higher in the central area than in the peripheral area.

MATERIALS AND METHODS

A birth cohort of all Quebec chrysotile miners and millers born 1891–1920 who had worked in the industry for at least one month has been followed from 1904, when the first man started work, through 1992 (Liddell *et al.*, 1997). Vital status was determined for 9780 men, of whom 8009 had died; for 657 deaths, the cause had been coded for official statistical purposes as malignant neoplasm of trachea, bronchus or lung (three-digit categories 162–164 in the Seventh Revision and 162 in the Eighth and Ninth Revisions of the International Classification of Diseases; see World Health Organisation, 1977), which is termed *lung cancer* in this report. It was decided to eliminate from the study the 66 cases who had been employed by one or other of six small companies (4–9 in Liddell *et al.*, 1997) because of the very few cases at each. Also excluded were the 52 cases who were recorded as having commenced work in the industry after age 35. These comparatively late starters might well have had substantial earlier exposure to carcinogens and, in view of the long latency averaging over 45 years, were unlikely to have developed asbestos-related malignancy.

For each of the remaining 539 cases, we sought four referents with the following criteria. Relative to the case, the referent must have:

1. worked at the same *place of employment*,* that is either at Company 3 in Thetford Mines or at the mine and mill in Asbestos or in the factory there;
2. survived to a greater age;
3. had a similar cigarette smoking habit;
4. started work at a similar age; and
5. had a similar date of birth.

For nearly 85% of the cases, it was possible to find a pool of potential referents and a sample of four was selected by a strictly random process, in what is termed the first *tranche of selection*. In the second tranche, to find referents for the remaining cases, criteria (3), (4) and (5) were relaxed; however, two cases had to be omitted because of a computing error. There were 49 cases whose smoking histories could not be reliably

*The term 'place of employment' is preferred in this report to the strictly correct, namely the 'company from the records of which the man was registered in the cohort' (see Liddell *et al.*, 1997).

Table 1. Place of employment, smoking habit, age started work, and date of birth, with era of death of case

	488 Cases	1941 Referents
PLACE OF EMPLOYMENT		
Thetford Mines: Company 3	243	970
Asbestos: Mine and mill	206	824
Factory	39	147
SMOKING HABIT		
1st tranche (411 cases: 1642 referents)		
Non-smoker of cigarettes or ex-smoker	88	350
Smoker of less than 20 cigarettes a day	88	352
Smoker of 20 or more cigarettes a day	235	940
2nd tranche (77 cases; 299 referents)		
Non-smoker of cigarettes or ex-smoker	11	44
Smoker of less than 20 cigarettes a day	18	134
Smoker of 20 or more cigarettes a day	48	121
All subjects		
Non-smoker of cigarettes or ex-smoker	99	394
Smoker of less than 20 cigarettes a day	106	486
Smoker of 20 or more cigarettes a day	283	1061
AGE STARTED WORK (years: average)		
1st tranche	22.56	22.57
2nd tranche	23.51	23.37
DATE OF BIRTH (average)		
1st tranche	1910.11	1909.95
2nd tranche	1904.86	1904.60
ERA OF DEATH OF CASE		
before 1975	146	581
1975–1984	199	795
1985–1992	143	565

classified and, although their referents had been chosen as also having unreliable histories, there was no guarantee that the actual habits of case and referents were similar; these 49 were also eliminated*.

There were now 488 cases left in the study and for all but six of them, we had found four referents each. For three of the others we had three referents each and for a fourth two referents, but for the last two cases we had only one referent each. Thus the total number of referents was 1941. Some men were included more than once as referents for different cases, but in what follows each referent was treated on each occasion as a separate subject. See also Table 1 and the first paragraph of the Discussion.

Liddell *et al.* (1997) describe how an annual exposure record for each of the 10,918 men in the complete cohort had been compiled. This was prepared by calendar year, from the year in which the man started work up to and including the year in which he finished. The annual record was of how many months in the year the man had worked, expressed as the fraction of the year and the dust level, in millions of particles per cubic foot (*mpcf*). The dust level for the man's job in the specific year up to 1 November 1966 was taken from the equivalent of a 5783×63 matrix (job class $\times$ year) provided by Gibbs and Lachance (1972), who had placed each dust level on a 13-point scale. In each of the 13 *dust categories*, a representative value, approximating to the mean, had been allocated as follows: 0.5, 2, 7, 12, 17, 22, 27, 32, 37, 42, 47, 70 and 140 mpcf. For the period 1967–1985, dust levels were estimated as explained by Liddell *et al.* (1997).

The work-week was 60–72 hours before 1938, 48 hours 1938–1949 and 40 hours thereafter. As *work-week adjustments*, we adopted the factors: $66/40 = 1.65$: $48/40 = 1.2$; and 1, for these three periods. In the exposure records, it was indicated into which of these periods the specific year fell and so it was possible to adjust the fractions of years worked by multiplying the recorded fraction by the appropriate factor.

For all 2429 subjects we calculated 15 *measures of exposure* as follows:—

- net service (adjusted for work-week): the sum of the adjusted fractions of years.
- years (adjusted) worked in dust category i ($i = 1, 2, \ldots, 13$): the sum of the adjusted fractions of those years in which the dust level had been in category i.
- accumulated dust exposure (mpcf $\times$ years): the sum of (adjusted fraction of year) $\times$ (dust level).

For a case, the calculations were carried out up to ten years before his death and, for a referent, up to ten

*In preliminary analyses, it was shown that inclusion of these 49 cases and their referents made no noticeable difference.

years before he reached the age at which the relevant case died.

For study of the 'tremolite effect', the detailed work histories of all cases at Company 3 and of one referent for each, selected strictly at random from those defined above, were examined. For every subject, periods of service in the central and in the peripheral areas were calculated up to 10 years before the age of the case's death; the periods were obtained as calendar years (without adjustment for work week)*. Years spent in the central area were expressed as proportions of total years and each man was categorised according as the proportion was: 0; greater than 0, but less than 1/2; at least 1/2, but less than 1; or 1. Subsequently, the three higher categories were grouped to form a two-point *C/P class*: all years in peripheral areas; and some or all years in central areas.

Smoking habits were classified as: non-smoker of cigarettes or ex-smoker; smoker of less than 20 cigarettes a day; or smoker of 20 or more cigarettes a day, but later the two classes of smoker were combined. Three *eras of death of cases* were defined as follows: before 1975; 1975–1984; and 1985–1992.

Exposure-response relationships were examined by means of conditional logistic regression using the EGRET package (Statistics and Epidemiology Research Corporation, 1989) and assuming multiplicative relative risks†. The output from the program includes *regression coefficients*, which are logarithms of the *odds ratios*, themselves estimates of the relative risks. The program also gives the standard errors of the regression coefficients and these can be used to calculate approximate confidence intervals, on the assumption that the coefficients are normally distributed; the confidence coefficient was set at 90%. In the tables, each odds ratio is an estimate of the relative risk that would have arisen from employment for 10 years adjusted for the length of the working week; there are two exceptions: Table 3, last line—see note (g)—and Table 5—see footnote.

