

Asbestos Fiber Type in Malignant Mesothelioma: An Analytical Scanning Electron Microscopic Study of 94 Cases

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* Although the association between asbestos exposure and malignant mesothelioma is indisputable, controversy continues regarding the relative contribution of the various types of asbestos fibers to the development of mesothelioma. We examined the types of asbestos fibers recovered from lung parenchyma in more than 90 cases of malignant mesothelioma from the United States, using an analytical scanning electron microscope. Almost half of the patients were former asbestos insulators or shipyard workers. The fibers were recovered from lung tissues obtained at autopsy or surgical resection by means of a sodium hypochlorite digestion procedure. Amosite asbestos was identified in 81% of the cases and accounted for 58% of all fibers 5 μ m or greater in length. Tremolite/actinolite anthophyllite were identified in 55% of the cases and accounted for 10% of all fiber types. Chrysotile was identified in 21% of the cases and accounted for 3% of fibers exceeding 5 μ m in length. Crocidolite was found in 16% of the cases and accounted for 3% of fibers exceeding 5 μ m in length. Nonasbestos mineral fibers (commonly found in the lungs of the general population) were observed in 71% of the cases and accounted for 25% of all fibers 5 μ m or greater in length. The findings in this study are at odds with the assertion that crocidolite asbestos is responsible for most mesotheliomas in the United States. © 1993 Wiley-Liss, Inc.

Key words: lung tissue burden, amosite, crocidolite, chrysotile, tremolite

INTRODUCTION

The association between exposure to asbestos and subsequent development of malignant mesothelioma is indisputable. However, controversy continues regarding the types of fibers that contribute to the development of mesothelioma. Conventional wisdom has taught us that all of the commercially valuable forms of asbestos—including amosite, crocidolite, and chrysotile along with its contaminant, tremolite—are capable of producing mesotheliomas in humans and experimental animals, but that the potency of the various fiber types differs with regard to their potential for producing mesotheliomas [Hammar and Bolen, 1988; Hillerdal, 1983; Roggli et al., 1987]. This so-called fiber gradient concept suggests that crocidolite is the most

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potent, chrysotile the least potent, and amosite somewhere in between with regard to their ability to produce mesotheliomas in humans, although no such gradient has been observed in experimental animal studies [Wagner et al., 1974]. Nonetheless, not all investigators have agreed with this conventional wisdom, with some taking the position that there is no evidence for differences in fiber potency with respect to mesothelioma [Nicholson et al., 1990], whereas others have argued that pure chrysotile does not produce mesotheliomas at all in humans [Craighead and Mossman, 1982; Mossman et al., 1990]. Some have taken the extreme position that crocidolite asbestos alone is the cause of practically all mesotheliomas in the world, including most cases in the United States [Wagner, 1991a,b].

The authors have had the opportunity to examine the mineral fiber content of the lungs in more than 90 patients with malignant mesothelioma from the United States. These cases were referred from throughout the country, and thus represent a wide variety of exposures. However, a large proportion of the cases were either insulators or shipyard workers [Roggli, 1991], which have accounted for a substantial percentage of mesotheliomas seen in this country. The purpose of the present study is to examine the relative proportion of the various mineral fiber types that were present in the lung either at the time of thoracotomy for diagnosis or at autopsy (usually within a year of diagnosis) in this group of patients with malignant mesothelioma.

MATERIALS AND METHODS

The authors' files were reviewed for cases of malignant mesothelioma for which lung tissue was available for analysis of mineral fiber content by means of analytical scanning electron microscopy (SEM). The diagnosis of malignant mesothelioma was confirmed by one of the authors (VLR) in all but three cases using our previously published criteria [Roggli et al., 1987], which include consideration of the gross distribution of tumor, histologic appearance, and histochemical and immunohistochemical findings. Histochemical studies using periodic acid Schiff (PAS) with and without diastase predigestion and alcian blue with and without hyaluronidase predigestion and/or immunohistochemical studies using antibodies directed against cytokeratins, carcinoembryonic antigen (CEA), or Leu-M1 were performed in most cases and ultrastructural studies were performed in a few cases [McCaughy et al., 1991]. In the three cases noted above, no histologic slides or blocks of tumor were referred to the authors' laboratory, but the diagnosis of mesothelioma was confirmed at autopsy at another institution. Records were reviewed for information regarding age, sex, location of tumor (pleural or peritoneal), and exposure history. The diagnosis of mesothelioma was made independent of asbestos exposure history or tissue mineral fiber content in all cases.

