Occupational Exposure to Chrysotile Asbestos and Cancer Risk: A Review of the Amphibole Hypothesis

ABSTRACT

Objectives. This article examines the credibility and policy implications of the "amphibole hypothesis," which postulates that (1) the mesotheliomas observed among workers exposed to chrysotile asbestos may be explained by confounding exposures to amphiboles, and (2) chrysotile may have lower carcinogenic potency than amphiboles.

Methods. A critical review was conducted of the lung burden, epidemiologic, toxicologic, and mechanistic studies that provide the basis for the amphibole hypothesis.

Results. Mechanistic and lung burden studies do not provide convincing evidence for the amphibole hypothesis. Toxicologic and epidemiologic studies provide strong evidence that chrysotile is associated with an increased risk of lung cancer and mesothelioma. Chrysotile may be less potent than some amphiboles for inducing mesotheliomas, but there is little evidence to indicate lower lung cancer risk.

Conclusions. Given the evidence of a significant lung cancer risk, the lack of conclusive evidence for the amphibole hypothesis, and the fact that workers are generally exposed to a mixture of fibers, we conclude that it is prudent to treat chrysotile with virtually the same level of concern as the amphibole forms of asbestos. (*Am J Public Health.* 1996;86:179–186)

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Introduction

Chrysotile is the predominant type of asbestos produced and consumed in the world today, and it accounted for over 98.5% of US asbestos consumption in 1992.[1] Although asbestos consumption has declined in North America and Europe, sales in other countries (e.g., Southeast Asia, South America, and Eastern Europe) have increased primarily due to the use of asbestos-based construction materials.[2]

Chrysotile is a serpentine (curly) form of asbestos that is distinguished from other amphibole forms of asbestos (i.e., crocidolite, amosite, tremolite). It has been hypothesized that (1) the mesothelioma risk observed among workers exposed to chrysotile asbestos may be explained by the relatively low concentrations (<1%) of tremolite fibers in commercial chrysotile asbestos fibers and (2) that chrysotile asbestos may be less potent than amphiboles in the induction of asbestosis and lung cancer. This has been dubbed the amphibole hypothesis.[3] It has even been suggested that exposure to chrysotile asbestos in the absence of tremolite may present little or no carcinogenic hazard.[4]

The arguments advanced to support the amphibole hypothesis have been primarily based on pathologic studies of burdens of asbestos fibers in human lungs and on toxicologic, mechanistic, and epidemiologic studies. This article presents a critical review of these arguments and of the literature on the carcinogenic hazards associated with exposure to chrysotile asbestos and considers the implications of these findings for the development of occupational health policies.

Lung Burden Studies

The development of methods that involve electron diffraction and energy dispersive analysis of x-rays (EDAX)[5] has made possible the measurement of the amounts of different fiber types in the lung. The results from lung burden studies have provided the primary basis for the advancement of the amphibole hypothesis.

Case studies of individuals who have worked in industries using or producing chrysotile asbestos revealed an unexpectedly high proportion of amphibole (primarily tremolite) fibers, considering the relatively low percentage of amphibole fibers in commercial chrysotile asbestos.[6] In one of the earliest studies, Pooley observed a greater number of amphibole fibers than chrysotile fibers in 7 of 22 patients with asbestosis who had worked in the Canadian chrysotile mining industry.[7] Rowlands et al. also reported a nearly equal concentration of tremolite fibers and chrysotile fibers in the lungs of 47 workers employed as miners or millers in Quebec.[8] Similarly, in population-based studies the percentage of chrysotile fibers found in the lungs has been surprisingly low considering the fact that chrysotile is the major source of exposure for the general population.[9]

Most case–control studies that evaluated the potential relationship between

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TABLE 1—Summary of Epidemiological Cohort Studies of Workers Exposed to Predominantly Chrysotile Asbestos

Study	Industry	Lung Cancer Deaths		Mesothelioma Cases	
		Observed	Expected	Observed	Deaths, %
Acheson et al.[27]	Gas masks	6	4.8[a]	1	0.6
Cheng and Kong[28]	Textiles, friction materials, and cement	21	6.7*	0	0
Dement et al.[29]	Textiles	126	64.0*	2	0.2
Finkelstein[30]	Electrical conduit pipe	6	3.7	1	1.0
Finkelstein[31]	Automotive	11	7.9	1–2[b]	1.0–1.9
Hughes et al.[32,c]	Cement manufacturing	70	53.2	1	. . .
Huilan and Zhiming[33]	8 asbestos factories	65	15.6[a]*	2	0.4
McDonald et al.[34]	Friction products	73	49.1*	0	0
McDonald et al.[35,36,d]	Mining and milling	518	389.7*	28	0.4
Piolatto et al.[37]	Mining	22	19.9	2	0.5
Shiqu et al.[38]	Mining	6	. . .	3	4.5
Weiss[39]	Paper and millboard	4	4.3	0	0
Total		922[e]	618.9	41.0	0.3

Note. SMR = the standardized mortality ratio, which is the ratio between the observed and expected.
[a]The expected number is for cancer of the lung and pleura combined.
[b]One or two cases of mesothelioma were reported. Only one was included in the totals.
[c]Results are for workers exposed only to chrysotile from one of two plants studied. The total number of deaths was not reported; thus, the percentage of mesothelioma deaths could not be estimated.
[d]Observed and expected numbers exclude observations from the asbestos factory.
[e]The Shiqu et al. study was not included in the total number of lung cancer cases because expected numbers were not reported.[67]
*Significantly different from the observed number, $P < .05$ (two tailed).

mesothelioma risk and lung concentrations of the different fiber types of asbestos demonstrated a clear relationship with amphibole lung burdens but failed to find a relationship with lung chrysotile concentrations.[10–14] McDonald et al. reported an association between mesothelioma and lung concentrations of long (≥ 8 μm) chrysotile fibers in univariate analyses but not in multivariate analysis, which controlled for the other fiber types.[15] Rogers et al. reported a significant association between mesothelioma risk and lung concentrations of short chrysotile fibers (<10 μm) in multivariate models and a significant trend for lung concentrations among mesothelioma case and control subjects who had only chrysotile detected in their lungs.[16]

