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Asbestos Fibre Concentrations in the Lungs of Brake Workers: Another Look

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Objective: To reanalyse data on the lung content of asbestos fibres among brake mechanics.

Methods: I re-analysed data published by Butnor, Roggli and colleagues on the lung content of chrysotile and tremolite asbestos fibres among brake mechanics and controls. Statistics of the distributions were estimated by maximum likelihood to accommodate observations below the detection limit. Mean concentrations were compared by the *t*-test, bootstrap resampling and interval-censored survival methods.

Results: The mean concentrations of fibres were higher among the brake workers than the controls. The concentration of tremolite fibres was higher than the concentration of chrysotile, a pattern similar to that observed among Quebec chrysotile miners and millers.

Conclusions: Re-analysis of published data does not support the interpretation that, in automotive brake repair workers with malignant mesothelioma, asbestos content is within the normal range. The alternative interpretation that brake mechanics have a greater than background burden of asbestos fibres, attributable to occupational exposure to dusts from friction products manufactured from Canadian chrysotile, appears more credible. This asbestos burden might be associated with an increased risk of asbestos-associated cancers.

Keywords: asbestos brakes; friction products; lung fibre content

INTRODUCTION

Mesothelioma is a rare tumour strongly associated with exposure to asbestos. During most of the 20th century, asbestos was an important constituent of vehicular braking systems (Paustenbach *et al.*, 2004). In 1973, the US Environmental Protection Agency reported that brake linings contained 33–73% asbestos by weight and estimated that 32 million kg of asbestos were worn away from brake linings each year (Jacko and DuCharme, 1973). Automotive and brake mechanics have occasionally been diagnosed with mesothelioma, and the attributability of these tumours to asbestos exposure has become a contentious legal issue in the US. A number of reviews have been published by authors working for lawyers or involved with litigation. Lemen (2004) concluded that 'even the so called "controlled" use of asbestos containing brakes poses a health risk to workers, users, and their families'. Laden *et al.* (2004) concluded that 'the evidence did not support an increase in risk of either lung cancer or mesothelioma among male automobile mechanics occupationally exposed to asbestos from brake repair'. Goodman *et al.* (2004) concluded that 'employment as a motor vehicle mechanic does not increase the risk of developing mesothelioma'. I was asked by a defence-side law firm to examine the literature on mesothelioma and friction materials. Following review and discussion, I was not asked to prepare a written report. Other than this instance, I have had no involvement with friction-materials litigation.

During my reading, I noticed that both Laden *et al.* (2004) and Goodman *et al.* (2004) referred to a study of the analysis of asbestos fibres in the lungs of subjects with mesothelioma published by Roggli *et al.* (2002). Both sets of reviewers interpreted the data as being consistent with the opinion that 'brake dust is unlikely to cause mesothelioma'. 'Individual' data for 10 cases from this series of subjects with mesothelioma were published in 2003 (Butnor *et al.*, 2003). Commenting on these data, Butnor *et al.* write 'Lung burden analyses in automotive brake repair workers with malignant mesothelioma in our series reflect asbestos content within the normal range or elevated commercial amphiboles'. I have examined

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the brake worker data reported in Butnor *et al.* (2003) and the data for 19 control subjects without occupational asbestos exposure published by Roggli *et al.* (2002) from the same laboratory. I believe that a different interpretation of these data is credible, and my analysis and interpretation are presented below.

METHODS

The data used in this study were abstracted from published reports. The study subjects were selected by Roggli and Butnor from the consultation files of Victor Roggli (Butnor *et al.*, 2003). The control subjects were a convenience sample of subjects without occupational asbestos exposure (Roggli *et al.*, 2002). The counting methodology was described by Butnor *et al.* (2003). 'Fibre analyses were performed on formalin-fixed or paraffin-embedded lung parenchyma using the sodium hypochlorite digestion procedure described (Roggli *et al.*, 2004). Digested lung tissue was collected on 0.4 μm pore size Nuclepore filters. For scanning electron microscopic (SEM) analysis, the filter was mounted on a carbon disc with colloidal graphite and then sputter-coated with gold. Only fibres ≥5 μm in length with a length to width ratio of at least 3:1 and approximately parallel sides were counted. Fibres meeting these criteria were quantified by examining 100 consecutive fields, with a total area of ~2.53 mm^2, or until a 200 fibre count was reached. The limit of detection is ~400 fibres/g for a 0.3 g sample. For cases in which no asbestos fibres were detected, the value was reported as less than the detection limit for that case. The chemical composition of fibres was determined by energy dispersive X-ray analysis. Asbestos fibres were classified as commercial amphiboles, specifically amosite + crocidolite (AC), non-commercial amphiboles, including tremolite, anthophyllite and actinolite (TAA), or chrysotile (Roggli *et al.*, 1992b)'.

