differentiative expression.... [M]yeloid leukemogenesis is a multistep process during which a clone of cells acquires a succession of abnormalities that ultimately leads through subclonal evolution to overt leukemia.

Philip J. Fialkow, Clonal Evolution of Human Myeloid Leukemias, GENES AND CANCER 215 (1984). With this language, Fialkow seems to recognize that AML has several forms and that only one form is like CML in developing clonally in stem cells. He also seems to suggest that myeloid, in contrast to lymphoid, leukemia undergoes a multistep process, thus recognizing several distinctions among various types of leukemia. We fail to read this passage as providing sufficient support for Teitelbaum's contention that all types of leukemia are so closely related in terms of how and why they develop that they can be treated interchangeably. The Austins have not indicated whether Teitelbaum's theory can be or has been tested and have not directed us to any location in the record where other scientists espouse this theory.

*291 The Austins cite the testimony of Kerr-McGee's toxicology expert, Dr. Gary Krieger, who testified that benzene can affect the pluripotential stem cell. However, Krieger testified that benzene can attack at a variety of places and that benzene-related leukemias have been recognized at slightly more differentiated cell levels. He testified that while benzene affects the pluripotential stem cell, it has never been shown to cause the lesion called the Philadelphia Chromosome, which he opined is what causes CML. Furthermore, to refute Kerr-McGee's theory that benzene does not cause the development of the Philadelphia Chromosome, the Austins point only to Fialkow's paper, in which Fialkow merely suggests that the initial hit or mutation occurs before the Philadelphia Chromosome develops. The Austins give no further explanation regarding the possibility that the Philadelphia Chromosome may cause CML independently of other possible causes.

The Austins also contend that the epidemiological studies' authors' grouping choices demonstrate that the different leukemia cell-types are so closely related in terms of how and why they develop that they can be treated interchangeably. They cite Dr. Otto Wong's epidemiological study, [FN9] in which Wong stated that based on the conclusion that transformation events occur at an early multipotent stem cell level, it was appropriate to combine lymphoma and leukemia in some of his analyses. But Wong's opinion is not so one-sided. Despite the similarity between lymphoma and leukemia that Wong recognized in his study, Wong testified at the Robinson/Havner hearing that leukemia consists of different types of diseases that have different patterns and different etiological agents. Simply because the authors group their findings under broad headings like "lymphatic and hematopoietic cancers" does not mean that the authors believe all leukemias are derived from the same source. In one study, the author, recognizing that very few studies reviewed medical records or histologic data to ensure correct categorization of diseases, expressed a need for more accurate categorization. Travis, supra, at 92.

FN9. O. Wong, An Industry-Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene, 44 BRITISH JOURNAL OF INDUSTRIAL MEDICINE 365 (1987).

Additionally, we find persuasive the rulings on a similar issue in two cases tried in the federal courts. In the cases of Mitchell v. Gencorp Inc., 165 F.3d 778 (10th Cir.1999), and Chambers v. Exxon Corp., 81 F.Supp.2d 661 (M.D.La.2000), the plaintiffs sought to establish that the exposure of the deceased worker to benzene or chemicals defined as benzene derivatives caused him to contract CML. In both cases the courts excluded the plaintiffs' scientific evidence because it was not shown to be reliable. Although the scientific studies relied on in those cases are not the same as those relied on in our case, they all suffer from the same defects, inadequacies, and inconclusiveness. In those cases the courts found

that the experts' estimates and conclusions were little more than guesswork, and that the experts' assurances that the methodology and supporting data were reliable would not suffice. In fact, in Chambers the court pointed out that while no study found a statistically significant association between CML and exposure to benzene, to the contrary, there were several scientifically-significant studies that demonstrated no association between benzene exposure and the development of CML. Chambers, 81 F.Supp.2d at 664-65.

The Austins concede that there is insufficient reliable data to establish an association between exposure to benzene and CML. In their brief to this Court, they state that CML is a relatively rare disease and "there simply are not enough cases of the disease for epidemiologists to generate a statistically- significant relative risk. .... No benzene-exposed population is significantly large to generate the numbers ... required to create statistical significance." [292] A similar concession was made by the plaintiffs in Chambers. 81 F.Supp.2d at 664 n. 3. The Austins also state, "Epidemiology as a science is ... handcuffed by the persistent problem of misclassification of disease, and that problem is particularly relevant in the context of CML." This lack of scientific evidence is unfortunate, but as stated by the Texas Supreme Court in Havner, "Our legal system requires that claimants prove their cases by a preponderance of the evidence." Havner, 953 S.W.2d at 728. The lack of reliable scientific evidence cannot be an excuse for imposing liability without proof of causation.

[21][22][23] Likewise, the Austins did not offer scientifically reliable evidence of specific causation, i.e., that Austin was exposed to benzene at all, or if he was, to what degree or level. Specific causation requires that a plaintiff show that the injured person is similar to those in the epidemiological studies, that he was exposed to the same substance, and that the exposure or dosage levels were comparable to or greater than those in the studies. Havner, 953 S.W.2d at 720. The Austins concede that none of the actual mineral spirits used by Austin was ever tested for benzene. The Austins' experts only assumed that because most solvents contain benzene, the solvents Austin used also contained benzene. But this is inadequate to show that there was any exposure, and certainly it is inadequate to show a level of exposure. It is fundamental that a plaintiff in a toxic tort case must prove the levels of exposure that are dangerous to humans generally, and must also prove the actual level of exposure of the injured party to the defendant's toxic substances. See id.; Mitchell, 165 F.3d at 781.

The Austins must show that benzene probably, or more likely than not, caused Austin's CML. See Havner, 953 S.W.2d at 720. In addition to showing general and specific causation, if there are other plausible alternative causes of CML that could be negated, the Austins must affirmatively exclude those causes with reasonable certainty. See id.; Robinson, 923 S.W.2d at 558.

Before he worked at Tuboscope and Sumrall, Austin held a job where he was a bystander to pipe inspection activities involving radiographic techniques. The job required that Austin wear a radiation badge that monitored the levels of radiation he received. Teitelbaum requested data regarding Austin's radiation exposure from his employee badge.

Teitelbaum suggested that radiation exposure could not have been an independent cause of Austin's CML, stating, "[T]he contributing cause [benzene exposure] stands whether we model it [radiation] or not." However, he also suggested that radiation may have been an alternative cause. He stated that he did not find any alternative cause, "other than the radiation issue," and he further testified, "Because radiation is always ... or potentially a 'one-hit' kind of experience, single ionization could cause a genetic change and remains a viable possibility...." Teitelbaum went on to opine that radiation exposure was unlikely or less likely than benzene to have caused

Austin's CML because of the size of the dose of radiation that Austin received. However, like the Austins' treatment of the Philadelphia Chromosome as an alternative cause of Austin's CML, the record does not contain a full explanation of the dose-size or the duration of Austin's radiation exposure, or a full explanation of the reason for Teitelbaum's decision to exclude radiation as a cause. Teitelbaum stated that he received Austin's badge but did not have data from which to model a radiation dose, suggesting at best that the dose of radiation was insignificant.

[24] We conclude that the Austins' scientific evidence does not adequately exclude exposure to radiation as a cause of CML. The Austins concede that exposure to radiation is a recognized cause of leukemia generally. Yet, their evidence only assumes that Austin, who admittedly "293 worked in an atmosphere that exposed him to radiation, did not receive sufficient exposure to cause him to develop leukemia. These assumptions, in turn, are based on "estimates" made by the Austins' experts. These estimates, however, are not based on scientifically reliable data. As noted in Mitchell, 165 F.3d 778, absent supporting scientific data, estimates and assumptions are "little more than guesswork. Guesses, even if educated, are insufficient to prove the level of exposure in a toxic tort case." Id. at 781.

After thorough and careful review of the Austins' contentions, as well as the record testimony and exhibits they cite, we conclude that the Austins have failed to demonstrate the reliability of their scientific evidence as to either general or specific causation. They also have failed to exclude other plausible causes with reasonable certainty. We conclude that the trial court acted within its discretion in excluding the Austins' causation evidence on the basis that it failed to satisfy the requirements of Robinson and Havner. Accordingly, we affirm the judgment.

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CHRYSOTILE, TREMOLITE AND CARCINOGENICITY

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Abstract—It has been suspected for many years that amphibole fibres in the tremolite series, a low level contaminant of chrysotile asbestos, may contribute disproportionately to the incidence of mesothelioma and perhaps other exposure-related cancers. A cohort of some 11 000 Quebec chrysotile workers, 80% of whom have now died, provided the opportunity to examine this hypothesis further. An analysis was made of deaths from mesothelioma (21), cancers of the lung (262), larynx (15), stomach (99), and colon and rectum (76), in men employed by the largest company in Thetford Mines, with closely matched referents. Risks were estimated by logistic regression for these five cancers in two groups of mines—five mines located centrally and ten mines located peripherally; tremolite contamination had been demonstrated to be some four times higher in the former than in the latter. Odds ratios for work in the central mines were raised substantially and significantly for mesothelioma and lung cancer, but not for the gastric, intestinal or laryngeal cancer sites. In the peripheral mines, there was little or no evidence of increased risk for any of the five cancers. The hypothesis that, because of the difference in distribution of fibrous tremolite, cancer risks in the central area would be greater than in the periphery was thus substantiated. That the explanation may lie in the greater biopersistence of amphibole fibres than chrysotile is important in framing policies for the use and control of asbestos and is directly relevant to the selection of man-made mineral fibre substitutes. © 1997 British Occupational Hygiene Society. Published by Elsevier Science Ltd.

INTRODUCTION

Since the observation by Dr Chris Wagner 40 years ago of malignant mesothelial tumours in crocidolite miners and millers and their family contacts, but rarely in miners of chrysotile or amosite, the history of asbestos-related research has been dominated by efforts to assess the relative carcinogenicity of the main mineral fibre types (see McDonald and McDonald, 1996). While this aim was largely achieved for chrysotile in an extensive and continuing research program in the mines and mills of Quebec, and by numerous cohort studies of factory workers exposed to chrysotile only, until quite recently there had been no comparable data for crocidolite or amosite. Meanwhile, confusion was created by the inevitable difficulty of interpreting findings in workers usually exposed to amphibole–chrysotile mixtures in manufacturing and product use; this in turn gave rise to much bitter controversy. There were those investigators (the 'chrysophiles') who believed the evidence to show a major difference between the relatively low carcinogenicity of chrysotile and the much higher risk, particularly of mesothelioma, usually associated with amphibole exposure; others (the 'chrysophobes') concluded from much the same

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evidence that all types of asbestos were equally dangerous. These arguments seem likely to continue (for example see Smith and Wright, 1996).

During the past 20 years the suspicion has grown, at least among the chrysophiles, that the frequent contamination of chrysotile deposits by amphibole fibres in the tremolite series may contribute disproportionately to the carcinogenic effects of occupational exposure. Beginning in the 1970s, newly applied techniques for lung burden analysis revealed the unexpected finding that despite the overwhelming exposure of Quebec miners and millers to chrysotile, tremolite was usually the predominating fibre present at death (Pooley, 1976; Rowlands *et al.*, 1982). Wagner *et al.* (1982) reported that the carcinogenicity of tremolite in experimental animals was similar to that of the other fibrous amphiboles and in a study by Churg *et al.* (1984) of six cases of mesothelioma in Quebec mine workers tremolite was reported as the predominating fibre type. The fibrogenic and carcinogenic potential of fibrous tremolite was confirmed a few years later by both mortality and radiographic studies of American vermiculite miners and millers exposed to tremolite, but to no other type of asbestos. The risk of mesothelioma, lung cancer and pulmonary fibrosis among these men was many times higher than that experienced by Quebec chrysotile workers (Amandus *et al.*, 1988; Armstrong *et al.*, 1988). Later, carefully controlled case–referent studies of deaths from mesothelioma across Canada, with detailed lung burden analyses, showed that while tremolite was indeed the dominant fibre in cases from the Quebec mining area its aetiological contribution to cases elsewhere was probably fairly similar to that of amosite and of crocidolite (McDonald *et al.*, 1989).

Given that chrysotile and tremolite tend to occur together it has not been easy to assess separately their effects on mortality. Even in our Quebec mortality cohort, until recently the number of mesothelioma and lung cancer deaths was not large enough for a sufficiently detailed study. However, the most recent update of deaths in the cohort to the end of 1992 (see Liddell *et al.*, 1997) identified a much larger number of such cases among the 8000 deaths from all causes. From this total, 38 deaths were considered due to mesothelioma and it was estimated that some 65 deaths from lung cancer were in excess. Also important was the growing evidence that neither the risk of these two diseases nor the level of tremolite contamination was equally distributed across the Quebec mining region, both being higher at Thetford Mines than at Asbestos (McDonald *et al.*, 1994).