The interpretation of the results from the studies of lung burden is complicated by differences in the respiratory clearance rates of the different forms of asbestos. Experimental studies demonstrated that chrysotile fibers are cleared far more rapidly from the lungs than are amphibole fibers.[17–19] The retention half-life of chrysotile in human lungs is unknown, but a half-life of 90 days has been reported in experimental studies of baboons.[20] If the half-life for chrysotile is similar for humans and baboons, then clearly the vast majority of the dose received in early years would not be reflected in the lung burdens measured at the time of autopsy. This is of particular concern for mesothelioma, which has been estimated to have a latency period of at least 20 years.[21] For example, assuming a 90-day half-life and first-order kinetics, only approximately $1/(8 \times 10^{22})$ of the dose received 20 years earlier would be predicted to be present in the lungs at the time of the autopsy. Hence, lung burdens of chrysotile may be a poor measure of the integrated exposures to chrysotile.

The high degree of correlation between the lung concentrations of the different fiber types, which has been noted by several investigators, further complicates the interpretation of the lung burden analyses.[15,16,23] Churg reported that the correlation coefficient between the numbers of chrysotile and crocidolite fibers in lungs of asbestosis patients was .88 ($P < .05$).[23] Rowlands et al. reported a stronger correlation between cumulative asbestos exposure and lung fiber counts for tremolite than between cumulative asbestos exposure and lung burdens of chrysotile in their study of Quebec miners and millers.[8] The high degree of correlation might explain the negative findings in some of the case–control studies if amphibole exposures are simply acting as a surrogate for integrated lifetime chrysotile exposure in these studies. As Churg et al. suggested, "It may be true that the tremolite serves as a better measure of past chrysotile than the chrysotile itself."[19]

Finally, studies of fiber counts in extrapulmonary sites raise serious questions about the validity of using lung burden studies for assessing mesothelioma risk. Several investigators reported cases in which short chrysotile fibers were the predominant fiber found in the pleura, pleural plaques, or pleural fibrotic tissue when amphiboles were the predominant fiber found in the lung.[22,24–26] These results suggest that chrysotile may be preferentially translocated to the pleura and that the fiber counts found in the lung may not accurately reflect the concentrations found at the site for mesothelioma induction.

Epidemiologic Studies

Lung Cancer

There have been 12 retrospective cohort mortality studies of workers who were predominantly exposed to chrysotile asbestos fibers. Results for mortality from lung cancer (and mesothelioma) from the most recent updates of these cohorts are summarized in Table 1. Mortality from lung cancer was greater than expected in nearly all of the studies. Combining the results from these studies, there were 928 observed and 618.9 expected lung cancer deaths, resulting in a pooled standardized mortality ratio for lung cancer of 1.50 (95% confidence interval [CI] = 1.40, 1.60). The observed excesses of lung cancer mortality did not appear to be explained by differences in cigarette smoking habits in the studies that had information on tobacco consumption.[28,33,35,36,40,41] Collectively, these studies provide strong evidence that exposure to chrysotile asbestos is associated with an excess risk of lung cancer.

There is little, if any, evidence to suggest that the excess in lung cancer mortality observed in these cohorts may be attributable to tremolite contamination. In fact, this hypothesis is strongly contradicted by the fact that the lung cancer response in the studies of populations with relatively pure chrysotile exposures is similar to that in studies of cohorts with amphibole or mixed exposures. Estimates of the increase in excess relative risk per unit of exposure (i.e., potency) for lung cancer based on cohort studies by industry and fiber type are presented in Table 2. Variations in risk according to

industry type appear to be far more remarkable than variations according to fiber type. The potencies for lung cancer risk are similar among the cohorts with pure chrysotile and mixed exposures in the textile industry and are generally higher than the potencies observed among workers in the mining or asbestos products industries. The studies of asbestos products industry workers all show very low potencies, with the lowest unit risks observed among friction product workers. One study of cement workers, which provided separate analyses for workers exposed to chrysotile asbestos and workers exposed to a mix of chrysotile and crocidolite fibers, produced remarkably similar potency estimates for these two groups.[32] Among the studies of miners, lung cancer potency was substantially lower among workers in the Quebec mining industry who were exposed to chrysotile ores than among crocidolite or tremolite miners.

It has been suggested that the high lung cancer mortality observed among South Carolina textile workers might be explained by exposure to mineral oils.[47] However, Dement et al. demonstrated in case–control analyses that the risk of lung cancer observed in this cohort is unrelated to mineral oil exposure.[29,48] In addition, studies of workers exposed to mineral oils have generally not demonstrated an excess of lung cancer.[49] There is evidence that asbestos fibers in the textile industry were considerably longer than the fibers measured in chrysotile mining and milling and other industries.[50] Thus, differences in fiber dimensions would appear to be a more likely explanation than mineral oil exposures for the higher lung cancer rates observed in textile workers.

TABLE 2—Estimates of Asbestos Potency for Lung Cancer from Studies with Individual Exposure Estimates, by Industry and Fiber Type

Study	Industry	Fiber Type	Excess Relative Risk per Fiber/cc × Yr
Dement et al.[29]	Textiles	Chrysotile	0.031
McDonald et al.[12]	Mainly textiles	Chrysotile, amosite, crocidolite	0.017[a]
Peto et al.[42]	Textiles	Chrysotile, crocidolite	0.015[b]
McDonald et al.[43]	Mining	Tremolite	0.013
de Klerk et al.[44]	Mining and milling	Crocidolite	0.010
McDonald et al.[36]	Mining and milling	Chrysotile	0.0006[a,c]
Henderson and Enterline[45]	Asbestos products	Chrysotile, amosite, crocidolite	0.002[a]
Hughes et al.[32]	Cement products	Chrysotile,[a] chrysotile,[b] and crocidolite	0.0071,[a] 0.0076[b]
Berry and Newhouse et al.[46]	Friction products	Chrysotile	0.00058
McDonald et al.[34]	Friction products	Chrysotile	0.00053[a]

