

NAIMA
NORTH AMERICAN INSULATION
MANUFACTURERS ASSOCIATION

8EHQ-0296-1359

RECEIVED FEB 27 1996

February 27, 1996

BY HAND --
FILE STAMPED COPY REQUESTED



8EHQ-96-13595
INIT 02/27/96

(A)

TSCA Document Processing Center (7408)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

ORIGINAL

Attention: Section 8(e) Coordinator

Dear Sir or Madam:

The North American Insulation Manufacturers Association (NAIMA) has just received preliminary information on an ongoing inhalation study in hamsters being conducted for NAIMA by the Research and Consulting Company in Basel, Switzerland.

Administration of the test articles to the animals began on August 7, 1995. The test articles are MMVF 10a (an insulation glass fiber), MMVF 33 (a special purpose glass fiber), and amosite asbestos. Detailed specifications for MMVF 10a and MMVF 33 are enclosed (Attachment A).

The MMVF 10a is being administered at one dose: 30 mg/m³ (approximately 250 WHO fibers/cc); the MMVF 33 at one dose: 37 mg/m³ (approximately 250 WHO fibers/cc); and the amosite at three doses: 0.7, 3 and 7 mg/m³ (approximately 25, 125 and 250 WHO fibers/cc). Fiber arithmetic mean diameters through 13 weeks of aerosol exposure were 0.94 microns for MMVF 10a, 0.84 for MMVF 33, and 0.58 for amosite. The median diameters were 0.87 microns for MMVF 10a, 0.57 microns for MMVF 33, and 0.52 for the amosite (Attachment B). Some preliminary lung burden data has been collected. Lung burdens of long (>20 micron) fibers found in the animals at 13 weeks of exposure were for MMVF 10a: 7,800 fibers/mg dry lung weight and for MMVF 33: 26,000 fibers/mg dry lung weight. Amosite lung burdens were: low dose 14,000 fibers/mg; mid dose 39,000 fibers/mg; and high dose 53,000 fibers/mg (Attachment C).

Preliminary histopathology has been conducted on animals at the three-month sacrifice and on animals who have died from a bacterial infection during the three months since that sacrifice. The data are insufficient for statistical analyses and have not undergone QA/QC review.



88960000075

RECEIVED
EPA/PT/MCIC

FEB 28 1996 8:22

The summary of the reports from the three reviewing pathologists, Drs. Ernest E. McConnell, Hans-Jörg Chevalier and Paul Kotin (Attachment D), includes the following findings in the hamsters treated with MMVF 33: While there was no evidence of pulmonary fibrosis at three months, in some animals there was a slight amount of pulmonary fibrosis at the level of the bronchoalveolar junction, which involved about 20-30% of the lobules, after five to six months exposure. Focal areas of collagen deposition (fibrosis) were found in the pleura at six months, but not at three months exposure. These were covered by hypertrophied mesothelial cells. No lung tumors or mesothelioma were observed. In the recovery animal exposed for three months and held another three months without exposure, no fibrosis was seen; this finding suggests that continuing exposure is necessary for fibrosis to develop.

The summary pathology report also includes observations on the other treated animals.

With respect to MMVF 10a fibers, the report finds that the inflammatory lesions produced by this insulation glass are consistent with the introduction of high levels of a foreign body into the lung. There is no progression from three to six months. No pulmonary fibrosis or pleural changes have been noted to date. No apparent pathology was seen in the recovery animal that had been exposed for three months and then held unexposed. The changes seen thus far are considered reversible.

With respect to amosite asbestos, the report finds there was a dose-related increase in the severity of lung pathology, which is much more severe than with either type of glass fiber. Pulmonary fibrosis was found as early as three months in all dose groups and has shown progression at five to six months. Pleural fibrosis, mesothelial hypertrophy and hyperplasia are prominent and are suggestive of pre-neoplastic change, especially at 125 and 250 fibers/cc. One of the reviewing pathologists identified an early mesothelioma in one of the 250 fibers/cc amosite animals.

The MMVF 33 glass fiber was chosen for testing because it was considered (based upon its lower solubility) more durable than insulation glass fiber. The 250 fiber/cc dose of MMVF 33 fibers might exceed the Maximum Tolerated Dose for this durable fiber. That will have to be determined and its effect on the study and its results assessed.

Manufacturers report that the special purpose fiber is used primarily in some high performance filtration products. MMVF 33 is not used in the general home, commercial and industrial insulation products that are commonly found in many U.S. buildings. Manufacturers also report that their workers participate in regular medical surveillance programs, that no adverse effects have been noted, and that current exposures to MMVF 33-type fibers average below 1 fiber/cc in manufacturing and fabrication.

BEST COPY AVAILABLE

TSCA Document Processing Center (7408)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
February 27, 1996
Page 3

Fibrosis has not been observed in workers manufacturing glass fibers. The most recent update of the comprehensive survey of U.S. workers at five manufacturing plants (Hughes, *et al.*, Attachment E), including two plants that manufactured special purpose fibers, found "no adverse clinical, functional or radiographic signs of effects of exposure" to glass fibers. As the principal investigator, Dr. Hans Weill of Tulane University has written, "after ten years of these investigations, we have failed to demonstrate any adverse effect of MMMF [man-made mineral fiber] exposure on respiratory health."

EPA and OSHA scientists are being notified of these findings. Manufacturers of these special fibers have notified their employees who manufacture the fibers and are notifying their customers.

The RCC hamster study is continuing. A final report is expected in late 1997. NAIMA will be providing EPA with additional information as it develops.

Sincerely yours,



Kenneth D. Mentzer
Executive Vice President

Enclosures

NAIMA DESIGNATED TEST ARTICLE MMVF 10a
FOR RCC STUDY 363442

Analysis provided by Schuller International Inc. Mountain Technical Center (MTC)

<u>CHEMISTRY</u>		<u>MORPHOLOGY</u>	
SiO ₂	57.21	A.M. DIA. μm	1.01
Al ₂ O ₃	5.10	A. S. DEV. μm	0.45
Fe ₂ O ₃	0.049	A. M. LEN. μm	24.4
TiO ₂	0.008	A. S. DEV. μm	22.1
ZrO ₂	0.023		
Cr ₂ O ₃	0.020	G M. DIA. μm	0.92
CaO	7.17	G. S. DEV. μm	1.57
MgO	4.48	G. M. LEN. μm	16.8
SrO	0.004	G. S. DEV. μm	2.42
BaO	0.007		
Na ₂ O	15.84	MEDIAN DIA. μm	0.95
K ₂ O	1.04	MEDIAN LEN. μm	15
B ₂ O ₃	8.4		
SO ₃	<0.03	% 0-0.5 μm	8.5
F	0.36	% 0.5-1.0 μm	44.8
L.O.I.	0.73	% 1.0-1.5 μm	30.4
		% 1.5-2.0 μm	14.9
		% > 2.0 μm	1.5
		% 0-5 μm	11
		% 5-10 μm	18.4
		% 10-15 μm	20.9
		% 15-20 μm	10
		% > 20 μm	39.8
		Part./Fiber	0.17

K_{dls} under test

Test Article Preparation: MMVF 10a is a blend of MMVF 10 fibers size separated from Schuller 901 glass made on a rotary process at Richmond Indiana during April, 1989 and fibers size separated from Schuller 901 glass made on the same equipment during October, 1994. This blend of fibers was made to achieve the morphological characteristics described above. The chemical analysis represents the final lot of fiber after blending.

**NAIMA DESIGNATED TEST ARTICLE MMVF 33
FOR RCC STUDY 363442**

Analysis provided by Schuller International Inc. Mountain Technical Center (MTC)

<u>CHEMISTRY</u>		<u>MORPHOLOGY</u>	
SiO ₂	58.63	A.M. DIA.	1.14
Al ₂ O ₃	5.87	A. S. DEV.	1.02
Fe ₂ O ₃	0.043	A. M. LEN.	23.0
TiO ₂	0.012	A. S. DEV.	22.9
ZrO ₂	0.034		
Cr ₂ O ₃	0.004	G M. DIA.	0.83
P ₂ O ₅	0.035	G. S. DEV.	2.19
CaO	1.74	G. M. LEN.	15.3
MgO	0.236	G. S. DEV.	2.5
SrO	0.106		
BaO	4.98	MEDIAN DIA.	0.68
MnO	0.001	MEDIAN LEN.	14.7
ZnO	4.02		
Na ₂ O	9.55	% 0-0.5 μm	36.3
K ₂ O	3.07	% 0.5-1.0 μm	25.5
SO ₃	<0.05	% 1.0-1.5 μm	11.3
B ₂ O ₃	11.02	%1.5-2.0 μm	10.3
F	0.62	% > 2.0 μm	16.7
L.O.I.	0.31		
		% 0-5 μm	11.8
		% 5-10 μm	18.6
		%10-15 μm	20.1
		%15-20 μm	10.8
		% > 20 μm	38.7
		Part./Fiber	0.2

K_{dis} 20 ng/cm²hr

Test Article Preparation: MMVF 33 was sized from a blend of code 104, 108B, and 110 Schuller 475 glass fibers made by the pot and marble flame attenuation process produced at Schuller plants between 1989 and 1995.

