DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

CERTIFICATE

Pursuant to the provisions of Rule 44 of the Federal Rules of Civil Procedure, I hereby certify that, John Wright, Division of Dockets Management, United States Food and Drug Administration, whose affidavit is attached, has custody of official records of the United States Food and Drug Administration.

In witness whereof, I have, pursuant to the provision of Title 42, United States Code, Section 3505, and FDA Staff Manual Guide 1410.23(1)(A)(6)(b), hereto set my hand and caused the seal of the Department of Health and Human Services to be affixed this 4th day of December, 2015.

Dynna Bigby,
Supervisory Administrative Proceedings Officer
Division of Dockets Management
FDA/Office of the Executive Secretariat (OES)

By direction of the Secretary of
Health and Human Services

DEFENDANT'S EXHIBIT
D-7214

Food and Drug Administration
Rockville MD 20857

AFFIDAVIT

John G. Wright, first duly sworn, deposes, and says:

1. I am, Administrative Proceedings Specialist, Division of Dockets Management, Office of Management, United States Food and Drug Administration.

2. In this capacity I have custody of official records of the United States Food and Drug Administration.

3. Enclosed is a reproduced certified copy of documents requested by LexisNexis CourtLink classified by the FDA as FOIA Request 2015-9061.

4. Copies of the administrative record are part of the official records of the United States Food and Drug Administration.

John G. Wright, JD

County of Montgomery
State of Maryland

Subscribed and sworn to before me this 4th day of December, 2015

Yatta Florence Yarjah, Notary Public
My Commission Expires 4/16/2018

JUL 11 1986

1986 JUL 21 PM 3:00

Phillippe Douillet
One Holyoke Lane
Stony Brook, New York 11790

Re: Docket No. 83P-0404

Dear Mr. Douillet:

This responds to your November 8, 1983, petition requesting that cosmetic talc be labeled with an asbestos warning statement, information on asbestos particle size, and the proportion of talc impurities in the product.

You assert that, because the mining of talc almost invariably includes the mining of asbestos as well, cosmetic talc may contain significant amounts of asbestos particles that present an inhalation hazard to humans. Also, you cite references to substantiate that significant amounts of asbestos have been found in commercial talc samples, that asbestos inhalation is hazardous to humans, and that asbestos contaminants in talc will produce toxicological responses when inhaled.

FDA recognizes that asbestos inhalation over extended periods is hazardous to humans. The agency is also aware that some cosmetic talc produced in the 1960s and early 1970s did contain asbestiform minerals. However, your petition has not persuaded us that the cosmetic talc that is presently being produced contains significant amounts of asbestiform minerals.

During the early 1970s, FDA became concerned about the possibility that cosmetic talc did contain significant amounts of this material. The agency received several reports about such contamination. However, at that time, the analytical procedures for determining asbestos in talc were not fully developed, and most of the analytical work was conducted without scientific agreement as to which methods were well-suited for the identification of asbestiform minerals in talc. Consequently, FDA considered all analytical results to be of questionable reliability. This assessment proved to be correct because many questions were subsequently raised about results reported in the literature in the early 1970s (see enclosed copy of National Bureau of Standards Special Publication 506 entitled "Misidentification of Asbestos in Talc"). Because of the questionable nature of the analytical results, the agency was not able to assess reliably the levels of asbestiform minerals in cosmetic talc then in the marketplace.

83P-0404

PDN1

Under these circumstances, FDA decided that the most appropriate actions that it could take to protect the public health would be to make the reports public and to request assistance from the affected industry in developing acceptable analytical procedures. This approach apparently has led to considerable improvement in the quality of this talc.

After FDA took these actions, many cosmetic manufacturers began to analyze their talc for asbestiform minerals as part of their quality control programs, and talc suppliers began to sell higher purity talcs to the cosmetic industry. By 1976, asbestos analytical methodology was sufficiently developed that the Cosmetic, Toiletry, and Fragrance Association (CTFA) could issue a specification (copy enclosed) for cosmetic talc. This specification required that such talc be free of fibrous amphibole (e.g., asbestos in the form of asbestiform tremolite) using a CTFA method of analysis that is capable of detecting 0.5 percent of amphibole asbestos. This specification contributed to the continued improvement of cosmetic talc quality.

In addition, FDA surveillance activities that were conducted in the latter portion of the 1970s showed that the quality of cosmetic talc had significantly improved, and that even when asbestos was present, the levels were so low that no health hazard existed. Our scientists recently reviewed data from these surveillance activities and concluded that the risk from a worst-case estimate of exposure to asbestos from cosmetic talc would be less than the risk from environmental background levels of exposure to asbestos (non-occupational exposure) over a lifetime.

Consequently, we find that there is no basis at this time for the agency to conclude that there is a health hazard attributable to asbestos in cosmetic talc. Without evidence of such a hazard, the agency concludes that there is no need to require a warning label on cosmetic talc.

FDA should also point out that, in reviewing your petition, we found several problems with the information on which you relied. The publication "Asbestiform Impurities in Commercial Talcum Powders," which you cite in your petition, appears to contain a number of significant errors that lead us to question the accuracy of the findings that were reported. For your information, we have enclosed a copy of a June 8, 1973, rebuttal of this publication that was written by the Chief Mineralogist of the Colorado School of Mines Research Institute in Golden, Colorado. Also, your petition's 1978 book reference to the Mt. Sinai School of Medicine findings is too old to reflect present contamination levels. Further, we are not convinced that the Mt. Sinai findings pertained to cosmetic talc. Your reference states that common commercial talcs were analyzed, but it does not specify whether these commercial talcs were industrial grade or cosmetic talc.

For all of these reasons, your petition is denied. This denial is without prejudice to the future filing of a petition on this matter, accompanied by all relevant data in support of the petition.

Sincerely yours,

/s/ J. W. Swanson

Acting Associate Commissioner
for Regulatory Affairs

Enclosures

cc: HFC-1
HFC-200 (#G-86-182)
HFC-220 (Rogers/file)
HFF-1
HFF-100
HFF-152
HFF-300
HFF-302
HFF-310
HFF-440
GCF-1 (Horton/Derfler)
HFA-224
HFA-305

Prepared:JRTaylor:5/15/86
Initialled:JRTaylor:5/15/86, 6/5/86
EJCampbell:5/15/86, 6/5/86
HJEiermann:5/16/86, 6/9/86
JAWerninger:5/19/86
WGFlamm:5/29/86, 6/9/86
IRLake:5/29/86, 6/12/86
RJLenahan:5/29/86, 6/10/86
LBBrock:6/10/86
RWGill:6/12/86
F/T:JRTaylor:sag:6/4/86
Concurred:EBrisson:6/27/86
Retype:RLSpencer:cdk:6/27/86:disk 26 (#1.32)
Revised:PSDerfler:7/3/86
Retype:RLSpencer:cdk:7/7/86
Concurred:PDerfler:7/8/86
Revised:Concurred:LHorton:7:9/86
F/T:RLSpencer:bka:7/10/86

COSMETIC TALC

CTFA Adopted Name:
TALC

DEFINITION: Cosmetic Talc is an essentially white, odorless, fine powder, ground from naturally occurring rock ore. It consists typically of 90% hydrated magnesium silicate, having the ideal formula $Mg_6[Si_8O_{20}](OH)_4$, with the remainder consisting of naturally associated minerals such as calcite, chlorite, dolomite, kaolin and magnesite, and containing no detectable fibrous, asbestos minerals.

TEST	SPECIFICATION	METHOD
Color	As specified by the buyer and showing no change after heating	Heat 1 to 2 g at 200°C for 5 minutes
Odor	As specified by the buyer	
Identification	Positive: 1. Close match to CTFA Spectrum—IR with no indication of foreign materials *OR* 2. (Alternate) Close match to X-ray Powder Diffraction File No. 19-770, published by ASTM, showing the most intense reflections at d values about 9.35, 1.53 and 4.59 Å	CTFA G 3-1 ASTM D 934-74
Slip	As specified by the buyer	
Lustre	Do.	
Water-Soluble Iron	Passes test	USP XIX, page 487
Screen Test	100% through 100 mesh 98% minimum through 200 mesh Finer grades: as specified by the buyer	CTFA C 6-1
Water Soluble Substances	0.1% maximum	USP XIX, page 487 See test for "Reaction and Soluble Substances"
Acid Soluble Substances	As specified by the buyer 6.0% maximum	CTFA E 32-1
Loss of Ignition	5.0% maximum	USP XIX, page 487
Arsenic (as As)	3 ppm maximum	CTFA F 1-1, Parts I-A and II
Lead (as Pb)	20 ppm maximum	CTFA F 2-1, Parts I-A and II
Fibrous Amphibole (Asbestiform Tremolite et al)	None detected	CTFA J 4-1
Free Crystalline Silica (Quartz)	As specified by the buyer	CTFA J 5-1 (DTA) Alternate: CTFA J 6-1 (X-ray)

* * * * *

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National Bureau of Standards Special Publication 506. Proceedings of the Workshop Asbestos: Definitions and Measurement Methods held at NBS, Gaithersburg, MD, July 18- 1977. (Issued November 1978)

MISIDENTIFICATION OF ASBESTOS IN TALC

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Abstract

Both optical microscopy and x-ray diffraction (XRD) are widely used to detect minerals associated with talc. Optical microscopy can determine the morphology of a particle, but cannot always fully identify the specific mineral. Although XRD is an excellent screening technique for the detection of minerals associated with talc, the method can misidentify minerals due to interferences, interpretive errors, and the inability to determine morphology.

Methods for reduction or elimination of these problems include special techniques of sample preparation and x-ray diffraction, combined with microscopic examination (both optical and electron).

Key Words: Amphiboles; asbestos; chlorite; electron microscopy; fiber; morphology; optical microscopy; x-ray diffraction; talc.

Introduction

There are many ways to analyze and study any naturally occurring material. The conclusions reached will often vary widely depending on the expertise and specific interest of the investigator. That situation sums up the present status of "asbestos"; it is also the status of minerals which are associated with "asbestos"; and it is becoming the status of other minerals which can be naturally associated with talc.

Popular methods of analysis can give the wrong answer – namely that asbestos is present when it certainly is not. That problem (misidentification) is not so much one of limitations of the methods, but rather one of misinterpretation of data, and failure to recognize the mineralogical background required to certify mineral purity, for example, when analyzing sheet silicates for asbestos. Unfortunately, one main factor is that asbestos has now developed variable definitions, depending on whether the point of view is mineralogical, industrial, medical, or regulatory. The medical definition is most concerned with whether or not the particles are biologically active; the industrial definition is dependent upon flexibility and weavability; the mineralogical definition upon crystallography; and the regulatory definition upon size and aspect ratio.

The word "asbestos" stems from ancient Greek and has always referred to a very fibrous industrial mineral product. Since asbestos has historically related to a mineral exploited as an important industrial commodity, we think a combined mineralogical and industrial definition should take precedence [1,2][1]. Other presentations during this

[1]Figures in brackets indicate the literature references at the end of this paper.

workshop have amply covered the aspects of asbestos terminology, and it is not our intent to provide comprehensive coverage of that subject. Our primary objective is to review some of the basic principles of analysis, and to point out problem areas where identification of "asbestos" has been abused.

Analysis Methods and Misidentification of Asbestos

It is useful to categorize the various analytical methods which have been applied to talc to highlight inherent principles which lead to misidentifying asbestos as being present. We offer the following general comments on the three principle determinative properties (chemical composition, morphology, structure).

Chemical Composition

It is well known that every mineral has a specific chemical composition, and that each mineral has an ideal theoretical chemical formula (configuration). Unfortunately, many investigators overlook the fundamental point that chemical composition does not identify a specific mineral. A simple example will bring that point into focus:

> A pearl, an oyster shell, a slab of marble, a piece of chalk, and the minerals aragonite and calcite are obviously different materials, and yet each will be identified as calcium carbonate. That is to say, chemical analyses will identify them all as the same substance, where everyone knows that a pearl is not a piece of chalk.

The same situation exists in certain phases of asbestos analysis. For example, chrysotile, antigorite, lizardite, sepiolite, chlorite, and talc are all hydrous magnesium silicates. But a Meerschaum pipe (sepiolite) is certainly not chrysotile asbestos in spite of the fact that chemical analysis alone could lead to that misidentification.

Accordingly, chemistry alone does not identify a mineral, nor do those sophisticated instrumental methods which are based on chemical principles, such as:

Wet Chemical Analysis

- Classical (gravimetric, volumetric)
- Instrumental (atomic absorption, flame emission)

Microprobe (electron and ion)

Emission Spectrograph

Mass Spectrograph

X-Ray Fluorescence

Morphology

Although the shape of a mineral particle is one of the key characteristics in the identification of a mineral, shape alone cannot be the sole determinant of a specific mineral species. There are hosts of minerals in different mineral classes whose particles have the same shape. They exist across the spectrum of all classes of minerals and the possibilities are beyond comprehension. Even if we limit ourselves to minerals which occur in the true fibrous state, we would estimate there are up to 100. There have been instances where nonasbestos particles have been misidentified as chrysotile in talc because shape alone was the index used.

Methods based on morphology include:

- Optical Microscopy
- Automated Image Analyzers
- Electron Microscopy (SEM and TEM)

Structure

The configuration of atoms in the crystal lattice of a mineral does not necessarily determine a mineral species. The atomic arrangement at the molecular level does not always carry through to the external visible physical form. That is to say that methods based on molecular structure can misidentify a mineral. For example, chrysotile asbestos is classified with the sheet silicates because of its crystal structure arrangement, but it certainly does not occur in flat sheets like the micas or its sibling, antigorite.

Methods of identification which relate to molecular structure are:

Infrared Spectroscopy

Differential Thermal Analysis

X-ray Diffraction

Electron Diffraction

In general then, no single property defines a mineral, and no single method which depends on one property can identify a specific mineral.

Conversely, methods which depend on a single factor or characteristic of a mineral can give misidentifications.

Two Popular Methods

Optical microscopy and x-ray diffraction methods require some additional discussion primarily because they have received widespread attention by industry and government laboratories as possible monitoring techniques.

Although both these methods are fundamental to the science of mineralogy and are highly reliable in the hands of experts, complications arise when shortcuts are taken in the professional procedures.

Optical Microscopy

When an experienced optical mineralogist or crystallographer identifies a mineral with a petrographic microscope, he can come to a remarkably accurate conclusion. The reason for high accuracy is that not one but several specific properties are determined, such as refractive indices, extinction angle, birefringence, and optical orientation. Specific training and wide mineralogical background are required to get the right answer.

In contrast, current optical methods in federal regulatory proposals relating to asbestos presume that asbestos is present in the first place. The analyst then merely observes the mineral particle for size/shape. Consequently, those methods which depend solely on aspect ratio give misidentification. They misidentify the presence of asbestos by such simple oversights as looking at a platelet on edge and counting it as an asbestiform particle. It is not necessary to elaborate on the other shortcomings of those methods in view of the recent NBS report on the analysis of 80 industrial talcs [3] evaluating that methodology. The same shortcomings were also recently corroborated in a study conducted by Harvard University and NIOSH [4].

However, there are a few rare cases where abnormal crystal habit can be misleading and subtly can lead to a misidentification. Optical microscopy is most vulnerable to this type of misidentification. For example, talc normally occurs as micaceous plates, but rare acicular talc does exist, and one must be very careful to avoid misidentifying the rare occurrence as asbestos. As an example, our XRD examination of an industrial acicular talc sample has identified the presence of significant amphibole (probably tremolite). However, when the material was subjected to thorough petrographic examination it was found to be composed of free grains of columnar amphibole and acicular talc and composite talc-amphibole. The significance is that an erroneous conclusion could be reached by misidentifying such a rare talc variety as asbestos, if only aspect ratio and simple optical microscopy were used.

Thus, simple optical microscopy can determine the morphology of a particle, but if used alone it cannot always fully identify the specific mineral observed.

X-Ray Diffraction

Although x-ray diffraction (XRD) is a valuable technique, it cannot determine the physical shape of a mineral particle, and for that reason it cannot determine whether or not a sample is asbestos. Furthermore, it cannot distinguish between two mineral varieties in the same mineral class in cases such as the asbestos minerals and their nonasbestiform analogues. It is surprising that such a basic shortcoming continues to be overlooked by responsible investigators alleging to have identified asbestos by XRD.

One result of the inability of powder XRD to differentiate between the asbestiform and nonasbestiform varieties of a mineral is the potential error of prejudging an XRD detected phase to be the asbestiform variety. For example, preparing calibration standards of mixtures of talc plus chrysotile could have the effect of causing a serpentine peak in an unknown sample to be prejudged as the asbestiform variety, i.e., chrysotile. A mixture of talc spiked with the serpentine mineral chrysotile will give the same XRD pattern as a mixture of talc spiked with the very common platy serpentine mineral antigorite. It should be obvious that an unknown talc showing a serpentine peak cannot be prejudged or branded as containing chrysotile asbestos under such circumstances. Unfortunately, the literature has articles by responsible authors who have overlooked that error in logic [5,6,7].

For research purposes only, single crystal XRD can provide information as to whether or not the specimen could be asbestos. However, due to the difficulty of handling minute specimens, single crystal XRD is inadequate for particles smaller than about 20 x 5 μm, and, of course, is also inadequate for routine monitoring procedures.

Amphiboles

Each of the five amphibole minerals, anthophyllite, cummingtonite-grunerite, riebeckite, tremolite, and actinolite has an asbestiform variety, namely anthophyllite asbestos, amosite, crocidolite, tremolite asbestos, and actinolite asbestos, respectively. Tremolite asbestos is quite rare, and actinolite asbestos is so rare that a recent NIOSH project to prepare reference standard minerals has been unable to locate a source of pure actinolite asbestos [8].

The amphiboles (named from the Greek "amphibolos," meaning ambiguous) are characterized by similar crystal structure and wide variation in chemical composition and appearance. All amphiboles have XRD patterns which are similar, and are characterized by having their (110) or (210) diffraction peaks occur within ±0.2Å of each other (Table 1, Figure 1). Reliable identification of individual amphibole species is difficult in the absence of confirming composition data.

Examination of Table 1 and Figure 1 illustrates that attempted identification of a specific amphibole on the basis of $d_{(110)}$ or $d_{(210)}$ has good potential for being in error. For example, selection of Joint Committee on Powder Diffraction Standards (JCPDS) card 13-437 as being definitive of tremolite presents serious problems. Twenty-nine additional JCPDS amphiboles have their (110) or (210) peaks within ±0.1°2θ of this tremolite (110) peak at 10.56°2θ. Identification of an amphibole as tremolite on the basis of a peak at 10.56°2θ is obviously an identification with very low reliability. In other words, a peak at that location is not necessarily the mineral tremolite since it could be one of 29 other minerals.

Table 1. Amphibole JCPDS Card No's., $d_{(110)}$ or $d_{(210)}$ peak position, and relative intensity.

JCPDS card #	Å[a]	2θ(Cu)	I	Name
23-118	8.58(1)	10.31	100	prieskaite
10-456	8.55(1)	10.35	100	richterite
20-734	8.53(1)	10.37	70	mboziite
20-378	8.52(1)	10.38	100	dashkesanite
14-633	8.51(1)	10.39	70	arfvedsonite
21-149	8.51(1)	10.39	55	hornblende
19-467	8.50(1)	10.41	100	ferropargasite, syn
20-982	8.50(1)	10.41	65	richterite, syn
23-665	8.48(1)	10.43	45	richterite, calcian, syn
23-664	8.47(1)	10.44	35	edenite, sodian, syn
23-667	8.47(1)	10.44	45	richterite, calcian, syn
23-663	8.46(1)	10.46	40	eckermanite, calcian, syn
9-434	8.45(1)	10.47	50	hornblende
13-499	8.45(1)	10.47	100	magnesioriebeckite
20-656	8.45(1)	10.47	100	magnesioriebeckite
20-470	8.44(1)	10.48	100	crossite
23-666	8.44(1)	10.48	40	tremolite, sodian, syn
20-469	8.43(1)	10.49	100	hastingsite
23-1405	8.43(1)	10.49	80	edenite
23-1406	8.43(1)	10.49	40	paragasite
20-1310	8.43(1)	10.49	40	tremolite, syn
10-428	8.42(1)	10.51	100	richterite, fluor, syn
23-603	8.42(1)	10.51	100	tirodite
10-431	8.41(1)	10.52	80	edenite, fluor, syn
19-1061	8.40(1)	10.53	100	riebeckite
20-481	8.40(1)	10.53	100	hornblende
20-1390	8.40(1)	10.53	90	winchite
23-302	8.40(1)	10.53	100	cummingtonite, mangoan
19-1063	8.39(1)	10.54	70	richterite
13-437	8.38(1)	10.56	100	tremolite
17-478	8.38(1)	10.56	65	kaersutite
23-495	8.38(1)	10.56	80	eckermanite
9-330	8.37(1)	10.57	100	tremolite, fluor, syn
17-750	8.36(1)	10.58	25	richterite, ferrian
20-386	8.35(1)	10.59	40	eckermanite, syn
22-531	8.35(1)	10.59	30	joesmithite
16-401	8.33(2)	10.62	70	anthophyllite, magnesian, syn
17-725	8.33(1)	10.62	100	grunerite
17-745	8.33(1)	10.62	100	grunerite
20-376	8.31(1)	10.65	100	crossite
17-726	8.30(1)	10.66	100	cummingtonite
20-484	8.29(1)	10.67	100	richterite
13-506	8.27(2)	10.70	80	gedrite
23-679	8.27(1)	10.70	90	glaucophane
9-455	8.26(2)	10.71	55	anthophyllite
20-453	8.26(1)	10.71	100	glaucophane
11-253	8.23(2)	10.75	100	ferrogedrite
23-310	8.20(1)	10.79	75	richterite, ferrian
13-401	8.11(2)	10.91	100	holmquistite

[a] $(110)^1$ or $(210)^2$.

Maximum $\Delta 2\theta(Cu)$ = 10.91° - 10.31° = 0.6°

Table 1 illustrates the very close proximity of the (210) or (110) XRD peak of all amphiboles, showing the inability to identify a specific amphibole on the basis of $d_{(210)}$ or $d_{(110)}$.

