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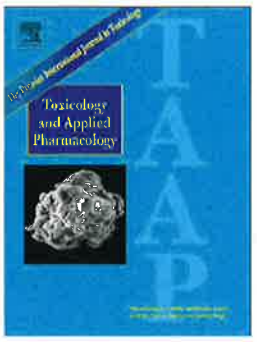

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The Role of Fiber Type and Cumulative Exposure in Controlling Mesothelioma Risk

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Abstract.

The acceptance of primary tumors arising on the serosal surface of body cavities and its association with asbestos exposure was established in 1960. Epidemiological studies followed in an effort to determine if all asbestos fiber types produced the same malignancy and with the same mortality incidence. Three asbestos mortality studies were published in 1979 authored by the same research team from the Mount Sinai School of Medicine. The studies followed the same design making their datasets internally consistent and uniquely comparable. Insulation workers who were exposed to three commercial fiber types (amosite, chrysotile, crocidolite), factory workers who manufactured amosite-containing insulation for U.S. warships, and chrysotile miners and millers from Thetford Mines, Quebec, comprised the three cohorts.

Lifetime cumulative exposures for these three cohorts (expressed in fiber/mL-years) were available from different source materials. Mortality data were obtained on these workforces and ascertainment of their cause(s) of death was based on medical-pathology evidence rather than information available on death certificates. Depending on the exposure estimates for the three cohorts the calculated mesothelioma risk for mid range mixed fiber exposure (insulators) is about 269 times (range 157 to 490) that of chrysotile exposure alone and for amosite at mid range exposure about 139 times (range 30 to 213) that of chrysotile exposure alone. Risk comparisons are the result of range in cumulative exposure estimates. Based on the available data from three Mt. Sinai studies, these differences in mesothelioma risk regarding fiber type were apparently knowable to

the asbestos community as early as 1979. The amphibole asbestos exposures carry far greater mesothelioma risk than chrysotile exposure alone. Mixed fiber exposure (chrysotile and amphibole asbestos) is associated with the highest mesothelioma mortality among the workforces studied.

Key Words

chrysotile, cumulative exposure, amosite, mesothelioma, crocidolite, mesothelioma risk, tremolite asbestos, risk ratio, exposure estimates, assignable risk

Background. Primary Tumors on the Serosal Membrane Surface. Pre-1960.

Prior to 1960 there was no consensus among pathologists that primary tumors of the serosal membrane actually existed, e.g., Rudolph Willis (1953). Further, the few "primary" tumors that were reported were not linked with a specific agent of causation or specific trade. The first details of a case involving "an asbestos-exposed worker" with mesothelioma were taken from the Case Records of Massachusetts General Hospital (Castleman et al., 1947). The case involved a 37-year old Swedish worker who entered the hospital complaining of chest pain, cough, and shortness of breath. There was evidence of a large tumor mass outside the lung that displaced the esophagus. The tumor diameter was larger than the tumor mass found in the upper lung field supporting the impression that the origin of the tumor was outside the lung. During the treatment of the patient the site of the tumor's origin remained unknown.

Diagnosis of the malignancy was made after the patient expired and an autopsy performed. Tumor was found on both the pleural and pericardial surfaces with thicknesses ranging from 3 – 8 cm. No evidence of cancer was found in the lung or bronchi. No evidence of a primary malignancy was found in any vital organ elsewhere in the body. The evidence concluded that the cause of death was primary mesothelioma. The patient had given in his occupational history that he had cut asbestos-containing "insulation boards" in his work as an insulator. Acceptance and causation of this tumor remained to be established, even though case reports of death from mesothelioma appeared in the literature from time to time.

Asbestos and Mesothelioma. An Association.

Dr. Christopher Wagner was a resident pathologist in Kimberley Hospital, Republic of South Africa (RSA), in the late 1950s. The institution lay between the Rand gold field to its east and the asbestos producing areas along the Asbestos Hills of the Cape Province to its west. Sick miners and millers from both regions found their way to the Kimberley facility complaining of shortness of breath and chest pain. Clinical workup found they suffered with pleural effusion. The Rand gold miners were quartz exposed (crystalline silica) and suffered a high incidence of silicosis and tuberculosis. Treated with newly available antibiotics, the Rand miners eventually improved in health, their pleural effusions resolved, and they returned to the mines. The miners from the Cape were similarly treated but their condition continued to deteriorate. They expired and at autopsy, performed by Dr. Wagner, large tumor masses were found in the chest surrounding and crushing the lungs. They appeared to have succumbed with a rare malignancy that Wagner called mesothelioma.

As a result of these observations, a cluster of thirty-three malignant mesotheliomas were reported among the workforce and inhabitants in and around the asbestos mines and mills of Kuruman, Cape Province, South Africa (Wagner et al., 1960). This report specifically implicated crocidolite asbestos (asbestiform riebeckite) as the causative agent of these tumors. Elsewhere, the community of asbestos investigators began to question if all exploited asbestos fiber types might play a similar role in the etiology of this tumor.

