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November 8, 2006

John W. Kelse, Corporate IH
Mgr. Corporate Risk Mgt. Department
R. T. Vanderbilt Company, Inc.
30 Winfield Street
P.O. Box 5150
Norwalk, Connecticut 06856-5150

Dear Mr. Kelse:

At your request I have reviewed four Workers' Compensation Claims alleging mesothelioma.

[redacted]

Mr.[redacted] worked for R. T. Vanderbilt as a miller operator and laborer from August, 1954 to January, 1955, during which time he was involved in crushing talc. Subsequently until 1970 he worked in quality control, spending only five percent of his time in the mill. From 1970 until 1994 he worked 25% of his time in the mill as a supervisor of quality control and was assigned a respirator in 1974. He smoked a pack of cigarettes a day since age 16. Chest x-rays on 02/29/88 were described as showing scarring in the pulmonary parenchyma or pleura of both lower lobes. In a letter dated 12/01/94 Dr. Ashraf diagnosed cancer of the lung and a pleural effusion, with a mention of alleged mesothelioma. Mr.[redacted] also suffered carcinoma of the prostate. A right-sided pleural effusion was noted on 03/22/94, and the PSA level was high. On 06/03/94 was PSA level was 9.7 and pleural fluid cytology was suspicious for adenocarcinoma. Biopsy on that date was reported to show malignant mesothelioma with calcified pleural plaques and "pulmonary ferruginous bodies." Dr. A. L. Katzenstein "felt that there was a mesothelioma present." Dr. W. K. C. Morgan attributes calcified pleural plaques to talc dust while working for R. T. Vanderbilt which did not become evident until mid or late 1980s. He cannot say whether the malignant effusion was caused by carcinoma of the lung or prostate, or whether it was a mesothelioma. In favor of a lung cancer was the presence of a nodule in the right middle lobe, which was not biopsied. Dr. Morgan notes that Mr[redacted] may have been exposed to asbestos before beginning to work for R. T. Vanderbilt. Before he developed a pleural effusion, pulmonary function tests indicated a restrictive impairment, consistent with pulmonary fibrosis.

On 07/06/95 a letter from Dr. Bertha Garcia of University Hospital, London, Ontario, states that the cytology from two cell blocks were suggestive of adenocarcinoma. In a report dated 06/07/95, Dr. Garcia notes "immunohistochemical stains are equivocal." On 01/17/96 Dr. Brian Boehlecke, Associate Professor of Medicine at the University of North Carolina sees "nothing which specifically suggests a mesothelioma."

On 06/03/94 Mr.[redacted] was admitted to St. Joseph's Hospital Health Center because of shortness of breath. The discharge diagnoses included pleural effusion, prostate cancer, and "malignant mesothelioma vs. benign asbestosis pleural disease." He was described as a 63-year old man with a 45-year history of smoking one pack of cigarettes a day. A Workers' Compensation Board Report dated 09/09/94, signed by Dr. Ashraf, lists "carcinoma lung, pleural effusion."

Mr[redacted] died on 09/06/95, and the Death Certificate lists the cause of death as mesothelioma.

Based on the information available to me, it is not possible to distinguish lung cancer from mesothelioma in this case, particularly in view of the long smoking history. If blocks of biopsy tissue are available, a careful immunohistochemical study would be advisable.

[redacted]

Dr. W. K. C. Morgan, in a letter of 02/01/95, states that a Mr. [redacted] worked for R. T. Vanderbilt from 03/19/54 to 06/30/87. He worked briefly as a talc crusher and then in quality control, spending 20% of his time in a dusty area. He was given a respirator in 1974. Mr[redacted] smoked a pack of cigarettes per day from the age of 18 to 43. The claims examiner stated that Mr.[redacted] chest x-ray showed calcified pleural plaques consistent with prior exposure to asbestos or talc. A chest film on 08/05/81 mentions pulmonary fibrosis and a possibility of cardiomegaly. Emphysema was diagnosed on 02/18/86. Dr. Boehlecke described right-sided pleural thickening and possible fibrosis of the base of the left parenchyma on 02/18/86. Mr.[redacted] was admitted to a hospital in Ogdendsburg, New York on 05/06/94 because of right-sided pleural effusion, and a CT scan showed two masses in the right lung. A biopsy was diagnosed as fibrosis mesothelioma, but "the basis for this diagnosis is uncertain." However, the initial diagnosis was pulmonary carcinoma with a right pleural effusion. The pathology report by Dr. Roark is compatible with lung cancer and mesothelioma. Bilateral calcified pleural plaques were diagnosed at the Mayo Clinic on 07/14/94, which could be related either to inhalation of asbestos or talc. A note indicates Mr.[redacted] had smoked 45-pack years. His date of birth was 1924. A slight restrictive impairment was noted on pulmonary function tests on 09/15/81. Dr. Morgan concludes that Mr. Evans had pleural plaques and pleural calcification related to his exposure to talc. He believes the malignancy is most likely lung cancer rather than mesothelioma. In a letter by Dr. Morgan dated 08/08/95 he notes that Mr. [redacted] died as a result of carcinoma of the lung, related to cigarette smoking.

[redacted]

Mr. [redacted] died on 05/17/01. The Certificate of Death lists the immediate cause of death as respiratory failure secondary to pleural effusion due to pleural tumor. "Talcum exposure" is also noted. A letter from Carl B. Friedman, M.D. (01/03/03) notes that Mr. [redacted] was exposed to "non-asbestiform amphibole (sic) consistent with tremolite." He points out that the "carcinogenicity of these materials is not associated with an increasing risk factor for mesothelioma or lung cancer in cohorts inside and outside of the talc industry." Vanderbilt talc is composed of non-asbestiform tremolite from 40-60%.

An autopsy was restricted to the chest. Lesions secondary to talc pleurodesis were present. The lower lobe and medial aspect of the lung was encased by a large, firm, white nodular mass, adherent to the diaphragm. Bulky masses were noted over the medial and upper lung. Microscopically, both lungs contained ferruginous bodies "consistent with asbestos bodies." In some foci, four or five asbestos bodies were present per high-power field. The tumor that involved the right pleura and lung showed a diffuse proliferation of atypical pleomorphic cells with sarcomatous and epithelioid patterns, "consistent with diffuse, malignant mesothelioma." The decedent was 87 years old at the time of death. A Workers' Compensation Form noted that "the death was found related to exposure to talcum dust." It is more likely that Mr. [redacted] was exposed to asbestos.

[redacted]

On 02/02/05 Mr. [redacted] was 73 years old. While in the Army from 1952-1954 he worked with dynamite and plastic explosives. He did mechanical work including brake adjustments as a service station attendant from 1956 to 1963. In 1964 he began employment with Gouverneur Talc from 1964 to 1997 (34 years). For 26 years he worked in a rotary mill operating a bulk loader. He smoked two packs of cigarettes per day for an approximate 76-pack year history. On 07/25/04 a CT scan had shown increased pleural thickening and an anterior mediastinal mass. He had previously been diagnosed with COPD. A note from Dr. Inhaber on 07/15/04 stated that Mr. [redacted] had significant exposure to asbestos and was on compensation for pleural thickening. On 08/05/04 a needle biopsy of the left upper lobe pleural-based mass was diagnosed by Dr. Abraham as consistent with mesothelioma. X-rays showed pleural plaques that were mildly calcified and bilateral lower lobe fibrotic changes with interstitial densitys. On 01/20/05 an anterior mediastinal mass was seen, together with an opacity at the right base.

Dr. Abraham noted that the tumor is predominantly an epithelial pattern malignancy. The tumor was positive for cytokeratin on both epithelial and spindle components, making it a biphasic mesothelioma. The tumor was positive for calretinin and WT-1 and stains for adenocarcinoma (CD15, CLA, B72.3, BerET4 and TTF-1) were negative. The study by Honda, et al. of talc miners is reviewed in detail. Mesothelioma is probably related to asbestos exposure.

Please feel free to call upon me for any further information.

Sincerely,

Emanuel Rubin, M.D.

MESOTHELIOMA W.C. CASE CHARACTERISTICS

DOD	Age at Death	Yrs GTC	Other Work	Wrong Diagnosis Likely: Yes	Wrong Diagnosis Likely: No	Wrong Diagnosis Likely: Unsure	Actual Asbestos Exposure: Yes	Actual Asbestos Exposure: No	Actual Asbestos Exposure: Unsure
1995	64	40 (54-94)	4 yrs Navy repairman	X (Tissue re-analysis supports adenocar.vs meso but poor specimen – 25 yr. smoker- had prostate cancer)					X (possible in navy -50-54
Death Certificate: "Mesothelioma, Thoracic, right"									
1995	71	33 (54-87)	4 yrs repairman			X (MD questions - may be matas. from underlying lung cancer)			X
Death Certificate; "Cardio-pulmonary arrest metastatic terminal cancer – meso. right lung"									
2001	86	20 (56-76)	15 yrs. Other area mines.			X (no tissue)	X GTC mine mucker brake pads conf. asbest		
Death Certificate: "Respiratory failure with pleural effusion – Pleural tumor"									
2005	74	34 (64-97)	10 yrs. Auto garage 2 yrs. Army demolition		X (confirmed)		X GTC wheeler with conf. asbest. In pads. Pos. brake work at auto garage Likely exp. Demol Of structures in army.		
Death Certificate: "Respiratory failure – mesothelioma"									

RJ Lee*Group*, Inc.

350 Hochberg Road
Monroeville, PA 15146
Tel: (724) 325-1776
Fax: (724) 733-1799

The Materials Characterization Specialists

Mr. John Kelse
R.T. Vanderbilt Company, Inc.
30 Winfield Street
PO Box 5150
Norwalk, CT 06856-5150

November 5, 2002

RE: Project No.: Lab hood panel board samples
R J Lee Group Project LBH201727

Dear Mr. Kelse:

RJ Lee Group has completed our analysis of the bulk samples submitted for analysis. The samples were received at RJ Lee Group on October 24, 2002 and assigned our laboratory numbers.

The samples were analyzed for asbestos content using polarized light microscopy (PLM) following a modified method as outlined in EPA/600/R-93/116, Method for the Determination of Asbestos in Bulk Building Materials. The results are included in the attached table. Photographs of the asbestos found in the samples follow the results table.

RJ Lee Group is accredited by the National Voluntary Laboratory Accreditation Program (NVLAP, #101208-00) for asbestos fiber analysis. This report may not be used to claim product endorsement by NVLAP or any agency of the US government.

These results are submitted pursuant to RJ Lee Group's current terms and conditions of sale, including the company's standard warranty and limitation of liability provisions. No responsibility or liability is assumed for the manner in which the results are used or interpreted. Unless notified in writing to return the samples covered by this report, RJ Lee Group will store the samples for a period of ninety (90) days before discarding. A shipping and handling fee will be assessed for the return of any samples.

If you have any questions on this report or if we can be of further assistance, please feel free to call me.

Sincerely,

Drew R. Van Orden, PE
Senior Scientist

Table I. **Polarized Light Microscopy (PLM) Results, EPA/600/R-93/116 Method**
RJ Lee Group Project No. LBH201727

Analyst: WHP

Analysis Report for R.T. Vanderbilt, Company

Client Sample ID	RJ Lee Group Sample ID	Non-Asbestos Components		Asbestos Content		Comments
#1 Pad under glass of photovolt - lab	3037351	Cellulose Opaques	95 % 5 %			White Fibrous Material
#2 Lab Glove Material Heater use	3037352	Fiberglass	100 %			White Fibrous Material
#3 Pipe Insulation Feed from boiler room to oil house	3037353	Mineral Wool Diatomaceous Earth	50 % 40 %	Chrysotile	10 %	White Fibrous Pipe Insulation
#4 Welding Pad	3037354	Opaques Sythentic Fibers	10 % 10 %	Chrysotile	80 %	Gray Woven Material
#5 Pipe Insulation First Aid Room	3037355	Mineral Wool Diatomaceous Earth	50 % 40 %	Chrysotile	10 %	White Fibrous Pipe Insulation

RJ Lee Group, Inc.
350 Hochberg Road
Monroeville, PA 15146

Date Analyzed 10/31/02

Table I. **Polarized Light Microscopy (PLM) Results, EPA/600/R-93/116 Method**
RJ Lee Group Project No. LBH201727

Analyst: WHP

Analysis Report for R.T. Vanderbilt, Company

Client Sample ID	RJ Lee Group Sample ID	Non-Asbestos Components		Asbestos Content		Comments
#6 Pipe Insulation Mez off generator area	3037356	Mixed Clays Calcite Quartz Cellulose	40 % 5 % 5 % 5 %	Chrysotile	45 %	White Fibrous Pipe Insulation
#7 Boiler Insulation	3037357	Mixed Clays Opaques Quartz	35 % 10 % 5 %	Chrysotile	50 %	Gray Fibrous Boiler Insulation
#8 Pipe Insulation Out of boiler room	3037358	Mixed Clays Calcite Opaques	30 % 10 % 10 %	Chrysotile	50 %	Gray Fibrous Pipe Insulaton
#9 Boards that line the wheeler	3037359	Cement Opaques Quartz	55 % 10 % 5 %	Chrysotile	30 %	Gray Fibrous Cement Board
#10 Gasket sheets on wheeler - blocks	3037360	Mineral Wool Mixed Clays Opaques	40 % 15 % 5 %	Chrysotile	40 %	White Fibrous Gasket

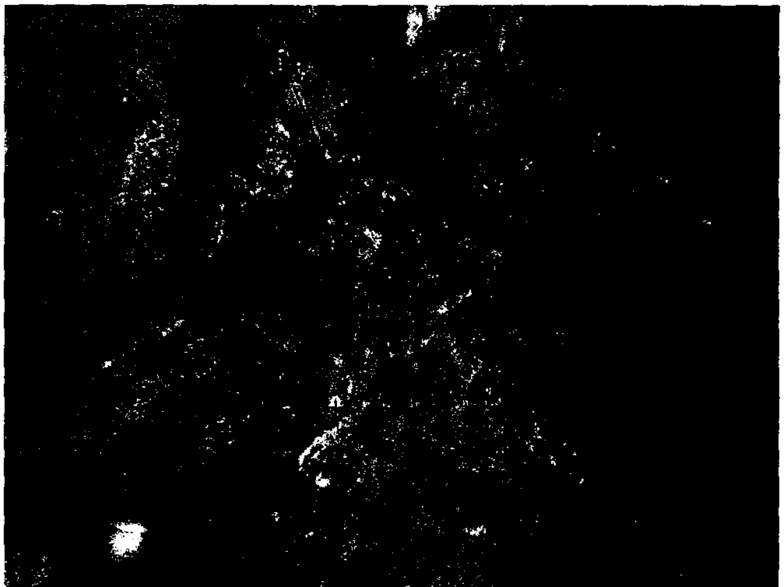
Table I. **Polarized Light Microscopy (PLM) Results, EPA/600/R-93/116 Method**
RJ Lee Group Project No. LBH201727

Analyst: WHP

Analysis Report for R.T. Vanderbilt, Company

Client Sample ID	RJ Lee Group Sample ID	Non-Asbestos Components		Asbestos Content		Comments
#11 Brake pad material	3037361	Cellulose	50 %	Chrysotile	50 %	Brown Fibers - Brake pad