The EGRET program also provides the *deviance* before and after the fit of any model, the difference being treated as a *likelihood ratio (LR) statistic* with degrees of freedom (df) equal to the number of variables in the model; when a model is extended by the inclusion of one or more variables, the reduction in deviance is also an LR statistic with the same df as the number of additional variables (Armitage and Berry, 1994). A close estimate of the LR statistic for a single variable is provided by the Wald statistic, i.e. $[(\text{regression coefficient})/(\text{standard error})]^2$.

For all subjects and for each of the three places of employment, analysis of the model with 13 exposure measures led to at least one negative regression coefficient, which taken at face value would imply a protective effect of exposure. Negative coefficients were eliminated by pooling years in adjacent dust categories as described in the Appendix. Each of the variables smoking habit, era of death of case and C/P class was analyzed, where appropriate, as a *factor* so that its interaction with exposure measures could be evaluated. Even with the original variables replaced by the dichotomies explained above, most of the interactions were minuscule and therefore deleted.

A rough guide to statistical significance may be obtained by referring any LR statistic to the χ^2 distribution with the same degrees of freedom. However, the *P* value found in this way is only nominal and it is essential that removal of negative and minuscule effects and the fact of simultaneous inference are taken into account in any attempt to evaluate significance. Also, where the lower 90% confidence limit on an odds ratio is greater than 1, the *P* value is less than 0.10, but, for the same reasons, only nominally so.

RESULTS

The 2429 subjects in the enquiry are described in Table 1 according to the criteria by which the referents were selected, taking account of the tranche of selection. Also shown is the distribution of subjects by era of death of cases. In Table 2, we present all the exposure measures, incorporating adjustment for the length of the work-week, for the 488 cases and the 1941 referents. The material consists of means, standard deviations (sds) and coefficients of variation (CVs), together with the differences between the means and the corresponding t-statistics. The matrix of the 78 coefficients of correlation between the 13 measures relating to the different dust categories is extremely complex; because of the very large number of degrees of freedom (2427), any value greater than 0.04 would be considered significant at the 0.05 level and values above, say, 0.1 of enormous significance, and there are several such values. This means that all variables have to be analysed simultaneously.

Likelihood Ratio statistics, each with 1 degree of freedom, from three different forms of matched analysis of the complete data set are given in Table 3. Those in column (a) are quite close to the squares of the t-statistics of Table 2, which correspond to the LR statistics in unmatched analysis. The initial deviance, i.e. before fitting any model, of 1564.79 was reduced to 1552.02 by including only net service in the analysis, yielding the LR statistic of 12.77 shown in column (a). In the analysis of the model including years in each of the 13 dust categories, there were two negative regression coefficients (indicated by brackets round the LR statistics). Pooling was carried out as outlined above and explained in the Appendix and this led to a reduced model with nine variables; regression coefficients are in column (d) of Table 3. When this

*The great effort involved in calculations for more than one referent per case, and especially for work week adjustment, was not considered justified.

†It would have been preferable to assume additive relative risks, but convergence could not be obtained with these models.

Table 2. Exposure measures for 488 cases and 1941 referents

	488 CASES Mean	(sd)	CV	1941 REFERENTS Mean	(sd)	CV	DIFFERENCE of means	t-statistic
Net service (years: adjusted *)	18.56	(16.92)	91.2%	15.76	(16.06)	101.9%	2.80	3.40
Years (adjusted) in dust category:								
1 (0.5 mpcf)	1.13	(3.78)	335.9%	1.13	(4.39)	389.1%	−0.001	−0.004
2 (2 mpcf)	7.86	(10.85)	138.0%	7.08	(10.39)	146.8%	0.78	1.47
3 (7 mpcf)	3.06	(5.51)	180.1%	2.54	(5.11)	201.5%	0.53	2.00
4 (12 mpcf)	1.63	(3.72)	228.9%	1.44	(3.67)	254.2%	0.18	0.99
5 (17 mpcf)	0.54	(1.51)	277.5%	0.41	(1.52)	369.6%	0.13	1.72
6 (22 mpcf)	0.37	(1.20)	322.0%	0.24	(0.84)	349.7%	0.13	2.80
7 (27 mpcf)	0.58	(2.19)	377.0%	0.29	(1.14)	391.4%	0.29	4.06
8 (32 mpcf)	0.51	(1.53)	299.1%	0.36	(1.34)	368.3%	0.15	2.16
9 (37 mpcf)	0.81	(2.21)	272.0%	0.63	(2.05)	323.3%	0.18	1.69
10 (42 mpcf)	0.29	(0.99)	346.3%	0.34	(1.48)	428.1%	−0.06	−0.83
11 (47 mpcf)	0.81	(2.38)	293.2%	0.52	(1.77)	341.7%	0.29	3.04
12 (70 mpcf)	0.39	(1.45)	374.9%	0.34	(1.39)	402.4%	0.04	0.58
13 (140 mpcf)	0.58	(2.46)	427.9%	0.43	(1.95)	452.7%	0.14	1.38
Accumulated dust exposure (mpcf × years)	293.6	(492.4)	167.7%	227.3	(402.6)	177.2%	66.4	3.10

*All years have been adjusted for length of working week; see text.

Table 3. Likelihood ratio statistics from different forms of analysis, with odds ratios: 488 cases and 1941 referents

	Likelihood Ratio statistic: Independent (a) (b)	Dependent: 13-variable model (c) (b)	Dependent: 8-variable model (c) (d)	Odds Ratio (e): Estimate	90% Confidence limits	
Net service (years: adjusted)	12.77	—	—	1.125 (f)	1.066	1.188
Years (adjusted) in dust category:—						
1 (0.5 mpcf)	(0.00)	0.00	—	1	—	—
2 (2 mpcf)	2.10	1.23	1.13	1.055	0.971	1.146
3 (7 mpcf)	4.55	2.52	2.72	1.189	1.001	1.413
4 (12 mpcf)	0.99	0.04	0.04	1.028	0.812	1.300
5 (17 mpcf)	2.83	0.14	0.23	1.180	0.670	2.078
6 (22 mpcf)	7.59	2.15	1.73	2.058	0.836	5.069
7 (27 mpcf)	15.59	9.85	10.16	3.121	1.735	5.614
8 (32 mpcf)	4.34	2.67				
9 (37 mpcf)	3.27	0.26	0.05	1.039	0.787	1.372
10 (42 mpcf)	(0.74)	(3.07)				
11 (47 mpcf)	8.73	4.70	4.60	1.728	1.136	2.628
12 (70 mpcf)	0.31	(0.05)				
13 (140 mpcf)	1.86	0.63	0.30	1.111	0.809	1.526
Accumulated dust Exposure (mpcf × years)	9.47	—	—	1.036 (g)	1.017	1.055

(a) Each variable analyzed separately.
(b) Figures in brackets indicate negative regression coefficients and hence odds ratios less than unity.
(c) As given by the Wald statistic, i.e. [(regression coefficient)/(standard error)]².
(d) Model reduced by setting odds ratio in relation to dust category 1 to unity and by the least degree of pooling of variables that ensured no other estimated odds ratio was less than unity.
(e) Estimate of relative risk arising from 10 (adjusted) years of employment.
(f) Independent analysis.
(g) Estimate of relative risk arising from exposure of 100 mpcf × years; independent analysis.

model was fitted, the deviance was further reduced to 1533.94, yielding the LR statistic 18.08, with 8 df. This statistic, associated with $P \approx 0.02$, relates to the improvement in fit arising from subdividing net service into nine components and indicates that such subdivision is meaningful.