The Wagner report was provocative on every level. Eleven (11) of the cases were in females with asbestos contact established in ten (10). Personal histories and asbestos bodies and fibers found in many of these tissues at autopsy strengthened the link between

the tumor and mineral fiber. Twenty-eight (28) of the cases were placed in the Cape Asbestos field while four (4) had handled and used asbestos products. A father-daughter relation both succumbed with pleural mesothelioma. Perhaps the most unsettling observation by Wagner and colleagues was that the malignancy occurred in some individuals who showed no signs of asbestosis and who had no direct occupational contact with the Cape fiber. They "were born in and lived in the area" that produced and processed crocidolite fiber, they occasionally "hand-cobbed" crocidolite ore for supplemental income, or transported sacks of crocidolite by cart to a rail head. Occupational direct and heavy exposure to crocidolite fiber was missing from these cases.

By 1961 sixty-seven (67) mesothelioma cases were accumulated in the regions in and distant from Kuruman, but among persons who lived along the extent of the Asbestos Hills. Although some reports of the same rare malignancy were made following exposure to other agents and mineral commodities in the decade before (e.g., Bonser et al., 1955), the recognition of the asbestos-mesothelioma association belongs to Wagner and colleagues.

The Search for Mesothelioma. Other Fiber Types.

. An explosion of investigations followed Wagner's report. Surveillance by the South African Ministry of Mines and its Pneumoconiosis Research Unit in Johannesburg reported that miners and millers of amosite asbestos (asbestiform grunerite) and chrysotile asbestos elsewhere in South Africa failed to find any case reports of mesothelioma among its workforces (Webster, 1965). Studies in other parts of the world were also initiated and included miners and millers of anthophyllite asbestos in Finland

(Kiviluoto, 1965) and chrysotile asbestos in Italy (Vigliani et al, 1965). The preliminary data released by investigators at that time found that asbestosis and some excess cases of lung cancer were found, but not mesothelioma. Apparently only crocidolite asbestos was associated with mesothelioma risk (Wagner, 1965; 1991). Methods and protocols for the identification of mesothelioma, and the ability to distinguish the tumor from secondary metastatic cancers, were studied in detail at this time (see Section IX, pages 603 – 684, in Selikoff and Churg, 1965). At this same time mesothelioma began to be reported among trades using and manipulating asbestos-containing products in the workplace (Selikoff et al., 1964). The fiber type in these instances was largely unappreciated or unreported although Dr. Selikoff insisted that his insulator cohort was exposed only to chrysotile prior to 1930 (Selikoff et al., 1965, 1970). His earliest mesothelioma cases were attributed to this fiber alone.

The series of papers from Mt. Sinai Hospital at that time reported exceptional mortality from mesothelioma among insulators in union locals number 12 and 32 (New York City and Newark, New Jersey), and among the international union members in the United States and Canada. The data were overwhelming as no other cohort at that time rivaled the observed proportional mesothelioma mortality except for crocidolite-exposed workers. Dr. Selikoff remained firm in his condemnation of chrysotile asbestos.

During this year, 1964, the issue of minerals associated with chrysotile ore as agents of pleural disease was discussed at an Asbestosis Conference, held in Caan France (April, 1964). The chrysotile region of specific interest was Thetford Mines, Quebec, and the issue was discussed by Dr. Paul Cartier then Director General of the Thetford Industrial Clinic. He presented data showing that miners and millers with asbestosis

(scarring of the lung parenchyma) did not manifest with pleural plaques, while those workers with pleural plaques did not show asbestosis. He surmised that asbestosis and the pleural effects, which included three cases of pleural mesothelioma, were produced by different minerals present in the dust cloud. No further information or explanation was offered at that time. [Read the discussion following Cartier's presentation in the Conference Proceedings]. Mesothelioma was of special interest to these investigators because of the observation that the tumor occurred in some individuals who showed no clinical signs of scarring of the lung parenchyma (by chest x-ray) or histological evidence of asbestosis at the time of their death (Wagner et al., 1960; Webster, 1965). These observations were interpreted to indicate that the required exposure to produce the malignancy was significantly less than was required to produce the asbestos-associated pneumoconiosis (asbestosis). This position has held to the present time for pleural mesothelioma. Greater cumulative exposure is thought to be necessary for the appearance of the tumor in the peritoneal cavity (e.g., Ribak and Ribak, 2008). The initial standards written to protect workers were based on prevention of pneumoconiosis, not cancer.

The issue of fiber type and mesothelioma risk was raised here in the United States in the fall of 1964 (Selikoff and Churg, 1965). Convened in New York City in October of 1964, the international community of asbestos investigators was encouraged by Dr. John Gilson, Director of the Pneumoconiosis Research Unit in Wales, to include in their studies urgently needed information concerning fiber type (Gilson, 1965). Three working groups, one of the three, the Geographical Pathology group, were convened following the meeting under the aegis of the Union Internationale Contra Cancer (UICC). Although much was known about asbestosis, much was unknown concerning the other asbestos

diseases. Mesothelioma was accepted as a separate reportable asbestos disease but its incidence among workers exposed to different fiber types remained unknown. Its' importance increased as the malignancy was considered pathognomonic for asbestos exposure.