Of the 38 deaths from mesothelioma in the cohort, 33 were in miners and millers—25 from Thetford Mines and 8 from Asbestos, and the remaining 5 were in an associated asbestos products factory. Thetford Mines offered the best opportunity for study, partly because of the higher levels of tremolite thought to prevail there than at Asbestos but mainly because the industry at Thetford originally comprised 21 mining companies, some located centrally and the others at varying distances peripherally. Six of the 21 companies were small and independent: the remaining 15 had been amalgamated many years ago into a large complex where 80% of the cohort in the Thetford area had been employed.

In a preliminary study, (see McDonald and McDonald, 1995), the work histories of the 22 cases of mesothelioma in men who had been employed by the largest company at Thetford Mines were compared in detail with similar data for a large series of comparable referents. The total number of years worked by the case series

in the clearly definable group of five centrally located mines (area A) was six times greater than in 10 mines located peripherally (area B), whereas the ratio for the referent series was 1.5. That this difference might be related to the distribution of fibrous tremolite in the ore body was supported by observations made by Sébastien *et al.* (1989) of mineral fibres in lung tissue from 83 cohort members who had worked in the same mines and died from causes other than mesothelioma. In that investigation, the geometric mean concentration of mineral fibres 5 μm or more in length was for tremolite four times higher in area A than in area B, a difference of very high statistical significance ($p = 0.0002$), whereas for chrysotile it was lower in A than in B.

Although this preliminary study thus provided evidence of a strong geographical correlation between the distribution of tremolite and the incidence of mesothelioma, the question of risk in relation to duration and intensity of exposure in the two areas was not addressed, and in retrospect it was felt that the referent series had not been matched sufficiently closely. The present paper describes a study designed to test the question of risk not only for mesothelioma but also for lung cancer and other malignant diseases potentially associated with chrysotile exposure.

MATERIALS AND METHODS

Cases

The cohort of 10 918 men born 1891–1920 who had worked for a month or more in the chrysotile mines and mills of Quebec, included over 4^00 employed by the largest company in the region of Thetford Mines (Liddell *et al.*, 1997). Of these more than 80% had died by the end of 1992, giving the following numbers of cancer deaths for the current analysis: mesothelioma 22 (as before), lung 266, larynx 16, stomach 99, colon and rectum 79.

Referents

For each death in the five categories of malignant disease, referents were selected from men who had survived the case, closely matched individually for year of birth and age at first recorded employment in the industry. Ten referents were sought for each mesothelioma, four for each laryngeal cancer and one for each cancer of lung, stomach, colon or rectum. In three cases of mesothelioma only six, five and three adequately matched referents could be found. A total of nine cases (mesothelioma, one; lung cancer, four; laryngeal cancer, one; colon and rectum cancer, three) had to be eliminated from the analysis, usually because either the case himself or his only referent had had frequent changes of employment between areas A and B which had not been recorded. The number of cases analysed is shown in Table 1.

Analysis

From the detailed work histories for each subject, periods of employment in central (area A) or peripheral (area B) mines were calculated. Periods of service within 10 years of death of the case were excluded for all cases and referents; these exclusions were made to reduce dilution by periods of exposure generally believed to be aetiologically unimportant. For the mesothelioma cases and referents, the periods

Table 1. Odds ratios from conditional logistic regression analyses of matched case-referent sets of selected malignant disease deaths at Thetford Mines

Cause of death	No. of matched sets analysed	Central mines (Area A) OR*	(90% confidence interval)	Peripheral mines (Area B) OR*	(90% confidence interval)	Likelihood ratio comparing areas
Mesothelioma	21	2.55	(1.52–4.27)	1.11	(0.47–2.62)	4.50
Lung cancer	262	1.98	(1.53–2.57)	1.09	(0.78–1.51)	8.25
Laryngeal cancer	15	0.48	(0.15–1.56)	1.16	(0.38–3.55)	1.20
Stomach cancer	99	1.36	(0.86–2.16)	0.99	(0.56–1.75)	0.71
Colo-rectal cancer	76	1.18	(0.73–1.91)	0.85	(0.42–1.73)	0.48

*Based on 20 yr employment in central or peripheral mines derived as (odds ratio associated with one year of employment)[20].

were adjusted for the length of the working week, as fully described by Liddell *et al.* (1997). This was not done for the other cancers because the considerable amount of work required did not appear to be justified. Cases and referents were compared for years of employment in areas A and B by conditional logistic regression, and odds ratios were calculated with 90% confidence intervals.

The results are summarised in Table 1, from which it can be seen that the odds ratios for mesothelioma and lung cancer were raised quite substantially in relation to work in the central mines (area A) but not for work in the peripheral mines (area B). The differences in risks between the two areas are reflected in likelihood ratios, also in Table 1, which can be referred to the χ^2 distribution with 1 degree of freedom, implying *p*-values of approximately 0.03 for mesothelioma and 0.004 for lung cancer; that the latter is much the lower is probably a reflection of the larger number of subjects. Table 1 also shows there was little relationship between the other cancers (laryngeal, stomach or colo-rectal) and work in either area.

That the main findings do not arise from greater intensity of exposure in area A than in area B is demonstrated by the time-weighted average levels of exposure of the referents during the same period, namely for mesothelioma referents 17.4 million particles per cubic foot (mpcf) in area A and 16.3 mpcf in area B, and for lung cancer referents 15.1 and 20.7 mpcf, respectively. As each average has a large standard error, all four can be considered quite similar.

DISCUSSION

Our studies of Quebec chrysotile miners and millers have consistently shown little evidence of a cancer risk except at very high levels of exposure and conclusively only for lung cancer and mesothelioma; it is important to note that the evidence presented in this paper on the role of tremolite also applied only to these two diseases. With the exception of a cohort of asbestos textile workers in Charleston, South Carolina, where a high risk of lung cancer but not of mesothelioma was observed (McDonald *et al.*, 1983a; Dement *et al.*, 1994), this has been the experience of the many other cohorts exposed to chrysotile only, in marked contrast to the far more serious effects of work with amphiboles (crocidolite and amosite) or chrysotile–amphibole mixtures (Hughes, 1991; McDonald and McDonald, 1996). Tremolite is also an amphibole and, although its fibres are seldom used commercially, it has been shown in the several studies mentioned earlier in this paper to share much the same carcinogenic potential for lung and pleura as crocidolite. Our findings are thus plausible and consistent with the view that amphibole fibres are considerably more hazardous than chrysotile in man.

If the incidence of mesothelioma and of lung cancer resulting from exposure to commercial chrysotile is mainly attributable to low but varying levels of tremolite fibres, effective steps are needed to minimise such contamination. In the meantime it must be accepted that for practical purposes chrysotile asbestos, as used commercially, may contain low but varying concentrations of fibrous tremolite. The extent to which this increases the potential carcinogenicity of the commercial product must be kept in proportion. As stated earlier our most recent findings indicate that the excess mortality from malignant disease in our cohort, some 80% of whom had then died, amounted to 38 deaths from mesothelioma and some 65

from lung cancer (Liddell *et al.*, 1997). These men, born 1891–1920, had worked through years of very high dust exposure yet with no discernible effect on mortality from lung cancer below an accumulated exposure of about 1000 (fibres/ml)×years and no case of mesothelioma among over 4000 men employed for less than 2 years. At present-day levels of exposure to commercial chrysotile, whether or not contaminated with tremolite, the risk must be vanishingly small. Full reports on mortality from mesothelioma and from lung cancer in the cohort, with emphasis on the estimation of risk in relation to quantitative and qualitative aspects of exposure, will be published shortly.

The discrepant risks of lung cancer in textile workers are not explained by our findings but tend to suggest that the factors responsible were specific to asbestos textile processes, not only in Charleston, South Carolina, but also in Mannheim, Pennsylvania (McDonald *et al.*, 1983b) and in Rochdale, England (Peto *et al.*, 1985), where important amounts of crocidolite were incorporated in the process. All three textile plants showed a similar high level of lung cancer risk, with few cases of mesothelioma in Charleston but many in both Mannheim and Rochdale.

The far greater durability in lung tissue of amphibole than chrysotile fibres underlines the importance of biopersistence in carcinogenicity and of avoiding this quality when selecting man-made fibres for industrial use.

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Pathology of Occupational Lung Disease

❖ Second Edition

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Intraperitoneal and Intrapleural Inoculation Studies. Some investigators have adopted the technique, originally used by Stanton et al. [12], of instilling fibers into the peritoneal or pleural cavities of experimental animals and observing tumor incidence. The most extensive studies were done by Pott et al. [13, 14] using intraperitoneal instillation of fibers in rats.

The results of such studies are in a general sense similar to those seen with in vitro monolayer cultures. Virtually all fibers produce mesothelioma. The effect depends on dose and to a certain extent fiber length. Only fibers that are extremely soluble fail to produce tumors. Fibers that on the basis of human epidemiologic studies are thought to produce quite different tumor incidences—for example, chrysotile and amosite or crocidolite asbestos—produce essentially the same tumor incidence by intraperitoneal inoculation.

Although intrapleural and particularly intraperitoneal inoculation tests form the basis for the classification of glass fibers as possible human carcinogens [15, 16], they are extremely controversial and have been the subject of considerable criticism [5–10, 17]. The intraperitoneal test in particular appears to depend on a marked and very nonspecific sensitivity of the rat peritoneum to foreign materials. This sensitivity is so extreme that even instillation of saline has been shown to produce a 6% incidence of mesotheliomas [5], compared with large control series of untreated rats in which the incidence of peritoneal mesothelioma is less than 1% [18]. Other fibrous and nonfibrous particulates that have never been suggested to be mesothelial carcinogens in man, for example calcium–sodium metaphosphate, gypsum, sepiolite, basalt, silicon carbide, and even iron oxide, also produce increased incidences of mesothelioma in this system [14].

Use of inoculation tests also bypasses normal fiber defense mechanisms, which prevent most fibers, particularly relatively soluble fibers such as glass, from ever reaching the pleura. These tests also allow extremely long fibers, which may be highly carcinogenic, to reach the pleura by a totally nonphysiologic route, whereas such fibers could never reach the pleura or even the lung parenchyma by inhalation. Moreover, the doses used in inoculation tests often are massive. Last, inoculation tests by definition produce only mesotheliomas, and although some claim that this indicates the potential of the fibers to cause carcinomas [13, 14], carcinoma of the lung has numerous other well defined etiologies, and probably is associated (at least in the rat) with parenchymal fibrosis. There is no rational mechanistic basis for using mesothelioma incidence by intraperitoneal inoculation to predict the parenchymal carcinogenicity of fibers. For these reasons most reviewers [5–10, 17] have concluded that inoculation tests are not suitable for predicting the carcinogenicity of fibers in man.

Inhalation and Intratracheal Instillation Tests. There are numerous in vivo studies on MMVF, most using long-term inhalation and a few using intratracheal instillation. Much of this material has been reviewed recently [7, 8, 19]. The most extensive and carefully designed studies are those summarized by Bunn et al. [19] and described in more detail in Hesterberg et al. [20] and others [21–23]. In these experiments rats were exposed by inhalation to glass fibers, slag wool, rock wool, and refractory ceramic fibers at concentrations up to about 250 fibers per cubic centimeter for periods up to 24 months. Of note are the facts that the MMVF fiber sizes and exposure levels in these studies were roughly the same and that analysis of lung content revealed high burdens, indicating plainly that the fibers were respirable.

Table 11.1 summarizes fibrogenicity and carcinogenicity of the various MMVF fiber types as determined from these and other published experiments.

as low as 37 f-yr/cc (this level produced a 1% prevalence of crepitations) and is consistent with the predictions made above. During the hearings, several witnesses stressed the range of physical and mental disability/impairment which may occur long before even radiologic evidence of disease appears. Typical of these comments were those made by Dr. Irving Selikoff of the Mount Sinai School of Medicine. He stated:

> So, what you're seeing on x-ray is always very much less than is really present pathologically. So that, when you see a positive x-ray, there's a fair amount there in the lung . . . I've seen people with comparatively little on x-ray, who can't walk across a room. But by and large, all it means is that there's been scarring [TR. 7/2, p. 170].