When the nine exposure variables were analysed in a single step, i.e. without the intervening stage of fitting net service, the LR statistic, with 9 df, became (1564.79–1533.94 =) 30.85 and the nine relevant odds ratios together with 90% confidence limits, are shown in Table 3, column (e); the odds ratios for net service and accumulated dust exposure were found in independent analyses. These last two variables were omitted from the analyses for Tables 4, 6, 7 and 8.

In the fit of the 13-variable model to the data for the 243 cases of Company 3 and their 970 referents, four of the 13 regression coefficients were negative and the necessary pooling resulted in a 5-variable model. Part (A) of Table 4 shows regression coefficients, with standard errors*; odds ratios are not given because they were all modified to some extent by the inclusion of other variables. In fact, all the interactions between smoking habit and/or era of death of case on the one hand and exposure on the other hand were very slight, except that between smoking habit and years spent in dust categories 5–7. Regression coefficients and odds ratios for the 6-variable model are in Part B of the table. Deviances were as follows:— initial 781.29; reduced to 764.95 after fitting the five exposure variables (LR statistic 16.34:5 df); and finally to 762.03 (LR statistic 2.91:1 df) when the interaction was included.

For 240 of the cases† at Company 3 and for a single referent each, it was known how long each man had worked in central and peripheral areas up to ten years before the death of the case and to the corresponding age for referents: regression coefficients are presented in Table 5, together with odds ratios in relation to 10 calendar years of net service. The deviances before and after analysis of net service alone were 332.71 and 319.43 and the effect of differentiating between service in the two areas was to reduce the deviance to 311.54, giving the LR statistic (1 df) as 7.89.

Because part of this undoubted statistical significance could have arisen from differences in dust levels in the two areas, the data for the same 240 cases and their referents have been re-analyzed; see Table 6, which is on the same lines as Table 4, Part (B), with the same pooling of dust categories, except that category 1 was retained because the relevant coefficient was not negative. After fitting the six exposure variables, the deviance was 313.71, which was reduced to 300.04 (LR statistic 13.67: 2 df) when the two interactions were included. Regression coefficients and odds ratios for all eight variables are given in this table, but only those for the interactions are relevant; see note (c).

Tables 7 and 8 present the analyses of the data from Asbestos, the former concerning the 206 cases from

Table 4. Lung cancer risks in relation to years worked, by dust category, at Company 3 in Thetford Mines: 243 cases; 970 referents

Years (adjusted) in dust category(ies):—	A. Without regard to interactions: Regression coefficient: Estimate	A. Standard error	B. Taking account of interaction between smoking habit and years in dust categories 5–7: Smoking habit	B. Regression coefficient: Estimate	B. Standard error	Odds Ratio (a): Estimate	90% Confidence limits	
1 (0.5 mpcf)	—	—	(b)	—	—	1	—	- -
2 (2 mpcf)	0.00032	0.0083	(b)	0.00011	0.0083	1.001	0.873	1.148
3–4 (ca. 9 mpcf)	0.01225	0.0083	(b)	0.01167	0.0083	1.124	0.980	1.289
5–7 (ca. 20 mpcf)	0.04695	0.0247	Non- and ex-smoker	0.1812	0.0821	6.123	1.587	23.63
			Cigarette smoker	0.03415	0.0261	1.407	0.916	2.162
8–10 (ca. 36 mpcf)	0.03337	0.0272	(b)	0.03825	0.0276	1.466	0.931	2.308
11–13 (ca. 92 mpcf)	0.02852	0.0148	(b)	0.02478	0.0151	1.281	0.999	1.642

(a) Estimate of relative risk arising from 10 (adjusted) years of employment.
(b) All interactions with smoking habit except that shown were very small; all interactions with era of death of case were very small.

*Regression coefficients, and their standard errors, are presented with 4–5 decimal places only so that odds ratios close to unity can be calculated with reasonable precision for 10-year periods of employment.

†The other three cases had to be eliminated, two because of frequent unrecorded moves between the two areas, the other because of a missing work history.

Table 5. Lung cancer risks in relation to years worked in central and peripheral areas of Thetford Mines: 240 cases; 240 referents

Net service (calendar years, without adjustment for length of working week)	Regression coefficient		Odds Ratio (a)		
	Estimate	Standard error	Estimate	90% Confidence limits	
Without differentiation by area	0.02454	0.0070	1.278	1.139	1.434
In central areas	0.03423	0.0082	1.408	1.231	1.610
In peripheral areas	0.00396	0.0102	1.040	0.880	1.230

(a) Estimate of relative risk arising from 10 years of service.

the mine and mill, with 824 referents, the latter the 39 cases and 147 referents from the factory. For Table 7, the necessary pooling of dust categories led to a 4-variable model: regression coefficients, with standard errors, are in Part A. All but one of the interactions with smoking habit and era of death of case were very small. Part B gives regression coefficients and odds ratios, with 90% confidence limits, after taking into account the interaction between smoking habit and years in dust categories 7–13. Deviances were as follows:— initial 663.09; reduced to 658.27 after fitting the four exposure variables (LR statistic 4.81:4 df); and then to 655.87 (LR statistic 2.40:1 df) by the fit of the one non-trivial interaction. Pooling for Table 8 reduced the number of dust categories analyzable to three and all interactions were small. The deviances before and after the fit of the three exposure variables were 120.40 and 118.81 and the LR statistic was 1.59 (3 df).

The odds ratios, with confidence limits, from Tables 4(B), 6, 7(B) and 8 are summarised in Table 9.

DISCUSSION

Methodology

We obtained four referents from the same place of work for all cases, except two at Company 3 and four at the factory in Asbestos. Matching by smoking habit was nearly perfect in the first tranche of selection and remained so for non- and ex-smokers in the second tranche. Overall, there was a shortfall of 71 referents who had smoked 20 or more cigarettes a day, with an excess of 62 lighter smokers. Matching by age started work had been within eight bands mainly two or three years wide in the first tranche and in the second within four bands of average width 6 1/2 years. The outcome was extremely close agreement on average between cases and referents. Similarly, matching by date of birth had been first within quinquennium and then within decade, leading to very close agreement on average.