Malignant Tumor Diagnosis Improves. Mesothelioma Incidence Increases.

Dr. Selikoff published updated information on the New York and New Jersey union locals in 1976 (Selikoff et al., 1976). There were now 31 deaths from mesothelioma accounting for ~ 13.9 % of the mortality in the cohort. Peritoneal mesothelioma increased dramatically as the SMR for gastrointestinal cancer decreased suggesting previous malignancy misclassification. The question was raised as to whether the dramatic increase in mesothelioma mortality was attributed to better diagnostic tools or to the introduction of amphibole in insulation products (1930), or both? According to Dr. Selikoff it was more than 40-years into onset of exposure to amphibole asbestos.

The early reports concerning the status of fiber type and mesothelioma found its way into the Federal hearings which framed the national asbestos standard. All fiber types produced mesothelioma and their biological potencies were claimed to be about the same per fiber exposure. The Federal Asbestos Standard, published in 1972, immortalized this position. The document was the product of agreement and convenience.

Amphibole Asbestos. Appearance in U.S. Commerce.

. Varieties of amphibole asbestos found its way into many products in the United States before the time proposed by Selikoff (Bowles, 1937, Table 7A). Crocidolite apparently found its way into U.S. commerce before 1900. In the trade journal Steam, the

best locomotive boiler insulation was advertized as "African Blue" (circa 1898). Anecdotal exposures and sources are reported in Langer and Nolan (1998, p. 178-179).

In 1979, insulation products in the United States consisted of both low and high-temperature fibrous components, spanning the spectrum between cellulose and ceramic fiber. Chrysotile, amosite and crocidolite were considered the most common asbestos varieties consumed by the insulation manufacturing industry at that time. Tremolite asbestos and anthophyllite asbestos were consumed in the stream of commerce but in very much lower quantities in the modern era.

Mt. Sinai Mortality Studies: 1964 – 1979.

There are three Mt. Sinai studies, all presented at the same meeting in 1978 and subsequently published in 1979, that may be used to compare cumulative exposure, fiber type and mesothelioma risk (Table 1). They are virtually identical in study design and were carried out by the same group of Sinai investigators. Any study flaws or biases would have been internally consistent and similarly affect all three studies. Dr. Irving Selikoff of Mt. Sinai Hospital provided the clinical data; Drs. E.Cuyler Hammond and William Nicholson, and Mr. Herbert. Seidman of the American Cancer Society provided both study design and data analysis. Drs. Jacob Churg, Yasunosuki Suzuki and Milton Kannerstein, all pathologists, ascertained cause of death in each case. In this regard, causes of death were reviewed and found that information given on many Death Certificates frequently required "correction." Cause of death on most death certificates in many regions of the United States at that time, more often that not, was incorrect,

especially in the case of mesothelioma. For example, death certificates obtained for insulators indicated that mesothelioma had caused 49 deaths among 2,271 deaths in the cohort (2.21%). Review of materials available in the cases indicated that 175 mesotheliomas (7.71%) had actually occurred, a more than 3-fold corrected increase (Selikoff et al., 1979). This correction was also underscored in the evaluation of the amosite cohort in the insulation producing factory located in Paterson, New Jersey, where only one mesothelioma was recorded on 528 death certificates but 13 additional cases were ascertained on tissue and medical document review. The cause of death was difficult to distinguish at that time from a number of more common metastatic tumors, e.g., adenocarcinoma in the chest and pancreatic cancer in the peritoneal cavity in men. The cause of death frequently could not be determined without an autopsy. Examination of tissues from autopsies and surgical procedures and review of clinical records, determined the "best evidence" concerning cause of death. Consider the range of immunochemical, histochemical and cytochemical stains used today in modern facilities that help distinguish among tumor types (e.g. adenocarcinoma and pleural mesothelioma, see Table 5-2 in Pavlisko and Sporn, 2014). Determination of fiber exposure based on tissue burden studies assisted as well (Langer,1974).

Parenthetically, the use of "best evidence" for mortality comparison has been criticized, e.g.,,by Doll and Peto (1985). The data produced by Dr. Suzuki and colleagues only increased the number of asbestos-related deaths without reporting any downward correction (elimination of false positives). This internal study design flaw is consistent for all Sinai studies in which mortality comparisons are made. For full disclosure, further critique of the comparability of the cohort data, it is well known that standardized

mortality ratios (SMRs) for specific diseases within different regions of the United States vary considerably (MacMahon and Pugh, 1970). The Sinai cohorts differ in age distribution as well (the Paterson workforce is much older that the other two workforces), in geographic locale (New York-New Jersey v. Quebec Canada), in socioeconomic condition. We assumed the cohorts were similar in several regards: they were exposed to some variety of asbestos fiber in their work environment, the mesotheliomas were caused by asbestos, and their mortality was determined for only those men who had achieved a lapsed period of twenty years or more from onset of exposure. The follow up of cohort members was virtually 100 % as no one was lost to observation. We can make no further claims as to other population characteristics. Exposure was verified by tissue analysis (Langer, 1970; 1974; Langer and Nolan, 1989a, 1989b, 1998).

