

Chrysotile Asbestos is the Main Cause of Pleural Mesothelioma

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In contrast to amphibole forms of asbestos, chrysotile asbestos is often claimed to be only a minor cause of malignant pleural mesothelioma, a highly fatal cancer of the lining of the thoracic cavity. In this article we examine the evidence from animal and human studies that relates to this issue. Reported data do not support widely quoted views regarding the relative inertness of chrysotile fibers in mesothelioma causation. In fact, examination of all pertinent studies makes it clear that chrysotile asbestos is similar in potency to amphibole asbestos. Since asbestos is the major cause of mesothelioma, and chrysotile constitutes 95% of all asbestos use world wide, it can be concluded that chrysotile asbestos is the main cause of pleural mesothelioma in humans. © 1996 Wiley-Liss, Inc.

KEY WORDS: chrysotile, asbestos, mesothelioma, epidemiological studies, animal studies, amphibole hypothesis, Stanton hypothesis

INTRODUCTION

Asbestos inhalation is an established cause of cancer in humans, particularly malignant mesothelioma and lung cancer. It is the main cause of cancer resulting from workplace exposure to carcinogens.

Despite extensive cancer studies in humans, certain controversies remain about asbestos exposure and human cancer. The primary controversy is the question of fiber type in causation of mesothelioma. Commercial use of asbestos mainly involves the two amphibole fiber types, crocidolite and amosite, and one serpentine fiber type, chrysotile. However, chrysotile asbestos is often contaminated with small amounts of tremolite, an amphibole fiber. The key questions concern whether or not, and to what extent, exposure to chrysotile asbestos (including its natural contaminant tremolite) causes mesothelioma in humans. While there is evidence that chrysotile asbestos is not a potent cause of malignant peritoneal mesothelioma [EPA, 1986; Doll and Peto, 1983], the role of chrysotile in the causation of pleural mesothelioma is still disputed.

Chrysotile asbestos is established to be a cause of asbestosis and lung cancer. In fact, one of the highest risks of asbestos-related lung cancer was observed in textile manufacturing where 100% chrysotile was used [Dement et al., 1994]. However, the opinion is held by some that chrysotile asbestos is much less hazardous than crocidolite, amosite, and tremolite, particularly where malignant mesothelioma is concerned. McDonald et al. [1989] state: "Amphibole asbestos fibers could explain most mesothelioma cases in Canada and other inorganic fibers, including chrysotile, very few." Wagner [1991] states: "There is overwhelming evidence that crocidolite is the main fibre associated with mesotheliomas. There is no clear evidence that exposure to uncontaminated chrysotile or anthophyllite is associated with these tumors." Two recent articles, however, have concluded that chrysotile is, in fact, an important cause of malignant mesothelioma [Huncharek, 1994; Nicholson and Landrigan, 1994]. Nicholson and Landrigan conducted a thorough review of the evidence concerning the carcinogenicity of chrysotile asbestos. In particular, they utilized the strong time dependence of mesothelioma risk to apportion the contribution of the different exposure periods, and thus of different fiber types, to the observed risk. Huncharek addresses some current controversial issues surrounding asbestos health effects and their relationship to cancer risk assessment and risk management. As these articles point out, the question of the carcinogenic potential of chrysotile

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asbestos is not only of scientific interest, but also has legal, public policy, and public health importance.

The purpose of this paper is to further examine both human and animal evidence concerning the importance of chrysotile asbestos in causing malignant pleural mesothelioma. Specifically, we have identified the 25 epidemiologic cohort studies having the highest ratio of pleural mesotheliomas per 1,000 deaths, and have assessed the type(s) of asbestos fiber exposure in the highest risk cohorts. We have also reviewed those lines of evidence often cited in support of the theory that amphibole asbestos, not chrysotile, is the primary, if not sole, cause of malignant mesothelioma. Such lines of evidence include: results of certain epidemiological studies (such as the gas mask studies), and the "Stanton" and "amphibole" hypotheses.

A REVIEW OF THE EPIDEMIOLOGICAL DATA

A review of the literature was undertaken to identify available asbestos epidemiological studies. Cohort studies (most recent follow-up available as of October 1994) were reviewed for the following data: industry, primary asbestos exposure (the fiber type to which the cohort or subcohort had the greatest exposure), secondary asbestos exposure (fiber types to which the cohort or subcohort had lesser exposure), number of workers in the cohort, number of deaths, number of lung cancer deaths, excess lung cancer deaths, and numbers of mesotheliomas. Pleural mesothelioma incidence within the cohort was determined in terms of the number of pleural mesothelioma deaths per 1,000 deaths as well as the ratio of pleural mesotheliomas to excess lung cancer deaths. When possible, the mortality data for subcohorts with greater than or equal to 20 years since start of employment were used in determining mesothelioma incidence. Cohorts were rank ordered from the highest to lowest ratio of pleural mesotheliomas per 1,000 deaths.

Table I summarizes the data for the 25 top-ranking asbestos cohorts. Other studies which were considered but which ranked below the top 25 cohorts are listed in Table II. Chrysotile was the primary exposure for at least two of the 10 top-ranking cohorts [Mancuso, 1988; Peto et al., 1985] and was the secondary exposure or identified as part of a mixed exposure in six of the 10 top-ranking cohorts. Crocidolite was the primary exposure for three of the top 10 cohorts [Jones et al., 1980; Talcott et al., 1989; McDonald and McDonald, 1978] and was the secondary exposure or identified as part of a mixed exposure in another five cohorts. Amosite was identified as part of a mixed exposure in three of the top 10 cohorts, but was not the primary exposure in any of them. These findings suggest that chrysotile is a major cause of pleural mesothelioma. They are inconsistent with the claim that amphibole fibers are much more potent than chrysotile. If that were the case, one would

expect all the top 10 risk cohorts to be predominantly amphibole exposure cohorts.

The highest ratio of 88.1 pleural mesotheliomas per 1,000 deaths was for railroad machinists exposed to chrysotile [Mancuso, 1988]. This study has been criticized for attributing the mesothelioma incidence to chrysotile exposure rather than possible amphibole exposure [Ohlson, 1989; McDonald and McDonald, 1989; Churg and Green, 1990]. Mancuso's responses to such criticism demonstrate that the principal exposure of the railroad machinists was to lagging or removal of lagging, which was chrysotile. While other jobs may have used amphiboles, leading to the possibility of secondary exposure to the railroad workers, he made a strong case that chrysotile was the overwhelming exposure to the machinists [Mancuso, 1989a,b, 1990].