[a]A conversion factor of three fibers per cubic centimeter being equivalent to 1 million particles per cubic foot was assumed.
[b]Data are based on results for workers employed after 1951.
[c]Slope was estimated by fitting a linear relative risk Poisson regression model to the standardized mortality ratio results reported by McDonald et al.[36]

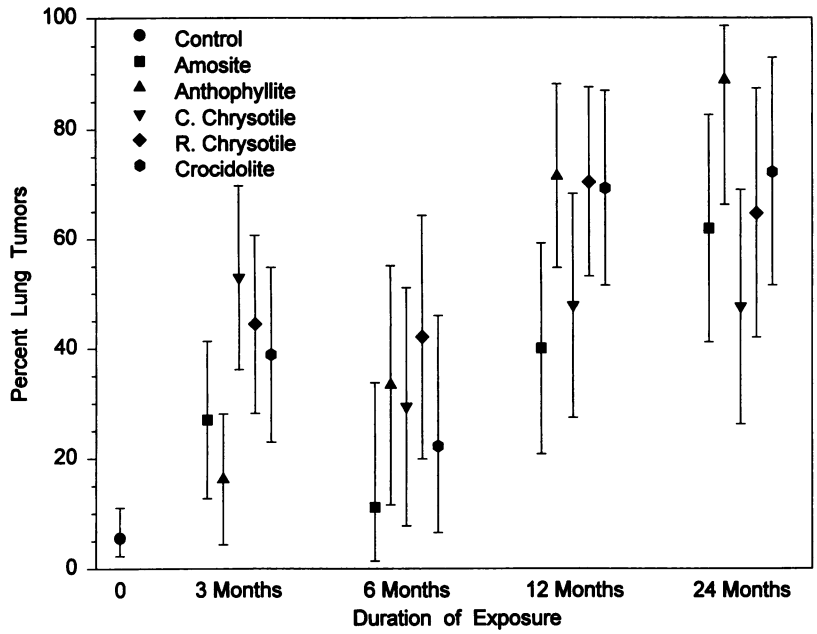
Mesothelioma

A total of 45 cases of mesothelioma (primarily pleural) were reported in the epidemiologic studies of workers who were predominantly exposed to chrysotile asbestos (Table 1). Although it has generally not been possible to estimate expected numbers of mesothelioma deaths, the percentage of deaths due to mesothelioma may be estimated and compared with background percentages. This percentage is 0.3% for all studies combined. In contrast, the percentage of deaths due to pleural malignancies (most of which are mesotheliomas) was only 0.02% in the United States in 1988.[51]

Although the evidence of excess mortality of mesothelioma among workers exposed to commercial chrysotile is compelling, the critical issue is whether this excess may be attributable to trace contamination by tremolite. All of the asbestos workers studied (Table 1) are likely to have potential exposures to tremolite, although in minute concentrations compared with their chrysotile exposures.

In a few studies the percentage of tremolite is known and varies. Contrasting the results from these studies provides some information on the plausibility of the amphibole hypothesis. Two cases of mesothelioma have been reported among chrysotile asbestos miners and millers in Zimbabwe, where the chrysotile ores are believed to be free of tremolite contamination.[52] Begin et al. noted that although exposure to tremolite may be as much as 7.5 times higher in Thetford than in Asbestos, the incidence of mesothelioma in these two Quebec mining towns was proportional to the size of their work forces.[53] He suggested that this fact may indicate that tremolite contamination may not be a determinant of mesothelioma risk in Quebec. In the most recent update of the study of Quebec miners and millers, McDonald et al.[36] presented separate exposure–response analyses for workers at the Thetford and Asbestos mines and mills. There is no indication in their findings that these two facilities exhibit a different exposure–response relationship for mesothelioma. On the other hand, McDonald and McDonald[54] recently reported that the average concentration of tremolite fibers in the lungs of miners was higher in one area of the Thetford mine, which also demonstrated a stronger association with mesothelioma risk than another area of the mine.

Informative comparisons may also be made between the proportion of deaths from mesothelioma observed in the South Carolina textile workers study and that observed in the Quebec miners and millers study. Based on lung burden studies, Sebastien et al. estimated that the proportion of tremolite in dust was probably 2.5 times higher in the Thetford mines of Quebec than in the Charleston textile facility.[47] The percentage of deaths due to mesothelioma in the most recent reports was one half as high in the South Carolina textile workers (0.2%) as it was among Quebec miners and millers (0.4%) (Table 1). However, in making this comparison one needs to consider the fact that the incidence of mesothelioma is known to increase exponentially with follow-up time,[55] and 72% of the Quebec miners and millers had died,[36] compared with 42% of the workers in the South Carolina study,[29] in the most recent updates of these cohorts. In the previous



Note. Data are from Wagner et al.[17]; approximate 95% confidence intervals for a binomial outcome have been added. C = Canadian; R = Rhodesian.

FIGURE 1—Lung tumors in rats exposed to 10 mg/m³ concentrations of asbestos for 3, 6, 12, or 24 months.

update of the Quebec miners and millers study, the percentage that had died was 41% and the percentage of deaths due to mesothelioma was 0.2%, which is nearly identical to the percentage of deaths from mesothelioma in the most recent update of the South Carolina textile workers.[35] The fact that these percentages are so similar is even more remarkable when it is recognized that the fiber exposure levels were approximately ten times higher in the Quebec miners and millers than in the South Carolina textile workers.[47] Thus, comparison of the mesothelioma results from the study of Quebec miners and millers with those from the study of South Carolina textile workers does not provide support for the hypothesis that tremolite exposure explains the mesothelioma excess observed in these studies.