While several participants commented in general on the risk of asbestosis, there was little direct comment on OSHA's quantitative estimates of risk. Hence, for these revised rules, OSHA has relied on the models developed for the proposal to predict the risk of asbestosis at the new PEL of 0.2 f/cc. Using OSHA's best estimate of risk, that from the Finkelstein data, OSHA predicted that exposure over a working lifetime to the 2 f/cc level will result in approximately a 5% incidence of asbestosis. Reducing the exposure to 0.2 f/cc would result in a lifetime incidence of asbestosis of 0.5%. While OSHA did not make predictions of risk at levels below 0.5 f/cc in the proposed rules, testimony received during the rulemaking increases OSHA's confidence that the Agency's estimates of risk at 0.2 f/cc are valid and reasonable. This is due primarily to the comments noting the validity of the model in the low dose region. Given the difficulties in accurately diagnosing cases of asbestosis and the fact that OSHA's estimates only take the risk of disabling asbestosis into account, OSHA believes that the Agency's estimates may be underestimates of the true risk of asbestosis to exposed workers.

VI. Significance of Risk

As discussed above in Section III (Pertinent Legal Authority), the Supreme Court in the Benzene case (*Industrial Union Department, AFL–CIO* v. *American Petroleum Institute* 448 U.S. 607, (1980)) ruled that, prior to the issuance of a new or revised standard regulating occupational exposures to toxic materials, OSHA must make a determination that a "significant" health risk exists and that the new standard will reduce or eliminate that risk. OSHA's analytical approach to making a determination that a significant risk of material impairment exists from exposure to hazardous workplace chemicals takes into consideration a number of factors that are consistent with recent court interpretations of the OSH Act and rational, objective policy formulation. As prescribed by Section 6(b)(5) of the Act, OSHA examines the body of "best available evidence" on the toxic effects of hazardous chemicals to determine the nature and extent of possible health consequences resulting from exposure to the hazardous agent in question. Quantitative risk assessments are conducted, where possible, and the results are considered along with other relevant information, such as the nature and severity of the health consequences, to determine whether a hazardous agent poses a significant risk to workers at the current permissible exposure level. The Agency also determines whether a reduction in the permissible exposure level for the hazardous agent will substantially reduce that risk.

The Court gave some general guidance to the Agency for arriving at findings of the significance of an occupational health risk. It recognized that the Agency's determination that a particular level of risk is "significant" will be based largely on policy considerations (*IUD* v. *API*, 448 U.S. 655, 656, n. 62). To illustrate how one may make a determination from quantitative information that a health risk is significant, the Court stated as follows:

> It is the Agency's responsibility to determine in the first instance what it considers to be a "significant" risk. Some risks are plainly acceptable and others are plainly unacceptable. If, for example, the odds are one in a billion that a person will die from cancer by taking a drink of chlorinated water, the risk clearly could not be considered significant. On the other hand, if the odds are one in a thousand that regular inhalation of gasoline vapors that are 2% benzene will be fatal, a reasonable person might well consider the risk significant and take appropriate steps to decrease or eliminate it (*IUD* v. *API* 448 U.S. at 655).

Although the Court's example is based on a quantitative expression of the risk, the Court indicated that the significant risk determination required of OSHA is not "a mathematical straitjacket," and that "OSHA is not required to support the finding that a significant risk exists with anything approaching scientific certainty." "A reviewing court [is] to give OSHA some leeway where its findings must be made on the frontiers of scientific knowledge [and] . . . the Agency is free to use conservative assumptions in interpreting the data with respect to carcinogens, risking error on the side of overprotection rather than underprotection." (448 U.S. at 655, 656)

OSHA has followed these guidelines in making a determination that the risk of material health impairment resulting from occupational exposure to asbestos is significant. The epidemiological and toxicological evidence and testimony presented in the November notice and in Section IV (Health Effects) of this preamble clearly show that exposure to asbestos is carcinogenic to humans and additionally causes disabling fibrotic lung disease. Lung cancer constitutes the greatest health risk to asbestos workers; in some occupational cohorts, this disease has been responsible for more than half of the excess mortality from asbestos exposure. Malignant mesotheliomas of the pleura and peritoneum, which are extremely rare among non-exposed persons, have been conclusively linked with asbestos exposure. Some studies of asbestos-exposed workers have also shown increases in mortality from gastrointestinal and other types of cancer. It has been known for years that exposure to asbestos is the only known cause of asbestosis, a progressive, fibrotic lung disease causing effects ranging from shortness of breath during exertion to complete disability, respiratory and cardiac failure, and death. OSHA's determination that the health risks from asbestos exposure is significant is based, in part, on the irreversible and ultimately fatal nature of these diseases, particularly of lung cancer and mesothelioma.

The finding that a significant risk exists is primarily supported by OSHA's quantitative risk assessment, which is based on studies of asbestos-exposed worker populations. OSHA's risk assessment (discussed in Section V of this preamble) estimates that 84 excess cancer deaths (including those from lung and gastrointestinal cancer and mesothelioma) will occur among 1,000 workers exposed at the existing permissible exposure limit of 2 f/cc for 45 years, a working lifetime. The estimates of mortality risk from mesothelioma, lung cancer, and gastrointestinal cancer are 16, 44, and 4 excess deaths, respectively, per 1,000 workers exposed for 45 years at 2 f/cc.

OSHA also estimated the risk of lung cancer, mesothelioma, and gastrointestinal cancer for 20-year and 1-year durations of exposure to asbestos at 2 f/cc. From this analysis, OSHA estimates that the risk from all asbestos-related cancers among workers exposed from 20 years to 2 f/cc is 44 excess deaths per 1,000 workers. The estimated cancer risk from all cancers among workers exposed to 2 f/cc for one year

1994 OSHA Standards. Preamble:

. . . .

There are at least three reasons for OSHA's decision not to separate fiber types. First. OSHA believes that the evidence in the record supports similar potency for chrysotile and amphiboles with regard to lung cancer and asbestosis. The evidence submitted in support of the claim that chrysotile asbestos is less toxic than other asbestos fiber types is related primarily to mesothelioma. This evidence is unpersuasive, and it provides an insufficient basis upon which to regulate that fiber type less stringently.

As OSHA explained in the preamble to the 1986 standards.

* * * to summarize the data on risk differential by asbestos fiber type. human epidemiological studies have suggested that occupational exposure to amphiboles is associated with a greater risk of mesothelioma than is exposure to chrysotile * * * No clear risk differential for lung cancer or other asbestos-related disease has been demonstrated by epidemiological studies. Animal experiments, however, have indicated that chrysotile is a more potent carcinogen than amphiboles when administered by inhalation or intrapleural injection * * * (51 FR at 22628).

OSHA agreed with the testimony of Dr. Davis. who stated that "the evidence cannot answer * * * with certainty * * * if "one fiber * * * of amphibole (is) more dangerous than one fiber * * * of chrysotile." (Ibid).

Second. as stated in the 1986 asbestos standard, even if OSHA were to accept the premise (which it does not), that chrysotile may present a lower cancer risk than other asbestos fiber types. occupational exposure to chrysotile asbestos still presents a significant risk of disease at the revised PEL (See 51 FR 22649. 22652). In particular. asbestosis. the disabling and often fatal fibrosis of the deep portions of the lung. is caused by exposure to all types of asbestos. The evidence on this is strong and no new information has been presented to contradict this. As stated above, OSHA estimated asbestosis risks at 0.2 f/cc exposures as an unacceptably high 5 cases per 1000 workers. Thus. asbestosis risks alone justify the regulation for chrysotile.

Lung cancer risks associated with chrysotile exposures are also high -- 6.7 lung cancer deaths per 1000 workers exposed to 0.2 f/cc for a full working lifetime. OSHA notes that SBA's witness. Dr. K. Crump acknowledged that "(t)here's not a clear difference. * * * even in humans. for lung cancer * * * in terms of distinguishing the potency of amphiboles vs. chrysotile." (Tr. 4220).

Third. the record shows that employees are likely to be exposed to mixed fiber types at most construction and shipyard industry worksites most of the time. Assigning a higher PEL to chrysotile would present the Agency and employers with analytical difficulties in separately monitoring exposures to different fiber types. Thus. regulating different fiber

types at differing levels, would require more monitoring all the time and would produce limited benefits (51 FR 22682).

Consequently, OSHA believes that its conclusion to treat all asbestos fibers as having a similar potency in the occupational setting remains valid. Most of the evidence submitted to the remand rulemaking duplicated evidence submitted to the 1986 standards record, or was cumulative to the earlier body of evidence. For example AIANA appended its 1988 submission to the EPA, consisting of numerous studies and reports. Some of these documents were considered by OSHA in the prior rulemaking. There, OSHA had stated that the 1983 Berry and Newhouse study of friction materials manufacturing workers which found nonsignificant increases in lung cancer mortality, was inconsistent with other studies showing that low level asbestos exposure resulted in excess lung cancer mortality, because of the relatively short follow up period used (51 FR 22618).

Other studies involved lung burden analyses of mesothelioma victims, apparently showing that the pulmonary content of chrysotile was within the range of the general population, whereas amphibole content was significantly elevated compared to the general population (see e.g. Churg, Malignant Mesothelioma in British Columbia in 1982, Cancer, 2/85, 672). OSHA noted in the preamble to the 1986 rule, that there is a difference in tissue retention which would account for the autopsy results and cited a study by Glyseth et al. (Doc. 33-C, Ex. 312) which supported that explanation. OSHA also noted that "the differential lung retention of various fiber types has been demonstrated in animals," citing a study by Wagner which found that animals exposed to chrysotile fibers developed lung cancer even though a smaller amount of chrysotile was retained in the lung compared to similar tests with amphiboles.

Dr. Weill believed that "these differences in tissue persistence may wholly or partially explain the observations [that exposure to amphiboles are associated with a higher prevalence of mesothelioma] in human * * * population * * *. Non-confirmation of fiber type differences in animal experiments may be related to the much shorter life span * * * [of experimental animals, which would not allow] the effects of varying tissue-persistence to be expressed" (Doc. 33-C, Ex. 99, p.18; 51 FR 22628). Therefore OSHA had reviewed and evaluated in the earlier rulemaking a portion of the evidence submitted by proponents of differential regulation of fiber types, and had rejected the claim that chrysotile should be regulated less stringently.

Some new evidence on the issue of differential risks of asbestos fiber types was submitted by both supporters and detractors of that theory.

In support of the position that chrysotile asbestos exposure is equivalent in risk to amphibole asbestos exposure, BCTD submitted studies which indicated excess mesothelioma cases in workers exposed solely to chrysotile asbestos (see Ex. 119 C, 1-136, 125, Att.6, 143 Att C, 143 Att. D1. In support of the opposing claim that chrysotile has reduced carcinogenic potential, AIANA and SBA submitted additional evidence. For example, AIANA submitted the World Health Organization's 1989 working report which recommended that the

exposure limit for chrysotile should be reduced to 1 f/cc or below (8 hour TWA), where it was recommended that exposure to crocidolite and amosite asbestos be prohibited (Ex. 21 A, p. 9). In particular, two papers by Mossman, et. al. are cited as the basis for the claim that a scientific "consensus" believes that chrysotile carries a reduced carcinogenic risk (Ex. 1-153, 151). Thus ALANA states that "since OSHA issued its 1984 asbestos risk assessment, the scientific consensus that chrysotile asbestos poses lesser risks has solidified" (Ex. 142 at 3).

However, OSHA notes that various participants in this rulemaking, including NIOSH and Dr. Nicholson, disputed the existence of such a consensus. Dr. Nicholson and others including Dr. Landrigan, in a letter to Science, (Ex. 1-155), dispute various interpretations of data in Mossman et al.'s paper, and challenge the conclusion that chrysotile asbestos carries little cancer risk. Nicholson et al, point out that human studies show excess lung cancer risk that is proportionate to exposure across all fiber types, and that animal tests confirm these relationships. OSHA believes that the scientific community has not achieved "consensus" on these issues.