A number of other epidemiological studies have been published but lack data that would allow calculation of pleural mesothelioma incidence. Bégin et al. [1992] described a series of mesothelioma cases in Canadian asbestos workers. All of these cases were seen and accepted by the Quebec Workman's Compensation Board for work-related compensation of industrial disease. There were 49 cases in miners and millers of the Quebec Eastern Township region. Twenty mesotheliomas occurred in miners and millers from Asbestos, where tremolite contamination was similar to background urban levels. Twenty-nine mesotheliomas occurred in workers from Thetford Mines, where higher levels of tremolite occur. The authors stated that, on the basis of the number of workers exposed at each mine site, the incidences in Asbestos and Thetford Mines were similar despite the differing levels of tremolite contamination. McDonald et al. [1980, 1993] conducted a cohort study of the miners and millers from Thetford Mines and Asbestos. Only 33 (25 in the period 1976-1988) mesotheliomas have been identified in the entire cohort of about 11,000 men, 80% of whom had died as of 1992. According to the authors, preliminary analysis of mesotheliomas suggests that the risk of mesothelioma was higher in the mine and mills at Thetford Mines (higher tremolite exposure) than in those at Asbestos (lower tremolite exposure). Their data, however, do not clearly support this conclusion, especially in the high exposure groups where the rates of mesothelioma were 0.97 per 1,000 person-years for Asbestos and 0.92 per 1,000 person-years for Thetford Mines.

A number of other studies have demonstrated risks of mesothelioma due to chrysotile exposure. Borow et al. [1973] reported 72 cases of malignant mesothelioma in persons exposed primarily to chrysotile in an asbestos mill. Fifty-three acceptable cases of chrysotile-induced mesotheliomas were identified by Churg et al. [1988]. Two malignant mesotheliomas were reported in a small group of former chrysotile miners and millers in Zimbabwe [Cullen and Baloyi, 1991]. A case series of 80 mesotheliomas in railroad rolling-stock machinists and others in the Italian

TABLE I. Asbestos Cohort Studies

Reference	Industry	Primary asbestos exposure	Secondary asbestos exposure	Number in cohort	Number of deaths	Lung cancer deaths	Excess lung cancers	Perit. mesoth.	Pleural mesoth.	Pl. meso/ 1,000 deaths	M. meso/rate lung cancers	Comments
Mancuso [1968]	Railroad machinists	Chrys	Possibly some amphibole	181	159	11	NA	1	14	58.1	NA	Expected lung cancer rates were not reported. Primary servicing of steam locomotives. Greater than 20 years since first employment. Mancuso [1969] emphasized that principal exposure was lagging or removal of lagging, which was chrysotile. However, other jobs may have used amphiboles, so secondary exposure is possible.
Reinstein [1964]	Cement products	Chrys/croc		683	136	29	21.4	3	11	30.9	0.51	20+ years from onset. Production and maintenance.
Jones et al. [1980]	Gas mask manufacture	Croc		951	166	12	5.7	4	13	78.2	2.29	20+ years from onset. Females only.
Falcon et al. [1969]	Cigarette filter manufacture	Croc		23	28	11	10.3	3	2	71.4	0.19	
Elmes and Simson [1977]	Insulation (luggers)	Unknown mix		162	122	14	NA	5	3	65.6	NA	20+ years from onset. Eleven additional lung cancers or mesotheliomas could not be categorized. EPA [1986] lists 27 cases, 22 excess lung cancers for this cohort.
Peto et al. [1965]	Textiles	Chrys	Croc	145	123	20	14.3	0	7	56.9	0.48	Subcohort, men only, employed 20+ years with some service before 1933. High exposure group. Crocidolite made up 5% of asbestos used between 1932 and 1969.
McDonald and McDonald [1973]	Gas mask manufacture	Croc	Chrys	199	56	7	4.6	9	3	51.6	0.65	Males and females combined. 20-26 years since onset of exposure to crocidolite. Exposure to chrysotile likely to have occurred before and after. Cohort includes workers from three factories. Filter pad workers in Montreal (n = 32) were exposed to croc from 1940 to 6/41 only. This factory used chrysotile since 1928 for mural, of 3754 bricks. Filter pad workers from Asbestos, Quebec (n = 113) were exposed to croc 1939-1941 only. This factory had been in operation since WWI processing chrysotile. Gas mask assembly was performed in Ottawa (n = 34). An additional two cases of pleural mesothelioma from Montreal plant were identified from a mail survey. Note that Table 2 in McDonald and McDonald [1973] incorrectly presents two pleural mesotheliomas.
Newhouse et al. [1985]	Textiles/cement products	Mixed amos/chrys/croc		700	274	37	32.0	11	14	51.1	0.44	Women only. Greater than 10 years follow-up.
Newhouse et al. [1985]	Luggers	Mixed amos/chrys/croc		1,400	157	38	27.3	6	7	44.6	0.26	Men only. Greater than 10 years follow-up. No complete data for 20+ years since last employ.
Selikoff et al. [1979a]	Shipyards	Chrys/amos		389	73	20	24.9	5	3	41.1	0.12	Shipyards insulator cohort 20+ years from onset. Amos+ croc to chrysotile just before and during WWII.
Sluis-Cremer et al. [1992]	Mining	Croc		1,430	423	27	13.7	2	17	40.2	1.24	Cohort of miners exposed only to crocidolite. No subcohort data for 20+ years since last employ.
Nicholson [1976]	Production and textiles	Not stated		689	199	27	18.6	7	6	40.2	0.43	20+ years from onset.
Armstrong et al. [1968]	Mining/milling	Croc		6,506	820	91	56.5	1	32	39.0	0.57	Men only. Includes entire cohort. Update to Hobbs et al. [1980].
Newhouse et al. [1985]	Textiles/cement products	Mixed amos/chrys/croc		1,000	818	158	94.8	29	31	37.9	0.33	Men only. >10 years follow-up.
Seidman and Selikoff [1950]	Insulation	Chrys	Amos	17,800	4,951	1,168	899.3	285	173	34.9	0.19	Entire cohort. Workers were exposed to chrys in early years and chrys + amos in later years.
Reisner et al. [1980]	Shipyards	Mixed		6,076	1,043	84	16.3	2	29	27.8	-1.78	
Albin et al. [1990]	Asbestos cement manufacture	Chrys	Crocidolite	1,458	592	15	15.8	0	13	22.0	0.33	
Seidman et al. [1986]	Insulation manuf.	Amos		820	366	76	62.8	9	8	21.9	0.13	20-40 elapsed years since onset of work.
Peto et al. [1965]	Textiles	Chrys	Croc	3,211	727	93	28.4		10	13.8	0.35	Subcohort of men first employed in 1933 or later. 20+ years since last employ.
Sluis-Cremer et al. [1992]	Mining	Mixed amon		673	154	NA	NA	3	2	13.0	NA	Cohort of miners exposed to mixed amphiboles. The number of pl mesos could be two or three. Unclear.
Newhouse and Sullivan [1989]	Friction materials	Chrys	Croc	2,222	743	88	5.7	NA	9	12.1	1.58	20+ years from onset.
Kolonel et al. [1985]	Shipyards	Chrys	Amos	3,191	668	81	4.9	7	8	12.0	1.63	Nonexposed group excluded.
Acheson et al. [1984]	Insulation manufacture	Amos		4,820	313	57	27.3	1	4	12.0	0.15	Includes all latency period. Includes two pl. mesoth. with less than 20 years since first exposure.
Acheson et al. [1982]	Gas mask manufacture	Croc		757	219	13	6.8	0	2	9.1	0.29	Crocidolite cohort only. Some chrysotile chrysotile gas masks were also made by this cohort.
Raffin et al. [1989]	Mixed, i.e., cement	Chrys	Amos/croc	7,996	1,305	162	72.2	0	10	7.7	0.14	89% chrysotile used. 100% chrys. 1923-1946.

