

Review Article

The Carcinogenicity of Chrysotile Asbestos—A Review

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Received December 23, 2000 and accepted January 17, 2001

Abstract: The world production of asbestos has been declining dramatically in recent years, particularly in Europe and the United States. However, increases have occurred in Asian nations and chrysotile is the dominant fiber used. Important uses are in cement products, wallboards, friction products and textiles. From studies in the United States and Great Britain, chrysotile has been shown to increase the risk of lung cancer and to produce mesothelioma in exposed workers.

Key words: Lung cancer, Chrysotile, Mesothelioma, Exposure, Risk

Introduction

There have been dramatic changes in the production, use, and exposure to asbestos in recent years. Table 1 gives representative production data for the past three decades¹⁾.

The numbers in Table 1 have substantial uncertainties because of limited information on early Russian production, but they clearly indicate a rising world asbestos output until the late 1970's after which a continuing decline set in. Between 1963 and the middle 1970's amphibole minerals constituted from 5% to 7% of the above asbestos production. In 1978, when a decline in the total usage of asbestos began, the individual amphibole composition was 3.8% crocidolite, 1.3% amosite and 0.2% anthophyllite. In the subsequent years, the percentage drop in amphibole usage was considerably greater than that for chrysotile. For example, at peak production South Africa mined 269,000 tonnes of amphibole in 1978, but less than 47,000 in 1991, of which 20,000 was crocidolite. Amosite production ceased in 1992. Currently, approximately 99% of all new asbestos use involves chrysotile, with crocidolite being used only for very specialized purposes. From the late 1970's to 1996, total asbestos production declined by more than two-fold, but amphibole usage decreased by greater than a factor of ten.

Because of its dominant presence in new materials, the following discussion will be confined to consideration of trends in chrysotile use, exposure and effects. Table 2 shows

the 17 top chrysotile consuming nations in 1994²⁾. Europe has since banned asbestos from new uses. Thus, the current primary users of chrysotile are countries in Asia and Central/South America. Substantial use also continues in some Middle Eastern nations.

While there has been an overall decline in asbestos usage, it has not occurred in all countries. The decline has been dramatic in Western Europe and the United States, but a general increase has taken place in Asian nations. Some explicit regional changes with time can be seen in the annual imports and production of asbestos in selected nations, which are shown in Table 3¹⁾. The countries chosen were major using countries whose production was small in comparison

Table 1. World production of asbestos

Year	Production (tonnes)
1963	2,922,000
1973	4,614,000
1978	5,159,000
1983	4,276,000
1988	4,323,000
1993	2,650,000
1994	2,410,000
1995	2,308,300 (a)
1996	2,140,000 (a)

(a) Chrysotile only²⁾

Table 2. Principal chrysotile consuming countries, 1994

Nation	Annual usage (tonnes)
Russia	700,000
China	220,000
Japan	195,000
Brazil	190,000
Thailand	164,000
India	123,000
South Korea	85,000
Iran	65,000
France	44,000
Indonesia	43,000
Mexico	38,000
Columbia	30,000
Spain	29,000
USA	29,000
Turkey	25,000
Malaysia	21,000
South Africa	20,000
Total above	2,021,000

to imports. Among the major producers, Canada and the nations of the former U.S.S.R. have reduced their output by about 70% from their respective peaks, while China and Brazil have increased production, but by less than a factor of two from the early 1980's to now.

As there have been dramatic changes in the global distribution of asbestos output, so there have been changes in uses of the fiber. From earlier use in a wide variety of products, asbestos use is now largely concentrated in relatively few products, which vary from nation to nation. Worldwide, the dominant use of asbestos in most nations is in cement products. In developing nations, such as those in Southeast Asia, asbestos cement pipes are of importance

for expanding water supply and sewage systems. However, in Japan 93% of all asbestos is used in various fire-retardant wallboards and 3.6% in friction products³⁾. South Korea has extensive asbestos textile and friction product industries and ships the finished products to Japan, West Europe and the United States⁴⁾.