Cohort Comparisons, Gross Mesothelioma Mortality, and Exposure to Asbestos Dust.

The differences in size of cohorts, the number of deaths in each, and number of deaths attributed specifically to mesothelioma, are stark (Table 1). The mesothelioma mortality adjusted for population size is given in the discussion and in Table 4.

(1) Insulation Workers: Exposure to Mixed Fiber Types (1979).

The first mortality report considered here is the mortality experience of unionized insulators who were members of the International Association of Heat and Frost Insulators and Asbestos Workers (IAHFIAW – AFL), of the United States and Canada. Their mortality status was reported in 1979 (Selikoff et al., 1979). Among 2,271 deaths that occurred in the union, mesothelioma accounted for 175 deaths, or ~ 7.71% of the total mortality (Table 1). (Tissue assays carried out by Langer and Nolan (1989a; 1998)

and Kohyama and Suzuki (1991) confirmed unpublished observations made more than a decade before that amosite, crocidolite and chrysotile, generally in combination, was present in the lung and pleural tissues of these workers. Langer and Nolan (1998) reported that amosite was observed in the lung tissues of all insulation workers they studied, while chrysotile was observed in only half their cases. Crocidolite fiber was present in a percentage of these cases at low concentrations. Crocidolite was found in greatest concentration and frequency in trades that worked in shipyards and shipboard. Noted among the shipboard trades were insulators.

Nicholson (1976) estimated exposure to members of this cohort ranged between 10 and 20 f/mL of air based on historical product formulation data and different workplace environments. Fiber content was normalized to modern product formulations and measured fiber release data for these modern products were used in the generation of reconstructed exposures. In his report, the value of 15 f/mL of air was used as a time-weighted average for insulation work prior to the establishment of Federal Standard in 1972. The exposure value is considered to have been maintained over a 25-year occupational history, the time period determined by the individual's active and continuous payment of union dues. The average cumulative exposure experienced by the workforce is estimated to have ranged between 250 and 500 f/mL-years. Mid-range exposure is estimated to have been about 375 f/mL-years (Table 3).

During the decade before 1979, five studies on the West Coast of the United States, e.g., Balzer and Cooper (1968), and on the East Coast of the United States. e.g., Ferris et al. (1971), measured far lower exposures for the insulators. Their average was 5.9 f/mL of air (range 1.7 – 8.9) with an SD of ~ 1.5 f/mL of air. These values are viewed

as "modern" and may have little bearing on the risk outcomes observed following long clinical latencies that involved pre-OSHA exposure standards in the past.

(2) Insulation Manufacturing: Exposure to Amosite Asbestos (1979).

The second Mt. Sinai mortality study considered here is that of factory workers who made pipe, boiler, and turbine insulation for U.S. naval warships during WW II (Seidman et al., 1979, Table 2). The cohort consists of men who were employed in the facility for some period between June 1941 and December 1945, the war years (WW II). The factory was operated by the Union Asbestos and Rubber Company (UNARCO). By 1978 there were 528 deaths in the cohort of 820 men. All had been exposed to amosite dust while working in this plant, the fiber identified and characterized by chemistry and mineralogical techniques (Langer, 1970). In addition to the amosite, the insulation formulation included large amounts of diatomaceous earth cemented with water glass (liquid sodium silicate).

The factory group experienced 14 mesothelioma deaths (~ 2.7 %) by 1978, (Tables 1, 2). The Seidman study found that 215 men, who worked less than five months in the facility, none had died of mesothelioma. Of 156 men who worked some portion of time between 6-months and one-year, seven (7) died of mesothelioma. Men who worked some time between 2 and 4.5 years (157) there were an additional seven (7) mesothelioma deaths. Seidman described the cohort as one of "short-term exposure." Cumulative exposure was indexed as the product of length of employment and average plant exposure (23 f/mL of air) during the employment period (Tables 2, 3).

There are no known direct environmental measurements that were made during this period although if dust measurements had been made the standard under which the

plant operated would have been the United States Public Health Service standard proposed by Dreessen et al., in 1938, i.e., five million particles per cubic foot of air (conversion of values to fiber/mL yields an estimate with a range of ~15 - 30 f/mL of air.

The facility ceased operation in December 1954 and the machinery dismantled and shipped to Texas where it was eventually re-assembled in Tyler (Ribak and Ribak, 2008). Exposure during amosite insulation production in Texas was reported by Levin et al. (1998). The highest dust levels were measured in the fiber opening area of the plant.