I have made several assumptions in the analysis and interpretation of the Roggli and Butnor data. These are

1. I assume that most of the friction material products used in the North American market during the 20th century would have been manufactured using chrysotile from the mines of Quebec (Virta, 2000).
2. Quebec chrysotile is known to be contaminated with fibrous tremolite (McDonald and McDonald, 1997). I assume that both chrysotile and tremolite fibres would be constituents of respirable brake dust.
3. Roggli and Butnor report counts of non-commercial amphiboles, including TAA as a single group. According to Roggli *et al.* (1993), the vast majority of these fibres had the typical composition of Si–Mg–Ca which is the chemical signature for tremolite. I have presumed that TAA is predominantly tremolite.
4. I assume that counts of asbestos fibres would be lognormally distributed in the lungs of both case and control subjects in the Roggli series. This assumption is confirmed by the Shapiro–Wilk test of normality on the log-transformed data for the tremolite content of the lungs of both the cases ($P > 0.75$) and controls ($P > 0.87$). Figure 1 shows, for the control series, the fit of the tremolite data, above the detection limit, to the lognormal distribution. There were too few subjects

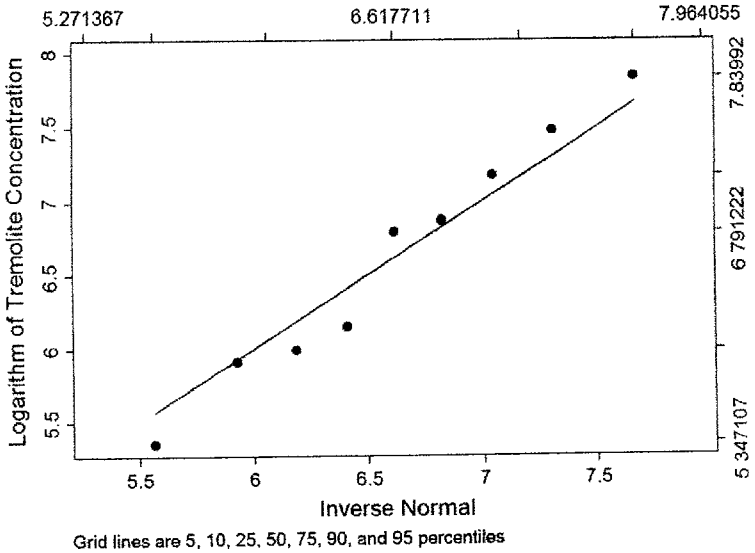


Fig. 1. The fit of the observed tremolite data to a lognormal distribution.

with counts above the detection limit to examine in detail the statistical distribution of the chrysotile fibres.

One important feature of the fibre count data in the Roggli and Butnor publications is that many observations, particularly for chrysotile, were below the detection limit of the analytical method. Roggli and colleagues dealt with this issue by presenting the 'median' as the summary of the data distribution. Comparison of point estimates of the median, without consideration of its sampling distribution, is not an optimal method for comparing distributions between two series of subjects. It is possible, however, to estimate the parameters (mean and standard deviation) of the distributions using the method of maximum likelihood (ML) and to make quantitative comparisons of the distributions of fibre concentrations among the case and control subjects. In 2001, a colleague and I published a methodology, implemented in spreadsheet software, to perform the ML calculations (Finkelstein and Verma, 2001). The ML method was used here to compute the parameters of the distributions of the counts of tremolite and chrysotile fibres in the lungs of the case and control subjects, assuming that the distributions were lognormal.

It is of interest to compare the distributions of fibre concentrations in the lungs of cases and controls. The standard method would be to use a *t*-test to compare the estimated means of the logarithmic distributions. However, because of the data points below the detection limit, it is not clear what are the correct degrees of freedom to be used in the *t*-test. The standard method was thus supplemented here by two other methods.

In the second method, the means of the (log-transformed) distributions among mesothelioma and control subjects were compared using the bootstrap method (Davison and Hinkley, 1997). Thirty bootstrap samples were drawn from each of the case and control series and the ML method was used to compute estimates of the means of the log-transformed data for each series. The difference between the means of the case and control series was then calculated for each bootstrap sample.

