

Both the long and short samples were prepared from ore by a wet grinding method, then sieved and washed by a technique described from this laboratory (Gibbsite, M.S., and M.S. Grant. Preparation of Amphibole Fibers for Experimental Use. Annals of N.Y. Acad. Sci. 132 (Part 1): 61-65, 1965). Fibers thus prepared were ground in a Wig-L-Bug to produce the short fiber samples. The Wig-L-Bug process was monitored by phase microscopy and stopped before destruction of the fibrous nature of the material.

These samples were furnished to Dr. U. Reineweber at Johns-Manville Research & Engineering Center for electron microscopy. From his photomicrographs it was learned that the long fiber samples contained relatively few fibers less than 5 microns in length, whereas the short fiber samples contained relatively few fibers more than 5 microns in length. Dr. Reineweber noted that the short fiber samples had not been reduced to amorphous material but preserved the fibrous structure of chrysotile. Further discussion of length measurements is offered later in this report.

3. Tests of long and short fiber anthophyllite gave results consistent with an hypothesis that reduction in fiber length reduces carcinogenicity.

though findings were not statistically significant. These samples were not tested at the 25mg level. At the 10mg level, long fiber anthophyllite induced 3 mesotheliomas (Group 20). Short fiber anthophyllite induced 1 mesothelioma (Group 21).

The short fiber sample was prepared by grinding the long fibers in a Wig-Bug, the process being stopped before the fibrous nature of the material was destroyed.

5. At the 10 mg dose level, mesotheliomas resulted from a sample of microquartz with mean fiber length of 24.7 microns (Group 12), but not from glass fibers with or without phenol-formal binder (Groups 13, 22). Mean fiber lengths of these two samples were 24.9 and 10.9 microns, respectively.

6. At our highest (25mg) dose level, mesotheliomas were induced in hamsters by diatomaceous earth and by calcined diatomaceous earth, but not by talc, nemaline or, except for a single case, by serpentine rock dust (Groups 15, 15A, 14, 13, 11). The sample of talc contained a large amount of tremolite.

7. Mesotheliomas were induced by powdered nickel dust at a 10mg dose level. The yield of mesotheliomas in response to nickel was closely comparable to the yield

obtained with the low level of chrysotile and
is limited, and less than the yield obtained with high
level of crocidolite.

8. No mesotheliomas have been found in the untreated
control groups.

9. Lymphoid tumors occurred in 14 of the 23 treated
groups, and in 1 of the 2 untreated control groups.
These tumors were regarded as spontaneous tumors
unrelated to treatment.

10. Tumors of the adrenals were common in both untreated
control groups and in treated groups. Nephromas were
found in 2 control and in 4 treated animals. Adeno-
carcinoma of the ductless was found in single animals
in groups 2, 5, 13, 15, 16 and 18.

11. Thrombi in the left cardiac atrium were a common
cause of death in hamsters in our experiments. Such lesions
occurred in untreated control groups, but in some
of the treated groups they were found earlier and more
frequently, as shown in Table 2 of addendum A (3).

Computer programming and analyses on data from necropsy
done for animals in groups shown in Table 1 has been done by
Dr. Thomas Nelson, our Consultant in Statistics. For each

he has made in the analyses broken down into
100 and 50 day intervals as follows:

L_i = number of hamsters at start of period

D_i = dead in period

V_i = lost in period

W_i = withdrawn in period

E_i = effective number at risk in the period = $L_i - \frac{1}{2}(D_i + V_i + W_i)$

q_i = probability of dying in the period

s_i = probability of surviving in the period

R_i = survival rate

SD = standard deviation

From these analyses, the group size used for tests in
Table 1 (50 hamsters per group) seems satisfactory for com-
parison of relative carcinogenicity of the tested samples
in the 100 day periods.

Dr. Dayton's report on his statistical studies is attached
as Addendum A.

In the preceding text, fiber lengths cited for our samples
1 and 2 (Table 1) were determined by light microscopy using a
40X objective and 10X ocular. These measurements were made in
the laboratory of the Occupational Health Program, Dept. of
Health, State of New Jersey, at the start of our tests of
these samples in animals. Also at the start of our animal
tests, very similar measurements were reported to us for

... supplied by the U.S. Department of Health, Education and Welfare, National Institute of Environmental Health Sciences, Research Triangle Institute in Durham, N.C. where 40X objective, 10X ocular and phase contrast illumination were used. Recently, these samples were furnished to Johns Manville Research and Engineering Center, Manville, N. J., where they were studied with a 12X objective and a 5X ocular by dark field microscopy, images being projected to a final magnification of 100X, photographed, then enlarged 24X for measurement of lengths and diameters. Mean lengths reported under these latter conditions were considerably longer. Measurements of samples studied under the 3 optical conditions are shown in Table 1.

Also shown in Table 3 are measurements made on these and other samples by electron microscopy at EMRI. For EM work, the original photograph was made at 2000X and was then enlarged 24X for measurements. Fibers extending beyond the EM field were excluded from measurements, hence mean lengths reported in Table 3 for samples 1 and 2 are much smaller than mean lengths reported for these samples by optical microscopy. In EM photographs, fibers less than 5 microns in length were relatively scarce in samples 1 and 2, which were samples that proved highly carcinogenic in hamsters.

In samples 4, 5 and 6 which proved non-carcinogenic in hamsters, most fibers were too short for meaningful measurement by optical methods. EM measurements of sample 4 gave mean fiber length of 0.71 microns. EM photographs of samples 5 and 6 look about the same as sample 4, but have not yet been

(Cumulative data to 650 days except where noted)
 50 hamsters per group
 INTRALIBOPAL INJECTION

GROUP	MEAN FIBER LENGTH microns	DOSE mg.	MESOTHEL- IOMA	SARCOMA INJECTION SITE	LYMPHOID TUMORS	REMARKS
WHITE ERIC	25	0	0	0	0	700 days
WHITE LONGS	25	3	2	2	2	
WHITE SUSC (Combined)	25	4	2	1	1	
WHITE SS WITH 24.9 INTRALIBOPAL INJECTION	10	0	0	5	5	
WHITE 14.3	10	4	4	0	0	
WHITE U.I.C.C.	10	10	5	1	1	
WHITE U.I.C.C.	1	2	0	4	4	700 days
WHITE Long (URCC)	10	3	0	2	2	
WHITE Short (3.7)	10	1	0	0	0	
WHITE 15.9	10	0	0	5	5	
WHITE 20.3	20.3	0	0	0	0	700 days
WHITE 20.3	20.3	0	0	4	4	650 days (survivors are being followed to 700 days)

TABLE 2. YIELD OF MESOTHELIOMAS IN HAMSTERS AT SITES OF INDUCTION OF CHLOROMYCELS

Group	Sample	151 days	340 days	372 days	450 days	500 days	550 days	600 days	650 days
2	B2 (Harsh)	1/41	4/26	4/21	7/16	7/13	7/9	8/5	9/1
3	C2 (Soft)	0/44	0/33	1/30	1/20	4/11	4/9	7/3	8/1
3	C2H1 (Soft)	0/37	1/35	1/22	1/27	4/17	5/15	8/4	10/1

1st row: Cumulative number of hamsters having mesotheliomas.

2nd row: Number of surviving hamsters.

3. All survivors at 550 days were killed on that day. Pleural adhesions, but no tumors, were found in them. For statistical treatment, see Addendum A.

Measurements of Selected Samples.
(For measurements of other samples see Table 1)

Sample	Lab.	OPTICAL MICROSCOPY	ELECTRON MICROSCOPY
		Mean fiber length microns	Mean fiber length microns
1	A	30	
	B	32.54	
	C	52.5	6.9
2	A	30	
	B	30.85	
	C	63.5	5.3
3	C		0.75
	C	56.7	7.33

Sample nos.
are as those
in Table 1

* Lab A: 40X objective, 8X ocular (phase contrast)
Lab B: 40X " 10X " (dark field)
Lab C: 32X " 5X " " "

Fiber lengths of sample 1 were too small for measurement by optical methods.

for optical and x-ray studies of these samples. Further, we are indebted to Dr. James Laineveber, Allan Burns, Don Bailey and Tom Brown.

Samples of soft and marsh chrysotile prepared in our laboratory from Arizona ores were sent to Dr. Cralliey in 1961 for analysis of trace elements by atomic absorption spectroscopy. The following report was received from him on these samples, which were the "long fiber" samples that subsequently proved highly carcinogenic in our intrapleural tests in hamsters (Groups 1 and 2).

Sample No.	Material	Microgram element/ gram sample			
		Ni	Cr	Co	Mn
92b	Chrysotile (marsh)	N.D.	N.D.	N.D.	220
92c	Chrysotile (soft)	N.D.	N.D.	N.D.	100

From these results, it can be seen that no detectable amounts of nickel, chromium or cobalt were found in the samples as injected into hamsters.

Subsequently, Dr. Cralliey's group developed a microsieve method for separating "longer than 10 micron" (>10 μ) and "Less than 10 micron" (<10 μ) fractions of asbestos and found certain trace elements in higher concentration in the short fractions. In 1969, we resubmitted our samples to Dr. Cralliey. They were fractionated by the microsieve method in his laboratory and he has reported the following analyses:

		Chromium		Nickel		Cadmium	
		ppm	%	ppm	%	ppm	%
Long (32-39 micron)	+10% <10	<1	100	<10	7.5	0.1	
Long (32-39 micron)	-10% <60	42	60	230	1800	8.1	
Short (1-5 micron)	+10% <80	<1	310	<5	185	4.5	
Short (1-5 micron)	-10% <50	157	500	46	118	2.9	

In these analyses, the symbol < means not detectable at the stated limit of sensitivity of tests. From these data, it has been seen that detectable amounts of chromium and nickel were not found in the +10% fractions but were found in the -10% fractions. The -10% fractions constituted 6 to 7% by weight of the samples. These fractionations were made on our "long" (32-39 micron mean fiber length) samples that proved highly carcinogenic in hamsters. If trace elements in the "less than 10 micron" fractions were important in carcinogenesis, then high carcinogenicity would have been expected in our "short" (1-5 micron) preparations of these ores, but such was not the case, our short preparations proving essentially non-carcinogenic.