Among the studies submitted in support of the lowered risk of chrysotile asbestos, are those of Churg, and others showing that the lung burden of mesothelioma victims is predominantly amphibole, even though high chrysotile exposure levels were reported. As noted above, this line of argument was presented in the earlier asbestos rulemaking, and OSHA had concluded that lung burden studies are inconclusive. Additional response to this argument is provided by Dement who notes that "(t)he biological significance of post-mortem lung fiber burden data has yet to be established. These data are not useful as a predictor of disease for several reasons. Chrysotile is known to split longitudinally and partially dissolve in the lung whereas amphiboles remain in the lungs for years without significant dissolution * * *. Measurements of tissue fiber burdens many years after first exposure may bear no relationship to the carcinogenic events which likely have taken place many years before clinical manifestation of cancer." (Ex. 1-273) BCTD pointed out in its post-hearing brief, that "Dr. Landrigan testified, while the observation that chrysotile does not last as long in the lungs as other forms of asbestos is not new knowledge (Tr. 1074), there is recent evidence that chrysotile is "the most effective of the three major fiber types at migrating to the pleura, that it is present in substantial amounts in pleural plaques and mesotheliomas, even in circumstances where it is not present or minimally present in the lungs themselves" (Tr. 1074).

The Agency also notes that the HEI report, in summing up its discussion of its literature search of studies examining the issue of the relative potency of chrysotile in inducing mesothelioma, stated: "(t)he evidence that chrysotile rarely causes pleural mesothelioma is not conclusive "* * * and concluded that the absence of mesothelioma in one of the "two cohorts of heavily exposed asbestos workers who worked only with chrysotile * * * seems likely to be due at least in part to chance" (Ex. 1-344 p. 6-23).

HEI concluded that "the mesothelioma risk for chrysotile was an issue of disagreement: some members of the Literature Review Panel held the view that a lower estimate should be

recommended. as it would be more consistent with available data. The crucial issues. neither of which can be resolved unequivocally. are (1) what proportion of the mesotheliomas observed in groups such as the U.K. textile workers and the U.S. insulation workers were caused by their exposure to crocidolite or amosite: and (2) whether the best general estimate of the ratio of mesothelioma to excess lung cancer caused by chrysotile is provided by the Quebec miners and millers (about 1:4 or 1:5). or by the South Carolina textile workers handling Quebec fiber (zero)" (Ex. 1-344 p. 6-32).

Thus. although there is some evidence linking chrysotile to a lower mesothelioma rate than some amphibole fiber types. OSHA believes that there is insufficient evidence to show that chrysotile does not present a significant mesothelioma risk to exposed employees. Furthermore. the major disease linked to asbestos exposure, lung cancer. occurs at the same frequency among employees exposed to equivalent doses of chrysotile or to amphibole asbestos fiber types. Indeed. evaluation of all of the evidence indicates that chrysotile asbestos presents a similar significant risk of lung cancer and asbestosis as other forms of asbestos. Since these adverse health effects constitute the majority of diseases related to asbestos exposure. OSHA is still of the opinion that chrysotile exposure should be treated the same as other forms of asbestos.

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NONOCCUPATIONAL EXPOSURE TO CHRYSOTILE ASBESTOS AND THE RISK OF LUNG CANCER

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ABSTRACT

Background Heavy industrial exposure to asbestos causes lung cancer and mesothelioma, but it remains unknown whether much lower environmental exposure to asbestos also causes these cancers. Nevertheless, regulatory agencies, including the Environmental Protection Agency (EPA), have assessed the risk of lung cancer by extrapolating known risks from past industrial exposure to asbestos to today's much lower environmental asbestos levels (roughly 100,000 times lower). We also tested the EPA's model for predicting the risk of asbestos-induced lung cancer in a population of women with relatively high levels of nonoccupational exposure to asbestos.

Methods Mortality among women in 2 chrysotile-asbestos–mining areas of the province of Quebec was compared with mortality among women in 60 control areas, and age-standardized mortality ratios were derived. With the help of an expert panel, we estimated past exposure to asbestos among women in the mining areas and used these data with the EPA's model to predict the relative risk of lung cancer. We then compared this prediction with the observed mortality ratios.

Results On the basis of the estimated exposure in the asbestos-mining areas, a relative risk of death due to lung cancer of 2.1 was predicted by the EPA's model, amounting to about 75 excess deaths from lung cancer in this population. By contrast, we calculated a standardized mortality ratio of 1.0 and a standardized proportionate mortality ratio of 1.1 ($P>0.05$), suggesting that there were between 0 and 6.5 excess deaths from lung cancer among the women with nonoccupational exposure to asbestos. Seven deaths from pleural cancer were observed (relative risk, 7.62; $P<0.05$).

Conclusions We found no measurable excess risk of death due to lung cancer among women in two chrysotile-asbestos–mining regions. The EPA's model overestimated the risk of asbestos-induced lung cancer by at least a factor of 10. (N Engl J Med 1998; 338:1565-71.)

ASBESTOS is a commercial group of strong, ductile, and fire-resistant mineral fibers. These properties, which differ among different mineralogic types of asbestos, strongly affect its in vivo persistence and toxicity.[1-3] Chrysotile asbestos, which constitutes about 99 percent of airborne asbestos fibers in the general environment, is cleared much more rapidly from the lung than amphibole asbestos.[3,4]

It has been recognized for several decades that exposure to asbestos at high levels, as was common among asbestos workers in the first half of this century, can cause lung cancer and mesothelioma of the pleura and peritoneum.[5] Among asbestos workers, nearly all mesotheliomas are induced by exposure to asbestos, whereas most lung cancers are attributable to smoking. Yet because mesothelioma is so rare, asbestos-induced cases of lung cancer greatly outnumber cases of mesothelioma among asbestos workers.[5-12]

In the 1980s, after labor-union campaigns and governmental regulations had greatly reduced occupational exposure to asbestos, public attention turned to environmental exposure.[13] Pressed to recommend preventive regulations and remedial measures, public health authorities assessed the risks of asbestos-induced cancers in the general population on the basis of occupational data.[5-12] The validity of such estimates of risk has been questioned for several reasons.[14-22] Extrapolations were made to environmental exposure to asbestos at levels that were 1/100,000 of those to which workers had been exposed in the past. The amphibole content of airborne dust containing asbestos (aerosols) is much lower in the general environment now than in historical occupational settings. In addition, past studies of occupational

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exposure to asbestos were methodologically limited, dose–response estimates varied by a factor of 1000 among studies, and estimates of the risk of asbestos-induced cancer have not been validated in nonoccupationally exposed populations.

We tested the Environmental Protection Agency's (EPA's) dose–response model for asbestos-related lung cancer in a population exposed to asbestos at levels intermediate between those encountered by asbestos workers and those encountered by today's urban populations. A small region of the province of Quebec, Canada, produced most of the world's asbestos until 1954 and remains the world's largest exporter of asbestos. Between 1891 and 1980, asbestos-dust emissions and fallout were usually visible. Asbestos aerosols were similar mineralogically to those found in cities today; more than 98 percent were chrysotile.[25] Our study was restricted to women in order to exclude most asbestos workers.[24] In contrast to previous studies of general populations,[25,26] we estimated levels of exposure to asbestos in order to quantify the relation between asbestos and lung cancer. We used data obtained from death certificates, which are adequate to study the risk of lung cancer but not that of mesothelioma.[27,28] Mesotheliomas are currently being investigated in a separate study.

METHODS

The study comprised three distinct components, a mortality study to measure the actual relative risk of death due to lung cancer and other causes, a historical exposure assessment, and a risk assessment to predict the relative risk of lung cancer on the basis of the exposure assessment and the EPA's risk model. We assumed, as in the EPA's risk-assessment model, that the risk of death due to lung cancer was nearly identical to the risk of lung cancer — a commonly accepted approximation for diseases in which survival is short.

Mortality Study

We determined the number of deaths that occurred between 1970 and 1989 among women at least 30 years of age who lived in 2 chrysotile-asbestos–mining areas or 60 reference areas in the province of Quebec. An area was defined as a group of contiguous municipalities with a total population of at least 4500. The areas where the population was exposed to asbestos were Thetford Mines (population, 29,093 in 1981) and Asbestos (population, 14,225); these two areas comprised eight towns, of which three (Thetford Mines, Black Lake, and Asbestos) contained nearly all the asbestos mines and mills. The residents of these areas lived within 10 km of a mine or mill, and 80 percent lived within 4 km. Among the other 65 areas in Quebec, 4 large urban centers and 1 shipbuilding area were excluded. The remaining 60 reference areas were spread across the province and had populations ranging from 8000 to 41,000 (total population, 1,375,370 in 1981).

To compute the relative risk of death due to specific causes in the asbestos-mining areas, we compared the observed numbers of deaths with the numbers expected on the basis of the rates in the unexposed areas. Since there was migration in and out of the asbestos-mining areas during the period of observation, the study population actually consisted of different people each year. The annual population numbers, which we used as denominators for mortality rates, were based on Canadian census data. Over the entire observation period, among women 30 years of age or older, there were 222,375 person-years in the asbestos-mining areas and 8,629,630 person-years in the reference areas.

The numerators for our calculations came from Quebec's mortality registry. We obtained the death certificates of women 30 years old or older who died from 1970 to 1989 in Quebec Province. The municipality where each woman resided at the time of her death was used to assign the death to an asbestos-mining area, to an unexposed reference area, or to a municipality excluded from the analysis.

The conventional standardized mortality ratio and standardized proportionate mortality ratio were estimated for the two asbestos-mining areas separately and together, as compared with the reference areas. Both measures are ratios of the numbers of observed deaths in the population under study to the expected numbers, with adjustment for age and calendar year. For the standardized mortality ratio, the expected number is based on the absolute mortality according to cause in the reference population. For the standardized proportionate mortality ratio, the expected number is based on the proportion of all deaths in the reference population that are due to each cause. The confidence intervals for the standardized mortality ratios were computed with use of Byar's approximation; the confidence interval for each standardized proportionate mortality ratio was computed with use of an approximation of the standard error of its natural logarithm.[29]

Estimates of Exposure to Asbestos

To predict the risk of lung cancer according to the risk model, we estimated the population's average cumulative exposure to asbestos, which is the product of the intensity and the duration of exposure. These two components were estimated separately for each of three possible types of exposure: neighborhood exposure, resulting from emissions from asbestos mining or milling in the towns' outdoor air; household exposure, resulting from dust brought home by asbestos workers; and occupational exposure. We present here a brief summary of the rather complex process of assessing exposure, described in detail elsewhere.[30]

Neighborhood Exposure

Our objective was to estimate historical levels of asbestos in the mining towns and to derive time-weighted average exposure levels for the "average" female resident. Information on airborne asbestos levels in the asbestos-mining towns was obtained from continuous measurements of dust made by a government agency beginning in 1972; annual measurements of asbestos fibers in the air, made by the asbestos industry since 1974; and two recent surveys.[31,32] To derive estimates of exposure for earlier periods, we took the following steps to obtain evidence.

Annual production volumes were computed for each asbestos-mining town from 1900 to 1984.

Detailed information about determinants of asbestos pollution going back to 1900 was obtained — specifically, the classes of fibers produced, controls on emissions, location of mining or milling sites and tailing piles in relation to inhabited areas, urbanization, topographic maps, and the directional distribution of winds.

The relation among levels of airborne dust, annual asbestos production, and dust controls was estimated for each mining town for the period from 1972 through 1984, and extrapolations were made back to 1900.

The frequency and intensity of past visible asbestos depositions and the distance of residences from mines and mills were estimated on the basis of the responses of a representative sample of 817 elderly female residents to a survey.

The volume and characteristics of asbestos dust currently retained by the plants' dust-emission filtration systems were entered into

a standard aerosol-dispersion model to estimate airborne asbestos levels in the town of Asbestos, Quebec, before the onset of dust controls in the 1950s.

We analyzed the relation between the lung burden of asbestos and the histories of occupational exposure among 89 Quebec miners and millers studied at autopsy by Sébastien et al.[3] We then applied that relation to the lung burdens of 22 deceased residents of the mining area who had no occupational exposures to asbestos, as reported by Case and Sébastien,[36] to estimate past exposure levels.

We then asked an international panel of five experts on the measurement of exposure to asbestos to consider the evidence. After evaluating the data critically, the panel estimated average neighborhood exposure levels in the three main mining towns for four key years (1945, 1960, 1974, and 1984), which cover the important phases in the implementation of dust-emission control. The panel also provided guidelines for estimating yearly average levels from 1900 to 1989, based on the values for the key years and on town-specific asbestos-production levels (Fig. 1). Average annual ambient levels were estimated to have peaked at 1 fiber per milliliter or more (this value reflects the number of fibers longer than 5 μm and visible on optical microscopy per milliliter of air) between 1940 and 1954 and to have been above 0.2 fiber per milliliter from about 1905 to about 1965. The panel thought that the true values were unlikely to be below 33 percent or above 300 percent of their best estimates, thereby providing subjective plausibility ranges. Furthermore, it was estimated that the three main towns were 5 to 20 times more polluted than the five other municipalities in the two asbestos-mining areas.