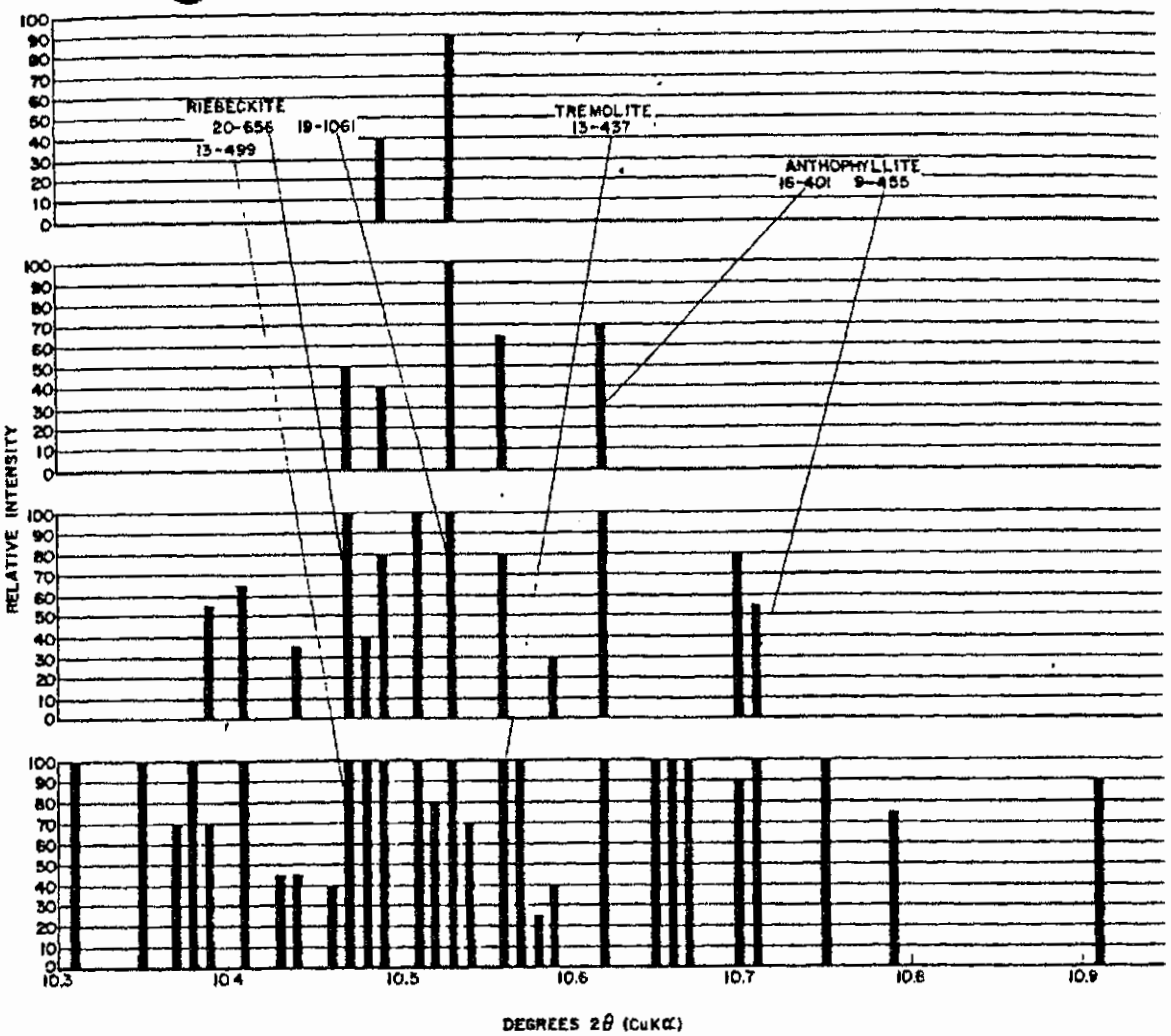

Figure 1. Amphibole $d_{(110}$ or $d_{(210)}$ – peak positions (2θ for CuK) and relative intensity.

An additional problem further affecting the reliability of identification by XRD is the effect of shift in peak position caused by slight mispositioning of the sample surface in the instrument. For example, a 100 μm mispositioning of the specimen surface will result in a shift of approximately 0.6-0.7 Å in d-spacing at low 2θ angles [9]. A slight shift in the position of the peak (from a different amphibole or mispositioning of the sample surface, for example) could go unnoticed, resulting in misidentification of an amphibole that is not even present.

In order to conclusively identify an amphibole by XRD, it is necessary to have an essentially complete diffraction pattern. In order to obtain such an XRD pattern, the sample must have a relatively high amphibole content and the pattern must be acquired with a time-consuming slow scan. Acquisition and interpretation of such patterns is time-consuming, and discourages proper application of the full procedure, especially for routine monitoring where large numbers of samples require analysis. Shortened procedures, such as single peak identification of amphiboles, provide good opportunity for misidentification. The shortened procedure of single peak identification was apparently used in a 1972 paper [7], where our examination of some of the same samples disagreed with identifications of serpentine, tremolite-actinolite anthophyllite, and anhydrite.

Chlorite is one of the most common accessory minerals found associated with talcs. The chlorite group of minerals are somewhat analogous to amphiboles in that they exhibit a wide variation in chemical composition and all have a similar crystal structure. The diagnostic chlorite basal XRD peaks (001), (002), and (004) are characteristic, and occur at about 14Å, 7Å, and 3.5Å, respectively. As in the case for the amphiboles, specific identification of a particular chlorite species by XRD is difficult. The XRD problem with chloritic talcs is that the serpentine first order basal peak overlaps the chlorite (002) peak, and the corresponding serpentine second order basal peak overlaps the chlorite (004) peak. Generally, however, the chlorite (004) and serpentine second order peaks are separate enough to allow unambiguous determination of the presence of both phases when present in adequate amounts to give definable peaks. Tables 2 and 3 and Figures 2, 3, and 4 are compilations of JCPDS data for the positions of the (004) basal peak for chlorites and (002), (004), or (0012) basal peak for serpentihes, respectively.

Table 2. Chlorite JCPDS Card No's., $d_{(004)}$ peak positions, and relative intensity.

JCPDS card #	Å	2θ(Cu)	I	Name
10-183	3.60	24.73	100	penninite
20-671	3.60	24.73[a]	90	kämmererite
16-351	3.59	24.80	70	chlorite 1b
12-185	3.57	24.94	85	kotschubeite
7-160	3.58	24.87	60	kotschubeite
19-749	3.56	25.01	80	clinochlore
7-77	3.558	25.03	50	sheridanite
16-362	3.55	25.08	80	chlorite 1a
19-751	3.55	25.08	65	sudoite
22-712	3.55	25.08	45	nimite
7-165	3.545	25.12	60	grochauite
7-78	3.541	25.15	60	thuringite
7-171	3.541	25.15	80	diabantite
12-242	3.54	25.16	100	leuchtenbergite
7-76	3.537	25.18	50	ripidolite
13-29	3.53	25.23	80	thuringite
7-166	3.523	25.28	50	daphnite
12-243	3.52	25.30	92	aphrosiderite
21-1227	3.52	25.30	100	thuringite
3-67	3.49	25.52	100	thuringite

[a] $d_{(115)}$.

Table 2 illustrates variation in position of the chlorite $d_{(004)}$ XRD peak. Table 2 should be compared with Table 3 to see that the chlorite and serpentine XRD peaks overlap and interfere with each other. Identification and quantification of serpentine in the presence of chlorite is extremely difficult at best.

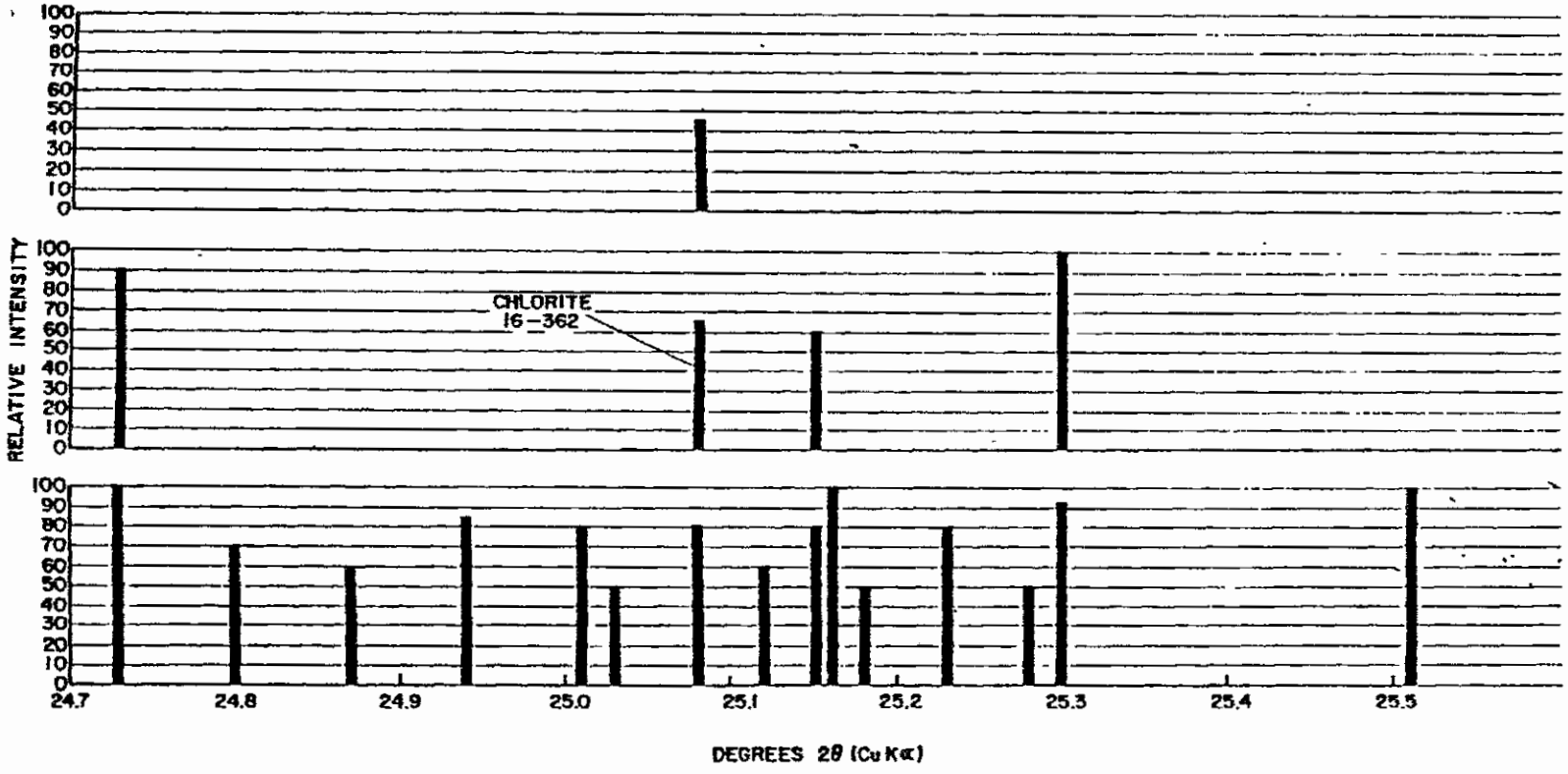

Figure 2. Chlorite $d_{(004)}$ — peak positions and relative intensity. The data of Table 2 are presented in graphical form showing the variation in position of the $d_{(004)}$ XRD peaks for different chlorites. Selection of JCPDS card 16-362 as diagnostic for chlorite can obviously result in misidentification.

Table 3. Serpentine, Kaolinite, Halloysite, and Dickite JCPDS Card Nos., peak position, miller index (hkl), and relative intensity.

JCPDS Card #	Å	2θ(Cu)	I	(hkl)	Serpentines
18-779	3.67	24.25	80	(002)	lizardite, 1M
9-444	3.66	24.32	100	(0012)	antigorite, 6O
21-543	3.65	24.39	70	(004)	chrysotile, 2M
7-417	3.63	24.52	300	(102)	antigorite, 6M
11-386	3.62	24.59	60	(002)	lizardite, 1O, aluminian
21-963	3.61	24.66	80	(002)	antigorite, 6M
12-583	3.56	25.01	80	(0012)	antigorite, 6O, aluminian
13-4	3.56	25.01	70	(0012)	antigorite, 6O, aluminian
7-339	3.55	25.08	100	(002)	berthierine
11-388	3.55	25.08	100	(0012)	antigorite, 6O, syn
7-315	3.52	25.30	100	(002)	berthierine
9-493	3.52	25.30	100	(004)	amesite
					Kaolinites
6-221	3.58	24.87	100+	(002)	kaolinite, 1Md
14-164	3.579	24.88	80	(002)	kaolinite, 1T
12-447	3.56	25.01	50	(002)	kaolinite, 1T
					Halloysite
9-453	3.63	24.52	90	(002)	halloysite, dehydrated
					Dickite
10-446	3.58	24.87	100+	(004)	dickite $2M_1$

Chlorite 2θ Range: 24.73 - 25.52

Table 3 illustrates variation in position of XRD peaks of serpentine, kaolinite, halloysite, and dickite. The XRD patterns of these minerals interfere with each other and with chlorite (see Table 2).

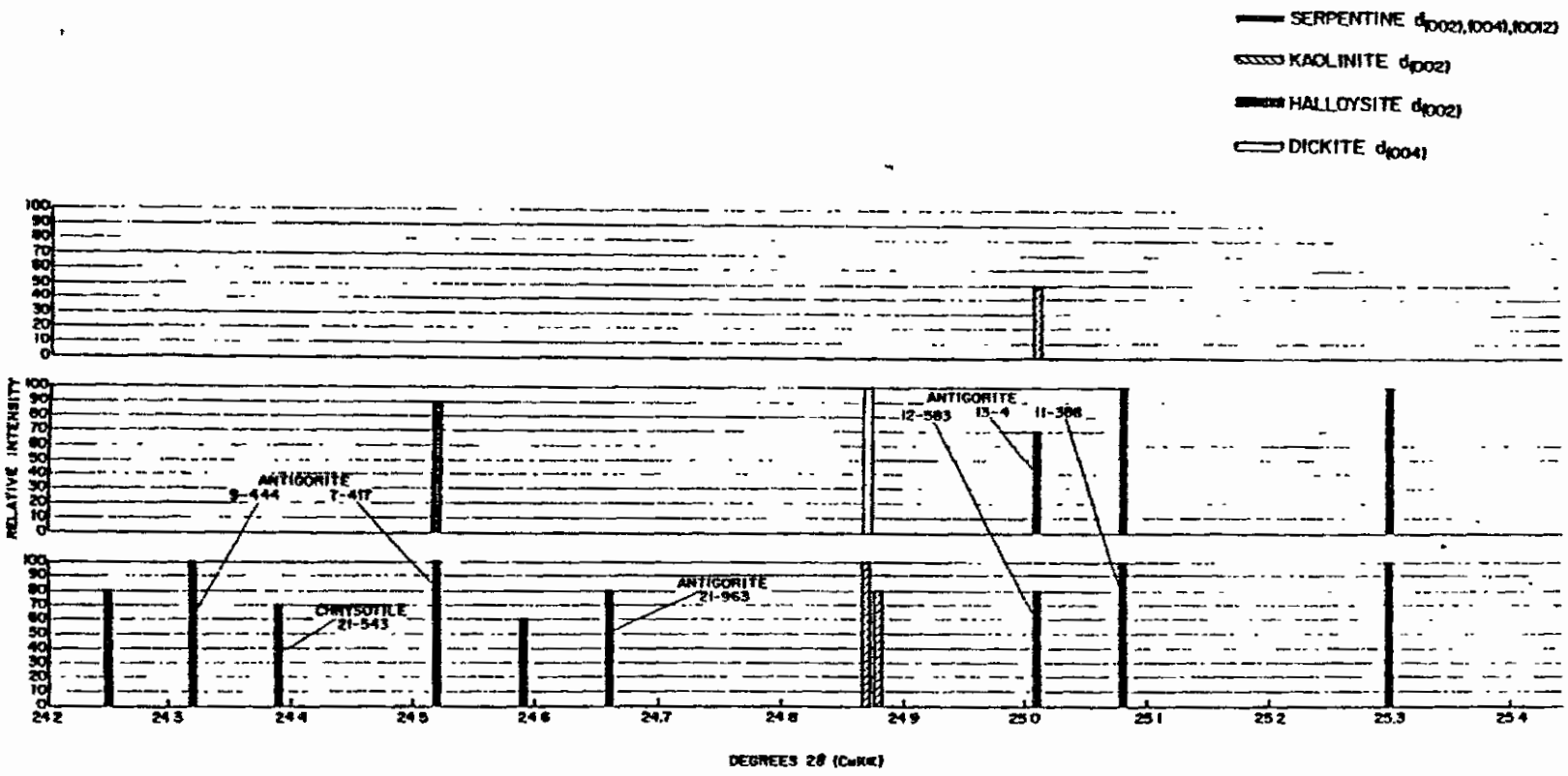

Figure 3. Peak positions and relative intensities. The data of Table 3 are presented in graphical form to illustrate the variation in position and interferring overlap of XRD peaks of serpentine, kaolinite, halloysite, and dickite.

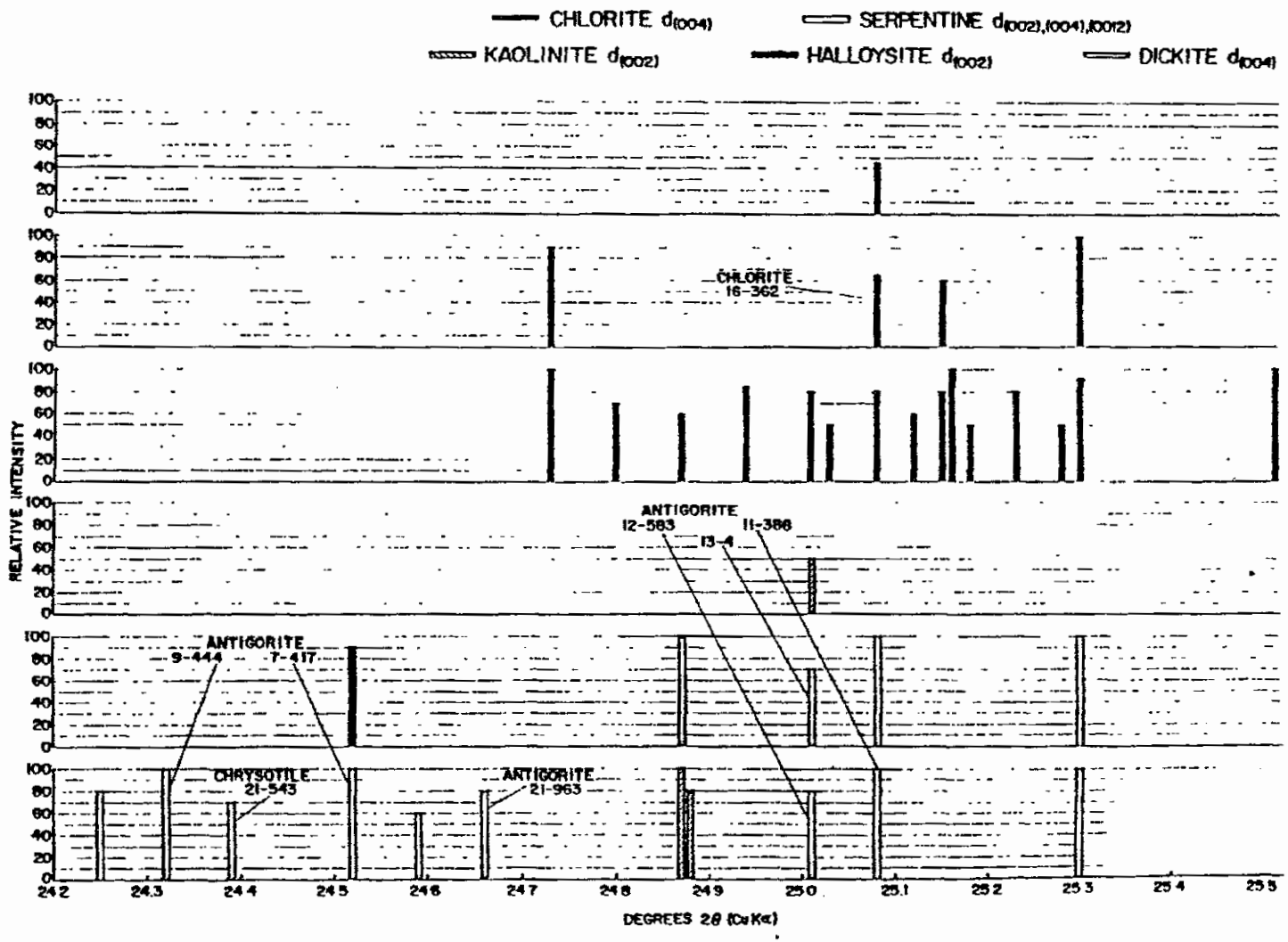

Figure 4. Peak positions and relative intensities. The data of Tables 2 and 3 are presented combined, illustrating the problems of XRD identification when chlorite and serpentine, and possibly kaolinite, halloysite, or dickite are also present.

Three essential features are demonstrated in Tables 2 and 3, and Figures 2, 3, and 4:

1. The diagnostic peaks show considerable variation in the position in which they occur ($\Delta 2\theta = 0.79°$ for chlorites and 1.05° for serpentines).

2. The chlorites and serpentines overlap and interfere with each other.

3. Basal peaks of the clay minerals kaolinite, halloysite, and dickite overlap the positions of the chlorite and serpentine peaks, and will interfere when present.

The significance of the chlorite-serpentine interference is increased by the fact that chlorite is a very common accessory mineral associated with talcs, whereas serpentine is much less commonly associated.

In spite of the chlorite-serpentine problem, numerous investigators have performed XRD identification and/or quantification of serpentine in chloritic talcs. It is obvious to us that they have misidentified asbestos as being present by overlooking the chlorite/serpentine interference and by misconcluding that a chlorite peak was serpentine.

Other Methods

Infrared Spectroscopy (IR)

The infrared absorption spectrum of a material results from vibrational and bending frequencies of various atomic bonds within the structure. For example, Si-O stretching frequencies produce similar IR peaks for all silicate minerals. As a result, IR spectra are not particularly useful for identifying the minerals present in a mixture, and the method certainly is not capable of determining whether or not a detected mineral is the asbestiform variety.

Differential Thermal Analysis (DTA)

The rearrangement or decomposition of mineral crystal structures due to thermal heating is a characteristic and reproducible reaction. It follows that DTA can identify specific minerals in a mixture but the method is not capable of determining morphology. Therefore, any DTA data which might point to the presence of a serpentine mineral could lead to misidenfying chrysotile asbestos in a talc when the mineral could well be a normally occurring platy antigorite having the same DTA pattern.

Electron Microscopy

Electron microscopic techniques of identification of asbestos have been amply covered in other presentations during this workshop. We do not intend to cover that subject again, but rather to point out some areas where asbestos can be misidentified.

The high magnification attainable with electron microscopy is, in itself, inadequate as the sole index of mineral identity. For example, chrysotile is often identified by the presence of a hollow central core and streaked electron diffraction spots. But the clay mineral halloysite also crystallizes in that form and will produce a similar electron diffraction pattern. Therefore, in the absence of exact chemical composition, halloysite can be misidentified as asbestos. Similar care must be exercised to avoid misidentifying other fibrous clay minerals as asbestos, e.g., attapulgite and alpha sepiolite. In addition, talc ribbons can be mistaken to be asbestos, especially when some talcs have particles which roll up into spiral tubes giving the appearance of a chrysotile particle.