The following studies were not part of the aims stated for this project in our original proposal but were carried out as ancillary work:

- a. In a previous project, we had carried out "line-spar" studies on hamsters given repeated intratracheal injections of chromium with and without some copper. These

pathologic studies. Lung from these animals were
completed in the course of the present project with
results presented in an attached publication (4).

b. Hamsters given a single intratracheal injection of
chrysotile were sacrificed at intervals for examination
of lungs by electron microscopy with results described
(5), (6), (7).

c. For chemotherapeutic trials, a fast-growing meso-
thelioma induced by chrysotile and a slow-growing meso-
thelioma induced by crocidolite have been established
and are being carried in serial transfer in new hosts
(hamsters).

d. Squamous cell carcinomas and adenocarcinomas were
induced from mouse pulmonary tissue exposed to chrysotile
(8). For chemotherapeutic trials, 2 lines of these
pulmonary squamous cell carcinomas and one line of
pulmonary adenocarcinoma have been established and are
being carried in serial transfer in new hosts (BALB/c
mice).

STATE OF RESULTS

a. After single intrapleural injection of hamsters, tumors
with gross and microscopic characteristics of pleural meso-
thelioma were found after injection of both chrysotile, and
chrysotile, amosite, crocidolite, anthophyllite, diatomaceous

graphite, nickel powder and mesopneumous fibers, but not with
 exposure of tremolite and talc or glass fibers. Car-
 pene rock dust (antigorite), induced only a single case
 of mesothelioma.

2. Native harsh chrysotile induced tumors more rapidly than
 soft chrysotile. Heat treatment of soft chrysotile increased
 fibrogenicity but not carcinogenicity.

3. With reduction in dose, there was reduction in fibrogenic
 and carcinogenic response to chrysotile, amosite and croci-
 dolite. Hence, hazards associated with exposures to asbestos
 should be controllable by measures to reduce amounts of ex-
 posure.

4. At the lowest dose level tested (1mg), no tumors arose
 in response to chrysotile or amosite, but tumors were found
 in response to crocidolite.

5. With each of 3 samples of chrysotile, treatment to reduce
 fiber length reduced fibrogenic responses and eliminated car-
 cinogenic responses. Electron microscopy revealed that the
 treated samples were fibrous in nature and had not been re-
 duced to amorphous material. These findings afford informa-
 tion pertinent to design of masks and to monitoring of dusts
 for industrial hygiene purposes.

6. Polyvinylpyrrolidone-K-25 did not inhibit fibrosis induced
 by asbestos injected intraperitoneally into hamsters.

7. After intratracheal injection of chrysotile into hamsters,
 the rate of clearance of asbestos fibers

... only by macrophages but also by epithelial cells.

Changes in fibers and in epithelial cells were described.

8. After intratracheal injection of benzo(a)pyrene plus chrysotile into hamsters, the incidence of lung tumors was greater than after benzo(a)pyrene alone.

9. After exposure of fetal mouse lung tissue to chrysotile by tissue transplant technique, squamous cell carcinomas and adenocarcinomas resulted.

10. For chemotherapeutic trials, two lines of transplantable mesotheliomas were established in serial transfer in hamsters, two lines of pulmonary squamous cell carcinomas and one line of pulmonary adenocarcinoma were established in serial transfer in mice.

11. Statistical treatment of responses of hamsters to intrapleural injection of tested minerals is described.

12. Additional manuscripts are in preparation for publication.

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Paper Presented at the Metal and Nonmetallic Mine Health
and Safety Symposium on Talc Dust Hazards Held in
Washington, D.C. on Tuesday, May 2, 1973 By
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Division of Industrial Hygiene, New York State

My former colleagues in the Division of Industrial Hygiene of New York State and I have had the opportunity to conduct numerous studies of talc workers in New York State, including, clinical, physiological, radiological and environmental observations⁽¹⁾. In addition, we have also studied the mortality experiences among workers in talc mining and milling. In most instances, we have had the invaluable opportunity to correlate the clinical with the environmental data. In general, we have found that sustained inhalation of significant amounts of commercial talc dust over an extended period of time, or where there was a significant elapsed time from initial exposure, can produce a symptomatic form of pneumoconiosis. The commercial talc to which the talc workers were exposed contained not only the mineral talc, but also other silicates such as vermiculite, tremolite, anthophyllite and other ingredients, as well as carbonates. Moreover, free silica was often present in the dust in variable amounts, usually not averaging more than 3 percent.

Specifically with regard to our mortality experiences among talc workers, we found in an earlier study of talc workers (miners and millers) who had 15 or more years of exposure to talc dust that the proportional mortality from carcinoma of the lung and pleura among these workers was four times that of the general population. However, the significant increase in incidence of malignancy appeared in the older talc workers, namely, those in the 60 to 79 year age group, rather than in the 40 to 59 year age group⁽²⁾. This observation in the talc workers was in variance with those found in a group of asbestos insulators who had the same duration of exposure covering a similar time period⁽³⁾. The asbestos insulators showed an increased incidence of mortality from lung cancer in both age categories. The incidence of carcinoma of the gastrointestinal tract and peritoneum among talc workers was not significantly different

from that of the general population, whereas among the asbestos insulators the incidence of gastrointestinal malignancy was significantly higher than that of the general population. He postulated that the earlier occurrence of malignancies among the asbestos insulators was due to two factors. The first was the relatively greater carcinogenicity of the chrysotile asbestos as compared to commercial talc. The second factor was the exposure of the insulators to greater quantities of chrysotile asbestos as compared to the talc workers who were exposed to lesser quantities of commercial talc dust which was admixed with appreciable amounts of tremolite and anthophyllite asbestos. Our observations favored the first factor. The earlier study⁽²⁾ also showed an increased incidence of deaths due to talc pneumoconiosis and/or its complications.

A follow-up study was made to bring our mortality data among the talc workers up to date and to provide additional information not reported in the earlier study. The pertinent data is indicated below.

All the talc workers employed in 1940 who had accumulated 15 or more years of exposure to commercial talc dust as well as those who achieved a minimum of 15 years of such exposure between 1940 and 1969 were included in the follow-up study. The group totaled 230 workers and it is believed that the overall number constituted the total work force in the worker population under study. The data were obtained from a number of sources. Plant records were examined and the work history of each individual was obtained to include changes of job and specific years of employment. Death certificates were studied in all instances where they were available. The records of the physicians who had attended the workers privately were reviewed. Substantial medical information on the majority of the workers was available in the files of the Division of Industrial Hygiene and was used as an additional source of

data. Hospital records, including autopsy reports and histological specimens, were examined wherever available. Autopsy or biopsy records were obtained in 38 of the 103 deaths.

A comparison was made of the observed proportional mortality rates from the specific causes with the expected rates among similar population groups and was found satisfactory for a descriptive study of this nature. The proportion of observed mortality attributed to cancer of the lung and pleura and of the gastrointestinal tract and peritoneum and cardiac diseases were compared to the expected mortalities due to the above causes in the various age groups. The expected mortality for the total group represents the proportion of deaths among white men in the United States due to the specific causes in the year 1955. This particular year was chosen as standard because it was the median year of death among the 103 deaths. For each of the 5-year periods, the median years, namely, 1942, 1947, 1952, 1957 and 1962 were selected.

In the group of 260 talc workers studied, there were 103 deaths. There were a total of 25 deaths from malignancies. Of these 25 deaths, 13 were due to lung and pleural malignancies; 9 were due to gastrointestinal and peritoneal malignancies and 3 were due to other malignancies. Thirty deaths resulted from cardiac disease, other than cor pulmonale, and 20 deaths were attributable to pneumoconiosis and its complications. Accidents and suicides accounted for 3 deaths and there were 16 deaths due to other causes (Table 1). The average age at death of the 103 talc workers was 60.3 years, with a range of 38 to 84 years. Environmental exposure data was available in 97 of the 103 death records. The mean duration of exposure for this group was 24.1 years, with a range of 13 to 47 years. The dust exposure was predominantly to talc, tremolite, anthophyllite, carbonate dusts and a small amount of free silica.

Comparative dust counts at the talc mines and mills prior to 1945 and between 1946 and 1969 were obtained (Table 6).

With regard to the deaths due to malignancies, 12 of the 13 malignancies of the lung and pleura were carcinomas of the lung and 1 was a fibrosarcoma of the pleura. Of the 9 malignancies of the gastrointestinal tract and peritoneum, 3 were cancers of the stomach; 2 were cancers of the liver, 1 of which was a primary hepatoma of the liver and the other a metastasis from a gastrointestinal malignancy; 1 was a cancer of the colon; 2 were cancers of the pancreas; and 1 was a peritoneal mesothelioma. The 3 malignancies involving other sites included 1 retroperitoneal reticulum cell sarcoma, 1 chronic lymphatic leukemia and 1 Hodgkins' disease (Table 3). The overall proportional mortality of carcinoma of the lung and pleura was four times that expected. Consistent with our previous observation, a significant increase appeared to occur in the age group of 60 to 79 years rather than in the 40 to 59 year age group (Table 2). As I have already mentioned, this finding among talc workers was at variance with what we had observed among asbestos insulators where the observed values in both the 40 to 59 and 60 to 79 year age groups were significantly different from the expected values. In the absence of adequate smoking data, one cannot assess the role played by smoking in accounting for the differences in the occurrence of malignancies.

When carcinoma of the lung and pleura was related to each of the six 5-year periods, namely, from 1940 to 1969, it is important to note that the observed proportional mortality from carcinoma of the lung was approximately four times as much as the expected mortality during the years 1945 to 1949 and dropped to approach the expected mortality in the years 1960 to 1964 and 1965 to 1969 (Table 4). The differences between the observed and expected mortality rates were significant in 1950-54 and insignificant in 1960-64 and

1968-69. The improved mortality experience between 1960 and 1969 and to date (1973) in the case of lung and pleural cancers is particularly pertinent since environmental controls have resulted in an appreciable reduction in the dust counts in the mines and mills, although the fiber counts still exceed the present threshold limit value for asbestos dust by approximately four to five times (Table 6). This finding indicates that the present threshold limit value of 5 fibers/ml with a fiber length greater than 5 microns for fibrous talc, including tremolite and anthophyllite, is basically adequate.

With regard to cancer of the gastrointestinal tract and peritoneum among the talc workers, we did not find any significant difference between the observed and expected values in the overall and specific age groups studied (Table 2) and are consistent with findings reported by Kiviluoto and Hammond⁽⁴⁾ among anthophyllite workers. These findings differ from those observed in asbestos insulators where a significant increase in the observed incidence of gastrointestinal malignancy was found in the overall and specific age groups studied⁽²⁾. Our findings among asbestos insulators were similar to those reported by Selikoff, Hammond and Churg⁽⁵⁾.