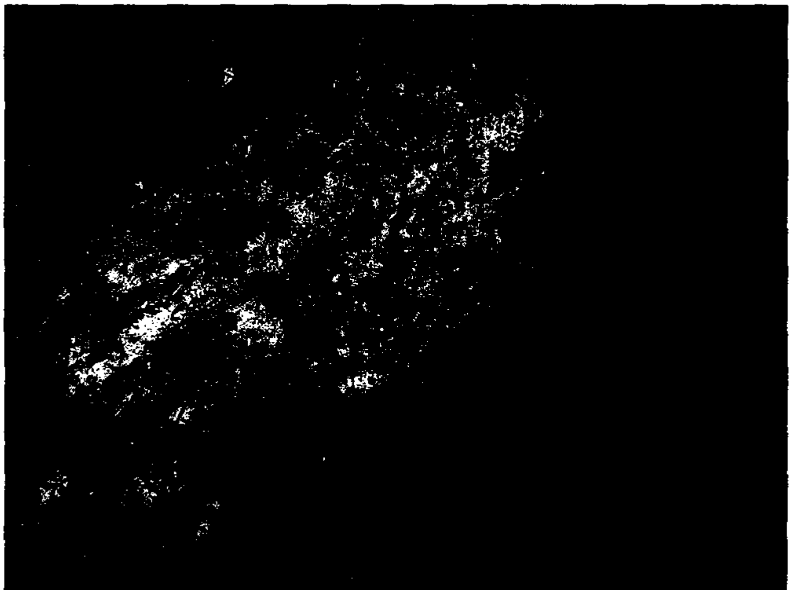
Project No.: LBH201727
Vanderbilt



Pipe Insulation
Sample No. 3037353

Welding Pad
Sample No. 3037354

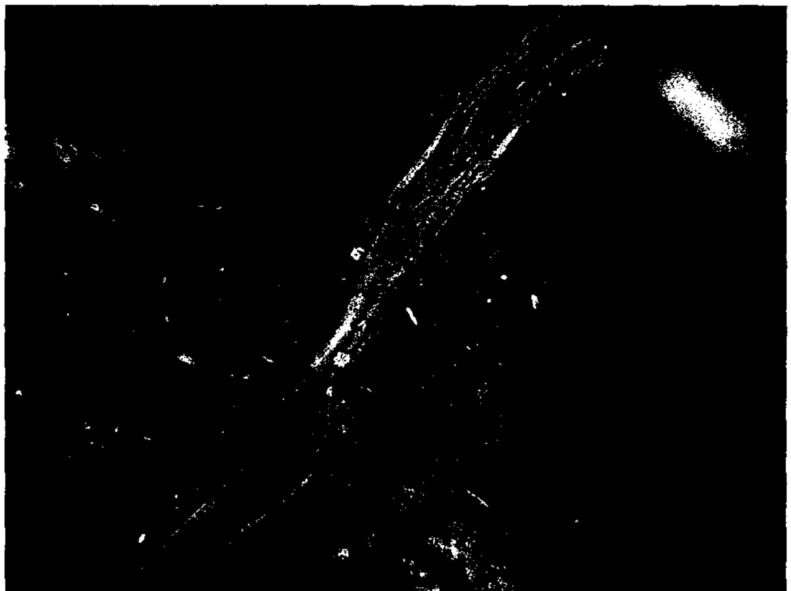
Project No.: LBH201727
Vanderbilt



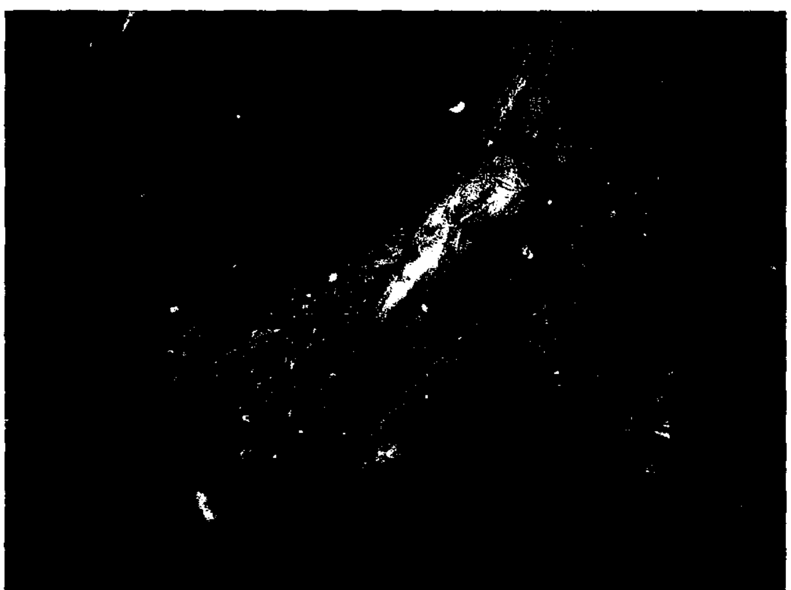
Pipe Insulation
Sample No. 3037355

Pipe Insulation
Sample No. 3037356

Project No.: LBH201727
Vanderbilt

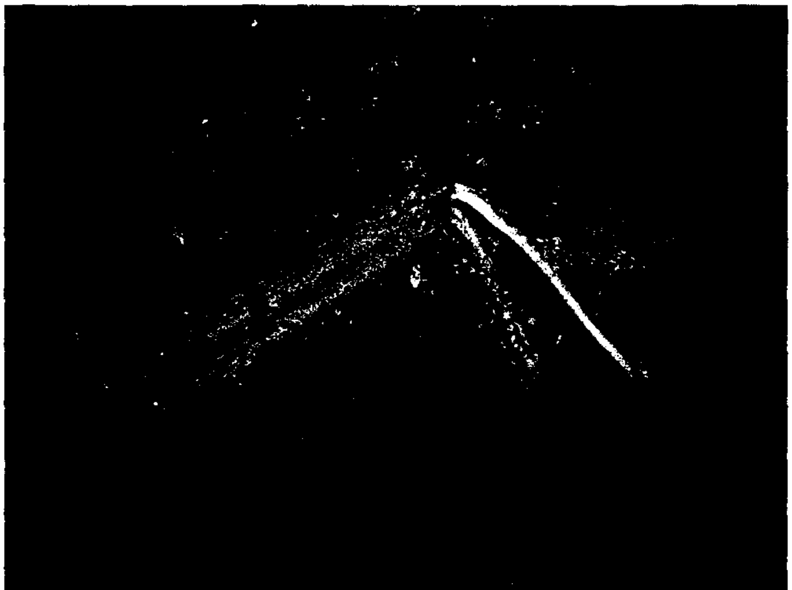


Boiler Insulation
Sample No. 3037357



Pipe Insulation
Sample No. 3037358

Project No.: LBH201727
Vanderbilt



Cement Board
Sample No. 3037359

Gasket
Sample No. 3037360

Project No.: LBH201727
Vanderbilt

Brake Pad
Sample No. 3037361

TO: John Kelse July 15, 2005

FROM: T. Jacobs

SUBJECT: Review of ACM's - Asbestos Containing Material

July 15, 2005: John, we have finished Phase I and II listed below. We are looking at Phase III, which is from the First Aid Room through the shop area.

February 16, 2005: John, we brought in a contractor to look at the listed sites; per the attached quotes from AAPEX Environmental Services #3, #6, #7, #8 and #9 will be taken care of by mid-summer 2005.

February 2, 2005: John listed below is a review of ACM's study at No. 1 Mill. Per your request I am listing the locations as to "still in use", "remain unprotected", and "still present an exposure".

Client Sample ID:	Still In Use:	Remain Unprotected:	Still Present's an Exposure:
# 3 Pipe Insulation - Feed from boiler house to oil house	X	X	Contract Removal
# 4 Welding Pad			Have Replaced with non-asbestos material
# 5 Pipe Insulation - First Aid Room	X	X	
# 6 Pipe Insulation Mezzanine off generator area	Half Done	Half Done	Contract Removal Partial Removal - 4/26/05 **PHASE I**
# 7 Boiler Insulation			Contract Removal Removed 7/14/05 **PHASE II**
# 8 Pipe Insulation - Out of Boiler Room			Contract Removal Removed 4/26/05 **PHASE I**
# 9 Boards that line Wheeler Mills			Contract Removal Removed 4/26/05 **PHASE I**
# 10 Gasket sheets on wheeler mills - blocks	X **Partial**	X	Replacing old gaskets with non-asbestos material. Three of the twelve wheelers have been rebuilt.[1]
# 11 Brake Pad Material	X	X	

[1] Chesterton 860 Gasket making material is being used to make the 6 gaskets for each wheeler mill.

Ann. occup. Hyg., Vol. 46, Supplement 1, pp. 132–135, 2002
© 2002 British Occupational Hygiene Society
Published by Oxford University Press
DOI: 10.1093/annhyg/mef651

Mesothelioma among Workers in Asbestiform Fiber-bearing Talc Mines in New York State

MINDY J. HULL[1], JERROLD L. ABRAHAM[1]* and BRUCE W. CASE[2]

[1]*State University of New York; Upstate Medical University, Pathology, Syracuse, NY 13210, USA;*
[2]*School of Environment, McGill University, Montreal, Canada*

Asbestos-related disease among talc miners and millers in a group of mines in two counties of northern New York State has been noted and disputed since the 1930s. One of the two counties was identified as among the 10 in the USA with the highest mesothelioma mortality up to 1981 for both men and women. Eight talc miners had been identified in previous studies as having mesothelioma. In the current study we: (i) report five new cases of mesothelioma among talc workers; (ii) present the results of and demonstrate the similarity between lung fiber burden analyses for selected cases and controls; and (iii) update mesothelioma mortality in this district using demographic and cause of death-cancer information from 1950 to 1997. Our results indicate that New York talc exposure is associated with mesothelioma, and deserves further public health attention.

Keywords: mesothelioma; talc; pathology; epidemiology; mortality; scanning electron microscopy; asbestos

BACKGROUND

In 1878 talc mining introduced an economic boon to the rural agricultural counties of St Lawrence and Jefferson in northern New York State. The hub of this industry was Gouverneur, home of several talc mines, at least one of which is still operational. We believe that occupational exposure to dust from the talc mines and mills caused the mesothelioma excess in these counties. We support this by examining the similarity between the lung fiber burden of talc miners with and without mesothelioma, and determining the presence or absence of retained fibers indicative of commercial amphibole asbestos exposure. There are at least eight histologically confirmed cases of mesothelioma among New York State talc miners and millers reported as of 1986, and increased pleural mesothelioma mortality in Jefferson County. Here we report five new mesothelioma cases and epidemiological data to determine if this trend continues. St Lawrence - our county

In the 1930s Merewether (1930) and others begin to describe asbestos exposure and its role in fibrotic lung disease. Pathology related to talc exposure also was being investigated, with a reported range of lung findings from nodular, silicosis-like to diffuse, asbestos-like patterns (Porro *et al.*, 1942). By 1943, Siegal and co-workers were studying New York State talc miners and millers (Siegal *et al.*, 1943). They described the mined talc 'of a fibrous variety…with it is found tremolite…a similar appearing mineral occurring in a fibrous or asbestiform state which… changes over to talc'. Midget impinger concentrations of particles ranged from 6 to 5000 million particles per cubic foot (mpcf) in mining and from 20 to 215 mpcf in milling. They found evidence of marked pulmonary fibrosis on chest roentgenograms in 32, all of whom had a >10 yr exposure history, out of a total of 221 talc workers. This established a clear relationship between lung fibrosis and duration of talc exposure. Fourteen of these workers also had pleural plaques, providing the first documentation of 'talc plaques'. In 1967 Kleinfeld *et al.* documented 9/220 talc workers with lung cancer; this represented a >4-fold excess. In addition, the first pleural 'fibrosarcoma' and peritoneal mesothelioma in talc miners were described in this cohort. Vianna *et al.* (1981) conducted an incidence study of all histologically confirmed mesos in New York State between 1973 and 1978. They found that Jefferson County had a mesothelioma rate twice that of the rest of the state. A total of six cases of mesothelioma (four male, two female) occurred in talc miners. Enterline and Henderson (1987) also concluded a mesothelioma excess in Jefferson County after looking at national mesothelioma incidence by county from 1968 to 1981. They observed four cases

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Table 1. Diagnosis and immunohistochemical results (where applicable) of three mesothelioma cases

	Description of pleural mesothelioma	Immunohistochemistry
Case 1	Biphasic, diffuse	Pan-cytokeratin (+++), calretinin (+++)
Case 2	Sarcomatous	Cytokeratin (+++), calretinin (–)
Case 3	Epithelial, with rare biphasic areas	CEA (–), alcian blue (+ cellular), mucicarmine (+ rare focal)
Case 4	Diagnosis of mesothelioma made by New York State Worker's Compensation Board. No tissue available	
Case 5	Diagnosis of mesothelioma made by death certificate. No tissue available	

(+++) strongly positive; (+) weakly positive; (–) negative.

Table 2. Pertinent data from New York talc miners diagnosed with malignant mesothelioma

Case	Birth	Death	Smoking history[a]	Relevant occupation(s) in the talc industry[b]	First year on job	Job duration (yr)
1	1931	1989	10	Mucker, driller, Hardinge operator	1952	22
2	1937	1990	0	Packed talc into trucks	1955	4
3	1912	1984	0	Mechanical engineer—helped construct two talc mines	Unknown	2
4	1923	1981	Unknown	Unspecified employment at a single talc company	1953	22
5	1925	1994	Unknown	Roustabout, foreman, packhouse worker	1949	25

[a]In pack-yr (no. of packs per day × no. of yr smoking).
[b]Includes all known dusty jobs (talc or otherwise).

females (0.6 expected), and seven cases in males (1.4 expected). This gave Jefferson County the second and sixth highest mortality rates from mesothelioma for females and males, respectively, in the USA.

METHODS AND RESULTS

Subjects

The SUNY Upstate Medical University serves the catchment area of Jefferson and St Lawrence counties. From 1984 to 1987, 36 biopsy and/or autopsy samples were recovered from talc workers with lung disease. Hospitalization, employment and (when applicable) death information were collected. From the 36 miners, five mesothelioma cases were documented. For three of these, the diagnosis of mesothelioma was histologically and immunohistochemically confirmed using hematoxylin & eosin, alcian blue, mucicarmine, calretinin, carcinoembryonic antigen (CEA) and cytokeratin staining (see Table 1). Case 1 is described in detail as a representative clinical course of mesothelioma. Table 2 contains demographic data for the five mesothelioma cases.

Observed and expected pleural mesothelioma mortality in mining counties

Calculations of mortality were performed at the University of Pittsburgh using the same protocol as that described by Enterline and Henderson (1987). Observed and expected values were updated to include the most recent years available (overall, from 1968 to 1997). Figure 1a,b presents the mesothelioma mortality for males and females, respectively.

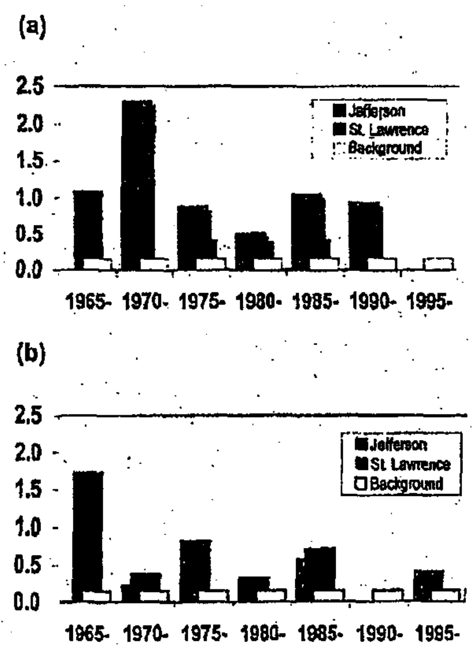

Fig. 1. Yearly mesothelioma mortality rate per 100000 (a) males and (b) females.