Analysis of tissue mineral fiber content was performed using a JSM-35C SEM equipped with a Kevex energy dispersive spectrometer using techniques described previously [Roggli, 1989b, 1991; Roggli et al., 1986]. Lung tissue samples that had previously been fixed in formalin were digested in 5.25% sodium hypochlorite solution and the residue collected on 0.4 μ m pore-size Nuclepore filters. The filters were mounted on carbon discs with colloidal graphite and sputter-coated with gold prior to examination by SEM. From 5 to 50 fibers were analyzed by means of energy dispersive x-ray analysis (EDXA) in each case; in most cases, 10–20 fibers were examined (only five fibers were analyzed in a few cases because of very low fiber



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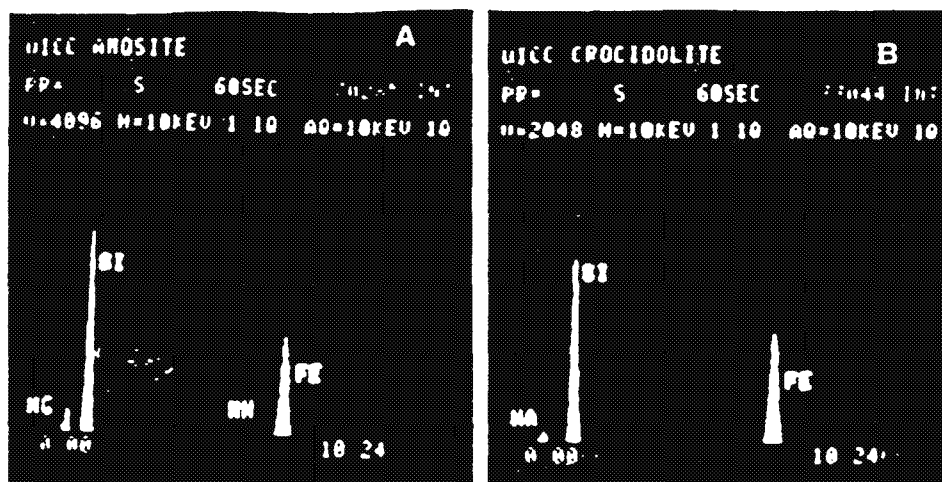


Fig. 1. A. Energy dispersive X-ray spectrum for amosite shows a prominent peak for silicon, an intermediate peak for iron, and smaller peaks for magnesium and, in this case, manganese. B. Spectrum for crocidolite shows a prominent peak for silicon, an intermediate peak for iron, and smaller peaks for sodium and magnesium.

counts and difficulty finding fibers 5 μm or greater in length: 50 fibers were analyzed in two cases because of a special study). Fibers were identified and examined consecutively using a screen magnification of 1,500 $\times$. Quantitative analyses for asbestos body content and uncoated fiber concentration for fibers 5 μm or greater in length were also performed in each instance, and these data have been reported previously for most of the cases [Roggli, 1991; Roggli et al., 1986, 1992]. They are not considered further in the present study.

Fibers were defined as mineral particles with a length-to-diameter (aspect) ratio of at least three-to-one and roughly parallel sides. Only fibers that were greater than or equal to 5 μm in length were included in the analysis. At the magnification used, most of the fibers observed were 0.2 μm or greater in diameter. Fibers were classified as amosite, crocidolite, chrysotile, tremolite, actinolite, anthophyllite, or nonasbestos mineral fibers based on their morphology and elemental composition as determined from energy dispersive x-ray spectra [Roggli, 1989b, 1991; Roggli et al., 1986]. Standard spectra were obtained for comparison using the U.I.C.C. (International Union Against Cancer) asbestos standard samples obtained from Dr. V. Timbrell [Roggli et al., 1982]. These standards include samples of amosite, crocidolite, chrysotile, and anthophyllite asbestos. The spectra for amosite and crocidolite are somewhat similar, being distinguished by a prominent magnesium peak for amosite and a prominent sodium peak for crocidolite (Fig. 1). For fibers recovered from the lungs of mesothelioma patients, spectra were collected on each fiber until sufficient numbers of magnesium or sodium X-rays had been accumulated to distinguish between amosite and crocidolite. In a few instances, the distinction could not be made due to the presence of a substantial chlorine peak along with the sodium. Under this circumstance, it is not possible to determine whether the sodium peak derives from crocidolite or from contamination of the filter with residual sodium hypochlorite

