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

Leslie T. Stayner, PhD, David A. Dankovic, PhD, and Richard A. Lemen, PhD

ABSTRACT

Introduction

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

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

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

Lung Burden Studies

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

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

Most case-control studies that evaluated the potential relationship between

The authors are with the Risk Assessment Program and Office of the Director, National Institute for Occupational Safety and Health, Cincinnati, Ohio.

Requests for reprints should be sent to Leslie T. Stayner, PhD, National Institute for Occupational Safety and Health, Robert A. Taft Laboratories, 4676 Columbia Parkway, Mail Stop C15, Cincinnati, OH 45226.

This paper was accepted August 16, 1995.

Editor's Note. See related annotation by Cullen (p 158) in this issue.

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

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

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

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

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

Mesothelioma

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

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

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

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

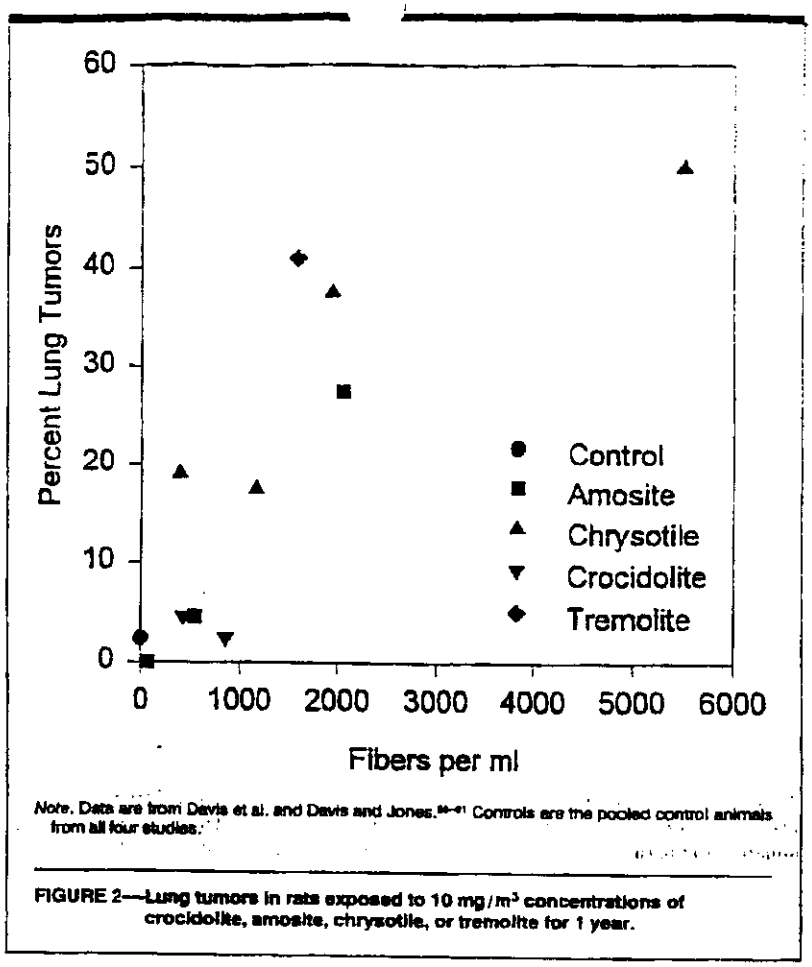
lung carcinomas in 18.3% of t. .imals tested vs 4.6% for crocidolite.[62]

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

Mesothelioma

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

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



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

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

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

Mechanistic Studies

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

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

References

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