Household Exposure

Seventy percent of the women in the asbestos-mining areas had each lived in the same household as an asbestos worker,[34] but there were very few data regarding indoor exposure. We estimated indoor exposure on the basis of the results of autopsies of 10 residents who had lived with asbestos workers. Using data on the relation between the lung burden of asbestos and lifetime exposure to asbestos among workers, we calculated that the asbestos lung burden of those 10 residents had resulted from indoor asbestos levels that were roughly 0.5 fiber per milliliter higher than the outdoor levels. This estimate was consistent with the meager documentation on indoor asbestos levels (0.1 to 6.0 fibers per milliliter) in the homes of asbestos miners in Quebec,[37] in the homes of chrysotile-asbestos miners elsewhere,[38] in urban buildings polluted with asbestos,[39-41] in homes in naturally contaminated areas of the world,[42-45] and in an experiment with clothes contaminated with asbestos dust.[46]

Occupational Exposure

From our survey in the area, we estimated that about 5 percent of local women had worked in the asbestos industry or had mended bags used for shipping asbestos. A large occupational study in the local asbestos industry estimated that the few female workers had worked in less dusty jobs than male workers and had accumulated less than 50 fiber-years per milliliter (fiber-years are calculated by multiplying average annual exposure by years of exposure).[33] We used this value to estimate cumulative exposure for the proportion of person-years spent by the population in work in the asbestos industry.

Duration of Exposure

In 1989, we interviewed 817 elderly female residents of the asbestos-mining areas about their lifetime residential and employment histories and those of the persons they had lived with. This inquiry gave us information about the numbers of person-years of residence in the area, residence with an asbestos worker, and asbestos-related work for women of different birth cohorts in each of the asbestos-mining areas.

Cumulative Lifetime Exposure

For each woman in the 1989 survey, the lifetime cumulative neighborhood exposure was estimated by multiplying years of exposure by the estimated asbestos levels for each year and town in which she had lived. Cumulative household and occupational exposure was computed in the same way but adjusted for discontinuous exposure. We extrapolated values for the cumulative exposure of the women we surveyed to the entire exposed population and the study period (1970 through 1989) by assuming that the women interviewed in 1989 were representative of the entire population with regard to their history of exposure.

Table 3 shows the estimated cumulative exposure for the population in the asbestos-mining areas according to the type of exposure. Neighborhood exposure represented about 65 percent of the study population's average cumulative exposure, household exposure about 30 percent, and occupational exposure about 5 percent. The estimated average cumulative level of exposure was 25 fiber-years per milliliter. Considering the range of plausible values around the expert panel's neighborhood-exposure estimates, the greater uncertainty of the household-exposure esti-

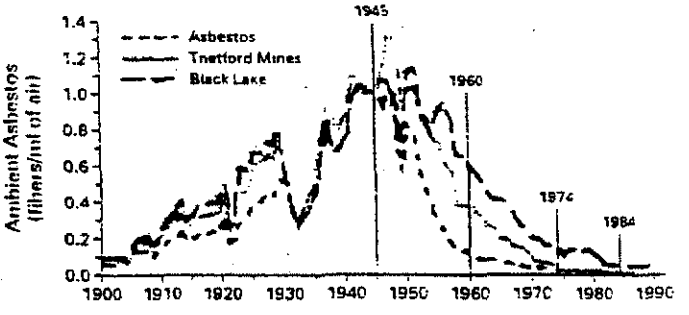

Figure 1. Mean Ambient Asbestos Levels in Three Asbestos-Mining Towns in the Province of Quebec, 1900 through 1985, Based on Estimates by an Expert Panel.

Asbestos levels are expressed as the numbers of fibers longer than 5 μm and visible on optical microscopy per milliliter of air. The vertical lines indicate the years for which the panel estimated asbestos levels (1945, 1960, 1974, and 1984); other values were interpolated on the basis of local asbestos production volumes.

TABLE 1. AVERAGE CUMULATIVE LIFETIME EXPOSURE OF THE POPULATION IN THE ASBESTOS-MINING AREAS ACCORDING TO TYPE OF EXPOSURE, 1970 THROUGH 1989.*

TYPE OF EXPOSURE	ESTIMATED CUMULATIVE EXPOSURE
	fiber-years/ml
Neighborhood exposure	16.0
Household exposure	7.8
Occupational exposure	1.2
Total cumulative exposure	25.0
Subjective plausible range of exposure†	5–125

*Values shown are averages for women 30 years of age or older who were living in the two asbestos-mining areas during the follow-up period, with adjustment for the duration of exposure. Values are expressed in fiber-years per milliliter of air, calculated by multiplying years of exposure by the average exposure level, and reflect cumulative round-the-clock exposure (1 fiber-year per milliliter is equivalent to 4.2 fiber-years per milliliter of cumulative exposure calculated for workers exposed 40 hours per week).

†The subjective plausible range provides for errors in estimating past environmental and household exposure levels and for errors in sampling and measuring in our exposure-history survey. The lower limit of 5 fiber-years per milliliter corresponds, for example, to 50 years of exposure to asbestos at a level of 0.1 fiber per milliliter (the actual mean ambient airborne-asbestos level in the area in 1974); the upper limit of 125 corresponds, for example, to 50 years of exposure to 2.5 fibers per milliliter — a relatively low exposure level in local asbestos-mining and asbestos-milling industries before 1960.

mates, and the uncertainty in our extrapolation from the sample of women surveyed in 1989 to the entire population in the asbestos-mining areas. We determined a subjective plausible range extending from 20 percent to 500 percent of this estimate.

Estimates of Risk

The dose–response model used by the EPA expresses the relative risk of lung cancer in a population as a linear function of its average cumulative exposure to asbestos,[4] as follows:

$$R = 1 + K_L \cdot \bar{E}$$

where K_L is the slope gradient, or the increase in the relative risk of lung cancer for each additional fiber-year per milliliter of cumulative exposure, $\bar{E}$ is the estimate of mean cumulative occupational exposure based on a workweek of 40 hours, and R is the risk of lung cancer in an exposed population as compared with that in a comparable unexposed population with similar smoking habits (we used the standardized mortality ratio and the standardized proportionate mortality ratio as estimates of this relative risk).

The EPA's estimate of K_L (0.01) is the geometric mean of relative-risk gradients estimated on the basis of data from 11 occupational studies.[7] The model requires that the exposed and reference populations have similar smoking habits, regardless of the smoking habits of workers in the original cohort studies. According to the model, a continuous exposure of 168 hours a week is equivalent to 4.2 40-hour workweeks of exposure to the same level of airborne asbestos. We applied this model to the exposure levels estimated for the populations in the asbestos-mining areas to predict its relative risk of lung cancer.

RESULTS

Given the estimated average cumulative exposure of the population in the asbestos-mining areas (Table 1), the EPA model predicted a relative risk of lung cancer of 2.05 (plausible range, 1.21 to 6.25).

Table 2 shows the standardized mortality ratios and standardized proportionate mortality ratios for death from selected causes in the exposed population. The standardized mortality ratio in the two asbestos-mining areas combined was 0.91 for death from all causes (2242 deaths observed) and 0.92 for death due to all cancers (595 deaths observed). There were 71 deaths due to lung or bronchial cancer among the exposed women. The standardized mortality ratio for lung cancer was 0.99 (95 percent confidence interval, 0.78 to 1.25), whereas the standardized proportionate mortality ratio was 1.10 (95 percent confidence interval, 0.88 to 1.38). The confidence intervals barely overlapped with the plausible range of the relative risk predicted from the EPA's model.

The difference between the expected number of deaths, based on rates in the reference population, and the observed number of deaths yields an estimate of the excess number of deaths in the exposed population. Applying the relative risk predicted by the EPA's risk-assessment model to the same expected numbers, it is possible to derive the number of excess deaths that would be predicted by the model. Table 3 shows these computations. Depending on whether one bases the computation of expected numbers on the standardized mortality ratio or the standardized proportionate mortality ratio, the risk-assessment model predicts between 68 and 75 excess deaths from lung cancer, whereas we observed 0 to 6.5. Thus, the EPA's risk-assessment model overestimated the mortality attributable to asbestos by a factor of at least 10 (68÷6.5).

There were, however, two significant elevations in risks associated with residence in the asbestos-mining areas. The standardized mortality ratio for pleural cancer was 7.65 (95 percent confidence interval, 3.06 to 15.78), and the standardized mortality ratio for asbestosis was 23.49 (95 percent confidence interval, 2.64 to 84.83).

DISCUSSION

Regulatory policies regarding asbestos are influenced by estimates of the risk of lung cancer and mesothelioma attributable to environmental exposure to asbestos. Such estimates are controversial because they rely on unverified assumptions and imprecise data. In this study, the EPA's model overestimated the risk of asbestos-induced lung cancer among women who lived in chrysotile-asbestos–mining areas between 1970 and 1989 by at least a factor of 10. Such risk assessments may also overestimate the risk of asbestos-induced lung cancer in other populations with nonoccupational exposure.

Our units of observation were clusters of towns, not individual residents, since it was not feasible to identify a large cohort of individual residents and ascertain their exposure levels and vital status. The ap-

TABLE 2. STANDARDIZED MORTALITY RATIO (SMR) AND STANDARDIZED PROPORTIONATE MORTALITY RATIO (SPMR) FOR DEATH FROM SELECTED CAUSES AMONG WOMEN IN THE ASBESTOS-MINING AREAS, AS COMPARED WITH MORTALITY AMONG WOMEN IN THE REFERENCE POPULATION, FROM 1970 THROUGH 1989 *

CAUSE OF DEATH	NO. OF DEATHS	SMR (95% CI)	SPMR (95% CI)
All causes	2242	0.91 (0.87–0.95	1.00 —
Circulatory diseases	1057	0.89 (0.83–0.94	0.98 (0.94–1.02
Respiratory diseases	184	0.81 (0.66–0.98	0.89 (0.75–1.08
Asbestosis	2	23.49 (2.64–84.82	24.10 (6.06–95.81
All cancers	595	0.92 (0.85–1.00	1.02 (0.96–1.10
Digestive cancer	205	0.96 (0.83–1.10	1.06 (0.95–1.21
Oral cancer	4	0.68 (0.18–1.74	0.75 (0.28–2.00)
Breast cancer	120	0.88 (0.75–1.06	0.97 (0.82–1.15
Genital cancer	64	0.55 (0.65–1.08	0.93 (0.73–1.18
Urinary cancer	19	0.84 (0.51–1.32	0.94 (0.60–1.46
Lymphatic or hematopoietic cancer	42	0.78 (0.56–1.05	0.85 (0.65–1.15
Respiratory cancer	82	1.06 (0.84–1.32	1.17 (0.95–1.45
Larynx	2	0.64 (0.07–2.32	0.72 (0.18–2.53
Lung or bronchus	77	0.99 (0.78–1.25	1.10 (0.88–1.38
Pleura	7	7.63 (3.06–15.73	8.21 (3.92–17.18

*There were no noticeable differences in mortality between the two asbestos-mining areas for death from any cause, except for the fact that all seven deaths from pleural cancer occurred in the Thetford Mines area. CI denotes confidence interval.

proach we used was nevertheless adequate, because exposures to asbestos differed much more between the exposed and reference populations than within either one. Furthermore, risk estimates such as these are applicable to group averages.

The study populations were dynamic; during the study period, people migrated between asbestos-mining areas and reference or excluded areas. For cultural and linguistic reasons, the population of Quebec was very stable until quite recently. The prosperity of the asbestos-mining areas attracted migrants until 1980. Those who left this area most often moved to large cities that were excluded from this study. Migration patterns would have been similar in the reference areas, albeit with somewhat less in-migration. Migration from exposed to reference areas would not significantly have affected mortality in the reference population, since it greatly outnumbered the exposed population (by 40 to 1). Migration from reference areas to asbestos-mining areas was not substantial, according to our survey of elderly female residents of the asbestos-mining areas. Finally, exposed and reference areas had similar health services, making it unlikely that out-migration from an asbestos-mining area would have been more strongly related to lung cancer than out-migration from reference areas. For these reasons and because of the results of simulations with various plausible assumptions, we concluded that in- and out-migration could not have distorted the relative risk substantially.