A value of 23 f/mL of air is the estimated average given by Seidman and colleagues (1979). The first mesothelioma observed in the cohort occurred in workers employed for 6 - 11 months. We have used the lowest employment period in our calculation of range of exposure (0.5 years x 23 f/mL of air). The work force of 126 men who worked for 1-year at the plant experienced an exposure of 1-year x 23 f/mL (Table 3). The next group of workers in the facility, N = 157, were employed between 2 and 4.5 years at the facility (Table 2) The risk calculation employs the greatest value (4.5-years x 23 f/mL of air, = 103.5 f/mL). The fourteen mesotheliomas occurred in men exposed in the extreme range of 12.5 f/mL and 103.5 mL of air. The mid-range value is ~ 75 f/mL of air. The risk calculation is therefore based on mesothelioma mortality of short-term employees (mid-point at 3.25 years (Table 3).

(3) Mining and Milling. Exposure to Chrysotile Asbestos (1979).

The third Sinai cohort included in this study was that of Nicholson et al. (1979) carried out on the miners and millers of chrysotile in Thetford Mines, Quebec. The study was of 544 senior members of the local union (25 or more years employment) who had worked for four asbestos producers in and around the town involving work in multiple

mines (at least 4) and five or six local mills that processed the ore. Based on "best evidence" one (1) mesothelioma was found in 178 deaths in the cohort (~ 0.6 %). Tables 1, 3.

Environmental measurements during the 1970s were made employing the membrane filter technique and an average of 18 f/mL of air was calculated for 5 mills assayed. In an unpublished earlier report by Nicholson he commented that environmental values for a sixth mill drove the average mill air up to 28 f/mL of air. The average employment for the members of the cohort was estimated at 25-years. The cumulative exposure to chrysotile is estimated to have been between 450 and 700 fiber-years (18 f/mL x 25 years, 28 f/mL x 25 years) with a mid-range value of 575 f/mL-years (Table 3). These values may appear to be high to some readers but the asbestosis mortality in this cohort was ~ 14.6 %. Consider that the same disease caused the death of about 8% of the insulators (average exposure experienced by the workforce was estimated as 15 f/mL of air, cumulative exposure of 375 f/mL) and the estimated exposure to chrysotile dust appears plausible. Anecdotal reports suggest that the mines and mills had been "cleaned and environmentally improved" before the Nicholson survey was undertaken (Dr. Jacque Dunnigan, personal communication). Both low- and high-range values are used in mid-range calculation (Table 3).

Chrysotile Alone or an Amphibole Complication?

Chrysotile ore from the study area, Thetford Mines Quebec, has been reported to be contaminated with tremolite fiber. Tremolite particles (amphibole in atomic structure) have been found in the lungs of Quebec miners and millers (Pooley, 1976) and the mineral has been associated with cases of mesothelioma found in that region (e.g., Case

et al., 1997). Some investigators have opined that the etiology of mesothelioma following chrysotile exposure may actually be caused by the tremolite mineral associated with the ore. This issue is not considered here for calculation of risk. Further, the amphibole minerals associated with chrysotile ore are now recognized as a far more complex assemblage than had been reported in the past (Germine and Puffer, 2015). The issue may carry greater meaning when comparing mortality studies from the different chrysotile deposits globally. While it cannot be proven that chrysotile alone does not cause mesothelioma, the extent of its risk appears to be orders of magnitude less when compared to the common amphibole asbestos fiber types in commerce. Tremolite presence in chrysotile ore is non-homogeneously distributed and its habit may not be asbestiform (Williams-Jones et al., 2001). These factors appear to complicate the hypothesis that chrysotile ore contaminated with tremolite is a universal concern. These features were noted in the contribution of Williams-Jones et al. (2001) in their study of the chrysotile ore body in Asbestos, Quebec located some 40-miles SW of Thetford Mines. The Manville ore body was found to be essentially "tremolite free."

Discussion.

The three Mt. Sinai mortality studies discussed in this paper show great differences in population size, total deaths, and total mesothelioma deaths. On a gross level the adjusted metrics, i.e., cohort size and expected number of mesothelioma deaths underscores these differences (Table 4A). Using Study 3 as the comparative unit for population size and expected number of mesothelioma deaths, the populations of studies 1 and 2 are adjusted to the expected number of mesotheliomas. The observed number of mesothelioma deaths far exceed the expected number of cases. It is so much greater that

other factors must be considered to account for this. Fiber type and cumulative exposure are considered critical in this regard.

Hodgson and Darnton (2000) in their meta-analysis of asbestos cohorts found that a strong association existed between mesothelioma risk and exposure to different asbestos fiber-types. When viewed in context with cumulative exposure, different workforces exhibited mesothelioma mortality, or risk, that was very different as well. Fiber type was observed to be the most significant factor controlling outcome. Gibbs and Berry (2008) amplified on this association and discussed factors that appeared to explain variation in risk following exposure to one fiber type, e.g., natural dimension variation among the fiber types, dimension variation superimposed on a single fiber type resulting from the industrial process, and character of the different cohorts. For example, men in the Paterson factory cohort began employment at far older age than the insulators or chrysotile miners and millers. As a war-time cohort, with a severe shortage of manpower, older men were those available for employment. The younger more fit men were siphoned off for military service (Seidman et al., 1979).