There are also differences in national responses to the health hazards of asbestos. Some Scandinavian and other Western European nations have prohibited all new uses of asbestos. In the United States the permissible exposure level is 0.1 f/ml and asbestos use has been dramatically curtailed. In contrast, Japan currently has a 2 f/ml for chrysotile but a recommendation has been made to lower the Permissible Exposure Level to 0.15 f/ml by the Japan Society for Occupational Health. The uses of amosite and crocidolite are prohibited in Japan. South Korea has a 2 f/ml standard for chrysotile but lower standards apply for amosite (0.5 f/ml) and crocidolite (0.2 f/ml). Generally, developing nations have permissible exposure levels greater than 1 f/ml.

With the use of asbestos being predominantly in cement products, a good opportunity for control of workplace and environmental exposures exists. In installation of pipes and boards exposures during sawing or other abrasive actions can be well controlled with the use of appropriate dust collectors or wetting techniques. However, these precautions may not always be taken and workplace monitoring by regulatory agencies is important. Uncontrolled sawing produces concentrations in the tens of f/ml. During normal use of such asbestos cement products there is limited release of fibers because of the strong binding of the cement. Again, however, abrasion of the cement will lead to fiber release.

One feature of current occupational exposures is that there has been a substantial decrease of the use of asbestos in thermal insulation. Such products are particularly dangerous because asbestos is readily released. Such release during

Table 3. Annual imports and production of asbestos, in tonnes in selected countries, by year

Country	1970	1975	1980	1985	1994(b)
Japan	311,274	261,841	309,305	264,619	195,000
Thailand	21,271	43,024	58,756	75,516	164,000
India	56,008	63,240		99,010	123,000
South Korea	35,292	56,960	36,787	57,143	85,000
Taiwan	6,589	13,363	31,247	24,519	
Mexico	40,460	60,981		54,871	38,000
France	151,846	138,637	127,123	68,827	44,000
United States	660,000	538,000		162,000	29,000

(b) Chrysotile only; from reference (2).

installation, repair or removal not only exposes the insulator, but also many other nearby workers in shipyards and construction sites. In the United States it has been estimated that approximately 70% of current asbestos-related cancers can be attributed to fibers released from thermal insulation materials⁵⁾.

A general feature of current asbestos use is a lesser concern for exposures to chrysotile than the amphiboles. This is a serious mistake. Available data indicate a similar lung cancer risk per fiber exposure for chrysotile, amosite and crocidolite⁶⁾. There is no question concerning the greater carcinogenicity of crocidolite for mesothelioma, but very strong data from an analysis of the time course of mesothelioma risk among U. S. insulators indicates similar, substantial risks for exposures to amosite and chrysotile⁶⁾. Let us consider some of that information.

Asbestos-Related Lung Cancer

It is widely accepted that exposure to chrysotile asbestos increases the risk of developing lung cancer in proportion to the cumulative exposure to asbestos up to a time 10 years prior to evaluation⁷⁾. The relationship can be expressed formally by:

$$I = I_0 (1 + K_L \cdot f \cdot d_{(t-10)}), \quad \text{Eq. 1}$$

where I is the lung cancer incidence or mortality in a study population at time of evaluation, t years from first exposure; I_0 is the age- and calendar year-specific lung cancer incidence or mortality expected in the same population in the absence of asbestos exposure (ideally, I_0 would explicitly consider smoking habits of each study individual); f is the intensity of asbestos fibers longer than 5 μ m per ml; d is the duration of exposure in years up to a period 10 years prior to evaluation; and K_L is a proportionality constant that is a

measure of the carcinogenic potency of the asbestos exposure. K_L represents the fractional increase in lung cancer incidence or mortality that occurs from a 1-year exposure to 1 fiber/ml.

Exposure-response relationships have been developed between asbestos exposure and lung cancer risk in several epidemiological studies. These are summarized in Table 4.