In contrast to the evidence for lung cancer, there is epidemiologic evidence indicating that exposure to chrysotile may be less potent than exposure to some amphiboles with regards to the induction of mesothelioma. Hughes and Weill estimated that the risk of mesothelioma was approximately five times lower among workers exposed to chrysotile fibers than among workers with mixed fiber exposure.[56] The percentage of deaths due to mesothelioma among South African asbestos miners was recently reported to be 4.7% among those exposed to crocidolite, which is substantially greater than the percentage of deaths due to mesothelioma observed in either the Quebec miners (0.4%) or the South Carolina textile workers (0.2%) exposed to predominantly chrysotile fibers.[57] The percentage of deaths due to mesothelioma was only slightly higher among South African miners exposed to amosite (0.6%) than among the chrysotile-exposed cohorts.[57] McDonald et al.[43] reported that the percentage of deaths due to mesothelioma was 2.4% among vermiculite miners who were predominantly exposed to tremolite fibers, which is approximately six times higher than the percentage (0.4%) reported in the study of Quebec miners and millers.[36] It must be recognized that the usefulness of these comparisons is limited by our inability to control for potential differences in exposure concentrations, fiber size distributions, and length of observation and are thus difficult to interpret. Nonetheless, the differences in mesothelioma response observed among chrysotile- and amphibole (primarily crocidolite)-exposed workers are so striking that alternative explanations for these differences appear unlikely.

Toxicologic Studies

Lung Cancer

Toxicologic studies demonstrated that all forms of asbestos can induce lung cancers in experimental animals. For example, the lung tumor response to 3- to 24-month exposures to Union International Contre le Cancer reference amosite, anthophyllite, Canadian chrysotile, Rhodesian chrysotile, and crocidolite is shown in Figure 1.[17] The overlapping 95% confidence intervals suggest that there is no significant difference in potency among the five types of asbestos (i.e., the amphiboles are not systematically more or less potent than the chrysotiles).

Davis and co-workers also compared the carcinogenic potencies of chrysotile and amphibole asbestos by exposing rats to 10 mg of amosite, crocidolite, and Zimbabwe chrysotile per m³ for 1 year. These investigators found that chrysotile actually produced more lung tumors than the other forms of asbestos.[58] These results obviously differ from those of Wagner et al.[17] and may point to the need to consider differences in fiber length when comparing the potencies of different types of asbestos. Davis et al. noted that 5% of the chrysotile in their study consisted of fibers greater than 20 μm in length vs 0.5% of the fibers for the amosite and crocidolite exposures.[58] Other studies by Davis et al. showed that long-fiber samples of amosite[59] and chrysotile[60] are considerably more active than short-fiber samples in inducing lung tumors.

Davis et al. also showed that tremolite,[61] crocidolite,[58] and long-fiber chrysotile[60] produce similar numbers of lung tumors. Figure 2 represents lung tumors due to amosite, crocidolite, chrysotile, or tremolite from the 1-year inhalation studies of Davis et al. and Davis and Jones, plotted against the exposure concentration in units of fiber count.[58–61] Inspection of Figure 2 suggests that the tumor incidence is strongly related to the concentration of fibers 5 μm or greater in length, regardless of which type of asbestos is involved.

More recently, Coffin et al.[62] reported the results from studies of rats exposed via intratracheal instillation of chrysotile or crocidolite. Although these investigators focused primarily on mesotheliomas, it is worth noting that (summed across all dose groups) intratracheal instillation of chrysotile asbestos produced

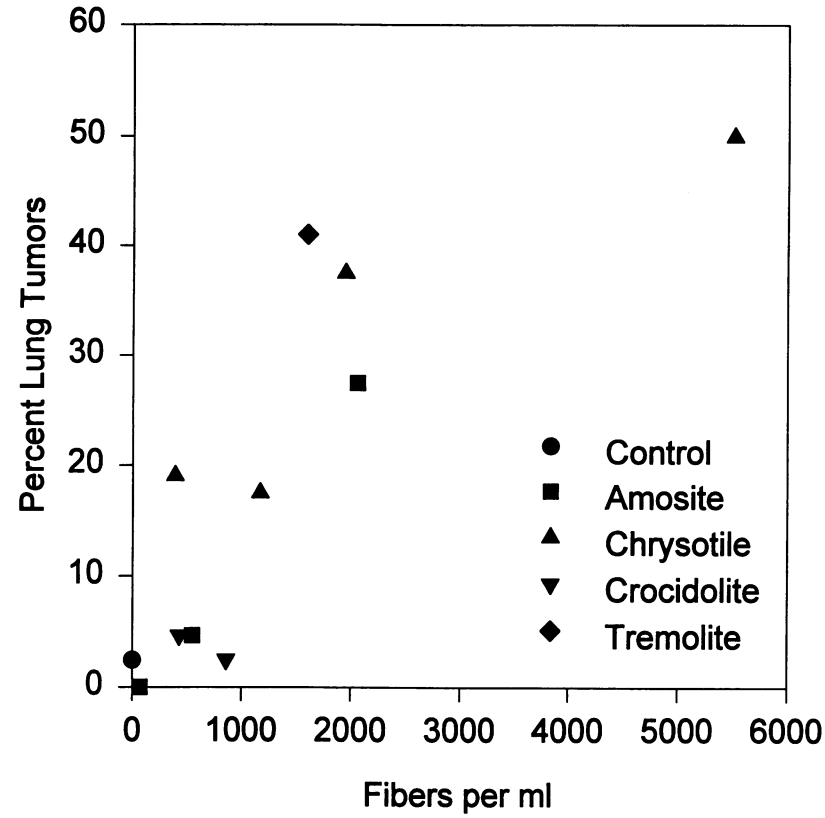
lung carcinomas in 18.3% of the animals tested vs 4.6% for crocidolite.[62]

Overall, the toxicologic data suggest that chrysotile asbestos is at least as potent, if not more so, as the amphibole forms in the induction of lung tumors on a per-milligram basis. The data shown in Figure 2 further suggest that the carcinogenic potencies of the various types are similar when the dosage is measured in terms of the number of fibers greater than 5 μm in length, as is customary in epidemiologic studies.