As a reminder, reports concerning fiber type, intensity and duration of exposure, and *asbestosis* were made as early as 1930 (Merewether and Price, 1930. Amphibole asbestos in the forms of tremolite asbestos (California) and anthophyllite asbestos (North and South Carolina) were exploited and consumed in the United States as early as 1880 (Bowles, 1937). Amphibole asbestos fibers of various kinds were present in many work environments in the United States for more than a century. Early reports focused on asbestosis not malignancies.

Tissue studies have confirmed the presence of the three major fiber types used in asbestos insulation products. Tremolite and anthophyllite have also been found in lung tissues in many cases although mineral habit (asbestiform or fragment) is frequently unreported or unknown (Langer and Nolan, 1998), The time of inhalation of each fiber type during the lifetime of the individual, and the nature of the source product, are also unknowns. The reasonable conclusion is that the exposure to insulators in the U.S. was to mixed-fiber dust (at least amosite, chrysotile, and crocidolite asbestos). Parenthetically, insulation products were studied in older buildings in New York City in the early 1980s and it was confirmed that chrysotile, amosite and crocidolite, either separately or in mixed-fiber combination, were present in the products analyzed (Langer and Nolan, 1989b).

It was not until 1972 that amosite was first reported to be a human carcinogen (Selikoff et al., 1972, based on the experience of the men who worked in the Paterson facility). The Selikoff et al. (1972) report was not in agreement with the observations made in the fiber's source area, the Penge region within the eastern Transvaal Basin, RSA. A possible explanation for this suggests the processing of the amosite fiber at the Paterson plant altered its size distribution character (diameter and expressed surface area) thereby increasing its inhalation potential, and enhancing biological potential. Alteration of a mineral fiber's biological properties and disease-producing potential as a result of altered properties was advanced in, e.g., by Langer and Nolan, 1986; Gibbs and Berry, 2008.

The experience of the Quebec miners and millers following exposure to chrysotile dust has been observed in association with low mesothelioma mortality. This mortality is

frequently ascribed to the presence of an ore contaminant, the amphibole mineral tremolite. The concentration of tremolite in the chrysotile ore body is difficult to ascertain accurately (presence in the host rock or ore body, or both, concentration in the processed ore, and the form of the tremolite, whether the habit is massive or asbestiform).

Support in comparing exposures among the three cohorts and mesothelioma outcome is based on the presumed presence of a large proportion of fibers/fibrils equal to or less than 0.1 um in width in their respective dust clouds. Fibers of this dimension have been shown to penetrate cell membrane "windows" and transport into body cavities. Data concerning widths of UICC amosite and crocidolite are available in the literature (Langer et al., 1974). Analysis of photomicrographs obtained by transmission electron microscopy (TEM) showed that about 67.1 % of the crocidolite particles were less than 0.2 um in width, with 26.5 % of the particles less than 0.1 um in width. Amosite prepared and examined in the same way displayed 56.1 % and 17.7 % of the particle population in the same width groupings. Of interest is chrysotile that showed that almost 98 % of the particles displayed widths of less than 0.1 um (particle population of fibrils and thin fibers) (Langer et al., 1978). The original particle size studies selected width groups that allowed us to gauge what phase contrast light microscopy "missed" in the asbestos dust aerosols generated in the workplace. All three workforces in these cohorts were exposed to asbestos aerosols containing fibers of critical dimension. The critical width fibers escape detection by light microscopy (Lippmann, 2017) and require electron optical techniques (TEM, SEM) to count directly (Langer, 2008). This critical metric was postulated for mesothelioma causation by amphibole asbestos by Timbrell et al. (1971).

The observation that the highest mesothelioma mortality occurred following exposure to mixed fiber types is perplexing. We are not advocating at this time that amphibole-chrysotile fiber synergy may exist. Synergy with additional agents has been limited for mesothelioma causation. It was suggested several years back by Dr Michele Carbone of University of Hawaii's Cancer Center that a virus (SV 40)-crocidolite combination acted to increase risk. Lifestyle factors have also been suggested to act in this capacity. No epidemiological evidence for these actions has been found.

Conclusions.