The individual studies in the above table vary substantially in their statistical quality. Some, such as those of textile production or insulation work, involve substantial exposures and large study populations. In such cases, the measures of risk are relatively good. In other, such as those of brake products manufacturing, the exposures were low and large uncertainties exist. In one of the brake studies¹⁷⁾, a high overall SMR was seen, but there was not a clear dose-response relationship according to exposure, although we are dealing with only 18 cases for four dose categories. In all studies we must use a relatively limited number of exposure estimates made from particle counts in earlier years.

Considering all studies, except those of mining and milling, the geometric mean value of K_L , the percentage increase in lung cancer for a 1-year exposure to 1 f/ml is 1.0. The value for chrysotile mining and milling is approximately ten-fold less. Comparing chrysotile mining and milling with chrysotile textile production, the difference is even greater. The complete understanding of this difference is not known at this time. Some of the difference may be the result of numerous fiber bundles being present in the mining and milling environment. These are easily counted, but some of them may not be inspired. In the textile environment, the bundles are opened, producing an environment with a greater percentage of individual carcinogenic fibers, which may not be counted, but which are readily inspired.

Table 4. Risks of lung cancer in workers exposed to asbestos minerals

Asbestos exposure circumstance	Study refs	Type of asbestos	Percentage increase in lung cancer for 1-y exposure to 1 f/ml
Textile manufacturing	8, 9, 10	98% chry	1.0–2.6
Amosite insulation mfg.	11	Amosite	4.3
Insulation application	12	Chrys/amo	0.8
Asbestos products mfg.	13, 14, 15	Mixed	0.5–6.7
Friction products mfg.	16, 17	Chrysotile	0.01–0.06
Chrysotile mining	18, 19, 20	Chrysotile	0.06–0.17
Crocidolite mining	22	Crocidolite	1.0

Malignant Mesothelioma

The risk of mesothelioma by fiber type can be analyzed in three ways. Firstly, since the lung cancer risk is very similar for all fiber types, excluding mining and milling of chrysotile, one can use the excess number of lung cancers as a measure of cumulative fiber exposure. With comparable follow-up periods, the ratio of the number of mesotheliomas to excess lung cancers is a measure of the relative fiber exposure mesothelioma risk. Secondly, one can use the unique time dependence of mesothelioma in mixed exposure circumstances to attribute risk to different fiber exposures in different periods of time. Finally, by utilizing a mathematical risk model, in an analogous fashion to what was done for lung cancer to produce Table 4, one can directly calculate a mesothelioma unit fiber exposure risk. We will utilize each of these procedures to assess the mesothelioma risk from different fiber exposures.

Estimates of relative mesothelioma risk by fiber type

The Asbestos Health Assessment Update of the U S Environmental Protection Agency⁷⁾ used the first method to estimate the relative mesothelioma potency for asbestos fibers. In studies where the mesothelioma risk cannot be estimated directly, it is found that the ratio of the number of mesotheliomas to excess lung cancers is very similar for most studies, within the uncertainties of the estimations. Were mesotheliomas produced only by amphiboles, one would have expected large differences in the mesothelioma risk between pure chrysotile studies and those with extensive amphibole use. Table 5, from Nicholson and Raffn⁶⁾, summarizes this ratio, by fiber type usage, for the more than 40 studies for which little or no exposure information is available.

In Table 5, we use the excess number of lung cancers as

a measure of exposure and compare the ratios of mesothelioma to excess lung cancer across these studies. In doing so, however, one has to adjust the excess numbers of lung cancer to the same underlying risk of lung cancer. This is necessary because the excess number of lung cancers is proportional to both the cumulative exposure and the expected lung cancer risk. It can be seen that the ratio of mesothelioma to excess lung cancer is the same for exposures to 100% chrysotile, 97%+ chrysotile, 100% amosite and mixtures of chrysotile, amosite and crocidolite, within statistical uncertainty. Only 100% crocidolite exposures appear to have a greater ratio, about two to four times that of predominantly chrysotile. This relatively small difference in the potential for crocidolite to produce mesotheliomas compared with other fiber exposures cannot explain the high risk seen in chrysotile exposures accompanied by a very small crocidolite exposure. The data speak strongly that much of the mesothelioma risk in predominantly chrysotile exposures is from the chrysotile.