TABLE II. Additional Studies Considered*

Acheson et al. [1982]—chrysotile cohort
Cement et al. [1982]
Finkelstein [1989]
Henderson and Enterline [1979]
Hughes and Weill [1980]
Hughes et al. [1987]
McDonald et al. [1980, 1993]
McDonald et al. [1983a]
McDonald et al. [1983b]
McDonald et al. [1984]
Nicholson et al. [1979]
Pioatto et al. [1990]
Puntoni et al. [1979]
Robinson et al. [1979]
Sluis-Cremer et al. [1992]—amosite cohort
Thomas et al. [1982]
Weill et al. [1979]
Weiss [1977]

*Studies which were reviewed but were not included in Table I due to low ratios of pleural mesotheliomas to total deaths.

railroad industry, where chrysotile was the primary exposure, has also been reported [Maltoni et al., 1991]. Fifty malignant mesothelioma cases have been identified in the manufacturing, insulation, and shipbuilding trades, and 21 cases in the construction and building maintenance trades [Begin et al., 1992]. In all of these trades, chrysotile constituted the primary exposure and amphiboles the secondary exposure. Sanden et al. [1992] conducted a cancer incidence study of shipyard workers exposed primarily to chrysotile, with lesser exposure to amosite and crocidolite. Eleven of the 168 cancers were pleural mesothelioma, including eight of the 70 cancers in persons with 20 or more years latency. In addition, eight cases of malignant mesothelioma were reported following household exposure to the dusty clothing of asbestos workers [McDonald and McDonald, 1980]. Three of these eight cases were children of chrysotile mine employees. The above data demonstrate that chrysotile exposure, even at the relatively low levels expected in household exposures, can cause malignant mesothelioma.

Gas Mask Studies

Studies of workers who assembled gas masks during World War II have been widely quoted as indicating that crocidolite is much more potent than chrysotile asbestos in causing mesothelioma [Doll and Pero, 1985; Harington, 1991]. Table III presents data abstracted from the three gas mask studies where workers have been exposed to one fiber type only [Jones et al., 1980; McDonald and McDonald,

1978; Acheson et al., 1982]. The expected number of lung cancer deaths for the McDonald and McDonald [1978] study was not given, but we have assumed it was one since it makes very little difference to the overall consideration of the studies.

The last row of Table III gives the summed data from the three gas mask studies. There were 19 pleural mesothelioma cases in the crocidolite group with a lung cancer excess of about 13.5. There was only one case in the chrysotile-only category, but the excess lung cancer number was only 1.2. Since chrysotile is a potent cause of lung cancer, this low excess makes it clear that the chrysotile gas mask workers had relatively low exposures. In fact, the total length of exposure to chrysotile in the Jones et al. study was shorter than 5 months. In the Acheson study, the exposure to chrysotile was probably much lower than the exposure to crocidolite, since the crocidolite filters were made by hand while the manufacture of chrysotile filters was mechanized. Thus these three studies provide no evidence whatsoever that crocidolite is more potent in causing mesothelioma than chrysotile asbestos.

Fiber Type Risk Comparisons

Hughes and Weill [1986] have suggested that crocidolite is about 14 times more potent than chrysotile in causing combined pleural and peritoneal mesotheliomas. This finding is based on combined data from selected cohorts with chrysotile, amosite, crocidolite, or mixed exposures. The results indicated that the number of mesotheliomas was 12% of the excess lung cancers among chrysotile-exposed populations, but 165% for crocidolite exposure, 22.2% for amosite exposure, and 65.9% for mixed fiber exposure.

Table IV presents our reanalysis of the above findings. The same cohorts are included, but the most recent follow-up data from these cohorts were used in the analysis. Where possible, data from subcohorts with 20+ years since first exposure were used. Furthermore, since it is generally agreed that chrysotile asbestos is not a potent cause of peritoneal mesotheliomas, only pleural mesotheliomas are included in the table. Our analysis indicates very different results from Hughes and Weill [1986]. The number of pleural mesotheliomas is 20% of the excess lung cancers among chrysotile-exposed populations, 72% for crocidolite exposure, 13% for amosite exposure, and 27% for mixed exposures. The longer follow-up period makes a large difference between the Hughes and Weill [1986] analysis and that presented here. Rather than appearing to be 14 times less potent than crocidolite, based on this selection of studies chrysotile may be only three or four times less potent in causing malignant mesothelioma. This is in close agreement with the conclusions of Nicholson [1991], who looked at comparative dose-response relationships of asbestos fiber

TABLE III. Pleural Mesotheliomas, Lung Cancer, and Excess Lung Cancers in Gas Mask Manufacturers Using Only Crocidolite or Only Chrysotile

	Crocidolite only			Chrysotile only		
	Pleural mesotheliomas	Lung cancer	Excess lung cancers	Pleural mesotheliomas	Lung cancer	Excess lung cancers
McDonald and McDonald [1978] ^a	1	2	1	—	—	—
Jones et al. [1980]	15	11	5.7	0	0	—
Acheson et al. [1982]	3	13	6.8	1	6	1.2
Total	19	26	13.5	1	6	1.2

^aOttawa cohort with exposure to crocidolite only.

types and included more studies than Hughes and Weill [1986]. His conclusion was: that "There appears to be no difference in the potency of chrysotile and amosite in producing mesothelioma. However, exposures to pure crocidolite, which has been and is rarely used in the U.S., may carry a two- to three-fold greater risk" [Nicholson, 1991].