Substantial bias due to confounding is unlikely in this study. Both the exposed and the reference populations were small-town homemakers of French-Canadian ancestry (93 percent) who were born in the early part of this century in a society that was culturally and socioeconomically homogeneous until the 1960s. According to the 1987 Quebec Health Survey[54] and our local survey in 1989, the women in the exposed and reference populations were similar in ethnic background, lifestyle, and socioeconomic characteristics. However, the population in the asbestos-mining areas may have smoked slightly less (25 percent were current smokers and 54 percent had smoked at some time) than the women in the reference areas (31 percent and 55 percent, respectively). According to Axelson's method of correcting risk ratios,[55] differences in smoking status should not have distorted the relative risk of lung cancer by more than 7 percent. In view of possible confounding and bias due to migration, and given the low mortality from all causes and from cancer in the asbestos-mining areas, we believe that the best estimate of the relative risk of lung cancer falls between the standardized mortality ratio of 1.0 and the standardized proportionate mortality ratio of 1.1.

The results of the eclectic and varied methods used as the basis for the retrospective estimate of exposure were sufficiently coherent that five experts agreed easily on past levels of neighborhood exposure. Our assessment of exposure was similar to the assessment in historical cohort studies of asbestos

TABLE 3. EXCESS DEATHS FROM LUNG CANCER AMONG WOMEN IN THE ASBESTOS-MINING AREAS, AS COMPARED WITH THE EXCESS PREDICTED ON THE BASIS OF THE EPA'S RISK-ASSESSMENT MODEL.*

VARIABLE	SYMBOL OR FORMULA	BASES FOR ESTIMATING EXPECTED DEATHS FROM RATES IN REFERENCE AREA†	
		SMR	SPMR
Expected deaths	E	71.4	64.5
Observed deaths	O	71	71
Observed relative risk‡	O/E	1.0	1.1
Observed excess deaths	O−E	−0.4§	6.5
Predicted relative risk‖	R	2.1	2.1
Predicted deaths	P=R·E	146.4	135.2
Predicted excess deaths	P−E	75.0	67.7
Ratio of predicted to observed excess deaths	(P−E)/(O−E	Undefined¶	10.4

*E denotes the expected number of deaths in this population, based on the death rates or proportion of deaths in the reference population. O the observed number, and R the relative risk that is predicted in the population by applying the EPA's model to the estimated exposure level in this population.

†The estimate of the number of excess deaths in the population depends on the number that was expected on the basis of the rates of cancer in the reference population. Since we derived two versions of the expected number — one based on the standardized mortality ratio (SMR) and one based on the standardized proportionate mortality ratio (SPMR) — the excess numbers corresponding to each of these calculations are shown. Observed deaths and predicted relative risk are the only variables in this table that do not depend on the expected number of deaths; they are therefore necessarily equal in the two columns.

‡The negative value for O−E was interpreted as an absence of effect (O−E=0), leading to an undefined value for the ratio (P−E)/(O−E).

to asbestos may be lower among nonsmokers than among smokers, contrary to the model's assumption of constant relative risks.[29] And finally, the EPA's statistical analysis may have overestimated the dose–response gradient; a recent meta-analysis found the EPA's estimate to be between 4 and 24 times too high.[30]

The results of this study are reassuring with respect to lung cancer, but there were significant excess numbers of deaths due to pleural cancer (seven deaths) and asbestosis (two deaths). The instances of pleural cancer suggest an excess risk of mesothelioma. However, since historical death certificates reflect the incidence of mesothelioma poorly,[31,32] we have launched a separate study based on a province-wide survey of hospital records.

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workers, which also relied on incomplete data and on subjective and imprecise retrospective estimates. These uncertainties and those resulting from the estimation of cumulative exposure on the basis of a survey conducted in 1989 were accommodated by assigning a large plausible range to our best estimate of exposure levels.

There are several possible reasons for the overestimation of the risk of lung cancer by the EPA model. First, the risk in the low-dose range may be less than would be predicted by a linear model. Second, cumulative exposure may be a poor measure of the biologically effective dose of asbestos (the actual dose that contributes to the risk of disease). Third, exposure–risk gradients in occupational studies may have been overestimated because exposure was underestimated, because of confounding by smoking, or because inappropriate reference populations were used. Fourth, chrysotile fibers may be less carcinogenic than amphibole asbestos, which was proportionately more prevalent in the environment of the occupational cohorts used to estimate the dose–response gradient than in the general environment today. Fifth, the relative risk of lung cancer due

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EDITORIAL

Asbestos -- Still a Carcinogen

Asbestos is an important cause of human illness. Clinical and epidemiologic studies have established incontrovertibly that asbestos causes cancer of the lung, malignant mesothelioma of the pleura and peritoneum, cancer of the larynx, and certain gastrointestinal cancers. (1) Asbestos also causes asbestosis, a progressive fibrotic disease of the lungs. The risk of these diseases increases with cumulative exposure and also with the length of time since the first exposure. Asbestos has been declared a proven human carcinogen by the Environmental Protection Agency (EPA) and by the International Agency for Research on Cancer of the World Health Organization. (2,3) The total number of deaths in the United States that will eventually be caused by exposure to asbestos is estimated to exceed 200,000. (4)

Asbestos is a generic term applied to a group of minerals, all of them fibrous. There are four commercially important forms: chrysotile, crocidolite, amosite, and anthophyllite. Chrysotile is the most important. It accounts for more than 95 percent of current world production. Nearly all asbestos used in North America has been chrysotile from the province of Quebec, Canada. (2)

All forms of asbestos are carcinogenic. All have been shown in clinical, epidemiologic, and laboratory studies to be fully capable of causing lung cancer, mesothelioma, and the full range of asbestos-related diseases. (3) Although crocidolite appears to be two to four times more potent than chrysotile or amosite in its capacity to induce mesothelioma, all forms appear to be equally potent in their capacity to cause cancer of the lung. (5)

New use of asbestos has almost completely ended in the United States and in most other developed nations as the result of government bans and market pressures. Those forces were stimulated by the landmark epidemiologic studies of Selikoff and colleagues (6) and by the release of information on the carcinogenicity of asbestos that had previously been suppressed by the industry. (7) By contrast, extensive and aggressive marketing of asbestos by Canada and other exporting nations continues in the developing world, where sales remain strong. (8)

With the virtual cessation of high-dose occupational exposure to asbestos, medical and public health attention has turned to the risks of exposure at lower doses in the general environment. Particular concern focuses on the asbestos that remains as a legacy of past construction practices in many thousands of schools, homes, and commercial buildings. (2)

Mistakes were made initially in dealing with asbestos in buildings. Parents in a few communities caused great harm by tearing out asbestos from schools with little regard for proper safety procedures. With the passage in 1986 of the federal Asbestos Hazard Emergency Response Act (AHERA), a rational set of legally enforceable controls was put in

place. The guidir. nciple of AHERA is that asbestos in. ilding is deemed to pose no hazard to health unless fibers become airborne and can be inhaled. (9) So long as asbestos remains in place and is protected from disturbance, it can safely be left alone.

AHERA requires all school authorities to conduct visual inspections to identify asbestos-containing materials: air sampling is inaccurate and is not required. The results of inspection and plans for dealing with any asbestos detected must be made public. Overall, AHERA has been a success. In the great majority of schools, it has been feasible to manage asbestos in place. Removal (also referred to as abatement) is required only when asbestos-containing materials are visibly deteriorating or when renovation is imminent. Yet debate continues about the risks of low-dose exposure to asbestos.

In a study reported in this issue of the Journal, (10) Camus et al. used two epidemiologic approaches to assess the risks of nonoccupational exposure to asbestos. Both analyses were undertaken in a population of women in townships in the province of Quebec that have long been the major sites of asbestos mining in North America. Camus et al. first compared mortality among women in these communities with that among women in 60 other areas of Quebec (after excluding cities and shipbuilding areas). They then compared the number of deaths due to lung cancer among women in the mining areas with the number predicted by a risk-assessment model developed by the EPA. (3)

Camus et al. found no excess mortality due to lung cancer among women in the mining communities. In addition, they found the number of excess deaths due to lung cancer among women in these areas to be smaller by at least a factor of 10 than the number predicted by the EPA model. Beyond lung cancer, Camus et al. observed that the rate of death due to "pleural cancer," presumably mesothelioma, was more than seven times the rate in the nonmining areas. They also found substantial excess mortality due to asbestosis.

How can these findings be explained? Why does there appear to be no excess mortality from lung cancer among these women? One possibility, noted by Camus et al., is that the dose-response relation between asbestos and lung cancer may be less steep at low doses than is assumed in the EPA model. Indeed, it has been suggested that there may exist a threshold level of exposure to asbestos below which no carcinogenicity is evident. (10) While interesting, this explanation is entirely speculative and not based on data.

Another possibility is that the past exposure of the Quebec women may have been overestimated; such overestimation would inflate their calculated risk. It seems most unlikely, though, that this factor could account for more than a small fraction of the difference observed in mortality due to lung cancer. A third possible explanation is based on the fact that the populations of workers on which the EPA model was based are known to have been exposed to the amphibole forms of asbestos; the women studied by Camus et al. were exposed only to chrysotile asbestos, however, and the model may therefore not apply to the study group. Although it is true that exposures differed, there is no evidence that chrysotile is less potent in causing lung cancer than other types of asbestos. (11,12)

The most plausible explanation of the low mortality from lung cancer observed in this study is that women in the mining areas were exposed to an asbestos aerosol in which many particles were too large to reach their lungs. Previous studies have established that the risk of cancer in the mining and milling industry is much lower than that in the industries that process and use asbestos, such as textile manufacture and insulation. (13) In mining and

milling, many [illegible] agglomerates and long curly fibers a[illegible]uspended in the air. These large particles are easily seen and counted under the light microscope, but they tend not to reach the pulmonary alveoli as efficiently as small particles. Thus, air sampling based on light microscopy in the mining environment produces a spuriously high estimate of true alveolar exposure.

By contrast, in the asbestos-processing industries, large mineral bundles are broken up into shorter, thinner fibers. Many of those smaller fibers are invisible under the light microscope and can be seen only with an electron microscope. They are, however, readily inhaled and retained in the alveoli. It is this fundamental difference in actual pulmonary exposure -- at the same level of exposure as measured with a light microscope -- that accounts for the profound difference in the risk of lung cancer observed between asbestos-mining workers and those in the industries that process and use asbestos; these risks differ by a factor of 10 to 50. (13) The EPA was fully aware of this difference when its model was constructed, and accordingly, the data from studies of workers in asbestos mining and milling were excluded. (2)

Camus et al. (10) go beyond their data when they assert, without qualification, that the EPA's model overestimates the risk of lung cancer among persons with nonoccupational exposure to asbestos by at least a factor of 10. The EPA's current regulatory controls embody a level of caution commensurate with the hazard. The data of Camus et al. from their study of a population in rural Quebec with highly atypical exposure to asbestos would be an inappropriate basis for revamping regulatory standards for asbestos in buildings throughout the United States.

A final, take-home lesson from this report is that chrysotile asbestos is still indisputably a human carcinogen. The observation by Camus et al. of a more than sevenfold mortality rate (relative risk, 7.63) from pleural cancer in mining areas, as compared with nonmining areas, corroborates an enormous body of literature showing that Canadian chrysotile, like all forms of asbestos, is a potent carcinogen. (1,6) This finding is sufficient by itself to argue against any relaxation of public health controls on chrysotile asbestos. Moreover, it underscores the inaccuracy of recent efforts to portray chrysotile asbestos as safe. (14) Assertions that chrysotile can be used without risk in developing nations are contrary to fact and extremely dangerous. (15)

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To the Editor:

Landrigan is wrong in concluding that "a more than sevenfold mortality rate... from pleural cancer in mining areas, as compared with nonmining areas, corroborates an enormous body of literature showing that Canadian chrysotile... is a potent carcinogen." This mortality rate (seven cases) is entirely explained by the few cases among women in the area who had occupational exposure to amphiboles in the manufacture of gas masks, (1) the repair of burlap bags that contained imported fibers, (2) and possibly, in one case, the tremolite brought home on miners' clothes. (2) Seven such women received workers' compensation in Quebec during the period of the study by Camus et al. Indeed, there is now a scientific consensus that chrysotile asbestos is not a cause of malignant mesothelioma, even among chrysotile-asbestos miners and millers. (1) Reasonable caution should continue to be used in exposing workers or bystanders to chrysotile, but if the levels of exposure currently recommended by the Occupational Safety and Health Administration and the National Institute for Occupational Safety and Health can be maintained, public health workers can concentrate their work on lung cancer where it belongs: on smoking.