It had been decided from prior considerations to truncate all exposure measures 10 years before the case's death and to adjust years worked to allow for the length of the working week. In a preliminary investigation, LR statistics were obtained for net service, both adjusted for work-week and not adjusted, and accumulated dust exposure, each with four amounts of truncation: 15, 10, 5 and 0 years before the death of the case. The LR statistics for adjusted service were higher than for unadjusted; those for 15- and 10-year truncation higher than for the other amounts of truncation. There was therefore no contra-indication to the use of the work-week adjustments and no strong contra-indication to truncation at 10 years before the

Table 6. Lung cancer risks in relation to years worked in central and peripheral areas of Thetford Mines, by dust category: 240 cases; 240 referents

Years (adjusted) in dust category(ies):—	C/P class *	Regression coefficient			Odds Ratio (a)		
		Estimate	Standard error		Estimate	90% Confidence limits	
1 (0.5 mpcf)	(b) (i)	{0.00921	0.0242	(c)	1.096	0.736	1.633}
2 (2 mpcf)	(b) (ii)	{0.01014	0.0112	(c)	1.107	0.921	1.331}
3–4 (ca. 9 mpcf)	Some or all years in central area	0.04014	0.0143		1.494	1.181	1.890
	All years in peripheral area	−0.01669	0.0224		0.846	0.585	1.223
5–7 (ca. 20 mpcf)	(b) (iii)	{0.01387	0.0359	(c)	1.149	0.636	2.073}
8–10 (ca. 36 mpcf)	Some or all years in central area	0.1188	0.0622		3.281	1.179	9.126
	All years in peripheral area	−0.03861	0.0472		0.680	0.313	1.477
11–13 (ca. 92 mpcf)	(b) (iv)	{0.05028	0.0232	(c)	1.653	1.129	2.422}

*See text.

(a) Estimate of relative risk arising from 10 (adjusted) years of employment.

(b) The interaction with C/P class was associated with a small LR statistic, namely: (i) 1.19; (ii) 0.03 [negative coefficient]; (iii) 0.72 [negative coefficient]; (iv) 0.37.

(c) These estimates are given only for the sake of completeness and are in no way substitutes for estimates in Table 4, which are more reliable, being based on four times as many referents: the two sets are entirely compatible given that those in Table 6 are based on a subset of referents.

Table 7. Lung cancer risks in relation to years worked, by dust category, at mine and mill in Asbestos: 206 cases; 824 referents

Years (adjusted) in dust category(ies)	A. Without regard to interactions: Regression coefficient Estimate	A. Standard error	B. Taking account of interaction between smoking habit and years in dust categories 7–13: Smoking habit	B. Regression coefficient Estimate	B. Standard error	Odds Ratio (a) Estimate	90% Confidence Limits	
1 (0.5 mpcf)	0.01059	0.0201	(b)	0.01139	0.0201	1.121	0.805	1.560
2 (2 mpcf)	0.00770	0.0071	(b)	0.00770	0.0071	1.080	0.962	1.213
3–6 (ca. 11 mpcf)	0.01350	0.0183	(b)	0.01429	0.0184	1.154	0.852	1.561
7–13 (ca. 40 mpcf)	0.01959	0.0143	Non- and ex-smoker	0.05312	0.0258	1.701	1.113	2.600
			Cigarette smoker	0.00505	0.0176	1.052	0.787	1.405

(a) Estimate of relative risk arising from 10 (adjusted) years of employment.
(b) All interactions with smoking habit except that shown were very small; all interactions with era of death of case were very small.

case's death: both these devices have been used throughout.

An important finding (Table 2) is the extremely high coefficients of variation of all the exposure measures: most subjects spent no time in most specific dust categories; and very few men spent more than five years in any one of the dust categories 5–13. Some implications are discussed in the Appendix; in particular, a different (chance) selection of referents might have led to rather different odds ratios for the higher dust categories.

The differences between the first two columns of Table 3 arise from the correlations between the exposure measures, which require these measures to be considered simultaneously, i.e. in dependent analysis. Accumulated dust exposure was omitted from all further analyses and net service from all except for Table 5. The odds ratios in Table 3 for these two variables correspond to column (a); the others correspond to column (c).

The materials to be analyzed are essentially the exposure measures, rather the differences, between cases and referents, in the mean measures, taking into account the correlations between them. In Table 2, the 13 differences of mean years in specific dust categories are seen to fluctuate greatly without discernible pattern and the correlations between the 13 differences of means, although mainly quite small, include several that have major influence. As a result, the corresponding odds ratios in Table 3 also exhibit great fluctuations, leading to major difficulties of interpretation, which are not decreased in the later tables.

In the only earlier study on broadly similar lines, Vacek and McDonald (1990) demonstrated a steady increase in differences (obtained from their Table I) between cases and 'controls' in 'durations' as average 'dust values' increased through six steps from 0.6 to 105.0 mpcf: the odds ratios (calculated from Table II) for 10 years work in the six dust ranges were 0.71, 1.14, 1.02, 1.26, 2.02 and 1.68. Comparison between the two sets of results is, however, vitiated by *inter alia* two major differences in methodology: how variation in the length of the working week was treated (see Appendix); and consideration of the age at which employment started. In the earlier report, the referents were on average 5.2 years older than the cases when they started work; their initial dust exposure would thus tend to be less severe because of the continuing improvement in conditions and, compared with cases who died only a few years after last employment, their duration of employment could not be as long*. Indeed, although matching by age at which employment commenced might appear 'over-matching', it is

*If only for these reasons, cases would accumulate more dust exposure than controls: Vacek and McDonald (1990) reported cumulative dust exposure for cases as 2 3/4 times that of controls, whereas we found cases to have had only 30% more exposure (Table 2).

Table 8. Lung cancer risks in relation to years worked, by dust category, at factory in Asbestos: 39 cases; 147 referents

Years (adjusted) in dust category(ies):—	Regression coefficient Estimate	Regression coefficient Standard error	Odds Ratio (a) Estimate	Odds Ratio (a) 90% Confidence limits	
1 (0.5 mpcf)	—	—	1	—	—
2 (2 mpcf)	0.01868	0.0150	1.205	0.942	1.543
3–6 (ca. 11 mpcf)	0.00441	0.0513	1.045	0.449	2.430
7–13 (ca. 42 mpcf)	0.00384	0.0433	1.039	0.510	2.118

(a) Estimate of relative risk arising from 10 (adjusted) years of employment.
(b) All interactions with smoking habit and era of death of case were very small.

Table 9. Odds ratios (a), with 90% confidence limits, by dust category and place of employment, taking account of interactions, and classified by Likelihood Ratio statistic.