To summarize the epidemiological findings as they relate to chrysotile and pleural mesothelioma, the following points can be made: (1) If crocidolite were much more potent, the highest mesothelioma risk cohorts should involve predominantly exposure to crocidolite. In fact, the highest risk cohorts do not show this differentiation. (2) Limited data concerning exposure of household members suggest chrysotile is a highly potent cause of mesothelioma. (3) The widely quoted gas mask workers studies do not provide evidence that crocidolite is more potent than chrysotile. (4) Considered overall, the evidence suggests chrysotile may be less potent than crocidolite by a factor in the range of 2–4. However, the epidemiological evidence does not support chrysotile being less potent than amosite.

A REVIEW OF AVAILABLE ANIMAL DATA

Chrysotile, amosite, crocidolite, and tremolite can cause pleural mesotheliomas in experimental animals exposed by inhalation, intrapleural injection, or surgical implantation. Table V summarizes data from long-term studies of experimental animals exposed via inhalation, the most relevant route for human exposure.

In order to get an overall incidence of pleural mesotheliomas in rats following inhalation, incidence data were added together for each of the three asbestos types (i.e., chrysotile, amosite, and crocidolite). The overall incidence of pleural mesothelioma in rats exposed via inhalation is 1.3% (13/733) for chrysotile, 1.3% (5/377) for amosite, and 1.2% (4/328) for crocidolite. Thus, inhalation studies in rats do not support the argument that chrysotile is far less potent than amphiboles in pleural mesothelioma causation.

Since only one inhalation experiment has been done for tremolite, it is not included in this comparison.

Intrapleural injection studies have also demonstrated that chrysotile is a potent cause of pleural mesotheliomas in rats [Reeves et al., 1971; Wagner et al., 1973]. In fact, Wagner et al. found that finely milled chrysotile was more potent than the crocidolite and amosite samples tested.

Surgical pleural implantation of fine chrysotile, crocidolite, amosite, or tremolite fibers also induced significant numbers of pleural sarcomas in rats [Stanton et al., 1972, 1981]. The cumulative incidence of deaths with mesothelioma from chrysotile, amosite, and two types of crocidolite was similar at the maximum dose level of 40 mg [Stanton et al., 1972].

In conclusion, there is clear evidence in animal inhalation and pleural injection/implantation studies that chrysotile asbestos causes pleural mesothelioma. Indeed, if one considers the dose of asbestos in terms of mass, chrysotile asbestos is generally the more potent fiber when compared to crocidolite and amosite. However, the data do not permit estimation of potency per fiber. The data for tremolite is quite limited, but do not support the conclusion that tremolite is a more potent mesothelial carcinogen than chrysotile.

THE STANTON AND AMPHIBOLE HYPOTHESES REVISITED

Two lines of evidence have led some researchers to believe that chrysotile is not an important cause of pleural mesothelioma in asbestos workers, and that the risk is attributable to amphibole exposure. The "Stanton Hypothesis" suggests that mesothelioma incidence is strongly correlated with longer, thinner fibers. The "Amphibole Hypothesis" states that amphibole fibers are responsible for causing mesothelioma, since these fibers are found in the lungs of mesothelioma cases at autopsy, but chrysotile fibers are not. The evidence leading to these hypotheses is summarized below.

TABLE IV. Mesothelioma in Populations Exposed to Different Fiber Types^{a,b}

Fiber type	Observed deaths	Lung cancer		Pleural mesothelioma	
		Observed	Excess	Observed	As % of excess lung cancer
Chrysotile ^c	10,245	726	186.9	39	20.3
Amosite ^d	1,153	133	90.2	12	13.3
Crocidolite ^e	1,042	110	86.8	48	71.9
Mixed fiber ^f	9,532	1,722	1,106.2	301	27.2

^aBased on Table 1 of Hughes and Weil (1986).^bIncludes subcohorts with 20+ years since first employment, where possible.^cMcDonald et al. (1983, 1984, 1993), McDonald and McDonald (1980), Rubino et al. (1979), Pianto et al. (1990), Weiss (1977), Acheson et al. (1982), Thomas et al. (1982).^dSeidman et al. (1979, 1986), Acheson et al. (1984).^eHoods et al. (1980), Armstrong et al. (1988), McDonald and McDonald (1978), Jones et al. (1980).^fMcDonald et al. (1983), Berry and Newhouse (1983), Newhouse and Sullivan (1989), Selikoff et al. (1979), Seidman and Selikoff (1990), Acheson et al. (1982), Newhouse and Berry (1979), Newhouse et al. (1985), Finkelstein (1983, 1984), Elmes and Simpson (1977), Thomas et al. (1982), Rossiter and Coles (1980).

Stanton and his colleagues conducted a series of experiments in which a number of durable minerals in the form of respirable particles were implanted in the pleura of rats for periods of more than 1 year (Stanton and Wrench, 1972; Stanton, 1973; Stanton et al., 1977, 1981). Significant numbers of pleural sarcomas were induced in rats with a wide variety of fine, durable fibers including chrysotile, crocidolite, amosite, and tremolite. The two earlier studies showed no difference in potency between standard UICC samples of chrysotile and crocidolite (Stanton and Wrench, 1972; Stanton, 1973). The primary conclusion of these studies was that the ability of mineral particles to cause tumors is mostly a function of the dimensional properties of the particles, rather than physicochemical properties.

The later studies, which did not include chrysotile, attempted to further characterize the importance of dimensional aspects of fibers (Stanton et al., 1977, 1981). According to the authors, the incidence of malignant mesenchymal neoplasms correlated well with the dimensional distribution of the particles. The probability of pleural sarcoma correlated best with the number of fibers that measured 0.25 μm or less in diameter and more than 8 μm in length. Relatively high correlations were also observed with fibers in other categories having a diameter up to 1.5 μm and a length of greater than 4 μm .