The third method was that of interval-censored survival analysis. In this method, we conceive of each fibre concentration data point as analogous to a 'length of survival' in a hypothetical survival analysis. Observations below the detection limit are treated as 'left censored'; that is, in the survival framework, they are thought to have occurred at an unknown time before entry to the study, where the time of entry is here the analytic detection limit. The program INTCENS (Griffin, 2005) written for the Stata statistical software package (StataCorp, 2005) was used to perform the regression calculations. Case or control status was used as the independent variable in the survival regression model and the distribution of the 'survival times' (that is, the lung fibre concentrations) was taken to be lognormal.

RESULTS

Table 1 shows the individual counts (fibres per gram wet lung tissue) of uncoated tremolite and chrysotile fibres ≥5 μm in length, for the 10 brake workers and 19 control subjects, abstracted from the papers of Butnor *et al.* (2003) and Roggli *et al.* (2002). Table 2 shows the means and standard deviations of the distributions of fibre counts from the lungs of brake workers and control subjects computed by the method of ML. The concentrations of both chrysotile and tremolite were higher in the lungs

Table 1. Tremolite and chrysotile asbestos fibre counts (>5 μm in length per gram wet lung) in the lung tissues of brake workers (n = 10, labelled C) and control subjects (n = 19, labelled CL)

Subject number	Number of fibres: tremolite >5 μ	Number of fibres: chrysotile >5 μ
C1	2180	2180
C2	440	<440
C3	4630	<660
C4	720	<720
C5	1160	<580
C6	490	<490
C7	<340	<340
C8	240	<120
C9	3280	2180
C10	2170	720
CL1	<990	<990
CL2	1770	<1770
CL3	210	<100
CL4	400	<400
CL5	<570	<570
CL6	2540	<2540
CL7	470	<470
CL8	<760	<760
CL9	890	<300
CL10	<170	<170
CL11	<1000	1000
CL12	1310	<650
CL13	960	<960
CL14	<790	<790
CL15	<430	<430
CL16	<510	510
CL17	370	<370
CL18	<600	<600
CL19	<600	<600

Data are obtained from the publications of Butnor *et al.* (2003) and Roggli *et al.* (2002).

of the brake workers than in the lungs of the control subjects.

Comparison of the fibre concentrations in the lungs of case and control subjects

The t-test comparison. The t-test of the hypothesis that the concentration of chrysotile was greater in the lungs of the brake workers than in the lungs of the control subjects had a P-value = 0.13. The t-test of the hypothesis that the concentration of tremolite was greater in the lungs of the brake workers than in the lungs of the control subjects had a P-value = 0.023.

Comparisons by the bootstrap method. In the bootstrap comparisons, I drew 30 bootstrap samples among the cases and controls. For each bootstrap sample, I computed the ML estimate of the mean of the log-transformed data and subtracted the estimate of the mean (log concentration) for the controls from that of the estimate of the mean (log concentration) for the cases. Because only a few of the chrysotile measurements exceeded the limit of detection, among the 30 bootstrap draws for chrysotile were five (three case draws, two control draws) in which none of the data points were greater than the detection limit. In those instances, the ML method did not converge to a positive value and those draws were omitted from the case–control comparisons.

Table 2. Means and standard deviations of the distributions of logarithmically transformed fibre counts in the lungs of brake workers and control subjects

	Brake workers (n = 10)	Control subjects (n = 19)
Chrysotile		
Mean (standard deviation) of logarithmically transformed data	5.1 (1.9)	4.3 (1.4)
Tremolite		
Mean (standard deviation) of logarithmically transformed data	6.9 (1.1)	6.0 (1.0)

Statistics are computed by the method of ML.

Figure 2 shows the distributions of the means of the log-transformed tremolite fibre concentrations for the 30 bootstrap draws among the case and control subjects. For each bootstrap draw, the mean concentration among the controls was subtracted from that of the case subjects. Figure 3 shows, for chrysotile, the results of the subtraction of the estimates of the mean log(concentrations) for the controls from those of the cases for each of the 25 bootstrap samples. In 14 of 25 bootstrap samples, the mean concentration was higher among the cases and in 11 the mean concentration was higher among the controls. This small difference in proportions is consistent with no significant differences between the chrysotile concentrations among the case and control subjects. Figure 4 shows the results of the same computation for the 30 bootstrap draws for the tremolite counts. In all 30 bootstrap samples, the mean concentration was higher among the cases than among the controls. This difference in proportions is consistent with a significant difference between the mean tremolite concentrations among the case and control subjects.