Selected area electron diffraction is routinely used to identify a mineral particle as amphibole. Many investigators simply observe the electron diffraction pattern in the microscope and decide on the basis of general pattern geometry whether or not the particle is an amphibole. This can lead to misidentification, since numerous other minerals can give electron diffraction patterns with amphibole pattern geometry [10,11]. Careful measurement of an electron diffraction pattern is required in order to identify the type

of mineral which produced the pattern. Chemical composition is further required in order to have a chance at identifying the particular species when the mineral is a member of a complex group such as the amphiboles. Otherwise, misidentification will result.

Cosmetic Talc Free from Asbestos

In the United States, we have a self-regulating association known as the Cosmetic Toiletry and Fragrance Association. In certifying the purity of the talcs which they use, they are aware that no single method can identify asbestos and their most recent specification for cosmetic talc [12] combines two methods (XRD and optical microscopy) for monitoring their types of talc.

The rationale is that a talc is first examined by XRD, and if even the smallest amount of amphibole is indicated, then the test proceeds into optical microscopy using a dispersion staining technique to determine whether or not the material contains asbestiform particles in the amphibole group.

Summary

This paper has categorized the main methods which have been used for detection of asbestos in talcs. The basic principles of the various methods were categorized to explain how asbestos has been and can be misidentified in talc. Generally, misidentifications arise by jumping to a conclusion from a single mineral characteristic, when, in fact, many characteristics are required to fully identify a mineral species and/or its variety.

Both optical microscopy and XRD required a more detailed review than other methods since they have received the most attention from a monitoring point of view.

This review is presented with the hope that our guidelines will enable analysts to avoid the misidentification of asbestos in talcs.

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Discussion

A. WILEY: You said that instantaneous recognition of SAD patterns is difficult. Could you give some examples as to what kind of confusions could exist in this? Can you confuse amphibole with serpentine or amphibole with talc, or is that kind of a gross mistake possible?

J. KRAUSE: Those kinds of mistakes probably would not generally happen if you are looking at pyroxenes or olivine. Electron diffraction is not one of my areas of real expertise, but I think that you could possibly get feldspars that would give confusing patterns, depending upon their orientation in the microscope.

L. MADSEN: We are using all the methods that have been talked about today for identification for asbestos materials and do not in any way limit ourselves to fiber length and aspect ratios.

J. WAGMAN: I would like to comment that it is possible by x-ray diffraction and through a special technique to identify and measure the presence of asbestos fibers even when they are in the presence of their non-fibrous counterparts. About two years ago this was demonstrated in a study which we supported at the Naval Research Laboratory in which samples were pre-treated so that fibers were first aligned and then the x-ray diffraction intensities measured at two different orientations with respect to the x-ray beam and in this way the intensity due to the non-fibrous counterparts could be subtracted from the total diffraction intensities.

KRAUSE: You were putting the fibers in some specific preferred orientation in the sample and then looking for those orientations by XRD.

WAGMAN: That is correct, and this had the advantage of not only making possible corrections, that is correcting for the non-fibrous material present, but also it greatly enhances the detectability for the fibers themselves.

KRAUSE: Is this method being currently used?

WAGMAN: This is a method whose feasibility was demonstrated and there are two publications on this in the literature. Actually our objective was to apply this method to airborne samples, which is a much more difficult application incidently, I should think than in the case of talc. The problem here is a preparative problem in that an air sample usually has a lot of organic material, sticky material present which interferes with the ability to orient the fibers. This is a preparative problem which will have to be overcome. But I should think that in the case of talc samples you probably would not have that problem.

COLORADO SCHOOL OF MINES RESEARCH INSTITUTE
P.O. BOX 112
GOLDEN, COLORADO 80401

TO: W. H. Ashton

DATE: June 8, 1973

FROM: W. T. Caneer

PROJECT NO. C10704

SUBJECT: Meeting with Bowling Green State University Geological Staff

A paper entitled "Asbestosform Impurities in Commercial Talcum Powders," published in the January 1972 issue of The Compass of Sigma Gamma Epsilon (Vol. 49, No. 2) stated that 18 commercial talcum powders examined contained from 4% to 46% asbestiform minerals. The average asbestiform content was 18%. The data in this paper has subsequently been quoted and has been a source of inquiry by interested individuals both in and outside of government agencies. The amount of asbestiform minerals reported is so large that the data could initiate costly FDA hearings on the matter. Since our general observations at the Research Institute relative to asbestiform minerals in talc are at such a large variance to those reported in the paper, an investigation of the paper was undertaken. To date we have reviewed the paper and have discussed the data with the authors. The people involved in the investigation were W. T. Caneer and Dr. Jerry Krause of the Research Institute and Dr. Maynard Slaughter of the Colorado School of Mines.

REVIEW OF THE PAPER

A review of the paper suggested that a number of errors are present. Some of these apparent errors may be illustrated by the following table which appeared in the paper:

Table I

Qualitative Mineral Analyses by X-ray Diffraction

Sample Number	Talc	Asbestosform Minerals (Serp.	Trem-Act.	Anth.)	Carbonates	Anhydrite	Clay (Mica)	Misc. Mins.*
1	x	x	x			x	x	x
2	x	x				x	x	x
3	x	x				x	x	x
4	x	x	x	x	x	x	x	x
5	x	x	x			x	x	x
6	x	x		x	x	x	x	x
7	x	x				x	x	x
8	x	x	x	x	x	x	x	x
9	x	x					x	x
10	x	x				x	x	x
11	x		x		x	x	x	x
12	x				x	x	x	x
13	x		x	x	x		x	x
14	x	x			x	x	x	x
15	x	x	x			x	x	x
16	x		x					x
17	x		x	x		x	x	x
18	x	x		x		x	x	x

*Additives and inert minerals and compounds.

According to this table, asbestiform minerals were identified by X-ray diffraction. By the method of X-ray diffraction used, one could only expect to identify mineral groups to which asbestiform minerals belong. Numerous common non-asbestiform minerals also occur in these groups.

A differentiation is shown for tremolite-actinolite and anthophyllite. It is not likely that these minerals could be differentiated by the X-ray methods used.

The mineral anhydrite ($CaSO_4$) is also reported by X-ray diffraction for all except three of the samples. We have never found anhydrite in any talc samples examined at the Research Institute. Furthermore, from the standpoint of geological occurrences and rock genesis, one would not expect to find anhydrite associated with talc. With these factors in mind, a study was made to determine how one may possibly make an identification of anhydrite in talc.

It soon became apparent that a talc k-beta diffraction peak was being interpreted as belonging to anhydrite. A filter is used to screen out k-beta radiation in X-ray diffraction analysis. However, the filter is not 100% efficient and some of the k-beta passes through the filter and can lead to erroneous interpretation.

The table also shows serpentine as one of the asbestiform minerals identified by X-ray diffraction for most of the samples. This is usually based on the occurrence of a 7-angstrom peak. However, chlorite also gives a 7-angstrom peak and chlorite is a common constituent of talc. A differentiation of the two minerals can usually be made based on other diffraction peaks. Since chlorite is a common constituent of talc and none was reported for the 18 samples, it is likely that chlorite was misidentified as serpentine.

Table II was presented in the paper and shows quantitative mineral analyses by petrographic microscopic techniques.

Table II

Quantitative Mineral Analyses by Petrographic Microscope
(Volume Percent)

Sample Number	Percent Talc Flakes	Percent Carbonate Grains	Percent Asbestosform Minerals
1	73	5	22
2	92	*trace	8
3	**79	trace	21
4	57	20	23
5	82	trace to 1	18
6	72	13	15
7	89	5	6
8	61	5	34
9	80	4	16
10	92	4	4
11	86	trace	14
12	76	20	4
13	48	6	46
14	90	4	6
15	74	4	22
16	80	trace	20
17	70	6	24
18	76	trace	24

*Less than 1 percent. **Includes muscovite.

It is perhaps significant that no anhydrite was observed by microscopic techniques even though it was reported in 15 of the 18 samples by X-ray diffraction. It is perhaps also significant that no specific asbestiform minerals were reported in Table II -- only a total percent of asbestiform minerals. This led us to suspect that any grain with a high length to thickness ratio observed under the microscope would be classified as asbestiform. This could lead to the misidentification of the edges of talc plates and of talc shards as asbestiform minerals.

DISCUSSIONS WITH THE AUTHORS

Of the three authors, two were graduate students (Snider and Pfeiffer) at the time the paper was written. J. Mancuso is on the Geology Department staff and acted as advisor for the research and the paper. Snider is presently with the Michigan Geological Survey in Mt. Pleasant, Michigan, and Pfeiffer is a geologist for Texaco in Midland, Texas. We discussed the paper with Mancuso in Bowling Green and held telephone conversations with Snider and Pfeiffer. We made it clear to these people that the data presented in their paper could lead to very serious charges against the products. They readily agreed that their data could easily have errors, and if so it would save them much possible embarrassment at a later date by correcting their errors now.

Apparently the paper was submitted for publication to fill an issue of the journal which was being devoted entirely to the Bowling Green Geology Department. Apparently a Dr. I. I. Oster (a fruit fly expert in the Biology Department) told them that he had been conducting experiments related to the injection of talc products into mice for the purpose of determining the effects of the injections upon the mice. He requested that the Geology Department make mineralogical determinations of the asbestiform minerals in the talc products. None of the three authors had had any previous experience with talc mineralogy, but they decided that it would be a suitable subject for a paper. Our discussions yielded the following significant results.

1. All three authors readily admitted that they did a "rush-job." About 2 weeks was spent in gathering data for the paper.

2. They agreed that asbestiform minerals cannot be identified by X-ray diffraction. X-ray diffraction is capable only of identification of a mineral group which contains both asbestiform and non-asbestiform minerals.

3. They admitted that they did not adequately check the "talc edge effect" which could lead to the misidentification of talc plate edges as asbestiform minerals by microscopic analysis.

4. They did not take into account the possible presence of chlorite in the talc and could have well misidentified chlorite as serpentine (which of course includes chrysotile).

5. Relative to the identification of anhydrite, they admitted that they probably misidentified a k-beta talc peak.

6. They counted only 100 grains for their quantitative microscopic analyses. Though their data is presented in terms of volume percent they neither measured the size of the grains counted nor considered the difference in the volume of a fiber as opposed to a plate. We pointed out that the statistics involved are totally unacceptable.

7. They admitted that they probably made many errors in conducting the project and seem anxious to rectify them before there is a possible accounting with the FDA or some other agency.

8. The following list identifies the talc products examined in the Bowling Green Study.

Sample No.	Brand Name	Quoted % Asbestiform Minerals
1	Mennen Talc Powder	22
2	J&J Baby Powder	8
3	Corn Silk	21
4	Estee Lauder	23
5	Cuticura (South Africa)	18
6	Coty-Muquist de Boio	15
7	April Showers (N.Y.)	6
8	Remington Shave Talc	34
9	Cashmere Bouquet	16
10	Imprevu	4
11	Avons Sachete Occur	14
12	Heaven's Scent	4
13	Excalibur Spray (Avon)	46
14	Loves Fresh Lemon	6
15	Mennens Baby Magic	22
16	Ammens Medicated Powder (ZnO)	20
17	ZBT Baby Powder	24
18	Cuticura (U.S.A.)	24

9. About a year ago Howard Jack, who was with the American Geological Institute at the time, requested and got the list of various brands of talc examined in the Bowling Green study. His motivation is unknown to us. We have determined that Jack is now apparently with some governmental agency and we are trying to determine his interest in the samples.

We asked to see their X-ray diffraction patterns and also requested splits of the samples. They could not locate the diffraction patterns and found only two samples (Nos. 8 and 13) while we were there. They are still trying to locate the others and said that they would send them to us when and if they find them.

They spent an inadequate amount of time and have admitted to making errors relative to the identification and amount of asbestiform minerals. They apparently will not stand behind the data presented in the paper if they are pressed to do so. ' I also believe that they will retract the data after we present them our data and after they have had time to do some checking on their own.

/nkr

Memorandum

Date June 6, 1985

From QRAC (Quantitative Risk Assessment Committee)

Subject Asbestos in Talc

To W. Gary Flamm, Ph.D.
Director, Office of Toxicological Sciences (HFF-100)

Using Linda Taylor's report [1] and other information on asbestos and talc, we conclude that the added human risk of lung cancer and mesothelioma from possible asbestos in talc is less than 10^{-8} lifetime risk and quite possibly orders of magnitude less. We have used, as our population at risk, infants that may be routinely dusted with talcum powder for an estimated period of 2 years.

Infant Dose and Worker Exposure:

Based upon one experimental 2 yr. exposure scenario for talcum powder dusting, babies would apparently inhale no more than about 6.5×10^3 asbestiform fibers per year (4.95 talc fibers/cc x 1000cc/l x .58 1/min. breathing rate x 43.8 min/wk powdering x 52 wk/yr. x .1% asbestos in talc). The asbestiform fibers are difficult to detect, poorly defined in shape, and of a highly variable subtype. We assume .1% tremolite or anthophyllite asbestos in talc based on 1977 FDA measurements and other recent samples [1, 10, 11]. To be called asbestiform fibers, the fibrous silicates must be greater than 5 um. and have length/width ratio greater than 3. These inherent detection and geometrical measurement limitations for asbestos in talc make comparisons with worker exposure to a different type (mainly amosite, crocidolite and chrysotile) and shape of asbestos highly problematical [5]. In fact there is a

general consensus that current talc mines are virtually free of asbestos (offending mines have gradually been abandoned) and that any residual silicates in talc are so finely and smoothly ground as to represent virtually no risk to humans whatsoever even where an occasional fiber just barely satisfies the technical definition for asbestiform fibers. However, this consensus belief would require better geometric measurements than currently exist for both current commercial talc fibers and for workplace asbestos fibers during the past 50 years. Nevertheless, baby exposure in fibers per year is crudely estimated at about 0.3×10^{-6} times that of worker exposure in several well known epidemiological studies (e.g., Selikoff study: 15 f/ml in workplace x 12,000 ml/min breathing rate x 60 min/hr x 8 hr/day x 5 days/wk x 50 wks./yr. = 2.16×10^{10} f/yr. vs 6.5×10^{3} f/yr for baby) [1].

A complicating factor, however, is that human cancer risk from these studies seems to follow different time-dose response patterns for the two main cancer endpoints (lung cancer and mesothelioma). Although several human epidemiological studies exist which could be utilized for quantitative risk assessment purposes, it is most illustrative to consider the largest of these occupational studies, namely, that of Selikoff, et. al. [7,8] in which 17,800 insulation workers were exposed to a mixed variety of asbestos fibers (mainly amosite and chrysotile) for about 25 years on average. Through 1976, 2,271 deaths (12.7% of total) had occurred.

Lung Cancer:

Lung cancer rates were about 4.6 times average (486 observed/106 expected). Since this nearly 360% excess lung tumor

rate seems to apply to nonsmokers alone as well as smokers and nonsmokers combined [6], then, assuming hypothetically that one can extend excess relative risks to very low asbestos exposures, one would expect to see an excess lifetime lung tumor rate among asbestos exposed nonsmokers of about 1.8% (360% x the normal lifetime nonsmoker lung tumor rate of about .5% - integrating 1979 survival rates against Garfinkel's 1960-1972 nonsmoker age-specific lung tumor rates [12, 13]). Excess lung cancer rates appear to be proportional to dose and duration of exposure, but not to some high power of time-since-first-asbestos exposure [6]. Thus, excess lifetime lung cancer risk for talc exposed babies who will never smoke would appear to be approximately the product of 1) an excess 1.8% lifetime risk for nonsmoking asbestos exposed workers, 2) a baby/worker yearly exposure ratio of 0.3×10^{-6}, and 3) a baby/worker exposure duration ratio of 2 yrs/25 yrs. This product yields a value of $.4 \times 10^{-9}$ added lifetime risk for lung tumors. Similarly, averaging eventual smokers in with the lifelong nonsmokers assumed above, the average added lifetime lung cancer risk for the talc exposed baby will be at worst about 10 times higher or about $.4 \times 10^{-8}$. We note that current (1979) lifetime total respiratory cancer rates are about 5% and have nearly doubled since 1960, possibly reflecting rapidly changing smoking patterns during and after World War II, primarily among women. However, decreased tar levels in cigarettes and decreased per capita use of cigarettes since about 1965 should result in a gradual leveling off or decline in the total respiratory and/or lung cancer rate of the general population [14].

Mesothelima:

The estimation of lifetime risk of mesothelioma is somewhat more difficult since the mesothelioma response data appears quite nonlinear in time since first exposure. We have investigated four different methods of mathematically modelling the nonlinear mesothelioma data. They all indicate an upper bound on lifetime risk for talc powdered infants of about 10^{-8} risk and quite possibly a much lower upper bound if the conservative assumptions upon which they were based do not hold. These four methods consisted of mathematically treating mesothelioma as 1) a nonincidental tumor with no time lag between tumor initiation and death, 2) a nonincidental tumor with a 10 year time lag between tumor initiation and clinical observation, 3) an incidental tumor, and 4) treating asbestos as a first stage intervener in an Armitage-Doll multistage carcinogenic process [9].

In fact methods 1-3 yielded virtually identical risks (.5-.75 x 10^{-8} risk). While method 4 yielded a risk 2-3 times higher (1.5 x 10^{-8} risk), it could easily have yielded a risk up to several orders of magnitude lower than 10^{-8} if we had simply assumed asbestos intervenes at a later stage of the carcinogenic process in this hypothetical Armitage-Doll multistage model. There was general concurrence among these four methods, and it suffices to briefly summarize Method 1.

Method 1: based upon fitting $bt^{3.1}$ (nonincidental analysis) to a 1922-1946 cohort of the Selikoff, et. al. data.

A reasonably simple way to estimate the median life (ML) risk to median survival age 77 (in 1979) for humans exposed 2 yrs. to talcum

powder during infancy is given by the product of the following terms:

(a) (77 yrs. since first exposure for infants/37 yrs. since first exposure for 1922-46 cohort as of 1978*)$^{3.1}$ = 9.70.

(b) (2 yr. infant exposure duration/34 yrs. approx. worker exposure duration for 1922-1946 worker cohort) = .059.

(c) (infant/worker) yearly exposure ratio = 0.3×10^{-6}.

(d) 1922-1946 cohort cumulative mesothelioma response of 3.75% (180 mesotheliomas/4,800 cohort members).

This product yields a median life risk of $R_{ML} = 0.64 \times 10^{-8}$.

Tumors other than Lung and Mesothelioma: (Selikoff study)

Although significant tumor increases were observed at other sites in the workers (e.g., esophagus, stomach and colon), their risk is dominated by that of the lung (less than 10^{-9} or 10^{-8} risk, depending upon whether or not the baby becomes a smoker) and by mesothelioma risk (less than 10^{-8} risk).

Other Comments on Total Cancer Risk:

These estimates of added lifetime human cancer risk are 2 orders of magnitude below those implied in Linda Taylor's memo 1) due to the fact that the more recent detection studies suggest .1% or less asbestos in talc on average rather than the 1% assumed by Dr. Taylor: and 2) due to a 10 fold conversion error going from fibers/cc in the air to fibers inhaled/yr by the infant.

Although mothers may receive an exposure for each infant powdered, their added lifetime risk from talc should be relatively smaller than the infant's since their mouths and noses are considerably further from the densest portion of the talc cloud than is the case for the captive infant during the daily powdering period (the inverse square law for exposure may apply).

Finally, the risks implied by the Selikoff study are generally on the high side of those implied by the other smaller epidemiological studies and we see little value in repeating calculations here for those studies (see reference 6 for details).

Ovarian Talc Study:

For completeness, a discussion is presented on a human epidemiological study purporting to show an association between talc use (talcum powder used for genital dusting on the perineum or on sanitary napkins) and ovarian cancer.

The Cramer et.al. study [2], which purported to show a significantly increased relative risk for ovarian cancer associated with talc use, 1) appears to have been misinterpreted statistically, 2) was uncorrected for several likely biasing factors and 3) appears to have been strongly contradicted by another study showing a reduced relative risk as significant in the negative direction as the Cramer study was in the positive direction.

The Cramer study's most prominent analysis (Mantel-Haenszel) was adjusted for only 2 factors and gave a relative risk (RR) of around 1.92 (p less than .003) and 95% confidence limits of 1.27 to 2.89 for 215 cases (talc users for genital or sanitary napkin dusting) vs 215 controls. Cramer's more comprehensively adjusted but seemingly de-emphasized multivariate regression analysis for 9 possible simultaneously confounding variables yielded a smaller and much less significant relative risk of 1.61 (p=.03), with 95% confidence limits of 1.04-2.49. It should be noted that the crude relative risk with no adjustments whatsoever was 1.89. In any case, if the authors had limited their logistic regression analysis as they subsequently did for their Mantel-Haenszel analysis, to those 121 cases where the first chosen control did not refuse to participate

(refusal bias), then the resulting p-value can be predicted through extrapolation of the other reported analyses to be greater than .05 and perhaps greater than .1. Unfortunately, the authors did not report this analysis. Instead they selectively chose to point out only that the relative risk of those exposed to talc both as a genital dusting powder and through sanitary napkins declined from a relative risk of 3.28 (p less than .001) to 2.44 (p less than .05) when the potentially biasing control refusals were eliminated from analysis. Apparently the authors felt it unnecessary to report those p-values that were greater than .05.

Since there were twice as many singles among the cases (21%) as among the controls (11%), the life style of singles might easily have biased the original overall relative risk of 1.92 [3]. However, the multivariate logistic analysis (RR=1.61) using all of the original 215 cases and 215 controls clearly adjusted for marital status along with such variables as religion, educational level, ponderal index, age at menarche, exact parity, oral contraceptive or menopausal hormone use, and smoking. The partially adjusted Mantel-Haenszel analysis (RR=1.92) only adjusted for menopausal status and crude parity.

Furthermore, it is generally assumed that any real positive cancer effect will show an increased risk with increased dose. Cramer only reported one subanalysis where he crudely considered dose response. He divided the small group of talc-dusted diaphragm users into those using diaphragms less than 5 years and into those using diaphragms more than five years. However, rather than showing an increased relative risk with increased dose (increased length of usage), the relative risk actually decreased noticeably

though not in a "statistically significant" fashion from 1.82 to 1.23 as diaphragm use increased from less than 5 years to more than 5 years.

In addition to the above interpretations of Cramer's own results, several potentially biasing factors could not be adjusted for by the logistic analysis. First, a possible positive correlation between talc use and ovarian disease etiology due to patient-perceived hygenic or cosmetic reasons would bias the relative risk upwards [4]. Second, a recall bias among hospital cases relative to community controls is quite plausible since cases may have greater incentive as well as opportunity to recall whether they should classify themselves as talc users [3]. Talc users from the community may well be modest in either participating as controls (the refusal bias already discussed) or in subsequently admitting talc use as a control subject. The recall bias might be expected to be even greater - as was possibly observed - for estimation of the relative risk for those using talc both on sanitary napkins and as a dusting powder (RR=3.28, p less than .001; or RR=2.44, p less than 0.05, after the refusal bias is eliminated) than for those engaged in only a single type of use.