This evidence led to the "Stanton Hypothesis," which states that durable fibers (provided they subscribe to well defined ranges of diameter and length), of which asbestos is but one sample, cause cancer irrespective of their physicochemical nature simply because they are fibers. Stanton also stated, however, that direct application of the results of his experiments to the problems in humans would be unwise given the deficiencies in the method of application and the massive amounts of fibers used (standard dose, 40 mg). In fact, if one were to exclude all fiber types other than asbes-

tos from Stanton's data, there appears to be little or no relationship between the probability of tumor and the number of particles measuring $\leq 0.25 \mu\text{m}$ diameter and $\geq 8 \mu\text{m}$ length (Fig. 1).

Other researchers have studied the correlation between dimensional properties of fibers and mesothelioma. In experiments similar to Stanton's, Jaurand (1991) determined the percentage of mesotheliomas occurring after intrapleural inoculation of 20 mg asbestos samples into rats. She found a fairly good correlation ($r = 0.643$, $p < 0.01$) between the risk of mesothelioma and the number of "index" fibers (i.e., $\leq 0.25 \mu\text{m}$ diameter and $\geq 8 \mu\text{m}$ length) inoculated according to Stanton's criteria. However, there was only a 30% difference (20% vs. 50%) between the percentage of mesotheliomas produced by samples with the smallest number of index particles compared to samples with a higher number of index particles. Furthermore, when Jaurand (1991) combined all of her available data from previous studies of amosite, crocidolite, and chrysotile (Monchaux et al., 1981), there was no correlation between the percentage of mesotheliomas and the number of index particles ($r = 0.164$).

Despite Stanton's warning and the findings described above, many researchers have utilized the Stanton hypothesis to link mesothelioma cases to particular asbestos fiber types and sizes. Churg, for example, stated: "Given the very high exposures experienced by the Quebec workforce, the short size and low aspect ratio of the tremolite fibers found in the ore may be a fortunate accident which 'protects' these workers from mesothelioma" (Churg, 1988).

Churg's statement, however, also assumes that it is the tremolite, not the chrysotile, that is responsible for those mesotheliomas that did occur. This assumption is based on the finding that, although tremolite comprises only a tiny fraction of the asbestos dust in the Quebec mines and mills,

TABLE V. Long-Term Asbestos Inhalation Studies in Animals

Reference	Species	Fiber type	Dose ^{a,b} mg/m ³	Number tested	No. of pleural mesotheliomas
Reeves et al. (1971) ^{c,d}	Rats	Amos	~48	63	0
		Croc	~48	61	0
		Chrys	~48	49	0
	Rabbits	Amos	~48	20	0
		Croc	~48	18	0
		Chrys	~48	26	0
	G. pigs	Amos	~48	17	0
		Croc	~48	33	0
		Chrys	~48	21	0
	Hamsters	Amos	~48	50	0
		Croc	~48	45	0
		Chrys	~48	49	0
Wagner et al. (1974)	Rats	Amos	11-14	146	1 ^e
		Croc	10-13	141	3 ^e
		Chrys (Can.) ^f	10-12	137	4
		Chrys (Rh.) ^g	10-15	144	0
Reeves et al. (1974)	Rats	Chrys	~50	34	1
		Croc	~50	43	0
		Amos	~50	43	2
	Gerbils	Chrys	~50	40	0
		Croc	~50	31	0
		Amos	~50	45	0
Davis et al. (1978)	Rats	Chrys (Rh.)	2	42	0
		Chrys (Rh.)	10	40	0
		Amos	10	43	0
		Croc	5	43	1
		Croc	10	40	0
		Tremolite (Kor.) ^h	?	40	2
Davis et al. (1985)	Rats	Short amos	10	42	0
Davis et al. (1986a)	Rats	Long amos	10	40	2
Davis et al. (1986b)	Rats	WDC yarn ⁱ	4	41	0
		Factory WDC ^j	4	44	0
		Chrys yarn ^k	4	42	1
		Exp WDC ^l	4	43	4
		Exp WDC/RO ^m	4	37	1
		Short chrys	10	40	0
Davis and Jones (1988)	Rats	Long chrys	10	40	2
		Chrys		733	13 (1.8%)
Total	Rats	Amos		377	5 (1.3%)
		Croc		328	4 (1.2%)

^aNo pleural mesotheliomas were observed in any control group.

^bSimilar doses in mg/m³ may be very different in terms of fibers/ml.

^cMesothelioma occurred with just 1 day exposure (>2 years followup).

^dOne mesothelioma occurred with just 1 day exposure (>2 years followup).

^eRh. Rhodesian.

^fCan. Canadian.

^gKor. Korean.

^hWDC is wet dispersed chrysotile.

ⁱDust from factory air.

^jStandard chrysotile textile yarn.

^kExperimental WDC process.

^lExperimental WDC "reversed daylight."