Aerosol Fiber Dimensions RCC Study 363442

SAMPLE ID	SAMPLE DATE	EXP GROUP	SAMPLE TYPE	ARITHMETIC MEAN		GEOMETRIC MEAN		MEDIAN		PF ratio				
				DIAMETER	LENGTH	DIAMETER	LENGTH	DIA.	LEN.					
				X(μm)	SD	X(μm)	SD	X(μm)	(μm)					
MSMF 10														
667:02	8/7/95	2	Stock	1.02	0.45	24.4	22.2	0.92	1.57	16.7	2.4	0.95	15.0	0.17
664:02	8/9/95	2	Aerosol	1.04	0.48	21.0	24.7	0.95	1.54	13.0	2.6	0.94	12.1	0.34
666:02	8/16/95	2	Aerosol	0.89	0.44	21.2	24.0	0.78	1.17	12.9	2.9	0.83	14.3	0.29
668:02	8/23/95	2	Aerosol	0.96	0.47	19.9	22.7	0.85	1.65	12.3	2.6	0.88	10.8	0.30
671:08	9/20/95	2	Aerosol	0.90	0.42	19.3	21.9	0.81	1.58	12.0	2.6	0.81	11.6	0.30
684:02	11/1/95	2	Aerosol	0.92	0.38	17.8	16.6	0.85	1.51	12.2	2.4	0.88	12.1	0.44
475														
Average				0.94	0.44	19.8	22.8	0.85	1.49	12.5	2.6	0.87	12.2	0.33
Stdev				0.06	0.04	1.4	3.2	0.06	0.19	0.4	0.2	0.05	1.3	0.06
667:03														
Stock				1.14	1.01	23.0	22.8	0.83	2.20	15.3	2.5	0.68	14.7	0.21
664:03														
Aerosol				0.87	0.72	15.2	13.0	0.68	1.97	11.6	2.1	0.59	11.5	0.80
Aerosol				0.94	0.94	16.9	17.3	0.67	2.13	11.2	2.5	0.53	11.1	0.62
Aerosol				0.73	0.59	16.4	18.5	0.59	1.87	10.0	2.7	0.51	9.4	0.58
Aerosol				0.74	0.56	17.6	15.5	0.59	1.91	12.5	2.3	0.53	13.2	0.46
Aerosol				0.92	0.65	19.2	17.7	0.75	1.85	14.0	2.2	0.70	14.0	0.51
Average														
Stdev				0.04	0.09	17.1	10.4	0.66	1.95	11.9	2.4	0.57	11.8	0.59
				0.09	0.15	1.5	2.1	0.07	0.11	1.5	0.2	0.08	1.8	0.13

Aerosol Fiber Dimensions RCC Study 363442

SAMPLE ID	SAMPLE DATE	EXP GROUP	SAMPLE TYPE	ARITHMETIC MEAN			GEOMETRIC MEAN			MEDIAN DIA.	MEDIAN LEN.	P/F ratio		
				DIAMETER	SD	X(μm)	DIAMETER	SD	X(μm)				LENGTH	LENGTH
Amesite Low														
667:01	8/7/95	3,4,5	Stock	0.57	0.24	28.7	36.3	0.52	1.46	16.4	2.8	0.49	14.7	0.20
664:04	8/8/95	4	Aerosol	0.53	0.20	17.3	20.2	0.50	1.43	10.6	2.7	0.51	9.5	0.51
666:04	8/15/95	4	Aerosol	0.53	0.19	14.9	16.6	0.50	1.42	9.5	2.5	0.50	8.8	0.11
668:04	8/22/95	4	Aerosol	0.61	0.28	13.6	32.1	0.56	1.52	7.1	2.7	0.57	5.8	0.80
671:10	9/20/95	4	Aerosol	0.57	0.20	14.7	15.4	0.54	1.42	10.0	2.4	0.54	9.4	0.52
684:04	11/3/95	4	Aerosol	0.66	0.56	13.0	11.5	0.62	1.40	9.6	2.2	0.59	10.0	0.35
Average														
				0.58	0.29	14.7	19.2	0.54	1.44	9.4	2.5	0.54	8.7	0.46
Stdev				0.06	0.16	1.7	7.9	0.05	0.05	1.3	0.2	0.04	1.7	0.25
Amesite Med														
667:01	8/7/95	3,4,5	Stock	0.57	0.24	28.7	36.3	0.52	1.46	16.4	2.8	0.49	14.7	0.20
664:08	8/10/95	5	Aerosol	0.56	0.19	15.1	21.1	0.53	1.41	9.6	2.5	0.55	9.0	0.43
666:05	8/15/95	5	Aerosol	0.53	0.23	16.0	19.9	0.48	1.54	10.4	2.4	0.49	9.9	0.14
668:05	8/24/95	5	Aerosol	0.55	0.23	9.6	17.2	0.51	1.48	6.0	2.3	0.51	5.5	0.39
671:11	9/19/95	5	Aerosol	0.54	0.26	14.5	18.3	0.50	1.52	9.2	2.4	0.48	9.7	0.31
684:05	10/30/95	5	Aerosol	0.62	0.19	11.0	11.2	0.60	1.35	7.9	2.1	0.59	6.8	0.31
Average														
				0.56	0.22	13.2	17.5	0.52	1.46	8.6	2.3	0.52	8.2	0.32
Stdev				0.04	0.03	2.8	3.8	0.05	0.08	1.7	0.2	0.05	1.9	0.11

Aerosol Fiber Dimensions RCC Study 363442

SAMPLE ID	SAMPLE DATE	EXP GROUP	SAMPLE TYPE	ARITHMETIC MEAN		GEOMETRIC MEAN		MEDIAN		F/F ratio				
				DIA. (μm)	SD	DIA. (μm)	SD	DIA. (μm)	LEN. (μm)					
Amosite 1gh														
667:01	8/7/95	3,4,5	Stock	0.57	0.24	28.7	36.3	0.52	1.46	16.4	2.8	0.49	14.7	0.20
664:06	8/8/95	6	Aerosol	0.61	0.23	14.3	19.2	0.57	1.43	8.7	2.6	0.54	7.8	0.23
666:06	8/15/95	6	Aerosol	0.55	0.24	16.3	18.5	0.49	1.56	10.6	2.4	0.51	9.8	0.14
668:06	8/24/95	6	Aerosol	0.54	0.20	13.9	15.8	0.51	1.43	9.4	2.3	0.54	8.1	0.20
671:12	9/19/95	6	Aerosol	0.57	0.25	17.5	20.7	0.52	1.51	10.7	2.6	0.50	9.2	0.34
684:06	10/31/95	6	Aerosol	0.63	0.20	11.1	11.7	0.60	1.36	8.2	2.1	0.59	7.3	0.34
Average				0.58	0.22	14.6	17.3	0.54	1.46	9.5	2.4	0.54	8.4	0.25
Stdev				0.04	0.02	2.5	3.6	0.05	0.08	1.1	0.2	0.04	1.0	0.09

Fibers/mg dry lung data through 13 weeks of RCC Study 363442

Study Group	F/cm ³ Aerosol F/cm ³ AD*	19 Week lungs	26 Week	52 Week	78 Week
Air Control					
WHO F/Lung > 20 F/Lung		2.7±1.8x10 ² 3.0±4.1x10 ¹			
MMVF 10a					
WHO F/Lung > 20 F/Lung	357±53 150±21	216±32 37±5	6.8±2.4x10 ⁴ 7.8±2.9x10 ³		
MMVF 33					
WHO F/mg > 20 F/mg	290±53 100±20	185±34 53±10	1.0±0.3x10 ⁵ 2.6±0.9x10 ⁴		
Amosite Low					
WHO F/mg > 20 F/mg	29±27 9±8	27±25 6±5	5.3±1.0x10 ⁴ 1.4±0.2x10 ⁴		
Amosite Mid					
WHO F/mg > 20 F/mg	148±72 34±17	125±61 26±12	1.8±0.2x10 ⁵ 3.9±1.0x10 ⁴		
Amosite Hi					
WHO F/mg > 20 F/mg	246±117 70±34	197±93 40±19	2.3±0.4x10 ⁵ 5.3±1.1x10 ⁴		

* Number of WHO F/cc that have aerodynamic diameter < 3.15 μm

OVERVIEW OF THE PATHOLOGY RESULTS (THROUGH 6 MONTHS) OF THE NAIMA-SUPPORTED CHRONIC INHALATION STUDY OF AMOSITE, MMVF 10a GLASS INSULATION WOOL AND MMVF 33, A SPECIAL PURPOSE GLASS FIBER, IN HAMSTERS

Ernest E. McConnell, DVM, MS (Pathology), DACVP, DABT
Science Advisor to NAIMA

OBJECTIVES OF THE STUDY

This study was designed to evaluate the effects of chronic (life-time) inhalation in hamsters of two types of glass fibers, one typical of the type of most commonly used in the insulation of houses/buildings and the other a "special purpose" glass fiber. The study also includes exposure to similar levels of amosite asbestos of similar length for comparative purposes. The hamster was chosen as the animal model to serve as a second species and because it has been observed to be a sensitive indicator of the potential toxic effects to the lung pleura.