Comparisons by interval-censored survival analysis. The test of the hypothesis that the concentrations of chrysotile were greater in the lungs of the cases than in the lungs of the controls had a P-value = 0.095. The test of the hypothesis that the concentrations of tremolite

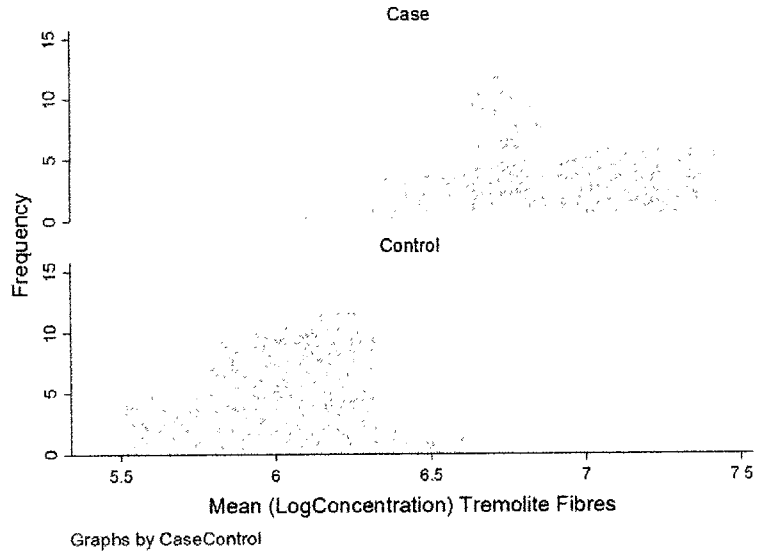


Fig. 2. Comparison, for brake workers and controls, of the distributions of ML-estimated means from 30 bootstrap results using tremolite data as source.

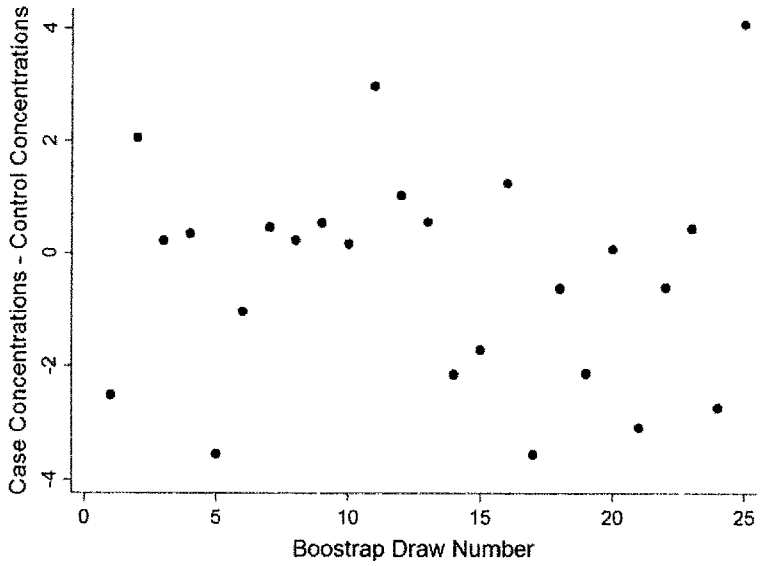


Fig. 3. For chrysotile, the results of the subtraction of the estimates of the mean log(concentrations) for the controls from those of the cases for each of 25 bootstrap samples.

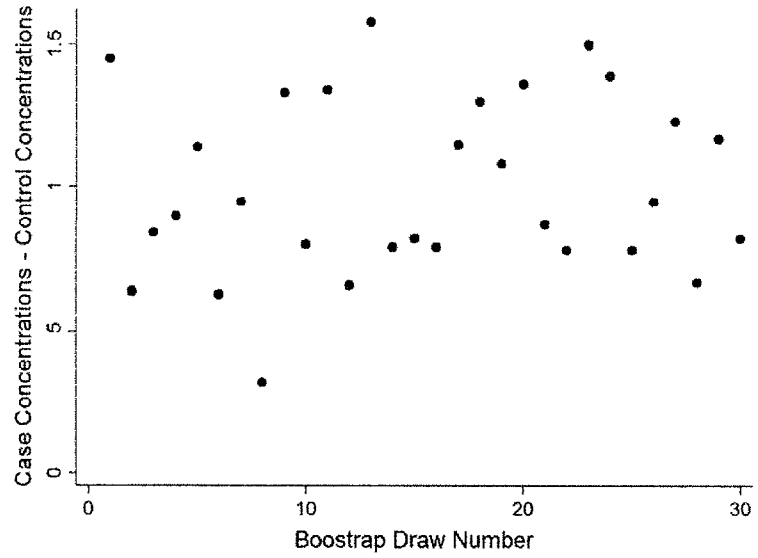


Fig. 4. For tremolite, the results of the subtraction of the estimates of the mean log(concentrations) for the controls from those of the cases for each of 30 bootstrap samples.

were greater in the lungs of the cases than in the lungs of the controls had a P-value = 0.017.