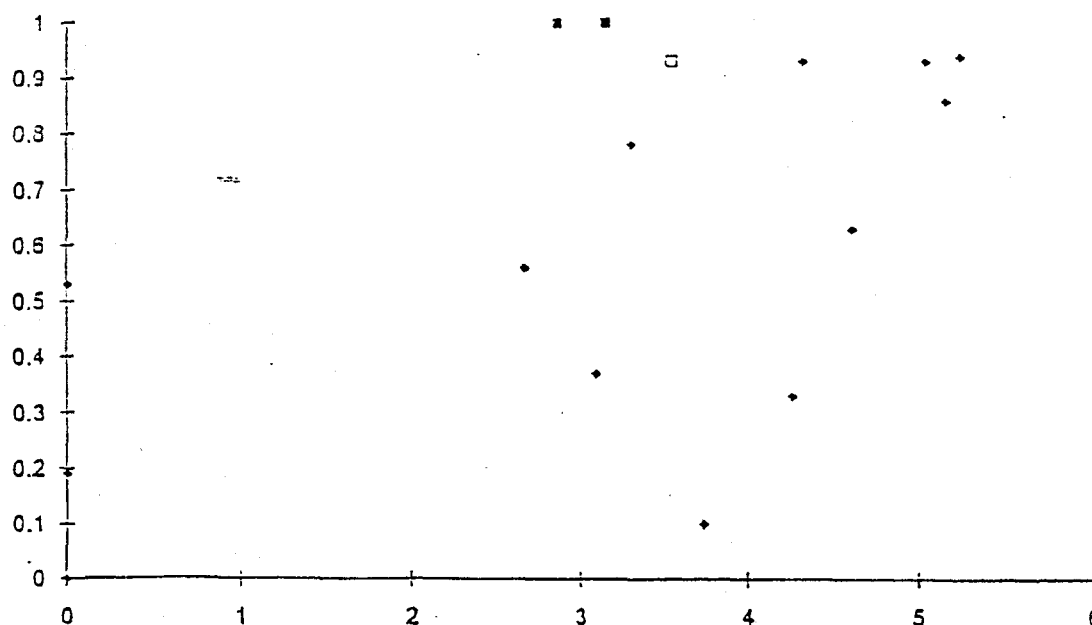


FIGURE 1. Stanton et al. (1981) data for asbestos fibers only. X-axis: Log number particles measuring $\leq 0.25 \mu\text{m}$ width by $> 8 \mu\text{m}$ length per microgram. Y-axis: Probability of tumor. ■, tremolite; □, amosite; +, crocidolite.

high tremolite lung burdens were associated with the presence of mesothelioma in miners and millers from Thetford Mines [Churg, 1994]. After adjustment for the presence of tremolite, no correlations between chrysotile concentration and disease could be found.

This leads us to the "amphibole hypothesis," which attributes the mesotheliomas observed in various groups of workers to the asbestos fibers present in their lungs at the time of death rather than to the fiber exposure earlier in life [McDonald et al., 1989; Mossman et al., 1990; Churg, 1988]. The "amphibole hypothesis" is based on the findings that workers exposed to asbestos have more amphiboles in their lungs than chrysotile at autopsy. This occurs because chrysotile fibers (but not amphiboles) break down and split apart longitudinally in tissue, leading to a loss of fibers in lung tissues that are visible by electron microscopy [Nicholson and Landrigan, 1994]. Some suggest that some (if not most) of the chrysotile fibers further fragment into shorter fibers and are then cleared from the lungs [Churg, 1994].

A number of studies have examined fiber content in lungs of mesothelioma cases. Those of Churg et al. [1984] and McDonald et al. [1989] are often referenced in support of the "amphibole hypothesis." Other important studies include Roggli et al. [1993], Morinaga et al. [1989], Rogers et al. [1991], and Sakai et al. [1994]. In fact, the results of these studies are inconsistent, as demonstrated in the following reviews.

Lung tissues of six mesothelioma cases from the Quebec chrysotile mining regions were examined by Churg et al. [1984]. The five cases that had only chrysotile ore components in their lungs had larger amounts of tremolite (i.e., tremolite/actinolite/anthophyllite) than chrysotile. The mean levels of chrysotile and tremolite in mesothelioma cases were higher than their respective mean levels in nine chrysotile miners without mesothelioma or the mean levels in nonexposed controls. Assuming that the fibers present in lung tissue at autopsy are responsible for mesothelioma, this study would support the conclusion that tremolite is responsible for the mesotheliomas occurring in this cohort.

McDonald et al. [1989] examined lung tissue samples from 78 mesothelioma cases in Canada and from matched referents. Chrysotile fiber distributions in the two series were similar. Relative risk was related to the concentration of long amphibole fibers. The proportion of long amphibole and chrysotile fibers was higher in cases than referents. According to the authors, amphibole asbestos fibers could explain most mesothelioma cases in Canada, and other inorganic fibers, including chrysotile, very few. McDonald et al. [1989] concluded that fibrous tremolite probably explained most cases in the Quebec mining region.

In a more recent study, Roggli et al. [1993] analyzed the mineral fiber content of the lungs in 94 patients with malignant mesothelioma from the United States. A large proportion of the cases were either insulators or shipyard workers. Only fibers that were greater than or equal to $5 \mu\text{m}$

in length were included in the analysis. Amosite was identified in 76 cases (31%), the noncommercial amphiboles (primarily tremolite) were identified in 32 cases (55%), chrysotile was detected in 20 cases (21%), and crocidolite in 15 cases (16%). Another five cases (5%) could not be distinguished between amosite and crocidolite. According to the authors, tremolite fibers are probably a marker for the much greater numbers of chrysotile fibers which were deposited but subsequently cleared.

The authors found that, assuming it is the fibers that accumulate within the lung that are responsible for the development of mesothelioma, the order of importance of fibers is amosite > tremolite > chrysotile = crocidolite. However, they were unable to exclude a greater role for the long chrysotile fibers found in their cases, especially since they probably constitute only a small fraction of the long fibers actually deposited. One issue raised was that the methods used might have underestimated the numbers of chrysotile fibers 5 μ m or greater in length, because chrysotile tends to undergo longitudinal splitting with many of the resulting fibers having diameters less than 0.1 μ m. The techniques used in Roggli et al. primarily detected fibers that are 0.2 μ m or greater in diameter.

A study of asbestos fiber content of lungs with mesothelioma in Osaka, Japan was conducted by Morinaga et al. [1989]. Chrysotile was observed in 12 of the 23 mesothelioma cases, amosite in 13, crocidolite in three, and actinolite-tremolite in three cases examined. Six of the mesothelioma cases had only chrysotile fibers. This study provides evidence that, if indeed it is the fibers present in the lung at death that are responsible for mesothelioma, then chrysotile asbestos is a potent cause of this cancer.

Rogers et al. [1991] examined lung tissues from 221 definite and probable cases of malignant mesothelioma reported to the Australian Mesothelioma Surveillance Program, and from an age-sex frequency-matched control series of 359 postmortem cases. A progressive increase in relative risk with increasing fiber content was observed for all fiber content measures. The relative risks for chrysotile, crocidolite, and total amphibole fibers which were 10 μ m or longer were greater than the corresponding risks for fibers less than 10 μ m in length. When cases and controls were compared in relation to exposure to single-fiber types only (all lengths), increased relative risks were observed for both chrysotile and crocidolite.

Pulmonary fiber content was analyzed by Sakai et al. [1994] in 16 patients with malignant mesothelioma and in 16 case-matched controls. Amphibole, chrysotile, and nonasbestos fiber contents were significantly higher in patients than in the control subjects.