Mesothelioma

Rats exposed to asbestos by inhalation also develop mesotheliomas, albeit at a low incidence. Wagner et al.[17] exposed rats to 10 mg/m³ of Union International Contre le Cancer reference asbestos[63] for periods of 1 day to 2 years; the mesothelioma yields were amosite, 0.7%; anthophyllite, 1.4%; crocidolite, 2.8%; and Canadian chrysotile, 2.9%. No mesotheliomas were observed in control animals or animals exposed to chrysotile from Zimbabwe.[17] Similarly, Davis et al. and Davis and Jones reported small numbers of mesotheliomas in response to 1-year inhalation exposures to amosite, crocidolite, Canadian chrysotile, and Zimbabwe chrysotile.[58–60] The highest mesothelioma incidence in these studies, 7.5%, was produced by exposure to long-fiber chrysotile.[60] Although the low incidence rates and small numbers of animals make quantitative comparisons uncertain, it cannot be said that these studies provide convincing support for the amphibole hypothesis.

The mesothelioma-inducing potential of asbestos fibers that reach pleural surfaces has also been examined via implantation studies. Union International Contre le Cancer reference amosite, anthophyllite, crocidolite, Canadian chrysotile, and Zimbabwe chrysotile all produced mesotheliomas in rats after intrapleural inoculation.[64] Extensive studies by Stanton and co-workers suggest that all long, thin, durable fibers have the potential to induce mesotheliomas after surgical implantation and that fiber dimensions have much more influence on mesothelioma yield than any differences that may exist between types of asbestos.[65] However, it is certainly possible that different types of asbestos fibers may have differing probabilities of reaching pleural surfaces when inhaled into the lungs. Overall, the implantation studies suggest that chrysotile asbestos does have the potential to induce mesothelioma, but these studies do not resolve the question of whether or not chrysotile is less potent in this regard than the amphibole forms.



Note. Data are from Davis et al. and Davis and Jones.[58–61] Controls are the pooled control animals from all four studies.

FIGURE 2—Lung tumors in rats exposed to 10 mg/m³ concentrations of crocidolite, amosite, chrysotile, or tremolite for 1 year.

Coffin et al. recently reported that both chrysotile and crocidolite produce mesotheliomas when administered intratracheally.[62] No consistent dose–response relationship was observed in these experiments, but (summing across all dose groups) chrysotile asbestos produced mesotheliomas in 9.5% of the animals vs 5.1% for crocidolite. This suggests that chrysotile may have greater mesothelioma-inducing potential than crocidolite on a per-milligram basis. However, the chrysotile preparation used in this experiment contained more fibers per milligram than the crocidolite preparation, as well as a larger proportion of long fibers. If the experimental exposures are expressed on the basis of the number of fibers greater than 5 μm in length, it appears that crocidolite produced nearly 12 times more mesotheliomas per fiber than chrysotile. It should be noted that the fiber preparations in the Coffin et al. experiments consisted primarily of short fibers, with median fiber lengths on the order of 1 μm for both chrysotile and crocidolite. If short fibers do in fact have some mesothelioma-inducing potential, the attribution of all mesotheliomas to the small fraction of the fibers that were greater than 5 μm in length may lead to an exaggerated estimate of the difference in potency of crocidolite vs chrysotile. In addition, reliance on the quantitative responses in this study should probably be limited due to the lack of dose–response. Nevertheless, these data do provide some support for the hypothesis that chrysotile may have lower mesothelioma-inducing potential than the amphibole forms of asbestos.

Mechanistic Studies

It has been hypothesized that the cytotoxic, genotoxic, and proliferative effects of asbestos are in part mediated by the production of reactive oxygen species released by alveolar macrophages in response to engulfment of long fibers and

that this process may be catalyzed by iron on the fiber surface. Furthermore, it has been suggested that the needle-like configuration, durability, and increased iron content of crocidolite render it more pathogenic than either amosite or chrysotile.[66] Experimental support for this hypothesis is primarily derived from in vitro studies, which suggest that iron could potentially act as a source of free radicals, an inhibitor of tumoricidal defense mechanisms, and a nutrient for unrestricted tumor cell replication.[67] However, comparison of the carcinogenic potencies of fibers in the rat in vivo does not support the hypothesis that carcinogenic potency is related to iron content. As discussed above, Wagner et al.[17] observed similar numbers of tumors in rats with crocidolite, amosite, and chrysotile, even though these fibers have an elemental iron content of 40%, 28%, and less than 1%, respectively.[67] The nonasbestos mineral erionite does not include iron as a constituent[68] but is nonetheless a potent mesothelioma inducer in rats.[69] Silicon carbide "whiskers," with an iron content of essentially zero, induce pleural tumors in rats after intrapleural implantation.[65] Therefore, no obvious correlation between iron content and carcinogenicity is apparent in the rat.

Summary

Our review of both the toxicologic and epidemiologic literature strongly supports the view that occupational exposure to chrysotile asbestos is associated with an increased risk of both lung cancer and mesothelioma. The hypothesis that these observations may be attributable to trace amounts ($<1\%$) of tremolite contamination may seem to be primarily of academic interest, because chrysotile exposures in workers and the public are also contaminated with tremolite. However, the percentage of tremolite has been reported to range from 0.5% to 6.9% in one analysis of eight commercial chrysotile asbestos samples,[6] and it has been suggested that chrysotile from Zimbabwe[70] and other countries may be free of contamination by amphiboles. Hence, the amphibole hypothesis may be of some public health relevance.

In our view, the currently available scientific literature does not provide persuasive evidence for the hypothesis that tremolite contamination explains the mesothelioma excesses observed in the studies of chrysotile-exposed workers. The primary evidence for this hypothesis comes from pathologic studies in which lung burdens were measured. However, interpretation of these studies is hampered by the fact that chrysotile lung burdens are a poor reflection of integrated exposures and the fact that chrysotile exposure is highly correlated with lung burden of the amphiboles (e.g., tremolite). In addition, the pattern of asbestos fiber deposition in the lung does not appear to be consistent with the pattern of deposition in the target tissue (i.e., pleura). The previously reviewed empirical data from toxicologic studies and comparisons of mesothelioma mortality and lung cancer mortality between epidemiologic studies with differing levels of tremolite contamination do not provide support for this hypothesis. Mechanistic arguments that have been made to support the amphibole hypothesis, which are based on in vitro studies of iron content, appear to be contradicted by the lack of correlation between iron content and carcinogenic potency observed in experimental studies.