Of the 29 deaths due to pneumoconiosis and its complications, 20 were due to cor pulmonale, 5 to advanced tuberculosis and 4 to bronchopneumonia. The lapsed time from the first commercial talc dust exposure to death in this group averaged 30.9 years with a range of 13 to 46 years. All 29 had their initial exposures prior to 1945 at which time more effective engineering controls, including wet drilling in the talc mines, were introduced. The percentage of deaths due to pneumoconiosis and its complications has decreased by more than 50 percent in the last 5-year period studied, namely, 1968-69, as compared to the preceding period (Table 3). The number of deaths probably reflects the greater exposures which occurred in the earlier

years of employment. A longer interval must elapse, however, before the effect of controls on the incidence of pneumoconiosis can be appraised more definitively in the plant studied. It is noteworthy, however, that in another study of a different plant processing a similar mixture of talc, tremolite and anthophyllite, but wherein controls were installed at the inception of operations in 1948, only 1 of 39 workers had a chest roentgenogram consistent with pneumoconiosis. The mean exposure of the 32 workers was 16.2 years with a range of 11 to 22 years. The worker whose chest roentgenogram was consistent with pneumoconiosis was a 75-year old man who had a non-productive cough, a Grade 1 dyspnea and who worked as a janitor for 11 years. The low incidence of pneumoconiosis was found despite the presence of relatively high fiber and dust counts in this plant⁽⁶⁾. The fiber counts exceeded by two to six times the present threshold limit value of 5 fibers/ml with a length greater than 5 microns. In terms of time-weighted averages, Murphy and associates⁽⁷⁾ found no asbestosis among workers exposed less than 60 mppcf-years to chrysotile and amosite in ship construction. In the study of the plant having controls since the start of operations⁽⁶⁾, it was found that an appreciable number of workers exceeded the 60 mppcf-years, but did not show any evidence of pneumoconiosis as determined by the criteria of Murphy and associates. The findings from the study of the plant having controls from the onset of operations suggest that tremolite and anthophyllite are less fibrogenic than chrysotile or amosite at comparable dust exposures.

Of the 30 cardiac deaths, excluding cor pulmonale, 22 had coronary artery disease, 5 had hypertensive heart disease and 3 had rheumatic heart disease. Rather surprising was the observation that the observed proportional mortality from cardiac diseases was lower than the expected

mortality in all 5-year periods except the first, namely, 1940-1944 (Table 5). It seems reasonable to state on the basis of the remaining data that the overall observed proportional mortality from cardiac disease among talc workers was lower than the expected mortality. The decreased mortality from cardiac disease among talc workers cannot be attributed to a predisposition to lung cancer which generally results in the death of these workers at earlier ages before they might be expected to succumb to cardiac disease. As demonstrated, the decreased proportional mortality from cardiac disease was present in both the 40 to 59 as well as the 60 to 79 year age groups (Table 2). If malignancy of the lung was a factor, one would have expected a difference in incidence between these two age groups. The true explanation for the lower incidence of cardiac disease is open to conjecture. The rural environment in which the talc workers lived, as well as the possibility that they smoked less, may account for the lower mortality due to cardiac disease as compared to the national rate.

I trust that the information I have submitted this morning will provide the Bureau of Mines with essential data relating to the occupational hazards of exposure to talc, fibrous talc and tremolite dusts in order to evaluate the adequacy of the existing threshold limit values for pure talc and talc mixed with tremolite and anthophyllite.

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Table 1

2. Kleinfeld, M., Massite, J., Keown, C. and Greenman, L.: **Talc Miners Causes of Death in 108 Talc Workers During Period of 1940 to 1969** 693-67, 1967.

3. Kleinfeld, M., Massite, J. and Keown, C.: **Causes of Death in Talc Miners.** Arch Environ Health 1967; 23: 1-10.

Cause of Death	No.	%
Malignancies	25	23.1
Lung and Pleura	13	12.0
Gastrointestinal and peritoneal	9	8.3
All other malignancies	3	2.8
Cardiac Deaths (other than cor pulmonale)	30	27.8
Pneumoconiosis and Complications	22	20.6
Accidents or Suicides	8	7.4
All Other Causes	16	14.8
Total	108	100.0

6. Kleinfeld, M., Massite, J. and Keown, C.: **Causes of Death in Talc Miners.** Arch Environ Health 1967; 23: 1-10.
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Table 2

Deaths and Proportional Mortality From Carcinomas of the Respiratory Tract, of the Gastrointestinal Tract, and From Cardiac Diseases Among Talc Workers by Age, 1940-1969

Age Group	Total Deaths	Deaths and Proportional Mortality From Respiratory Cancers			Deaths and Proportional Mortality From Gastrointestinal Cancers			Deaths and Proportional Mortality From Cardiac Diseases		
		No	(%) Observed	Expected	No	(%) Observed	Expected	No	(%) Observed	Expected
40	3	0	0	1.6	0	0	2.5	1	33.3	21.1
40-59	47	4	8.5	5.2	3	6.4	5.7	11	24.4	44.2
60-79	54	9	16.6	3.6	4	7.4	7.2	17	31.5	47.8
80-84	4	0	0	1.1	1	25.0	5.3	1	25.0	47.1
Total	108	13	12.0	3.7	8	7.4	6.5	30	2.8	45.8

Table 3

**Causes of Death in 108 Talc Workers*
During the Period 1940-1969**

Cause of Death	1940-44	1945-49	1950-54	1955-59	1960-64	1965-69	Total
Malignancies							
Lung and Pleura	-	2	1	5	3	2	13
Stomach	-	1	-	1	-	1	3
Liver	1	-	-	1	-	-	2
Colon	-	-	1	-	-	-	1
Pancreas	-	-	-	-	1	1	2
Peritoneum	-	-	-	1	-	-	1
Other Malignancies	-	-	2	-	-	1	3
Cardiac Diseases	3	6	-	6	8	7	30
Pneumoconiosis and Complications	2	4	2	8	9	4	30
Accidents and Suicides	1	1	1	2	2	1	8
Others	-	3	1	1	5	6	16
Total	7	17	8	25	28	23	108

*who had at least 15 or more years of exposure to talc dust.

Deaths and Expected Mortality from Cancer of the Lung and Pleura and of the Gastrointestinal Tract and Peritoneum Among Talc Workers 1940-1969

Deaths and Expected Mortality from Cancer of the Lung and Pleura and of the Gastrointestinal Tract and Peritoneum Among Talc Workers 1940-1969

	Lung and Pleura				Gastrointestinal Tract and Peritoneum			
	Deaths	Proportional Mortality (%)		P	Deaths	Proportional Mortality (%)		P
		Observed	Expected			Observed	Expected	
1940-44	0	0	2.0	1	1	14.3	7.8	NS
1945-49	2	11.7	3.1	S	1	5.8	7.8	NS
1950-54	1	12.5	4.3	S	1	12.5	7.1	NS
1955-59	5	20.0	5.7	S	3	12.0	6.7	NS
1960-64	3	10.7	6.7	NS	1	3.6	6.3	NS
1965-69	2	8.7	7.7	NS	2	9.5	6.1	NS
Total	13				9			

P = probability
S = significant
NS = not significant

Table 5

Deaths and Expected Mortality From Cardiac Disease
Among Talc Workers 1940-1969

	Deaths	Proportional Mortality (%)	
		Observed	Expected
1940-44	3	42.8	37.4
1945-49	6	35.3	41.0
1950-54	0	0	46.0
1955-59	0	20.0	40.5
1960-64	8	28.6	46.6
1965-69	3	30.4	45.5
Total	30		

Table 6

Comparative Dust and Fiber Counts at the Various Tale Mining and Milling Operations

	Pre 1945 through 1969						1972		
	Dust Counts*						Dust Counts*		Fiber Count
	Pre 1945		1946-1965		1966-1969				
	Ave.**	Med.**	Ave.**	Med.**	Ave.**	Med.**	Ave.**	Med.**	
Drilling	618	413	5	3	19	19	7	7	3
Mucking	120	30	5	5	9	9	3	3	2
	Pre 1948		1948-1965						
Crushing	180	69	42	13	20	20	33	15	62
Screening	69	61	37	37	--	--	--	--	--
Milling	92	75	25	20	40	24	7	7	28
Garnering & Separating	278	70	27	27	--	--	13	9	27
Pulverizing	--	--	28	28	--	--	--	--	--
Bagging	151	129	27	23	29	25	27	27	47
RR & Truck Loading	--	--	73	63	43	20	36	28	24
Blow Room***	1227	1196							
Open Chutes***	125	83							

*Dust counts in mppcf; fiber counts in no. fibers/ml. > 5 μ in length

**Ave. - average; Med. - median

***Operation discontinued after 1948

...medically oriented
"detective story."

TALC-COATED

R I C E

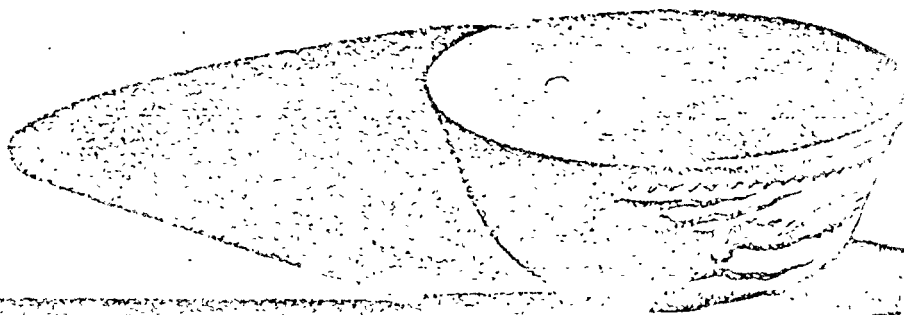
Last summer I walked through a ceramics plant to see how dusty it was because one of my patients had developed lung trouble after working there for several years. Within the plant itself the air seemed fairly clean. However, when I walked outside, I saw piled against a shed a number of open sacks of talc powder which the manager told me was talc. It was to be added to the clay. A small breeze stirred the surface of the talc, picking up some dust and blowing it throughout the back yard. Some blew into my face and onto my clothes. I asked whether the workmen inhaled the talc, and the answer of the manager, who appeared an intelligent and careful man, suggested he believed that the talc constituted no hazard.

I worried about this since California talcs, as well as other talcs, are mixtures of minerals, of which a large percentage is asbestos. Asbestos causes lung can-

cer in workmen who inhale it, and, interestingly enough, these workmen also have an increased incidence of cancer of the gastrointestinal tract, particularly of the stomach.