Lung-retained particulate and fiber analysis

Lung parenchyma from two mesothelioma cases and eight non-mesothelioma cases was available for analysis. The non-fibrous inorganic particulate lung burden was measured using morphometric *in situ* analysis of tissue sections (Abraham and Burnett, 1983). For fiber analysis, lung tissue was digested with sodium hypochlorite and the residue collected on polycarbonate filters for analysis of asbestos bodies by light microscopy or fibers by scanning electron microscopy/energy dispersive X-ray spectroscopy (Abraham *et al.*, 1991). The analytical results are displayed in Table 3. For fibers >1 μm, length, width and chemistry were recorded. Log normalized lengths and widths of the fibers found in the mesothelioma cases and the non-mesothelioma cases were compared using Student's *t*-test (Analyze-It Software, Ltd). Significance was defined as $P < 0.05$. Finding no difference between dimensions of each fiber type would support similar dust exposure between miners with and without mesothelioma.

Case 1 illustrates a representative medical history. This was a 43-yr-old, 5′8″, 190 lb, white, hypertensive male, with a 10 pack-yr smoking history who presented in 1974 with 'hardness of breathing' for 4–5 yr. He reported nocturnal wheezing, persistent anterior chest pressure, chronic cough (1 oz daily sputum), occasional hemoptysis, and difficulty walking ~200 m. He had a 22 yr talc dust exposure history, working at times as a mucker, driller and Hardinge™ operator at two New York talc mines. He had optional access to a respirator that proved too cumbersome to work with. Both his father (now deceased) and brother had been diagnosed with talc pneumoconiosis. His physical examination showed a symmetrical chest wall with an increased anteroposterior dimension and diminished inspiratory expansion. Auscultation revealed harsh inspiratory and expiratory bilateral diffuse rhonchi and fine scattered expiratory wheezing. A chest X-ray showed bilateral prominence of mediastinal/cardiac shadows and increased reticular pulmonary markings, particularly over the lower lung zones. He had markedly restricted ventilatory function on spirometry, with FVC = 3.3 l (75% predicted), FEV_1 = 2.5 l (74% predicted) and V_{max} = 60 l/min (39% predicted). Like his brother and father, he was diagnosed with talc pneumoconiosis. His disease progressed, and in <2 yr he was placed on permanent total disability. He died at age 58, 15 yr after presentation. The post-mortem revealed a biphasic diffuse pleural mesothelioma encasing the left lung, which had not been suspected during life. It is noteworthy that 'congestive heart failure' was the only listed cause of death—there was no mention of mesothelioma on the death certificate.

DISCUSSION AND CONCLUSIONS

We have found a continued trend of increased mesothelioma mortality at 5–10 times the background rate in Jefferson County from 1982 to 1997, with five new male cases (two expected) and three new female cases (0.5 expected). We also show that increasing talc exposure duration is associated with an increase in lung burden of both fibrous and non-fibrous talc. Asbestos bodies were also seen in elevated concentration in most men with >10 yr exposure who had not been diagnosed with mesothelioma. The concentrations of each fiber type from mesothelioma and non-mesothelioma cases were similar, except for a high tremolite concentration in case 2. There was no significant difference found between non-mesothelioma and mesothelioma miners with regard to length and width of the tremolite and talc fibers (Tables 4 and 5), supporting our hypothesis that they were exposed to dust with similar

Table 3. Lung-retained particulate analyses of mesothelioma and non-mesothelioma cases

	Mesotheliomas		Non-mesotheliomas							
	1	2	A	B	C	D	E	F	G	H
Age at death	58	52	49	58	60	63	66	71	71	76
Years of talc mining	22	4	21	21	18	30	23	25	2	10
Diagnosis[a]	ATM	ATM	ATSC	ATS	ATP	ATSP	ATPC	ATP	Nl	Pn
Asbestos bodies[b]	350	93	200	10	980	890	417	4850	1	10
Asbestos fibers[c]										
Anthophyllite	5	n/d	12	85	64	4	14	n/d	0.04	0.4
Tremolite/actinolite	2	1110	1	105	7	17	31	43	0.07	0.9
Chrysotile	5	21	7	188	10	21	9	19	0.18	2.6
Talc (fibrous)[c]	46	96	24	716	4 7	157	195	233	0.1	3.1
Talc (non-fibrous)[d]	37	146	511	60	n/a	139	n/a	51	1	1
Silica[d]	7	n/d	.15	10	n/a	68	n/a	n/d	1	.1

n/a, not available; n/d, not detected.
[a]Nl, normal; Pn, pneumonia; A, asbestosis; T, talcosis; S, silicosis; P, pleural plaques; M, mesothelioma; C, lung cancer.
[b]Thousands of bodies/gram dry lung.
[c]Millions of fibers/gram dry lung.
[d]Millions of non-fibrous particles/ml lung.

Table 4. Dimensional analysis for lung fibers in two New York State talc miners with immunohistochemically diagnosed malignant mesothelioma

Fiber type	n[a]	Width (µm)			Length (µm)			AR[b]
		X[c]	Min	Max	X	Min	Max	
Actinolite	1	0.20	–	–	4.6	–	–	23
Anthophyllite	6	0.15	0.06	0.30	10.6	3.9	30.2	90
Chrysotile	5	0.05	0.03	0.06	4.1	1.9	6.1	93
Tremolite	38	0.22	0.10	0.40	4.5	1.7	10.6	26
Talc	54	0.20	0.05	1.00	5.3	1.4	53.0	43

[a]Number of fibers measured.
[b]Mean aspect ratio = length × width^{-1}.
[c]Geometric mean.

Table 5. Dimensional analysis for lung fibers in eight New York State talc miners with pulmonary disease other than mesothelioma

Fiber type	n[a]	Width (µm)			Length (µm)			AR[b]
		X	Min	Max	X	Min	Max	
Actinolite	7	0.18	0.12	0.25	3.4	2.5	5.4	20
Anthophyllite	85	0.24	0.05	1.60	7.7	1.6	146.0	56
Chrysotile	33	0.08	0.04	0.40	7.4	2.1	36.1	133
Tremolite	51	0.34	0.04	1.00	5.3	1.5	17.0	24
Talc	284	0.33	0.06	2.80	6.4	1.3	219.0	30

[a]Number of fibers measured.
[b]Mean aspect ratio = length × width^{-1}.
[c]Geometric mean.

fiber dimensions. Finally, in all of the 10 cases analyzed, only a single commercial amphibole fiber was found.

New York talc miners are exposed to a mixture of platy talc, silica and fibrous minerals, resulting in a disease process much more complex than pure talcosis. The asbestiform fibers in the New York talc miners' lungs are a mixture of talc, tremolite and related mineral series. Our results indicate that mesos continue to occur at high rates in counties where New York talc mining occurs. Furthermore, New York talc miners without evidence of commercial amphibole asbestos exposure develop mesos. Talc miners with mesos have lung fiber burdens similar to those without, indicating comparable exposures. Increased public health attention to the risks of exposure to New York talc is indicated.

Acknowledgements—M.J.H. was a Post Sophomore Fellow in Pathology during part of this work. Supported by Department of Pathology, SUNY Upstate Medical University.

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THE CITY UNIVERSITY OF NEW YORK
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Executive Summary

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Hull MJ. Abraham JL & Case BW (2002)
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Is there an Association between Mesothelioma and Tremolitic Talc from New York State?

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Executive Summary

Hull et al. 2002 reviewed a series of mesothelioma cases among NY State tremolitic talc miners and millers and two reports in the medical literature of increased mortality from mesothelioma. These occurred in two NY State counties, one with tremolitic talc mining (St Lawrence) and the county next to it without (Jefferson). They conclude that an association exists between exposures to asbestiform fiber bearing talc and human mesotheliomas. For the following reasons this association is weak and does not support a claim that tremolitic talc is an etiological agent in human mesothelioma:

- *Pathology and Lung Content Analyses.*

1. The mesothelioma case series consists of only five cases collected in a 13-year period. Histological slides needed to diagnose the tumor were available in just three cases. In the two cases without histology, the diagnosis in one case was obtained from worker compensation records and in the other from a death certificate. In a mesothelioma case series, such as Hull et al., cases in which the diagnosis can not be histologically confirmed are generally excluded from the series.

2. In the three cases in which histology is available the immunological markers used were so limited, that diagnoses other than mesothelioma could not reasonably be excluded.

3. Parenchymal tissue for lung content analysis was available in only two of the mesothelioma cases.

4. The identification of the minerals in the lung was done using scanning electron microscopy (SEM), which relies on morphology and determination of elemental composition using energy dispersive spectroscopy. Two of the phases present in tremolitic talc –talc and transitionals (intergrowth of talc and anthophyllite) have elemental compositions indistinguishable from each other by elemental composition.

5. These two mineral phases can be reliably differentiated only on the basis of crystal structure, which for individual fibers needs to be obtained using selected area electron diffraction (SAED). The use of this technique requires an analytical transmission electron microscopy and knowledge of mineralogy and crystal chemistry well beyond that of a pathologist.

6. Anthophyllite asbestos also has elemental composition indistinguishable from talc and transitionals. Hull et al. report the presence of only two of these three mineral fiber-types.

7. The method of instrumental analysis selected by Hull et al. 2002 cannot be used to meaningfully characterize the types of fibers found in tremolitic talc.

8. Hull et al. places the magnesium silicate fibers into two classifications – anthophyllite and talc, with no mention the third type of magnesium silicate fiber– transitionals.

9. The lung content analyses in these cases have been published in a number of different reports. Comparison of these various reports show that fibers counted as anthophyllite in the early reports are later changed to talc fibers. These changes are consistent with the analytical limitations of the SEM methodology to differentiate between the various magnesium silicate phases in tremolitic talc.

10. One case in Hull et al. appears to have already been reported in Abraham et al, (1990a). The age at death, years of exposure and concentration of all minerals were identical in both reports, except the concentration of tremolite/actinolite is an order of magnitude higher in Hull et al. 2002 than in the earlier report.

11. The results of the lung content analyses are not consistent between the various reports published by Abraham and his co-workers.

- *Geology and Occupational Histories*

1. The occupational histories are incomplete in of all the mesothelioma cases. In the two cases where occupational exposure to tremolitic talc was only for a brief period, the lack of a complete history is particularly significant. What did these individuals do for the rest of their working careers? Did they develop mesothelioma because they were exposed to commercial amphibole asbestos?

2. Occupational exposure to tremolitic talc is reported in all five cases with durations of employment ranging from 2 to 25 years. Exposures in the cases began between 1949 and 1955 and ended no later than 1974. In the case with only 2 years of exposure, it is not known over which two-year period the exposure occurred. But as this individual was the oldest in the case series by 11 years (having been born in 1912), it is reasonable to assume he was exposed in the 1950s or earlier.

3. Numerous mining operations involving a number of mineral commodities would have been active in St Lawrence County at the time when the exposure in these five cases occurred. Tremolitic talc is present in many, if not all, of the ore bodies mined.

4. It is not known, if any, of these five individuals were exposed at the Gouverneur Talc Company, where their exposures occurred, or if they were all exposed in the same mine. The mineral assemblage in Gouverneur Talc mine has not been compared to any of the other ore bodies in St Lawrence County or compared to the results of the lung content in the case series reported by Hull et al.

5. It is unlikely that any of the Hull et al. mesothelioma cases were occupationally exposed to mining or milling tremolitic talc in Jefferson County, as this mineral type has not been mined in Jefferson County since the closing of the Natural Bridge Mine more than 100 years ago.

6. Hull et al. assign the high incidence of mesothelioma in Jefferson County to the tremolitic talc mines. But these mines are only in St Lawrence County. Hull et al. provide no explanation for why the mines in St. Lawrence County produce mesotheliomas in Jefferson County.

7. In the two mesothelioma cases where lung content analysis is available, the results are strikingly different. The case with 2 years of occupational exposure to tremolitic talc has a lung content about 90-fold higher than the case with 22 years of "similar" exposure.

8. In the case with 2 years of exposure, 98% of the fibers present are reported to be tremolite/actinolite (none are anthophyllite) and in the case with 22 years of exposure, 16% (or 1.6% depending on which Abraham and co-worker reports you "rely" on). These results are not consistent with both these individuals having been exposed in remotely similar workplaces.

9. Hull et al. rely on similarities in the fiber morphology among the 10 lung content analyses to associate the cases into a similarly exposed group, rather than the more meaningful association of duration of exposure correlated with fiber number and/or fiber-type.

10. The comparison of the lung content analyses in the two mesothelioma cases with the 8 other cases provides little or no useful information about the possibility (or lack) of an association between tremolitic talc and mesothelioma.

11. Not knowing the complete occupational history in the 5 mesothelioma cases and having lung content analysis in only two cases leaves open the possibility that exposure to commercial amphibole asbestos is the predominant cause of mesothelioma where the etiology can be identified, particularly for males.

12. We also note that the reports by Abraham and co-workers on the lung content in miners and millers exposed to tremolitic talc are inconsistent with regard to the presence or absence of commercial amphiboles. In the most recent report Hull et al. state a "single commercial amphibole fiber" was found in the lung content of the ten tremolitic talc cases. They do not report the fiber-type or concentration, or if it was found in one of the two mesothelioma cases.

13. Most significantly they do not specify the sensitivity or the concentration of commercial amphibole asbestos in the lung below which no increased risk of mesothelioma would be expected.

14. Even if the lung content analyses were repeated using analytical transmission electron microscopy and a protocol with the proper sensitivity, the presence of commercial amphibole asbestos cannot be eliminated in 40% of the cases, owing to a lack of parenchymal tissue.

- *Observed and Expected Pleural Mesothelioma Mortality in Mining Counties.*

1. Hull et al. mischaracterize Jefferson as a mining county and claim mining tremolitic talc is associated with the county's increased mesothelioma mortality. Tremolite talc has not been mined in this county for over 100 years.

2. Analysis of mesothelioma incidence from New York State Cancer Registry during 1998-2002 found no statistical differences between male mesothelioma incidence in St Lawrence and Jefferson County and background for New York State (excluding NYC). The number of cases is too small to conclude that the incidence in these two counties is greater than background.

Comments on

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Introduction

Hull et al. 2002 report mesotheliomas are occurring among New York State (NYS) miners and millers occupationally exposed to asbestiform fiber-bearing talc. The term asbestiform fiber-bearing talc is not defined by the authors and we will assume the authors are referring to tremolitic talc. Hull et al. discuss mesothelioma incidence in two counties northwest of the Adirondacks Mountains of New York State - Jefferson and St. Lawrence. While little mining was done in Jefferson County industrial grade talc, zinc, wollastonite and lead has been mined in St Lawrence County for more than a century (Brown and Engel, 1956). The talc mined in St Lawrence County is referred to as tremolitic talc due to the high concentration of this amphibole. Tremolite imparts industrially desirable characteristic to the mineral commodity. There is only one talc mining company currently operating in St Lawrence County and its tremolitic talc contains non-asbestiform tremolite, platy talc, serpentine minerals principally in the forms of lizardite and antigorite, non-asbestiform anthophyllite and talc in fibrous form (both as pure talc fiber (agalite) and a mixture of talc and anthophyllite referred to as transitional fibers). None of these minerals commonly found in tremolitic talc are asbestos and are therefore not regulated asbestos under any of the federal asbestos standards (OHSA, CPSC, MSHA or EPA).

Geology and Mineralogy of St Lawrence County

The commercially important mineral deposits of St. Lawrence County are found in a series of highly metamorphosed sedimentary rocks of pre-Cambrian age. Together they are called the Grenville Series and are defined by 16 stratigraphic units distinguished by their mineralogy and mappable field character (Brown and Engel, 1956). The Grenville series is formed largely of 15 carbonate units of silicated limestone and dolomitic marble. Of these 15, 8 contain the tremolite. One unit contains grunerite and cummingtonite, the former referred to as amosite when occurring in the asbestiform habit.