MATERIALS AND METHODS

Fiber Characteristics: Two types of glass fibers were used: MMVF 10a (a building insulation glass fiber) and MMVF 33 (a special purpose glass fiber). MMVF 33 is the designation for a blend of 475 glass fibers as described in the study material specifications. Bulk fibers with chemical compositions typical of commercial products were size-separated to be largely animal respirable (<1.5 μm diameter and <80 μm length) and to have average dimensions (average aerosol geometric mean diameter <1.0 μm and length >15 μm) that are comparable to other MMVF inhalation studies reported previously (Hesterberg et al., 1993). Amosite asbestos was used for comparative purposes and hopefully to serve as a positive control. It was size-separated in a similar manner to the glass fibers so that the average length was comparable to the glass wools used in this study.

Fiber Aerosol Exposure: The hamsters were exposed by nose-only inhalation to a single target exposure level of $\sim 30 \text{ mg/m}^3$ (MMVF 10a) and $\sim 37 \text{ mg/m}^3$ (MMVF 33) which would be equivalent to ~ 250 WHO f/cc. The dose level of MMVF 10a was chosen as the maximum tolerated dose based on a 90-day dose range study of this glass insulation wool in hamsters at this laboratory. Three exposure levels of amosite asbestos were used to approximate 25, 125 and 250 WHO f/cc. Advanced techniques of non-destructive aerosolization were used to maximize the number of respirable fibers, *i.e.*, fibers of a size able to reach the alveolar region of the lung (Hesterberg et al., 1991). Temperature, relative humidity, and oxygen concentrations were monitored continuously. The animals were confined separately in tubes which were positioned radially around the exposure chamber (Cannon et al., 1983). This flow past nose-only system provides a positive pressure laminar flow to each animal individually so that each is supplied fresh aerosol and the air exhaled by one animal does not contaminate the air of others in the chamber.

Experimental Design: The study was conducted at the Research and Consulting Company, Basel, Switzerland, using 13-15 week old (150g \pm 20%) Syrian golden male hamsters (Charles River Laboratories, St-Constant, Quebec, Canada). There were 125 hamsters in all of the fiber exposed groups and 140 in the control group. They are being exposed for 6 hours/day, 5 days/week for 18 months. Groups of 5 or 6 randomly selected hamsters, identified at the start of the study, from each exposure group are being killed at 3, 6, 12 and 18 months for lung fiber burden measurements and to follow the progression of the pulmonary lesions. Additional groups of 6 hamsters from each group were removed from exposure at 3, 6 and 12 months and held until 18 months (recovery groups), at which time they were sacrificed to ascertain whether there was progression or regression of lesions and to determine lung fiber burdens following cessation of exposure. Following the 18 month exposure period, the animals will be held for lifetime observation (until ~20% survival).

Aerosol Monitoring and Characterization: Fiber concentrations (mass) were measured at least 4 times/week. Each aerosol sample from each fiber type and dose level, as well as the control aerosols, was collected on a Gellman membrane filter from one of the laminar flow ports in the exposure chamber. Additionally, aerosol concentrations were monitored continuously during the exposure period to assure uniformity. The aerosols were analyzed for WHO fibers/cc and number of fibers >10, >15 and >20 μ m in length once each exposure week during weeks 1-13 and every other week thereafter.

Clinicopathology: The hamsters were observed daily for clinical signs, morbidity, and mortality throughout the study. They were individually examined and weighed once/week during the first 13 weeks and at least once/month thereafter. A necropsy was performed on all animals and a complete set of tissues (NTP, 1984) was obtained and fixed in 10% neutral buffered formalin. The lungs were removed, weighed, and examined under a dissecting microscope. After fixation, a consistently uniform transverse (horizontal) section (2mm diameter) of the right apical and diaphragmatic lobes were obtained from each animal for routine histopathology. Replicate sections were routinely stained with hematoxylin and eosin (H&E) and Masson-Goldner's trichrome stain to highlight collagen.

The lungs were examined and classified histopathologically and given a Wagner score for inflammatory change and fibrosis (McConnell et al., 1984). In this system a grade of 10 is considered normal, grades 2 to 3 are evidence of focal cellular change, while grades 4 to 8 represent the former lesions plus increasing degrees of fibrosis.

RESULTS TO DATE

Clinical Observations: No treatment related clinical signs were observed in any exposure groups during the course of the study to date, although there has been increased mortality due to a concurrent infectious disease, which has been tentatively diagnosed as "wet tail," a common disease of hamsters. Tetracycline was administered to the animals for 17 days. There have been no treatment related effects on body weight gain and survival.

Pathology: The lesions described below are a consensus opinion of three pathologists (Dr. Jörg Chevalier, Experimental Pathology Services, Muttenz, Switzerland; Dr. Ernest E. McConnell, Raleigh, NC; and Dr. Paul Kotin, Denver, CO) who examined the slides independently and without knowledge of the others' diagnoses. The lesions are graded into one of five categories of increasing severity, *i.e.*, minimal, slight, mild, moderate and severe. A three month sacrifice occurred per the protocol; the six month sacrifice was not conducted due to the number of animals dying between 3 and 6 months from wet tail.

Chamber Controls: The negative controls showed no significant macroscopic lesions, although microscopically a few pulmonary macrophages were noted scattered randomly throughout the parenchyma. No lesions were observed in the pleura. There was no progression in severity from 3 to 6 months exposure.

MMVF 10a (250 f/cc): No treatment-related macroscopic (gross) lesions have been observed in the lungs or pleura to date. Microscopically, no abnormalities were noted in the airways to the level of the bronchioles. The only lesion found in these lungs after 3 months exposure was the presence of a slight to mild excess in the number of pulmonary macrophages and presence of micro granulomas randomly scattered throughout the parenchyma, although most were concentrated in the area of the proximal alveoli. Many fibers were observed, most of which were within these macrophages and micro granulomas; some of the fibers appeared quite long. Overall, the lesion is consistent with Wagner Grade 2. There was little if any progression from 3 to 6 months exposure. No treatment related lesions were found in the pleura. Of particular interest were the findings in a "recovery" animal which died spontaneously at ~6 months in this group. This hamster had been exposed for 3 months and was being held (unexposed) until a scheduled sacrifice at 18 months. The lungs from this animal were almost normal, *i.e.*, comparable to control lungs at this time point. This indicates that the lesions at 3 months are completely reversible.

MMVF 33 (250 f/cc): No macroscopic abnormalities were noted to date. Microscopically, no lesions have been observed in the airways to the level of the terminal bronchioles. The primary lesion found in these lungs was the presence of a slight to mild excess in the number of pulmonary macrophages, which were randomly scattered throughout the parenchyma, although most were concentrated in the area of the proximal alveoli. There were also a number of micro granulomas and occasional multinucleated giant cells, most of which were located along the alveolar ridges of the proximal portion of the alveolar duct. There were many fibers, most of which were within these macrophages, micro granulomas and giant cells; some of the fibers appeared quite long. It was also not unusual to find fibers in macrophages just beneath the pleura. While none of the hamsters showed evidence of pulmonary fibrosis at 3 months and, at that time were considered to be Wagner grade 2, a majority showed a slight amount of collagen deposition after 5-6 months exposure in the area of the bronchoalveolar junctions. Approximately 20-30% of the lobules were so affected. This degree of pulmonary fibrosis qualifies the lesion as Wagner Grade 4. No treatment related changes were observed in the pleura after 3 months exposure to MMVF 33 fibers. However, at 5-6 months a slight amount of focal collagen deposition was noted in all of the hamsters. A minimal amount of mesothelial hypertrophy (mesothelial cells were round compared to their normal flat appearance)

was noted in a majority of the animals. In addition, slight "mesothelial activation," as evidenced by cell enlargement and hyperchromatic nuclei, was observed in most of the hamsters. A recovery animal (3 months exposure and then held unexposed for up to 18 months) died at ~6 months. Again, the inflammatory response had decreased during the nonexposure period. More importantly, there was no evidence of pulmonary fibrosis, which suggests that continuing exposure is necessary for fibrosis to become manifested and that the residual levels of MMVF 33 were not sufficient to stimulate fibroblast activity.

Amosite Asbestos:

~25 f/cc: No macroscopic lesions were observed. The inflammatory response to amosite was qualitatively different from the MMVFs in this study. At 3 months a moderate number of neutrophils (not seen with MMVFs), macrophages, clumps thereof, many well defined micro granulomas and a few multinucleated giant cells were found, primarily in the area of the terminal bronchioles and along the ridges of the proximal alveolar duct, although some were also found in peripheral alveoli. Of note was that these giant cells were "dirty" gray and "aggressive" appearing, unlike those found in response to MMVF 33. Although difficult to discern at this time point, a few fibers were observed in the micro granulomas and giant cells. A minimal amount of early bronchiolization was observed in most of the hamsters in this group (again this was not found with either MMVF). There was an indication of early interstitial fibrosis in the walls of the alveoli subjacent to micro granulomas in a majority of the hamsters. This lesion is compatible with Wagner grade 4. Focal pleural fibrosis was definitely observed in one and possibly a second hamster. It was more comparable to focal fibroplasia just beneath the pleura, rather than true pleural thickening. The lesions had progressed in severity after 5-6 months exposure. The inflammatory response was much more intense and pulmonary fibrosis (found in all of the animals), while slight, affected all of the bronchioles and extended some distance into the alveolar duct and adjacent alveoli and was present in nearly all of the bronchioles. However, because of the restrictions of the Wagner grading system, the lesion was still consistent with Grade 4. The pleural lesions had also progressed in severity and were found in all of the hamsters at this time. Also, mesothelial hyperplasia was observed in a majority of the hamsters.