Then, with this entire subject still fresh in my mind, I went shopping with my wife at a market near our beach home in Laguna. There is a Japanese population in Laguna, and this particular market carries food intended for the Japanese purchaser. I was startled to see a sack of rice intended for Japanese consumption bearing on it the label "coated with glucose and talc." Japanese people have a high incidence of stomach cancer. Talc coating on rice meant that the Japanese, at least in the Los Angeles area, were eating talc with their food. The obvious question was whether the two facts were related. Later, in Los Angeles I visited several markets, and in each I found that rice intended for Japanese

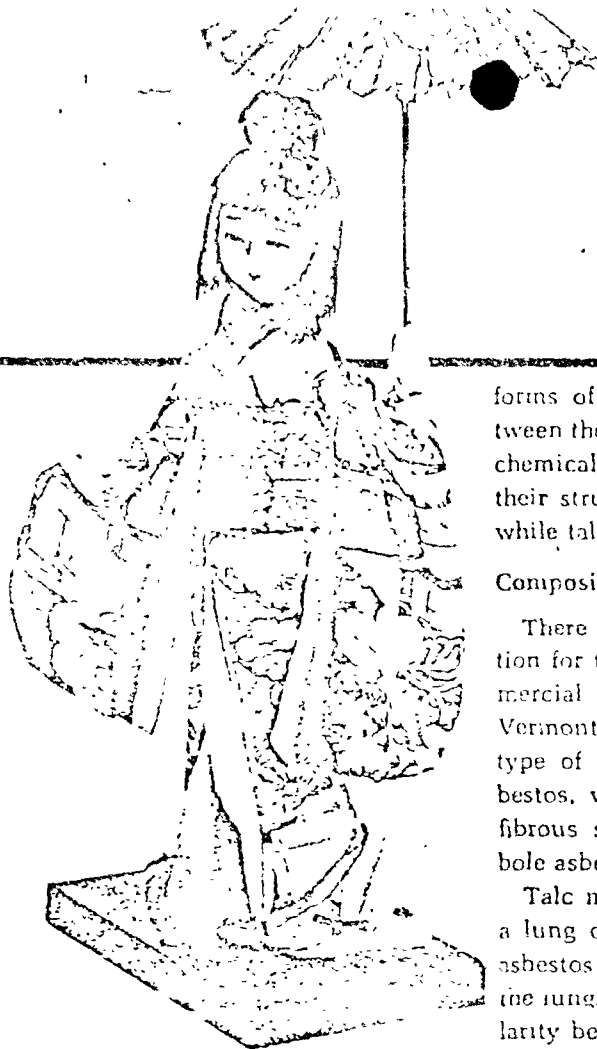
by R. R. MERLISS, M.D.



consumption bore the label "coated with glucose and talc." The next piece of information needed was how widely used talc-coated rice is in Japan itself. I found I could not buy Japanese imported rice in Los Angeles. The United States, at least in this area, does not import rice from Japan. However, I bought a sack of California-produced talc-coated rice, and visited several stores in the Japanese area of Los Angeles, asking in each case the Japanese owner whether this is the type of rice commonly used in Japan. In each case he told me that it was.

Beginning of a hypothesis

This, then, represented the genesis of a hypothesis: that the high incidence of cancer of the stomach in Japanese is due to their eating of asbestos-contaminated talc adhering to the rice. The further development of the hypothesis led me to spend a number of evenings away from home reading relevant studies. I learned that the age-adjusted rate of cancer of the stomach in Japanese men from 1962 to 1963 was the highest for all nations. It was 67.96 per 100 thousand men and was seven times the frequency of that in men in the United States. Investigation of the original report on the health problems of asbestos workers by Irving Selikoff of Mount Sinai Hospital showed that the workmen exposed to this mineral had a significant increase in gastrointestinal cancer, especially



stomach cancer. Presumably the increase came from the inhalation of fibers of asbestos, which then settled in the pharynx or the nasopharynx (that part of the respiratory tract shared with the mouth), and were swallowed, becoming trapped in the glands of the stomach, causing development of cancer there.

Rice meant for the American consumer is milled mechanically. On the other hand, California rice prepared for the Japanese consumer is treated with glucose, which forms a sticky film, to which the talc is applied. The talc is thought to preserve the flavor of the rice. About 2 per cent of all the talc produced in the State of California from 1959 to 1963 was used as a rice additive. I had a sample of the sack of rice I bought examined. Study of the ash demonstrated close to about four million asbestos-form fibers per gram.

I found that the mineral talc is defined in the geologic texts as a hydrous silicate of magnesium. So are some

forms of asbestos. The difference between these two minerals is not in their chemical composition but rather in their structure, asbestos being fibrous while talc is flaky or granular.

Composition of talc

There is no firm commercial definition for talc. The composition of commercial talc varies with the deposit. Vermont talcs are said to be a granular type of mineral relatively free of asbestos, while California talc contains fibrous silicates, classified as amphibole asbestos.

Talc miners and processors develop a lung disease called talcosis, just as asbestos miners develop asbestosis of the lungs. There is a good deal of similarity between talcosis and asbestosis. In one study¹ older talc workers showed more than four times the expected incidence of lung and pleural cancer. The presence of pleural cancer, or mesotheliomata, is especially revealing, since this particular type of tumor is very rare, and occurs primarily as a result of asbestos inhalation. Autopsies on six talc workers with talcosis showed the presence of the characteristic "asbestos body" in the lungs of every one.² This is a fiber of asbestos, coated with iron-containing protein material, which will give a positive stain for iron.

Up to 30 per cent of various talcs, depending on their points of origin, are classifiable as fibrous silicates, which are largely varieties of amphibole asbestos. *Chrysotile*, the classical form of asbestos, has a fiber more suitable for weaving and has been used in making asbestos caskets, blankets and so forth. *Chrysotile* has recently been found as a contaminant of talc.

However, amphibole asbestos fibers,

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... "the information I collected appeared to support the hypothesis that eating rice coated with asbestos-contaminated talc might contribute to cancer."

which are usually shorter than chrysotile fibers, are no safer. In one study I saw from Holland amphibole asbestos mineral predominated in asbestos bodies in the sputum of a group of men exposed to asbestos and having a high incidence of malignant tumors of the pleura (the membrane that lines the lungs and chest cavity). Moreover, miners of talc that contains more amphibole asbestos than chrysotile have a substantial increase in the incidence of cancer of the lung.

At this point the information I collected appeared to support the hypothesis that eating rice coated with asbestos contaminated talc might contribute to cancer.

The next step in the investigation of the hypothesis was to examine the geographical occurrence. Studies within Japan showed that in prefectures in which rice is the major staple, stomach cancer is higher. It is lower where the population eats heavily of other staples such as soybeans or yams. The death rate from stomach tumors is greater in Japanese who eat rice with every meal than in Japanese who eat it not as frequently.

Finally, the stomach-cancer incidence of Japanese cannot be considered a hereditary or genetic disorder, since as Japanese migrate westward, the incidence of stomach cancer falls. Thus the incidence of stomach cancer among Japanese in Hawaii is greater than among their non-Japanese neighbors, but is roughly only a little over half as much as in Japan.

History of talc coating

The most difficult aspect of the development of this hypothesis was the determination of the nature of the rice currently being eaten in Japan, and the

history of talc coating of rice in Japan. While storekeepers have told me that to their memory, talc-coated rice was customarily eaten in Japan, information directly from official sources in Japan has been slow in coming. When it finally did come it was incomplete and only partially revealing. I have learned that talc-coated rice was the classical form of Japanese rice preparation in the past. However, officially, this has stopped in recent years. The Japanese Ministry of Agriculture and Forestry writes that with enforcement of food sanitation laws in 1947, the addition of talc to rice has stopped. This same Japanese official source indicates that there is no current contamination of rice by talc. I have had five specimens of Japanese rice, imported from Japan or purchased here by visitors, examined for asbestos. Four of these demonstrate no asbestos. However, one specimen of canned cooked rice, currently prepared and cooked in Japan and imported to America from Japan, contains a substantial amount of asbestos, even after the cooking and washing process. Consequently, it would seem that while the use of talc-coated rice in Japan has officially been abandoned, at least one sample of rice from Japan is still currently contaminated with talc.

At the moment, then, the hypothesis remains neither proven nor disproven. With all carcinogens, or co-carcinogens (other substances that work with carcinogens to cause cancer), the period between injury and the development of clinical cancer is always long. In the human being such a period between injury and development of cancer may run up to twenty to thirty years. This is what makes the identification of carcinogens difficult, and why

it took us so long to recognize that smoking causes cancer. The latent period between exposure and development of the cancer is particularly long with asbestos. In one study¹ lung cancer appeared more than twenty years after the beginning of occupational exposure to asbestos inhalation. In another study² the increase of lung cancer first appeared about twenty-five years after first exposure.

Consequently, I expect now, should the hypothesis be correct, that sometime in the future, after the expiration of the latent period necessary for carcinogenesis, cancer of the stomach in Japanese in Japan will begin to decrease. Exactly when this drop occurs will depend on the length of the latent period, and the time when widespread application of talc to rice in Japan stopped.

The value of this hypothesis, then, will be decided by the death rate from cancer of the stomach in Japan in the future. Consequently, the next ten years will tell whether this hypothesis is valid. If the death rate drops, it will be strongly supported. If not, one will then have to conclude that one more seemingly attractive hypothesis on the genesis of a form of cancer will have been disproved. □

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2. ———, C. Gell, J. Macnamowski, and J. Messure. Talc Pneumonomias—a report of six patients with postmortem findings. *Arch Environ Health* 7:101-115, 1963.
3. L. Selikoff, J. Chung, and J. C. Hammond. Asbestos exposure and mesothelioma. *JAMA* 191:22-26, 1964.
4. T. Koos, et al. Mortality from lung cancer and other causes among workers in an asbestos textile factory. *Brit J Indust Med* 17:1-10, 1960.

TITLE: MODIFIED FDA OPTICAL FOR ASBESTOS IN TALC

1. The method is essentially similar to the procedure as outlined by A. E. Schulze and W. V. Eisenberg of the U. S. Food and Drug Administration, Washington, D.C., August 20, 1973. Considerable experience is necessary to obtain a uniformly well-dispersed sample on the slide.
2. Equipment, etc.:
 - A. Leitz Orthoplan Petrographic Microscope.
 - B. Magnification 500X. Resolution is 0.4 micron.⁽¹⁾
 - C. Diameter of field at 500X is 0.350 mm.
 - D. Area of the field at 500X is 0.096mm².
 - E. Area of 100 fields (which are taken at random) is equal to 9.60 mm².
 - F. Use 18 x 18 mm square cover slip over 1 mg of sample. Area of the cover slip is 342 mm².
 - G. For each fiber detected in 100 fields, multiply by 34 for total number of fibers in 1 mg sample.
 - H. If the population of asbestos is heavy, only 5 to 10 fields are necessary for counting which is then extrapolated to the entire sample under the cover glass.
 - I. Use OSHA definition of fiber: 5 microns or greater in length and a length-to-width aspect ratio of at least 3:1.