The Brown and Engel paper of 1956 notes the location of two zinc mines and three talc mines within one mile of the Gouverneur (RT Vanderbilt's currently worked tremolitic talc mine) known as the Gouverneur Talc Company (GTC) (Table 1); they are comprised of the American, Woodcock and Wight Talc mines. A recent paper by Webber et al. (2004) noted the existence of "historical" mine workings in the Balmat-Edwards region of New York State in the twentieth century, but located only three talc mines in the Sylvia Lake area near GTC (there are four). They noted the existence of the Hyatt zinc mine, worked ~ 4 miles to the east of GTC (in the Grenville units cdm 14, cdm 15, both containing tremolite), a talc mine, worked ~ 1.5 miles east of Fowler (in the Grenville units dm 1, ps 2, dm 3, containing tremolite, cummingtonite and grunerite) and six talc mines worked around the town of Talcville, ~ 4.3 miles east of GTC (in the Grenville unit ts 13, containing tremolite, anthophyllite, serpentine and talc). All of these workings occur within units of the Grenville between Balmat Corners and Edwards, New York, a distance of ~ eight miles. All are confined to three, or possibly four, units of the Grenville series, and all of contain tremolite. As of 1974, GTC is the only remaining talc mine in the region. *None of the tremolite, serpentine or anthophyllite occurrences have been described in the literature as asbestiform.*

Based on the mineralized units in the Grenville, every mining operation would have necessarily encountered tremolite during exploitation, either as a gangue mineral or as a desired component of the recovered ore. Anthophyllite is variable in occurrence and concentration as are the transitional fibers too, the variation of minerals within a single mine might be significant as well (Table 2). Tremolite exposure to a mining cohort may have occurred in many places, while working many ore bodies. It is unlikely to have been restricted to talc workers.

Epidemiology of Human Mesothelioma

Human mesothelioma is a rare disease. In the United States, mesothelioma accounts for approximately one-tenth of one percent (0.10%) of deaths annually (Price and Wilson, 2001). For the year 2000 in the United States, Price and Ware (2004) estimated that a total of 2,550 mesothelioma deaths occurred (2,000 males and 550 females). That year the population of the US was about 280,000,000. Therefore the mesothelioma incidence (not adjusted for age) was about 0.92 cases of mesothelioma (pleural and peritoneal) per 100,000 population. For males, the mesothelioma rate in the year 2000 was 1.4 per 100,000; for females the rate was 0 .39 per 100,000. One expects this difference as the asbestos fiber exposure tends to concentrate in occupational environments where the working populations are predominately male.

The etiology of mesothelioma in the United States and Europe has been linked with heavy, occupational exposure to the commercial amphibole asbestos minerals (crocidolite and amosite) A few anthophyllite related cases have been reported among workers with anthophyllite exposure that was sufficiently intense to produce asbestosis in the same individual. Tremolite-actinolite asbestos and other calcium and magnesium asbestiform amphiboles (which depending on the concentration of sodium would be called either winchite or richterite asbestos) have produced mesothelioma among the miners and millers of Libby, Montana who were vermiculite exposed. Although tremolite asbestos is likely the predominant fiber present there, the most recent reports indicate the asbestiform fibers at Libby may also include a mixture of asbestiform winchite and richterite (Nolan et al. 1991, Wylie and Verkouteren 2000, Gunter et al. 2003). Often these asbestiform fibers have been referred to only as tremolite asbestos or Libby amphiboles.

Based on meta-analysis of cohort data, chrysotile asbestos is thought to be about 500-fold less potent as an agent in mesothelioma causation than crocidolite asbestos (Hodgson and Darnton, 2000). Information on anthophyllite asbestos and tremolite-actinolite asbestos are too limited (too few or no environmental measurements) to develop asbestos-related cancer risk assessment models for either asbestos fiber-type. Epidemiology, experimental animal studies and cell studies indicate that non-asbestiform amphibole and non-fibrous serpentine minerals do not have the biological potential as their asbestos mineral analogs (Nolan et al. 1991).

There is substantial scientific evidence that heavy exposure to amphibole asbestos is *not the only cause* of human mesothelioma. It can occur in individuals with no history of exposure to any specific source of or type of asbestos. Price and Ware 2004 list 21 reports in the medical and scientific literature in support of this position. A few potential causes or mesothelioma other than asbestos have been identified, including: therapeutic radiation, scar tissue proliferation, inflammation, and other types of mineral fibers e.g. fibrous zeolites, specifically erionite (Gibbs et al. 1989, Hillerdal and Berg 1985, IARC 2002, Lerman et al. 1991). However, for the majority of mesotheliomas where a sufficient asbestos exposure cannot be ascertained the etiology of mesothelioma is unknown and referred to as idiopathic. In this latter respect, mesothelioma is no different than other notable cancers. For example, the causes of breast, pancreatic, colon, rectal, prostate, and ovarian cancer all remain largely unknown. Price and Ware (2004) have estimated the background spontaneous rate for mesothelioma in the United States to be approximately 0.50 per 100,000 population (1 mesothelioma in 2,000 deaths).

Hull et al. are attempting to establish that a significantly increased risk of mesothelioma is occurring specifically among NYS talc workers and justify adding asbestiform fiber-bearing talc to the list of etiological agents for mesothelioma. Hull et al. argue three points in attempting to establish their claim:

1. They report that five new cases of mesothelioma have occurred in workers occupationally exposed to NYS talc. These are in addition to what Hull et al. describe as eight historical cases already reported in the literature by Kleinfeld et al.1967 and Vianna et al.1981.

2. Lung content analyses were carried out on lung parenchyma in two of the five new mesothelioma cases. The authors claim these persons were exposed only to tremolitic talc and this is the etiological agent for the mesothelioma. The results of these two lung content analyses were compared to a population of fibers found in eight NYS talc workers without mesothelioma. Based on the similarity, Hull and co-worker's claim that a miner's risk of developing fiber-related mesothelioma is significantly higher than background risk and is talc exposure related.

3. An update was made of the incidence of mesothelioma occurring in St. Lawrence and Jefferson Counties where Hull et al. indicate talc mining began in 1878. Using demographic and cause of death information from 1950-1997, the authors report a 5 to10-fold higher than background incidence of mesothelioma in Jefferson County and claim occupational exposure to asbestiform fibers from the talc mines is the cause of this increase.

From an analysis of these three points the authors conclude "our results indicate that New York State talc exposure is associated with mesothelioma, and deserves further public health attention". We have accepted their challenge and what follows is our evaluation of the same data set.

Comment on the Hull et al. 2002

We have examined the claims in the report by Hull et al. and comment on their scientific and medical evidence, offered in support of their claims. We will focus our comments on the approaches they used - a pathology case series, a comparison of lung content analysis of talc workers with and without mesothelioma, and population-based mesothelioma incidence data. We will not address epidemiology studies, experimental animal studies and mineralogical studies not mentioned by Hull et al. although these are generally not supportive of their position. Some of these have been addressed elsewhere (Langer et al. 199l, Nolan et al. 1991, Honda et al. 2002, Ross and Nolan 2003).

Analysis of the Three Points

Point 1: Number of Cases: Analysis of the Five New Mesothelioma Cases. Hull et al. is the latest in a series of reports on the occupational health effects among NYS talc worker published by Dr Abraham. The first, Abraham et al. 1989, appeared in a conference proceeding. Reviewing an earlier report we noticed *one of the new mesothelioma cases* (called Case 1 in Hull et al.) was presented at an OSHA Hearing in 1990 and published in an abstract as Case 7 in Abraham, 1990a. The new case had been published 12 years earlier a fact that Hull et al. failed to report in their 2002 paper.

The dates of death in the five new mesothelioma cases were given as between 1981 and 1994, the most recent of the new cases occurring eight years prior to the publication in 2002 (Table 3). We concluded that the five cases collected over 20 years are consistent with our earlier statements concerning the rare nature of this type of tumor certainly at or below the idiopathic number of mesothelioma case, 20, anticipated for St Lawrence and Jefferson Counties population (Figure 1 & 2).

Point 2: Tissue Studies. The tissues in the ten cases reported by Hull et al. were selected from 36 cases of talc workers with lung disease obtained between 1984 and 1987. The initial report by Abraham (1990b) was of six cases of non-malignant disease in talc workers followed by a report of a mesothelioma and a lung cancer to bring the series to eight in total (Abraham 1990a). Hull et al. report adds two more malignancies – also a mesothelioma and a lung cancer – bringing the series to ten cases. Hull et al. 2002 do not reference the two earlier reports.

In the 12 years between publications it appears that only *two new cases were identified.* Have new cases occurred after 1987 that might not have been referred to Upstate Medical University? Hull et al. reports on a *subset of only 10* talc worker cases from among the 36 cases where biopsy and/or autopsy materials were provided to the Upstate Medical University prior to 1987. The reader is left to ponder what criteria were used to reject the other 26 cases? Were lung content analyses carried out on any of the other cases? Were commercial amphibole asbestos fibers found? We are left to our own conclusions.

Point 3: Pathology. No pathology materials were available for *both diagnosis and lung content analyses in the two latest cases making it uncertain whether the cases were* referred for treatment or for pathological review (Table 4). The authors do not comment on why no tissue was available in Case 4 and 5. From a research prospective the two cases with no tissues of any kind are of limited value in addressing the question of asbestiform fiber-bearing talc as a sole etiological (or causative agent) in human mesothelioma. Neither the mesothelioma diagnosis nor the fiber type can be verified.

In the remaining three mesothelioma cases with tumor tissues, it is unclear as to whether the tissues were provided as unstained slides and/or blocked tumor tissue or whether stained slides were forwarded from another hospital (Table 4). Sufficient lung parenchyma was available for lung content analysis in two of the three mesothelioma cases where slides of the tumor tissue was also available (Table 5). It appears that sufficient parenchymal tissue was available for the diagnosis of asbestosis and talcosis in 8 of the 10 cases, including all the cancer cases, and to rule out these diseases in the remaining two cases.

The diagnosis of the mesothelioma in the series is adventuresome in that of the five cases only three had tissue available (as discussed earlier). It is not specified what types of samples – percutaneous biopsies, open biopsies, lobectomies or autopsy were received. It is not possible to independently establish, for the two cases without any tissue or cytological material available, a diagnosis of mesothelioma. The immunohistochemical work-up uses too few markers to exclude some diagnoses.

To establish a mesothelioma diagnosis currently it is recommended that at least two epithelial and two mesothelial markers be employed when one is dealing with epithelioid or biphasic tumors (as in Cases 1 and 3). Mesothelial markers that should be employed include calretinin, cytokeratin 5/6, WT-1, thrombomodulin; epithelial markers include CEA, CD15, BerEP4, B72.3, MOC31 and TTF-1. Care has to be taken with assessing calretinin since the specific staining has to be nuclear – cytoplasmic staining is non-specific. For sarcomatoid tumors (Case 2) the panel of stains should include cytokeratin and vascular markers such as CD31 and CD34 because of, e.g., angiosarcoma mimicking mesothelioma. In addition synovial sarcoma has not been excluded in the second case. There is some doubt concerning the validity of diagnoses in Cases 2 and 3. No tissue in Cases 4 and 5 cast serious doubt on any statement of causation. The pathological work-up of the mesothelioma cases do not satisfy current standards of diagnostic criteria.

The reception date for the tissues predates the year of death in two cases. All the samples were received at SUNY over a very limited time period (1984-87).

In the mesothelioma cases where immunohistochemistry was carried out, no standard protocol of staining was used for diagnosis. The immunohistological staining was different in three of the five cases where histology was available (Table 4). *The diagnoses in these five cases have not been established to the degree of pathological certainty one would want if trying to credibly establish a casual association between exposure to tremolitic talc and mesothelioma.*

Were tissues obtained at autopsy in both of the mesothelioma cases where lung content analysis was carried out (Case 1 and Case 2 died in 1989 and 1990 respectively)? If so, it must have been performed after the 1984 to 1987 period for tissue collection discussed above (Table 3). Case 1 died in 1989 and Hull et al. report the mesothelioma as an incidental finding at autopsy. This is inconsistent with the time line for obtaining the biopsy/autopsy tissues. We are puzzled that the biopsy material found prior to 1987 to establish mesothelioma yet the tumor was not discovered until autopsy in 1989? No co-author on the Hull et al. report is from a hospital(s) in St. Lawrence or Jefferson Counties nor is anyone listed in the acknowledgements for providing the biopsy and/or autopsy materials and medical records in the 36 cases. The materials are unspecified in this regard and information regarding differential diagnosis and related issues were not given.

We assumed that the lung tissues available for the 10 lung content analyses were obtained from biopsy and/or autopsy samples, consistent with the 1984-1987 collection period given in the report. In the two mesothelioma cases it is possible that only small amounts of tissue obtained at biopsy were available for the lung content analysis. Autopsies, if they occurred, were only performed after the cut-off date for the collection of pathology materials. Small biopsy samples can lead to non-representative sampling of the lung content and a very significant concern arises that commercial amphibole asbestos fibers which might be present were missed.

The same internal error exists with samples laden with many fibers. For example assuming 50 or 60 fibers were counted in Case 2, with well over a billion fibers per gram dry lung, this would equate to 1 fiber representing about 17 million fibers. Therefore a count of commercial amphibole asbestos fibers below a background (less than 17 million fibers per gram dry lung) could be present that would not be detected by the analysis. It is therefore not surprising that only a *single commercial amphibole fiber* was found in only one of the 10 cases analyzed. The dimensions of the fiber and the case in which it was found, were not reported. If there is commercial amphibole asbestos fiber in one of the mesothelioma cases it would further weaken the tremolitic talc causation argument. This claim about a single commercial amphibole is inconsistent with earlier reports (Abraham 1990a, b) concerning low concentrations of commercial amphibole in Cases 1, 2 and 5.

Occupational details concerning the cases are very limited. e.g., Case 2 only 4 years in the talc industry, and Case 3 a mechanical engineer (with potential exposure to commercial amphiboles) with only two years in the talc industry. Both cases underscore the importance of obtaining a complete occupational history for all the working years in the case which was not done.

The results of the lung content analysis for fibrous minerals in the two mesothelioma cases do not present a consistent pattern (Table 5). Case 2 with 4-years of tremolitic talc exposure has a tremolite concentration more *than 90-fold higher than in the lung of* Case 1 reported to have 22-years of exposure. Case 2 had either a much more intense exposure, *or was exposed elsewhere.* These findings are not supportive of the Hull et al. conclusion that "increasing talc exposure duration is associated with an increase in lung burden and both fibrous and non-fibrous talc". The pattern is *inconsistent with talc only exposure.* Sampling error (discussed above) might be an equally plausible explanation for the tremolite concentration differences.

All the fiber concentrations (except for anthophyllite asbestos where none was detected) including talc fibers were higher in the mesothelioma case with *4-years of exposure* (Case 2) than in the case with *22-years of exposure* (Case 1) (Table 5). *The difference in concentration would be an order of magnitude higher if the Abraham (1990a,b) report had the correct concentration of 0.2 million fibers/gram dry lung of tremolite/actinolite asbestos in Case 1* (Table 6). Abraham (1990a, b) and Hull et al. report different results, by an order of magnitude, for tremolite asbestos in what appears to be the same mesothelioma case (Case 7 & Case 1 bold in Table 5).

There are inconsistencies in the authors' published work. The first inconsistency is found in Abraham (1990a, b) where Case 5 is reported as having 49 million fibers/gram dry lung of anthophyllite asbestos while Hull et al. re-publishes what appears to be the same asbestosis/talcosis/pleural plaque case (this time calling it Case F) and now report *no anthophyllite asbestos detected* (Case F in Table 5 showing only Hull et al. data and broken out to compare Abraham (1990a, b) to Hull et al. in Table 6). Hull et al. refers to this as Case F and the 49 million fibers/ gram dry lung of anthophyllite asbestos reported earlier now seem to be counted as talc fibers which are reported as 233 million fibers/gram dried lung (bold in Table 5). This number is arrived at by adding 49 million fibers/gram dry lung of anthophyllite asbestos to the 184 million fibers/ gram dry lung of talc fibers reported in Case 5 in Abraham (1990a,b) (Table 6). Case 2 (a mesothelioma) and Case F (or 5) are the only two of the ten cases with no anthophyllite asbestos detected. Similar changes appear in Case 6 (Abraham 1990a,b) and Case D (Hull et al.) where the concentration of anthophyllite asbestos in earlier reports is reduced and the number of talc fiber increased in the later report in what appears to be the same manipulation.