Dust category(ies) (with average dust level)	Likelihood Ratio statistic class (b) <1.64 {$P>0.2$}	1.65, <2.70 {$0.2>P>0.1$}	>2.71 {$0.1>P$}	Source (c)	LR (Wald) statistic (1 degree of freedom)
Category 1: (0.5 mpcf)					
Factory in Asbestos	1 (d)			[8]	
Mine and mill in Asbestos	1.1 (0.8, 1.6)			[7B]	0.32
Company 3 at Thetford Mines	1 (d)			[4B]	
Category 2: (2 mpcf)					
Factory in Asbestos	1.2 (0.9, 1.5)			[8]	1.55
Mine and mill in Asbestos	1.1 (1.0, 1.2)			[7B]	1.18
Company 3 at Thetford Mines	1.0 (0.9, 1.1)			[4B]	0.00
Categories 3–4: (ca. 9 mpcf)					
Company 3 at Thetford Mines					
all years in peripheral area	0.8 (0.6, 1.2)			[6] (e)	0.56 (f)
some or all years in central area			1.5 (1.2, 1.9)	[6] (e)	7.88
Categories 3–6: (ca. 11 mpcf)					
Factory in Asbestos	1.0 (0.4, 2.4)			[8]	0.01
Mine and mill in Asbestos	1.2 (0.9, 1.6)			[7B]	0.60
Categories 5–7: (ca. 20 mpcf)					
Company 3 at Thetford Mines					
cigarette smokers		1.4 (0.9, 2.2)		[4B]	1.75
non- and ex-smokers			6.1 (1.6, 23.6)	[4B]	4.87
Categories 8–10: (ca. 36 mpcf)					
Company 3 at Thetford Mines					
all years in peripheral area	0.7 (0.3, 1.5)			[6] (e)	0.67 (f)
some or all years in central area			3.3 (1.2, 9.1)	[6] (e)	3.65
Categories 7–13: (ca. 40 mpcf)					
Factory in Asbestos	1.0 (0.5, 2.1)			[8]	0.01
Mine and mill in Asbestos					
cigarette smokers	1.1 (0.8, 1.4)			[7B]	0.08
non- and ex-smokers			1.7 (1.1, 2.6)	[7B]	4.24
Categories 11–13: (ca. 92 mpcf)					
Company 3 at Thetford Mines		1.3 (1.0, 1.6)		[4B]	2.69

(a) Estimate of relative risk arising from 10 (adjusted) years of employment.
(b) Nominal P values are given in curly brackets.
(c) Table 4B, 6, 7B or 8, as indicated in square brackets.
(d) There is neither confidence interval nor LR statistic, because the odds ratio was 'forced' to unity.
(e) Estimate of relative risk arising from 10 calendar years of service; based on only one referent per case.
(f) Based on a negative regression coefficient.

considered essential for valid comparisons (see, for example, Liddell, 1988) and its lack—until rectified—can be disastrous in leading to impossibly high relative risks (Sluis-Cremer *et al.*, 1992).

Epidemiology

Accumulated dust exposure, which was a useful measure in the subject-years analyses of the cohort (Liddell *et al.*, 1997), discriminated reasonably well between the 488 cases and 1491 referents*, but not as well as net service and the inclusion of nine dust-related measures improved the discrimination greatly (Table 3). Although these measures allow some examination of response to different intensities of exposure, the pattern of exposure-response was quite irregular, even after the pooling described above; for example, the most 'significant' odds ratios were for years in dust categories 7 and 11 (averaging 27 and 47 mpcf), but there was little sign of 'significance' in relation to the adjacent categories 8–10 (ca. 36 mpcf) and 12–13 (ca. 92 mpcf).

It is not surprising, in the light of the material in the Appendix, that the relationships between odds ratio and dust category were nowhere clear-cut. The hypothesis we would have liked to test was that the odds ratio was related to intensity of exposure measured in fibres ml, but the lack of a reliable fibre/dust ratio rendered such an approach impossible, forcing the use of mpcf as a surrogate†. Further, it must be emphasised that dust exposure in any extractive industry is likely to be highly variable, with little discernible pattern: this is well illustrated in Table 10, which shows not only large differences between the places of employment but also several sporadic peaks at all three places, probably associated with changes in work practices.

Although interactions between dust measures and era of death of case were very small at all three places of employment, the pattern of exposure-response was affected at least slightly by smoking habit both at Company 3 and at the mine and mill in Asbestos. However, considerably the most important interactions related to whether work was in the central or peripheral area of Company 3.

Odds ratios in relation to 10 years of employment are summarised in Table 9, in three columns according to the value of the LR statistic (with 1 df), which is quoted in the final column. The columns of odds ratios are also headed by nominal P values, but it should be borne in mind that these are considerably lower than if due regard were paid to the selection of effects 'tested' and simultaneous inference. Thus the odds ratios in the first column must be considered as differing from unity only trivially and those in the central column cannot be thought of as statistically significant at any level normally adopted.

~~In the~~ light of the information in the Introduction, inferred from the data of Liddell *et al.* (1997), about where the excesses of deaths from lung cancer, as a result of exposure in the industry, must have occurred, it was to be expected that risks would be elevated at Company 3 and, to a lesser extent, at the mine and mill in Asbestos, but probably not at the factory. This is clearly borne out by the findings in Table 9.

*Accumulated dust exposure also differentiated cases and referents at Company 3, but not at the other two places of employment.

†See **Dust–fibre relationships** in the Appendix.

It is also important to appreciate that excess lung cancer was apparently confined to men with substantial exposure, of the order of 300 mpcf × years (Liddell *et al.*, 1997). The longest net service recorded in the current study was less than 68 years (after adjustment) and to accumulate 300 mpcf × years even in such a long period would have required the dust level to average over 4 mpcf throughout. It was thus to be anticipated that even long employment in dust categories 1 or 2 (averaging 0.5 and 2 mpcf) would not appear hazardous. This also is clearly borne out in the first six lines of Table 9: the lowest value of P for category 1 was greater than 0.5 and even that for category 2 was about 0.25.

Much has been written on the interaction of smoking and asbestos exposure in the causation of lung cancer, summarised by Berry *et al.* (1985), who defined a 'Relative Asbestos Effect' (RAE) which would be unity if the interaction were multiplicative, i.e. if smokers and non-smokers had closely similar relative risks from exposure. They found the RAE averaged over six studies as 1.8, indicating that the relative risk of lung cancer due to exposure to asbestos is greater for non-smokers than for smokers. One of those studies was of the 245 cases in the Quebec cohort before 1976, with 735 referents (Liddell *et al.*, 1984) and it had the same RAE (1.8) as the average. In subject–years analysis of deaths 1976–1988 in the Quebec cohort (McDonald *et al.*, 1993), RAEs could be found in several ways but all were much greater than unity. In the current study, the direct effects of cigarette smoking on the risks of lung cancer were effectively eliminated by the matching in the selection of referents. However, the interactions of smoking and asbestos exposure could be examined; the only two that were not trivial indicated higher lung cancer relative risks for non- and ex-smokers than for cigarette smokers.