Finally a talc and ovarian cancer study by Hartge, et. al. [4], appears to strongly contradict the reportedly positive Cramer study. Overall 135 cases and 171 control women matched by age, race and hospital were questioned on talc use. The estimated relative risk of ovarian cancer by talc users was reported to be 0.7 (95% confidence interval of 0.4 to 1.1). Adjustments for race, age, and gravidity (pregnancy) had no effect upon the estimate. No subanalyses

resulted in relative risks significantly greater than 1. It would appear that no refusal bias was operative in the Hartge study since none was reported. Also it would appear that recall bias was non-existent since there appeared to be no recall bias on the use or nonuse of douching.

SUMMARY

In summary, any hypothetical systemic added lifetime cancer risk (e.g., mesothelioma and lung cancer) to humans due to asbestos fibers in talc (principally for babies subject to 2 years of talc dusting) appears to be less than 10^{-8} added lifetime risk and possibly several orders of magnitude lower risk still, depending upon assumptions and uncertainties alluded to above, especially those regarding geometrical shape of any possible asbestos fibers in talc, and limits of detection for asbestos in talc. In addition, there appears to be no association between customary human talc use per se and ovarian cancer.

Robert Brown

Robert Brown

ATTACHMENT:

Signature Page

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Memorandum

Date May 21, 1985

From Robert Brown
BRAB, Division of Mathematics (HFF-118)

Subject Four methods of quantitating mesothelioma risk based on the Selikoff, et. al., insulation workers asbestos study. Technical support for QRAC's asbestos risk assessment.

To QRAC

In fig. 1 we have plotted on a log-log scale Selikoff's original mesothelioma incidence data vs. years since first exposure to asbestos. Incidence is defined as number of mesotheliomas/man-years exposure. The data do not seem to fit a single straight line. Uncertainties of exposure in the early part of the century and the general decline in intensity of asbestos exposure after World War II are possible sources of error. For these reasons, as well as general lack of fit of both recent data and distant past data, Peto recommended use of a more homogeneous subset of workers for quantitative purposes, namely those workers first exposed between 1922 and 1946 [8]. It can be inferred from Selikoff's report that this subset consists of about 4800 workers.

Peto reports 180 mesotheliomas (3.75%) among this subgroup out of a total of 236 mesotheliomas for all 17,800 workers followed from 1967 until about 1978 or 1979. Note that Selikoff only reported 175 mesotheliomas total; however, his reported follow-up period was also shorter (1967-1976).

Plotting Peto's homogeneous 1922-46 cohort subset, we see that $bt^{3.1}$ nicely fits the data (expressed as a straight line on log-log paper with a slope of 3.1). We also see that $b(t-10)^{2.1}$ nicely fits the data (with a different value for the constant b) and may be a reasonable

way of looking at mesotheliomas since the time lag from mesothelioma induction to death is not zero. The time of mesothelioma induction is not even a well defined concept and may be intimately entertwined with the concept of stage definition in, for example, a multistage cancer process. Nevertheless, both these model fits assume mesothelioma to be a nonincidental tumor (i.e., a life table where incidence is the ratio #tumor bearers/#survivors, re-expressed in man-years, per time interval). If we assume mesothelioma annual incidence to be better approximated by a prevalence or incidental definition, (#tumor bearers/#dead in interval), then $bt^{1.64}$ seems to be a rough though not very tight fit to the original Selikoff data. Peto's reported 1922-1946 data set does not easily allow determination of a prevalence fit. However, since the prevalence denominator is defined in terms of deaths per time interval rather than the much larger number of survivors to date, the first 2,271 deaths (12.7% of 17,800 workers) reported by Selikoff are very heavily weighted with the 1922-1946 cohort used exclusively in the two nonincidental curve fits above. Therefore comparisons of slightly different cohort subsets may still be useful. We estimate that the average time since first exposure for the Peto subset (1922-1946 first exposure) is about 37 years (Peto's 1978[+] follow-up) or 35 years (Selikoff's 1976 follow-up). This compares to 25 years average time since first exposure usually reported for all 17,800 workers. We also make the assumption that workers ceased exposure on average 3 years before death.

Method 1: based upon fitting $bt^{3.1}$ (nonincidental analysis) to a 1922-1946 cohort of the Selikoff, et. al. data.

A reasonably simple way to estimate the median life (ML) risk to median survival age 77 (in 1979) for humans exposed 2 yrs. to talcum powder during infancy is given by the product of the following terms:

(a) (77 yrs. since first exposure for infants/37 yrs. since first exposure for 1922-46 cohort as of 1978+)$^{3.1}$ = 9.70.

(b) (2 yr. infant exposure duration/34 yrs. approx. worker exposure duration for 1922-1946 worker cohort) = .059.

(c) (infant/worker) yearly exposure ratio = 0.3×10^{-6}.

(d) 1922-1946 cohort cumulative mesothelioma response of 3.75% (180 mesotheliomas/4,800 cohort members).

This product yields a median life risk of $R_{ML} = 0.64 \times 10^{-8}$.

Method 2: based upon $b(t-10)^{2.1}$ (delayed observation or time lagged nonincidental analysis).

Note that to estimate real mesothelioma incidence (time of mesothelioma induction - the last stage of the multistage cancer process) at age x, the worker must be assumed to have been autopsied or surgically inspected at some average age, say x+10. Thus, assumming the worker stops exposure 3 years before death, the component relative and absolute risk factors for incidence at age 77 now are the following:

(a) ((87 yrs.-10 yrs.)/(37 yrs.-10 yrs.)$^{2.1}$ = 9.03.

(b) (2 yr. infant exposure duration/(37-10) yr. worker exposure duration) = .074.

(c) (infant/worker) exposure rate ratio = 0.3×10^{-6}.

(d) 3.75% mesothelioma response in 1922-1946 cohort

Thus $R_{ML} = 0.75 \times 10^{-8}$.

Method 3: based upon $bt^{1.64}$ (prevalence or incidental analysis):

The relative and absolute risk product factors are:

(a) (77 yrs. since first exposure for infant/35 yrs. since first exposure for the 2,271 deaths to 1976)$^{1.64}$ = 3.64.

(b) (2 yr. infant exposure/34 yr. ave. worker exposure duration for 2,271 deaths to 1976) = .059.

(c) (infant/worker) exposure rate ratio = 0.3×10^{-6}.

(d) 7.7% mesothelioma cumulative prevalence to 1976 (175 mesotheliomas/2,271 deaths).

Thus $R_{ML} = 0.50 \times 10^{-8}$.

Method 4: based upon $bt^{3.1}$ (nonincidental analysis) and a first stage effect in a generalized multistage process.

We assume that bt^{k-1} fits the time-response data of a nonincidental tumor and is consistent with a first-stage-only effect in a generalized multistage process (with K stages), where biological time t starts at age of first exposure and continues until death [9]. Although this is not precisely true for the 1922-46 asbestos worker cohort, it appears to be approximately true. Moreover the time lag from cessation of exposure to end of followup (1976 or 1978^{+}) is assumed to be small compared to total duration of exposure (i.e., exposure duration is a large fraction of time since first exposure). However, the exposure duration for infants is very small compared to median lifespan. Thus, while we fit worker yearly incidence data to bt^{k-1} we should extrapolate yearly incidence (I) for exposed infants using the expression $I = b(t^{K-1} - (t-d)^{K-1})$ for a K stage multistage process with duration of exposure d and time since first exposure t [9].

Now K-1 = 3.1 from Fig. 1 and b can be written as the product of a constant K_m and f where f is the time adjusted yearly dose of asbestos fibers in ml-yrs. K_m is a constant dependent upon the type and dimensions of the asbestos. Since f = 3.43 f/ml-yr. (15 ave. f/ml in workplace (1922-1946) x 8 hrs./24 hrs. x 5 days/7 days x 50 wks/52 wks) for the Selikoff study, K_m can be computed from the plot of $I = K_m f\, t^{3.1}$ in Fig. 1. At t = 20 yrs, $I = 5.6 \times 10^{-4}$, implying that the $\ln K_m = \ln(5.6 \times 10^{-4}) - \ln(3.43) - 3.1(\ln 20) = -7.49 - 1.23 - 9.29 = -18.01$.

Thus $K_m = 1.51 \times 10^{-8}$ (same as Peto obtains). Continuing, $I = K_m f(t^{K-1} - (t-d)^{K-1}) = K_m f t^{K-1}(1-(1-d/t)^{K-1})$ which roughly = $K_m f t^{K-1}(d/t)(K-1)$ for d much less than t (using Taylor expansions). Thus yearly incidence is approximately $I = K_m fd(K-1)t^{K-2}$. Integrating (without correcting for decreasing survival) over a total of T years yields a cumulative incidence of about $I_c = K_m fdT^{K-1}$. If d = 2 yrs. infant exposure duration, T = 77 yrs., K-1 = 3.1, f = 3.43 f/ml-yr. for worker x 0.3×10^{-6} (infant/worker exposure ratio) = 1.03×10^{-6} f/ml-yr., and $K_m = 1.51 \times 10^{-8}$, then $I_c = 2.2 \times 10^{-8}$.

However, this figure assumes no mortality from competing causes of death and does not even adjust for the effect of previous mesothelioma related deaths. Factoring in a standard population age-specific mortality or corresponding survival function into the above integral would yield a median life risk of about 75% of 2.2×10^{-8} or $R_{ML} = 1.6 \times 10^{-8}$. This correction for survival can vary depending upon the limits of integration and what functional forms are under the integral, but for median life risk estimates the correction ranges from 1.0 down to .5 at worst. We also note that integrating I out to 100 yrs. of life with

respect to a standard mortality curve should yield approximately the same risk as cumulative incidence to median age 77 yrs. without any mortality adjustments. These approximately cancelling effects of two mathematical refinements may support the utility of using the median lifespan in simple calculations.

Comments on the 4 Mesothelioma extrapolation methods:

First and most importantly, it should be noted that the first 3 methods yield virtually identical median lifespan risks for babies exposed to talc for 2 years ($.5-.75 \times 10^{-8}$). Thus many of the debates over the "correct model" appear somewhat superfluous. In particular heated debates over whether mesothelioma rates follow given high or low powers of time appear to be superfluous since the power of time is compensatingly related to other poorly defined and difficult to measure conceptual model parameters (e.g., tumor stage initiation and consequent time lag to clinical detection or death, and context of tumor observation (incidental or nonincidental)). Furthermore, small perturbations of the rough estimates of worker exposure or the power of time (K) have only a small effect on the overall risk.

All the above models appear to be reasonable summary descriptors of the observable data and result in simple extrapolatory tools for the given problem of inferring median lifetime risk from infant exposure. One can always make method 4 computationally more difficult if one avoids use of the approximations.

A second observation is that the rough mutual agreement of the results of the 4 extrapolation methods does not necessarily imply that

the obtained excess median life risk is accurate even if the infant and worker exposure were to the same type and dimension of asbestos fiber. For example, none of the four models take into account the possibility that accumulated dose rather than yearly dose rate might more accurately reflect the biological burden of asbestos due, for example, to its ability to reside in vivo in the lung, pleural or peritoneal lining for years without being excreted (although encystment may be possible). Note also that we did not define dose on a mg/kg body weight basis. Although, we prefer such a definition for routine compounds that are ingested and metabolized, we strongly suspect that routine approach to be inappropriate for asbestos. In addition, all 4 methods assume linearity in response vs. dose at all dose levels. However, we have virtually no reliable dose response data from any of the epidemiological studies.

Furthermore, some investigators have suggested that the nonconstant accumulated asbestos dose may be as conceptually consistent with a late stage multistage carcinogenic process as the more usually defined yearly asbestos dose rate appears to be consistent with a first stage Armitage-Doll multistage process [9]. Although the theory and computations are more complicated for nonconstant exposures, it does appear that median life risks from infant exposure to asbestos affecting only a late stage in the carcinogenic process will generally result in much smaller risks than those calculated above for a first-stage-only effect in the carcinogenic process.

Our third observation which we have just hinted at is that method 4 above (the first-stage-only effect in a multistage model) may be just another way of implementing method 1, but just slightly more computationally difficult and having a slightly higher risk, partially because it substitutes a theoretical risk integration against the current (1979) U.S. population's standard survival function for the implicitly observable but poorer asbestos worker's cumulative survival of an earlier era in a more toxic environment. For example, the method 4 risk is about 2.6 times greater than the average risk of methods 1-3. There are probably other reasons for this 2.6 fold increase in risk over methods 1-3. However, since even partial intervention of asbestos fibers at later stages of the carcinogenic process in the Armitage-Doll multistage model imply lower overall risks, we prefer the simpler methods 1-3 at this moment to the more complicated multistage models whose proper application with respect to the stage or stages affected is still very much in doubt.

In general, we do not put a lot of faith in mechanical use of sophisticated but unverifiable models, but we will occasionally refer to them as in method 4 where we can suggest implicit and perhaps elucidative connections to apparently more humble and simpler procedures.

Summary:

All four mathematical methods of modelling the nonlinear mesothelioma response data from the Selikoff study indicate a lifetime added human risk to infants exposed 2 years to talc powdering of at most about 10^{-8} risk, and quite probably far less risk, if for example, asbestos intervenes in the carcinogenic process at a later stage than the first stage which was assumed in method 4 for the Armitage-Doll multistage process.

Robert N. Brown

Robert N. Brown

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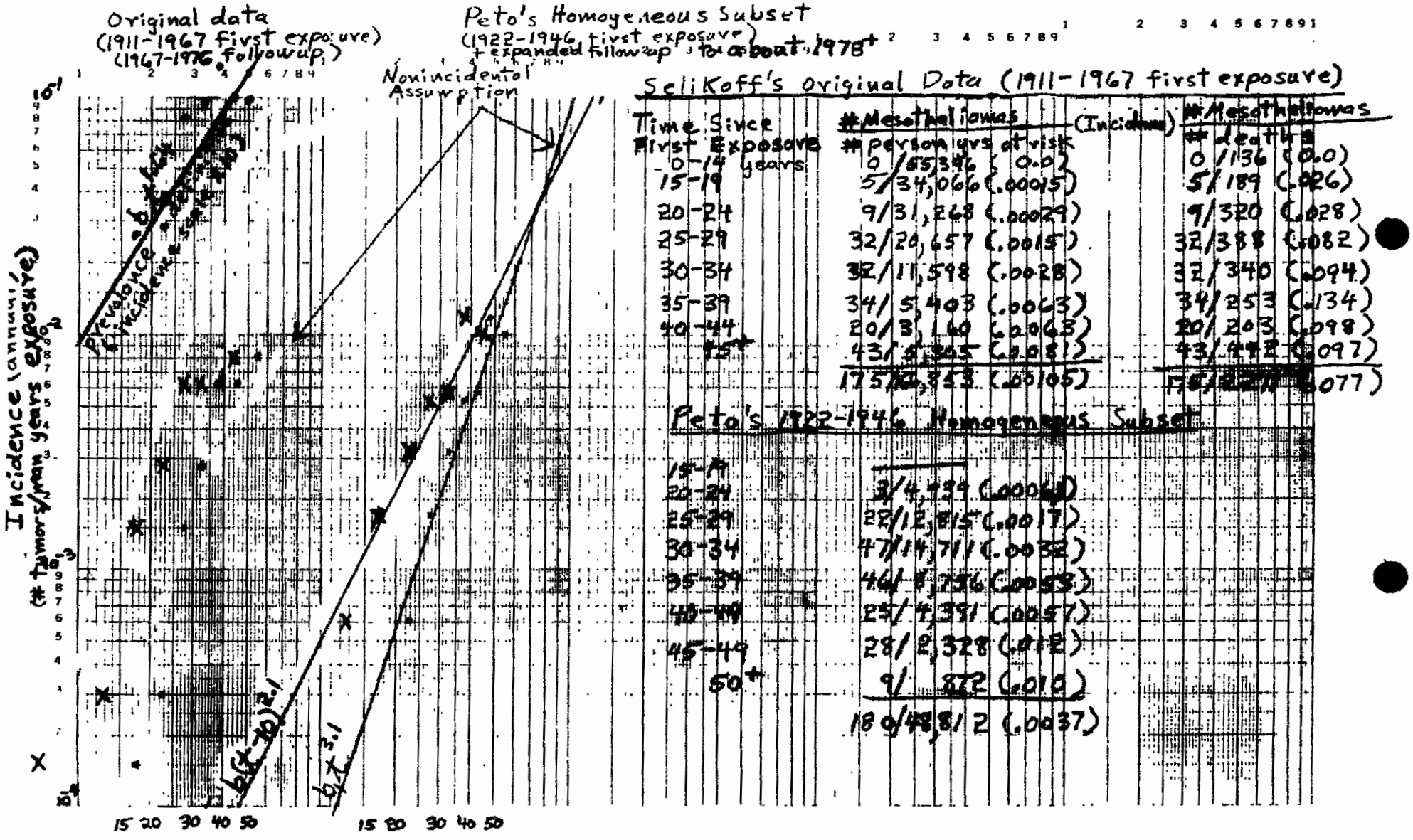
K-Σ LOGARITHMIC 3 × 5 CYCLES KEUFFEL & ESSER CO. MADE IN U.S.A. **Fig 1** 46 7520

SeliKoff Asbestos Study (17,800 workers an asbestos union. roles as of Jan. 1, 1967)

Mesotheliomas



SeliKoff's Original Data (1911-1967 first exposure)

Time Since First Exposure	# Mesotheliomas / # person yrs at risk (Incidence)	# Mesotheliomas / # deaths
0-14 years	0 / 65,346 (0.0)	0 / 136 (0.0)
15-19	5 / 34,066 (.00015)	5 / 189 (.026)
20-24	9 / 31,268 (.00029)	9 / 320 (.028)
25-29	32 / 24,657 (.0015)	32 / 388 (.082)
30-34	32 / 11,598 (.0028)	32 / 340 (.094)
35-39	34 / 5,403 (.0063)	34 / 253 (.134)
40-44	20 / 3,160 (.0048)	20 / 203 (.098)
45+	43 / 4,305 (.0081)	43 / 442 (.097)
	175 / 182,953 (.00105)	175 / [illegible] (.077)

Peto's 1922-1946 Homogeneous Subset

15-19	3 / 4,739 (.0006)
20-24	22 / 12,815 (.0017)
25-29	47 / 14,711 (.0032)
30-34	46 / 8,756 (.0053)
35-39	25 / 4,391 (.0057)
40-44	28 / 2,328 (.012)
45-49	9 / 872 (.010)
50+	
	180 / 48,812 (.0037)

November 15, 1984

Food Additives Evaluation Branch (HFF-156)

Request for Quantitative Analysis of Risk from Potential Exposure to Asbestos from Cosmetic Talc Use.

Quantitative Risk Assessment Committee
Attention: Ronald Lorentzen, Ph.D. (HFF-100)

CITIZEN'S PETITION 83P-0404

Philip Douillet
1 Holyoke Lane
Stony Brook, N.Y. 11790

Mr. Philip Douillet has submitted a petition requesting certain mandatory labeling on cosmetic talcs to warn consumers of asbestos hazards associated with such products.

BACKGROUND

Cosmetic talc is used as a face powder and body powder by both adults and children to lubricate the skin and prevent chafing and discomfort caused by moisture and heat. The normal use of cosmetic talc in infants has not been reported to be harmful[1], although the accidental aspiration of excessive amounts in infants has been reported to cause serious but reversible acute respiratory disease in some instances and death in isolated cases.[2-5]

As discussed below, talc, a hydrous magnesium silicate, occurs fairly commonly in nature. Table 1 lists the minerals that are commonly found in talc deposits.

FDA STATUS

There are no regulations concerning the use of talc as an ingredient in cosmetic products. Under current law, the burden of proof that a cosmetic may be harmful in that it contains a harmful substance rests with FDA. FDA must have data or other information demonstrating that a product contains a poisonous or deleterious substance that is harmful under customary conditions of use before any action can be taken either to restrict or prohibit the use of an ingredient or product.

TABLE I

	Mineral	Ideal formula
Carbonates	Calcite	$CaCO_3$
	Dolomite	$CaMg(CO_3)_2$
	Magnesite	$MgCO_3$
Amphiboles	Tremolite	$Ca_2Mg_5Si_8O_{22}(OH)_2$
	Anthophyllite	$(FeMg)_7Si_8O_{22}(OH)_2$
Serpentine	Antigorite	$Mg_3Si_2O_5(OH)_4$
	Chrysotile (uncommon)	$Mg_3Si_2O_5(OH)_4$
	Lizardite (uncommon)	$Mg_3Si_2O_5(OH)_4$
Others	Quartz	SiO_2
	Mica, e.g. Phlogopite	$K_2(Mg,Fe)_6[Si_6Al_2O_{20}](OH)_4$
	Chlorite, e.g. Penninite	$(Mg,Al,Fe)_{12}[Si,Al)_8O_{20}](OH)_{16}$

IDENTITY

Talc

Talc as a pure chemical compound is defined as hydrous magnesium silicate, $Mg_3Si_4O_{10}(OH)_2$ and consists of a brucite sheet containing magnesium ions sandwiched between silica sheets that are held together by relatively weak forces. A variety of elements such as nickel and iron may be included in the talc particle lattice but are so bound within the particle that they are not free to exert any biological action[6]. Talc can be tubular, granular, fibrous, or platy, but it is usually crystalline, flexible, and soft. Talc is a member of the family of silicate minerals that have a similar atomic structure and occur widely in a large number of different varieties. These silicate minerals are derived from metamorphic alteration of mineral rocks that sometimes include the amphibole and serpentine groups of asbestos after their exposure to specific temperatures, pressures, and circulating liquid solutions. Talc may be formed also by the thermal metamorphism of silicon dolomites.

The purity and physical form of any sample of talc dust as well as the other minerals that are associated with it are, therefore, directly related to the source of the talc and to the minerals found in the ore body from which it is mined. Talc commonly contains chlorites and carbonates, the former being sheet silicate minerals containing magnesium, aluminum, and iron. The carbonate mineral components of talc are mainly magnesite, dolomite, and calcite. Quartz (free silica), iron oxides, sulphides, and various silicates can also be associated with talc.

Since serpentine is one of the minerals from which talc has evolved, it can be associated with talc and is sometimes a contaminant of talc dust. Tremolite, a member of the amphibole group of asbestos, and chrysotile or antigorite of the serpentine group, are the commonest asbestos contaminants of industrial talc dust, although (according to Pooley, F.D., 1975) chrysotile has never been reported to be present in the high-grade talc used in health and cosmetic talc. As talc dusts are obtained from different sources, the amount and specific form of talc, as well as the amount and nature of mineral contaminants, will be different for each dust.

The U.S. Department of the Interior, in a letter dated February 24, 1984,[7] indicated that, with regard to talc deposits and whether any were asbestos free, talc deposits can contain the mineral tremolite. However, even for those deposits that do contain tremolite, it was stated that it is important to understand the distinction between non-fibrous (non-asbestiform) tremolite, which may be common to some talc deposits, and fibrous, asbestiform, tremolite, which is a very rare

form for that mineral. Similarly, actinolite and anthophyllite only very rarely have fibrous forms. Therefore, the presence of tremolite, actinolite, or anthophyllite in a talc deposit does not necessarily indicate the presence of asbestos, because they usually are not fibrous. Additionally, it was stated in the letter that the minerals crocidolite and amosite do not form in the same geological environment as talc; therefore, it is extremely unlikely that they would be found in any talc deposits. However, it is possible that chrysotile might occur in rocks in or around some talc deposits, but it would probably be in only very minor amounts.