The second inconsistency is in the same Case 5 where the tremolite/actinolite is reported as 34 million fibers/ gram dry lung (Abraham 1990a, b) and 43 million fibers/gram dry lung in Table 6 (Hull et al.). It appears these numbers were reversed from the earlier reports to the latest published report. *Inconsistencies between the different publications on the lung content analysis reduces our confidence in the reliability of Hull et al. and the data given in the earlier reports.*

Compare Lung Content for fibers in Talc-exposed Workers with and without Mesothelioma

Hull et al. compared the lung content analysis in the two mesothelioma cases with those of the eight other cases exposed to tremolitic talc (Table 5). Case G was described as normal and Case H died of pneumonia. The cases had two and ten years of exposure respectively in mining rather similar to one of the mesothelioma cases with two years of exposure (Table 5). These two cases contained the least amount of asbestos and talc fiber. The remaining six non-mesothelioma cases, where lung content analysis is available, had asbestosis and talcosis as did the two mesothelioma cases. Two of the six cases presented with lung cancer and three with silicosis. Plaques were found in four of the six cases although none of the mesothelioma cases had plaques or evidence of silicosis but one of the two lung cancer cases were diagnosed with silicosis (Table 5). Only two of the ten cases reported by Hull et al. did not appear in Abraham (1990a, b), the new cases being a mesothelioma and lung cancer.

Only limited mineralogical characterization can be accomplished by scanning electron microscopy (SEM). As a result no crystal structure information was determined on any of the fibers. Such analysis is required to differentiate between phases with similar elemental composition but different crystal structures, e.g. talc and anthophyllite. The resolution and imaging conditions of the SEM are not sufficient to detect the presence of thin diameter commercial amphibole asbestos, e.g. crocidolite. The elemental composition, crystal structural information and morphology needed for a definitive lung content analysis can only be obtained with an analytical transmission electron microscopy (ATEM). This is consistent with the US Environmental Protection Agency's requirement that ATEM be used for monitoring airborne asbestos. It logically follows that once the airborne asbestos fibers are inhaled the same analytical methodology should continue to be used.

SEM is generally operated in a mode that can provide elemental composition and some morphology information. It is therefore of limited value for characterization of the various magnesium silicate phases of similar elemental composition as found in NYS talc deposits. The type of fibers reported by Hull et al., and the choice of instrumentation, indicates a lack of appreciation of the mineral complexities associated with the Grenville metasediments. This may in part be the explanation as to why from one report to another they shift anthophyllite "asbestos" to talc fibers in a few cases (see discussion above and Table 6). The dimensional information provided is of interest but knowing the mineralogical complexity of NYS talc and the limitations of SEM for mineralogical analysis of lung content, establishing causation and agent based on SEM is virtually impossible.

Importantly, the authors have not convincingly eliminated the possibility that commercial amphibole asbestos exposure occurred. The possibility of selection bias also exists, by providing no selection criteria for the ten of the thirty-six cases provided. The occupational histories provided for these cases are scant. The ability of SEM to detect fine diameter commercial asbestos fibers(most commonly associated with the etiology of mesothelioma) is limited, the detection limit of the lung content analysis (as high as 17 million fiber/gram dried lung) is too high to detect etiologically important exposures to commercial amphibole asbestos and the occupational histories lack detail so that exposure to commercial amphiboles cannot be ruled out.

Update of the Mesothelioma Mortality in St. Lawrence and Jefferson County using Demographic and Cause of Death Information from 1950-1997

Hull et al. describe the mortality from mesothelioma in the general population in two counties in northern New York State, St. Lawrence County which is a tremolitic talc mining region and Jefferson Country which is just south of St. Lawrence. Our review found only one talc mine in Jefferson County at Natural Bridge which closed before 1900. Both counties border the St. Lawrence sea way and Lake Ontario, where ports abound (Figure 1).

Hull et al. claim a continued trend of increased mesothelioma mortality of 5-10 times the background rate in Jefferson County from 1982-1987. These authors do not provide the data necessary to confirm this assertion. Hull's accounting of when the mesotheliomas occurred involves overlapping time intervals. Without reliable data on the annual historical numbers of mesothelioma cases it is not possible to analyze the trends in Jefferson and St. Lawrence counties. However, summary data from the New York State Cancer Registry[1] for the period 1998-2002 provides one perspective on the relationship between mesothelioma in these two counties versus the background level in NYS (excluding NYC). For Jefferson County during 1998-2002, the mesothelioma incidence

[1] New York State Cancer Registry: Cancer Incidence in New York 1990-2002, NAACCR 10.1 format, New York State Department of Health, created April 2005, based on January 2005 data.

per 100,000 for males was 3.0 with 95% confidence limits of 1.1 to 7.2; for males in St. Lawrence County, mesothelioma incidence was 4.0 with 95% confidence limits of 1.9 to 7.9. The male mesothelioma incidence in NYS (excluding NYC), which represents background mesothelioma incidence, is 2.4 per 100,000 with 95% confidence limits of 2.2 and 2.6. Based the overlap in confidence intervals, there is no statistical difference between male mesothelioma incidence in the two targeted counties and background. The number of mesotheliomas in males in the two counties is too small to conclude that the incidence is greater in these counties than background.

Even if one assumes the diagnosis in all the mesothelioma cases in Hull et al. was correct, an increased mesothelioma incidence casually linked with exposure to tremolitic talc is a difficult argument to make with the information they presented. The data are based on where an individual died and the data are not informative about exposures to commercial amphibole asbestos.. Individuals who move to these two counties might have been exposed to a mesotheliomagenic agent somewhere else, and similarly a talc worker who retires and moves away and develops mesothelioma will not be counted. This is a serious consideration due to the few cases of mesothelioma expected. Still it would be cause for concern if the major tremolitic talc producing county, St. Lawrence, had a significantly higher than average incidence rate for mesothelioma.

Hull et al. describes the mesothelioma incidence data as mortality data. Mesothelioma is a very rare tumor therefore the incidence will be based on a very small number of cases. This is why Hull et al. were only able to identify five possible mesothelioma cases over a 13-year period (about 26 would be expected based on estimates of the NYS background incidence). And, as reported in Hull et al., with the Syracuse Medical Center as a mesothelioma "catchment institution" this certainly did not occur.

In their abstract Hull et al. state the mesothelioma mortality will be updated using demographic and cause of death cancer information from 1950-97. No further mention is made of any incidence data prior to 1965. Mesothelioma is a very rare tumor type with multiple histological presentations making the malignancy difficult to diagnose. Prior to the report by Wagner et al. 1960 describing a large case series of mesotheliomas occurring among crocidolite asbestos exposed individuals in 1960 many pathologists questioned if such a malignancy existed.

In the text the expected and observed values for mesothelioma are stated to be from 1968-1997 while in their Figure 2 the earliest year is 1965 with intervals of five years with the last interval starting in 1995. Does the last interval end in 1997 and only represent three years? Males and females are plotted separately and the background incidence for mesothelioma is reported to be the same for both sexes (Figure 2). The authors are silent on how the background was selected. The incidences are plotted as the number of cases per 100,000 and the background is constant at 0.16 cases per 100,000 population over all seven time intervals for both sexes. We assume these mesothelioma cases include pleural and peritoneal sites. Initially, we focus our attention on the mesothelioma incidence in St. Lawrence County as this is the location of the talc mines.

The incidence values reported by Hull et al. were compared to the values recently reported by Price and Ware (2004) for the US and those reported by Vianna et al. for NYS (excluding NYC)(Figure 2, Table 7). The incidence of mesothelioma among males in St. Lawrence County is indistinguishable from the US incidence for females. The incidence rates in St. Lawrence County are well below the 2000 average incidence rates for US mesothelioma of 0.92 per 100,000 not age-adjusted as discussed earlier. Vianna et al. report the NYS incidence rate (excluding NYC) is on average 0.45 cases per 100,000 and fluctuated from 0.37 to 0.52 over the six years of their study. Also, Vianna et al.

define high rates as twice the state average and reported St. Lawrence County had a mesothelioma incidence *lower than the average* for NYS (excluding NYC) (Figure 3).

Vianna et al. did report six mesotheliomas among talc workers, four in males and two in females, and reported these cases occurred in the six counties *with high mesothelioma incidence rate which did include St. Lawrence County.* Although the six are describe as talc miners they include two women. With the very small number of women in mining it seems unlikely with a 3:1 ratio of males to females that causation would be related to mining in general and talc mining specifically. The role of tremolitic talc in these six cases is not known and gender distribution suggests individuals experienced exposures elsewhere.

Although Vianna et al.'s results are suggestive of increased mesothelioma risk among talc miners it is inconsistent with the low incidence rates for the disease in St. Lawrence County (Figure 3). Hull et al. claim these as six of the eight historical mesothelioma cases; we would argue from these data that although mesotheliomas are occurring in St. Lawrence County, the incidence is similar to what one would expect based on US rates and less than the NYS average. Therefore it is not reasonable to assign a specific etiological agent to the "increase" as did Hull et al. *The increased incidence rates occurring among the males by year shown in Figure 2 are predominantly occurring due to increased rates in males over 70 years of age. The trend among females is flat over the same time period and similar to that of males and females in St. Lawrence County as a whole.*

The ages at death of the five cases reported by Hull et al. are 53, 58, 58, 69 and 72 (mean 62) we find them on average young for an occupationally exposed mesothelioma group. The mean age of mesothelioma in Great Britain is about five years older (Hodgson et al. 2005). It appears that the incidence of mesothelioma among females in St. Lawrence

County is less than that for males as is the pattern for the US population as a whole. We found no increase in the county where the mines with the asbestiform fiber-bearing talc are located we have not addressed in detail the higher incidence of mesothelioma in Jefferson County or any of the other counties in NYS which are in the highest incidence group (Table 7, Figure 3). As Jefferson County borders on Lake Ontario we suspect shipyards along it south and eastern borders are important in this regard (Figure 1).

Conclusions

Hull et al. report a causal association between human mesothelioma and exposure to NYS tremolitic talc based on a pathology case series of mesotheliomas, a comparison of lung content analysis of talc workers with and without mesothelioma, and population-based mesothelioma incidence data.

1. A series of five mesotheliomas are described as being caused by occupational exposure to tremolitic talc. In two of the cases no tumor histology or lung parenchyma was available and therefore neither the diagnosis nor exposure could be independently verified. We consider these cases of extremely limited value in establishing causation. Selikoff et al. 1979 reviewed histological slides and pathology materials in cases reported as mesotheliomas among insulation workers rather than simply rely on death certificates and compensation records. Death certificate information that identifies occupation of the deceased as "miner" or "talc miner" lacks critical information about complete occupational history. Any association of disease with an agent in a mining environment must recognize and take into account variables of mine location, mineralogy, and form of the implicated amphibole mineral. In addition to knowing if there was a potential for

exposure to commercial asbestos at the mining facility. Hull et al. have not provided convincing evidence of an increased mesothelioma risk among miners in St Lawrence County or provided evidence as to which of the many mines in the region the exposures occurred.

2. Reporting mesothelioma as a cause of death in a case series study requires reliable ascertainment which Hull et al. were not able to provide in two of the five cases. The lack of lung content analysis leaves open the possibility that the causative agent might have been commercial amphibole asbestos or the tumor was idiopathic in origin. Of the three remaining mesothelioma cases in the series where tumor tissues were available, the authors did not use a standard protocol for staining the histopathological tissue sections or the stains needed to eliminate other possible diagnoses.

3. By not making use of the most informative stains specifically for mesothelioma and other possible diagnoses the authors limit the diagnostic certainty in these three cases to a standard which most pathologists would consider questionable. Considering the lack of lung content analysis in three of the five mesothelioma cases and the limited occupational histories, commercial amphibole asbestos cannot be eliminated as a causative agent. Scanning electron microscopy analysis is an additional limiting factor.

4. The authors appear to have published the series of cases in at least three reports over a 12 year period. The first two reports appeared in 1990 with six and eight cases, and the last report, Hull et al. in 2002 with ten cases. The concentrations of asbestos fibers in the cases appear too have changed over time and the reports differ as to the presence or absence of commercial amphibole asbestos in at least 3 of the 10 cases. The lung content analysis although interesting is not of the robust

analytical standard one would need to support their causation claim. The authors report having collected 36 cases in talc exposed workers and report on only 10 cases. Among the 10 selected the research materials available in each case are not the same. Selection bias has not been properly considered and addressed.

5. The authors report an increased incidence of mesothelioma in two counties in northern New York –St Lawrence and Jefferson (Figure 1). They claim a 5 to 10-fold increased risk of mesothelioma in Jefferson County due to exposure to tremolitic talc. Our review of the literature found only a single talc mine in Jefferson County which closed over 100 years ago. The tremolitic talc mines are located in St. Lawrence County where the mesothelioma incidence is below the average for both New York State and the United States (Figure 2). Analysis of New York State Cancer Registry, for the period 1998-2002, found the mesothelioma incidence in St Lawrence County to be indistinguishable from background. We did not find any evidence of increased mesothelioma incidence due to tremolitic talc in St. Lawrence County.

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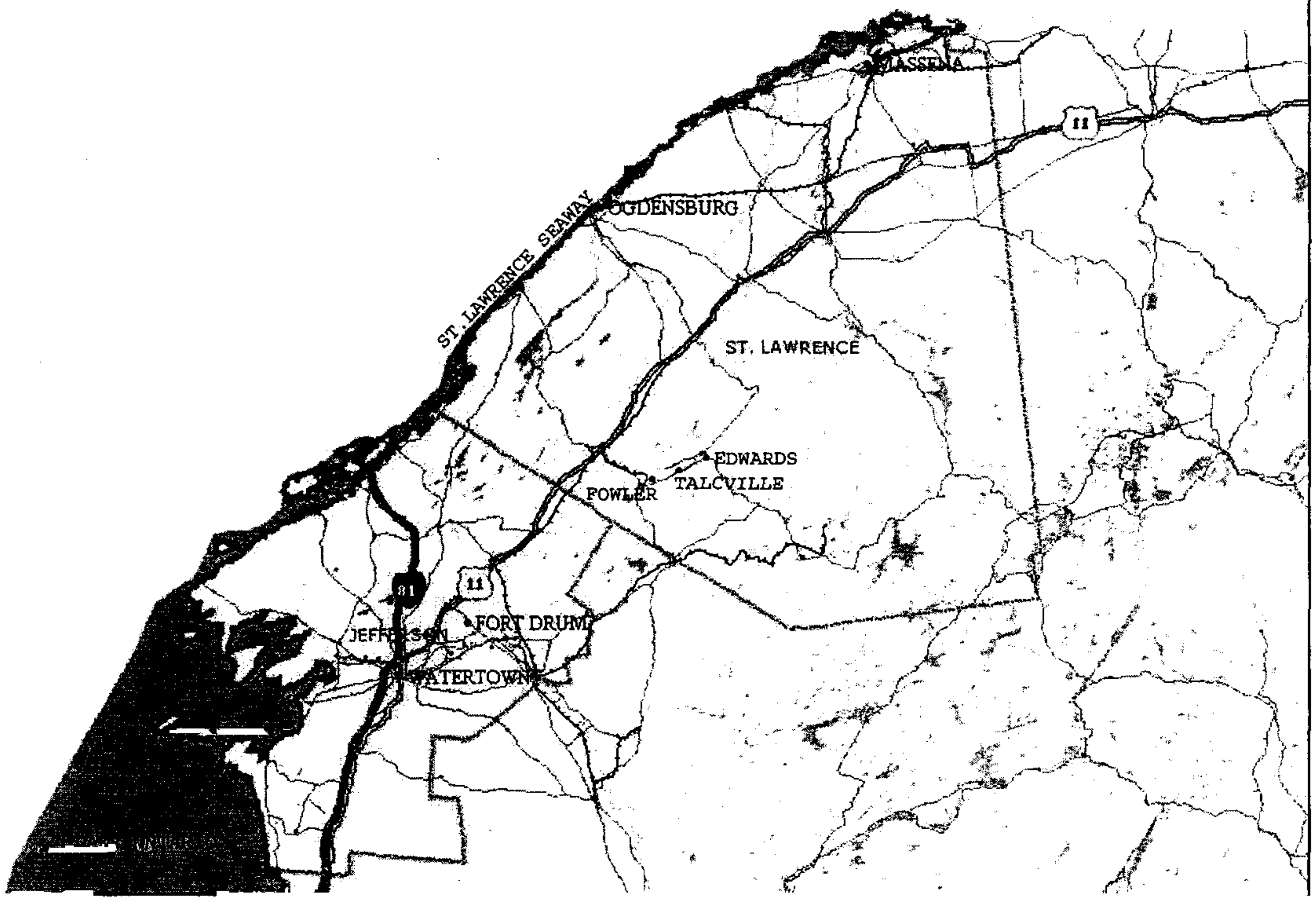

Figure 1: St Lawrence and Jefferson Counties, New York are along the St. Lawrence seaway with a population of 111,931 and 111, 738 respective in 2000 with about 51% males in both countries.