One of our most important findings is that the odds ratios relating to years worked in dust categories 3–4 and 8–10, but only in the peripheral area, were negligible, whereas for men some or all of whose years were spent in the central areas the corresponding odds ratios were substantial. It has been shown elsewhere (Sébastien *et al.*, 1989) that contamination of chrysotile by fibrous tremolite was much more serious in the group of five central mines of Company 3 than in the ten peripheral mines and no other reason has been found for the differences in odds ratios.

There were great improvements over the years in dust levels everywhere: from 1974, only about 4% of men in the complete cohort were working in more than 5 mpcf (Table 10); a few years later, concentrations had been brought to quite low levels virtually throughout the industry. However, it must be borne in mind that the 'average' case started work in 1929 when the mean dust levels were very high (see the 1904–1937 column in Table 10) and even in 1953, when the last of the 488 cases was first employed, the average dust level in the industry was still about 50 mpcf (Gibbs and Lachance, 1972), roughly equi-

Table

COMPANY 3 AT
Number of records
Percentage by dust
1: (0.5 mpcf)
2: (2 mpcf)
3: (7 mpcf)
4: (12 mpcf)
5: (17 mpcf)
6: (22 mpcf)
7: (27 mpcf)
8: (32 mpcf)
9: (37 mpcf)
10: (42 mpcf)
11: (47 mpcf)
12: (70 mpcf)
13: (140 mpcf)
Total
Mean dust level (t
MINE AND MI
Number of recor
Percentage by du
1: (0.5 mpcf)
2: (2 mpcf)
3: (7 mpcf)
4: (12 mpcf)
5: (17 mpcf)
6: (22 mpcf)
7: (27 mpcf)
8: (32 mpcf)
9: (37 mpcf)
10: (42 mpcf)
11: (47 mpcf)
12: (70 mpcf)
13: (140 mpcf)
Total
Mean dust level (
FACTORY IN
Number of reco
Percentage by d
1: (0.5 mpcf)
2: (2 mpcf)
3: (7 mpcf)
4: (12 mpcf)
5: (17 mpcf)
6: (22 mpcf)
7: (27 mpcf)
8: (32 mpcf)
9: (37 mpcf)
10: (42 mpcf)
11: (47 mpcf)
12: (70 mpcf)
13: (140 mpcf)
Total
Mean dust leve

Table 10. Distribution of 13 609 annual work records by dust categories and place of employment

	1904–1937	1938–1949	1950–1961	1962–1973	1974–1985	1904–1985
COMPANY 3 AT THETFORD MINES						
Number of records	1794	1864	1686	1107	334	6785
Percentage by dust category						
1: (0.5 mpcf)	4.3	5.3	11.3	13.0	38.9	9.4
2: (2 mpcf)	30.0	25.3	36.7	46.8	54.8	34.3
3: (7 mpcf)	20.5	19.0	24.7	33.2	5.4	22.4
4: (12 mpcf)	14.2	12.3	10.6	6.2	0.9	10.8
5: (17 mpcf)	4.7	3.8	3.7	0.4	—	3.3
6: (22 mpcf)	1.6	2.7	3.1	0.1	—	1.9
7: (27 mpcf)	0.9	1.6	1.4	0.2	—	1.0
8: (32 mpcf)	3.0	4.7	3.0	—	—	2.8
9: (37 mpcf)	0.6	2.1	2.5	0.1	—	1.4
10: (42 mpcf)	1.2	2.3	1.0	—	—	1.2
11: (47 mpcf)	1.6	15.2	0.5	—	—	4.7
12: (70 mpcf)	1.8	2.5	1.1	—	—	1.5
13: (140 mpcf)	15.8	3.3	0.5	—	—	5.2
Total	100	100	100	100	100	100
Mean dust level (mpcf)	30.8	21.8	9.5	4.2	1.7	17.3
MINE AND MILL AT ASBESTOS						
Number of records	2002	1493	1273	723	237	5728
Percentage by dust category						
1: (0.5 mpcf)	2.5	4.6	10.4	8.7	84.0	9.0
2: (2 mpcf)	41.5	49.6	69.0	87.6	16.0	54.5
3: (7 mpcf)	6.3	8.5	9.0	3.5	—	6.9
4: (12 mpcf)	7.7	10.0	4.6	0.1	—	6.4
5: (17 mpcf)	2.3	2.2	1.7	0.1	—	1.8
6: (22 mpcf)	1.8	1.7	2.7	—	—	1.6
7: (27 mpcf)	2.3	7.0	1.7	—	—	3.0
8: (32 mpcf)	1.7	5.5	0.7	—	—	2.2
9: (37 mpcf)	17.7	6.5	—	—	—	7.9
10: (42 mpcf)	5.9	3.9	—	—	—	3.1
11: (47 mpcf)	4.9	0.2	—	—	—	1.8
12: (70 mpcf)	5.3	0.1	—	—	—	1.9
13: (140 mpcf)	—	0.1	—	—	—	0.0
Total	100	100	100	100	100	100
Mean dust level (mpcf)	19.1	11.6	4.2	1.9	0.7	10.9
FACTORY IN ASBESTOS						
Number of records	293	343	245	172	43	1096
Percentage by dust category						
1: (0.5 mpcf)	9.2	9.3	15.5	16.9	83.7	14.8
2: (2 mpcf)	58.4	53.4	65.7	80.8	16.3	60.3
3: (7 mpcf)	11.6	25.1	14.3	2.3	—	14.5
4: (12 mpcf)	4.8	4.4	3.3	—	—	3.4
5: (17 mpcf)	2.4	0.9	0.4	—	—	1.0
6: (22 mpcf)	1.7	1.7	—	—	—	1.0
7: (27 mpcf)	0.7	2.0	—	—	—	0.8
8: (32 mpcf)	0.7	1.2	0.8	—	—	0.7
9: (37 mpcf)	6.1	0.6	—	—	—	1.8
10: (42 mpcf)	0.7	1.2	—	—	—	0.5
11: (47 mpcf)	1.7	0.3	—	—	—	0.5
12: (70 mpcf)	1.7	—	—	—	—	0.5
13: (140 mpcf)	0.3	—	—	—	—	0.1
Total	100	100	100	100	100	100
Mean dust level (mpcf)	10.4	5.8	3.1	1.7	0.7	5.1

valent to 175 fibres/ml. The interval between first exposure and death averaged 47 years, ranging from 15 to 71 years: thus many of even the latest cases would have been exposed before the industry had done very much to 'clean up its act'. The corollary is that there may be a continuing, though small and diminishing, excess of lung cancer at Company 3 arising from conditions in the 1950s and 1960s.

On the other hand, modern dust conditions are well below the average even of dust category 1 and so there can be considerable confidence that the risk of lung cancer as a result of such exposure has become vanishingly small.

ENVOY

In this paper, the last of a long series since 1971 on mortality in Quebec chrysotile miners and millers and the fourth of a recent quartet (the others being: Liddell *et al.*, 1997; McDonald and McDonald, 1997; and McDonald *et al.*, 1997), it is appropriate to present the main conclusions relating to both lung cancer and mesothelioma.