With respect to women in the mining area, it has been established that the content of chrysotile and tremolite in the lungs is directly proportional to the number of years lived in the mining region and inversely proportional to the distance between the place of residence and the mining region. (2) In fact, these women were exposed to levels of chrysotile as high as 1 fiber per milliliter of air as recently as one month in 1984. (2)

Editor's note:

Dr. Case has served as an expert witness in asbestos litigation during the past five years.

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To the Editor:

Landrigan misleads readers with the statement. "Clinical and epidemiologic studies have established incontrovertibly that asbestos causes cancer of the lung, malignant mesothelioma of the pleura and peritoneum, cancer of the larynx, and certain gastrointestinal cancers." To prove his point, he cites only one report. The cohort cited by Landrigan is only one of many asbestos-exposed cohorts described in the medical literature. That cohort has an atypical pattern of lung cancer, as compared with other cohorts. Our review of mortality from

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Chrysotile Asbestos is the Main Cause of Pleural Mesothelioma

Allan H. Smith, MD, PhD, and Catherine C. Wright, MPH

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

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

INTRODUCTION

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

Despite extensive cancer studies in humans, certain controversies remain about asbestos exposure and human cancer. The primary controversy is the question of fiber type in causation of mesothelioma. Commercial use of asbestos mainly involves the two amphibole fiber types, crocidolite and amosite, and one serpentine fiber type, chrysotile. However, chrysotile asbestos is often contaminated with small amounts of tremolite, an amphibole fiber. The key questions concern whether or not, and to what extent, exposure to chrysotile asbestos (including its natural contaminant tremolite) causes mesothelioma in humans. While there is evidence that chrysotile asbestos is not a potent cause of malignant peritoneal mesothelioma [EPA, 1986; Doll and Peto, 1985], the role of chrysotile in the causation of pleural mesothelioma is still disputed.

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

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

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

A REVIEW OF THE EPIDEMIOLOGICAL DATA

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

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

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

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

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

TABLE I. Asbestos Cohort Studies

Reference	Industry	Principal asbestos exposure	Secondary asbestos exposure	Number in cohort	Number of deaths	Lung cancer deaths	Excess lung cancers	Pleural mesoth.	Peritoneal mesoth.	Pt.-years/1,000 deaths	Est. mesoth./1,000 lung cancers	Comments
Mancuso (1958)	Railroad machinists	Chrys	Possibly some amphibole	181	159	11	NA	1	14	58.1	NA	Expected lung cancer deaths were not reported. Primary exposure at steam locomotives. Greater than 10 years since first employment. Mancuso (1966) emphasizes that principal exposure was scraping or removal of lagging, which was chrysotile. However, other work may have used amphibole. So secondary exposure is possible.
Finkelstein (1964)	Cement products	Chrys/ croc		665	136	29	21.4	6	11	60.9	0.51	20+ years from onset. Production and maintenance.
Jones et al. (1980)	Gas mask manufacture	Croc		951	166	12	5.7	4	13	78.3	2.28	20+ years from onset. Females only.
Talcott et al. (1989)	Cigarette filter manufacture	Croc		33	28	11	10.3	3	2	71.4	0.19	
Edwin and Simpson (1977)	Insulation (lagging)	Unknown mix		162	122	24	NA	5	4	65.6	NA	20+ years from onset. Seven additional lung cancers or mesotheliomas could not be categorized. EPA (1986) lists 27 cases. The excess lung cancers for this cohort.
Peto et al. (1985)	Textiles	Chrys	Croc	145	123	20	14.5	0	7	56.9	0.48	Subcohort from prev. employees 20+ years with some service before 1933, high exposure group. Crocidolite made up 5% of asbestos used between 1932 and 1969.
McDonald and McDonald (1978)	Gas mask manufacture	Croc	Chrys	198	56	7	4.8	6	3	53.6	0.65	Males and females combined, 20–36 years since onset of exposure to crocidolite. Exposure to chrysotile likely to have occurred before and after. Cohort includes workers from three factories. Filter gas workers at Montreal (n = 221) were exposed to croc from 1940 to 6/41 only. This factory used chrysotile since 1928 for manuf. of other things. Filter gas workers from Asbestos, Quebec (n = 113) were exposed to croc 1939–1941 only. This factory has been in operation since WWI processing chrysotile. Gas mask assembly was performed in Ottawa (n = 54). An additional two cases of pleural mesotheliomas from Montreal plant were identified from a mail survey. Note that Table 2 in McDonald and McDonald (1978) incorrectly presents two pleural mesotheliomas.
Newhouse et al. (1985)	Textiles/ cement products	Mixed amph/ chrys/ croc		700	274	37	22.0	11	14	51.1	0.44	Women only. Greater than 10 years follow-up.
[illegible] (1982)	Laggers	Mixed amph/ chrys/ croc		1,400	157	38	27.3	6	7	44.6	0.26	Men only. Greater than 10 years follow-up. No complete data for 20+ years since 1st employ.
Selikoff et al. (1979a)	Shipyard	Chrys/ amph		385	73	20	24.9	5	3	41.1	0.12	Shipyard insulator cohort 20+ years from onset. Amosite added to chrysotile just before and during WWII.
Sluis-Cremer et al. (1992)	Mining	Croc		3,430	423	27	13.7	2	17	40.2	1.24	Cohort of miners exposed only to crocidolite. No subcohort data for 20+ years since 1st employ.
Nicholson (1978)	Production and fabric	Not stated		668	198	27	16.6	7	6	40.3	0.43	20+ years from onset.
Armstrong et al. (1988)	Mining/ milling	Croc		6,506	820	91	56.5	1	32	39.8	0.57	Men only. Includes entire cohort. Update to Hobbs et al. (1980).
Newhouse et al. (1985)	Textiles/ cement products	Mixed amph/ chrys/ croc		3,000	818	158	94.8	29	31	37.9	0.33	Men only. >10 years follow-up.
Seidman and Selikoff (1990)	Insulation	Chrys	Amos	17,800	4,951	1,168	891.3	265	173	34.9	0.19	Entire cohort. Workers were exposed to chrys in early years and chrys + amos in later years.
Rossiter et al. (1980)	Shipyards	Mixed		6,075	1,943	84	−18.0	2	29	27.8	−1.78	
Albin et al. (1990)	Asbestos cement manufacture	Chrys	Crocidolite	1,456	582	35	15.6	0	13	22.0	0.83	
Seidman et al. (1986)	Insulation manuf.	Amos		820	366	76	63.8	5	5	21.9	0.15	20–40 exposed years since onset of work.
Peto et al. (1985)	Textiles	Chrys	Croc	3,211	727	93	28.4		10	13.8	0.35	Subcohort of men first employed in 1933 or later, 20+ years since 1st employ.
Sluis-Cremer et al. (1992)	Mining	Mixed amph		675	154	NA	NA	3	2	13.0	NA	Cohort of miners exposed to mixed amphiboles. The number of 30 mesotheliomas is two or three. Unclear.
Newhouse and Sullivan (1989)	Friction materials	Chrys	Croc	2,222	743	86	8.7	NA	9	12.1	1.58	20+ years from onset.
Kaschnitz et al. (1985)	Shipyards	Chrys	Amos	5,191	668	61	4.9	7	8	12.0	1.63	Mesothelioma/croc excluded.
Acheson et al. (1984)	Insulation manufacture	Amos		4,820	333	37	27.4	1	4	12.0	0.15	Includes all factory workers, including one in Penang, with less than 20 years since 1st exposure.
Acheson et al. (1982)	Gas mask manufacture	Croc		757	219	12	6.8	0	2	9.1	0.29	Crocidolite cohort only. Some known chrysotile gas masks were also made in this cohort.
Rafnsson et al. (1989)	Manuf. asb. cement	Chrys	Amos/croc	7,996	1,305	162	72.2	0	10	7.7	0.14	88% chrysotile used 1920–1946

TABLE II. Additional Studies Considered*

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

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

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

Gas Mask Studies

Studies of workers who assembled gas masks during World War II have been widely quoted as indicating that crocidolite is much more potent than chrysotile asbestos in causing mesothelioma [Doll and Peto, 1985; Harington, 1991]. Table III presents data abstracted from the three gas mask studies where workers have been exposed to one fiber type only [Jones et al., 1980; McDonald and McDonald, 1978; Acheson et al., 1982]. The expected number of lung cancer deaths for the McDonald and McDonald [1978] study was not given, but we have assumed it was one since it makes very little difference to the overall consideration of the studies.

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

Fiber Type Risk Comparisons

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

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

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

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

*Ottawa cohort with exposure to crocidolite only.

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

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

A REVIEW OF AVAILABLE ANIMAL DATA

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

In order to get an overall incidence of pleural mesotheliomas in rats following inhalation, incidence data were added together for each of the three asbestos types (i.e., chrysotile, amosite, and crocidolite). The overall incidence of pleural mesothelioma in rats exposed via inhalation is 1.8% (13/733) for chrysotile, 1.3% (5/377) for amosite, and 1.2% (4/328) for crocidolite. Thus, inhalation studies in rats do not support the argument that chrysotile is far less potent than amphiboles in pleural mesothelioma causation. Since only one inhalation experiment has been done for tremolite, it is not included in this comparison.

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

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

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

THE STANTON AND AMPHIBOLE HYPOTHESES REVISITED

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

TABLE IV. Mesothelioma in Populations Exposed to Different Fiber Types[a,b]

Fiber type	Observed deaths	Lung cancer		Pleural mesothelioma	
		Observed	Excess	Observed	As % of excess lung cancer
Chrysotile[c]	10,345	725	186.9	29	20.3
Amosite[d]	1,153	133	90.2	12	13.3
Crocidolite[e]	1,042	110	66.8	48	71.9
Mixed fiber[f]	9,532	1,722	1,106.2	301	27.2

[a]Based on Table 1 of Hughes and Weill (1986).
[b]Includes subcohorts with 20+ years since first employment, where possible.
[c]McDonald et al. (1983, 1984, 1993), McDonald and McDonald (1980), Rubino et al. (1979), Piolatto et al. (1990), Weiss (1977), Acheson et al. (1982), Thomas et al. (1982).
[d]Seidman et al. (1979, 1986), Acheson et al. (1984).
[e]Thomas et al. (1980), Armstrong et al. (1988), McDonald and McDonald (1978), Jones et al. (1980).
[f]McDonald et al. (1983), Berry and Newhouse (1983), Newhouse and Sullivan (1989), Selikoff et al. (1979), Seidman and Selikoff (1990), Acheson et al. (1982), Newhouse and Berry (1979), Newhouse et al. (1965), Finkelstein (1983, 1984), Elmes and Simpson (1977), Thomas et al. (1982), Rossiter and Coles (1980).

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

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

This evidence led to the "Stanton Hypothesis," which states that durable fibers (provided they subscribe to well defined ranges of diameter and length), of which asbestos is but one sample, cause cancer irrespective of their physicochemical nature simply because they are fibers. Stanton also stated, however, that direct application of the results of his experiments to the problems in humans would be unwise given the deficiencies in the method of application and the massive amounts of fibers used (standard dose, 40 mg). In fact, if one were to exclude all fiber types other than asbestos from Stanton's data, there appears to be little or no relationship between the probability of tumor and the number of particles measuring ≤0.25 μm diameter and ≥8 μm length (Fig. 1).

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

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

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

TABLE V. Long-Term Asbestos Inhalation Studies in Animals

Reference	Species	Fiber type	Dose[a,b] mg/m³	Number tested	No. of pleural mesotheliomas
Reeves et al. [1971]	Rats	Amos	~48	53	0
		Croc	~48	51	0
		Chrys	~48	49	0
	Rabbits	Amos	~48	20	0
		Croc	~48	18	0
		Chrys	~48	26	0
	G. pigs	Amos	~48	17	0
		Croc	~48	33	0
		Chrys	~48	21	0
	Hamsters	Amos	~48	50	0
		Croc	~48	45	0
		Chrys	~48	49	0
Wagner et al. [1974]	Rats	Amos	11–14	146	1[c]
		Croc	10–13	141	3[d]
		Chrys (Can.)[e]	10–12	137	4
		Chrys (Rh.)[f]	10–15	144	0
Reeves et al. [1974]	Rats	Chrys	~50	34	1
		Croc	~50	43	0
		Amos	~50	43	2
	Gerbils	Chrys	~50	40	0
		Croc	~50	31	0
		Amos	~50	45	0
Davis et al. [1978]	Rats	Chrys (Rh.)	2	42	0
		Chrys (Rh.)	10	40	0
		Amos	10	43	0
		Croc	5	43	1
		Croc	10	40	0
Davis et al. [1985]	Rats	Tremolite (Kor.)[g]	?	40	2
Davis et al. [1986a]	Rats	Short amos	10	42	0
		Long amos	10	40	2
Davis et al. [1986b]	Rats	WDC yarn[h]	4	41	0
		Factory WDC[i]	4	44	0
		Chrys yarn[j]	4	42	1
		Exp WDC[k]	4	43	4
		Exp WDC/RD[l]	4	37	1
Davis and Jones [1988]	Rats	Short chrys	10	40	0
		Long chrys	10	40	2
Total	Rats	Chrys		733	13 (1.8%)
		Amos		377	5 (1.3%)
		Croc		328	4 (1.2%)

[a]No pleural mesotheliomas were observed in any control group.
[b]Similar doses in mg/m³ may be very different in terms of fibers/mL.
[c]Mesothelioma occurred with just 1 day exposure (>2 years followup).
[d]One mesothelioma occurred with just 1 day exposure (>2 years followup).
[e]Rh. Rhodesian.
[f]Can. Canadian.
[g]Kor. Korean.
[h]"WDC" is wet dispersed chrysotile.
[i]Dust from factory air.
[j]Standard chrysotile textile yarn.
[k]Experimental WDC process.
[l]Experimental WDC "reversed daylight."