TABLE I. Demographic and Pathologic Information for 94 Patients With Malignant Mesothelioma

	No.
AGE (yr)	
Median	60
Range	31-89
SEX	
Male	84
Female	10
LOCATION	
Pleural	89
Peritoneal	5
SOURCE	
Autopsy	75
Surgical resection	19
EXPOSURE CATEGORY*	
Insulator	24
Shipyard worker (other than insulator)	22
Other asbestos	23
Household contacts	5
Building occupants	3
Other	5
Unknown	12

*See text for details.

adherent to organic residues [Roggli, 1989b]. Such fibers are classified as amosite/crocidolite (Amos/Croc) to acknowledge this confounding factor in fiber identification.

RESULTS

The demographic data for our 94 cases of malignant mesothelioma are summarized in Table I and are similar to those reported in other large series of patients with mesothelioma [Alberts et al., 1988; Chahinian et al., 1982; Ruffie et al., 1989]. The median age for the 94 cases is 60 years (range 31-89 years); 84 of the patients were men. In 89 cases, the tumor was of pleural origin, as opposed to a peritoneal origin in only five instances. Lung tissue for asbestos analysis was obtained at autopsy in 75 cases and from surgical resections in 19.

A history of asbestos exposure was elicited in 74 of the 94 cases (79%). Twenty-four of the patients were asbestos insulators, a category that includes the job descriptions of insulator, pipecoverer, pipefitter, boiler worker, asbestos sawer, and asbestos sprayer. Twenty-two patients were shipyard workers other than insulators, including such job descriptions as joiner, welder, rigger, engineer, estimator, sandblaster, machinist, carpenter, mason, fireman, service in the U.S. Navy or merchant marine, and shipyard worker not otherwise specified. Twenty-three patients had histories of exposure to asbestos other than as insulators or shipyard workers, and these included asbestos cement workers, chemical maintenance workers, asbestos textile workers, sheet metal workers, asbestos factory workers, electricians, construc-

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TABLE II. Number and Percentage of Cases in Which Various Fiber Types Were Identified in 94 Patients With Malignant Mesothelioma

Fiber type	No. cases	Percent
Amosite	76	81
Tremolite/anthophyllite/actinolite	52	55
Chrysotile	20	21
Crocidolite	15	16
Amos./Croc. ^a	5	5
Other ^b	67	71

^aCases in which amosite could not be distinguished from crocidolite with certainty by means of EDXA.

^bNonasbestos mineral fibers including talc, rutile, silica, aluminum silicates, other silicates, iron oxides, aluminum oxides, iron-chromium, fibrous glass.

tion workers, chemical engineers, nuclear or electrical power plant workers, jewelers, carpenters, painters and spacklers, inspection engineers, railroad workers (during steam locomotive era), brake repair workers, and industrial exposure to asbestos not otherwise specified [Roggli, 1991]. Five additional patients were household contacts of asbestos workers, and these accounted for half of the cases that occurred in women. For three patients, the only identified possible source of exposure was working or attending school in a building with asbestos-containing materials. Five patients had no identifiable exposure to asbestos, including a truck driver, a district sales manager, and a teacher. Information regarding exposure to asbestos was unavailable in the remaining 12 cases.

The number and percentage of the 94 cases among which each of the various fiber types were identified are summarized in Table II. Amosite was the most prevalent fiber type, identified in 76 cases (81%). The noncommercial amphiboles, tremolite, anthophyllite, or actinolite were identified in 52 cases (55%). The vast majority of these fibers had the typical composition of Si-Mg-Ca, which is the chemical signature for tremolite. Chrysotile fibers were detected in 20 cases (21%). Crocidolite was identified in only 15 of the 94 cases (16%). Among these 15 cases, there was only one in which crocidolite accounted for a greater percentage of the fibers than either amosite, chrysotile, or the noncommercial amphiboles. This case was an 82-year-old man who was a railroad worker and who had insulated his own home in the 1940s. There were five cases (5%) in which commercial amphiboles were identified, but a reliable distinction between amosite and crocidolite could not be made. Nonasbestos mineral fibers, including talc, rutile, silica, aluminum silicates, other silicates, iron oxides, aluminum oxides, iron chromium, or fibrous glass (in order of decreasing frequency), were identified in 67 cases (71%).