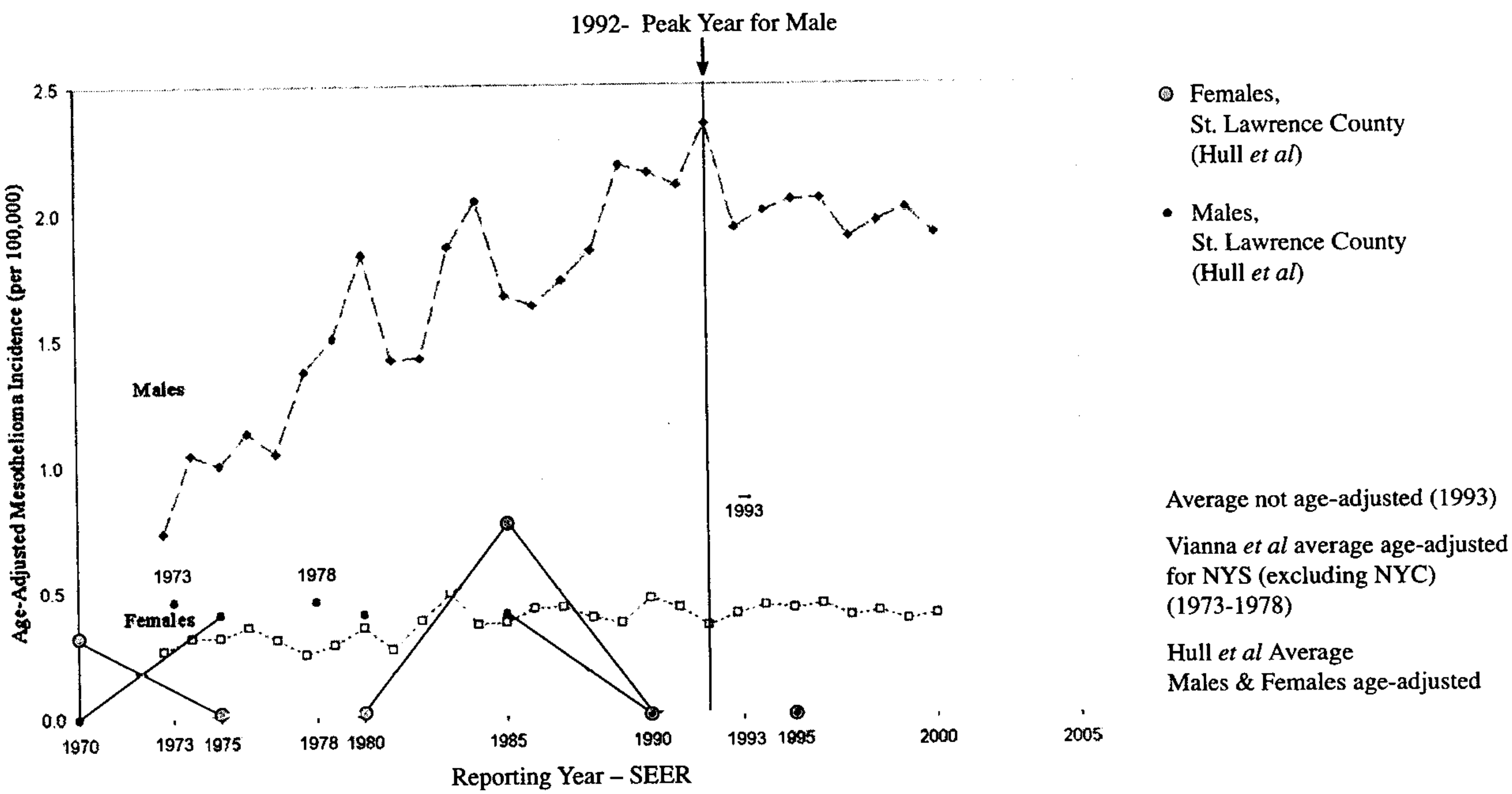

Figure 2: The US mesothelioma incidence for males and females is based on the SEER data 1970-2000 (Price & Ware, 2004), average incidence for both males and females in the US for 1993, average incidence for both males and females from NYS (excluding NYC) (Vianna et al) compared to St. Lawrence County the major tremolitic talc producing and background reported by Hull *et al.*

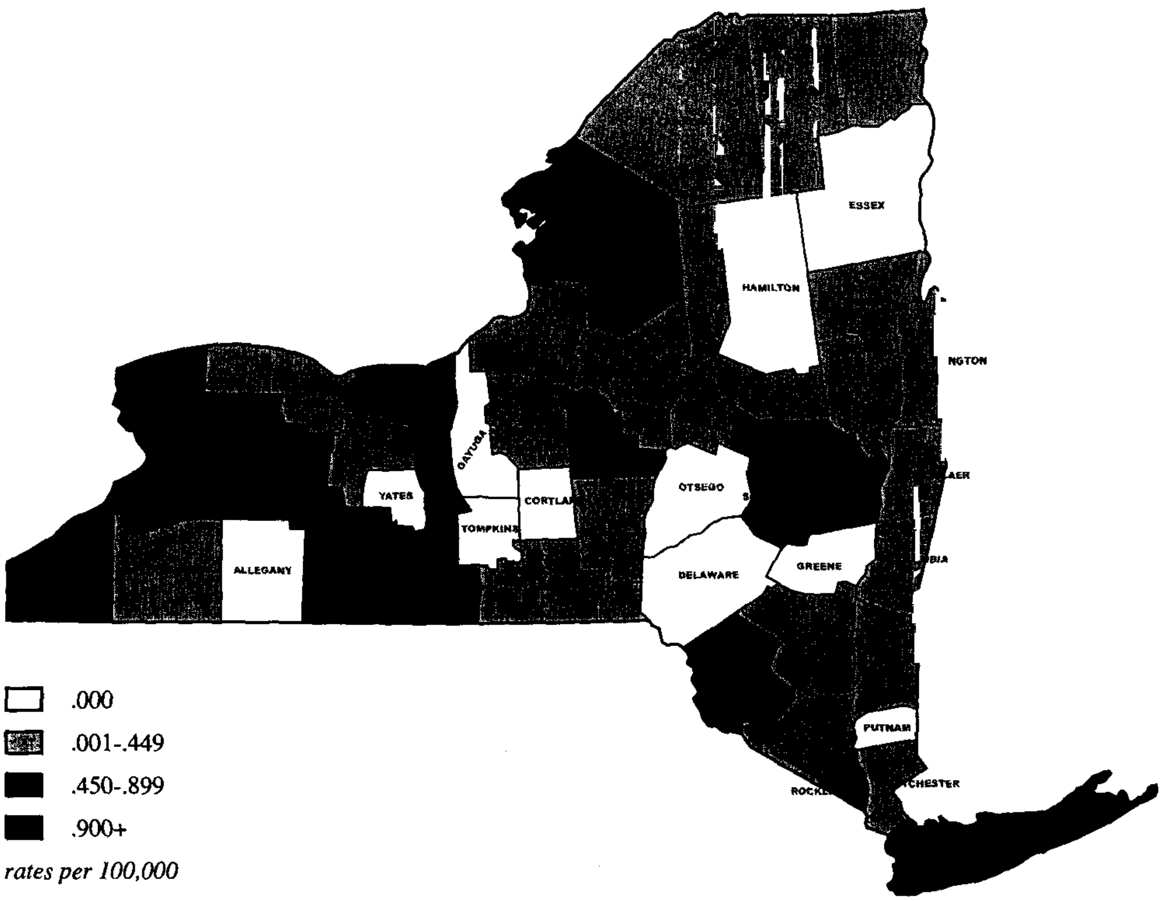

Figure 3. Average incidence rates for malignant mesothelioma in counties of New York State (excluding New York City) from 1973 through 1978.

Table 1: Five Mines Located Within One Mile of the Gouverneur Shaft, St Lawrence County, New York.

Mine	**Distance From Gouverneur Mine**	**Grenville Unit**	**Mineralogy**
Balmat Zinc	~1,173 ft SW	cdm 14	Partly calcitic, partly dolomitic marble; some tremolite.
American Talc	~ 880 ft SW	ts 13	Tremolite-anthophyllite-serpentine-talc schist.
Gouverneur Talc	Reference 0	cdm 14 ts 13	Calcitic-dolomitic-talc; Tremolite, anthophyllite serpentine schist.
Woodcock Talc	~ 1,222 ft N	ts 13	Tremolite-anthophyllite-serpentine-talc schist.
Wight Talc	~ 2,738 ft NE	ts 13	Tremolite-anthophyllite-serpentine-talc schist.
Balmat Zinc #2	~ 3,911 ft NNW	sm 6	Silicated dolomite, diopside layers; some tremolite.

This information was taken from Brown and Engel (1956). Note that the Gouverneur talc occurs essentially in stratigraphic unit cdm 14, but contains tremolite, some anthophyllite, talc, talc fiber and transitional structural-compositional fiber (sometimes also referred to as talcboles). Underground workings include some ts 13.

All carbonate units are marbles.

Table 2. Mineralogical Variation of the Talc Unit in Mines near Balmat, St Lawrence Country, New York.

Mineral	Mine 1	Mine 2	Mine 3	Mine 4
Tremolite	38.0	47.6	84.8	4.6
Anthophyllite	7.0	38.4	4.5	NR
Serpentine	12.0	4.1	4.2	11.7
Talc	24.0	5.4	3.2	3.8
Quartz	3.6	3.5	2.3	3.1
Calcite	14.4	2.0	0.2	71.4
Dolomite	TR	TR	NR	1.7
Others *	0.5	TR	0.8	3.7
	99.5	100.0	100.0	100.0

TR = trace, NR = not reported
Others* = oxides, sulfides, diopside, micas, and other minerals above trace.

Analyses based on polarized light microscopy modal analysis (volume percent).

Mine 1 is average composition, Woodcock Talc Mine, level 5.

Mine 2 is average composition, Woodcock Talc Mine, top level.

Mine 3 is average composition, Balmat Zinc Mine, talc unit.

Mine 4 is average composition, Woodcock Talc Mine, silicated calcic marble, separating talc units. Other analyses are of [ts 13] unit in mine.

Table 3: Pertinent data from NYS talc miners diagnosed with malignant mesothelioma

	Birth	Death	Smoking History	Talc Job	1^{St} Year on Job	Job Duration (yrs)
Case 1	1931	1989	10	Mucker, driller, Hardinge operator	1952	22
Case 2	1937	1990	0	Packer Talc into Trucks	1955	4
Case 3	1912	1984	0	Mechanical Engineer helped construct 2 talc mines	Unknown	2
Case 4	1923	1981	Unknown	Unspecified employment at a single talc mine	1953	22
Case 5	1925	1994	Unknown	Roustabout, foreman, pack house worker	1949	25

Table 4: Diagnosis and immunohistochemical results in three mesothelioma cases no tissue was available in two cases.

	Description of Pleural Mesothelioma	Immunohistochemistry
Case 1	Biphasic, diffuse	Pan-cytokeratin (+++). Calretinin (+++)
Case 2	Sarcomatous	Cytokeratin (+++) Calretinin (-)
Case 3	Epithelial with rare biphasic areas	CEA(-) alician blue(+ cellular), mucicarmine (+ rare focal)
Case 4	Diagnosis of mesothelioma made by NYS Workers Compensation Board	No Tissue Available
Case 5	Diagnosis of mesothelioma made by death certificate	No Tissue Available

Table 5: One of the two mesothelioma cases (shown as bold) reported as Case 7 in Abraham (1990a, b) appears as Case 1 in Hull et al. The tremolite/actinolite is an order of magnitude higher in Hull et al. 2002. Six of the seven Hull et al. cases all appeared in Abraham (1990a, b) including one of the two mesotheliomas where lung content was available. .

Cases*	**7**	**1**	2	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
Paper	(1990a)&(2002)		(2002)	(2002)			(1990a)	&	(2002)		
Age at Death	**58**	58	52	49	58	60	63	66	71	71	76
Years Mining	**22**	22	4	21	21	18	30	23	25	2	10
Diagnosis†	**ATM**	ATM	ATM	ATSC	ATS	ATP	ATSP	ATPC	ATP	N	Pn
Asbestos Fibers	**10.2**	**12**	**1,121**	**20**	**378**	**81**	**42**	**54**	**62**	**0.29**	**3.9**
Anthophyllite	**5**	5	n/d	12	85	64	4	14	**n/d**	0.04	0.4
Tremolite/Actinolite	**0.2**	**2**	1100	1	105	7	17	31	**43**	0.07	**0.9**
Chrysotile	**5**	5	21	7	188	10	21	9	19	0.18	2.6
Talc Fiber	**46**	46	96	24	716	47	157	195	**233**	0.1	3.1
Asbestos Bodies‡	**35**	35	9.3	200	1	98	89	42	485	0.1	1

† A is asbestosis, T is talcosis, M is mesothelioma, S is silicosis, P is plaque, C is lung cancer, N is normal and Pn is pneumonia.

n/d is none detected.

* Bold indicates the same case was reported in Abraham(1990) and Hull *et al.*

‡ Asbestos bodies used in the generic sense, coating could have a talc or transitional fiber core.

Table 6: The lung content analysis of Case 5 (Abraham 1990a, b) and Case F are compared (Hull et al.). The anthophyllite asbestos in Case 5 become talc fiber in Case F and the tremolite asbestos concentration is reversed from 34 million fibers/gram dry lung in Case 5 to 43 million fibers/gram dry lung in Case F. It appears to be the same case in both reports.

	Case 5 1989	Case F 2002
Age at Death	71	71
Years Mining	25	25
Diagnosis †	ATP	ATP
Asbestos Fibers	62	62
Anthophyllite	(49) —	n/d
Tremolite/Actinolite	(34) ←→	(43)
Chrysotile	19	19
Talc Fiber	(184) →	233
Asbestos Bodies	485	485

† A is asbestosis, T is talcosis, M is mesothelioma, S is silicosis, P is plaque, C is lung cancer, N is normal and Pn is pneumonia.
n/d is none detected.