As to what percentage of talc deposits might contain 0.5% or greater of asbestos, this would have to be evaluated for individual deposits. It is also stated that asbestos cannot be formed by shearing during mining. If asbestos minerals are not present to begin with, they will not be formed by mechanical means during mining or crushing operations. This last point is disputed by others.

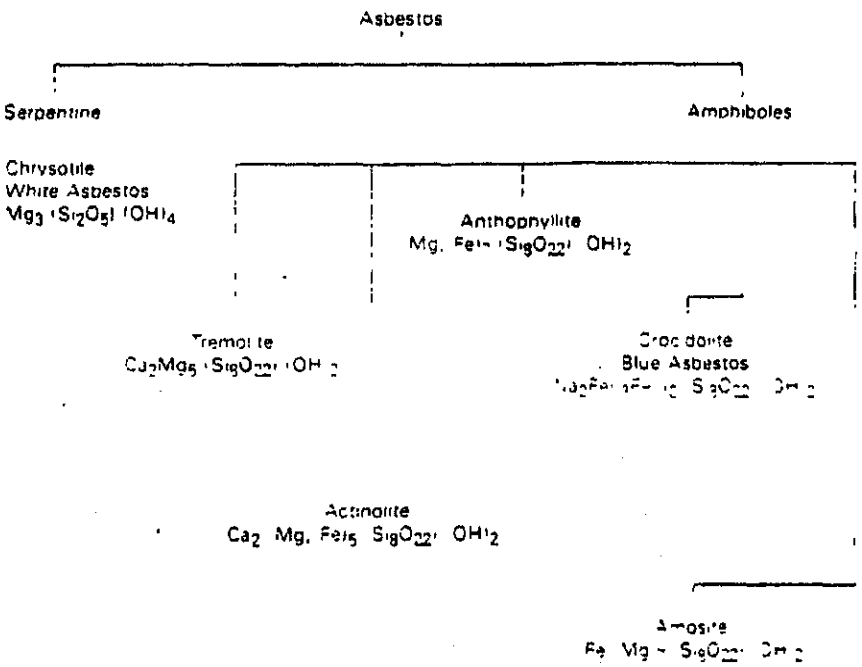
Asbestos

Asbestos is not one mineral but a generic term used to describe a family of naturally occurring fibrous hydrated silicates divided on the basis of mineralogical features into two groups: serpentines and amphiboles. The important property of asbestos as compared to non-asbestiform varieties of silicates is the presence of mineralogically long, thin fibers that can be easily separated. According to some definitions, there are as many as thirty varieties of asbestos, but only six are of commercial importance. These, together with their chemical composition, are shown in Figure 2.1.

The word "asbestos" is derived from the Greek word meaning "inextinguishable", and the origin of its name reflects one of its principle characteristics: fire resistance. But asbestos has many other qualities that enhance its commercial utility, among them tensile strength, durability, flexibility, and resistance to heat, wear, and corrosion. As an aside, because of its many uses (insulation material, as a fire retardant, linings for brakes and clutch facings, reinforcing agent in cement and pipes, as filters, etc.) and its natural occurrence, it is not surprising that asbestos is found in ambient air, in drinking water, and in foods.

The mineralogical classification of what is and what is not asbestos is complex, and as a result, many definitions of asbestos have appeared in the scientific literature. One definition of the term, asbestos, was published in the Federal Register in 1975 by the U.S. Occupational Safety and Health Administration (October 9, 1975, pp. 47652, 47760). According to this definition, asbestos is considered to include the naturally occurring minerals chrysotile, amosite, crocidolite,

Figure 2.1
Principal Varieties of Asbestos



SOURCE Dr. Eric J. Chatfield, "The Problems of Measurement of Asbestos," in Ontario, Royal Commission on Asbestos, *Proceedings of The Royal Commission on Asbestos, Second Public Meeting, Friday, December 12, 1980*, reported by Lydia Dotto (Toronto: Royal Commission on Asbestos, 1981), Appendix A, Figure 1, p. 2.

tremolite, actinolite, and anthophyllite, if the individual crystals or fragments are greater than 5 micrometers in diameter, and have a length to diameter ratio of 3 or greater.

Each of these six minerals included in OSHA's asbestos standard occurs in both an asbestiform and a non-asbestiform variety. Three of the six minerals have been given different names for each of their two forms. Chrysotile in its non-asbestiform variety is called antigorite. Crocidolite is called riebeckite. Amosite is called cummingtonite-grunerite. The other three minerals--because they occur in their asbestiform varieties so rarely in nature--are each called by only one name, regardless of their form. Tremolite, anthophyllite, and actinolite are labeled asbestos by OSHA in both their forms. According to mineralogists, this is incorrect, and it is poor science.

HEALTH EFFECTS

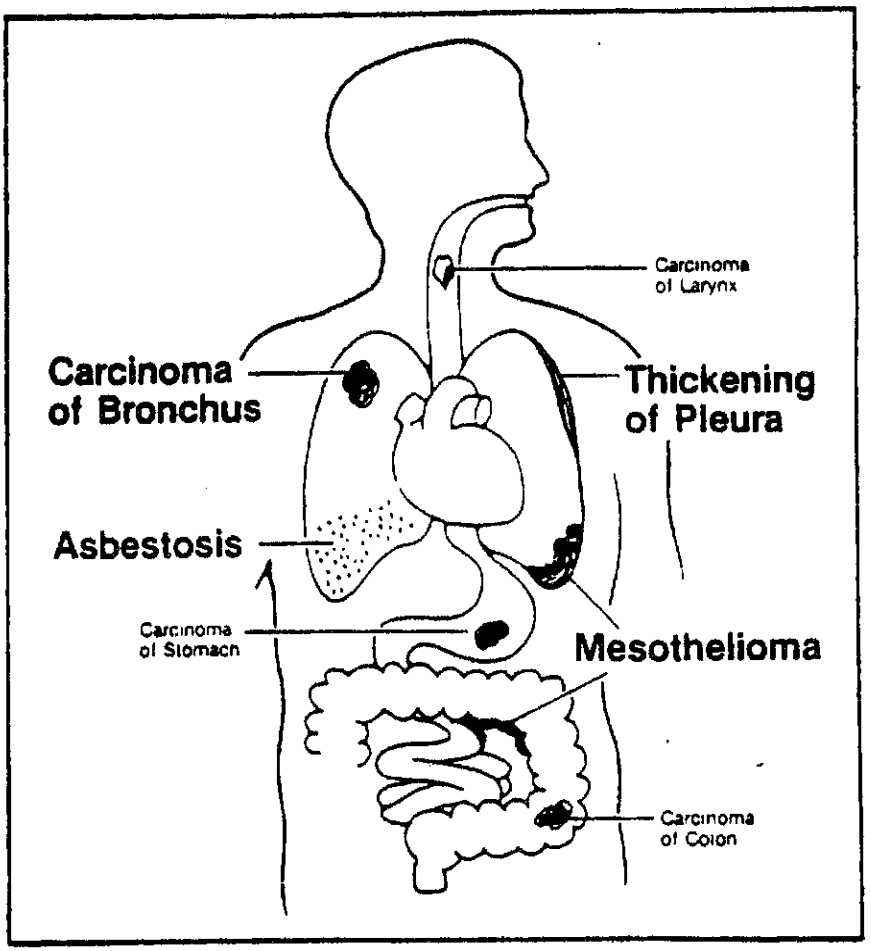
Evaluation of potential health effects from exposure to talc contaminated with asbestos and from other nonoccupational exposures to asbestiform fibers depends primarily on the results of epidemiological studies of occupational groups exposed to asbestos. Most of the data come from cohort studies (see Appendix I) of workers exposed to asbestos of various types and in a variety of industries and occupations. Much information has been obtained from these studies. However, they also suffer from limitations common to many epidemiological studies and from some additional problems related to determining dose (exposure) and response (health end point, such as death from a specific cause). Despite the limitations of individual studies, when all the studies are considered, exposure to asbestos increases the risk of developing lung cancer, mesothelioma, asbestosis, and possibly other cancers.

To quantify health risks from an exposure, it is necessary to obtain dose-response data, but exposure measurements are particularly difficult to obtain. Because of the long latency period for asbestos-associated diseases, investigators have found it necessary to try to reconstruct past exposures. Techniques of measurement vary from place to place and over time[8,9]. For example, fiber counts obtained by light microscope in various industrial settings may need to be multiplied by a factor varying from 2 to 8 to obtain a true count of fibers longer than 5 um.

Typically, a cumulative dose measurement is used. This does not take into account the time lapsed since last exposure nor does it distinguish between short exposures of high intensity and long exposures to low dust concentrations. In addition, a cumulative dose measurement does not change when exposure ceases. Variability in these exposure-related factors affects mortality responses in occupational cohorts. In some studies, exposure surrogates, such as type of job and duration of employment, are used to estimate exposure. These estimates may be less precise than actual measurements.

Figure 2.4

Principal Asbestos-Related Diseases and Conditions and Their Sites in the Human Body



SOURCE. Illustration by Mr. Jerry Farrell, Audio-Visual Centre, McMaster University, consultative assistance by Dr. David C. F. Muir, Director, Occupational Health Program, Health Sciences Centre, McMaster University, Hamilton, Ontario.

There may also be variability in reporting causes of death, ascertainment of deaths, and diagnostic accuracy of the reported cause of death. Inaccuracies are particularly likely for mesothelioma and asbestosis[10].

Methodological differences are a major source of variation in comparing studies[11]. For example, the results obtained will depend on the criteria for selecting the cohort, the choice of comparison groups, the influence of other environmental factors that may introduce competing disease risks, and the records available.

In addition, heterogeneity in the time at which onset of exposure begins can introduce additional distortion in the observed relative risks[12], especially because the types of exposure experienced by some workers in the distant past may differ from exposures experienced only more recently. Weiss also discussed how the results of lung cancer studies can be affected if persons who left a job are not included in the study cohort. He found that the exclusion of these workers could affect the relative risk by a factor of 2 to 3.

An additional difficulty is encountered when comparing dose-response results from mortality and morbidity studies, particularly if the morbidity studies are confined to active workers, which is usually the case. A bias is introduced in studies of active workers, since those with severe disease have probably already left employment. However, asbestosis generally progresses after cessation of dust exposures[13;14].

Numerous follow-up studies of asbestos-related mortality have been conducted on cohorts with varying intensity and duration of exposure, type of exposure, type of work, time and duration of follow-up periods, differences in the completeness of the cohort, completeness of mortality ascertainment, availability of smoking histories, geographic area of analysis. Because of the variations noted, it is not surprising that the standardized mortality ratios (SMRs) and dose-response results differ greatly among studies. In general, however, the same major diseases--lung cancer, mesothelioma, and asbestosis--have been observed, although not all investigators conducting these studies have reported or detected excesses of all three of these diseases.

Talc

The health effects of talc have been studied only in relation to occupational exposures[15-25]. Data available on the health hazards associated with occupational exposure to talc are not extensive. Exposure to talc itself in high concentrations has been shown to produce excess mortality, mainly due to respiratory diseases.

Workers from different geographic regions containing talc with or without fibers have been studied to determine if any adverse health effects are associated with the asbestiform fiber content of talc. Adverse effects have been found in some studies among workers exposed to talc both with and without fibers. These studies are discussed in the following paragraphs.

Epidemiological studies on workers exposed to talc containing fibers have demonstrated adverse effects on pulmonary function. In a study of 121 New York miners and millers exposed to talc containing tremolite and anthophyllite fibers, pulmonary function was found to be significantly decreased.[26] Reductions in forced vital capacity (FVC) and 1-second forced expiratory volume (FEV_1) were associated with employment duration and the amount of fiber present. Increased pleural thickening and calcification were detected in talc workers with 15 or more years of employment[26].

A mortality study of 398 New York miners exposed to talc containing fibers has demonstrated excess mortality from nonmalignant respiratory disease, excluding influenza, bronchitis, or pneumonia (5 observed/1.3 expected)[27]. An excess in lung cancer with an average latency of 20 years was also observed (9 observed/3.3 expected). Additional studies have had conflicting results. Some investigators have found no significant increases in lung cancer and nonmalignant respiratory disease[28], whereas others have reported significant increases in lung cancer, attributed to the silica content of talc.[29,30]

Morbidity and mortality studies have also been conducted on workers exposed to talc with low or undetectable levels of fibers. A study on the respiratory function of 103 Vermont talc workers indicated that there was a reduction in pulmonary function in smokers[31]. After adjusting for smoking, the effect of the exposure to talc was not statistically significant, although there was evidence of an exposure-related effect in workers with an annual dust exposure of approximately 1.5 mg/m^3. Exposure to talc dust was also associated with small opacities seen on chest radiographs.

Gamble et al.[26] conducted a cross-sectional study of 299 workers from Montana, Texas, and North Carolina who were exposed to talc containing low levels of silica and fiber. There was no significant difference in lung function, respiratory symptoms, or pneumoconiosis between workers and controls, although there was a significant increase in bilateral pleural thickening among the workers. Results of pulmonary pathology studies also have provided evidence of fibrosis in workers exposed to talc that does not contain fibers[33].

A mortality study of 392 Vermont workers exposed to talc not containing fibers showed that there were excess deaths from nonmalignant

respiratory disease, excluding influenza and pneumonia, among millers (11 observed/1.79 expected)[34]. This excess mortality was associated with small opacities seen on chest radiographs. An excess of respiratory cancer mortality among miners was also noted (5 observed/1.15 expected) but was attributed to exposures other than talc.

In a recent case-control study[37], increased risk of ovarian cancer was shown for women who regularly used talc either (or both) as a dusting powder on the perineum or on sanitary napkins compared to women who did not engage in either practice (See Table 4). No data with regard to asbestos contamination of the talc were provided. Studies of female asbestos workers are presented in Appendix I.

Table 4: Relative Risks (RR) for Common Epithelial Ovarian Cancers Associated with Talc Exposure in Perineal Hygiene

			Types of Perineal Exposure		
	No perineal exposure	Any perineal exposure	As dusting powder but not on napkins	On napkins but not as dusting powder	Both on napkins and as dusting powder
Cases (Total = 215)	123(57.2%)	92(42.8%)	43(20.0%)	17(7.9%)	32(14.9%)
Controls (Total = 215)	154(71.6%)	61(28.4%)	34(15.8%)	14(6.5%)	13(6.0%)
Crude rr	1	1.89	1.58	1.52	3.08
Adjusted RR*	-	1.92	1.55		3.28
95% confidence limits	-	(1.27-2.89)	(0.98-2.47)		(1.68-6.42)

*Adjusted for parity and menopausal status

Note: A study (reviewed in Appendix II) of mesothelioma incidence in domestic dogs concluded that there was an association between the incidence of mesothelioma and asbestos exposure; the source of exposure of the dogs was from the use of flea powders and/or the owners asbestos-related occupations (hobbies).

Additionally, an animal inhalation study (reviewed in Appendix II) with talc (Italian 00000 grade) did not indicate talc to be carcinogenic.

Asbestos

Asbestos associated diseases generally have been related to occupational exposures, such as those experienced by some miners, insulators, and factory workers (see Appendix I). Recently, however, there has been concern that exposures to asbestos and related fibers may present a health hazard to the general public.

Because asbestos and other asbestiform fibers appear to be ubiquitous, virtually everybody is exposed to some extent. During autopsy, asbestos fibers have been detected in the lungs of most urban residents studied. Reported concentrations of asbestos in urban air are shown in Table 7-6. Exposure to the general public is of concern because the population involved is large and includes unhealthy persons. Also, exposure may begin in childhood (as with baby powder application), leaving a longer time for the development of adverse effects. Additionally, asbestos may enhance the carcinogenic effects of other materials. There is little information about the health effects of most nonoccupational exposures to asbestos (see NAS report, Ref. 100). Although babies have been powdered with talc powder for many years, there is no evidence that this has resulted in an increase in asbestos-related disease.

Three principal diseases are related to exposure to one or more of the commercial asbestos minerals. These are: (1) lung cancer, which includes cancer of the trachea, bronchus, and the lung proper; (2) mesothelioma, a cancer of the pleural and peritoneal membranes that invest the lung and abdominal cavities, respectively; and (3) asbestosis, a diffuse interstitial fibrosis of the lung tissue often leading after long exposure to severe loss of lung function and respiratory failure. These diseases are not equally prevalent in the various groups of asbestos workers that have been studied; the amount and type of disease depend on the duration of exposure, on the intensity of exposure, and possibly on the type or types of asbestos to which the individual was exposed. Only lung cancer and mesothelioma will be considered here. Asbestos appears to act principally as a late stage carcinogen (promoting agent) that multiplies the underlying risk of lung cancer that occurs in the absence of asbestos exposure. The nature of the dose-response relationship for asbestos-related diseases is discussed below.

TABLE 7-6. Summary of Environmental Asbestos Exposure Samples[a]

Sample Sets	No. of Samples	Measured Concentration (ng/m^3) Median	Measured Concentration (ng/m^3) 90th Percentile	Equivalent Concentration (fibers/cm^3)[b] Median	Equivalent Concentration (fibers/cm^3)[b] 90th Percentile	Reference
1. Paris air	161	0.7	3.2	0.00002	0.00011	Sebastien et al., 1980
2. Paris (outdoor control)	19	0.7	5.2	0.00002	0.00017	Sebastien et al., 1980
3. Outdoor control samples, for U.S. schools	31	0.9	9.8	0.00003	0.00033	Constant et al., 1982
4. Air of 48 U.S. cities	187	1.6	6.8	0.00005	0.00023	Nicholson, 1971
5. Air of U.S. cities	127	2.3	7.8	0.00008	0.00026	U.S. Environmental Protection Agency, 1974
6. Air of five U.S. cities (outdoor control sample)	34	6.7	31.9	0.00022	0.00106	Nicholson et al., 1975, 1976
7. New York City air	22	13.7	42.9	0.00046	0.00143	Nicholson et al., 1971
8. Air 0.5 mile (0.8 km) from asbestos spraying	17	22.5	82.6	0.00075	0.00275	Nicholson et al., 1971
9. Air in U.S. schoolrooms without asbestos	31	16.3	72.7	0.00054	0.00242	Constant et al., 1982
10. Air in Paris buildings with asbestos surfaces	135	1.8	32.2	0.00006	0.00107	Sebastien et al., 1980
11. Air in U.S. buildings with cementitious asbestos	28	7.9	19.1	0.00026	0.00064	Nicholson et al., 1975, 1976
12. Air in U.S. buildings with friable asbestos	54	19.2	96.2	0.00064	0.00321	Nicholson et al., 1975, 1976
13. Air in U.S. schoolrooms with asbestos surfaces	54	62.5	550	0.00208	0.01833	Constant et al., 1982
14. Air in U.S. schools with damaged asbestos surfacing materials	27	121.5	465	0.00405	0.01550	Nicholson et al., 1978

[a]Adapted from Nicholson, 1983.
[b]Based on conversion factor of 30 µg/m^3 = 1 fiber/cm^3.

(1) Lung Cancer

Most epidemiological studies (reviewed in Appendix II) of asbestos workers that have demonstrated an excess lung cancer risk associated with the inhalation of asbestos have produced results consistent not only with a linear relationship between cumulative dose and mortality, but also consistent with the absence of a threshold. In all of these studies, there appears to be a progressive and proportional increase in the SMR (standard mortality ratio) for lung cancer with increasing dose and no evidence of a threshold level. This evidence cannot be accepted without some qualification, however. All of the studies have the intractable difficulty of separating out the effects of cumulative dose from duration of exposure.

Persons exposed to asbestos nonoccupationally can be at increased risk of contracting these asbestos-associated cancers. In one of the first studies linking asbestos exposure and mesothelioma, the disease was found among residents of an asbestos mining area in South Africa. These subjects had presumably inhaled the material in the surrounding air.[42] In another study, persons living in households with asbestos factory workers in New Jersey were reported to be at increased risk of asbestos-associated disease.[45]

There is debate about the carcinogenic risk at low exposure levels of asbestos because lung cancer risks at low doses over a working lifetime have not been estimated to date by observation but rather by extrapolation from observed risks at higher exposure levels.[44] Accordingly, there is no direct evidence of the existence or absence of a threshold for lung cancer. It may arguably be the case that with further inquiry and better information the scientific community will be able to demonstrate that there is a dose level for asbestos for which the body's defense mechanisms are effective, or that asbestos acts differently at lower rather than higher doses, thus demonstrating a threshold level for the induction of cancer. At the present time, that information does not appear to exist. Since a threshold dose level for asbestos-related lung cancer has not been established, many investigators conclude that it is prudent to assume that there is none and that any dose may induce lung cancer.[45] A linear non-threshold model is less likely to underestimate the risk at low doses than any other plausible model.

(2) Malignant mesotheliomas are rare cancers that appear as thick, diffuse masses inside any of the serous membranes (mesothelia) that line body cavities. Epidemiologic research has shown that exposure to asbestos can produce mesothelioma at two sites: the pleura (the serous membrane that surrounds the lungs and lines the thorax) and the peritoneum (the serous membrane that surrounds the abdominal organs and lines the abdominal and pelvic cavities).

The status of pleural and peritoneal mesothelioma as marker diseases for asbestos exposure stems from the fact that these diseases seldom occur in people who have not been exposed to asbestos in excess of normal ambient levels.

The nature of the dose-response relationship for mesothelioma has been less firmly established than that for either lung cancer or asbestosis. Indeed, it has been suggested that very trivial doses of asbestos are capable of inducing the disease and that as a result there is no dose-response relationship for mesothelioma at all.[46] That mesothelioma is associated with low levels of exposure for brief periods of time appears to be based upon isolated anecdotal case reports and upon more systematic case-series reports of mesothelioma arising from non-occupational household or neighborhood exposures.[47,48] Newhouse et al.[48] reported nine cases of mesothelioma in family contacts of asbestos workers and eleven cases among individuals whose only identified asbestos exposure was associated with living within one-half mile of an asbestos factory. In these cases of non-occupational exposure, pleural mesotheliomas predominated over peritoneal mesothelioma. The evidence is not inconsistent with the existence of a dose-response relationship for mesothelioma. Although deaths from mesothelioma have been reported after what appear to have been brief (for gas mask workers) or low (for family contact and neighborhood cases) exposures, the Ontario Commission[49] concluded that the evidence suggests that the actual exposures approached or were equivalent to corresponding occupational exposures; it further agreed with the IARC[50] conclusion that there is no evidence of risk of mesothelioma to the general population.

There is a time interval between the initial exposure to asbestos and the clinical manifestation of the diseases it causes. The latency period for cancer is thought to be long; rarely less than 10 years and often more than 20 years. Mesothelioma appears to have the widest range of latency--again, they rarely occur less than 10 years from the time of first exposure to asbestos, but they can occur as many as 40 years or more from the onset of exposure.[51] It has been suggested that the death rates from mesothelioma appear to rise at an exponential rate from the time since first exposure; death rate appears to rise at a rate between the third and fourth power of time since first exposure;[52,54] other work suggests the fifth power of time.[55] What the data demonstrate is that the incidence of mesothelioma rises rapidly the longer the time period since a person is first exposed to asbestos. As a result, the age at which a person is first exposed to asbestos becomes a very significant factor in determining the overall risk of contacting mesothelioma.