Summary of Lung Content Studies

The "amphibole hypothesis" is based on (1) the assumption that the fibers present in the lungs at death caused

the mesothelioma, and (2) the finding that workers exposed to asbestos have more amphiboles in their lungs than chrysotile at autopsy. Chrysotile fibers break down and split apart longitudinally in tissue and can be cleared from the lungs, while amphibole fibers are less attacked by body fluids and can be detected in the lungs of workers years after exposure [Nicholson and Landrigan, 1994]. In fact, complete fragmentation of a single chrysotile fiber may produce 1,000 fibrils [Wagner et al., 1973], and these fibrils may be so thin that they are no longer visible by electron microscopy in lung tissue.

Results of the lung content studies described above are inconsistent, and do not resolve the question of the importance of fiber type in mesothelioma causation. Some studies report significant amounts of chrysotile fibers in lung tissue. Furthermore, the results of Morinaga et al. [1989] demonstrate that mesothelioma can occur in the absence of amphibole fibers, since six cases had only chrysotile fibers in their lung tissues.

The limitations of using lung content studies in determining the role of chrysotile in mesothelioma causation are as follows: (1) The methods used often exclude fibers less than 5 μ m in length. (2) The potential for carcinogenic effects induced by large numbers of short fibers has not been investigated. (3) The methods may have underestimated the number of long thin chrysotile fibers actually present in the lungs due to an inability to detect very thin fibers. (4) The number of chrysotile fibers counted constitute only a minute proportion of the long fibers actually deposited and subsequently cleared. (5) Finding a significant number of tremolite fibers would indicate a major exposure to chrysotile, since tremolite is only a minor contaminant of chrysotile.

Dement [1991] makes the obvious point that measurements of lung fiber burdens made many years after first exposure may bear no relationship to the carcinogenic events that took place long before clinical manifestation of disease (lung cancer or mesothelioma). In addition, the fiber levels of tremolite measured in lung tissues of workers exposed to chrysotile may be a surrogate measure of cumulative dose of chrysotile. Case [1991], on the other hand, states: "*It is presumably necessary for fibers to be present in order for them to exert a carcinogenic effect!*" This point is often missed by those who regard tremolite—the more potent carcinogen—simply as a 'marker' for chrysotile."

However, we cannot presume that the fibers present in the lungs at death are responsible for mesothelioma. In view of the long latency between asbestos exposure and mesothelioma diagnosis (average of about 32 years in all studies), it is more likely that the effective target organ dose involves fibers in contact with the pleura many years before diagnosis. Data concerning fibers present in the pleural space are considered below.

Pleural Content Studies

A number of studies have addressed pleural fiber content, which is likely to be more biologically relevant to the development of asbestos-related pleural mesothelioma than lung tissue content.

One study comparing the retention of asbestos fibers in parenchymal and pleural tissues found that lung parenchymal retention is not a good indicator of pleural retention [Sébastien et al., 1980]. Although amphibole-type fibers longer than 8 μm were present in lung parenchyma, in parietal pleural tissues short chrysotile fibers greatly outnumbered long fibers of the amphibole type. The retention of asbestos dusts in the parietal pleura was related to type and size: 84% of the chrysotile fibers in the parietal pleura were from 0.4 to 4 μm in length and from 0.03 to 0.25 μm in diameter. If the fiber content of the pleura is responsible for pleural mesothelioma, then this study suggests that chrysotile fibers would be more important than amphiboles in causation of this cancer.

Tissue samples from 13 North American insulators were examined in order to investigate translocation of asbestos fibers [Kohyama and Suzuki, 1991]. These cases included three of asbestosis, three lung cancers, two malignant pleural mesotheliomas, and five malignant peritoneal mesotheliomas. The authors concluded that (1) translocation of inhaled asbestos fibers from the lung to other organs, such as the pleura and the peritoneum, seemed to occur frequently among asbestos insulation workers, although the route of the translocation has not been completely investigated; (2) chrysotile seemed to be more actively cleared from the lung and translocated into extra pulmonary tissues, compared with amosite; (3) chrysotile fibers cleared from the lung were not later eliminated from the host. The authors suggested that biological effects of the translocated asbestos fibers may be significant, and translocated chrysotile fibers may play an important role in the induction of either malignant mesothelioma and/or hyaline plaques. Asbestos fibers detected in both mesothelial tissue and hyaline plaques were mainly chrysotile.

Data from a study of lungs and pleurae of shipyard workers were reported by Bignon et al. [1978]. Larger fibers, often amphibole, were found in the lung tissue. In the pleura, the fibers were generally chrysotile, but shorter and thinner.

Le Bouffant [1980] observed a preferential migration of chrysotile fibers to the pleura, with a significant increase and accumulation in the pleura in comparison with the lung parenchyma. The median percentage of chrysotile fibers was 3% in the lung and 33% in the pleura. Similar results have been demonstrated in rats [Viallat et al., 1986]. Following intratracheal injection of rats with small amounts of UICC chrysotile, the shortest fibrils (mean lengths 0.44–1.32 μm , diameter 0.03 μm) reached the pleura very rapidly

and could be retrieved from the pleural fluid of rats within 1 month.

In summary, pleural content studies demonstrate that chrysotile fibers preferentially reach the pleura and are the predominant fiber found at this target site in asbestos-exposed humans. These findings are clearly more pertinent than lung content findings, and support chrysotile asbestos being a potent cause of pleural mesothelioma.

CONTRIBUTION OF CHRYSOTILE ASBESTOS TO PLEURAL MESOTHELIOMA INCIDENCE

In considering the contribution of chrysotile to pleural mesothelioma incidence, three factors will be addressed: (1) the relative potency of the three commercial asbestos fiber types; (2) the proportion of pleural mesotheliomas due to asbestos exposure; and (3) the extent of chrysotile production and use.

Potency of Chrysotile

To summarize the evidence presented concerning the potency of chrysotile asbestos in causing pleural mesothelioma, the following points can be made: (1) Studies of asbestos-exposed workers provide evidence that the chrysotile and crocidolite forms of asbestos are major causes of pleural mesothelioma in humans. Crocidolite asbestos may be 2–4 times more potent than chrysotile and amosite. (2) In rodents, chrysotile, amosite, and crocidolite asbestos have similar potencies, both in inhalation studies and in pleural injection studies. (3) Reexamination of the data on which the Stanton Hypothesis is based demonstrates that the data do not support the hypothesis that long thin amphibole asbestos fibers are the most potent in causing mesotheliomas. (4) Studies of lung tissue on which the "Amphibole Hypothesis" is based are inconsistent. In any case, findings in lung tissue at the time of diagnosis have no relevance to causal events which take place decades earlier. (5) Pleural content studies demonstrate that chrysotile fibers preferentially reach the pleural space, which is important since the pleura is the target site.