Whether chrysotile asbestos is less potent than the amphibole forms of asbestos is a question that has not yet been fully resolved. There is currently very little toxicologic evidence to support this hypothesis. There is evidence from epidemiologic studies that chrysotile may be less potent for mesothelioma induction than crocidolite. The proportion of deaths due to mesothelioma are strikingly lower in chrysotile-exposed miners and millers than in crocidolite miners. There is absolutely no epidemiologic or toxicologic evidence to support the argument that chrysotile asbestos is any less potent than other forms of asbestos for inducing lung cancer.

It should be recognized that comparisons of the potency of the different forms of asbestos are severely limited by uncontrolled differences in the bivariate distribution of fiber length and diameter (i.e., fiber dimensions). Experimental studies clearly demonstrated that fiber dimensions are a critical component of the carcinogenic potency of fibers.[65] This concern applies to most of the toxicologic studies in which exposure is determined on an equal mass basis and is particularly pertinent to the epidemiologic investigations. Historic exposures in most of the epidemiologic investigations were based on impinger samples that assessed the number of fibers, and conversion factors were applied to estimate the number of fibers longer than 5 μm. Concerns have been raised about the accuracy of these conversion factors and the potential impact of associated errors on the assessment of risk.[71] The current Occupational Safety and Health Administration (OSHA) method counts asbestos fibers that are longer than 5 μm and that have a length-to-diameter ratio of at least 3 to 1. This method implicitly assumes that fibers less than 5 μm in length are not carcinogenic and that all fibers greater than 5 μm in length are of equal carcinogenic potency. These assumptions are clearly inconsistent with the experimental data and most likely result in substantial misclassification of exposure in the epidemiologic studies.

Policy Implications

The American Conference of Governmental Industrial Hygienists and several countries (e.g., the United Kingdom) have adopted less restrictive standards for chrysotile asbestos than for the other forms of asbestos.[72] In our view, the currently available scientific evidence does not provide sufficient support for developing separate standards for the different forms of asbestos. As this article documents, the scientific evidence for the amphibole hypothesis is still tenuous. Furthermore, the fact remains that in practice workers in this country and other countries are not exposed to pure chrysotile, but rather to a mixture of chrysotile, tremolite, and other forms of asbestos. Thus, it is highly impractical to consider setting separate standards for the different forms of asbestos. Finally, even if one accepts the argument that chrysotile asbestos does not induce mesothelioma (which we do not), the risk of lung cancer (and asbestosis) can not be dismissed, and chrysotile appears to be just as potent a lung carcinogen as the other forms of asbestos. It is noteworthy that the risk of lung cancer is of greater concern than the risk of mesothelioma because in most studies there are at least two excess lung cancers for every mesothelioma observed (see Table 1). There is also the additional concern of asbestosis risk, which was not considered in this article but clearly adds to the risk associated with chrysotile exposure.

Therefore, given the clear evidence of a lung cancer risk, the lack of compelling evidence for the amphibole hypothesis, and the fact that workers are generally exposed to mixture of fiber types, we believe that it is prudent policy to treat chrysotile asbestos with virtually the same level of concern as the amphibole forms of asbestos. This view is consistent with the

past National Institute for Occupational Safety and Health Administration recommendation and the recently revised OSHA standard to limit occupational exposures for all forms of asbestos to 0.1 fiber/cc. □