Analyses utilizing the time course of mesothelioma risk

The mortality risk of mesothelioma from exposure to asbestos can be described by a mathematical model that is widely accepted. It was used for regulatory purposes by the U S Consumer Product Safety Commission²³⁾, the U S Environmental Protection Agency⁷⁾, and the US Occupational Safety and Health Administration²⁴⁾. It was the model in the recent review of the Health Effects Institute/Asbestos Research²⁵⁾. In this model the risk of mesothelioma, R_M , is given by:

$$R_M = K_M \cdot f \cdot [(t-10)^3 - (t-10-d)^3] \quad \text{for: } t > 10+d \quad \text{Eq. 2a}$$

$$R_M = K_M \cdot f \cdot (t-10)^3 \quad \text{for: } 10+d > t > 10 \quad \text{Eq. 2b}$$

$$R_M = 0 \quad \text{for: } 10 > t \quad \text{Eq. 2c}$$

Here R_M is the mesothelioma mortality rate at t years from

Table 5. Ratio of mesothelioma to adjusted excess lung cancer^a according to type of asbestos exposure

Type of exposure	Number of studies	Mesothelioma/excess Pleural cases	Lung cancer All cases
Chrysotile	8	0.13	0.14
Predominantly chrysotile	6	0.24	0.48
Amosite	2	0.13	0.22
Predominantly crocidolite	6	0.46	0.61
Anthophyllite	1	0.00	0.00
Talc (tremolite)	2	0.00	0.08
Mixed exposures	16	0.19	0.40

^a Adjusted to the U S male cancer rates in 1970

onset of exposure to asbestos for a duration d years at a concentration f fibers/ml. K_M is a proportionality constant related to carcinogenic potency and may depend on fiber type. For exposures that vary with time, risks for each separate period are additive. Alternative models have been used without the lag period of 10 years. These have similar formulas, but without the factor of 10, and a power of 4 or higher rather than 3.

Information is available from two groups of workers that allows consideration of the contribution of chrysotile to mesothelioma risk by consideration of its time of use compared with other fibers. United States insulation workers, while exposed to mixtures of chrysotile and amosite since 1940, also can provide information on health effects related to pure chrysotile. This arises because their exposure to asbestos prior to 1937 was to only chrysotile and until 1940 only occasionally to amosite. Because of the strong dependence of mesothelioma risk with time as indicated by Eqs. 2, exposures to amosite would not be expected to contribute substantially to a mesothelioma risk until the mid-1950's. Observations of insulator mortality in the period of low amphibole mesothelioma risk relate directly to chrysotile risk. This time course of mesothelioma risk was utilized by Nicholson and Landrigan²⁶⁾ to compare the expected and observed mesothelioma risks in the New York and New Jersey insulation worker cohort established by Selikoff, Churg and Hammond²⁷⁾. The comparison considered mesothelioma risks expected from the workers' total exposure to asbestos and to the exposure from amphiboles, predominantly amosite beginning in the late 1930's.

The 632 members of the New York and New Jersey locals of the insulator's union who were members on January 1, 1943 are an ideal group to study the effects of exposure periods with different asbestos types. The majority of the group were first employed prior to 1923. Follow-up of the group extends from 1943 until the present. First employment as an insulator began in 1888 for two members of the group; 38% were first employed before 1920. Through 1992, all but 40 of the 632 were deceased. Furthermore, substantial effort was made to obtain tissue specimens and medical records to validate the causes of death of cohort members deceased over the years. Pathological material was reviewed in the early years of follow-up by Drs. Jacob Churg and Milton Kannerstein, then members of the U. S. panel on mesothelioma, and since the 1970's by Dr. Yasunosuke Suzuki. Thus, the analysis does not suffer as much from the inadequacies of mesothelioma diagnosis that were common prior to the mid-1960's in the analyses of other groups for which only death certificate information was