~125 f/cc: No macroscopic lesions were observed at 3 months. The inflammatory infiltrate was much more apparent than at 25 f/cc. Again, neutrophils, macrophages, numerous well defined micro granulomas and many giant cells were found, primarily in the area of the terminal bronchioles and along the ridges of the proximal alveolar duct, although some were also found in the periphery of the lung. There were a few fibers in the micro granulomas and giant cells. A minimal amount of early bronchiolization was observed in all hamsters in this group. There was an indication of early interstitial fibrosis in the walls of the alveoli subjacent to micro granulomas in all of these hamsters and it affected most of the lobules. Although the lesion was certainly more severe than at 25 f/cc, by definition it is still consistent with a Wagner grade 4; again, a limitation of this grading system. There was no evidence of pleural fibrosis in any of these hamsters at this time. At 5-6 months there was macroscopic evidence of treatment related changes. The lungs did not collapse completely when removed from the thorax and small (1-2 mm diameter) greyish-white foci were found scattered

on the surface of the lung. However, they tended to disappear when the lungs were inflated with fixative. Microscopically, the overall lesion had progressed in severity at 5-6 months, although it was still in the Wagner grade 4 category. Also, the fibrotic lesion had extended peripherally along the alveolar duct and into the walls of the adjacent alveoli, almost to the level of the pleura. Of special note, was that numerous fibers could be found in macrophages, granulomas and giant cells at this time. The pleura showed a greater severity of pleural fibrosis, hypertrophy and there was evidence of mesothelial hyperplasia in a majority of the animals. One hamster showed focal pleural "sclerosis" (proliferation of fibroblasts).

~250 f/cc: No macroscopic lesions were observed at 3 months. The inflammatory infiltrate was about the same, qualitatively and quantitatively, as the 125 f/cc exposure group. Large numbers of neutrophils, macrophages, numerous well defined micro granulomas, many giant cells and foci of bronchiolization were found, primarily in the area of the terminal bronchioles and along the ridges of the proximal alveolar duct, although some were also found in the periphery of the lung. A few fibers were observed in the micro granulomas and giant cells. Early interstitial fibrosis in the walls of the alveoli subjacent to micro granulomas was found in all of the hamsters. Again, the lesion was consistent with a Wagner grade 4.0. There was evidence of pleural fibrosis in some of these hamsters at 3 months. At 5-6 months the lungs failed to collapse in a normal fashion when the thorax was opened and there were small (1-2 mm diameter) greyish-white foci scattered over the surface of the lung. Also, the pleura was focally thickened in some of the hamsters. Microscopically, the pulmonary lesions had progressed in severity and appeared somewhat more prominent in the 250 f/cc exposed animals compared to those in the 125 f/cc group. The most apparent difference was that interstitial fibrosis had progressed to a fibrotic "linking" of the lobules in a majority of the hamsters, which places the lesion in the Wagner grade 5 category. Moderate to severe mesothelial hyperplasia was also noted. In one animal the mesothelial cells were 3-4 cell layers thick and showed evidence of pseudo-vacuolation; a feature found in mesotheliomas. This lesion could, in fact, be considered by some pathologists to be an early mesothelioma.

Summary: The conclusions from this study to this time are as follows:

MMVF 10a: The inflammatory lesions produced by this insulation glass are consistent with the introduction of high levels of a foreign body particulate into the lung. There is no progression from 3 to 6 months. No pulmonary fibrosis or pleural changes have been noted to date. No apparent pathology was seen in the "recovery" animal that had been exposed for three months and then held unexposed. The changes thus far are considered reversible.

MMVF 33: The inflammatory lesion is more pronounced than with MMVF 10a. While there was no evidence of pulmonary fibrosis at 3 months, in some animals there was a slight amount at the level of the broncoalveolar junction, which involved about 20-30% of the lobules, after 5-6 months exposure. Focal areas of collagen deposition (fibrosis) were found in the pleura at 6 months, but not at 3 months exposure. These were covered by hypertrophied mesothelial cells. No lung tumors or mesotheliomas were observed. In the recovery animal exposed for 3 months and held another 3 months without exposure, no fibrosis was seen; this finding suggests that continuing exposure is necessary for fibrosis to develop.

Amosite Asbestos: There was a dose-related increase in the severity of lung pathology, which is much more severe than with either type of glass fiber. Pulmonary fibrosis was found as early as 3 months in all dose groups and has shown progression at 5-6 months. Pleural fibrosis, mesothelial hypertrophy and hyperplasia are prominent and are suggestive of pre-neoplastic change, especially at 125 and 250 f/cc.

References

Cannon, W.C., Blanton, E.F. and McDonald, K.E. (1983). The flow-past chamber: An improved nose-only exposure system for rodents. *Am.Ind. Hyg. Assoc. J.* 44, 923-928.

Hesterberg, T.W., Vu, V., Chase, G.R., McConnell, E.E., Bunn, W.B. and Anderson, R. (1991). Use of animal models to study manmade fiber carcinogenesis. In *Cellular and Molecular Aspects of Fiber Carcinogenesis*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY., pp. 183-205.

Hesterberg, T.W., Miiller, W.C., McConnell, E.E., Chevalier, J., Hadley, J.G., Bernstein, D.M., Thevenaz, P. and Anderson, R. (1993) Chronic inhalation toxicity of size-separated glass fibers in Fischer 344 rats. *Fund. Appl. Toxicol.* 20, 464-476.

McConnell, E.E., Wagner, J.C., Skidmore, J.W. and Moore, J.A. (1984). A comparative study of the fibrogenic and carcinogenic effects of UICC Canadian chrysotile B asbestos and glass microfibre (JM 100). In *Biological Effects of Man-made Mineral Fibres*, Proc. WHO/IARC Conference, Copenhagen, 20-22 April, 1982, Vol. 2, World Health Organization, Geneva, Switzerland, pp. 234-252.

NTP (National Toxicology Program) (1984). Report of the NTP Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation. National Toxicology Program, Research Triangle Park, NC, pp. 95-198.

Follow up study of workers exposed to man made mineral fibres

Janet M Hughes, Robert N Jones, Henry W Glindmeyer, Yehia Y Hammad, Hans Weill

Abstract

A survey of workers in seven man made mineral fibre (MMMMF) production plants, the subject of a previous report,¹ was conducted, with other blue collar workers serving as regional comparisons. Based on the median reading of chest radiographs by five readers, a low prevalence of small opacities, all at the 1/0 and 1/1 profusion levels, was again found: for workers with MMMFs, 23/1435 (1.6%); for comparison workers, 2/305 (0.7%). Spirometric measurements indicated generally healthy populations, and were not related to presence of opacities. Ninety three per cent (21/23) of MMMF workers with opacities worked at the two plants with the highest exposures to fine fibres, resulting in a dose-response relation across plants. For one location, the prevalences of opacities for the MMMF and comparison workers were not significantly different (5.9% (13/220) v 3.1% (2/65)). No comparison x ray films were obtained for the MMMF plant with the highest prevalence (6.6%), so a second phase of the study was conducted, with pre-employment films from these two plants. On this second reading, the prevalence of opacities was lower; there were no significant differences between the two groups of films, and no relation between opacities and exposure indices. There was considerable inter and intrareader variability. These results indicate no adverse clinical, functional or radiographic signs of effects of exposure to MMMFs in these workers.

(British Journal of Industrial Medicine 1993;50:658-667)

Tulane University School of Medicine, Department of Medicine, Section of Bioenvironmental Research, New Orleans, Louisiana 70112, USA

J M Hughes, R N Jones, H W Glindmeyer, Y Y Hammad, H Weill

A 1979-80 study¹ of male production workers in seven United States man made mineral fibre (MMMMF) production plants examined tests of lung function and readings of chest radiographs in relation to indices of exposure to MMMF. A low prevalence of radiographic small opacities was found, all at the lowest International Labour Office (ILO)² profusion levels (6.7% at 0.1 (63/941), 2.7% at 1/0 (25/941), 0.6% at 1.1 (6/941). The prevalence of opacities \geq 1/0 was highest, however, among employees at the two plants manufacturing both ordinary (nominal fibre diameter $> 3 \mu\text{m}$) and fine (nominal fibre diameter 1-3 μm) fibres (7.5% (22/292) compared with 1.4% (9/649) of the other plants combined). None of the 86 workers from the very fine fibre ($< 1 \mu\text{m}$) plant had small opacities \geq 1/0, but these workers had been employed, on average, for shorter durations than those in the other plants. Presence of small opacities was related to age and cigarette smoking. Among current smokers, after accounting for age, pack-years of smoking, and two plant categories (ordinary or fine fibre or not), presence of small opacities (profusion \geq 0/1) was related to several measures of fibre exposure, including cumulative exposure to fine fibres. There were no significant factors among ex or never smokers, possibly because of the few cases ($n = 33$).

Respiratory symptoms and measurements of pulmonary function indicated a generally healthy population, and were unrelated to either type of fibre or amount of fibre exposure. Radiographic small opacities were, however, associated with lower lung function.

The 1979-80 survey led to the conclusion that the minimal evidence for respiratory effects among these workers could not be considered clinically significant, and that the results were encouraging as regards potential health effects of exposure to MMMFs. Nevertheless, the possible relation between the occurrence of small opacities and exposure to fine fibres indicated the need for continued surveillance of these workers.