(1) Note: 500X magnification is recommended rather than the approximately 400X of the original procedure in order to (a) assure Becke Line determination; and (b) field contains fewer particles and is less confusing.

It should be recognized that theoretically we could observe at 500X some fibers which might not be determined at 400X, thus resulting in a slightly higher "asbestos fiber count" than for the same sample observed at 400X.

3. From a petrographic viewpoint, we prefer to go immediately after "culprits" with appropriate index oils rather than the two-slide method as proposed by Schulze and Eisenberg

in which asbestos fibers are counted relative to talc indices of refraction. This method presents too many technical (optical) problems and can be misleading. For example, if sepiolite fibers are present, and using the FDA 1.574 liquid slide, these fibers have to be counted as chrysotile.

4. Be sure the material is essentially talc. Use liquid with n of 1.590 for confirmation and at same time look for apparent gross contamination.
5. The Becke Line is extremely difficult to interpret on fibrous-appearing talc. More often than not, there is disagreement among petrographers in the same laboratory on precisely the same fibrous-appearing talc particle as to whether the Becke Line is moving in or out. With experience, however, the talc particles standing on edge can readily be determined by the relatively high interference order color. Also, in an oil of 1.556 under plane polarized light, the particles will match the oil from an angle of approximately 45° to 80° , but never in the N-S or E-W directions.
6. If not present as large bundles, the most difficult asbestos mineral to determine is chrysotile. The gamma index (X direction) we use is 1.556. Prepare 1 mg slide with 1.556 oil and proceed with determination. Under conditions of crossed Nicols and near maximum light intensity, proceed to look for chrysotile showing maximum interference color at 45° . Now check for parallel extinction. Switch to plane polarized light, reduce the light intensity and iris diaphragm for contrast and check the gamma index. If fiber is chrysotile, it will nearly disappear or show Christiansen effect for gamma index. Rotate the stage 90° to get relative bearing of Alpha index. The fiber should now stand out in high relief with Becke Line going into the oil. Then check for positive elongation.
7. The most common asbestiform amphibole to be associated with talc is tremolite. Prepare 1 mg slide with 1.622 oil (gamma index for tremolite) and proceed with determination (now, all non-tremolitic particles stand out in high relief). Go for tremolite's most characteristic feature which is inclined extinction of about 10° to 14° (gamma index to the Z direction). At position of extinction check for gamma index. If these match, rotate stage 90° to get relative reading of Alpha index which is below 1.622. Confirm tremolite with positive elongation.

8. If Step 7 indicates the presence of amphibole fibers other than tremolite by differences in extinction angle or index of refraction, then these can be determined by routine petrographic methods. Once species is established use same procedure as in (7) (1 mg of sample on slide in a characteristic oil of the mineral for counting purposes) giving due allowance for differences in extinction angle and elongation.

Reported by N. L. Wolkodoff
V. E. Wolkodoff

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Determination of Inapplicability

for

A Regulation Entitled

"Asbestos-Form Particles in Drugs for Parenteral Injection"

The environmental assessment of this action has been accomplished on the basis of a complete Environmental Impact Analysis Report. None of the Department of Health, Education, and Welfare initial criteria were met.



Christopher Schonwalder, Ph.D.
Primary Action Officer

Enclosures:

Environmental Impact Analysis Report
Environmental Assessment Report

ENVIRONMENTAL ASSESSMENT REPORT

A. Summary of the Action

The Food and Drug Administration (FDA), based upon accumulating evidence that parenteral injection of asbestos fibers may be harmful to human health, promulgated proposed regulations on the utilization of asbestos filters on September 23, 1973. These regulations have been modified, are now in final form, and attempt to minimize asbestos contamination in parenteral drugs by: (1) eliminating the use of asbestos filters in the manufacturing process where possible or (2) requiring an appropriate non-asbestos filter downstream of the asbestos filter to maintain a safe and efficacious product. Only with special permission from the appropriate Bureau within the FDA will the utilization of an asbestos filter without such subsequent filtration be permitted.

B. Evaluation

The attached Environmental Impact Analysis Report is complete in that it lists all of the effects likely to occur, and is accurate in that it describes the expected results within the limits of existing knowledge with respect to environmental relationships. The action and secondary effects of the action have been evaluated against the Department of Health, Education, and Welfare initial criteria, and no effects approach these levels of significance. The benefits to human health likely to be derived from this action, therefore, greatly outweigh the slight effects on the environment (the consequences of process changes). All reasonable alternatives to this action do not accomplish the health objectives of the chosen alternatives, nor do they result in less environmental impact.

C. Application of Initial Criteria

1. Natural Resource Use. The regulation does not meet this criterion in that it could not cause a 1% increase in mineral or fuel consumption nationally, due to the small scale of the industry being regulated. Conversely, a slight decrease in total asbestos mined will result from this regulation.

2. Pollution. This regulation does not meet this criterion in that no identifiable increase in ambient air or water pollution will occur from the action or its secondary effects due to the small scale of the section of the industries to be affected by the regulation; nor will any emission standards be violated by any resulting shifts in the filter production industries. Similarly due to the small nature of this action, no identifiable increase in waste or storage will result from the promulgation and implementation of this regulation.

3. Populations. Although this regulation is designed to diminish the possible adverse health effects of asbestos injection, a change in the overall age characteristic of the human population to the extent that requirements for health, education, transportation or welfare services would be altered probably will not occur. Although the number of people receiving parenteral medications in the USA at least once in their lifetime is indubitably quite significant, there is no way to quantify a cause-effect health relationship with the possible presence of asbestos in these medications. Even qualification of effects is subjective, at best. It is hoped that this action will result in a health benefit to a portion of the population receiving injections on a routine basis, but not even the most ardent supporters of limiting regulations would claim that asbestos fibers in parenteral drugs has a definite

demographic significance and that the removal of asbestos fibers from these products would cause human population parameters to noticeably change.

4. Services. The regulation is written in a manner to avoid the possibility of removing an important parenteral product from health services. Therefore, no change in capacity for health services will result.

5. Human Values. No effect on any historical structures or endangered species will result from this regulation, nor will any federal, state or local standards be violated by the regulation's implementation.

D. Recommendation

Whereas this action and the effects of the action do not meet any initial criteria, it is recommended that a Determination of Inapplicability be applied to the promulgation of the regulation entitled, "Asbestos-Form Particles in Drugs for Parenteral Injection."

ENVIRONMENTAL IMPACT ANALYSIS REPORT

1. Proposed Action

a. Purpose of the Action

The proposed action is the promulgation of regulations limiting the use of asbestos and microfibrous glass filters from the parenteral injectable drug and drug ingredient manufacturing processes by means of Food and Drug Administration Good Manufacturing Practices (GMPs) for these industries. The purpose of this action is to minimize the presence of asbestos and glass fibers as contaminants in injected drugs. The deleterious health consequences of injection of large quantities of these types of fibers has been demonstrated in laboratory animals, and thus prudence dictates that human exposure of this nature be minimized. The regulation accompanying this EIAR states that no asbestos containing or micro-fiberglass containing filter can be used in the preparation of parenteral drugs or drug ingredients in human use and allows for a 12 to 18 month period of process adaptation to permit the manufacturer to determine the best substitute for asbestos filtration without sacrifice in product safety or quality. Should no suitable substitute be found, a non-asbestos, non-fibrous glass filter of sufficient pore size will be required downstream of the fibrous filter to remove the fibers of sizes suspected to be the most hazardous. Only upon review and acceptance of submitted evidence that neither of the above procedures results in a safe and effective parenteral drug or drug ingredient will the FDA allow the continuation of present practices utilizing these types of fibrous filters.

b. Environments Affected

The primary environment to be affected by this action will be the environment of humans receiving parenteral drugs. Secondary affects of this action will be alterations in the demands for asbestos and non-asbestos filters and the raw materials for the production of these products.

2. Probable Impact of the Action on the Environment

a. Human Exposure

The environment of an organism can be defined as all external substances and forces which impinge upon that organism and thereby affect his existence. Therefore, the environment of patients receiving parenteral drugs includes the materials in those particular drugs, including the active ingredient, the solvent, salts, buffering agents, stabilizers, and impurities. This regulation is designed to eliminate or minimize the fibrous impurities in these drugs, as there are inferences from inhalation exposure to asbestos and from experiments in laboratory animals which imply that the parenteral administration of asbestos in humans can cause fibrosis and tumors. A "state of the art" review of the hazards of exposure to asbestos fibers was written for the preamble of the proposed regulations and is attached to this EIA as Appendix I (General Background).

The impact of this action would be to minimize the human exposure to injected asbestos fibers which may have a deleterious effect on both the directly exposed tissues and respiratory tissues subsequent to circulation. There is no acceptable method of extrapolating the present data on experimental animals to man in a quantitative manner, but this regulatory action is the

result of a prudent analysis of the risks, benefits and analytical techniques associated with the inhalation, ingestion and parenteral administration of asbestos fibers. The major environmental effect will be a reduction in exposure of humans to fibrogenic and tumorigenic materials, and will contribute to an unquantifiable reduction in incidence of these pathological occurrences.

b. Effects on Raw Materials Utilization

The National Association of Filter Material Manufacturers has informed us that at least ten grades of filter sheets or pads are provided by the asbestos filter industry and that these filters vary in asbestos content from 5-40%. The other basic ingredient is cellulose wood pulp. Approximately 40 million pieces of asbestos filter material are produced annually of which 6 million pieces go to parenteral or injectable drug producers. These items are typically smaller than those provided to other users, such as commercial beverage producers, and therefore, an estimate of 40 tons of asbestos and 80 tons of cellulose wood pulp (of the total 400 tons asbestos and 1,600 tons of cellulose wood pulp used by the asbestos filter manufacturers) are required to produce the filters which are subject to this regulation.