A total of 1,512 fibers were analyzed and identified by means of EDXA in these 94 cases, an average of 16 fibers per case. More than half (58%) of the total fibers identified had the characteristic chemical signature for amosite asbestos (Fig. 1A). An additional 10% of the fibers were noncommercial amphiboles, mostly tremolite. Only 3% of the fibers were crocidolite, which was similar to the percentage of chrysotile fibers detected. For 2% of the fibers analyzed, a reliable distinction between amosite and crocidolite could not be made. Nonasbestos mineral fibers accounted for 25% of

TABLE III. Number and Percentage of Mineral Fiber Types Among 1,512 Fibers Identified by EDXA

Fiber type	No. fibers	Percentage
Amosite	879	58
Tremolite/anthophyllite/actinolite	144	10
Crocidolite	43	3
Chrysotile	40	3
Amos./Croc.*	25	2
Other ^a	381	25

*See footnotes to Table II.

the total. Most of these were relatively low aspect ratio fibers, with lengths less than 10 μm and diameters of 1 μm or greater.

DISCUSSION

The present study indicates that among patients with malignant mesothelioma from the United States with a wide variation of exposure histories, amosite is by far the most predominant fiber type recovered from the lung for fibers 5 μm or greater in length. Crocidolite, by comparison, was identified about 1/20 as often (Table III). It is widely believed that fibers in this size range are the most relevant for the development of mesothelioma [Lippman, 1988; McDonald et al., 1989; Stanton et al., 1981; Wagner and Pooley, 1986]. Previous studies from our laboratory had presented data on fiber analysis as commercial amphiboles, with amosite and crocidolite combined [Roggli, 1989b, 1991; Roggli et al., 1986, 1992].

These findings are comparable to those of other investigators from the United States and abroad. Churg and Wiggs [1984] reported analyses from 10 patients with malignant mesothelioma from the Pacific Northwest who had amphibole-induced malignancies. In nine cases, the ratio of amosite to crocidolite ranged from 2.3 to 37 (median value of 14.3). In only one case did the concentration of crocidolite fibers exceed that of amosite. This patient was an asbestos insulator from 1945–1980. Warnock [1989] analyzed fiber burdens from 27 U.S. shipyard and construction workers with mesothelioma. The median amosite concentration was 1.2 million per gram of dry lung, whereas the median crocidolite concentration was 0.032 million per gram (a ratio of about 40:1) for fibers 0.25 μm or greater in length. In only two of the 27 cases did the concentration of crocidolite fibers exceed that of amosite. McDonald et al. [1989] reported results of lung tissue analyses from 78 Canadian patients with mesothelioma. As compared to a reference population, the risk increment and attributable risk for long ($> 8 \mu\text{m}$) amphibole fibers were 93.7 and 28% for amosite as compared to 24.9 and 10% for crocidolite in their group of patients with mesothelioma. Gaudichet et al. [1988] analyzed lung tissue samples from 20 French subjects with malignant mesothelioma and found a significant difference between amphibole fiber retention in mesothelioma cases vs. controls, but no preponderance of crocidolite over amosite. Rogers et al. [1991] analyzed fiber burdens from 221 Australian cases of mesothelioma and found the greatest risk to be associated with the presence of long ($\geq 10 \mu\text{m}$) crocidolite fibers, which these authors attributed to the

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wide distribution of Wittenoom crocidolite throughout Australia. However, a significant association between risk and amosite fiber burdens was also reported.

Noncommercial amphiboles were the next most commonly identified asbestos fiber type in our study, accounting for 10% of all fibers (Table III). Most of these were tremolite fibers, with smaller amounts of actinolite and anthophyllite. Tremolite is a known contaminant of chrysotile asbestos [Churg et al., 1984], which is the most common type of asbestos used commercially in the United States. Analysis of lung tissue from chrysotile miners and millers with malignant mesothelioma shows preferential retention of the contaminating tremolite fibers [Churg et al., 1984]. This is probably due to the tendency for chrysotile to break apart within the lungs into individual fibrils, which can then be more readily cleared [Roggli and Brody, 1984]. The study by McDonald et al. [1989] indicated that after excluding chrysotile miners and millers, ~22% of Canadian mesotheliomas are attributable to tremolite.