About seven years after the initial survey, a follow up was conducted to reassess the respiratory health of workers in these plants, to determine if there was progression of the radiographic indica-

tors, and to consider the question of whether the apparently increased prevalence of small opacities at two plants was indicative of a fine fibre effect or was an artefact, possibly reflecting factors related to geographic region or radiological laboratory.

Methods

STUDY DESIGN

The present study consisted of two phases: the first or primary phase, which included workers from all seven plants; and a second phase, which included workers from only two plants. The first phase, a cross sectional survey, was similar to the earlier study, but with these exceptions: (1) no minimum duration of employment was required for workers in the seven MMMF plants (in 1980, either five or 10 years of employment, depending on the size of the plant, was required); (2) at each geographic location, other blue collar workers, without exposure to fibre or other materials known to be hazardous to respiration, were recruited to serve as regional comparison populations; and (3) the number of x ray film readers was increased from three to five.

During the first phase of the study, radiographs of comparison workers could not be obtained at two locations. As will be described in the results section, this lack of comparison films, as well as the small number of comparison workers at one other location, made the interpretation of the radiographic findings difficult. Consequently, a second phase of the study was implemented in which chest radiographs taken for pre-employment screening at two plants were obtained to serve as (additional) comparison films.

DESCRIPTION OF THE MMMF PLANTS AND INFORMATION ON EXPOSURE

Descriptions of the seven MMMF plants, their processes, and the available information on exposure are provided in the report on the 1980 study.¹ There are five fibrous glass and two mineral wool manufacturing plants. These produce primarily insulation and building materials. The five fibrous glass plants included two producing only ordinary fibres, two producing both ordinary and fine fibres, and one producing only very fine fibres.

As in the 1980 survey, estimates of exposure are based on a University of Pittsburgh survey,² which classified all jobs as either involving no fibre exposure or to one of four categories of fibre concentration: 0.0032, 0.032, 0.32, or 1.5 fibres per millilitre of air (f/ml), based on fibre counting with electron microscopy.

Job histories and exposure estimates for individual workers were updated throughout 1986 when most of the radiographs were obtained.

EMPLOYEE ELIGIBILITY, MMMF PLANTS

In the seven MMMF plants, only male production workers with less than one month ever assigned to the batch or binder areas (where exposures to crystalline silica or potential carcinogens were possible) were eligible. In all plants, women constituted less than 5% of production workers and were excluded. For the five plants with 250 or fewer eligible employees, all were targeted for participation; in the two larger plants, all participants from the 1980 survey and a random sample of the other eligible employees were targeted.

COMPARISON WORKERS

For each of the six communities in which the seven MMMF plants were located (the two ordinary fibre plants, plants 1 and 2, were located in the same city), blue collar comparison workers were identified and agreement reached with management personnel for the employees' participation. These six comparison groups consisted of city workers for plants 1 and 2), glass products manufacturing workers (plant 3), city workers (plant 4), employees of two plastic container manufacturing plants (plants 5 and 6), and metal cabinet manufacturing workers (plant 7). Comparison workers never employed as electricians, welders, mechanics, or any other job with potential respiratory hazards were not included.

Workers in all six of these comparison groups participated in the spirometry and radiograph phase of the survey. Despite all recruitment efforts and release time from work, the two groups of plastic container workers (corresponding to the MMMF plants 5 and 6) refused to have chest radiographs taken. With only a few industrial workers in rural areas, no other comparison workers could be enlisted.

RESPIRATORY HEALTH ASSESSMENT

The procedures used in the MMMF and comparison plants were identical. The study physicians travelled to each location to administer spirometric testing and interview, while the radiographic version of the American Thoracic Society's Questionnaire of Lung Diseases questionnaire³ was completed. Spirometry was performed with a portable testing device supplied by the Informed Corporation, which meets the American Thoracic Society's specifications.

Plant personnel scheduled workers for chest radiographs taken at a local radiological laboratory, usually providing release time for the workers' transportation. The two plants located in the same city used the same facility.

After removal of identifying information and a coded study number, the assessment forms were thoroughly shuffled. Five readers, including two in the use of the ILO 1980 classification scheme,⁴ then

logical studies were employed. These were JC Gilson, ITT Higgins, RN Jones, WKC Morgan, and EN Sargent. Each reader was provided with the set of ILO standard radiographs and worked independently of the others and without knowledge of plant site or whether the individual films were those of exposed or reference workers. Batches of 50 to 60 films were presented in random order to each reader. Early batches contained certain study films, preselected for the possibility of divergent judgements as to quality or lung abnormality, for use as "trigger films".³ After the reader's initial classification of trigger films, which were not identified to the reader as such, they were inserted into later film batches. At subsequent readings, the recording clerk informed the reader that a trigger film was just classified, telling the reader how it was previously classified. The intention of trigger films is to provide feedback, so that readers can detect any drift in sensitivity over the course of a long reading exercise.

Films judged unreadable by three of the five readers were excluded from analyses. For each film, the median of all readings was used as the summary reading.

Radiographs from participants in the 1980 study were included in the random readings. After completion of the random readings, the films were paired and read side by side, in known order, to determine progression. Comparability was rated as good, fair, or impossible, and pairs receiving a majority rating of impossible were excluded from analysis. A seven part scale for change was used: no change, and three categories (possible, probable, and definite) for progression and regression. No change was scored as zero, possible regression as -1, possible progression as +1, etc, and the mean of all readers' scores was assigned as the progression score for the film pair.

PHASE TWO OF THE STUDY

As previously stated, no x ray films for comparison workers were obtained for plants 5 and 6. In the earlier survey, none of the 86 plant 5 workers and only one of the 32 plant 6 workers had small opacities profusion 1/0 (none higher); therefore, the lack of comparison x ray films at these locations was initially considered unlikely to be a serious limitation.

Increased prevalences of small opacities, at minimal profusion levels, were subsequently found for MMMF workers at two plants: plant 5, for which no comparison workers were available, and plant 3, for which only 65 comparison workers had participated. Because comparison films were considered essential for interpreting minimal radiographic findings, radiographs taken as part of pre-employment screening at these two plants were obtained. To maximise comparability, an individual worker's

pre-employment radiograph was included only if it was taken at the same radiological facility during 1985-7 (the years during which the study films were taken), and if the person had been hired by the plant (only a very few subjects with a pre-employment film were not subsequently hired). None of the workers with pre-employment radiographs from these years had participated in the main part of the study.

Four of the readers returned for a second reading. Regrettably, Dr Gilson died before the second reading took place, requiring the enlistment of another experienced reader (J Whot). Readers were told that the second reading was necessitated by the lack of comparison films for two locations.

This second reading included 157 pre-employment films, as well as the 342 from these two plants obtained for the main phase of the study (to control for possible changes in readings over time). These were shuffled together, and the set was independently read by each reader, with no knowledge of film sources, date, or whether the subject was an exposed worker or a control.

STATISTICAL ANALYSIS

Multiple logistic regression analysis was used to examine the presence of small opacities on x ray film opacities in relation to possible determinants—for example, age, smoking habit, and other indices. In these analyses, the actual values of continuous variables, such as age and most of the other indicators, were used for entry into the model. Multiple regression was used for relating the mean values to determinants after controlling for the approximate normality of these distributions.

Results

DESCRIPTION OF THE POPULATION
Overall, about 76% of the 1441 MMMF workers provided a chest x ray film for analysis. Of the 941 participants with x ray films from the earlier survey, only 64% (602) were subsequently employed. Of these 522 (87%) again participated in the study. 1441 workers provided spirometry assessments. 25 (1.7%) were judged non-comparable and excluded from analyses of spirometry.

For several MMMF plants, substantial numbers of workers who had not had spirometry and respiratory health questionnaires at the time of the study but later agreed to participate in a chest x ray film taken. For the MMMF plant with 1449 workers provided a chest x ray film, 1030 had (repeatable) spirometry assessments. For comparison workers, 305 had an x ray film and 207 provided repeatable spirometry assessments.

For each location, the mean age and percent ages of smokers for the MMMF and comparison

Table 1 Description of participants by location*

MMMf plant (category)†	MMMf workers				Comparison workers		
	No‡	Age (y) Mean (SD)	Ever smokers (%)	Years§ (conc)	No‡	Age (y) Mean (SD)	Ever smokers (%)
1 (Ordinary)	313 (208)	45.1 (9.8)	78	16.2 (0.0032)	123 (120)	41.0 (13.5)	74
2 (Ordinary)	269 (174)	47.3 (8.3)	76	20.5 (0.038)	—	—	—
3 (Ordinary/fine)	220 (155)	39.3 (10.7)	62	9.6 (0.314)	65 (77)	42.4 (10.8)	70
4 (Ordinary/fine)	335 (210)	43.0 (10.5)	68	15.7 (0.032)	84 (83)	39.6 (10.6)	65
5 (Very fine)	122 (128)	36.4 (9.5)	66	9.6 (1.41)	0 (17)	39.2 (8.7)	65
6 (Mineral wool)	86 (81)	34.2 (10.2)	61	8.6 (0.032)	0 (49)	34.8 (7.9)	58
7 (Mineral wool)	99 (74)	38.6 (10.7)	74	14.4 (0.032)	33 (40)	35.9 (12.4)	55
Total	1444 (1030)	42.2 (10.7)	71	14.7 (0.032)	305 (386)	39.6 (11.7)	69

*Description of workers who participated in any phase of the study (x ray film and/or spirometry/interview).