Table 7: Mesothelioma incidence rate per 100,000 persons for St Lawrence and Jefferson Counties given in 5-year intervals.

Time	Background	St Lawrence		Jefferson	
Interval	Males& Females	Males	Females	Males	Females
1965-69	0.16	1.0	1.7	---	---
1970-74	0.16	---	0.3	2.2	0.2
1975-79	0.16	0.4	---	0.9	0.8
1980-84	0.16	0.4	---	0.5	0.3
1985-89	0.16	0.4	0.8	1.04	0.6
1990-94	0.16	---	---	0.95	---
1995-97(?)	0.16	---	---	---	0.4

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Asbestos, Asbestos Health Effects, Industrial Minerals, Contaminated Land, Analytical Training, Expert Witness

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A Critical Review

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HU16 4NL

Mesothelioma among Workers in Asbestiform Fiber-bearing Talc Mines in New York State. Annals of Occupational Hygiene, 2002, Vol. 46, Supplement 1, pp 182-185. Mindy J. Hull, Jerrold L. Abraham, Bruce W. Case

A Critical Review

John Addison

Fiber analysis by SEM/ADXS

The analytical technique used to perform identification of the fibers is of serious concern. The Scanning Electron Microscope method is very limited in the information that it can provide for accurate identification of minerals. No crystal structural information can be deduced from SEM, so there is no means of differentiating minerals of similar chemical composition but different crystal structure. Quantitative chemical analysis using Energy Dispersive x-ray Spectrometry in SEM is only possible if the material under analysis is presented as an flat surface perpendicular to the electron beam. The computer algorithms used for converting crude element x-ray counts to chemical analysis can be applied successfully if the material is an infinitely thick plate (or effectively so) or if it is a thin film. In any other situation, such as in this method, with irregular particles scattered on a plastic substrate, the best that can be achieved is an approximation to the chemical composition. This is because of the lack of information about mass absorption coefficients, secondary fluorescence effects and the geometry of the particle surfaces with respect to the x-ray detector. In addition, if the particles are 0.2 µm thick or less the x-ray yield is very much reduced and the statistical reliability of x-ray yields from different elements in the mineral is very much reduced. The result is that small particles (0.2 µm) of minerals such as talc, anthophyllite, chrysotile, cummingtonite, forsterite and enstatite which all contain magnesium and silicon in slightly different proportions are effectively indistinguishable. The same would be true of the minerals tremolite, actinolite, diopside, pigeonite, and monticellite, all of which contain calcium magnesium and silicon. Furthermore, in my experience, the x-ray yield from fibers with diameters of 0.1 µm or less is so low as to make it impossible to identify fibers with any confidence. It is disconcerting then to observe that the geometric mean widths of mineral fibers identified in the mesothelioma cases as talc, anthophyllite and chrysotile are in the range from 0.05 to 0.20 µm. The same minerals in the non-mesothelioma cases range from geometric mean widths of 0.08 to 0.34 µm., and the minimum widths of fibers, cited as identified, are as low as 0.03 µm.

The authors provide no information as to how these identifications were achieved, what reference materials were used, or what the statistical reliability of the x-ray counts were. In view of this lack of information the identifications can only be considered as unreliable.

Fiber lung burdens

The paper provides Tables with lists of the lung burdens in terms of fiber numbers, asbestos bodies and mineral particles. These are expressed as fibers per gram of dry weight tissue (fibers and asbestos bodies) or as numbers of particles per millilitre of lung (talc and silica particles). There is no way of correlating these figures so the relationship between particles and fibers is unknown.

The lung fiber burdens are provided separately for the two mesothelioma cases and the eight non-mesothelioma cases, but the fiber dimensions, upon which much of the argument is based consists of the geometric mean widths, lengths and aspect ratios for all fibers of the different types in the two groups of cases. The statistical validity of making that calculation is questionable since the authors are actually trying to demonstrate whether any of these fiber populations are the same or similar. At this point they appear to have already decided that by grouping all the fiber types in the two sets of cases together. As a result, at first sight, there is little that can be done to assess the quality of the results.

The total numbers of fibers of each type found in the analyses (Hull et al, Tables 4 and 5) must relate in some way to the lung burden results (Hull et al, Table 3). The lung burden results report tremolite/actinolite concentrations in lung while the dimensional analysis of Table 4 and 5 report tremolite and actinolite separately, so there are still some difficulties.

Since the actinolite numbers are comparatively small, for this analysis the Table 4 and 5 fiber numbers of tremolite and actinolite will be grouped together.

Doing so produces Table 1 shown below. For the mesothelioma cases only, this shows the fiber burdens in each lung and the actual numbers of fibers found in both lungs together. The analysis is too complicated to apply to the non-mesothelioma cases

Table 1

Mineral	M1 F/g dwl	M2 F/g dwl	Number found (M1 + M2)
Anthophyllite	5	0	6
Tremolite/Act	2	1110	39
Chrysotile	5	21	5
Talc fibers	46	96	54

Understanding how these numbers must relate is complex but can be deduced from the analytical processes used in arriving at them. The fundamental number is the number of fibers actually found in the course of the SEM search which is shown in column 3 as the sum for the two mesothelioma cases. The lung concentration is calculated from the fibers found by simple arithmetic using the formula; $F_{lung} = n \cdot V/v \cdot A/a \cdot 1/W$, involving the weight of tissue, volumes of initial suspension of residue and any aliquots taken from it, the effective area of the filter and the area searched by SEM. Irrespective of the exact values of these factors, for any one case, the final factors must be exactly the same for each of the fiber types, effectively a constant, as in $F_{lung} = n \cdot K_1$.

From Table 1 we know that for the anthophyllite in case M1, $F_{lung} = 5 = 6 \cdot K_1$. The value of K_1, 0.833 must be the same for all of the other minerals in that sample since they were found in the same residue during the same search.

Similarly, for case M2, for the tremolite, $F_{lung} = n \cdot K_2$, so $1110 = (39 - X) \times K_2$ where X is the number of tremolite fibers found in case M1.

But we also know that for case M1, $2 = X \cdot K_1$, and $K1 = 0.833$, so the actual number of tremolite fibers found in the search of case M1 was $X = 2/0.833 = 2.40$. Assuming some arithmetical rounding of the numbers the number of fibers observed in M1 must have been 2.5 since only whole or half integer numbers can ever be found in such a search, and using 2.5 for X in the equation $F_{lung} = X \times 0.833$ gives 2.08 fibers in lung.

So now we know that for tremolite in Case 2, $1110 = (39 - 2.5) \times K_2$, therefore

K2 = 30.4.

Using these factors for the other fiber numbers in Table 1 of this document allows an iterative series of tests for the internal consistency of the data, remembering that these must be constant factors for all of the fibers in any one lung sample. Unfortunately there are no two constants that can produce the results as given by Hull et al, for all of the four fiber types listed. The data are not internally consistent, and this raises serious questions about their validity. A more detailed evaluation of these factors is given in the appendix.

Fiber dimensions

The authors consider that the similarity in the geometric mean dimensions of the fibers found in the lungs of the mesothelioma and non-mesothelioma cases to be very significant in ascribing the mesothelioma causation to the exposures in the talc mining industry. They specifically mention the similarity between the talc fibers and the tremolite fibers in the two sets of cases. These are shown below together with the anthophyllite dimensions in Table 2 below.

Table 2 Fiber dimensions as given in Hull et al (2002)

			Width (µm)			Length (µm)			
	Fiber type	n	GM	Min	Max	GM	Min	Max	AR
Meso	Tremolite	38	0.22	0.1	0.4	4.5	1.7	10.6	26
Non-Meso	Tremolite	51	0.34	0.04	1.00	5.3	1.5	17	24
Meso	Talc	54	0.20	0.05	1.00	5.3	1.4	53	43
Non-Meso	Talc	248	0.33	0.06	2.8	6.4	1.3	219.0	30
Meso	Anthophyllite	6	0.15	0.06	0.3	10.6	3.9	30.2	90
Non-Meso	Anthophyllite	85	0.24	0.05	1.6	7.7	1.6	146.0	56

Ignoring the fact that the grouping of these fibers may not be statistically valid for fibers found in 10 different lung residues with no known association, other than that the cases worked for some time in one of what may have been a number different talc mines in New York State, the figures cited do not appear to support the conclusions. The authors state that there is no significant difference between the size distributions of the mineral types in the two sets of cases based upon Student's t-test, with significance determined as $P < 0.05$. This assertion is made with no reference to what was actually tested and there is no way that the data presented can be used to confirm it. As the table above shows, the geometric mean widths of fibers of each type in the non-mesothelioma cases are consistently 50% or more greater than those in the mesothelioma cases. As fiber width is a critical characteristic of asbestos fibers it would seem that this difference should be examined more closely before reaching a judgement about the 'similar dimensions' of the dusts to which the miners were exposed. In addition, it seems unreasonable to make such assertions on the basis of a relatively small number of fibers in each class (with the exception of the talc fibers in the non-mesothelioma cases). A serious comparison of fiber size distributions ought to be made on the basis of at least 100 fibers, preferably more, and a Kolmogorov-Smirnov statistical test would be the preferred method of comparison. Asbestos fiber populations are bivariate log normally distributed and such a test is the only real way to test population similarities. Unfortunately the length and width of each fiber found is needed for this type of test and the authors do not provide this data.

The size distributions are unusual in other ways in comparison to asbestos and other mineral samples. The geometric mean lengths are considerably longer than most other asbestos samples; most asbestos samples measured by SEM or TEM have mean lengths of the order of 2 - 3 μm (for all fibers longer than 1 μm), rather than the 3 – 10 μm found here. Aspect ratios for whole populations of asbestos fibers are normally in the range of 7 – 10 rather than the 20 – 30 range found in most of these samples, and never near the extraordinary geometric mean aspect ratios of 90 to 133 found for the anthophyllite of the mesothelioma cases and the chrysotile of the non-mesothelioma cases. Such dimensional departure from the normal asbestos shapes and sizes lead to doubt about the credibility of the measurements. Finally, the dimensions of the fibers are not consistent with those found for NY talc as described by Siegrist and Wylie (1980) and as such it is suggested that other sources of mineral dust may have contributed significantly to the lifetime lung burdens of both the mesothelioma and non-mesothelioma cases.

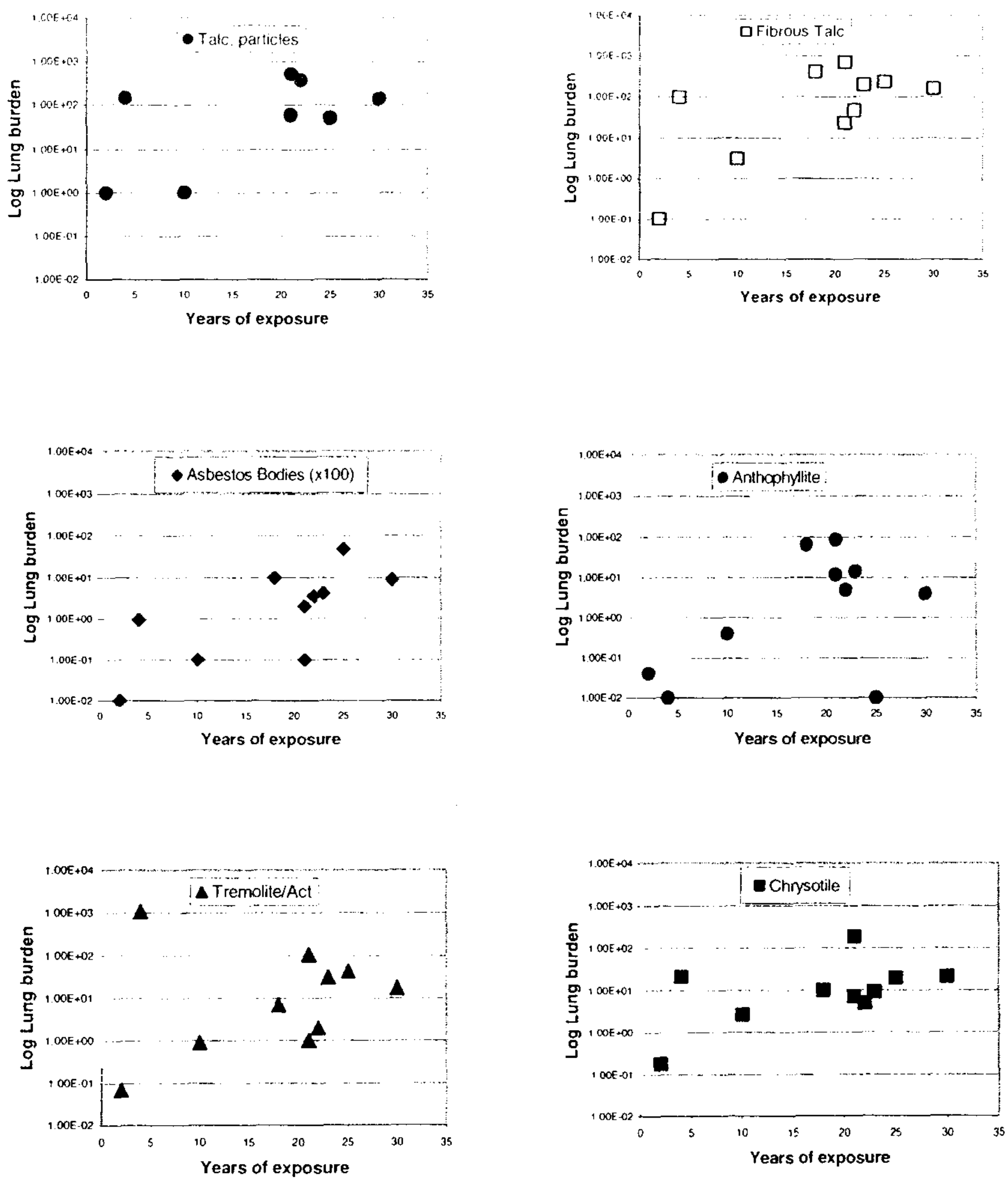
Lung burden and exposure

More evidence for this is found when the lung burdens are compared to the years of exposure in talc mining as shown in Figure 1.

It is apparent at first sight that whatever the relationship between lung burden and duration of employment is, it is not simple and it appears to differ between particle types and individuals. There is some general trend towards increasing lung burden with duration of employment but this is largely because the shortest duration burdens are , as expected, very low. Without this single point in each graph the trends are much less clear. Asbestos bodies and talc particles both appear to increase as expected with years of exposure. Tremolite fibers show no increasing trend; it is very low in the shortest exposure case and extremely high in the mesothelioma case (with the second lowest exposure period); for longer exposures it shows no increase at all. Anthophyllite is generally low, absent in two cases, including one of the mesothelioma cases, and very much higher in one case only. The same case also has the highest lung concentration of talc fibers and chrysotile as well as the second highest tremolite/actinolite.

Figure 1a -f. Showing the relationship between lung burdens of all types of particle and the duration of employment in the talc mines. The two mesothelioma cases are shown with blue symbols.

All of the data are from Table 3 of Hull et al (2002). The asbestos bodies are expressed as thousands per gram of dry lung (divided by 100 in the figure). The fibers are expressed as millions of fibers per gram of dry lung. The talc particles are expressed as millions per millilitre of lung.



An equally good case could be made for the tremolite/actinolite fibers being the result of environmental exposure: as shown in Figure 2 they appear to some extent to be a function of the age at death of the cases. Cases G and H, two of the oldest three cases at death, have very much lower lung burdens than any of the others and without any more information about their life or work histories it is difficult to draw any conclusions about their exposures. The remaining lung burdens do appear to show a progression with age.