It is abundantly clear that the risks of excess lung cancer in this industry, except after extremely high dust exposure, were very low. The overall excess, 1904–1992, in the cohort (which included the great majority of men recruited to the industry over several decades) is estimated as no more than 65 deaths (0.8% of 8009) and little or no excess was seen below 300 mpcf × years. To accumulate such exposure, a man would have had to spend his whole working life in dust levels of 5–6 mpcf, very roughly equivalent to 20 fibres/ml, orders of magnitude higher than permitted today—or of course a shorter period in even more severe conditions. Among miners and millers, there were just 33 mesothelioma deaths in a total of 7456 from all causes (0.4%) and none were in men employed less than two years. What has now become evident is that both these modest excesses were concentrated in men employed in the central area of Thetford Mines, with relatively little either in the periphery there or in the large mining and milling industry in Asbestos. This geographical pattern points to some important and clear-cut geological difference between areas of high and low risk; the distribution of amphibole fibres in the tremolite series offers a reasonable, biologically plausible and sufficiently specific explanation. While we accept that associations demonstrated epidemiologically cannot *prove* cause and effect, we believe the answer to the fundamental question posed by Bradford Hill (Hill, 1966)—"is there any other way of explaining the set of facts before us, is there any other answer which is equally, or more, likely than cause and effect?"—is "No".

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REFERENCES

Alderson, M. (1976) *An Introduction to Epidemiology*, pp. 27–29. Macmillan, London.

Armitage, P. and Berry, G. (1994) *Statistical Methods in Medical Research*, 3rd Edn, p. 428. Blackwell, Oxford.

Berry, G., Newhouse, M. L. and Antonis, P. (1985) Combined effects of asbestos and smoking on mortality from lung cancer and mesothelioma in factory workers. *Br. J. ind. Med.* **42**, 12–18.

Gibbs, G. W. and Lachance, M. (1972) Dust exposure in the chrysotile asbestos mines and mills of Quebec. *Arch. Environ. Health* **24**, 189–197.

Gibbs, G. W. and Lachance, M. (1974) Dust–fibre relationships in the Quebec chrysotile industry. *Arch. Environ. Health* **28**, 69–71.

Hill, A. B. (1966) *Principles of Medical Statistics*, 8th Edn, pp. 305–313. The Lancet Ltd., London.

Liddell, D. (1988) Maintaining progress in the analysis of cohort studies. In: *Progress in Occupational Epidemiology* (Edited by Hogstedt, C. and Reuterwall, C.), pp. 71–74. Elsevier Science Publications, Amsterdam.

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

Liddell, F. D. K., Thomas, D. C., Gibbs, G. W. and McDonald, J. C. (1984) Fibre exposure and mortality from pneumoconiosis, respiratory and abdominal malignancies in chrysotile production in Quebec, 1926–75. *Ann. Acad. Med. Singapore* **13**(2) (suppl.), 340–344.

McDonald, A. D., Case, B., Churg, A., Dufresne, A., Gibbs, G. W., Sébastien, P. and McDonald, J. C. (1997) Mesothelioma in Quebec chrysotile miners and millers: epidemiology and aetiology. *Ann. occup. Hyg.* **41**, 707–719.

McDonald, J. C., Liddell, F. D. K., Dufresne, A. and McDonald, A. D. (1993) The 1891–1920 birth cohort of Quebec chrysotile miners and millers: mortality 1976–88. *Br. J. Ind. Med.* **50**, 1073–1081.

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. *Ann. occup. Hyg.* **41**, 699–705.

Sébastien, P., McDonald, J. C., McDonald, A. D., Case, B. and Harley, R. (1989) Respiratory cancer in chrysotile textile and mining industries: exposure inference from lung analysis. *Br. J. Ind. Med.* **46**, 180–187.

Sluis-Cremer, G. K., Liddell, F. D. K., Logan, W. P. D., Bezuidenhout, B. N. (1992) The mortality of amphibole miners in South Africa, 1946–80. *Br. J. Ind. Med.* **49**, 566–575.

Statistics and Epidemiology Research Corporation (1989) EGRET. Reference Manual. Seattle.

Vacek, P. M. and McDonald, J. C. (1990) Effect of intensity in asbestos cohort exposure-response analysis. In: *Occupational Epidemiology* (Edited by Sakurai, H. *et al.*), pp. 189–193.

World Health Organisation (1977) *Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death*, Vol. 1. World Health Organisation, Geneva.

APPENDIX

Dust levels by period and by place of employment

Liddell *et al.* (1997) explain how an exposure file had been created containing, for each of the nearly 11,000 men in the cohort, an annual record consisting of: (a) the fraction of the specific year worked; (b) an indicator of the length of the work week in that year (taken as 66 hours before 1938, 48 hours 1938–1949 and 40 hours thereafter); and (c) an estimate of the level of dust, in millions of particles per cubic foot, or

Table 11. Distributions of 243 cases and 970 referents at Company 3 in Thetford Mines according to years worked in 13 dust categories

	Years* worked in specific dust category					
	0	>0, <1	1, <5	5, <20	20+	Total
Dust category 1:						
% of 243 cases	82.7	2.9	7.4	6.2	0.8	100
% of 970 referents	82.0	4.4	7.3	4.3	2.0	100
Dust category 2:						
% of 243 cases	29.2	14.4	20.6	26.3	9.5	100
% of 970 referents	37.0	12.4	14.8	25.3	10.5	100
Dust category 3:						
% of 243 cases	32.5	9.1	23.9	30.0	4.5	100
% of 970 referents	38.4	9.8	24.5	22.4	4.9	100
Dust category 4:						
% of 243 cases	55.1	6.2	20.6	16.0	2.1	100
% of 970 referents	62.5	5.6	17.5	13.1	1.3	100
Dust category 5:						
% of 243 cases	70.8	5.8	17.3	6.2	—	100
% of 970 referents	77.0	4.8	15.3	2.9	—	100
Dust category 6:						
% of 243 cases	82.7	1.2	13.6	2.5	—	100
% of 970 referents	88.1	0.6	10.0	1.2	—	100
Dust category 7:						
% of 243 cases	86.8	1.6	10.3	1.2	—	100
% of 970 referents	90.2	0.7	8.4	0.7	—	100
Dust category 8:						
% of 243 cases	73.7	2.9	19.8	3.7	—	100
% of 970 referents	84.1	3.1	10.9	1.9	—	100
Dust category 9:						
% of 243 cases	85.2	.	12.8	2.1	—	100
% of 970 referents	88.6	1.2	9.4	0.8	—	100
Dust category 10:						
% of 243 cases	86.8	1.2	11.5	0.4	—	100
% of 970 referents	91.2	1.6	6.4	0.5	0.2	100
Dust category 11:						
% of 243 cases	75.3	0.8	10.7	13.2	—	100
% of 970 referents	79.7	1.8	12.0	6.5	0.1	100
Dust category 12:						
% of 243 cases	85.6	0.8	11.9	1.6	—	100
% of 970 referents	87.7	1.9	8.7	1.8	—	100
Dust category 13:						
% of 243 cases	73.7	6.6	12.3	6.2	1.2	100
% of 970 referents	79.0	4.3	11.1	5.3	0.3	100

*adjusted for length of working week.