†Nominal fibre category for MMMf plants.

‡Number of workers with chest x ray films. Number with both a health interview and repeatable spirometry in parentheses.

§Mean years employed in MMMf plant; conc = mean concentration of fibre exposure in f/ml.

¶MMMf plants 1 and 2 were located in the same city; these 123 serve as comparison workers for both plants.

workers were similar (table 1). The most pronounced difference was in the percentage of smokers in plant 7 (74%) compared with the comparison manufacturing workers (55%).

The MMMf workers had been employed in the plants for an average of 14.7 years. For three plants (3, 5 and 6), the mean duration was less than 10 years; for the other four plants, the means ranged from 14 years (plant 7) to 20 years (plant 2).

There were substantial differences across the MMMf plants in the mean concentration of exposure to airborne fibres, with plant 3 (ordinary and fine fibres) and plant 5 (very fine fibres) considerably higher than the others.

Overall, 14% of participants reported previous occupational exposure to asbestos (for a mean of six years), 10% previous mining experience (two years), and 17% sandblasting (one year). The prevalences of previous exposures were similar for MMMf and comparison workers, with the exception of sandblasting (20% for MMMf workers, 7% for comparison).

SYMPTOMS AND SPIROMETRY

As expected, most respiratory symptoms were significantly related to cigarette smoking and age, and, among current smokers, to pack-years of smoking after accounting for age.

For MMMf plants 2 to 5, symptom prevalences were similar for the MMMf and comparison workers (see table 2 for prevalences of selected symptoms). For plant 1 (ordinary fibre) and the two mineral wool plants, several symptom prevalences were higher among MMMf workers.

In the two mineral wool plants, the higher prevalence of asthma among MMMf was largely accounted for by asthma diagnosed before working at the plants (14 of 17 cases diagnosed before hire, with 12 diagnosed in childhood). After accounting for smoking category (current, ex, never), none of the differences in symptoms between MMMf and comparison workers was statistically significant.

Workers in MMMf plant 1 had a significantly higher prevalence of symptoms than the comparison workers (after accounting for smoking and

Table 2 Prevalence of selected symptoms and mean FEV₁ by location

MMMf plant*	MMMf workers			Comparison workers		
	Not	Symptom prevalence‡	FEV ₁ Mean (SD)	Not	Symptom prevalence‡	FEV ₁ Mean (SD)
1	208	13,23,10,7	96.2 (17.4)	120	7,14,4,2	101.1 (16.2)
2	174	5,10,8,2	98.9 (17.0)	—	—	—
3	155	3,7,3,6	103.0 (14.7)	77	4,10,4,3	101.8 (17.6)
4	210	3,10,2,3	102.0 (16.0)	83	7,14,2,2	101.4 (14.2)
5	128	0,4,2,2	108.7 (14.4)	17	0,0,0,6	101.7 (14.0)
6	81	6,16,2,7	99.8 (15.8)	49	2,6,2,4	101.8 (10.3)
7	74	14,18,8,14	102.3 (15.2)	40	3,5,3,0	101.9 (9.9)
Total	1030	6,13,5,5	101.1 (16.4)	386	5,11,3,3	101.1 (14.9)

*See footnote, table 1, for fibre type category.

†Number with both a respiratory health interview and repeatable spirometry.

‡Prevalences of chronic bronchitis, chronic cough, dyspnoea > level 3 (having to stop when hurrying on level ground), and asthma respectively.

age), although workers in plant 2 did not. No factors investigated, including age, smoking, and previous exposures, could account for these differences, and among plant 1 workers, symptom prevalences were not related to any exposure index. Although these differences remain unexplained, it is considered unlikely that these higher prevalences are due to mineral fibres, as this plant had the lowest estimated levels of exposure to fibres.

The spirometric measurements, expressed as percentage of predicted⁶ (and incorporating the OSHA recommended adjustment of 0.85 for black subjects),⁷ indicated generally healthy populations: the mean values for forced expiratory volumes in one second (FEV₁), forced vital capacity (FVC), FEV/FVC, and forced expiratory flow (FEF₂₅₋₇₅) were 101, 103, 95, and 78, respectively for the MMMF workers overall and 103, 104, 96, and 81, respectively for comparison workers. Functional values showed the expected relation with cigarette smoking—for example, mean FEV₁ values of 105, 102, and 99 for never, ex and current smokers respectively.

There were some workers whose values were surprisingly low for an actively employed population—for example, five MMMF workers with FEV₁% predicted less than 40. However, most of these low values were in workers with active asthma or previous chest surgery.

Among MMMF workers, there were significant differences in functional values across the seven plants; the highest mean values were found for workers from plant 5, the very fine fibre plant (109% predicted for FEV₁), the lowest for those from plants 1 and 2, the two ordinary fibre plants (96 and 99% predicted for FEV₁). Functional values were not related to any of the exposure indicators, either across or within plants.

For some plants, there were significant differences between MMMF and comparison workers; however, when asthmatic workers and workers with previous chest surgery were omitted from the analyses, none of the differences remained significant.

CHEST X RAY FILMS

There was considerable variability between the five readers. For film quality, four of the readers were in close agreement, finding from 0% to 1% unreadable, but one reader judged 8% to be unreadable. The percentages of readable films judged to have small opacities $\geq 1/0$ were: 1%, 2%, 2%, 6%, and 11%.

Based on median reading for quality, nine of the 1749 films (0.5%) were judged unreadable and 244 (14%) of poor quality. The median assessments of quality differed substantially across the six radiological laboratories, with 26%, 2%, 1%, 5%, 5%, and 39% of the films judged to be poor or unreadable.

For each, however, the distributions by quality were similar for the MMMF and comparison workers.

As in the 1980 survey, there was only a low prevalence of small opacities, all at the lowest profusion levels. Of the 1435 readable films for MMMF workers, median readings categorised 14 (1.0%) and 9 (0.6%) as 1/0 and 1/1 respectively; for the 305 comparison films, one (0.3%) was categorised as 1/0 and one (0.3%) as 1/1. The primary type of opacity was irregular for 96% of these films. No films had large opacities.

Presence of opacities was not related to mean spirometry measurements among either the MMMF or comparison workers. Of the 1435 MMMF workers with a chest x ray film 956 had also performed repeatable spirometry. Mean FEV₁ values (% predicted) for the 938 without and the 18 with opacities ($\geq 1/0$) were 101.3 and 103.9 respectively; corresponding FVC values were 103.4 and 107.2.

For films taken for this survey, presence of opacities ($\geq 1/0$) was significantly related to film quality, with 2.9%, 1.1% and 0.4% of films of optimal, good, and poor quality having opacities respectively. Opacities were not related to cigarette smoking (prevalences of 1.2% and 1.6% among never and ever smokers), nor to previous occupational exposures such as asbestos, mining, and sandblasting.

Among MMMF workers, the two ordinary fibre plants (plants 1 and 2) had similar (and low) prevalences of small opacities, as did the two mineral wool plants (plants 6 and 7). These two sets of plants are combined in the summaries of x ray film findings by location.

Plants 3 (5.9%) and 5 (6.6%) had higher prevalences than the other five plants (table 3). Film quality could not account for these differences: the same patterns in prevalences across plant were seen for each grade of film quality.

For three of the four groups of comparison workers with x ray films, no opacities $\geq 1/0$ were seen; these findings are comparable with those for the corresponding MMMF plants, indicating no differences between the MMMF and comparison workers at these locations.

The 5.9% with small opacities for MMMF workers at plant 3 was higher than the 3.0% among the 65 comparison workers who were employed in the manufacture of glass products. This difference, however, was not significant, either alone or after accounting for possible differences in age and smoking between the two plants (one tailed $p > 0.14$). There were no comparison workers for MMMF plant 5, which had the highest prevalence of opacities (6.6%).

The distributions of readings for opacities across plants were similar for the individual readers: all

Table 3 Profusion of small opacities by plant

Plant (fibre)	MMMf workers			Comparison workers		
	No	1/0	1/1	No	1/0	1/1
1,2 (Ordinary)	576	1 (0.2)*	0	123	0	0
3 (Ordinary/fine)	220	8 (3.6)	5 (2.3)	65	1 (1.5)	1 (1.5)
4 (Ordinary/fine)	334	0	1 (0.3)	84	0	0
5 (Very fine)	122	5 (4.1)	3 (2.5)	0	—	—
6,7 (Mineral wool)	183	0	0	33	0	0
Total	1435	14 (1.0)	9 (0.6)	305	1 (0.3)	1 (0.3)

*Number as a percentage of films from plant.

five read substantially higher prevalences for MMMf workers at plants 3 and 5, and for the comparison workers corresponding to plant 3.

FACTORS RELATED TO SMALL OPACITIES AMONG MMMf WORKERS

Most (21/23) of the MMMf workers with small opacities were employed in plants 3 and 5, which had the highest average concentrations of exposure (table 1) and cumulative exposures (not shown). Considering all MMMf workers combined, each of the following exposure indicators was significantly related to the presence of opacities after accounting for film quality, smoking, and age: cumulative exposure ($p < 0.001$), time in jobs > 0.32 f/ml ($p < 0.01$), time in jobs at 1.5 f/ml ($p < 0.01$), and average concentration of exposure ($p < 0.01$).