While the mesothelioma incidence rates appear to be independent of the age at which exposure first took place, the practical result is that the risk of contacting mesothelioma is greater the earlier in life one is first exposed. (This is important to keep in mind when considering baby

powder exposure.) The magnitude of the risk will still depend on the amount and duration of exposure (and, possibly, fiber type); and where that exposure is minimal, the risk, albeit greater for exposures earlier rather than later in life, will also be minimal.

The disease rate of lung cancer among persons exposed to asbestos appears to be quite unlike that of mesothelioma. Rather than being time-dependent, lung cancer rates appear to be age-dependent.[56] The majority of lung cancer deaths, both in smokers and non-smokers, occur after age 50 and over half occur after age 60, irrespective of the time of first exposure. This suggests that the risk of contracting lung cancer is much greater in older groups than in younger groups. Asbestos exposure appears to have the effect of multiplying the risk of lung cancer that exists apart from that exposure; and the risk of lung cancer contributed to by asbestos exposure appears to be virtually independent of the age when that exposure took place and will be simply proportional to cumulative dose.

The consistency of an increased cancer risk at extrathoracic sites and its magnitude are less for cancer at other sites than for lung cancer. Nevertheless, many studies document significant cancer risks at various GI sites. Cancer of the kidney has also been found to be significantly elevated. Among female workers, ovarian cancer has been found in excess (Appendix I, #16). While no other specific sites have been shown to be elevated at the 0.05 level of significance, the category of "all cancers other than lung, GI tract, or mesothelial" is significantly elevated.

Several epidemiological investigations reported in the literature provide data on exposure levels of asbestos related to mortality and specific cause of death, while most do not provide exposure data. Those with relevant data are reviewed in Appendix I (see Summary table). In these investigations, different epidemiological approaches were used, various definitions of the study groups were adopted, observations took place over different periods of time, types of controls varied, time interval from first exposure was unknown, some workers exposed to more than one type of fiber, etc.

Several studies are briefly described below:

Mining and Milling

Chrysotile. Three cohorts occupationally exposed to chrysotile asbestos during mining and milling operations had a moderately increased risk for lung cancer (SMRs from 1.0 to 2.6). In the largest investigation, McDonald et al. (1980)[57] studied all employees who had worked for at least 1 month in Quebec mines. From 1950 to 1975, 3,291 deaths occurred among the 9,850 male employees successfully traced and followed for 20 years or more after initial employment. An increase in lung cancer

mortality was observed (SMR = 1.3, 230 observed vs. 184 expected), and the risk increased with duration of employment (SMR = 1.0 for < 1 year to 1.6 for ≥ 20 years) and level of exposure (SMR = 0.9 for < 30 mppcf(yr) to 2.3 for ≥ 300 mppcf(yr). Eleven cases of mesothelioma were observed.

Anthophyllite. Male and female employees of anthophyllite asbestos mines in Finland were studied by Meurman et al. (1974, 1979),[58,59] who reported a two-fold increase in lung cancer mortality (44 observed vs. 22.4 expected) and no mesotheliomas among the 1,045 persons successfully traced. All lung cancer deaths occurred among the male employees, and the risk was associated with estimated intensity of exposure (SMR = 1.4 vs. 3.3 for low and heavy exposures, respectively). Lung cancer risk among nonsmoking asbestos-exposed employees was 1.4 compared to a relative risk of 17.0 for the asbestos-exposed employees who smoked.

Crocidolite. For exposure associated with crocidolite mining in Western Australia, there was a similar increase in risk of lung cancer (SMR = 1.6, 60 observed vs. 38.2 expected) and a strong association with mesothelioma.[60] Twenty-six cases of pleural mesothelioma were observed among the 526 deaths, and the mesothelioma risk increased with increased duration and intensity of exposure. Follow-up period was relatively short.

No increases in gastrointestinal cancer were observed for any of the mining and milling cohorts reviewed.

Manufacturing

Chrysotile. Most asbestos exposures associated with manufacturing processes involve mixed fiber types, but Dement et al. (1982, 1983a,b)[9,61,62] examined the risks associated with exposure to chrysotile asbestos in textile factory workers. They observed a marked increase in lung cancer mortality (SMR = 3.2, 35 observed/11.1 expected), and the risk was strongly correlated with exposure level. There was also one peritoneal mesothelioma. Increased risks for both lung cancer and nonmalignant respiratory disease were observed at exposure levels lower than those reported in other studies.

Amosite. Mortality due to lung cancer was increased three- to four-fold (83 observed /22.8 expected) for 820 factory workers exposed to amosite asbestos.[63] The higher risks were observed for the subgroup followed 20 years or longer after initial employment (SMR = 5.1, 52 observed/10.1 expected). This cohort is a somewhat unusual population because of its limited duration of intense work exposure (1941-1945) and long period of observation. Other excess cancers, including 14 mesotheliomas, were also reported.

Mixed. Newhouse and Berry (1979)[64] reported increased risks of lung cancer mortality for both males (SMR = 2.4, 103 observed/43.2 expected) and females (SMR = 8.4, 27 observed/3.2 expected) in a follow-up study of 4,600 male and 922 female employees of an East London asbestos factory in which crocidolite and amosite were used. Approximately 10% of all deaths resulted either from pleural or peritoneal mesothelioma.

Except for 10 cases of mesothelioma, no increased cancer mortality was observed among more than 11,000 males and females employed during 1941 or later at a British factory producing friction materials.[65,66] In a case-control study that corrected for total asbestos exposure, 5 of 6 cases had definitely worked with crocidolite, whereas 2 of 10 controls had.

A cohort of 1,345 retired asbestos products workers employed from 1941 to 1967 had increased risks for lung cancer (SMR = 2.7, 63 observed/23.3 expected) and gastrointestinal cancer mortality (SMR = 1.4, 55 observed/39.3 expected).[67] Overall mortality among the 1,075 retirees successfully traced to 1973 was 73%. The lung cancer risk was strongly associated with the amount of exposure, expressed as million particles per cubic foot multiplied by number of years of exposure (mppcf-yr), ranging from a SMR of 2.0 up to 7.8. Lung cancer risk differed by type of asbestos exposure (SMR of 2.5 for chrysotile alone vs. 5.2 for mixed chrysotile and crocidolite exposures). Five mesothelioma deaths were observed. Study results suggest that effects of asbestos exposure on lung cancer risk may continue long after the termination of exposure. Studies of a retiree cohort may result in an underestimation of actual risks, since deaths among employees under age 65 would be omitted. The Consumer Product Safety Commission (1983)[68] suggests that the risks may be understated by as much as two-fold.

No increase in lung cancer mortality or cancer of any other site, except mesothelioma, was observed in the cohort of 5,645 employees of an asbestos-cement product manufacturing facility studied by Hughes and Weill (1980).[69] In the high exposure subgroup, lung cancer risk was increased for employees exposed to crocidolite, and two mesothelioma deaths were reported. The low overall mortality, 10.6%, and the low tracing rate, approximately 75%, suggest that this study may have resulted in an underestimate of mortality risks.

Finkelstein (1983)[70] studied 328 asbestos-cement workers hired before 1960 and employed for a minimum of 9 years. Mesothelioma was strongly associated with exposure level for production workers, whereas a dose-response relationship was not observed for lung cancer. Excess lung and gastrointestinal cancers were observed.

Clemmesen and Hjalgrim-Jenson (1981)[71] studied cancer incidence among 6,372 Danish males who worked in asbestos-cement factories between 1944 and 1976. There were 55 cases of respiratory cancer compared to 33

expected, based on Danish Cancer Registry incidence rates. Three mesotheliomas were observed in addition to excess prostate, laryngeal, and stomach cancers. Cancer incidence in the unexposed employees at the same factories was not increased.

Jones et al. (1980b)[72] studied a cohort of 578 females exposed to crocidolite from western Australia during the manufacture of gas masks. The 12 cases of lung cancer (SMR = 1.9, 12 observed/6.3 expected) and the 17 mesothelioma cases (13 pleural and 4 peritoneal) were all exposed to crocidolite, whereas no cases of mesothelioma or lung cancer occurred among the 102 females exposed only to chrysotile. Overall, 10% of deaths were due to mesothelioma. Risk of mesthelioma was strongly associated with duration of exposure, although no dose-response relationship was observed for lung cancer.

Similar results were reported among 1,304 females who manufactured gas masks at three locations followed from 1951 to June 30, 1980.[8] Deaths from lung cancer (SMR = 2.0, 22 observed/11 expected) and ovarian cancer (SMR = 2.2, 17 observed/7.8 expected) were increased. Lung cancer excess was higher for those exposed predominantly to crocidolite compared to those exposed predominantly to chrysotile. Five of the six mesotheliomas occurred in those exposed predominantly to crocidolite.

All studies of occupational cohorts exposed to asbestos during manufacturing processes had an overall increased risk of lung cancer or a dose-response relationship in the exposure subgroups.[69,77] Elevated risk ratios (1.1) for gastrointestinal cancer were observed in six of the nine cohorts reviewed.[62,63,65,67,70,71]

Insulation

Mixed. All three of the cohorts involved in end product use of asbestos as insulators were exposed to mixed types of asbestos. One of the largest studies is that of Selikoff et al. (1979),[74] who studied 17,800 members of an insulator's union. Overall mortality in this cohort was 12.8%; 2,271 deaths were reported through 1976. Lung cancer risk was increased four-fold (429 observed/105.6 expected) and increases were observed for gastrointestinal cancer (SMR = 1.6, 94 observed/59.4 expected), cancer of the larynx, pharynx, buccal cavity (SMR = 1.7, 25 observed/14.8 expected), and kidney (SMR = 2.2, 18 observed/8.1 expected). Dose-response relationships were not examined because of the lack of exposure data. Mesotheliomas (63 pleural and 112 peritoneal) accounted for 7.7% of the deaths. Analysis of the relationship between smoking and lung cancer risk using data from the American Cancer Society indicated a consistent multiplicative effect, in that a 10-fold increase in risk of lung cancer was associated with smoking in both asbestos-exposed and unexposed groups. A five-fold increase in lung cancer risk was associated with asbestos exposure in both smokers and nonsmokers.[10]

Elmes and Simpson (1977)[75] reported an unusually high risk of lung cancer (SMR = 7.0, 35 observed/5 expected) and gastrointestinal cancer (SMR = 5.9, 13 observed/2.2 expected) for a cohort of 162 insulators and pipe coverers employed in Northern Ireland during 1940. Overall mortality in this cohort was 75.3% by 1975; 54% of the deaths were due to cancer. Thirteen cases of mesothelioma (eight pleural and five peritoneal) were reported. No difference in cancer risk was apparent for workers first employed before or after 1933. Ascertainment bias is unlikely to explain the magnitude of the risks reported for this cohort.

Shipyards

Mixed exposures. Rossiter and Coles (1980)[76] studied 6,076 dockyard workers employed before 1947. They reported no increase in lung cancer mortality (SMR = 0.7, 84 observed/119.7 expected) or gastrointestinal cancer (SMR = 0.8, 63 observed/83.3 expected). Mesothelioma was reported for 31 (3%) of the 1,043 deaths. However, since less than 20% of this cohort have died, excess cancers may not be fully apparent.

In a study of 2,190 Italian dockworkers, Puntoni et al. (1979)[77] observed increased risks for lung cancer (SMR = 2.2, 123 observed/54.9 expected), gastrointestinal cancer (SMR = 1.3, 74 observed/58.6 expected), laryngeal cancer (SMR = 1.9, 15 observed/7.7 expected), and kidney cancer (SMR = 2.0, 29 observed/14.7 expected).

EXPOSURE

Talc

Values between 800,000 and 960,000 tons have been reported as the amount of talc used commercially in the U.S. each year.[78,79] Talc is used in a number of industries, for a variety of purposes; e.g., the manufacture of ceramics, paints, paper, rubber, roofing, insecticides, stucco, plastics, textiles, and soaps. Pulverized talc is also used as an ingredient in such consumer products as cosmetic talcums, paper mache, and modeling compounds, in spackling, patching compounds and putties, in automotive and boat body repair fillers, and caulking compounds. The uses of talc in food products include rice coating, peanut polishing, candy molding, and salami dusting. It is also used as a filler and excipient for pharmaceutical pills, and for dusting contraceptive diaphragms. Each product carries with it a distinct and individual inhalation and/or ingestion potential of the mineral components. An estimated 30,000 tons of cosmetic-grade talc are used in cosmetic, pharmaceutical, and food products.[80]

Talc Contamination

The table below shows the principal minerals that can be combined with talc in natural deposits.[89-91]

MINERALS COMMONLY ASSOCIATED
WITH TALC IN NATURAL DEPOSITS

Carbonates:	calcite, dolomite, magnesite
Amphiboles:	tremolite, anthophyllite
Serpentines:	chrysotile, antigorite, lizardite
Others:	quartz, mica, chlorite, rutile, pyrophyllite

A 1968 study conducted by United States researchers[92] on 22 talc samples for cosmetic use showed values between 8 and 39% fibrous particles, whereas a similar study on 80 industrial talc samples conducted by N.B.S. researchers[93] indicated the presence of fibrous particles in the samples in percentages which vary from 2 to 30%. In both cases the fraction of these percentages made up of asbestos was not specified. Research conducted in Great Britain[94] on talc powders for various uses has shown that of the 27 samples examined, 3 contained tremolite. More complete and significant data are indicated for 20 talcs for cosmetic use and one talc for pharmaceutical use sampled in the New York area from 1971 to 1975: of the cosmetic products analyzed, 10 contained tremolite and anthophyllite in amounts varying from 0.1 to 14 wt.%, and showed a detectable quantity of chrysotile. (This is in conflict with Pooley who stated that no chrysotile has been found in cosmetic talc.) In an Italian article published in 1982[96], 15 samples of talc products (for industrial, cosmetic, and pharmaceutical uses) were analyzed for asbestos contamination using transmission electron microscopy and the associated analytical techniques such as electron diffraction and x-ray microanalysis. In eight of the 15 samples, the presence of asbestos was detected; in seven cases tremolite fibers were observed and in one case, chrysotile (see Table 9).

TABLE 9. PERCENTAGE OF FIBROUS PARTICLES AND ASBESTOS FIBERS IN SOME COSMETIC TALCS.

KEY: (a) % fiber in the particular matter
(b) % fiber 5 um in the particular matter
(c) % asbestos fiber in the total fiber
(d) % asbestos fiber in the particular matter, and
(e) variety of asbestos

	(a)	(b)	(c)	(d)	(e)
A	6.1±0.9	1.6±0.5	<2	<0.1	--
B	21.6±1.6	5.0±0.9	<2	<0.4	--
C	11.1±1.1	3.2±0.6	<2	<0.2	--
D	4.9±0.5	0.7±0.2	32±4.7	1.6±0.3	Tremolite
E	10.3±0.7	3.2±0.4	<2	<0.2	--
F	5.1±0.6	1.8±0.4	10±3	0.5±0.2	Tremolite

Consumer talc products marketed before 1973 were variably contaminated by asbestos. In October, 1976, the Cosmetic, Toiletry, and Fragrance Association (CTFA)[97] revised their guidelines for talc and recommended that no sample containing asbestos detectable by x-ray diffraction and optical microscopy with dispersion staining should be sold. Adherence to the revised CTFA guidelines is voluntary and monitoring of samples is left to individual manufacturers.

Samples of cosmetic talc products were analyzed in 1979 by the Division of Cosmetics Technology using x-ray diffraction (XRD). Samples found to be contaminated with tremolite or anthophyllite by XRD were also examined by optical microscopy (OM) to determine crystal morphology. In all cases, the amphiboles found (tremolite and anthophyllite) were present in the massive (non-fibrous) form. The level of detectability is approximately 0.1% for tremolite and 2% for anthophyllite. None of the samples was found to contain serpentine at a detectability limit of 1-2% (XRD). These samples were submitted for SEM analysis and, if fibers were found, the samples were to be examined by energy dispersive x-ray analysis (EDXA) to determine the nature of any fiber-like particle detected. The results of the latter (SEM and EDXA) analyses are not known to this reviewer. No analyses of cosmetic talc have been performed by FDA since 1979. As noted previously, there are non-fibrous forms of minerals with essentially the same chemical composition as the asbestos varieties. In some cases the non-fibrous form has the same name as its fibrous counterpart; e.g., tremolite. According to the U.S. Department of the Interior, non-fibrous (non-asbestiform) tremolite is the common form of this mineral, while fibrous tremolite (asbestiform) is a very rare form for this mineral.[7]

Asbestos

As stated above, asbestos bodies can be recovered from the lungs of virtually everyone in the population, on autopsy. These observations suggest that the entire population is being exposed to asbestos.

Several studies have assessed the environmental air pollution by asbestos using the transmission electron microscope (TEM) or the scanning electron microscope (SEM). European cities have shown levels as follows: 0.1-1 ng (10^{-9} gm^{-3} or ng^{-3}) of chrysotile asbestos in English cities, 10^{-2}-10^{4} asbestos fibers per cubic meter of air in Dusseldorf,[R] and 0.1-10 ng^{-3} of chrysotile asbestos in Paris. Higher concentrations (0.1-100 ng^{-3} of chrysotile asbestos) have been found in U.S. cities. The highest concentrations have been found in New York City (see Table 7-6).

Asbestos fibers have been detected in rural locations (0.01-0.1 ng m^{-3}) removed from known sources of emission suggesting the existence of background air pollution by asbestos fibers (especially chrysotile) in industrial countries.

It is to be noted that an appreciation of the extent of air contamination by asbestos depends upon which of two approaches to its measurement is adopted. If the conventional practice of counting only fibers longer than 5 um is followed, the concentrations away from immediate industrial activities are low or undetectable and even some of those in and around asbestos industries approach tolerable levels. But, if the concentration of smaller fibers is taken into account and particularly the mass concentrations revealed by electron microscopy, the situation changes. Up to 10 ng/m^3 seems to be virtually ubiquitous in urban communities.

It is to be noted also that analysis of ambient air samples for asbestos has utilized techniques different from those used in occupational circumstances because typical urban air may contain up to 100 ug/m^3 of particulate matter in which one is attempting to quantify asbestos concentrations from about 0.1 ng/m^3 to perhaps 1000 ng/m^3. Thus asbestos may constitute only 0.0001 to 1% of the particulate matter in a given sample.

It is difficult to make quantitative estimates of exposure to asbestos. A common unit of cumulative dose for occupational exposures is obtained by multiplying the average concentration of fibers in workplace air by the number of years that an individual worked there (full-time equivalent). The concentration of fibers in workplace air is expressed as fibers > 5 μm long/cm^3, as counted by the light microscope (LM) under specified conditions ((U.S. National Institute for Occupational Safety and Health, 1977); (fibers/cm^3) yr. It is to be noted that cumulative exposure measures do not take into account dose rate per unit time,

duration of exposure, and ages at exposure. These three factors, particularly the third one, could be very important in determining effects on health.

Another measure of exposure that allows comparison of different exposure situations is expressed as "lifetime fibers." This quantity is derived by integrating over time the product of fiber concentration in air (the only source of exposure considered here) and the intake rate.

When interpreting health-effects information obtained from occupational studies, it may be necessary to convert nonoccupational exposures to equivalent occupational dose expressed in (fibers/cm^3) yr. Assuming an inhalation rate of 12000ml/minute; an 8-hour work day; 5 days/week; 50 weeks/year, the amounts of inhaled fibers workers could accumulate in one year, according to work group, are shown below.

worker group	exposure level	duration	exposure per year	total life-time exposure
insulation workers (amosite, chrysotile)	15 f/ml	25 yrs	2.16×10^{10} f/yr	5.4×10^{11} f
British textile workers (chrysotile)	15-30 f/ml	20 yrs	$2.16\text{-}4.32 \times 10^{10}$ f/yr	$4.32\text{-}8.64 \times 10^{11}$ f
amosite factory workers	35 f/ml	1.46 yrs	5.04×10^{10} f/yr	7.36×10^{10} f
cement workers (chrysotile, crocidolite)	9 f/ml	12 yrs	1.296×10^{10} f/yr	1.56×10^{11} f

Similar calculations for the general population are shown below:

If ambient air concentrations are assumed to be 10 ng/m^3, using the EPA conversion factor of 30 fibers (f)/ng, the population as a whole is exposed to 3×10^{-4} f/ml. Using the further assumptions:

(1) average breathing rate - 12.72 liters/min.
(2) 24 hours per day, and
(3) 52 weeks per year as the exposure duration;

It is calculated that an individual is exposed to 2.0×10^6 f/year.

Using the assumptions and the data generated in the baby-powdering experiment[114] (concentration - 8.58 f/cc during powdering; 4.38 f/cc during settling; with 13.6% and 86.4%, respectively, of the time - with exposure time of 43.8 minutes per week; breathing rate of 05.8 1/min.), exposure of a baby from baby powder could be 6.6×10^6 f/year. It is to be noted that these calculations assume that all of the talc is asbestos. If a more realistic value of 1% asbestos is used, the number of fibers is calculated to be 6.6×10^4 f/yr.

The carcinogenic potential and the hazards of exposure to asbestos have been well documented. Also, several types of asbestos are known to be geological contaminants in talc ore. Since the accepted best index of exposure to asbestos requires counting the respirable fibers in the worker's breathing zone, a problem arises in the methodology of distinguishing asbestos fibers from talc. Characteristically, talc has a tendency to curl and stand on its edge, which may result in many erroneous counts by optical microscopy.[98]

The latest USPHS/NIOSH method for counting asbestos fibers requires phase contrast microscopy at X400-500 magnification, and arbitrarily defines a fiber as a particulate with a length to width ratio of 3:1 or greater, and a maximum width and minimum length of 5 micrometers.[99] This method is a crude determination of total fiber exposure because of the resolution limitations of optical microscopy. Most airborne asbestos fibers are less than 5 um in length, and those that are longer may have diameters too small to be resolved by phase contrast microscopy. With regard to the measurement of asbestos exposure from talc, some authors have stated that scanning electron microscopy (SEM) should be considered as an adjunct to the USPHS/NIOSH method when counting fibers in a dust environment. Phase contrast microscopy may suffice in an asbestos environment, but the resolution limitations of optical microscopy and the inability to distinguish rolled talc particles and talc "shards" from actual asbestos fibers will allow only a crude determination of the total fiber exposure.

Other than what was presented above, it is not known whether cosmetic talc (used today) is contaminated with asbestos or asbestiform minerals, what form is involved (tremolite-fibrous or nonfibrous), or what levels of asbestos, if contaminated.