The three comparison methods were thus in agreement; the mean of the log(concentrations) of tremolite, but not of chrysotile, was significantly higher in the lungs of the cases than the lungs of the control subjects.

DISCUSSION

Measurements of asbestos fibre counts in the lungs of 10 brake workers were reported by Butnor *et al.* (2003) and data for a series of 19 control subjects were reported by Roggli *et al.* (2002). After analysing their data, Butnor *et al.* wrote 'lung burden analyses in automotive brake repair workers with malignant mesothelioma in our series reflect asbestos content within the normal range or elevated commercial amphiboles'. I believe that another interpretation of these data is credible.

Table 2 showed that, using the method of ML to deal with observations below the analytical detection limit, the mean concentrations of both chrysotile and

tremolite fibres were higher among the brake workers than among the control subjects. Three methods of comparison were in agreement that the mean of the log(concentrations) of tremolite, but not of chrysotile, was significantly higher in the lungs of the cases than the lungs of the control subjects. While the point estimate of the concentration of chrysotile in the lungs of the case subjects was higher than that in the control subjects, the difference in means did not achieve statistical significance for chrysotile. However, there were only 10 case and 19 control subjects and the statistical power of the *t*-test was consequently very low; the power to detect a significant difference in means at the 5% level was only ~22%.

The asbestos utilized in the manufacture of the friction products used in the North American market during much of the 20th century came from the mines of Quebec. It is well known that these ores were contaminated with fibrous tremolite and some authors have postulated that the incidence of mesothelioma and of lung cancer resulting from exposure to commercial chrysotile is mainly attributable to low but varying levels of tremolite fibres (McDonald and McDonald, 1997). Butnor and Roggli classified the non-commercial amphiboles that they counted as TAA. However, the vast majority of these fibres had the typical composition of Si–Mg–Ca which is the chemical signature for tremolite (Roggli *et al.*, 1993). I have thus presumed that TAA is predominantly tremolite. Tremolite fibres were present in the lungs of both the cases and controls in the Roggli series. In fact, the mean concentration of tremolite fibres was higher than the mean concentration of chrysotile in the lungs of both the cases and controls. How could it be possible for the concentrations of a minor contaminant to be higher than the concentrations of the principal commercial fibre? Does this exonerate occupational exposure to brake dust as the source of the fibres?

In 1999, a colleague and I published the results of an analysis of the asbestos fibre content of the lungs of 72 Quebec chrysotile miners and millers and of 49 control subjects, measured using analytical transmission electron microscopy (Finkelstein and Dufresne, 1999). We concluded that tremolite fibres persisted in lung tissue with a very long half-life, but chrysotile fibres were cleared from lung tissue with a clearance rate that varied inversely with the length of the chrysotile fibres. For chrysotile fibres >10 μm in length, the clearance half-time was estimated to be ~8 years and the clearance half-time was ~6 years for fibres 5–10 μm in length. I have returned to that data set and computed the mean concentrations of fibres in the lungs of the Quebec chrysotile miners and millers and the control subjects. The results are presented in Table 3. We have the result that, among the Quebec chrysotile miners and millers, the lung concentrations of fibres of the contaminant (tremolite) were higher than the concentrations of the principal fibre (chrysotile). This is the same pattern that was seen in the lungs of the brake mechanics occupationally exposed to dusts of Quebec chrysotile. Since chrysotile is cleared from the lungs of brake workers, tremolite is arguably a better marker of exposure to Quebec chrysotile than is chrysotile itself.

CONCLUSIONS

Further examination of the lung fibre data obtained by Butnor and Roggli data show that the 10 brake workers with mesothelioma had higher mean concentrations of tremolite and chrysotile fibres in their lungs than did the control subjects without occupational asbestos exposure. The pattern of higher tremolite than of chrysotile concentrations is consistent with occupational exposure to dusts of Quebec commercial chrysotile. The alternative interpretation of the data of Butnor and Roggli is thus that automotive mechanics have elevated concentrations of asbestos fibres in their lungs, consistent with occupational exposure to commercial chrysotile. I believe that this interpretation is more strongly supported by the data than is the interpretation proposed by the authors.