After allowing for a plant category effect, however (plants 3 and 5 *v* the others combined), the only significant indicator of exposure was duration of exposure (one tailed $p = 0.04$). On the other hand, after allowing for all exposure indices (as well as age, smoking, and film quality), plant category remained highly significant ($p < 0.0001$), indicating increased prevalences of opacities at these two locations not accounted for by the available exposure indices.

WORKERS AT MMMf PLANTS 3 AND 5

When only workers at plants 3 and 5 were included

in the analyses (thereby including 21 of the 23 workers with opacities), after accounting for age, smoking, and film quality, the prevalences of opacities did not differ between the two plants, and the only exposure indicator that was significant was duration (one tailed $p = 0.04$).

For plant 3 workers alone, after accounting for age, smoking, and film quality, the presence of opacities was significantly related to cumulative exposure ($p = 0.02$), time at 0.32 f/ml ($p = 0.02$), and duration of exposure ($p = 0.04$). For workers at plant 5 only, after accounting for age and smoking, no exposure variables were significant (one tailed $p > 0.16$).

Table 4 shows the prevalences of opacities among workers in these two plants by quartile of employment duration. Whereas the trend among workers at plant 3 was statistically significant, this trend held for profusion 1/0 but not for 1/1. In fact, two of the five workers with profusion 1/1 had been employed for only short periods (12 and 19 months).

As with the MMMf workers overall, presence of opacities was not related to the spirometry measurements among workers at plants 3 and 5; the mean FEV₁ values (% predicted) for those without opacities were 102.5 ($n = 125$) and 108.7 ($n = 114$), respectively and the corresponding means for those with opacities were 102.0 ($n = 9$) and 111.1 ($n = 8$).

Table 4 Profusion of small opacities by quartile of years employed, plants 3 and 5

Plant	Years employed				All Durations
	< 1.7	> 1.7- < 5.8	> 5.8- < 15.2	> 15.2	
Plant 3	61*	56	50	53	220
1/0†	0	1 (1.8)‡	2 (4.0)	5 (9.4)	8 (3.6)
1/1	2 (3.3)‡	1 (1.8)	0	2 (3.8)	5 (2.3)
Plant 5	25	29	35	33	122
1/0§	0	0	3 (8.6)	2 (6.1)	5 (4.1)
1/1	0	0	1 (2.9)	2 (6.1)	3 (2.5)
Plants combined	86	85	85	86	342
1/0	0	1 (1.2)	5 (5.9)	7 (8.1)	13 (3.8)
1/1	2 (2.3)	1 (1.2)	1 (1.2)	4 (4.7)	8 (2.3)

*Number in group.

†Significant ($p < 0.04$) relation for profusion \geq 1/0 (not for 1/1) and years employed after accounting for age and smoking; see text.

‡Number as percentage of films.

§No significant relation for any profusion levels and years employed after accounting for age and smoking; see text.

PROGRESSION OF OPACITIES

There were 512 workers with readable films from both the 1980 and current surveys. For the 1980 films, there was good agreement in the median readings for small opacities for the 1980 study and the current study, with no evidence of a systematic difference: the two medians agreed for 477 (93%), and the current reading was higher than the earlier reading for 18 films and lower for 17.

There was little evidence of progression of opacities, with only 10 pairs with possible progression and one with probable progression. Eight of these 11 workers were employed in plants 5 and 7; the prevalences of progression were 12.5% and 11.5% for workers from these two plants respectively, compared with 1% or lower for the other plants. These readings for progression do not seem to indicate important changes: for seven of these eight workers (including the one with probable progression), both the earlier and later films, when read independently, were read as 0/0; for the eighth worker, his later film was 1/0. Also, only age was a significant factor in progression among the workers from these two plants, with none of the exposure indicators approaching statistical significance.

STUDY EXTENSION, PLANTS 3 AND 5

Pre-employment films from plants 3 ($n = 87$) and 5 ($n = 70$) were obtained to provide comparison films for workers from plant 5 and additional comparison films for plant 3. Compared with the 342 workers who had participated in the main part of the study, these 157 hires were on average younger (33.0 *v* 38.5 years), with a lower percentage of ever smokers (44% *v* 64%).

The median readings for quality for the 157 pre-employment and 342 workers' films were similar.

The 342 films taken in the main phase of the study at these two plants had been read about 18 months previously; there were significant changes in the readings of these films. The second median reading for quality tended to be better than the earlier: the two medians agreed for 78% of the films, the second indicated better quality than the earlier for 14% and worse for 8%. This difference was primarily due to one repeat reader, who assessed the films as significantly better on the second reading, and the fifth reader, who classified the films as significantly better than the reader he replaced.

For the 341 readable films, there were also significant changes in the readings for small opacities. The two median readings agreed for 88% of the films (299/341), but the second reading indicated a lower profusion category than the previous reading for 11% (39/341) and higher for 1% (3/341). Two of the four repeat readers read significantly lower the second time, and the substitute reader read significantly lower than the original reader he replaced.

Because of the lower readings in the second phase, the prevalences of opacities (median readings) were lower for workers in both plants: during the main phase of the study, the prevalences were 5.9% and 6.6% respectively; in the second phase, these prevalences were 3.2% and 0.0% respectively.

In this phase, presence of opacities (median reading) was significantly related to smoking (2.8% (8/287) among ever smokers *v* 0.5% (1/210) among never smokers). At both plants, there were no significant differences in the prevalences of small opacities between pre-employment and workers' films. At plant 3, the prevalences were 3.2% and 1.1% whereas at plant 5 these were 0% and 1.4% (table 5).

For workers at plant 5, all eight films classified (by median) on the first reading as having small opacities (five at 1/0, three at 1/1) were classified on the second as lacking opacities. For workers at plant 3, all eight films first classified as profusion 1/0 were classified on the second reading as negative 1/0; of the five originally classified as 1/1, four remained positive (one at 1/0, three at 1/1), and one was classified as negative 1/1. Also, three plant 3 films originally classified as negative were classified as positive on the second reading (two at 1/0, one at 1/1).

Of the four workers at plant 3 with radiographic profusion 1/1, two had been employed for only one year (the others for 5.6 and 3.3 years). Consequently, when prevalences were examined by quartile of years employed (similar to table 4), there was no evidence of increasing trends: the prevalences for profusion $\geq 1/0$ were 3.3%, 3.6%, 2.0%, and 3.8%, respectively, and for 1/1 these were 3.3%, 1.8%, 0%, and 1.9%. When analysed by multiple logistic regression, none of the exposure indicators approached significance as factors in the occurrence of opacities.

As with the earlier readings, presence of opacities among MMMF workers was not associated with lower functional values. For example, the mean FEV₁ values were 105.4 among those with small opacities, and 106.6 among those without small opacities.

COMPARISON OF X RAY FILM READINGS IN 1980 AND CURRENT STUDY

In comparing the results of this survey with that of the survey seven years earlier, it is appropriate to impose the same minimum impairment criteria for participants used in the 1980 study: 10 years for plants 1-4, and five years for plants 5-7, primarily because of the relation often found between age and x ray film opacities.

With these restrictions, the prevalences of small opacities ($\geq 1/0$) in the two studies were low and reasonably similar for the ordinary diameter fibre

Table 5 Profusion of small opacities, pre-employment and MMMF workers' films, plants 3 and 5, phase two of study

Plant (fibre)	MMMF workers			Pre-employment				
	No (%)*	Age (y) Mean (SD)	1/0	1/1	No (%)*	Age (y) Mean (SD)	1/0	1/1
3 (Ordinary/fine)	220 (63)	39.7 (10.7)	3 (1.4)†	4 (1.8)	87 (47)	35.1 (9.2)	1 (1.1)	0
5 (Very fine)	121‡ (67)	36.4 (9.5)	0	0	70 (40)	30.4 (9.0)	1 (1.4)	0
Total	341 (64)	38.5 (10.4)	3 (0.9)	4 (1.2)	157 (44)	33.0 (9.4)	2 (1.3)	0

*Percentage ever smokers.

†Number as a percentage of films.

‡One of total of 122 films judged unreadable.

(plants 1 and 2) and mineral wool plants (plants 6 and 7): for the two ordinary diameter plants combined, a prevalence of 1.7% in 1980, compared with 0.2% currently; for the mineral wool plants, 1.2% and 0.0% respectively.

In the 1980 study, the prevalences were highest for workers in the two ordinary and fine diameter fibre plants (plants 3 and 4). For plant 3, the 1980 prevalence of 12.2% (10/82) was comparable with the prevalence of 10.7% (8/75) in the main phase of the current study (workers employed > 10 years). The prevalence was lower, however, in the second phase of the current study (2.7% (2/75)).

The primary differences in prevalences between the 1980 and the main phase of this study were found at plants 4 (ordinary and fine) and 5 (very fine). For plant 4, the 1980 prevalence was 5.8% (12/210) compared with 0.5% (1/217) in the main phase. This difference can partially be explained by variability in the readings: of 140 films read for both studies, six were judged to have small opacities previously, compared with only one in this survey.

For plant 5, the 1980 prevalence was 0.0% (0/86) compared with 10.8% (8/74) in the main phase of the current study (workers employed > 5 years) and 0.0% in the second phase.

Discussion

The results of this investigation are consistent with previously reported cross sectional studies that have failed to find persuasive evidence of respiratory effects of manufacture of MMMF. A review⁸ of the available studies concluded that, whereas occupational exposure to various types of MMMF may be associated with adverse effects on the respiratory tract, no consistent pattern of such effects has emerged.