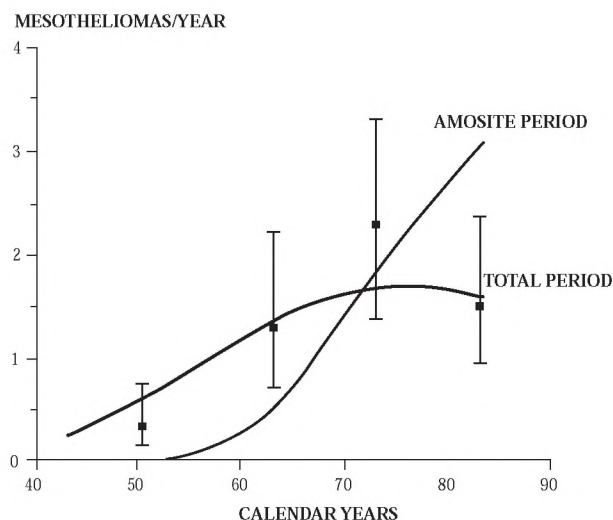


Fig. 1. Estimated and observed cases of mesothelioma/year, 1943-1987.

Estimated mesothelioma risk curves adjusted to yield 56 deaths. Of the four displayed points, the first represents 15 years of the followup and the remaining three 10 years each.

available.

The analysis of Selikoff's original cohort considered only the 56 identified deaths from mesothelioma, virtually all of which were confirmed by one of the above pathologists. The model given above for mesothelioma risk and estimates of insulation workers' exposure were used to calculate the expected numbers of mesotheliomas, 1943-1987, among the cohort of 632 NY-NJ insulators. This was done for two periods of time. In one, only exposures subsequent to 1935 were considered, reflecting exposure to amosite; in the other, all asbestos exposures to individuals in the group were considered, from their first exposure to chrysotile asbestos until termination of employment or death. Figure 1 shows the results of these calculations of expected mesothelioma cases, by year, compared with the actual numbers of mesotheliomas observed. Because of uncertainties in the relative amounts of amosite and chrysotile after 1935, the expected cases were adjusted to represent the observed 56 total mesotheliomas. The actual estimate for amosite alone was less than one-fifth that observed. Data points represent an average of 15 years for the first point and an average over ten years for the remaining three. As can be seen, the time course of mesothelioma risk is totally incompatible with an exposure pattern that begins in the late 1930's. Indeed, the 95% confidence limits on three of the four data points do not intercept the expected distribution for amosite exposure. Barring unknown exposures to amphiboles prior