In a recent (August, 1984) report[100] by the NAS Committee on Nonoccupational Health Risks of Asbestiform Fibers, who evaluated the human health risks associated with nonoccupational exposure to asbestiform fibers with emphasis on inhalation of outdoor and indoor air, it was concluded that nonoccupational exposure to asbestiform fibers in air presents a risk to human health. The Committee made a quantitative estimate of the risk of excess lung cancer and mesothelioma that might occur in persons breathing low levels of asbestos in the air. A concentration of 0.0004 fibers/cm^3 was deemed reasonable to use in

such calculations because a variety of measurements of indoor and outdoor air indicated that 0.0004 f/cm^3 is the approximate average level that may be encountered. If a person inhaled air containing asbestos at that level throughout a 73-year lifetime, the committee's best judgement is that the lifetime risk of mesothelioma would be approximately nine in a million (range 0 to 350 per million, depending on assumptions regarding the relationship of dose to risk). Risks for continuous lifetime exposures to higher or lower levels would be proportionately higher or lower. Epidemiological data and the estimates derived from them indicate that the corresponding lifetime risk for lung cancer would be about 64 in a million for male smokers (range 0 to 290), 23 in a million for female smokers (0 to 110), and 6 and 3 in a million, respectively, for male and female nonsmokers. The risk to nonsmokers appears greater for mesothelioma than for lung cancer. The Committee also emphasized the strong dependence of mesothelioma rates on time from first exposure and exposure of children to asbestos (although mainly from school exposure). (See NAS Risk Assessment - Attachment III.)

The only information available on cosmetic exposure is that of baby powder use noted above. Infants exposed to asbestos from talc could be exposed to an additional amount above background of the order of 0.04 to 0.08 f/cc for approximately 2 years. This would result in an increase of 0.05% in the cumulative lifetime exposure of 1.95×10^8f to 1.951×10^8f, with a similar increase in the lifetime risk (e.g., 9 to 9.0045 mesotheliomas per million). However this estimate is based on a linear dose response function, assuming no dose-rate effect. Cumulative exposure measures do not take into account dose rate, duration of exposure, or age at exposure. Although the cumulative amount of asbestos would appear to be of no consequence, the estimated exposure level is 100 to 200 times greater than background. Data on acute exposures of this magnitude are not available.

This memo is to request a risk assessment of the potential exposure to asbestos from use of cosmetic talc.

Linda L. Taylor, Ph.D.

APPENDIX I

Epidemiological Studies on Asbestos

1. In a follow-up study[57] of a birth cohort consisting of 10,939 men and 440 women (exposed for at least one month), dust exposure and mortality of chrysotile miners were analyzed using the "man-years" method and the "case- and multiple-control" approach.

   Among men the overall excess mortality was 2% at Asbestos and 10% at Thetford Mines, which was the dustier region (see Table 2). The women, mostly employed at Asbestos, had a standardized mortality ratio (SMR) of 0.90. During the five decades, 1926-75, 4350 men died compared with 4107 expected on the basis of Quebec age- and year-specific death rates, a SMR of 1.06. There had been a net excess of 33.9 deaths at Asbestos (1.6% of the 2074.1 expected) and 208.8 at Thetford Mines (10.3% of the 2033.2 expected); SMRs of 1.02 and 1.10, respectively. Table 2 provides data on deaths of the men by age and cause of death.

   Four exposure levels were used in these analyses; the mean concentrations were: low: 2.5 to 4.2; medium: 4.3 to 9.4; high: 14.4 to 23.6; very high: 46.8 to 82.6 million particles per cubic foot (mppcf). Quantitative exposure was estimated as cumulative dust exposure during the first 20 years from onset of employment. Tables 6 and 7 analyze the 3291 deaths, 20 or more years after first employment, occurring from 1951 to 1975. Comparison with Table 2 shows that, although 26.3% of all observed deaths were thus excluded from the analysis because they occurred before 1951 or within 20 years of first employment, over 90% of deaths from pneumoconiosis and from lung cancer were included, and percentages were also high for malignant neoplasms of other sites (except the larynx) and stroke.

   When account is taken only of length of service (Table 6), trends of risk, as measured by the ratios of observed to expected deaths--that is, SMRs in which the standardization was by both age and era--were generally without clear trends, probably reflecting differences in selection and other factors. Exceptions were deaths attributed to pneumoconiosis and accidents: of the 42 deaths from pneumoconiosis, 36 were in men with at least 20 years' service.

TABLE 2. Deaths of [redacted], by year, age, and certified cause of death

Cause of death (ICD code*)	Age at death	Year of death					
		Before 1946	1946-55	1956-65	1966-75	Total	
All causes	<45	564	136	54	--	754	4463
	45-64	111	438	842	702	2093	
	≥65	--	--	389	1227	1616	
Pneumoconiosis (523-524)	<45	0	0	1	--	1	46
	45-64	1	6	10	13	30	
	≥65	--	--	7	8	15	
Malignant neoplasms: Lung (162-164)	<45	2	2	2	--	6	250
	45-64	0	12	51	72	135	
	≥65	--	--	20	89	109	
Oesophagus and stomach (150-151)	<45	5	2	1	--	8	154
	45-64	4	22	34	17	77	
	≥65	--	--	12	57	69	
Colon and rectum (152-154)	<45	4	1	0	--	5	88
	45-64	1	8	20	18	47	
	≥65	--	--	6	30	36	
Other abdominal (155-159)	<45	5	2	1	--	8	80
	45-64	1	6	15	14	36	
	≥65	--	--	6	30	36	
Larynx (161)	<45	0	0	0	--	0	21
	45-64	2	5	6	5	18	
	≥65	--	--	1	2	3	

Other (140-148; 160; 165-205)	45	12	4	1	--	17	276
	45-64	2	28	52	48	130	
	65	--	--	28	101	129	
Heart disease (400-443)	45	28	25	18	--	71	1543
	45-64	25	154	355	285	819	
	65	--	--	166	487	653	
Respiratory tuberculosis (001-008)	45	118	30	1	--	149	248
	45-64	20	31	27	7	85	
	65	--	--	5	9	14	
Other respiratory (470-522; 525-527)	45	60	3	0	--	63	234
	45-64	5	12	28	37	82	
	65	--	--	17	72	89	
Cerebrovascular (330-334)	45	6	2	3	--	11	268
	45-64	4	12	42	38	96	
	65	--	--	39	122	161	
Accidents (800-999)	45	170	41	17	--	228	461
	45-64	18	44	71	51	184	
	65	--	--	9	40	49	
All other known causes	45	114	23	9	--	146	669
	45-64	25	82	112	82	301	
	65	--	--	67	155	222	
Cause not known	45	40	1	0	--	41	125
	45-64	3	16	19	15	53	
	65	--	--	6	25	31	

*Code in the 7th revision of the International Classification of Diseases

TABLE 6. Deaths, by cause, in relation to duration of service

Cause of death (see table 2)	Length of gross service (yr)									
	Very short (1)		Short (1 5)		Medium (5- 20)		Long (20)		Complete cohort	
	0	SMR	0	SMR	0	SMR	0	SMR	0	SMR
All causes	885	1.07	629	1.09	679	1.15	1098	1.07	3291	1.09
Pneumoconiosis	1	1.15	3	5.00	2	3.39	36	34.62	42	13.55
Malignant neoplasms:										
Lung	47	0.97	29	0.83	50	1.37	104	1.61	230	1.25
Oesophagus and stomach	37	1.30	25	1.27	18	0.91	50	1.47	130	1.27
Colon and rectum	22	0.78	13	0.67	23	1.16	21	0.62	79	0.78
Other abdominal	20	1.98	12	0.92	14	1.04	21	0.90	67	0.98
Larynx	6	1.48	5	1.75	1	0.34	4	0.78	16	1.07
Other	67	1.12	43	1.04	48	1.13	79	1.08	237	1.09
Heart disease	370	1.06	251	1.02	287	1.15	424	0.97	1332	1.04
Respiratory tuberculosis	7	0.62	7	0.89	21	2.68	22	1.56	57	1.39
Other respiratory	29	0.66	46	1.52	22	0.71	59	1.12	156	0.99
Cerebrovascular	62	0.95	49	1.12	50	1.13	82	1.11	243	1.07
Accidents	52	1.36	38	1.32	37	1.18	56	0.96	183	1.17
All other known causes	130	1.03	94	1.07	94	1.05	132	0.85	450	0.98
Cause not known	35	--	14	--	12	--	8	--	69	--

Columns headed 0 give the numbers of deaths of men, 20 years or more after first employment, occurring during 1951-75; figures under headings SMR are ratios of deaths observed to those expected on basis of male mortality in Quebec.

TABLE 7. Deaths, by cause, in relation to dust concentration

(a) Gross service: less than one year

Cause of death (see table 2)	Accumulated dust exposure (see table 4)							
	Low		Medium		High		Very high	
	0	SMR	0	SMR	0	SMR	0	SMR
All causes	311	1.12	260	1.13	162	0.95	152	1.03
Pneumoconiosis	0	0	0	0	1	5.66	0	0
Malignant neoplasms:								
Lung	19	1.17	12	0.91	9	0.88	7	0.80
Oesophagus and stomach	12	1.24	12	1.50	9	1.54	4	0.81
Colon and rectum	5	0.52	7	0.88	6	1.03	4	0.81
Other abdominal	3	0.48	6	1.17	4	1.04	7	2.12
Larynx	2	1.45	2	1.77	1	1.19	1	1.40
Other	20	0.99	23	1.38	13	1.05	11	1.04
Heart disease	136	1.15	112	1.15	63	0.87	59	0.94
Respiratory tuberculosis	4	1.05	1	0.32	1	0.44	1	0.48
Other respiratory	11	0.74	10	0.82	3	0.33	5	0.66
Cerebrovascular	25	1.14	18	0.98	9	0.67	10	0.90
Accidents	16	1.30	19	1.86	10	1.27	7	0.90
All other known causes	45	1.06	29	0.82	26	1.00	30	1.33
Cause not known	13	--	9	--	7	--	6	--

See footnote to table 6

7(b) Gross service: one year, less than five years

Cause of death (see table 2)	Accumulated dust exposure (see table 4)							
	Low		Medium		High		Very high	
	O	SMR	O	SMR	O	SMR	O	SMR
All causes	141	1.12	246	1.09	130	1.12	112	1.04
Pneumoconiosis	0	0	3	12.80	0	0	0	0
Malignant neoplasms:								
Lung	5	0.66	13	0.95	6	0.82	5	0.78
Oesophagus and stomach	8	1.83	7	0.90	4	1.03	6	1.64
Colon and rectum	2	0.46	4	0.52	4	1.04	3	0.82
Other abdominal	2	0.70	7	1.37	2	0.75	1	0.41
Larynx	2	3.17	1	0.89	1	1.71	1	1.90
Other	14	1.53	16	0.98	9	1.08	4	0.52
Heart disease	51	0.95	99	1.03	59	1.19	42	0.92
Respiratory tuberculosis	0	0	5	1.64	1	0.61	1	0.65
Other respiratory	10	1.49	16	1.34	10	1.66	10	1.78
Cerebrovascular	18	1.83	17	0.98	10	1.19	4	0.49
Accidents	11	1.89	12	1.10	3	0.47	12	2.14
All other known causes	16	0.83	40	1.16	16	0.91	22	1.33
Cause not known	2	--	6	--	5	--	1	--

See footnote to table 6

7(c) Gross service: five years, less than 20 years

Cause of death (see table 2)	Accumulated dust exposure (see table 4)							
	Low		Medium		High		Very high	
	0	SMR	0	SMR	0	SMR	0	SMR
All causes	161	1.10	194	1.07	170	1.22	154	1.26
Pneumoconiosis	0	0	0	0	1	7.36	1	8.42
Malignant neoplasms:								
Lung	13	1.41	14	1.22	7	0.83	16	2.17
Oesophagus and stomach	6	1.21	6	0.99	5	1.07	1	0.25
Colon and rectum	4	0.81	7	1.14	9	1.92	3	0.74
Other abdominal	6	1.78	3	0.72	3	0.95	2	0.75
Larynx	0	0	0	0	1	1.44	0	0
Other	9	0.85	19	1.44	11	1.10	9	1.03
Heart disease	66	1.06	81	1.05	72	1.22	68	1.31
Respiratory tuberculosis	3	1.55	9	3.94	5	2.64	4	2.28
Other respiratory	5	0.64	5	0.51	5	0.69	7	1.12
Cerebrovascular	8	0.73	13	0.94	14	1.34	15	1.67
Accidents	8	1.07	10	1.06	10	1.33	9	1.28
All other known causes	29	1.30	21	0.77	25	1.17	19	1.01
Cause not known	4	--	6	--	2	--	0	--

See footnote to table 6

7(d) Gross service: 20 or more years

Cause of death (see table 2)	Accumulated dust exposure (see table 4)							
	Low		Medium		High		Very high	
	0	SMR	0	SMR	0	SMR	0	SMR
All causes	367	0.98	253	0.89	183	1.07	295	1.50
Pneumoconiosis	4	10.49	7	23.75	5	30.10	20	101.52
Malignant neoplasms:								
Lung	28	1.21	20	1.08	24	2.20	32	2.65
Oesophagus and stomach	17	1.36	6	0.64	8	1.44	19	2.89
Colon and rectum	7	0.56	4	0.43	1	0.18	9	1.39
Other abdominal	10	1.18	3	0.46	2	0.51	6	1.35
Larynx	2	1.07	1	0.69	0	0	1	1.03
Other	33	1.23	16	0.79	11	0.90	19	1.36
Heart disease	138	0.87	115	0.95	77	1.06	94	1.12
Respiratory tuberculosis	5	1.01	5	1.31	3	1.27	9	3.06
Other respiratory	18	0.92	10	0.68	14	1.62	17	1.74
Cerebrovascular	32	1.15	18	0.89	10	0.84	22	1.58
Accidents	16	0.82	19	1.16	9	0.85	12	1.01
All other known causes	52	0.92	29	0.68	18	0.70	33	1.10
Cause not known	5	--	0	--	1	--	2	--

See footnote to table 6

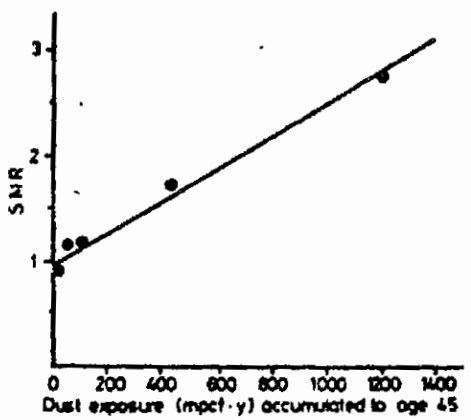
Among those in the very short and short service groups (those with gross service of less than 5 years (Tables 7(a) and (b)), careful study of differences between groups according to severity of exposure showed no consistent pattern. Table 7(c) deals with men with gross service between 5 and 20 years; their service had also been completed before the start of the study interval. There were fairly consistent trends for higher SMRs the greater the dust exposure for total mortality, for pneumoconiosis (although based on only 2 deaths), heart disease, and stroke. In addition SMRs were highest in the group with the most severe exposure, for lung cancer and "other" respiratory diseases. The authors stated that all these findings are understandable as pulmonary fibrosis could well contribute directly to cardio-pulmonary disease and, in addition, might adversely affect the probability of survival in any life-threatening condition. Table 7(d) concerns 3105 men with at least 20 years service, and an average of almost 32 years of employment. Here the most severely exposed had the highest SMR not only for total mortality but for all listed causes other than laryngeal cancer and accidents. Further, the tendency for increased risk with each augmentation in exposure was completely consistent for pneumoconiosis and for heart disease, and positive, although rather less consistent, for total mortality, lung cancer, respiratory tuberculosis, and other respiratory diseases.
The other form of a priori analysis, with exposure calculated to age 45 at which age the study interval started, is summarized in Table 8. The total number of deaths observed in this analysis was 3448 (77.3% of the deaths), with SMR = 1.07, very close to that for all causes in the complete cohort as seen in Table 6. Indeed, for each cause of death, SMRs from both methods of analysis were always close. Clear trends were found for SMRs to be higher the heavier the exposure, for total mortality, pneumoconiosis, lung cancer, cancer of the colon and rectum, respiratory tuberculosis, other respiratory diseases and stroke. The trends were most clear-cut in pneumoconiosis and lung cancer. The lung cancer trend was essentially linear as shown in the Figure below, where exposures of 30 mppcf-year or more have been broken down further, into 4 classes. The trend for respiratory tuberculosis was also consistent in the two areas, but not those for the other causes listed.

Dust exposure and mortality in chrysotile mining, 1910-75

TABLE 8. Deaths, by cause, in relation to dust exposure accumulated to age 45

Cause of death (see table 2)	Dust exposure (mpcf-y) accumulated to age 45					
	< 30		30 < 300		≥ 300	
	0	SMR	0	SMR	0	SMR
All causes	1668	1.02	1138	1.04	642	1.30
Pneumoconiosis	5	2.98	12	10.81	27	54.00
Malignant neoplasms:						
Lung	91	0.93	81	1.18	70	2.25
Oesophagus and stomach	68	1.22	42	1.14	26	1.58
Colon and rectum	34	0.62	28	0.77	18	1.11
Other abdominal	37	1.00	21	0.84	10	0.88
Larynx	9	1.11	6	1.08	2	0.81
Other	129	1.10	83	1.06	38	1.08
Heart disease	696	1.06	463	0.99	240	1.14
Respiratory tuberculosis	21	0.94	25	1.67	15	2.20
Other respiratory	71	0.84	55	0.98	40	1.62
Cerebrovascular	119	0.96	86	1.08	46	1.32
Accidents	104	1.28	60	1.00	33	1.16
All other known causes	237	0.95	154	0.92	74	0.99
Cause not known	47	--	22	--	3	--

See footnote to table 6



Lung cancer SMRs in relation to dust exposure accumulated to age 45. The line has been fitted by a modified least-squares technique.

Table 9 shows deaths from lung cancer.

TABLE 9. Deaths from lung cancer in relation to dust exposure and smoking habit

Smoking habit	Dust exposure (mpcf.y) accumulated to age 45							
	< 30		30 < 300		≥ 300		All	
	0	SMR	0	SMR	0	SMR	0	SMR
Non-smokers	5	0.18	6	0.36	8	1.24	19	0.38
Moderate smokers	73	1.14	64	1.35	52	2.31	189	1.41
Heavy smokers	13	2.12	11	2.39	10	4.50	34	2.63
All smoking habits	91	0.93	81	1.18	70	2.25	242	1.23

See footnote to table 6

Table 10 summarizes the findings from the Miettinen approach--that is, more than one control for each case, excluding those for smoking habit; the

TABLE 10: Dust exposure in deaths from pneumoconiosis and from malignant disease and in controls numbers of deaths areas table 2 (but see

	Dust exposure (mpcf.y) accumulated up to nine years before death of case				
	30	30 300	300 1000	1000	All
Pneumoconiosis					
Deaths	7	9	13	17	46
Controls(3)*	63	49	21	5	138
Relative Risk+	1	1.65	5.57	30.60	--
Lung cancer					
Deaths**	89	73	56	27	245
Controls(3)	333	243	127	32	735
Relative risk	1	1.12	1.65	3.16	--
Cancer of oesophagus and stomach					
Deaths	74	41	22	17	154
Controls(2)	143	105	53	7	308
Relative risk	1	0.75	0.90	4.69	--
Cancer of colon and rectum					
Deaths	39	29	13	7	88
Controls(2)	88	70	15	3	176
Relative risk	1	0.93	1.96	5.26	--
Other abdominal cancers					
Deaths	43	25	7	5	80
Controls(2)	83	46	26	5	160
Relative risk	1	1.05	0.52	1.93	--
Cancer of larynx					
Deaths	13	6	2	0	21
Controls(3)	36	21	5	1	63
Relative risk	1	0.79	1.11	0.00	--

*Figures in brackets are numbers of controls for each death. Method of selecting controls is described in text; those reported here were not matched for smoking habit.
+Risk calculated by method of Doll in relation to those with exposure less than 30 mpcf.y.
**Excluding five deaths coded to 162-164, but found to be due to malignant mesothelioma.

numbers of deaths are as in Table 2 (but see footnote ** in Table 10) because there were no restrictions on the start of the study interval. Four groups of dust exposure are distinguished, and the data are presented without regard to the matching. Matching was taken into account in the full analysis, however, which generally confirmed the tendencies shown in the two a priori approaches and relative risks were fairly similar at Asbestos and Thetford Mines.

Linear dose-response relations have been fitted (Berry, G., unpublished) for lung cancer (without regard to smoking habits); using the data on which Table 10 is based, but taking into account the matching of controls for each case in terms of date of birth and place of employment, the fitted line was:

$$\text{Relative risk} = 1 + 0.0014 \text{ (mppcf-y)}$$

the standard error of the estimate of the slope being 0.0005. The linear fit accounted for X^2, with one degree of freedom, of 21.37, leaving only a very low value for deviations from linearity.

There were in all 11 deaths (including one women) from malignant mesothelioma observed to the end of 1975. All were of the pleura and appeared to follow a clear exposure trend.

The authors concluded that essentially linear relations have been shown between indices of exposure, based on dust concentration (mppcf) multiplied by length of service, and lung cancer, pneumoconiosis, and total number of deaths.

Because of concern regarding the risk from concentrations of asbestos dust nearer current standards, the data for the 1904 men in the cohort employed for at least 20 years in the low and medium dust exposure groups were analyzed. The concentrations to which these men were exposed (Table 4) averaged 6.6 mppcf, or perhaps 20 f/ml. The total mortality was 620 deaths, and the SMR was 0.94. The authors stated that this might be a true healthy worker effect, but not all cause-specific SMRs were below unity. There were excesses for pneumoconiosis (10.3 excess deaths, leading to X^2 on the usual basis, and with one degree of freedom, of 159.27), for lung cancer (6.4, X^2 = 0.99); cancer of esophagus and stomach (1.1, X^2 = 0.06); "other" cancers (1.7, X^2 = 0.06); respiratory tuberculosis (1.3, X^2 = 0.17); and stroke (1.8, X^2 = 0.07). Apart from pneumoconiosis, these values of X^2 are so low, even for lung cancer (where the associated p-value is 32.0%), that the observed excesses do not reach conventional levels of statistical significance. Moreover, the lung cancer SMR for the low dust exposure group (1.21) was higher than that of the medium exposure group (1.08); the authors stated that only the greatly enhanced SMRs for those with high and very high exposure allow the conclusion that there was a

response to exposure. Nevertheless, the lung cancer SMR for all 1904 men was 1.15, in close conformity with that which might be predicted from the figure (about 1.20) or the relative risk of 1.16 from the fitted line (Berry, G., unpublished).

It is noted that exposure to asbestos was presented as dust exposure in mppcf. The current trend is towards providing information in terms of fibers rather that dust counts, although there is an almost complete lack of epidemiological data based on fiber measurements. The problem with this is there is no easy conversion. The authors note that studies showed that, at relevant dust levels, the conversion factors range from about 3 to 7 fibers/ml for each mppcf; although other data point to a lower range, 1 to 5. This is a recurring problem.