This follow up study of MMMF workers, studied previously in 1979-80, again found prevalences of respiratory symptoms and functional values generally consistent with a healthy population. Their radiographs showed small lung opacities only in the lower profusion categories, and in low prevalence. There was no persuasive evidence of radiographic

progression during the seven year interval between the two surveys.

There were, however, unexplained differences between prevalences of symptoms of MMMF and comparison workers, but without evidence that these differences were attributable to exposure to fibres. The minimal differences in mean values for lung function were explained by unrelated causes (previous chest surgery and asthma, most of which had been diagnosed before employment at these plants).

If the radiographic observations were available only for MMMF workers, a role for MMMF exposures in the occurrence of opacities could be inferred: almost all (21/23) of the workers with small opacities were employed at the two MMMF plants (plants 3 and 5) with the highest fibre exposures, resulting in an overall exposure-response relation. There were relations between opacities and several exposure indicators among workers at one of these plants (plant 3). There was no evidence of reduced functional values among workers with opacities, however, so a clinically important effect could not be inferred. Also, the relations found for workers at plant 3 were only for profusion 1/0; there were no relations for profusion 1/1.

The design of the study, however, included comparisons of the prevalences of opacities between MMMF workers and reference workers studied in the same radiological laboratories. Radiographs of reference workers were obtained for five MMMF plants (four locations), including plant 3; in all cases, there were no significant differences between the MMMF and reference workers in the prevalences of opacities. Whereas the prevalences of small opacities was higher among plant 3 workers than the reference workers (5.9% v 3.0%), as this difference was not statistically significant, it could have been a chance occurrence.

There were only a small number (65) of reference workers for plant 3, and none for plant 5. The study was therefore extended with pre-employment radiographs of other workers from plants 3 and 5 as reference films in a second reading for both plants. This second reading showed no persuasive evidence for a difference between workers exposed to fibres

and the reference group. The only suggestion of a possible difference was for opacities of profusion 1/1 among workers at plant 3. Again there was no evidence of a functional relation with the presence of opacities, nor of a relation between the presence of opacities and indicators of exposure among these workers. In fact, two of the four workers with profusion 1/1 had worked in the plant for only one year.

There are two problems in assessing the results of radiography. Firstly, the finding of small opacities in only the lower profusion categories poses difficulties in interpreting their significance. It is in these same categories that cigarette smoking and ageing, factors known to stimulate the appearances of interstitial fibrosis, have their effects.⁹

Secondly, the radiographic data in this study show notably large variability, both between different observers and within (some of) the same observers on different occasions. It has been known for a long time, however, that observer variability in grading radiographic lung abnormality is at its greatest when readers are trying to distinguish between normal and suspicious, or suspicious and minimally positive. In 1970, Reger and Morgan¹⁰ studied factors influencing consistency of readings and provided six tables showing all pairwise comparisons between four readers who independently classified a set of more than 2000 radiographs. Combining the tables and examining the categories of "zero" (normal), "suspect" (suspicious), and "simple pneumoconiosis" (positive), there were 401 instances in which both readers rated a film as suspicious, but there were 1211 instances of differing judgement as to suspicious *v* normal. Agreements at this level of abnormality were thus greatly exceeded by disagreements. At the next higher level, however, agreements far exceeded discordant judgements: 2033 instances of agreement as positive, and only 584 differing as to positive *v* suspicious.

As with between-observer variability, within-observer variability was long ago shown to vary with level of abnormality. In 1949, Fletcher and Oldham¹¹ reported a careful study of consistency in radiological judgements, within and among 10 readers of varying experience in pneumoconiosis work. They concluded that "the opinions of these observers were found to differ to a remarkable degree, both amongst themselves, and, to a lesser extent, from the one occasion to the other... The variation of opinion was greatest in films that were neither normal nor grossly abnormal."

It is also likely that systematic differences in the appearances of films from different radiological laboratories would have greater effect on deciding whether minimal changes were or were not present than on the detection of examples of normality or

advanced disease. Differences in film quality are not all reflected in gross departures from acceptable quality such as usually arise from errors in exposure settings or from developer malfunctions that produce either very light or very dark films. Less obtrusive differences can arise from various film and screen speeds, grids of differing efficiency, and the variations in the quality and maintenance of developers. Readers who often interpret series of films from different sources become aware of systematic differences attributable to technical factors, and try to allow for these to discount spurious appearances and detect only real abnormality. This tendency to compensate is so powerful that it has thwarted attempts to determine the biasing effects of even grossly over and underexposed films. Proof that more subtle differences could lead to over or under reading is thus not to be found in published work. The existence of the phenomenon is so likely, however, that it must be regarded as a potential source of confounding in a study such as this one, where fibre types are segregated by plant, and different plants are served by different radiological laboratories.

Systematic variations in film appearances associated with different radiological laboratories may thus be safely assumed to foster between observer disagreements, owing presumably to the varying efficiency with which different readers can compensate for them. This also furnishes a likely explanation for some of the within observer variability found in the present study. When the films from two sites that were reread in this study were initially read, they were mixed throughout the inclusive set comprising all films from all sites. The readers had less chance to perceive, and so to compensate for, any site specific differences in film quality than when rereading the set restricted to the two sites. According to a hypothesis that compensation for film defects reduces noise in the expression (signal + noise), which constitutes prevalence, a protocol that favours compensation at a second reading would be expected to produce a lower prevalence at the second reading.

In the final analysis, however, confidence in the results of a radiographic survey should rest mainly upon the integrity of the study design, the qualifications of the readers, and the adherence of the investigators to accepted methods of conducting radiographic surveys. In the present study, the design conforms to accepted principles of survey radiography. All readers had long experience in research use of the ILO classification, and all have contributed to publications on radiography of the pneumoconioses. The principles of independent reading, reference to standard radiographs, and blinding to non-radiographic data, were consistently followed. The observer variability found in

this study is probably a reflection of very low prevalence of "true abnormality" (or signal), in which case the observed prevalences (signal + noise) are mainly noise. The inherent randomness of noise then produces high rates of between and within observer variability.

The radiographic results of this study show the difficulty in striving to detect effects of exposure at the lower limits of radiographic detectability. Because of reader variability (within and among highly experienced readers), the readings of chest radiographs from such a population are necessarily of limited precision for the lower profusion levels for small opacities. Continued health surveillance of workers in this industry, especially those in fine fibre manufacture, is therefore prudent.

Nevertheless, the limited repeatability of the low level radiographic findings, suggests in itself that the observations are without clinical significance, and this is supported by the lack of a relation between small opacities and spirometry measurements. Moreover, the prevalences of these low profusion level opacities among MMMF workers were not significantly different from regional comparison workers, and for the two fine fibre plants where most opacities occurred, these prevalences exhibited no repeatable, consistent trend with indicators of exposure to fibre.

This work was supported by the Thermal Insulation Manufacturers' Association.

Requests for Reprints to: Janet M Hughes, PhD, Tulane University School of Medicine, Section of

Bioenvironmental Research, 1700 Perdido Street, New Orleans, Louisiana 70112, USA.

- 1 Weill H, Hughes JM, Hammad Y, Glindmeyer H, Sharon G, Jones RN. Respiratory health in workers exposed to man-made vitreous fibres. *Am Rev Respir Dis* 1983;128:104-12.
- 2 International Labour Office. *Guidelines for the use of ILO international classification of radiographs of pneumoconioses* (revised ed). Geneva: ILO, 1980. (Occupational Safety and Health Series No 22 (rev 80)).
- 3 Esmen N, Corn M, Hammad Y, Whittier D, Kotsk N. Summary of measurements of employee exposure to airborne dust and fibre in sixteen facilities producing manmade mineral fibres. *Am Ind Hyg Assoc* 1979;40:108-17.
- 4 Ferris BG. Epidemiology standardisation project. II. Recommended respiratory disease questionnaires for use with adults and children in epidemiologic research. *Am Rev Respir Dis* 1978;118(suppl):7-53.
- 5 Gilson JC, Jones RN. Radiography. In: Weill H, Turner-Warwick M, eds. *Occupational lung diseases: research approaches and methods*. New York: Marcel Dekker Inc, 1981:35-59.
- 6 Knudson RJ, Slatin R, Levowitz MD, Burrows B. The maximum expiratory flow-volume curve: normal standards, variability and effects on age. *Am Rev Respir Dis* 1976;113:587-600.
- 7 Occupational Health and Safety—Code of federal regulations. Office of the Federal Register; July 1, 1987;29 CFR Ch XVII; 1910.1043 Cotton Dust; 854-86.
- 8 World Health Organisation. *International programme on chemical safety; Environmental Health Criteria 77—Manmade mineral fibres*, Geneva:WHO,1988.
- 9 Castellon RM, Sanderson WT, Petersen MR. Prevalence of radiographic appearance of pneumoconiosis in an unexpected blue collar population. *Am Rev Respir Dis* 1985;131:684-6.
- 10 Reger RB, Morgan WKC. On the factors influencing consistency in the radiologic diagnosis of pneumoconiosis. *Am Rev Respir Dis* 1970;102:905-15.
- 11 Fletcher CM, Oldham PD. The problem of consistent radiological diagnosis in coal miners' pneumoconiosis. *Br J Ind Med* 1949;6:168-83.

Accepted for publication 7 September 1992.