Comparing mesothelioma mortality in three Mt. Sinai studies published in the same year, 1979, and appearing in the same published volume, showed fiber type and cumulative exposure were critically important factors in imparting mesothelioma risk (Tables 4A, 4B). Available information concerning historical exposure to these men allowed reasonable estimates to be made. The range of these estimates is large and the mid-range values were used to estimate risk and cumulative exposure. Mixed-fiber exposure to amosite, chrysotile, and crocidolite is associated with about 269-times greater mesothelioma risk than chrysotile exposure alone and amosite is associated with about 139-times greater risk than chrysotile exposure alone (Tables 3, 4A, 4B). Even so, assuming greatest exposure differences (lower for chrysotile, higher for the amphiboles) the mesothelioma risk for the fiber types retains very large and significant differences. (Table 4B). By .1979, this information was available, and therefore knowable, that exposure to different asbestos fiber types was associated with different risk of dying from malignant mesothelioma. The fiber type differential was qualitatively stated by Peto et al.

in 1982 in his paper that formulated the initial mesothelioma risk model. His co-authors included Dr. Selikoff and Mr. Seidman, and was based on their Mount Sinai data sets.

Although the data were available to the Mt. Sinai team, as well as Federal regulatory agencies here in the United States, their interpretation appeared to follow and embrace the original Federal Asbestos Standard premise published in The Federal Register in June 1972. The position at that time was that all fiber types were capable of producing mesothelioma (which may be true), but no risk distinction among fiber types was attempted. At that time some in the field argued that significant differences existed. Unfortunately, the position they articulated did not discern between low-risk chrysotile exposure and no-risk chrysotile exposure. The prevailing belief held at that time was that mesothelioma incidence in the United States was approximately proportional to fiber type consumption at that time (~95% chrysotile, ~5% amphibole asbestos).

Today, concerns have come out of Great Britain (Gilham et al., 2015) concerning widespread amosite exposure experienced by the general population. Transposing work place risk to large populations, albeit at very much lower exposures, may be important. Wagner et al.'s data suggested this was so (1960). Low-level exposure to amphibole asbestos dust and its association with elevated pleural mesothelioma incidence continues to occupy the attention of the international medical community. For the amphibole asbestos fibers of crocidolite and tremolite asbestos, the concern appears to be supported by reports in the literature.

The postulate that all fiber types were equally potent in inducing pleural mesothelioma was based on lack of specific mesothelioma data and convenience in establishing national asbestos standards. Consider this: Drs. Niles Eldredge and Steven

Gould challenged geological dogma in "Punctuated Equilibria" (1972): This paper challenged the dictum that evolutionary (biological) processes required long periods of geologic time to take place. They stated: "The expectations of theory color perception to such a degree that new notions seldom arise from facts collected under the influence of old pictures of the world. New pictures must cast their influence before facts can be seen in different perspective." They showed that evolutionary processes can and do occur abruptly. The concept shocked the established paleontology world. New pictures, for asbestos fibers and mesothelioma, were made available for us to see in 1979 by the Mt. Sinai team. Drs. Eldredge and Gould spoke to many disciplines.

Acknowledgement. The Mount Sinai Team.

It is appropriate to recognize the contributions to asbestos medicine made by the late Dr. Irving J. Selikoff and his Mt. Sinai colleagues during the period 1964 – 1979. Dr. Selikoff and his multi-disciplinary group of physicians and scientists studied the outcomes produced following asbestos exposure in many places and in many trades. This paper is based on three of their mortality studies. The integration, comparison, and interpretation of these data sets are ours alone. We assume responsibility for all errors of commission and omission.

The authors were members of the Mt. Sinai team and state they have no conflict of interest.

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Table 1. The Mount Sinai Mortality Studies – All Published in 1979*.

Study **Cohort Size**	**Fiber Type(s) Exposure**	**Total Deaths in Cohort**	**Mesothelioma Deaths (% in cohort)**
(1) Selikoff et al. (1979).			
Insulation Workers N = 17,800	Amosite Chrysotile Crocidolite	2,271	175 (7.7 %)
(2) Seidman et al. (1979)			
Insulation Factory N = 820	Amosite	528	14 (2.7 %)
(3) Nicholson et al. (1979)			
Miners and Millers N = 544	Chrysotile	178	1 (0.6 %)

The insulator study (1) comprises a cohort of ~ 17,800 men in which 2,271 deaths were recorded up to and including 1976 (Selikoff et al., 1979).There were 175 mesothelioma deaths accounting for ~ 7.7 % of the deaths that occurred.

The insulation manufacturing facility study (2) comprises a cohort of 820 men in which 528 deaths were recorded up to 1978 (Seidman et al., 1979). There were 14 mesothelioma deaths accounting for ~ 2.7 % of the deaths that occurred..

The chrysotile study at Thetford Mines, Quebec (3) comprised a cohort of 544 miners and millers of chrysotile in which 178 deaths were recorded up to 1978 (Nicholson et al., 1979). There was one mesothelioma death accounting for ~ 0.6 % of the deaths that occurred.

Ascertainment of cause of death in each cohort was based on "best evidence" rather than information provided on death certificates. All cohort members experienced more than twenty years from onset of exposure.