Only 3% of the total fibers in our study were long ($> 5 \mu\text{m}$) chrysotile fibers. This value of course does not include the much larger number of short chrysotile fibers, which are frequently found in lung samples from the general population [Churg and Warnock, 1980]. Studies from our laboratory have shown that chrysotile fibers $5 \mu\text{m}$ or less in length are rapidly cleared from the lungs of rats exposed by inhalation, whereas longer chrysotile fibers are preferentially retained [Coin et al., 1992]. Kimizuka et al. [1987] reported further fragmentation of long thin chrysotile fibers 2 years postexposure in hamsters, with a concomitant increase in the percentage of fibers less than $5 \mu\text{m}$ in length. These short fibers would then be expected to be rapidly cleared from the lungs. Tremolite fibers found in the lung tissues of our mesothelioma cases are probably a marker for the much greater numbers of chrysotile fibers, which were deposited but subsequently cleared. Rogers et al. [1991] concluded that the chrysotile lung burden contributed significantly to the risk of mesothelioma in Australia, whereas McDonald et al. [1989] found no difference in chrysotile content between cases and controls. We are unable to exclude a role for the long chrysotile fibers ($> 5 \mu\text{m}$) found in our cases in the production of mesothelioma, especially since they probably constitute only a minute proportion of the long fibers actually deposited.

Nonasbestos mineral fibers accounted for 25% of the total fibers identified in the present study (Table III). Such fibers are commonly found among members of the general population [Churg, 1983; Roggli, 1989a] and account for nearly 80% of fibers $5 \mu\text{m}$ or greater in length found in lungs of individuals with no identifiable exposure to asbestos [Roggli et al., 1992]. Most of these fibers had a low aspect ratio, and very few of them met the Stanton criteria for the most dangerous fibers, i.e., $\geq 8 \mu\text{m}$ in length and $< 0.25 \mu\text{m}$ in diameter. (Fibers that are $\geq 8 \mu\text{m}$ in length and $< 0.25 \mu\text{m}$ in diameter were the most efficient at producing mesotheliomas by means of implantation within the pleural cavities of rats [Stanton et al., 1981].) McDonald et al. [1989] could find no evidence that these nonasbestos mineral fibers contribute to the risk of mesothelioma.

It has been suggested that it is the fibers that reach the pleura that are the ones responsible for the development of mesothelioma. In this regard, studies by Sébastien et al. [1977] showed that large numbers of short ($< 5 \mu\text{m}$) chrysotile fibers accumulate in the pleura, whereas long ($> 5 \mu\text{m}$) amphibole fibers tend to accumulate within the lung parenchyma. However, a review of the pertinent human and experimental animal literature indicates that fibers less than $5 \mu\text{m}$ in length are unlikely to

be relevant to the pathogenesis of mesothelioma [Lippmann, 1988]. Furthermore, recent studies have shown that, in addition to short chrysotile fibers, some long amosite fibers also reach the pleura [Dodson et al., 1990]. Fibers that exceed 5 μm in length and have diameters less than 0.1 μm may be the ones that are most relevant to the development of malignant mesothelioma in man [Lippmann, 1988], although the pathologic changes induced by large numbers of short fibers have yet to be established in human lungs.

It could be argued that, since our technique primarily detects fibers that are 0.2 μm or greater in diameter, we could have overlooked substantial numbers of fibers that are 5 μm or greater in length and 0.1 μm or less in diameter. We think that this possibility is unlikely to affect our results or conclusions, because substantial numbers of crocidolite or amosite fibers less than 0.1 μm in diameter should be accompanied by substantial numbers of fibers 0.2 μm or greater in diameter. This opinion is supported by the observations of Churg and Wiggs [1984] and Warnock [1989], since these investigators used transmission electron microscopy and found ratios of amosite to crocidolite among U.S. mesothelioma cases similar to those found in our study. It is more likely that our analysis would underestimate the numbers of chrysotile fibers 5 μm or greater in length, because chrysotile tends to undergo longitudinal splitting with many fibers, as a result, having diameters less than 0.1 μm [Roggli and Brody, 1984].

There is a growing consensus that it is the fibers that accumulate within the lung that are responsible for the development of asbestos-associated diseases, including mesothelioma [Churg, 1988; Wagner and Pooley, 1986]. If this is indeed the case, then the results of the present study indicate that, with respect to the occurrence of malignant mesothelioma in the United States, the order of importance of the various asbestos fiber types is

Amosite > Tremolite > Chrysotile $\equiv$ Crocidolite.

Our findings are at odds with the assertion that crocidolite asbestos is responsible for most mesotheliomas in the United States.

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