The 1973 Bureau of Mines Minerals Yearbook lists apparent United States annual consumption of asbestos at 876,147 tons. The EPA, in correspondence accompanying their proposed standards for effluent guidelines for the pulp, paper and paperboard industries, has estimated that about 50 million tons of pulp were produced in the United States in 1973. Therefore, the asbestos demand for parenteral filter production is 0.0045% of the U. S. asbestos production. The amount of cellulose wood pulp required for this

production of the regulated filters is likewise insignificant (0.00016% of U. S. production).

Cellulose acetate or nitrate "membrane" filters are the most likely substitutes for asbestos filters. Roughly 90 percent of the U. S. production of these products is done by Millipore, Inc. and by the Gelman Company. These firms have provided information on their raw materials utilization and estimated market sizes which demonstrates the insignificance of increases in demand for natural resources, even assuming complete substitution of asbestos filters by membranes. The estimates are as follows:

At most, the regulations will increase the consumption of cellulosic materials by less than 130,000 lbs/year. These materials are derived from wood pulp (50 million tons produced in the U. S. in 1973) and are processed with a number of organic solvents (petroleum derivatives, alcohols, ketones). The precise identities of these solvents are confidential to these firms, but it can be estimated that if the regulation resulted in the replacement of all six million asbestos filters used annually, a maximum of one million pounds of solvents would be required to produce the membrane substitutes.

The 1973 U. S. production figures on common solvents have been provided by the U. S. Tariff Commission as follows:

	<u>Million lbs. produced</u>		<u>Million lbs. produced</u>
Methanol	7,064	Benzene	28,000
Isopropanol	1,635	Cyclohexane	2,122
Acetone	1,995		

Therefore, increased demand for solvents resulting from this regulation will amount to fractions of percents, even in the unlikely case of 100% conversion to cellulose acetate filters by the parenteral product industry. The actual conversion figures will depend on the success of process modifications.

3. Probable Adverse Effects Which Cannot be Avoided

The adverse effects of this action which cannot be avoided are minimal. The production of non-asbestos filters will of necessity increase. This will result in a shift in raw materials utilization from asbestos to cellulose and water-based solvents. The magnitude of these effects was discussed in the previous section.

4. Alternatives to the Proposed Action

a. Different Regulations

(1) A ban on the use of asbestos filters in the process of parenteral drug and drug ingredients without the phase-in period and without the allowances for the use of asbestos filters with subsequent downstream filtration, should the scientific filters sacrifice product quality, would result in the loss of a number of medically important parenterally administered materials. Asbestos filters are unique in their filtration properties in that the fibrous mesh can remove large proteins and other pyrogens without the rapid decline in filtering capacity associated with conventional surface filters. This "depth filtration" has been responsible for the successful purification of many blood fractionation products. It is not the intent of this regulation to remove all asbestos fibers from parenteral drugs, no matter what the cost. The loss of a lifesaving parenterals due to difficulties in adapting non-asbestos filters to the production scheme should be avoided.

(2) A regulation based on asbestos particle count rather than process requirements is not a viable option at this time due to the uncertainties

in predicting dose-response with carcinogenic materials and due to difficulties in quantification methodologies presently associated with asbestos fiber counting. Electron microscopy for both qualitative and quantitative fiber determination is a time-consuming, expensive technique requiring well-trained technicians for both measurement and interpretation. Even then, results are often capricious. Thus, the lack of standard methodologies for analyses precludes the promulgation of regulations based on fiber count in the product.

b. No Action

The "no action" alternative would allow the present use of asbestos filters in the manufacture of parenteral drug and drug ingredients to continue unrestricted. Although it has been argued that asbestos fibers are ubiquitous in the environment and that man has always been exposed to a background of asbestos in his air and water, we see a significant difference between this natural background and the presence of asbestos contamination in materials administered by subcutaneous, intravenous or intramuscular injection. These administration routes circumvent the natural barriers to internal contamination and have proven pathogenic in laboratory animal studies. Therefore, this alternative was rejected for an alternative which attempts to minimize the public's exposure to parenterally administered asbestos.

5. This action will not affect local, short-term use of the environment nor long-term productivity as the magnitude of resource use is negligible in comparison with other industrial activities.

6. Irreversible, irretrievable commitment of natural resources resulting from this action will be negligible due to the minor nature of the industries affected, as discussed in section 2(b).

7. All known objections to this regulation, as proposed, are discussed in the final regulation itself. The reader is referred to this document.

8. The Cost-Benefit Considerations of these Actions are Listed Below

a. Costs

The costs to the drug manufacturing industry of this regulation will not be prohibitive. No comments on the proposed regulation from the drug industry, directly or through trade associations, claimed that the cost of process modification for parenteral drug production would cause hardships. However, several vociferous communications from asbestos filter manufacturers indicate a fear of a significant loss in business.

b. Benefits

The benefit from this action is solely in the human health area. The minimization of public exposure to parenterally administered asbestos fibers is expected to have a positive long-term effect on public health, as discussed in previous sections of this EIAR.

APPENDIX I

GENERAL BACKGROUND

"Asbestos" is a generic term for a number of hydrated silicates that, when crushed or processed, separate into flexible fibers made up of fibrils. Although there are many asbestos minerals, only six are of commercial importance. Chrysotile, a tubular serpentine mineral, accounts for 95 percent of the world's production. The others, all amphiboles (crystals with three groups of metal ions), are amosite, crocidolite, anthophyllite, tremolite and actinolite. These asbestos minerals differ in their metallic elemental content, range of fiber diameters, flexibility, harshness, tensile strength, surface properties, and other attributes that determine their industrial uses and which may affect their respirability, deposition, retention, translocation and biologic reactivity (Ref. 1).

Many products such as cement, flooring, shingles, pipes, filters, textiles, etc. contain asbestos of one kind or another. There are great variations among such products with respect to the chances of fiber release during the use of the product. The likelihood of such fiber release depends predominantly on the ease with which the fibers can be dislodged and on the degree to which the use of the product destroys the fibers. Almost all asbestos fiber used in the United States for manufacturing products becomes tightly bound within the products and usually undergoes little actual abrasion or wear before being discarded. Asbestos cement products (accounting for most of the asbestos used in the United States), shingles and floor tiles are in this category. Some asbestos-containing products, such as brake linings, are subjected to great friction; their rate of wear is considerable, and at times they are almost completely worn away. In the case of brake linings, the application

of force is so intense and the heat created so great that most chrysotile fibers are destroyed by being converted into another substance which is non-fibrous. Nevertheless, an appreciable percentage (1 to 3 percent) remains as fibrous asbestos, and fiber release from products such as asbestos cloth, paper and sprayed fireproofing materials is a serious source of emission. This usually occurs in densely populated areas. Most of the pipes delivering drinking water are of a mixture of cement and asbestos.

Solid wastes produced during manufacture of asbestos-containing products, use of such products, and demolition can be emission sources. These waste materials are usually disposed of without regard to their potential as emission sources. Alternate methods of disposal often result in commingling of asbestos-containing wastes with municipal wastes in open dumps and thus create a long-term emission source.

Asbestos fibers thus are ubiquitous in air, water and a large percentage of the earth's crust. The amount of this material which additionally is added to the environment and to food and drugs by the use of asbestos filters is not known. Therefore, it is obvious that the presence of asbestos in these products is only one small source of exposure.

Asbestos inhalation has been known to be an occupational hazard in workers in asbestos mines. The asbestos is inhaled and lodges in the lungs causing the development of a fibrotic disease known as "asbestosis." Asbestosis, or abestotic pneumoconiosis, was the first clearly demonstrated adverse effect of asbestos in man. It is characterized by a pattern or roentgenographic changes in the lung consistent with diffuse interstitial fibrosis of variable degree and at times with fibrosis and calcification of the pleura; clinical

changes that include fine rales, finger clubbing and shortness of breath, each of which may be absent in an individual case; and physiologic changes consistent with a restrictive lung disorder (Refs. 2 through 8).

In these workers in asbestos mines, malignancies of the lung and of the body lining tissues, namely lung cancer and mesothelioma, occur at rates greater than in persons not so occupationally exposed. There is a 5 to 7 fold increase in lung cancer in asbestos workers which is noted as early as 10 to 14 years after onset of exposure and is significant at 20 years (Refs. 9 through 15). Seven percent of deaths in asbestos workers are caused by pleural and peritoneal mesothelioma (Refs. 16 through 33). This is a marked increase since this tumor is extremely rare in the general population. There is suggestive evidence concerning an increase in the rate of gastrointestinal malignancies in asbestos workers (Ref. 34).

There is considerable evidence that most human lungs harbor thousands or millions of asbestos fibers although most people do not have asbestosis (Refs. 35 through 37). This is due to the ubiquity of the substance. Some of these fibers are chrysotile asbestos, and amphiboles are probably present also. This number of fibers is relatively small in most persons not occupationally exposed to asbestos compared with the numbers found in the occupationally exposed. The systematic application of quantitative techniques, measuring both coated and uncoated fibers, is needed to define a gradient of accumulated fibers for correlation with incidence of disease, on the one hand, and history of environmental exposure, on the other.

The methodology for quantification of asbestos fibers of varying sizes is such that the results obtained in one laboratory may vary substantially

from those in another. An inter-agency governmental task force together with other scientists working in this field is currently attempting to develop standard technology which can be applied to the identification and qualification of asbestos fibers. The Environmental Protection Agency is currently investigating four separate techniques in order to establish the best method for identification, quantification, sizing and typing of asbestos particles and fibers. At present, the National Institute for Occupational Safety and Health (NIOSH) recommends, as a technique for sampling of air, a method based on counting fibers greater than 5 microns in length using phase contract illumination at 430x magnification with a 4 millimeter objective (Refs. 38 and 39). This technique is currently recommended for liquid materials until more accurate and sensitive practical methods are developed. Similarly, difficulties exist with other methods proposed for analysis of asbestos fibers in a material such as talc.

The evidence concerning the possible hazard from ingestion of asbestos particles is contradictory and inconclusive.

In an unpublished study by L. M. Swinburn (Ref. 40), asbestos particles were fed once a week to SPF Wistar rats for 16 and 18 weeks. The material was administered in butter. Although the particles were of the size range known to produce tumors by other modes of administration, no tumorigenic effect was noted. With a single large dose, the fibers were totally cleared by the gastrointestinal tract in 48 hours and no asbestos was detected in the animal tissues at the end of 1 week. The gastrointestinal tract of the rat seemed to provide an effective barrier to penetration.

In a published study by W. E. Smith et al. (Ref. 41), hamsters maintained on a diet of 1 percent chrysotile or amosite through life had no gastrointestinal tumors.