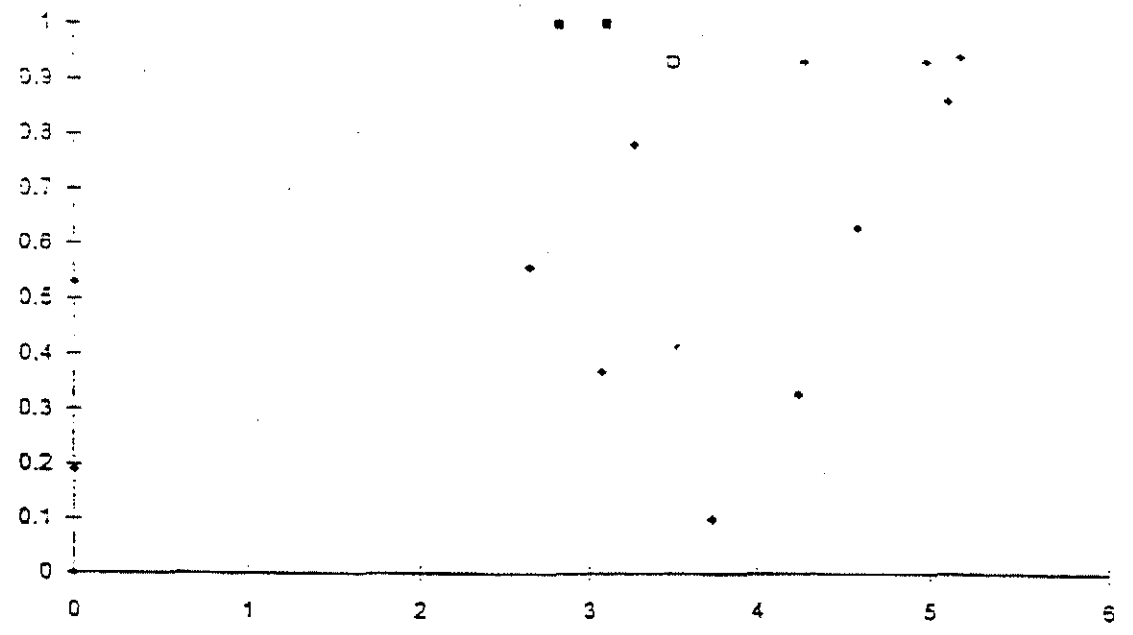

FIGURE 1. Stanton et al. (1981) data for asbestos fibers only. X-axis: Log number particles measuring ≤0.25 μm width by >8 μm length per microgram. Y-axis: Probability of tumor. ■, tremolite; □, amosite; ♦, crocidolite.

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

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

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

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

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

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

in length were included in the analysis. Amosite was identified in 76 cases (81%), the noncommercial amphiboles (primarily tremolite) were identified in 52 cases (55%), chrysotile was detected in 20 cases (21%), and crocidolite in 15 cases (16%). Another five cases (5%) could not be distinguished between amosite and crocidolite. According to the authors, tremolite fibers are probably a marker for the much greater numbers of chrysotile fibers which were deposited but subsequently cleared.

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

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

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

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

Summary of Lung Content Studies

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

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

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

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

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

Pleural Content Studies

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

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

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

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

Le Bouffant [1980] observed a preferential migration of chrysotile fibers to the pleura, with a significant increase and accumulation in the pleura in comparison with the lung parenchyma. The median percentage of chrysotile fibers was 3% in the lung and 33% in the pleura. Similar results have been demonstrated in rats [Viallat et al., 1986]. Following intratracheal injection of rats with small amounts of UICC chrysotile, the shortest fibrils (mean lengths 0.44–1.32 μm, diameter 0.03 μm) reached the pleura very rapidly and could be retrieved from the pleural fluid of rats within 1 month.

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

CONTRIBUTION OF CHRYSOTILE ASBESTOS TO PLEURAL MESOTHELIOMA INCIDENCE

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

Potency of Chrysotile

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

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

Proportion of Mesotheliomas Due to Asbestos

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

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

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

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

Production and Use of Asbestos in the U.S.

Chrysotile represents approximately 95% of the total world production of all forms of asbestos, with Canada its largest producer [Mancuso, 1988]. Amosite and crocidolite accounted for only 5% of the asbestos usage in the U.S. over the years (Table VI) (Minerals Yearbook, 936–950). For example, the percent amphibole usage ranged from ≤1% in 1935 to a peak of ≤5.9% (≤25,121 tons amphibole, 445,902 tons total asbestos consumed) in 1943, then decreased to less than 2% by 1950. During this period the U.S. depended mainly on Canada for its supply of nonspinning (short chrysotile) fiber and upon South Africa, Canada, and Russia for nearly all of its spinning (long chrysotile and amphibole) asbestos. The U.S. produced only small amounts of both chrysotile and amphiboles.

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

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

CONCLUSION CONCERNING THE CONTRIBUTION OF CHRYSOTILE ASBESTOS TO MESOTHELIOMA INCIDENCE

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

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

Year	Canadian chrysotile imported[a]	U.S. chrysotile produced	African amphiboles imported[a]	U.S. amphiboles produced	Total consumed in U.S.[b]	Percent that is chrysotile
1935	154,200	NA[c]	945	NA	174,555	99.5
1936	226,080	10,520	2,080	404	250,922	99.0
1937	276,002	13,284	4,247	612	316,260	98.5
1939	223,840	14,686	6,359	450	255,547	97.3
1940	225,653	17,481	8,752	1,693	262,199	96.8
1941	389,391	20,144	21,447	2,252	438,741	94.6
1942	386,647	13,109	20,424	2,208	434,121	94.8
1943	385,655	3,900	24,007	2,114	445,902	94.1
1944	353,228	6,296	19,162	317	407,148	95.2
1945	355,768	13,340	13,247	250	377,875	96.4
1946	442,073	4,438	6,324	437	459,752	98.5
1949	470,783	NA	22,720	NA	535,132	95.8
1950	678,358	NA	14,805	NA	728,785	98.0

[a]Data for years 1935–1950 obtained from the Minerals Year Book (1936–1950).
[b]Includes crude and milled fibers, as well as "stucco and refuse."
[c]May include some small amount of African Chrysotile.
[d]Includes all imported as well as domestic-produced amphiboles and chrysotile consumed in that year.
[e]NA, data not available.

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Occupational E osure 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 [illegible]

[illegible] evidence for the amphibole hypothesis. Toxicologic and epidemiologic studies provide evidence that chrysotile is associated with an increased risk of lung cancer and mesothelioma. Chrysotile may be less potent than amphiboles for inducing mesothelioma, but there is little evidence to indicate a 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, [illegible] 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.[6] 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.[5] In one of the earliest studies, Pooley observed a greater number of amphibole fibers than chrysotile fibers in [illegible] of [illegible] 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 Observed	Lung Cancer Deaths Expected	Mesothelioma Cases Observed	Mesothelioma 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[a]	0	0
Dement et al.[29]	Textiles	126	64.0[a]	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]	6 asbestos factories	65	15.6[a,b]	2	0.4
McDonald et al.[34]	Friction products	73	49.1[a]	0	0
McDonald et al.[35,36,c]	Mining and milling	516	389.7[a]	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[d]	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.[e]

[f]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.[15,16,22] 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."[16]

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.[26,33,35,36,40,41] 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 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 × Y[a]
Dement et al.[29]	Textiles	Chrysotile	0.03[b]
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	0.007[a], 0.007[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]

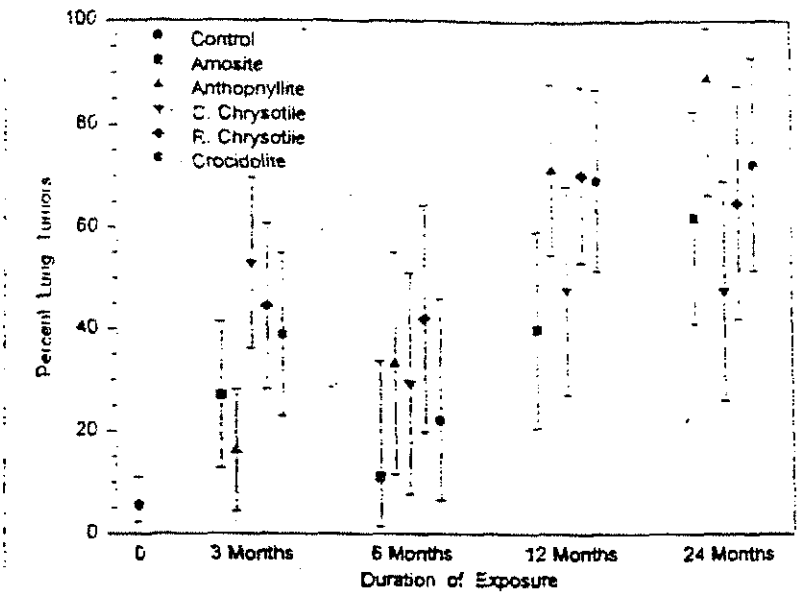
Mesothelioma

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.[5] 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[55] 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

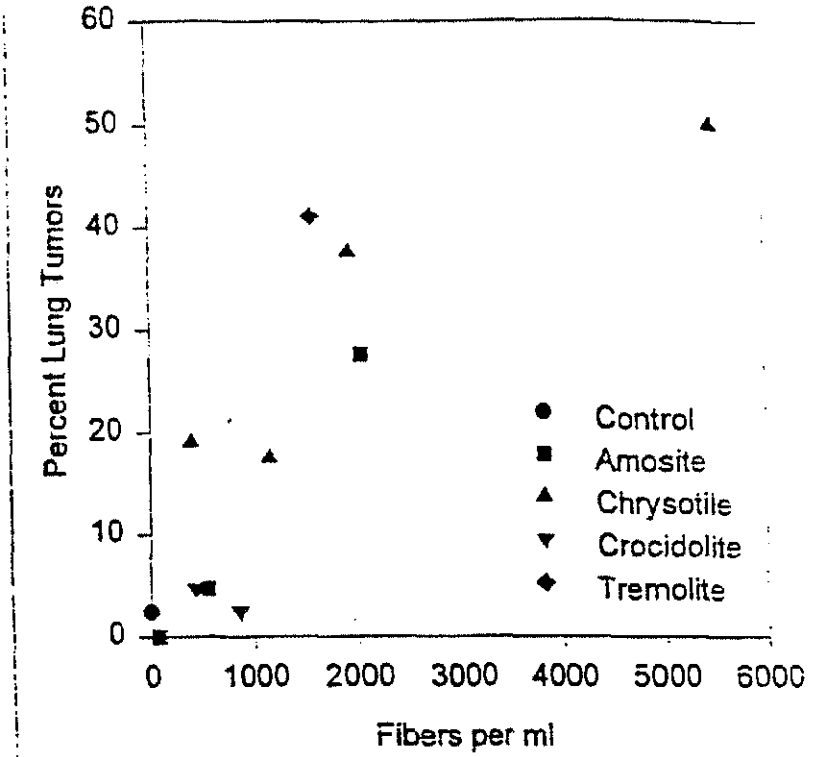
lung carcinomas in 18.3% of t... animals tested vs 4.6% for crocidolite.[65]

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.[57] 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.[57] 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.[59–61] 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,[5] 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.[66] 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