Based on these points it can be concluded that chrysotile asbestos is a potent cause of pleural mesothelioma. In light of the evidence regarding their relative potencies, it is reasonable to make the same regulatory policies for each of the three primary asbestos fiber types.

Proportion of Mesotheliomas Due to Asbestos

There has been wide variation in estimates of the proportions of mesotheliomas attributable to asbestos exposure. For example, Peterson et al. [1984] reviewed the literature

and noted that the proportions linked to asbestos exposure ranged from 13% in two studies [Ratzer et al., 1967; Brenner et al., 1982] to 100% in one study at the other extreme [Cochrane and Webster, 1978]. They concluded that there were large numbers of apparently nonasbestos-related malignant mesotheliomas.

Closer examination of the evidence does not support this conclusion. The studies which find a low proportion of cases linked to asbestos exposure tend to use poor exposure ascertainment methods, such as reviewing medical records [Ratzer et al., 1967; Brenner et al., 1982]. Assessment of the proportion of cases due to asbestos requires careful exposure ascertainment methods. This point was made very clearly by Cochrane and Webster [1978], who noted that "a history of exposure to asbestos can be established in a significant number of cases if histories are taken from the patient and recorded by a medical specialist with experience in the field of occupational medicine." In their own study, histories were taken from patients by one or other of the authors, usually by both. Where confirmation of exposure to asbestos was necessary, it was obtained from executive and government sources. All interviews were repeated at least once. These authors reported asbestos exposure in all but one of the 70 cases, and the one exception was a carpenter who claimed he had "worked with asbestos sheeting only very occasionally, and although he had always kept asbestos filling for screw holes on his workbench, he did not feel that this, or any other exposure, had been meaningful" [Cochrane and Webster, 1978].

Another early study with carefully obtained work histories found that 85% of 246 cases could be linked to asbestos exposure [Greenberg and Davies, 1974]. Living subjects were interviewed where possible. Occupational histories were also sought from coroners and from former employers and workmates. The final classification was made by two medical advisors in consultation. If one focuses attention solely on those epidemiological studies which have obtained careful work histories, then it is clear that the large majority of mesotheliomas in adult males are attributable to asbestos exposure. Since additional cases may occur from unknown occupational exposures, it is likely that at least 80% of pleural mesothelioma cases in adult males are attributable to asbestos exposure. That a large proportion is due to asbestos is also consistent with the evidence that the rate of mesothelioma prior to the 1930s was extremely low in the United States and in Europe [Mark and Yokio, 1991].

Production and Use of Asbestos in the U.S.

Chrysotile represents approximately 95% of the total world production of all forms of asbestos, with Canada its largest producer [Mancuso, 1988]. Amosite and crocidolite

accounted for only 5% of the asbestos usage in the U.S. over the years (Table VI) (Minerals Yearbook, 1936-1950). For example, the percent amphibole usage ranged from $\leq 1\%$ in 1935 to a peak of $\leq 5.9\%$ ($\leq 26,121$ tons amphiboles/445,902 tons total asbestos consumed) in 1943, then decreased to less than 2% by 1950. During this period the U.S. depended mainly on Canada for its supply of nonspinning (short chrysotile) fiber and upon South Africa, Canada, and Russia for nearly all of its spinning (long chrysotile and amphibole) asbestos. The U.S. produced only small amounts of both chrysotile and amphiboles.

Chrysotile had a wide variety of uses in the U.S. during the 1935-1945 period. The higher grade, long fibers were used in woven brake linings, textiles, and sheet packing. Lower grade, short fibers were used in asbestos shingles, paper, molded brake linings, fireproofing, floor tiles, etc. Rhodesian chrysotile was used for electric insulation, gaskets, and flameproof navy cable construction. Chrysotile was also used extensively in heat insulation [Minerals Yearbook, 1936-1950].

During the war years, amphiboles had specialized uses in the U.S. Amosite was used for insulation around steam machinery on warships, special pipe coverings, and block insulation. Crocidolite was used for asbestos-cement pressure pipes, chemical filters, acid-resistant packings, and gas masks [Minerals Yearbook, 1936-1950].

CONCLUSION CONCERNING THE CONTRIBUTION OF CHRYSOTILE ASBESTOS TO MESOTHELIOMA INCIDENCE

The three points made above can be summarized as follows: (1) chrysotile asbestos is a potent cause of pleural mesothelioma; (2) the large majority of mesothelioma is attributable to asbestos exposure; and (3) chrysotile asbestos has been the major fiber type used. Based on this evidence, we conclude that chrysotile asbestos is by far the main contributor to pleural mesothelioma causation in the U.S. and other countries in which it has been the predominant fiber type. Crocidolite may be 2-4 times more potent, but there is no valid evidence that amosite is more potent than chrysotile. Even considering an extreme that crocidolite and amosite were 10 times more potent than chrysotile, the extent of use of chrysotile means that it would still be the main contributor to pleural mesothelioma causation.

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TABLE VI. Estimated Quantities of Asbestos (Short Tons) Imported or Consumed in the United States*

Year	Canadian chrysotile imported ^a	U.S. chrysotile produced	African amphiboles imported ^a	U.S. amphiboles produced	Total consumed in U.S. ^a	Percent that is chrysotile
1935	154.200	NA ^b	945	NA	174.655	99.5
1936	226.080	10,520	2,080	404	250.922	99.0
1937	276.002	13,284	4,247	612	316.260	98.5
1939	223.840	14,686	6,359	450	255.347	97.3
1940	225.653	17,481	8,752	1,693	262.199	95.0
1941	389.391	20,144	21,447	2,252	438,741	94.6
1942	386.647	13,109	20,424	2,208	434,121	94.8
1943	385.655	3,900	24,007	2,114	445,902	94.1
1944	353,228	6,296	19,162	317	407,148	95.2
1945	355,768	13,340	13,247	250	377,875	96.4
1946	442,073	4,438	6,324	437	459,752	98.5
1949	470,783	NA	22,720	NA	535,132	95.8
1950	678,358	NA	14,805	NA	728,785	98.0

*Data for years 1935-1950 obtained from the Minerals Year Book (1936-1950).

^aIncludes crude and milled fibers, as well as "stucco and refuse."^bMay include some small amount of African Chrysotile.^cIncludes all imported as well as domestic-produced amphiboles and chrysotile consumed in that year.^dNA, data not available.

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