One must be cautious in generalizing these observations, based as they are on data from only 10 subjects with mesothelioma and 19 control subjects. While the dust exposures of automotive mechanics are likely to have been less than those experienced by chrysotile miners and millers, it has been estimated that 1 million American workers are involved in installing and repairing clutch facings and brake shoes (Huncharek, 1990). In this circumstance, even a mild increase in risk might have produced cases of

Table 3. Means and standard deviations of the logarithms (base 10) of asbestos fibre concentrations (fibres >5 μm in length) in the lungs of Quebec chrysotile miners and millers (n = 72) and of control subjects (n = 49)

	Chrysotile: 5 to <10 μ in length	Tremolite: 5 to <10 μ in length	Chrysotile: >10 μ in length	Tremolite: >10 μ in length
Miners and millers	2.97 (1.00) [2950 f mg^{-1} dry lung tissue][a]	3.39 (0.70) [4300 f mg^{-1} dry lung tissue]	2.58 (0.86) [900 f mg^{-1} dry lung tissue]	2.71 (0.65) [850 f mg^{-1} dry lung tissue]
Controls	1.71 (0.46) [65 f mg^{-1} dry lung tissue]	1.85 (0.57) [100 f mg^{-1} dry lung tissue]	1.64 (0.40) [50 f mg^{-1} dry lung tissue]	1.66 (0.33) [50 f mg^{-1} dry lung tissue]

[a]Arithmetic mean concentrations are presented in square brackets.

asbestos-associated cancer among workers in this trade.

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REFERENCES

Butnor KJ, Sporn TA, Roggli VL. (2003) Exposure to brake dust and malignant mesothelioma. a study of 10 cases with mineral fiber analyses. Ann Occup Hyg; 47. 325–30.

Davison AC, Hinkley DV. (1997) Bootstrap methods and their application. Cambridge Cambridge University Press.

Finkelstein MM, Dufresne A. (1999) Inferences on the kinetics of asbestos deposition and clearance among chrysotile miners and millers. Am J Ind Med; 35. 401–12.

Finkelstein MM, Verma DK. (2001) Exposure estimation in the presence of nondetectable values another look. Am Ind Hyg Assoc J; 62: 195–8.

Goodman M, Teta MJ, Hessel PA *et al.* (2004) Mesothelioma and lung cancer among motor vehicle mechanics: a meta-analysis. Ann Occup Hyg, 48: 309–26.

Griffin J. (2005) Intcens. Available at http.//ideas.repec.org/c/boc/bocode/s453501.html. Accessed 16 June 2008.

Huncharek M. (1990) Brake mechanics, asbestos, and disease risk. Am J Forensic Med Pathol; 11: 236–40.

Jacko MG, DuCharme RT. (1973) Emissions· Measurements from Brake and Clutch Linings from Selected Sources. 68-04-0020. US EPA. Washington DC.

Laden F, Stampfer MJ, Walker AM. (2004) Lung cancer and mesothelioma among male automobile mechanics: a review. Rev Environ Health; 19· 39–61.

Lemen RA. (2004) Asbestos in brakes. exposure and risk of disease. Am J Ind Med; 45. 229–37.

McDonald JC, McDonald AD. (1997) Chrysotile, tremolite and carcinogenicity. Ann Occup Hyg; 41: 699–705.

Paustenbach DJ, Finley BL, Lu ET *et al.* (2004) Environmental and occupational health hazards associated with the presence of asbestos in brake linings and pads (1900 to present): a "state-of-the-art" review. J Toxicol Environ Health B Crit Rev; 7: 25–80.

Roggli VL, Pratt PC, Brody AR. (1993) Asbestos fiber type in malignant mesothelioma: an analytical scanning electron microscopic study of 94 cases. Am J Ind Med; 23: 605–14

Roggli VL, Sharma A, Butnor KJ *et al.* (2002) Malignant mesothelioma and occupational exposure to asbestos: a clinicopathological correlation of 1445 cases. Ultrastruct Pathol, 26: 55–65.

Roggli VL, Oury TD, Sporn TA. (2004) Pathology of asbestos-associated diseases. New York: Springer.

StataCorp LP. (2005) Stata statistical software. College Station, TX Version 9.1.

Virta RL. (2000) Asbestos. Mineral Yearbook: US Geological Survey. Washington DC.