A report by Westlake, Spjut and Smith (Ref. 42) indicates that the rat colonic mucosa is penetrated by chrysotile after feeding a diet containing 5 percent asbestos for 3 months.

Cunningham and Pontefract (Ref. 43 and 44) injected chrysotile fibers (9.4 and 94×10^9) directly into stomachs of rats. Fibers were found in blood and other organs 2-4 days after treatment. Control rats, although having no asbestos in blood, also had high levels of asbestos in tissues.

These workers found that, whereas the tap water in Ottawa (having a filter plant) contained about 2 million fibers per liter, the quality of fibers in soft drinks and alcoholic beverages purchased in the Ottawa area ranged from 1 to 12 million fibers per liter. Even with the technical problems of methodology, this seems to indicate that in some beverages the asbestos content may be about the same as in water, whereas, in others, it may be increased. Thus, it is reasonable to conclude that water and many other beverages for human consumption contain substantial amounts of asbestos fibers.

There is some evidence that asbestos filters may remove some asbestos material. In a preliminary experiment performed by the Food and Drug Administration, asbestos was added to distilled water and dispersed evenly by the action of an ultrasonic generator. Electron microscopy of this material clearly showed large numbers of asbestos fibers. This material was then filtered through an asbestos filter, and electron microscopic examination of the filtered material showed a reduction in the number of asbestos fibers.

Nicholson and his colleagues (Ref. 45) investigated a number of samples of parenteral drugs and found asbestos fibers. Based on their report a study was undertaken by the Food and Drug Administration concerning contamination of parenteral drugs with asbestos. Although the data are still preliminary, the following observations are pertinent. Parenteral drug samples were collected from a number of firms. Based on phase contrast microscopy, 11 of 13 samples had clear-cut evidence of the presence of asbestos, one sample was questionably positive, and one was negative. The number of fibers ranged from 2 to 27 in the positive specimens of variable sample size. Using electron microscopy, 12 of the 12 samples examined were positive. Quantitation is not yet complete.

In this survey, seven of 13 manufacturers of parenteral drugs do not use asbestos filters; four firms use such filters followed by final membrane type filters (one of these uses asbestos filters for its rinse water without final filtration of such water); and two firms use asbestos filters only for their rinse water, without final filtration.

The preliminary report of these studies is on display at the Office of the Hearing Clerk. Any other scientific data in this regard should be submitted to the Hearing Clerk.

Certain parenteral drugs, such as blood fractionation products, may be filtered several times through asbestos filters. Thus far, it is not known with certainty whether the more viscous products could be successfully processed through terminal membrane filters without compromising safety, identity, strength, quality or purity. The precise effect of asbestos pad filtration on

removal of pyrogens (Ref. 46 and 47) is not completely known at the present time. Currently, the Food and Drug Administration is surveying the industry for information concerning the use of asbestos filters. Results of this survey will be incorporated in the public record.

Although the major experimental studies of asbestos have involved inhalation of fibers so as to simulate occupational exposure, several studies have been performed to investigate the effect of parenteral inoculation of asbestos fibers. In 1958, Schmahl (Ref. 48) reported that implantation of asbestos fibers and crumbs in either the subcutaneous tissue or in the peritoneum lead to the development of malignant tumors (sarcomas) in 11 of 30 rats which survived longer than 15 months after such implantation. Roe and his colleagues (Ref. 49, 50, 51) have performed a number of studies in which asbestos fibers were injected subcutaneously (Ref. 49) into the flanks of mice. In the first experiments, crocidolite, amosite and chrysotile asbestos fibers were used and each animal was injected twice subcutaneously in both flanks with 10 milligrams of fibers in saline with an interval of five weeks between the injections. Seven of seventy-one mice which survived 40 weeks or more developed injection site tumors. In addition, one mouse developed a mesothelioma of the peritoneum underlying the injection site. The injection site sarcomas were produced by all three types of fibers. In addition, Roe et al. (Ref. 49) showed that the asbestos fibers were widely disseminated from the local injection sites being deposited rather selectively on the serosal surfaces of the abdominal organs and the retroperitoneal structures as well as on the pericardium, diaphragm, pleura and adjacent parts of the lungs and heart. These serosal surfaces reacted

vigorously to the presence of the asbestos fibers and in 10 of 71 mice, malignant mesotheliomas of the thorax and/or abdomen developed. In a later study (Ref. 51) Kanazawa et al. showed that, after subcutaneous injection of asbestos fibers in mice, fibers could be found to have disseminated to regional and distant lymph nodes, spleen, kidneys and occasionally to brain tissue suggesting that some asbestos may enter the circulation.

Thus, there is experimental evidence that parenteral administration of asbestos fibers may lead to wide dissemination of such fibers in animals and to the development of local malignant tumors as well as malignant mesotheliomas of the pleura and peritoneum similar to those that occur after inhalation of asbestos fibers.

The problem of asbestos in the total environment, to which the worldwide scientific community is addressing itself, is very complex. The Environmental Protection Agency has published in the Federal Register of April 6, 1973 (38 FR 8820) national emission standards for asbestos milling and manufacturing based on the determination that asbestos is a hazardous air pollutant. This standard has been developed despite the fact the EPA also recognizes that a "standardized reference method has not been developed to quantitatively determine the content of asbestos in a material."

The present status of this problem is summarized by the report of a committee prepared subsequent to a meeting sponsored by the International Agency for Research on Cancer (Ref. 52). The Food and Drug Administration's review of this report indicates the following areas of further research are necessary:

- (1) Further epidemiology, particularly with respect to past exposure to asbestos and cancer of sites other than lung, pleura, and peritoneum.

(a) Assessment of excess cancer risks following exposure to only one type of fiber.

(b) Investigation of whether reduction of asbestos exposure in lungs below those causing asbestosis abolishes excess risk of carcinoma.

(c) Investigation of evidence of an increased risk of cancer resulting from asbestos in water, beverages, food, or liquids used for the administration of drugs.

(2) Development of methods of quantitative assessment, size analysis and characterization of particles and fibers.

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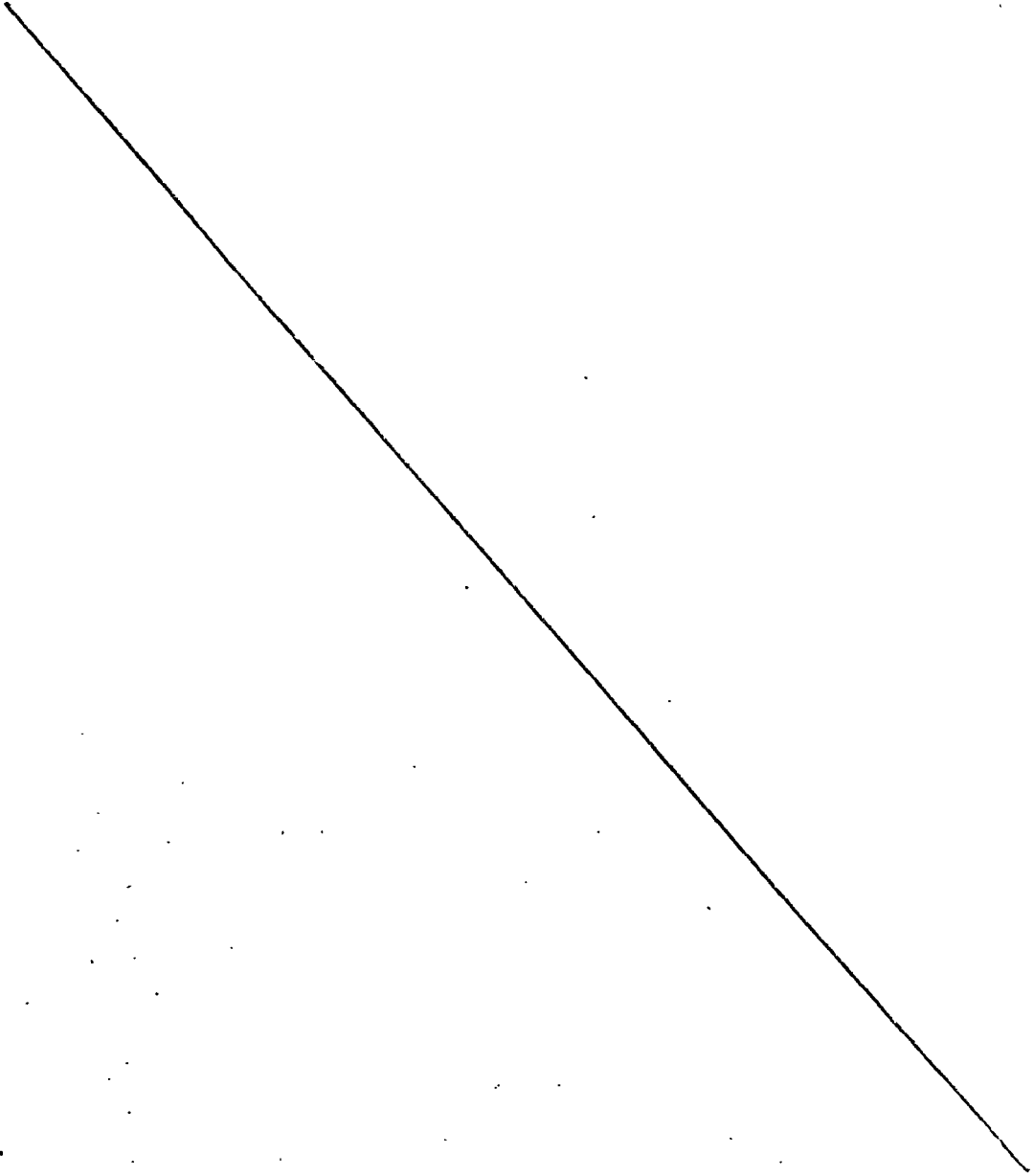
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MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Dr. Christopher O. Schonwalder
Office of Environmental Quality, FDA
HFS-30

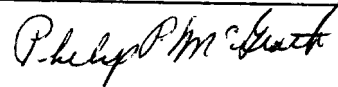
DATE: June 21, 1974

FROM : Philip P. McGrath, Electron Microscope Branch
Division of Pathology, Bureau of Biologics, FDA - HFB-400