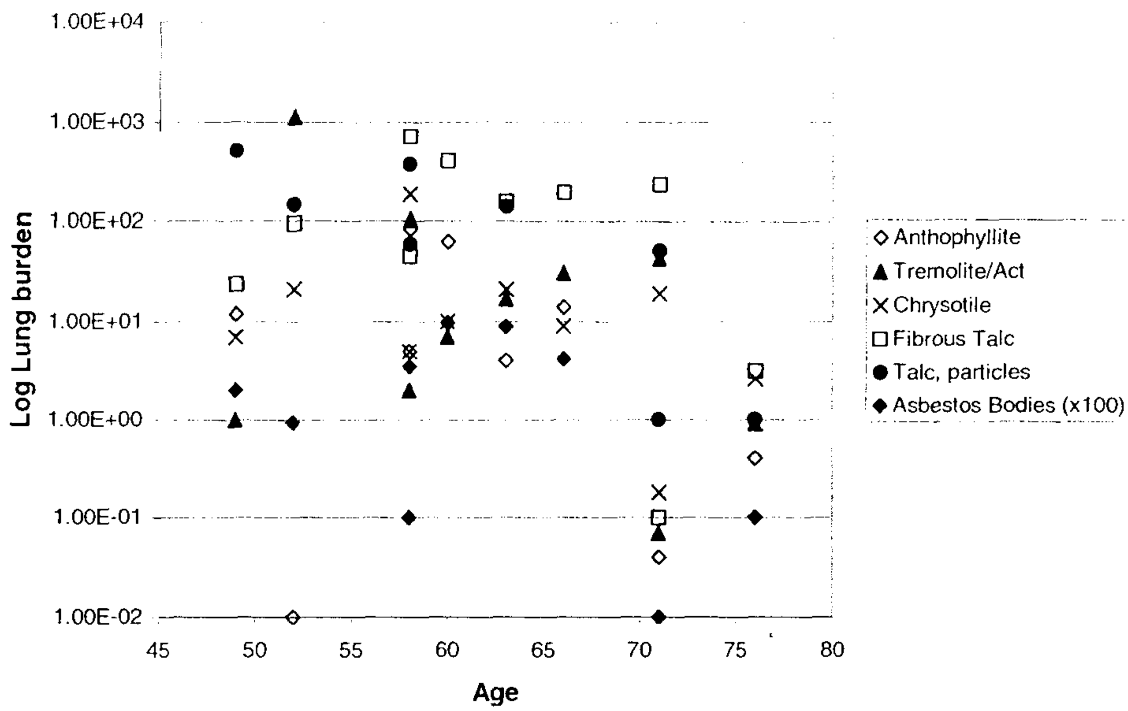


Figure 2. The relationship between lung burdens of all types of particles and the age of the case at death. (Same data as for Fig 1) Mesothelioma cases are shown in blue.

A different way of viewing the relative lung burdens with respect to duration of employment is to rank the lung burdens by assigning a value of 10 to the highest. 9 for the next highest and so on as shown in Table 3.

Table 3 Ranking of lung contents for each case; cases are ordered in terms of duration of work in the industry.

Case No	G	M2	H	C	A	B	M1	E	F	D
Actual Years	2	4	10	18	21	21	22	23	25	30
Rank years	1	2	3	4	5	5	7	8	9	10
Rank AB	1	4	2	9	5	2	6	7	10	8
Rank Anth	3	1	4	9	7	10	6	8	1	5
Rank T/A	1	10	2	5	3	9	4	7	8	6
Rank Chr	1	8	2	6	4	10	3	5	7	8
Rank Talc F	1	5	2	9	3	10	4	7	8	6
Rank Talc NF	1	8	1	Na	10	6	9	Na	5	7
Average Rank	1.3	6.0	2.2	7.6	5.3	7.8	5.3	6.9	6.5	6.7

Na – not analysed

If the only source of fibers was occupational exposure in the talc mining then a regular increase in rank should appear with age rank. Other than for cases G and H , the average ranks are scarcely different over the whole set, and indeed the highest ranks are found for the cases with intermediate duration of employment. While the conclusion that non-occupational exposures are significant is not possible, because there is no information about the severity of the exposures of each case, nevertheless the hypothesis that some other source of exposure must be playing a part is suggested and should not be excluded.

A similar approach can be taken with the order of concentration of the different fibrous minerals in each of the lung burdens as shown in Table 4.

Table 4 Ranking of fibrous minerals in the lung of each case. 1 is the lowest of the four minerals in the lung; 4 is the highest of the four minerals in the lung. All are the numbers of fibers per gram of dry lung as in Table 3 of Hull et al (2002)

	M 1	M 2	A	B	C	D	E	F	G	H	Average
Anthophyllite	2	1	3	1	3	1	2	1	1	1	1.6
Trem/actinolite	1	4	1	2	1	2	3	3	2	2	2.1
Chrysotile	2	2	2	3	2	3	1	2	4	3	2.4
Talc fibrous	4	3	4	4	4	4	4	4	3	4	3.8

If the four minerals were all the result of a consistent industrial exposure the ranking should be the same in each lung, and indeed three of the cases, B, D, and H have the same pattern of fiber burdens. However this pattern is not followed by any other cases and only two others, A and C have the same pattern. The talc fibers are the highest in 8 out of the ten cases and second highest in 2. Anthophyllite is the lowest in 6 out of ten, but second highest in 2. The tremolite and chrysotile are both very variable in their rankings, ranging from highest to lowest, and their average ranks are very similar. That the lung contents are inconsistent lends support to the hypothesis that at least some of the lung burdens are not related to occupational exposure in the talc mines. Other explanations for this could be that the miners worked at different mines with different mineralogy or that the mineralogy of the mines varied over time, leading to variation in the quality of the mineral exposures. There is no evidence for or against any of these propositions. Whatever the explanation the suggestion that the men all experienced the same mineral exposure is not strictly tenable.

It is speculative to suggest possible environmental exposures for any of the minerals found in the lung burdens. However, the geology of Northern New York State is complex, the Adirondaks being part of the Appalachian metamorphic belt, and outcrops of rocks bearing these minerals are probably not uncommon. So it is to be expected that many activities in agriculture or even gardening could result in environmental exposures that would not be negligible in the long term.

Conclusions

It is my opinion that the SEM analytical procedures used leave some doubt as to the validity of the mineral identifications in the paper. The fiber lung burdens can not be consistently derived from the observed fiber numbers given in the paper. The size distributions of the fibers lead to further questions about the quality of the data and do not support the conclusions drawn. The conclusion that the lung burdens represent a picture of a coherent pattern of occupational exposure is not justified by close examination of the lung burdens.

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August 2004

Appendix

It is difficult to check the validity of the final lung burden result given by Hull et al because the numbers of fibers found in the individual lung samples are not given, only the total numbers of fibers in each group that were used to calculate the geometric mean dimensions. However, if we assume that the fiber numbers given in Table 5 of Hull et al represent combinations of those used to calculate the lung burdens the mesothelioma cases at least can be checked for internal consistency.

The formula for calculation of lung burden from the numbers of fibers found during a systematic search of a sample prepared on a filter and examined by microscopy is usually given as follows: F_{lung} = n x **V/v x A/a x 1/W**

n – number of fibers found;

W - Dry weight of lung tissue digested, in grams;

V - total volume of solvent used in digestion of tissue, millilitre;

v - volume of aliquot filtered, millilitre;

A - Total area of filter deposit, square millimetres;

A - area of filter searched, square millimetres.

Irrespective of the exact values of these individual factors, for any one case, they can be grouped into a single constant which must be exactly the same for each of the fiber types in any one sample. This can be called x for Mesothelioma Case 1, and y for Mesothelioma Case 2. For any mineral the total number of fibers found in the search can be called T, and if the number found in Case 1 was n, then the number found in Case 2 was T – n. The lung burdens F1 and F2 calculated from these are

$F1 = n.x,$ (1)

$F2 = (T-n).y$ (2)

Equation 1 can be written to allow the term for n in equation (2) to be substituted as $n = F1/x$, giving:- $F2 = (T - F1/x).y$ (3)

This equation can be rewritten as $0 = F2.x - T.xy + F1.y$

This is a simple equation that contains only terms that are known or can be calculated from values provided by Hull et al.

The figures from Hull et al are:

Fiber Type	Mesothelioma Case 1 Lung burden F/g dwl	Mesothelioma Case 2 Lung burden F/g dwl	Number found (M1 + M2)
Anthophyllite	5	0	6
Tremolite/Act	2	1110	39
Chrysotile	5	21	5
Talc fibers	46	96	54

So the calculations must be as in the following table;

	Mesothelioma Case 1	Mesothelioma Case 2
Fiber Type	Lung burden,	Lung burden,
Anthophyllite	$5 = n_{ant*}\, x$	$0 = (6 - n_{ant})\, y$
Tremolite/act,	$2 = n_{/at}\, x$	$1110 = (39 - n_{t/a})\, y$
Chrysotile	$5 = n_{chr}\, x$	$21 = (5 - n_{chr})\, y$
Talc fibers	$46 = n_{talc}\, x$	$96 = (54 - n_{talc})\, y$

* n is the number of each fiber type found in the SEM search of Case 1; the number for Case 2 is the total number found minus the number for found in Case 1

The algebra used for equations 1, 2, and 3 above allows these to be recast as the following equations

For the Anthophyllite; $x = 5/6 = 0.833$

For the Tremolite/act, $1110x - 39xy + 3y = 0$

For the Chrysotile $21x - 5xy + 5y = 0$

For theTalc fibers $96x - 54xy + 46y = 0$

Case 2 contains no anthophyllite, so it is possible to calculate x from $F_{ant} = n_{ant}\, x$; 6 fibers found gives the result of 5 fibers per gram of lung tissue; therefore $x = 5/6$,

i.e. $x = 0.8333$.

Of course, because the analyst may have rounded numbers up or down after the calculation, the nmber 5 in the first of these equations could have been anything between 4.5 and 5.5 and the resulting value of x between 0.75 and 0.916.

Table 5 shows the best solutions for x and y in the equations for tremolite, talc and chrysotile found by iteration.

Table 5

	x	y
Tremolite.	0.915	30.15
Talc	0.905	30.3
Chrysotile	1.16	30.40

Theoretically these factors should be identical, and while those for tremolite and talc fibers are close, the factor for chrysotile in Case 1 can not be reconciled with the reported lung burdens and numbers of fibers found in the search.

It is possible to test these values by applying them back into the original equations to determine the actual numbers of fibers found in the Case 1, 'n'. For Case 2, 'n' will be the total numbers of fibers found minus Case 1 'n'. These should be whole or half integers if the factors x and y are correct.

	Case 1	Case 2
Anthophyllite	6.00	0
Tremolite	2.19	36.81
Chrysotile	4.31	0.69
Talc fibers	50.83	3.17

These are obviously not whole or half integers.

Unfortunately, no two constants have been found that can produce the results as given by Hull et al, for all of the four fiber types listed. The data do not appear to be internally consistent, and this raises serious questions about their validity.

Outline / Nolan
For Lawyer Review
Project accepted

Issue: RTV is routinely pulled into 3rd party asbestos suites. In the past two years, however, these suites have increasingly involved mesothelioma. Our ability to settle these cases cheaply (once we trot out the mineralogy and biology) has been adversely impacted by the "ambiguity" associated with mesothelioma and enhanced willingness of the plaintiffs bar to spend more time on RTV (fewer "deep pockets" left).

The articles by Andrew Schneider, NIOSH, problematic analytical reports (Rohl, RTI, etc.) and J. Abraham's lung burden work are our biggest problems.

Resolution: We have been reasonably successful dealing with the mineralogy issues and lung cancer claims. We do not yet have enough defenses when confronted with a mesothelioma case thanks in large measure to the 4-page paper by Hull et al (Abraham).

We believe it is critical that the Hull paper – the strength of the "causal association" suggestions behind it – be rigorously and fairly critiqued. This would include, but not be limited to, the following considerations:

- The strengths and weaknesses of lung burden studies as a causality predictive tool (in general). How does the Hull paper fair against these considerations?
- The strengths and weaknesses of the mineral analysis employed in the Hull paper. How complete is it? Is the discussion and conclusions in the paper reasonably supported by the mineral observations? How are current talc mining (RTV only) reasonably linked to "possible" historical exposures. Are they the same in type and concentration – do we know?
- The strengths and weaknesses of a case study like this to draw causal conclusions about a larger, more directly exposed RTV talc worker population and/or the population of entire counties.
- The strengths and weaknesses of a study like this contrasted to more direct studies (mortality, morbidity studies, animal studies, cell studies of the talc in question).
- How credible – how unbiased has J. Abraham been on this matter over time?

Basically: mineralogy, pathology and risk assessment as it pertains to this work.

Format: A formal report to RTV or an attorney that addresses the above. This would be used in response to being named in mesothelioma litigation when Abraham is cited. The document might be published at a later date.

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Hull MJ, Abraham JL, Case BW. Mesothelioma in asbestiform fiber-bearing talc mines in New York State. Annal Occup Hyg 2002; 46 (suppl 1) : 132-135 - critique

They report five new cases of mesothelioma among talc workers, present fibre burden data and update mesothelioma mortality in this district using cause of death information from 1950 to 1997.

Histopathologic diagnosis

Of the five cases only three had tissue available – in two there was no tissue diagnosis. The immunohistochemical workup is very poor with very limited range of markers employed. The recommendation these days is for at least two epithelial and two mesothelial markers to be employed. Case 1 is probably a mesothelioma but there is some doubt as to cases 2 and 3. No tissue in cases 4 and 5 casts serious doubt as to validity of diagnosis.

Occupational details

Very limited.

Case 2 only 4 years in the talc industry – what had he done the remainder of the time?

Case 3 - Mechanical engineer with potential exposure to commercial amphiboles – only two years in the talc industry.

Cases 4 and 5 presumably had periods of other employments prior to and after working in the talc industry.

Lung particle analyses

2 mesothelioma and 8 non-mesothelioma cases analysed. Very little detail as to what was actually done. I have seen a number of analyses by Abraham – Burnett in cases and they do not seem to employ a standardized protocol, reporting results at a range of magnifications, which makes it difficult to compare the results of one case with another.

Non-fibrous particle burden measured using in-situ analysis of tissue sections – this is crude and does not provide a good estimate of what types of particles are there – it provides poor characterization and by expressing the result in volume terms is problematic because the volume of the tissue will depend to a large extent on how well the lung has been inflated. This will vary with the technician, if the lung has been distended with formalin at all at the time of examination grossly and the disease present.

There will be problems with estimating "asbestos" bodies in this situation because of the large numbers of non-asbestos ferruginous bodies present – the cores need to be checked by EDAX.

There is a large difference in tremolite measured between case 1 and case 2 (mesotheliomas) which does not correlate with years of exposure. This is contrary to the results found in the Canadian chrysotile mining situation where tremolite lung burden increases with length of exposure. There may well be problems with differentiating between anthophyllite and talc in these analyses.

It would be interesting to see the raw data on these cases because I have no feel for how many fibres were counted and analysed for each case and what the detection levels were. The values obtained in control G were probably within background. However, Abraham has never reported what his background ranges are for the various asbestos fibres. It is possible that if he only analysed a small number of fibres for each case and controls that significant numbers of commercial amphibole fibres were missed because they would comprise a small percentage of the total fibres and might have been well out-numbered by the talc and other fibres present. It is surprising that only one commercial amphibole fibre was found in the 10 cases analysed and suggests to me inadequate detection levels.

Overview

In summary this paper provides very cursory and limited information concerning mineral particle burdens in workers employed in the talc industry. The update mesothelioma mortality in the district from death certificate information is also limited and would require close inspection of occupational records to make sense of in terms of whether these were related to talc exposure or to some confounding exposure to commercial amphiboles.