References

1. Pigg BJ. The uses of chrysotile. *Ann Occup Hyg.* 1994;38:453–458.
2. Lemen RA, Bingham E. A case study in avoiding a deadly legacy in developing countries. *Toxicol Ind Health.* 1994;10(1/2): 59–87.
3. Mossman BT, Bignon J, Corn M, Seaton A, Gee JBL. Asbestos: scientific developments and implications for public policy. *Science.* 1990;24:294–301.
4. Dunnigan, J. Linking chrysotile asbestos with mesothelioma. *Am J Ind Med.* 1988;14: 205–209.
5. Pooley FD, Clark NJ. Quantitative assessment of inorganic fibrous particulates in dust samples with an analytical transmission electron microscope. *Ann Occup Hyg.* 1979;22:253–271.
6. Addison J, Davies LST. Analysis of amphibole asbestos in chrysotile and other minerals. *Ann Occup Hyg.* 1990;34:159–175.
7. Pooley FD. An examination of the fibrous mineral content of asbestos lung tissue form the Canadian chrysotile mining industry. *Environ Res.* 1976;12:281–298.
8. Rowlands N, Gibbs GW, McDonald AD. Asbestos fibres in the lungs of chrysotile miners and millers—a preliminary report. *Ann Occup Hyg.* 1982;26:411–415.
9. Churg A, Warnock ML. Asbestos fibers in the general population. *Am Rev Respir Dis.* 1980;122:669–678.
10. Jones JSP, Roberts GS, Pooley FD, et al. The pathology and mineral content of lungs in cases of mesothelioma in the United Kingdom in 1976. In: Wagner JC, ed. *Biological Effects of Mineral Fibers.* Lyon, France: International Agency for Research on Cancer; 1980:188–199. Scientific Publication No. 30.
11. Wagner JC, Pooley FD, Berry G, et al. A pathological and mineralogical study of asbestos-related deaths in the United Kingdom in 1977. *Ann Occup Hyg.* 1982;26:423–431.
12. McDonald AD, McDonald JC, Pooley FD. Mineral fibre content of lung in mesothelial tumours in North America. *Ann Occup Hyg.* 1982;26:417–422.
13. Gaudichet A, Janson X, Monchaux G, et al. Assessment by analytical microscopy of the total lung fibre burden in mesothelioma patients matched with four other pathological series. *Ann Occup Hyg.* 1988; 32(suppl 1):213–223.
14. Wagner JC, Berry G, Pooley FD. Mesotheliomas and asbestos type in asbestos textile workers: a study of lung contents. *Br Med J.* 1982;285:603–606.
15. McDonald JC, Armstrong B, Case B, et al. Mesothelioma and asbestos fiber type: evidence from lung tissue analyses. *Cancer.* 1989;63:1544–1547.
16. Rogers AJ, Leigh J, Berry G, Ferguson DA, Mulder HB, Ackad M. Relationship between lung asbestos fiber type and concentration and relative risk of mesothelioma. *Cancer.* 1991;67:1912–1920.
17. Wagner JC, Berry G, Skidmore JW, Timbrell V. The effects of the inhalation of asbestos in rats. *Br J Cancer.* 1974;29:252–269.
18. Middleton AP, Beckett ST, Davis JMG. A study of the short-term retention and clearance of inhaled asbestos by rats, using U.I.C.C. standard reference samples. In: Walton WH, ed. *Inhaled Particles IV.* Edinburgh, Scotland: Institute of Occupational Medicine; 1975:247–258.
19. Churg A, Wright JL, Vedel S. Fiber burden and patterns of asbestos-related disease in chrysotile miners and millers. *Am Rev Respir Dis.* 1993;48:25–31.
20. Rendall RE. *Retention and Clearance of Glass Fibers and Different Varieties of Asbestos by the Lung.* Johannesburg, South Africa: University of Witwatersrand; 1988. Dissertation.
21. Selikoff IJ, Hammond EC, Seidman H. Mortality experience of insulation workers in the United States and Canada, 1943–1976. *Ann N Y Acad Sci.* 1979;330:91–116.
22. Sebastien P, Janson X, Gaudichet A, Hirsch A, Bigon J. Asbestos retention in human respiratory tissues: comparative measurements in lung parenchyma and in parietal pleura. In: Wagner JC, ed. *Biological Effects of Mineral Fibers.* Lyon, France: International Agency for Research on Cancer; 1980:237–246.
23. Churg A. Asbestos fiber content of the lungs in patients with and without asbestos airways disease. *Am Rev Respir Dis.* 1983; 127:470–473.
24. LeBouffant L, Martin JC, Duyif S, Daniel H. Structure and composition of pleural plaque. In: Bogovski P, Gilson JC, Timbrell V, Wagner JC, eds. *Biological Effects of Asbestos.* Lyon, France: International Agency for Research on Cancer; 1973:249–257. Scientific Publication No. 8.
25. Dodson RF, Williams MG, Corn CJ, Brollo A, Bianchi C. Asbestos content of lung tissue, lymph nodes, and pleural plaques from former shipyard workers. *Am Rev Respir Dis.* 1990;142:843–847.
26. Kohyama N, Suzuki Y. Analysis of asbestos fibers in lung parenchyma, pleural plaques, and mesothelioma tissues of North American insulation workers. *Ann N Y Acad Sci.* 1991;643:27–52.
27. Acheson ED, Gardner MJ, Pippard EC, Grime LP. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. *Br J Ind Med.* 1982;39:344–348.
28. Cheng W, Kong J. A retrospective mortality cohort study of chrysotile asbestos products workers in Tianjin 1972–1987. *Environ Res.* 1992;59:271–278.
29. Dement JM, Brown DP, Okun A. Mortality among chrysotile asbestos textile workers: Cohort mortality and case-control analyses. *Ann Occup Hyg.* 1994;38:525–532.
30. Finkelstein MM. Mortality among employees of an Ontario factory that manufactured construction materials using chrysotile asbestos and coal tar pitch. *Am J Ind Med.* 1989;16:281–287.
31. Finkelstein MM. Mortality rates among employees potentially exposed to chrysotile asbestos at two automotive parts factories. *Can Med Assoc J.* 1989;141:327–330.
32. Hughes JM, Weill H, Hammad YY. Mortality of workers employed in two asbestos cement manufacturing plants. *Br J Ind Med.* 1987;44:161–174.
33. Huilan Z, Zhiming W. Study of occupational lung cancer in asbestos factories in China. *Br J Ind Med.* 1993;50:1039–1042.
34. McDonald AD, Fry JS, Woolley AJ, McDonald JC. Dust exposure and mortality in an American chrysotile asbestos friction products plant. *Br J Ind Med.* 1984;41:151–157.
35. McDonald JC, Liddell FDK, Gibbs GW, Eyssen GE, McDonald AD. Dust exposure and mortality in chrysotile mining, 1910–1975. *Br J Ind Med.* 1980;37:11–24.
36. McDonald JC, Liddell FDK, Dufresne A, McDonald AD. The 1891–1920 birth cohort of Quebec chrysotile miners and millers: mortality 1976–88. *Br J Ind Med.* 1993;50:1073–1081.
37. Piolatto G, Negri E, LaVecchia C, Pira E, Decarli A, Peto J. An update of cancer mortality among chrysotile asbestos miners in Balangero, Northern Italy. *Br J Ind Med.* 1990;47:810–814.
38. Shiqu Z, Yongxian W, Fusheng M, Hongshuen M, Wenzhi S, Zhenhuan J. Retrospective mortality study of asbestos workers in Laiyuan. In: *Proceedings of the VII International Pneumoconioses Conference,* Part II; August 23–26, 1988; Pittsburgh, Pa. National Institute for Occupational Safety and Health; 1990:1242–1244. DHHS publication 90-109, part II.
39. Weiss W. Mortality of a cohort exposed to chrysotile asbestos. *J Occup Med.* 1977;19: 737–740.
40. Dement JM, Harris RL, Symons MJ, Shy CM. Exposures and mortality among chrysotile asbestos workers, part I: exposure estimates. *Am J Ind Med.* 1983;4:399–419.
41. Dement JM, Harris RL, Symons MJ, Shy CM. Exposures and mortality among chrysotile asbestos workers, part II: mortality. *Am J Ind Med.* 1983;4:421–433.
42. Peto J, Doll R, Hermon C, Binns W, Clayton R, Goffe T. Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. *Ann Occup Hyg.* 1985;29:305–355.
43. McDonald JC, McDonald AD, Armstrong B, Sebastien P. Cohort study of mortality of vermiculite miners exposed to tremolite. *Br J Ind Med.* 1986;43:436–444.
44. de Klerk NH, Armstrong BK, Musk AW, Hobbs MST. Cancer mortality in relation to measures of occupational exposure to crocidolite at Wittenoom Gorge in Western Australia. *Br J Ind Med.* 1989;46:529–536.
45. Henderson VL, Enterline PE. Asbestos exposure: Factors associated with excess cancer and respiratory disease mortality. *Ann N Y Acad Sci.* 1979;117–126.
46. Berry G, Newhouse ML. Mortality of workers manufacturing friction materials using asbestos. *Br J Ind Med.* 1983;40:1–7.
47. Sebastien P, McDonald JC, McDonald AD, Case B, Harley R. Respiratory cancer in chrysotile textile and mining industries: exposure inferences from lung analysis. *Br J Ind Med.* 1989;46:180–187.
48. Dement JM. Carcinogenicity of chrysotile