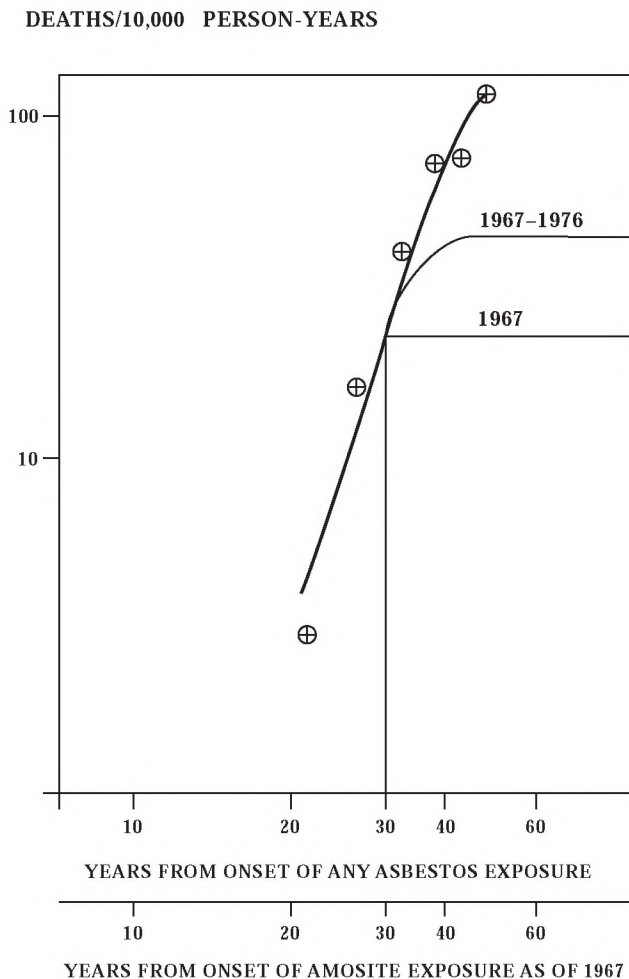


Fig. 2. The mortality rates, by five-year periods, for U S and Canadian insulation workers, 1967-1976, based on 175 deaths.

to 1935, the data present strong evidence that chrysotile is a substantial, indeed, the dominant contributor to the mesothelioma risk experienced by this group of insulation workers.

The study by Selikoff, Hammond and Seidman¹²⁾ of the entire union membership of U. S. and Canadian insulators also strongly reflects a chrysotile mesothelioma risk. Follow-up for the study began in 1967, 30 years after the earliest incorporation of amosite by insulation manufacturers into their products. Figure 2 displays the data on mesothelioma risk for the ten-year period, 1967-1976 (the crossed circles). The observed data match a risk estimate made using Eqs. 2 and a value of $K_M = 1.5 \times 10^{-8}$ (the heavy line) for the full asbestos exposure period of the insulators, as indicated by the (upper) "years from onset of any asbestos exposure." This match, considering all asbestos exposures, strongly suggests that the pre-1937 exposures of insulators solely to

chrysotile contributed substantially to the overall mesothelioma risk.

To fully appreciate the chrysotile effect, consider a hypothetical one-year follow-up during 1967 of these insulators with the assumption that only amosite contributes to their mesothelioma risk, according to Eqs. 2. Since we are considering at this time a one-year follow-up, let us also assume an amosite potency that would match estimated risks to the observed insulator mesothelioma risks for the first 30 years from onset of *any* asbestos exposure (that allows us to use the same graph). Note that these first 30 years correspond to first asbestos exposures in the calendar years, 1937-1966, the years in which amosite was contained in insulation and during which our hypothetical amosite can explain the observed risks. The vertical line identifies the risk for an individual first exposed to amosite in 1937. However, all individuals employed as an insulator before 1937 also had their first exposure to amosite in 1937 and *would have the same 30-years from amosite exposure risk*, even though their first exposure to chrysotile was 40, 50 or more years previously. The characterization of time from onset of amosite exposure would accord with the (lower) "years from onset of amosite exposure as of 1967." Thus, it would be expected that the risk for this hypothetical one-year follow-up of this cohort would follow the indicated horizontal line.

In actuality, the depicted insulator data are for a 10-year follow-up period and by 1976 some insulators would have had 40 years from onset of amosite exposure. Consideration of the full 10-year follow-up period results in a hypothetical amosite risk curve for the group indicated by the 1967-1976 curve. Considering risk according to time from onset of any asbestos exposure, there is a dramatic difference between an amosite only effect and a combined effect from amosite and chrysotile. Instead of a sharp break of the heavy line at 30 years from onset of exposure, there is an unwavering continuation indicating the substantial contributions of exposures prior to 1937. The data strongly indicate a chrysotile contribution to mesothelioma risk equal to that of amosite.

Direct calculation of mesothelioma risk

Finally, one can make an estimate of chrysotile mesothelioma risk from direct calculations of mesothelioma risk in mixed exposure circumstances. Data on duration and intensity of exposure are available in five exposure circumstances that allow one to utilize Eqs. 2 and calculate values of K_M . The results are shown in Table 6.