Table 12. Regression coefficients at various stages of pooling dust categories: 488 cases and 1941 referents

	Stage of pooling			
Years in dust category:—	Stage 1 (13 variables)	Stage 2 (12 variables)	Stage 4 (10 variables)	Stage 5 (9 variables)
1 (0.5 mpcf)	0.00006	−0.00002	−0.00093	—
2 (2 mpcf)	0.00561	0.00554	0.00535	0.00534
3 (7 mpcf)	0.01682	0.01668	0.01732	0.01733
4 (12 mpcf)	0.00290	0.00298	0.00271	0.00272
5 (17 mpcf)	0.01310	0.01340	0.01636	0.01645
6 (22 mpcf)	0.08091	0.08071	0.07223	0.07217
7 (27 mpcf)	0.1136	0.1134	0.1138	0.1138
8 (32 mpcf)	0.05931	0.05638		
9 (37 mpcf)	0.01407	0.01220	0.00378	0.00381
10 (42 mpcf)	−0.08373	−0.08730		
11 (47 mpcf)	0.05594	0.05754	0.05476	0.05468
12 (70 mpcf)	−0.00866	0.01064	0.01051	0.01054
13 (140 mpcf)	0.01933			

mpcf. in 13 categories (Gibbs and Lachance, 1972), in which the man was employed in that year. Each man's record was compiled from the (calendar) year in which he started work to the year in which he finished and for each year in between. The longest period of service was found to be 58 years and, as first and last years were incomplete, the file had to allow for 59 annual entries; to retain fixed record length, blank records were inserted for the years after each man finished work.

As the file was enormous (5.9 Megabytes), a systematic sample was taken as follows. First, we selected for every man the record for the year after that in which he started work, i.e. usually his first complete year of work. Then, we added the records for every tenth succeeding year, i.e. the 12th, 22nd, 32nd, 42nd and 52nd, giving six records for each man. As expected, most records were blank (71%), usually because service had been completed earlier but some because of a gap in service; a further 5% referred to less than a full year's service, while 3% were for men first employed in mines 4–9. The calendar year was entered by programme into the remaining 13,609 records, which were then classified into five periods, namely 1904–1937*, 1938–1949, 1950–1961, 1962–1973 and 1964–1985. Each of the small proportion of records of work in different dust categories within the year was allocated to the category the mean of which was closest to the (monthly weighted) average dust level which had been used in the basic 5.9 M-byte file.

As there is no good reason for believing the members of the cohort were employed in selected areas of the industry, it seems appropriate to accept the 13 906 records as reasonably representative of dust conditions in the three places of employment, 1904–1985. Table 10 shows the distribution of these records according to dust category, by period, for each place of employment. Also given are the mean dust levels calculated from the levels extracted from the basic file, i.e. before re-categorisation.

Distributions of exposure measures

Extremely high coefficients of variation of all the exposure measures were observed not only overall (Table 2) but also for both cases and referents at all three place of employment. Table 11 gives the distributions of the 1213 subjects first employed at Company 3 by (adjusted) years worked in each dust category. There were only four categories (2–4 and 11) in which substantial numbers of cases were employed for 5 years or more and there were six categories (6–10 and 12) which had been worked in for such periods by less than 10 cases each and by no more than 18 referents. Only slight variations in the numbers of referents, which would probably arise from different random selections, would have had substantial effects on the LR statistics.

Correlations between exposure measures

One important source of correlations between exposure measures was from men who were employed for long periods; they tended to stay in the same job, but the job itself would often be allocated to lowering dust categories as the environment improved. This led to correlations between the measures for adjacent categories, which would also have major effects on the LR statistics.

Adjustments for length of the working week

There are many reasons why the mean years spent at specific dust levels in Table 1 of Vacek and McDonald (1990) are quite unlike what might at first sight appear to be corresponding means in our Table 2; much the most important lies in the treatment of the adjustment for length of work-week. The earlier authors incorporated this adjustment into the 'dust value', so that, for example, a man who had been employed over a period 10 calendar years before 1938 in dust category 8 (averaging 32 mpcf) would have been allocated the dust value ($32 \times 1.65 =$) 52.8 mpcf (i.e. in 'level' 7, the highest: 50 or more mpcf) and 'duration' of 10 years, so that the cumulative exposure would be 528 mpcf × years. In the current paper, this example—with the same cumulative exposure of 528 mpcf × years—would have been treated as ($10 \times 1.65 =$) 16.5 adjusted years at 32 mpcf.

Dust-fibre relationships

Liddell *et al.* (1984) estimated a factor to convert dust counts to fibre counts as about 3.5 (fibres/ml)/mpcf, but stated this would be quite unreliable except applied to mean dust levels for substantial groups of Quebec asbestos workers. For the many jobs in which the 2217 men included in their study had worked, the fibre/dust ratios had ranged from 0.3 to 30 (fibres/ml)/mpcf, virtually independently of the dust level; in the current study ratios job by job must have varied similarly, so that the classification of jobs by dust category would not be a reliable classification by fibre count. The two important reports by Gibbs and Lachance (1972); Gibbs and Lachance (1974) give some indication of the inherent complexity; a simple example is that work on the tailings dump in 1968 was extremely dusty but, as most of the fibre would have been extracted, the fibre dust ratio must have been quite low.

Elimination of negative regression coefficients

In all the conditional regression analyses of the full model, i.e. with 13 exposure measures, there was at least one negative regression coefficient, which taken at face value would imply a protective effect of exposure. Years in the highest relevant dust category were pooled with those in the adjacent category and the analysis was repeated. This process was iterated until either all coefficients had become positive, when it was terminated, or until the only negative coefficient was for category 1; in that circumstance, category 1 was eliminated from the model, which was equivalent to setting the coefficient to zero and the odds ratio to unity.

The process is illustrated by Table 12, which was analyzed in five stages as follows:—

Stage	Pooling	Number of variables	Dust categories with negative coefficients
1	—	13	Cats. 10 and 12
2	Cats. 12 & 13	12	Cats. 10 and 1
3	Cats. 12 & 13 and Cats. 9 & 10	11	Cats. 9–10 and 1
4	Cats. 12 & 13 and Cats. 8–10	10	Cat. 1
5	Cats. 12 & 13 and Cats. 8–10 and eliminating Cat. 1	9	—

Admittedly, there was a degree of arbitrariness in some of the pooling carried out, but every effort was made to retain any 'significant' effects.

*Not surprisingly in view of the methods of evaluation, a three-way split of this period was not revealing.

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