CONCLUSION:

The study suggests an overall small increase in lung cancer associated with asbestos exposure. A consistent dose-response gradient was observed: SMR of 0.9 (low exposure 30 mppcf-yrs) to 2.3 for highest exposure category (300 mppcf-yrs.).

2. In this cohort study of chrysotile miners and millers, only workers with at least 20 years of employment were chosen.

Dust measurements after 1969 were reviewed but no quantitative exposure data were provided. Fiber concentrations for various areas of the mills and mines ranged from 9 to 36 fibers longer than 5 micrometers/ml of air.

Table 4 shows the various causes of death observed in 130 deaths.

TABLE 4: Categorization of causes of death according to death certificate information compared with categorization following review of all available medical records and pathological material in 130 cases

Cause of Death as Ascertained (BE)*	No.	Underlying Cause of Death as Categorized on Certificate of Death, (DC)*				
		Lung Cancer	Mesothelioma	All Other Cancer	Asbestosis Including Pneumoconiosis	All Other Causes
Lung cancer	25	18		3	2	2
Mesothelioma	1		1			
All other cancer	18	1		17		
Asbestosis	24	3			14	7
All other causes	62			1	1	60
Totals	130	22	1	21	17	69

*BE - best evidence
DC - death certificate cause

The expected mortality experience was calculated using national rates of Canada (Table 5).

TABLE 5: Expected and Observed Deaths Among 544 Asbestos Miners and Millers, Thetford Mines, Quebec, Jan.-Nov., 1961 ADG, 1977*

	Total		
	Exp.	Obs.	O/E
Total deaths	159.9	178	1.11
Total cancer all sites	36.7	49	1.34
Lung cancer	11.1	28	2.52
Pleural mesothelioma	**	1	--
Cancer of the gastrointestinal tract	9.5	10	1.05
All other cancers	16.1	10	0.62
Total Noninfectious pulmonary diseases	6.7	30	4.48
Asbestosis	**	26	--
All other causes	116.5	99	0.85
Person-years		7,408	

*Expected deaths are based upon age-specific death rate data for Canadian white males.
**Death rates not available but these have been rare causes of death in the general population.

Asbestosis and lung cancer were major causes of death among these workers. Table 7 details the mortality experience according to time from onset of exposure and shows an increase in mortality between 30 and 50 years from first exposure to asbestos. There is, however, little excess mortality after 50 or more years from first exposure. The authors stated that perhaps this occurred as individuals at high risk of death (because of their particular susceptibility or because of other associated factors, as cigarette smoking) may have died preferentially in earlier years.

TABLE 7: Ratios of Observed to Expected Deaths Among 544 Asbestos Miners and Millers, Thetford Mines, Quebec, Jan.-Nov. 1961 - Aug. 1977

	Ratio of Observed to Expected Deaths (Number of Deaths in Parentheses)			
	Years from Onset of Employment			
	20-29	30-39	40-49	50 +
Total deaths	0.65 (8)	1.27 (60)	1.28 (66)	0.91 (44)
Total cancer	0.00 (0)	0.98 (11)	1.95 (24)	1.30 (14)
Lung cancer	0.00 (0)	1.94 (7)	4.19 (16)	1.67 (5)
Noninfectious pulmonary diseases (incl. asbestosis)	-- (4)	5.29 (9)	3.64 (8)	3.60 (9)
Causes other than cancer or noninfectious pulmonary diseases	0.42 (4)	1.16 (40)	0.91 (34)	0.59 (21)
	Number of deaths			
Asbestosis	3	8	8	7
Mesothelioma	0	0	1	0
Person-years of observation	1,623	3,067	1,805	914

CONCLUSION:

The study results indicate that a small increase in lung cancer risk occurs as asbestos exposure increases, but the lack of quantitative exposure data makes it difficult to evaluate this association.

3. Mortality of Italian chrysotile asbestos workers was studied[82] using two different reference groups. In the first analysis the observed number of deaths was compared with the expected number in the population of all Italy. Person-years of observation were calculated according to the method of Case and Lea[35a] and multiplied by age-specific death rates to compute the expected number of deaths. Secondly, a case control study of carcinoma of lung and larynx was undertaken. Only two exposure categories were considered, the first with cumulative exposure up to 100 fiber-years and the second, all those with a cumulative exposure greater than 100 f/yr. (The lower of the two exposures corresponds to the British standard of 2f/cc for 50 years' working life).

In Table 3 the mortality of the cohort is divided into 2 groups according to period since first employment: deaths occurring up to 19 years since first employment and deaths occurring over 20 years since first employment. The overall mortality compared to the national figures is also shown.

One death from pleural mesothelioma occurred 35 years after starting employment in a worker with 33 years exposure.

A significant excess of laryngeal cancer is seen when examining mortality over the whole period of observation. Four of these deaths occurred after 20 years since first employment. Two of the six workers dying from laryngeal cancer had less than one year of exposure. There is also a marked excess of respiratory diseases, both influenza and pneumonia and "other" respiratory diseases, consisting chiefly of chronic obstructive lung disease. Asbestosis was reported in 9 cases.

Mortality from lung cancer is shown in Table 4. No deaths were observed before 1961, nor did any deaths occur from this cause in subjects under the age of 50. However, among those of 50 years or more, the SMR rises to 111 in the quinquennium 1966-70 and reaches 226 between 1971 and 1975; for men of all ages it is 206 in the same period.

TABLE 3: Number of deaths observed and expected by period since first exposure, and cause. (Period of observation from 1946 to 1975)

Period since first exposure (yr) over	Total			Up to 19			20 and		
Person-years observation	12683			8776			21459		
Cause of death	Observed	Expected	SMR	Observed	Expected	SMR	Observed	Expected	SMR
All causes	112	54.2	207**	220	160.2	137**	332	214.4	155**
All malignant neoplasms (140-205)	12	10.0	120	38+	37.0	103	50+	47.0	106
Lung and pleura (162-163)	1	1.7	59	10+	8.7	115	11+	10.4	106
Larynx (161)	2	0.4	500	4	1.5	267	6	1.9	316*
Gastrointestinal (151-159)	4	4.8	83	15	14.5	103	19	19.3	98
Other sites	5	3.1	161	9	12.3	73	14	15.4	91
Non-malignant respiratory diseases (470-527)	12	2.3	522**	20	11.8	169*	32	14.1	227**
Influenza and pneumonia (480-483)	8	1.6	500**	4	4.6	87	12	6.2	194*
Other respiratory diseases(470-475, 500-527)	4	0.7	571**	16	7.2	222**	20	7.9	253**
Asbestosis (523.2)	2	--	--	7	--	--	9	--	--
Tuberculosis of the lung (001-008)	13	3.9	333**	5	3.3	152	18	7.2	150**
Cardiovascular diseases (400-468)	22	14.8	149	100	67.7	148**	122	82.5	148*
Cirrhosis of the liver (581)	9	2.1	429**	22	7.8	282**	31	9.9	313**
Accidents (800-999)	30	7.8	385**	15	9.5	158	45	17.3	260**
All other causes	9	13.3	68	17	23.1	74	26	36.4	71
Unknown	5	--	--	3	--	--	8	--	--

*$p < 0.05$; **$p < 0.01$

+These numbers include one suspected case of mesothelioma of the pleura

Figures in parentheses are ICD (7th Revision) code numbers

TABLE 4: Observed and expected deaths from lung cancer (162-163) by age and calendar time

Age		Calendar years of follow-up				
		1946-60	1961-65	1966-70	1971-75	1946-75
Up to 49	Observed	0	0	0	0	0
	Expected	0.5	0.2	0.3	0.3	1.3
	SMR	--	--	--	--	--
50 and over	Observed	0	1	3	7*	11
	Expected	1.7	1.6	2.7	3.1	9.1
	SMR	--	63	111	226	121
All ages	Observed	0	1	3	7*	11
	Expected	2.2	1.8	3.0	3.4	10.4
	SMR	--	56	100	206	106

*These numbers include one suspected case of mesothelioma of the pleura

Table 5 shows the distribution of the deaths of men with lung cancer and their controls in the two exposure categories, in the upper part of the table, and the deaths from laryngeal cancer with their controls, in the lower half of the table. Ten of the deaths from lung cancer are in the higher exposure group with a relative risk of 2.89. However, tests of the significance of the association of lung cancer and high exposure gave a two-tailed P value of 0.18, thus demonstrating no statistically significant difference between the proportion of cases and controls reaching the higher exposure level. Nor is there a statistically significant excess of laryngeal cancer in the higher exposure categories (relative risk 3.33, two-tailed P value 0.28), although all but one of the deaths occurred in this group.

TABLE 5: Distribution of patients with lung and laryngeal cancer and their matched controls according to cumulative dust exposure.

Subjects	Dust exposure	
	Up to 100 fibre/yr	101 and over fibre/yr
Lung cancer	2	10+
Controls	22	38
Relative risk	1	2.89*
Laryngeal cancer	1	5
Controls	12	18
Relative risk	1	3.33**

+Including one case of lung cancer diagnosed in hospital but reported in death certificate as "cardiac failure" and one suspected case of mesothelioma of the pleura.
*two-tailed p value 0.18
**two-tailed p value 0.28

Table 7 shows the distribution of the whole cohort according to the selected exposure categories. For this analysis, workers included in the higher exposure category contributed to person-years observation in the lower category "up to 100 fibre/years" from the date of first employment to the date they reached the cumulative dust exposure of "more than 100 fibre/yr," after which they contributed to the higher category. The mean value of cumulative dust exposure in the higher category was about five times that in the lower (75 fibre/yr compared with 376 fibre/yr). About two-thirds of the cohort reached the higher exposure category. In Tables 7 and 8, man-years from 1 January 1946 only are included in the total. Thus, those who had accumulated a dose of 100 fibre/yr by 1946, immediately entered the higher exposure category.

The age-standardized death rates and the associate measure of risk for overall mortality and some selected causes of death are shown in Table 8. The relative risk for lung cancer obtained by examining the whole cohort (2.54) is similar to that calculated for the case control study (2.89, Table 5). A higher death rate for laryngeal and gastrointestinal cancer is also seen in the more highly exposed group, although comparison with the national statistics showed no

excess for gastrointestinal cancers. Non-malignant respiratory diseases, including asbestosis, tuberculosis and cardiovascular diseases, showed an increase in relative risk, whereas death rates for all other causes were almost equal in the two exposure groups.

TABLE 7: Distribution of workers according to cumulative dust exposure. Period of observation from 1946 to 1975

Dust exposure as fibre/yr	Up to 100 fibre/yr	101 and over fibre/yr	Unknown
Mean value within categories	74.7	376.2	--
Number in study	927*	611	6**
Person-years observation	8365	12976	118

*Including the 611 workers in the category "101 and over fibre/yr" before they had reached such cumulative exposure. Person-years are additive, whereas number of workers are not.
**Including 4 dead

TABLE 8: Crude and age-standardised death rates per 1000 person-years and relative risks by selected causes.

Cause of death	Cumulative dust exposure				Relative risk*
	Up to 100 fibre/yr		101 and over fibre		
	Death rate		Death rate		
	Crude	Age-standardised	Crude	Age-standardized	
All causes	11.72	13.31	17.73	16.73	1.26
Lung cancer (162-163)	0.24	0.28	0.77	0.71	2.54
Laryngeal cancer (161)	0.12	0.14	0.39	0.36	2.57
Gastrointestinal cancer (151-159)	0.48	0.57	1.16	1.09	1.91
Non-malignant respiratory diseases excluding influenza and pneumonia (470-475, 500-527)	0.48	0.46	1.39	1.28	2.21
Tuberculosis of the lung (001-008)	0.48	0.46	1.08	1.10	2.39
Cardiovascular diseases (400-468)	4.06	4.68	6.47	5.94	1.27
All other causes	5.86	6.60	6.47	6.24	0.95

*Based on age-standardised death rates

CONCLUSION:

The gradient of risk for lung cancer with time since onset of exposure (SMR 0.6 for < 20 years vs. 1.2 for > 20 years) and calendar time (SMR 0.6 for 1961-1965 vs. 2.1 for 1971-1975) was observed. Significantly higher risk was noted only for laryngeal cancer. Increased relative risk for lung cancer (2.9) and laryngeal cancer (3.3) was found when case-control groups were compared by exposure level.

4. Mortality of workers manufacturing friction materials using chrysotile was studied[65] on a population of 13460 workers. Exposure conditions are shown in Table 1.

Table 1 *Mean concentration of asbestos in air (f/ml)*

Period	*Office/ laboratory*	*Storage/ distribution*	*Grinding*	*Forming*
Pre-1931	10–20	>20	>20	>20
1932–50	<0·5	2–5	5–10	2–5
1951–69	<0·5	2–5	2–5	1–2
1970–79	<0·5	0·5–1	0·5–1	0·5–1

The observed mortality was compared with that expected, based on sex-, age-, and period-specific death rates for England and Wales, using the subject-years method. Attention was restricted to the period following 10 years exposure, and follow-up was to the end of 1979. In addition to mortality from all causes, the separate causes of death considered were cancer of lung and pleura, cancer of the gastrointestinal tract, and all other cancers. Table 7 shows the total mortality. Apart from 10 pleural mesotheliomas there was no sign of any excess mortality.

Table 7 *Observed and expected mortality after 10 years from first exposure (Number of pleural mesotheliomas included in parentheses)*

Cause of death	*No. subject-years*			
	Men [illegible]		*Women* [illegible]	
	Obs	*Exp*	*Obs*	*Exp*
All causes	[illegible]	1361·8	[illegible]	328·0
Lung and pleural cancer	151 (8)	139·5	8 (2)	11·3
Gastrointestinal cancer	[illegible]	107·2	[illegible]	27·4
Other cancers	77	87·7	[illegible]	60·0
Other causes	1008	1027·4	[illegible]	229·3

When the subjects were divided into groups according to duration of exposure, there was still no sign of excess mortality nor of any trend in mortality with duration of employment. Dividing the subjects according to the period of first employment again showed no excess mortality apart from the pleural mesotheliomas. This applied even to those with 30 years' follow-up who were first employed before 1950, when dust levels were high (Table 1).

Among deaths from other cancers, there were 2 in men due to cancer of the larynx (3.6 expected). Eight of the women died of cancer of the ovary (8.1 expected), and 22 of cancer of the breast (24.4 expected). The mortality experience of workers who completed 10 years' service is shown in Table 8.

Table 8 *Observed and expected mortality after completing 10 years' employment*

	Men				Women			
Follow-up after 10 years' exposure (years)	0–10		>10		0–10		>10	
No. subjects/years	2484/21 860		1808/19 028		627/5578		457/6877	
Cause of death	*Obs*	*Exp*	*Obs*	*Exp*	*Obs*	*Exp*	*Obs*	*Exp*
All causes	185	195.7	432	450.8	14	21.3	76	[illegible]
Lung and pleural cancer	23	21.3	58 ([illegible])	17.4	0	0.7	2 ([illegible])	2.2
Gastrointestinal cancer	23	16.3	25	35.8	0	1.8	8	[illegible]
Other cancers	7	12.6	21	28.2	1	4.5	14	[illegible]
Other causes	132	145.5	328	369.4	13	14.3	52	[illegible]

Except for deaths from mesothelioma, there was no excess in this group, even 10 years after completing 10 years' employment. A similar result was obtained when restricting attention to those who had completed 20 years' exposure.

An additional 187 deaths have occurred since the original analysis. Only one of 40 deaths in women and 12 of 147 in men were due to lung cancer. One of the men certified as dying from pleural mesothelioma was 50 and had worked at the factory for two weeks in 1960 (when aged 29) as a grinder exposed to chrysotile (only known asbestos exposure). With regard to mesothelioma, the cases observed here were analyzed in a case-control study using the method of Liddell, et al. The effect of exposure to crocidolite was examined. Four matched controls were chosen for each mesothelioma, where matching was for (1) sex, (2) year started work in factory (± 1 year), (3) year of birth (± 4 years), (4) survival up to time of death of mesothelioma, and (5) employed at factory during crocidolite period for same time as case.

Eighty percent of those dying of mesothelioma had worked on the crocidolite contract compared with only 8% of the controls. Those with mesothelioma, however, had also been exposed to higher levels of chrysotile than the controls; 90% had been exposed to more than 5 f/ml compared with 25% of the controls. The confounding effect of exposure to chrysotile was eliminated by considering only cases of mesothelioma and their controls who had been exposed to chrysotile at a level of at least 5 f/ml. This left 6 cases with 10 controls. Five of the 6 had had definite crocidolite exposure.

A case-control study of deaths due to lung cancer was carried out for males who had started work before the end of 1960 and who survived for at least 10 years after start of exposure. There were

106 deaths from lung cancer satisfying these criteria, and three controls were chosen for each case, matched for: (1) year started at factory; (2) date of birth; and (3) survival up to time of death from lung cancer. Within the restricted set of men there were 86 who had died of gastrointestinal cancer, who were also included in this study (without additional controls). Each occupational history was integrated with respect to time to give the cumulative exposure up to the date of death for the cases, and for controls up to the date of death of the corresponding case of lung cancer. The total duration was also calculated. These two measures were also evaluated up to 9 years before the above dates, on the basis that recent exposure is irrevalent to the risk of lung cancer. A fifth measure evaluated was the cumulative dose weighted by the time elapsed since the exposure occurred. This measure was evaluated up to the date of death and attaches most importance to the earliest exposure.

The distribution of duration of exposure and cumulative exposure up to death are given in Tables 13 and 14.

Table 13 *Distributions of duration of exposure up to death*

Duration of exposure (years)	*No of subjects*			*Odds-ratios*	
	Controls	*Lung cancers*	*Gastrointestinal cancers*	*Lung cancer*	*Gastrointestinal cancer*
0–0·9	74	26	16	1·00	1·00
1–4·9	86	29	24	0·96	1·29
5–9·9	26	9	9	0·81	1·49
10–19·9	77	26	26	1·03	1·56
20–44·5	32	15	11	0·82	0·98
Total	317	106	86		

Table 14 *Distributions of cumulative exposure to death*

Cumulative exposure (f-y ml)	*No of subjects*			*Odds-ratios*	
	Controls	*Lung cancers*	*Gastrointestinal cancers*	*Lung cancer*	*Gastrointestinal cancer*
0–9	132	50	36	1·00	1·00
10–49	124	37	40	0·79	1·18
50–99	40	13	9	0·86	0·83
100–356	15	5	1	0·88	0·24
Total	311*	105*	86		

*For [illegible] men (6 controls, 1 lung cancer) information available on dust levels was insufficient to calculate cumulative exposure (f-y/ml = fibre-years/ml)

The odds ratio, i.e., the approximate risks of cancer, relative to the lowest exposure group, are also given.

For lung cancer there is no indication of an increased risk with either duration of exposure or cumulative exposure. For gastrointestinal cancer, there is no sign of an increased risk with cumulative exposure, and although there appears to be a trend with duration of exposure up to 20 years, this trend is not supported by

the numbers with more than 20 years' exposure and could have occurred by chance. There was also no sign of increased risk with duration of exposure or with cumulative exposure calculated to nine years before death or with the measure of exposure weighted by elapsed time (tables not given). Restricting the analysis to cases who survived for at least 15 years after first exposure also did not show any dose-response relationship.

For lung cancers, a linear relationship between relative risk and cumulative exposure was fitted using methods appropriate to matched data. The coefficient was estimated as 0.00058 per fiber-year/ml. That is, for a cumulative exposure of 100 fibers-years/ml, the relative risk was estimated as 1.06; the upper confidence limit was 1.80.

CONCLUSION:

No gradient of risk was observed with quantitative exposure level.

No evidence of excess mortality due to cancer at any site, except mesothelioma, even when examined by duration of exposure or period of initial employment.

No increased risk of lung cancer or gastrointestinal cancer was associated with either duration or cumulative exposure in the case-control analysis.

5. A report[83] on dust exposure and mortality of workers in a chrysotile asbestos friction products plant consisted of data on a cohort of 3641 men employed for at least one month. Individual exposures were estimated (in mppcf-years) from impinger measurements. Table 1 shows deaths by cause and age at death.

Table 1 *Male deaths by age and certified cause*

Cause of death (ICD code)	*Age at death (y)*			*Total*
	<45	*45–64*	*≥65*	
All causes	139	616	511	1267
Malignant neoplasms				
Lung (162–64)	1	47	41	89
Oesophagus and stomach (150–51)	0	12	13	25
Colon and rectum (152–54)	3	9	20	32
Other abdominal (155–59)	4	9	12	25
Larynx (161)	0	3	1	4
Other (140–48, 160, 165–205)	11	50	40	101
Heart disease (400–443)	39	273	198	510
Respiratory tuberculous (001–008)	3	6	2	11
Other respiratory (470–522, 525–527)	2	27	24	53
Pneumoconiosis (523–24)	0	7	5	12
Cerebrovascular (330–34)	5	30	56	91
Accidents (800–999)	35	42	15	92
Other known causes	30	87	66	183
Cause not known	6	14	18	39*

*Including one age unknown

[redacted] information is presented in Tables 2 and 3.

Table 2 *Estimated average dust concentrations (mpcf) for main processes 1930–70*

	1930–9	1940–9	1950–9	1960–9
Pulverising waste asbestos products	6	4	2	1
Sheet packings				
Fibre room	13·4	10	6	6
Mixing	2·4	2	1·5	1
Other	2·0	1·5	1	0·5
Millboard wet machines	3·1	2	2	0·5
Wire mould extruded brake lining				
Mixing	8·2	3	2	1
Other	1	1	0·5	0·2
Paper				
Autotransmission etc	—	—	0·5	0·2
Nivabestos process	—	—	0·2	0·2
Grouving	—	—	0·5	0·2
Metal fabrication	—	—	1	0·5
Brake shoes	—	—	0·5	0·2
Core	—	—	0·5	0·2
Disc brake	2	1·5	1	0·5
Treat/cure	2	1·5	1	0·5
Brake finish/hot press				
Drymould mix	24	10	7·5	5
Grinding	4·3	3	2	1
Other	1·5	1·5	1	0·5
Ring finish (grinding)	5·6	4	2	1
Packing	1	1	0·5	0·1
Warehouse	2	2	0·2	0·1

Table 3 *Age at start, duration of employment, and dust exposure (men only)*

	Duration of gross service (y)				
	<1	1–<5	5–<20	≥20	Total
No	1253	938	577	747	3515
Average age at start (y)	29·62	31·96	33·95	29·64	30·95
Gross service (y)	0·38	2·53	10·58	30·59	9·05
Net service (y)	0·37	2·12	9·00	28·82	8·04
Average dust concentration (mpcf)	2·28	2·06	1·56	1·06	1·84

Table 4 summarizes the mortality experience of the cohort by duration of work. The SMR based on Connecticut rates was 108.5 (107.9 on U.S. rates). The excess was mainly due to people who had worked for less than 1 year (SMR 129.9); those who worked one or [redacted]ars had an SMR of 101.2. The lowest SMR (97.2) was for those [redacted] worked 20 or more years. SMRs were raised for the three [redacted]roups of malignant neoplasms. Again this was mainly due to high SMRs in men employed for less than one year; in none was there evidence of increasing risk with increasing duration of exposure. No mesotheliomas were observed.