These results show that risk of mesothelioma per fiber

Table 6. The risks of mesothelioma demonstrated in studies of workers exposed to various asbestos minerals

Asbestos exposure	Type of asbestos	Risk coefficient	Ref
Textile production	Chrysotile	1.0×10^{-8}	7
Insulation application	Chrysotile/amosite	1.5×10^{-8}	7
Factory workers	Amosite	3.2×10^{-8}	7
Cement workers	Chrysotile/crocidolite	12×10^{-8}	7
Miners and millers	Crocidolite	13.4×10^{-8}	29

The risk coefficient is K_M in the equation, $R_M = K_M \cdot f \cdot [(t-10)^3 - (t-10-d)^3]$.

exposure, as measured by K_M , is virtually the same for exposures to 97% chrysotile + 3% crocidolite, 60% chrysotile + 40% amosite, and 100% amosite. The value of K_M from the cement workers study of Finkelstein is higher than the chrysotile-amosite exposures as was a value of K_L in the same group of workers. As noted previously, there may be substantial errors in the exposure estimates of the study. The value for a pure crocidolite exposure, as calculated by de Klerk and Armstrong^{8, 11, 12, 15, 28)} for the mining population of Australia, is about ten times greater. As with the values of K_L in Table 4, K_M is uncertain because of uncertainties of exposures in the early exposure years of the groups under study and from uncertainties of small numbers. Indeed, from data to be considered below, the mesothelioma potency of crocidolite would appear to be less than ten times that of other fibers. Nevertheless, in contrast to the analysis of crocidolite lung cancer risk in comparison to other fibers, the data do indicate a clearly greater mesothelioma potency for crocidolite.

However, K_M is not so much greater for crocidolite that it is likely to be the dominant cause of the mesothelioma found among the textile workers of the Rochdale, England plant. There, crocidolite was brought into the plant as yarn and the raw fiber was not opened, carded or spun to a significant extent. Overall, from 1932–1968, 2.6% of the asbestos fiber purchased for use at Rochdale was crocidolite⁹⁾. Without evidence of overwhelmingly greater exposures to crocidolite, an estimate from the above data is that crocidolite might account for about 35% of the total mesothelioma risk at Rochdale. If $K_M(\text{croc.}) = 13 \times K_M(\text{Rochdale})$, for equal percentage use over time and a contribution to air concentrations equal to the percentage use, the $K_M(\text{chrys.})$ can be estimated from the relation:

$$(13 \times 0.026) \times K_M(\text{Rochdale}) + 0.97 \times K_M(\text{chrys.}) = K_M(\text{Rochdale}).$$

This yields a value for $K_M(\text{chrys.})$ equal to 0.68×10^{-8} and a contribution to the total mesothelioma risk at Rochdale of

66%. The chrysotile contribution to mesothelioma at Rochdale is substantial.

A direct estimate cannot be made of the exposure specific mesothelioma risk for Quebec chrysotile miners and millers. Among the miners and millers, the ratio of mesotheliomas to excess lung cancer suggests a lower risk comparable to that seen for lung cancer. In the case of the South Carolina textile workers with only two mesotheliomas, suggesting a low risk, the possibility of misdiagnosis of the disease on certificates of death must be considered.

Summary of malignant mesothelioma risks

The case that chrysotile is a potent causative factor in producing mesothelioma is a strong one. It is shown to be so in a comparison of more than 40 studies of different fiber exposure circumstances. It is shown to be so when the time course of risk is considered in mixed fiber exposures. Finally, it is shown to be so in direct calculations of risk. All available data suggest that it dominates the risk in those circumstances where it is the principal fiber used. The risk of chrysotile in producing mesothelioma is similar to that of amosite on a per fiber exposure basis. Crocidolite would appear to have a four to ten times greater potential to produce mesothelioma for equal exposure than chrysotile. However, the crocidolite risk is not so much greater that one can ascribe total causation to a small percentage of crocidolite fibers in a mixed fiber exposure setting.

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