Table 2. Insulation Manufacturing, Paterson, New Jersey – Seidman et al. (1979): Length of Employment and Exposure Calculation

Length of Employment	N Men Deaths in Cohort	Estimated Expo in f/mL-year	Mesothelioma Distribution Pl	Pe	Total
< 1 Month	19	< 1.9 f/mL-yr	0	0	0
1 Month	49	1.9 f/mL-yr		0	0	0
2 Months	51	3.8 f/mL-yr		0	0	0
3 – 5 Months	96	8.5 f/mL-yr		0	0	0

N =215 No mesotheliomas observed in men with < 5 months employment (< 8.5 f/mL-yr exposure)..

6 –11 Months	82	12.5 – 21.1 f/mL-yr	2	1	3
1 Year	74	23.0 f/mL-yr	2	2	4
				7	

N=156 Seven (7) mesotheliomas observed in men with employment between 6 months and 1 year (exposures between 12.5 and 23 f/mL-yrs.).

2-4.5 Years	157	3	4	7

N=157 Seven (7) mesotheliomas observed in men employed between 2.0 and 4.5 years (exposures between 46.0 and 103.5 f/mL-yrs).

N=528 Fourteen (14) mesotheliomas occurred following exposures ranging between 12.5 and 103.5 f/mL-yrs..

Note: 528 deaths occurred in the Paterson cohort employed in the period June 1941 and December 1945. Length of employment x 23 f/mL = cumulative exposure estimate. Exposure estimate 23 f/mL of air given in Seidman et al., 1979; 1986.

Note 157 men were employed in Paterson between 2 and 4.5 years. Mid-range value is 3.25 years. Exposure ranged from 46 f/mL to 103.5 f/mL. The mid-range value for exposure is 74.8 f/mL-years.

Table 3. Estimated Mid-Range Exposure and Mesotheloma Risk

Fiber Type	Cum Exp (f/mL-years) Mid-Range	Meso Deaths in Cohort	Meso:Exp Ratio	Meso/Fiber Year
(1) Insulators				
Amosite Chrysotile Crocidolite	375 f/mL*	175	175/375 = 0.4667	1 M per 2.14 f-yr
(2) Insulation Manufacturing				
Amosite	58 f/mL**	14	14/58 = 0.2414	1 M per 4.14 f-yr
(3) Miners/Millers				
Chrysotile	~ 575 f/mL***	1	1/575 = 0.0022	1 M per 450 f-yr

^ 375 f/mL-years represents an exposure (15 f/mL over a period of 25 years).. Nicholson (1976) range of exposure was given as between 10 and 20 f/mL of air over an average employment history in the union. Exposures range between 250 and 500 f/mL-years. Risk for low and high cumulative exposures are calculable but a mid range value of 375 f/mL-years is used in the risk calculation..

**The exposure unit used here for Paterson factory workers is based on an estimate of 23.0 f/mL of air in the plant during operation. Mesothelioma was first observed as a cause of death among men with more than six months of employment (>12.5 f/ml-years). It was reported that half of the 14 mesotheliomas (seven) occurred as a cause of death in men with short employment history (exposure), between 6 months and one year (12.5 – 23 f/ml-year). The risk ratio calculated above utilizes the lowest and highest exposure values.

***Chrysotile's exposure mid-range is 575 f/ml. [Noted: Exposure estimates range between average mill air in Nicholson et al.'s (1979) study of 18 f x 25 years and 28 f x 25 years. The mid-point average is 23 f/mL x 25 years that produces a cumulative exposure over a working lifetime of 575 f/mL=years.]

Table 4 A. Mesothelioma Risk and Method of Comparison.- Raw Data

	Number of Deaths	Mesothelioma Deaths	Number of Deaths Adjusted to (3)*	Mesothelioma** Deaths Adjusted to (3)	
(1)	2,271	175	~ 12.76	175/12.76	~14 x O/E
(2)	528	14	~ 2.97	14/2.97	~ 5 x O/E
(3)	178	1	1.0	1.0	1.0 O/E

Total deaths and mesothelioma deaths as given in study (1) by Selikoff et al. (1979) and in Study (2) by Seidman et al, (1979). Study (3) is the Thetford study by Nicholson et al. (1979). Deaths* and mesothelioma deaths** are "adjusted" (Columns 3 & 4) to reflect equivalent population number (deaths) in study (3).

Table 4 B. **Mesothelioma Risk Based on Unit of Cumulative Exposure**

Estimation of Exposure	Range of Exposures Over Work History	Mid-Range Value of Exposure	Meso Number to Mid-Range Exposure

~ 15 f/mL	10 – 20 f/mL	375 f/mL – yrs	175 M / 375 f/mL-yrs = 0.4667 = 1 M / 2.14 Fiber Years
~ 23 f/mL	12.5 – 103.5 f/mL	58 f/mL - yrs	14 M /58 f/mL- yrs = 0.2414 = 1 M / 4.14 Fiber Years
~ 23 f/mL	18 – 28 f/mL	575 f/mL - yrs	1 M / 575 f/mL – yrs = 0.0017 = 1 M / 575 Fiber Years

Study 1 to Study 3 ~ 269 times greater risk (mid-range value)

Study 2 to Study 3 ~ 139 times greater risk (mid-range value)