asbestos: a case control study of textile workers. *Cell Biol Toxicol.* 1991;7:59–65.
49. Tolbert P, Eisen E, Pothier LJ, Monson RR, Hallock MF, Smith TJ. Mortality studies of machining-fluid exposure in the automobile industry, II: risks associated with specific fluid types. *Scand J Work Environ Health.* 1992;18:351–360.
50. Dement JM and Wallingford KM. Comparison of phase contrast and electron microscopic methods for evaluation of occupational asbestos exposures. *Appl Occup Environ Hyg.* 1990;5:242–247.
51. *Vital Statistics of the United States, 1989,* Vol II—Mortality, Part B. Hyattsville, Md: National Center for Health Statistics; 1992. DHHS publication PHS 92-1102.
52. Cullen MR and Baloyi RS. Chrysotile asbestos and health in Zimbabwe, I: analysis of miners and millers compensated for asbestos-related diseases since independence (1980). *Am J Ind Med.* 1991;29:161–169.
53. Begin R, Gauthier J, Desmeules M, Ostiguy G. Work-related mesothelioma in Quebec, 1967–1990. *Am J Ind Med.* 1992;22: 531–542.
54. McDonald JC, McDonald AD. Chrysotile, tremolite and mesothelioma. *Science.* February 10, 1995;267:775–776.
55. Peto J, Seidman H, Selikoff IJ. Mesothelioma mortality in asbestos workers: implications for models of carcinogenesis and risk assessment. *Br J Cancer.* 1982;45:124–135.
56. Hughes JM, Weill H. Asbestos Exposure-Quantitative Assessment of Risk. *Am Rev Respir Dis.* 1986;133:5–13.
57. Sluis-Cremer GK, Liddell FDK, Logan WPD, Bezuidenhout BN. The mortality of amphibole miners in South Africa, 1946–80. *Br J Ind Med.* 1992;49:566–575.
58. Davis JMG, Beckett ST, Bolton RE, Collins P, Middleton AP. Mass and number of fibres in the pathogenesis of asbestos-related lung disease in rats. *Br J Cancer.* 1978;37:673–688.
59. Davis JMG, Addison J, Bolton RE, Donaldson K, Jones AD, Smith T. The pathogenicity of long versus short fibre samples of amosite asbestos administered to rats by inhalation and intraperitoneal injection. *Br J Exp Pathol.* 1986;67:415–430.
60. Davis JMG, Jones AD. Comparisons of the pathogenicity of long and short fibres of chrysotile asbestos in rats. *Br J Exp Pathol.* 1988;69:717–737.
61. Davis JMG, Addison J, Bolton RE, Donaldson K, Jones AD, Miller BG. Inhalation studies on the effects of tremolite and brucite dust in rats. *Carcinogenesis.* 1985;6: 667–674.
62. Coffin DL, Cook PM, Creason JP. Relative mesothelioma induction in rats by mineral fibers: comparison with residual pulmonary mineral fiber number and epidemiology. *Inhal Toxicol.* 1992;4:273–300.
63. Timbrell V, Gibson JC, Webster I. UICC standard reference samples of asbestos. *Int J Cancer.* 1968;3:406–408.
64. Wagner JC, Berry G, Timbrell V. Mesotheliomata in rats after inoculation with asbestos and other materials. *Br J Cancer.* 1973;28:173–185.
65. Stanton MF, Layard M, Tegeris A, et al. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. *J Natl Cancer Inst.* 1981;67: 965–975.
66. Mossman BT. Mechanisms of asbestos carcinogenesis and toxicity: the amphibole hypothesis revisited. *Br J Ind Med.* 1993;50: 673–676. Letter.
67. Weinberg ED. Association of iron with respiratory tract neoplasia. *J Trace Elem Exp Med.* 1993;6:117–123.
68. *Kirk-Othmer Encyclopedia of Chemical Technology.* 3rd ed. Vol 15. New York, NY: John Wiley & Sons; 1981:639.
69. Davis JMG. Mineral fibre carcinogenesis: experimental data relating to the importance of fibre type, size, deposition, dissolution, and migration. In: Bignon J, Peto J, Saracci R, eds. *Non-occupational Exposure to Mineral Fibers.* Lyon, France: International Agency for Research on Cancer; 1989:33–45.
70. Baloyi R. *Exposure to Asbestos among Chrysotile Miners, Millers and Mine Residents and Asbestosis in Zimbabwe.* Helsinki, Finland: University of Kuopio; 1989. Dissertation.
71. Peto J. Fibre carcinogenesis and environmental hazards. In: Bignon J, Peto J, Saracci R, eds. *Non-occupational Exposure to Mineral Fibres.* Lyon, France: International Agency for Research on Cancer; 1989:457–470.
72. *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices.* Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists; 1994–1995.