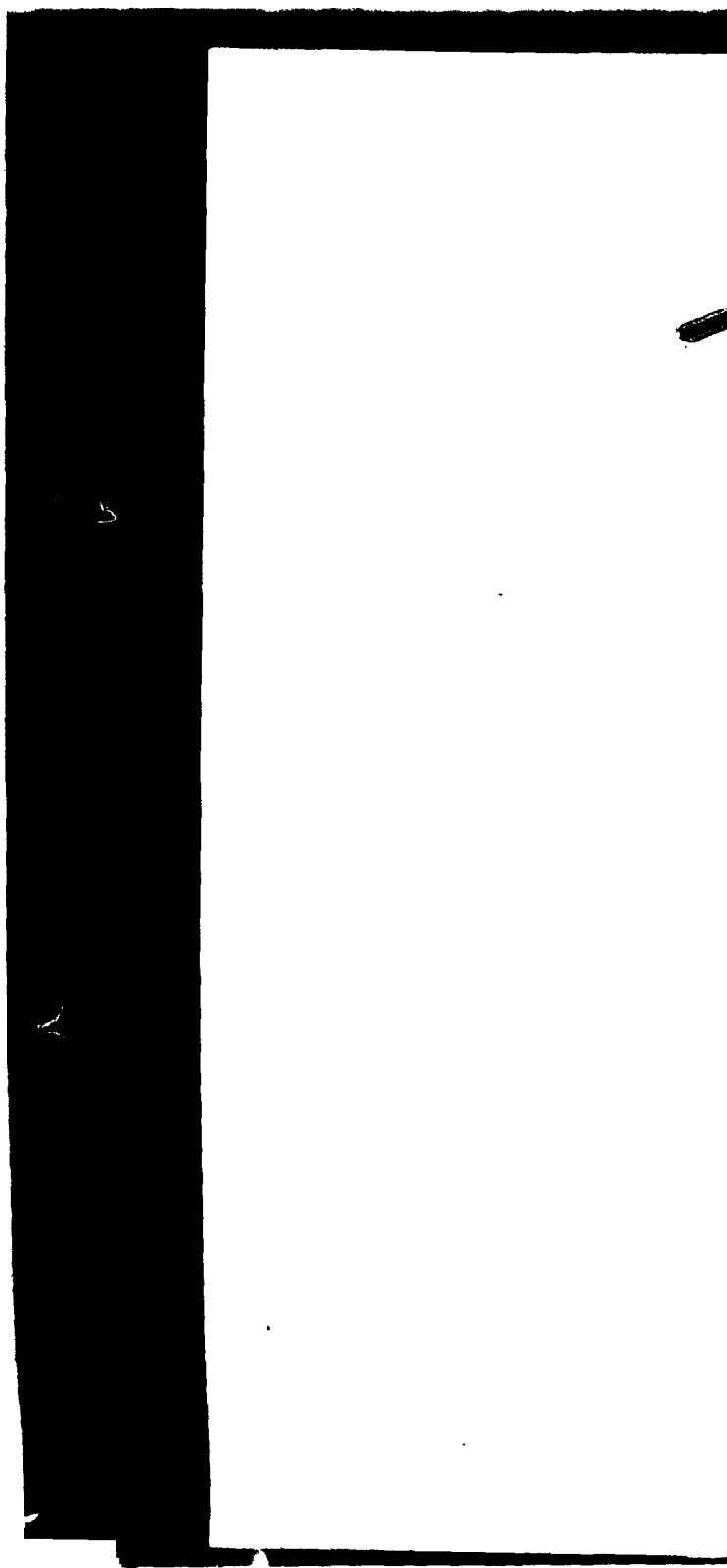
SUBJECT: Asbestos fibers in filtered, deionized water after passage through an asbestos filter pad

In response to your telephone request of June 6, 1974 for information concerning the release of asbestos fibers or fibrils by asbestos filter pads during the filtering process, we performed the following test: membrane filtered deionized water was filtered through an asbestos filter pad housed in a metal filter holder, see attached protocol. Examination of the filtrate in the transmission electron microscope revealed fibers and fibrils of varying sizes in 7 of 20 grid squares on one carbon coated grid containing a 5 microliter drop of the filtrate. Figures 1 and 2. A second grid examined had a similar distribution of asbestos fibers. Examination of filtered deionized water on carbon coated grids showed no asbestos fibers.

Philip P. McGrath



1. 3000 milliliters of filtered deionized water was filtered through a Millipore membrane filter with a pore size of 0.2 microns. The flask used to receive the filtered water was rinsed with filtered, deionized water.
2. A metal Seitz filter holder from the Republic Seitz Filter Company was carefully rinsed with filtered deionized water and a D-10 Steriflo asbestos filter pad from F. R. Harmon and Co., Milldale, Conn. was clamped in the metal Seitz filter holder.
3. Fifty milliliters of filtered deionized water was filtered through an asbestos pad in the metal holder using house vacuum at a negative pressure of twenty to twenty-five inches of mercury. This first filtrate was discarded.
4. Ten more milliliters of filtered deionized water was filtered through the same asbestos filter pad using house vacuum at a negative pressure of 20 to 25 inches of mercury. The water was filtered into a 700 milliliter erlenmeyer flask which had been rinsed with filtered, deionized water to reduce possible contamination with background asbestos fibers.
5. Five microliter drops of the filtrate were placed directly on carbon film supported on a 300 mesh copper electron microscope grids and examined in the electron microscope.
6. Two grids were examined. In one grid, 7 of 20 grid squares examined contained crysotile asbestos fibers. The second grid had a similar distribution of fibers. Figures 1 and 2 are representative photographs of the fibers seen in the first grid.
7. Carbon film grids or carbon film grids containing five microliter drops of filtered, deionized water were examined as controls. No asbestos fibers were seen in these controls.



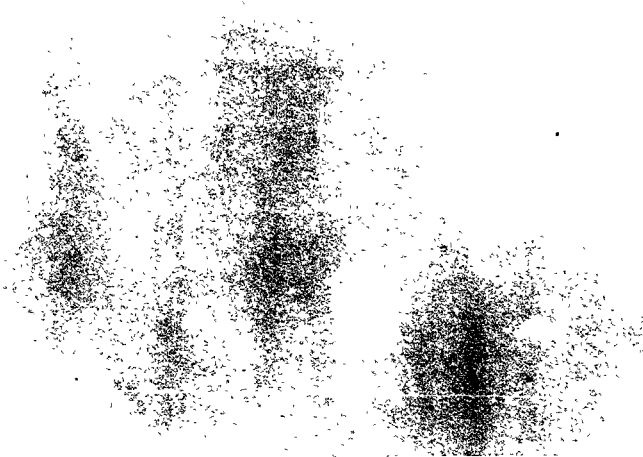


Figure 2

Crysotile asbestos fiber particles
introduced into filtered distilled
water during passage through an as-
bestos filter pad.
Magnification: 68,000

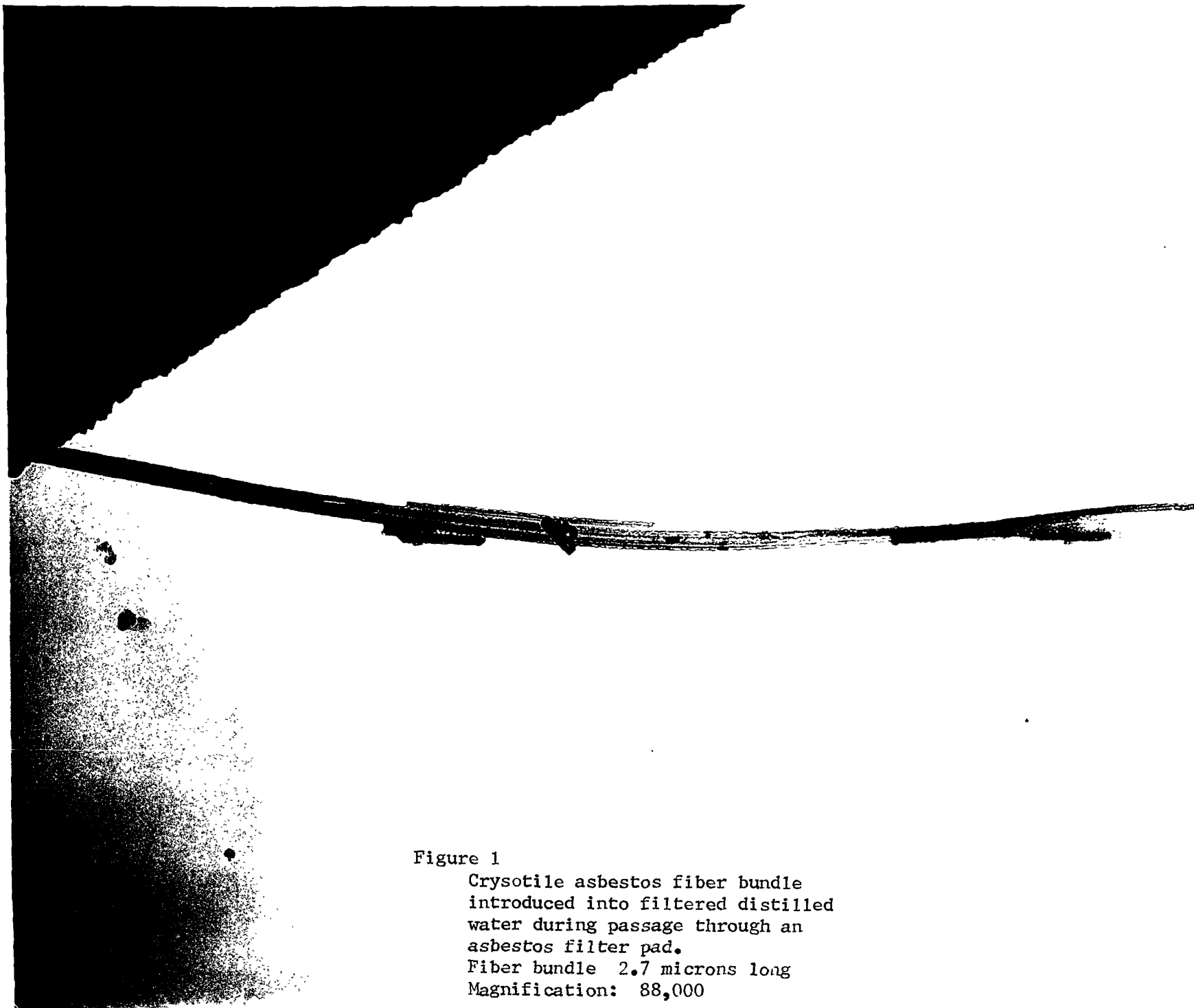


Figure 1

Crysofile asbestos fiber bundle
introduced into filtered distilled
water during passage through an
asbestos filter pad.

Fiber bundle 2.7 microns long

Magnification: 88,000