Commentary

Chrysotile Asbestos as a Cause of Mesothelioma:

Application of the Hill Causation Model

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Chrysotile comprises over 95% of the asbestos used today. Some have contended that the majority of asbestos-related diseases have resulted from exposures to the amphiboles. In fact, chrysotile is being touted as the form of asbestos which can be used safely. Causation is a controversial issue for the epidemiologist. How much proof is needed before causation can be established? This paper examines one proposed model for establishing causation as presented by Sir Austin Bradford Hill in 1965. Many policymakers have relied upon this model in forming public health policy as well as deciding litigation issues. Chrysotile asbestos meets Hill's nine proposed criteria, establishing chrysotile asbestos as a cause of mesothelioma. *Key words*: asbestos; chrysotile; amphiboles; causation; mesothelioma; Hill model.

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In determining cause and effect, epidemiologists are confronted with two distinct determinations, general causation and specific causation. General causation involves the determination of whether the particular substance under consideration causes the effect being studied. Specific causation, on the other hand, focuses on whether a particular individual's disease is attributable to exposure to that substance. In determining general causation, a variety of data sets are evaluated by researchers. The information that is processed includes mechanistic processes, biological principles, molecular studies, toxicologic studies, animal experimentation, and human epidemiologic studies, including case reports, case–control studies, cohort studies, and mortality and morbidity studies. It is not surprising that consensus about basic definitions and methods for causal inference is limited, even after three centuries of debate.[1]

One of the most widely acclaimed methods for determining cause and effect for general causation was proposed by Sir Austin Bradford Hill in 1965.[2] In using this method, researchers are asked to evaluate nine areas of consideration: strength of association, temporality, biologic gradient, consistency, specificity, biologic plausibility, coherence, experimental evidence, and analogy. None of these considerations, in and of itself, is determinative for establishing a causal relationship. As Hill himself noted, "[n]one of my nine view points can bring indisputable evidence for or against the cause and effect hypothesis, and none can be required as a sine qua non." In the same vein, it is not necessary for all nine considerations to be met before causation is established. Instead, Hill emphasized that the responsibility for making causal judgments rested with a scientific evaluation of the totality of the data. He further acknowledged that decisions on causation must be made in the absence of perfect data. As he stated,

> All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.

With respect to the issue of whether chrysotile asbestos is capable of inducing or contributing to the development of mesothelioma, the body of scientific evidence has long established a cause-and-effect relationship. Throughout the last 30 years, many governmental organizations have thoroughly and meticulously reviewed reams of published data and have concluded that all fiber types are capable of causing mesothelioma in American workers. Two publications highlight the fact that the majority of the world medical community considers chrysotile to be a cause of mesothelioma. In 1997, a multidisciplinary gathering of 19 pathologists, radiologists, occupational and pulmonary physicians, epidemiologists, toxicologists, industrial hygienists, and clinical and laboratory scientists held a meeting in Helsinki, Finland, to agree upon criteria for attribution of disorders of the lung and pleura in association with asbestos. Collectively, the group had published over 1,000 articles on asbestos and asbestos-associated disorders. The consensus of the

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group was that all types of malignant mesothelioma can be induced by asbestos, with the amphiboles showing greater carcinogenic potency than chrysotile.[3]

The second publication was a monograph devoted specifically to chrysotile asbestos that was prepared by the International Programme on Chemical Safety (IPCS) in conjunction with the World Health Organization. After an extensive review of the world's literature, this body concluded that "commercial grades of chrysotile have been associated with an increased risk of pneumonoconiosis, lung cancer and mesothelioma in numerous epidemiological studies of exposed workers."[4]

While these two publications represent the recent scientific consensus on the ability of chrysotile to cause mesothelioma, the International Agency for Research on Cancer (IARC), a part of the World Health Organization, came to similar conclusions in 1976. The IARC gathered a group of eminently qualified asbestos experts to review and then develop a consensus report on the carcinogenic effects of exposure to all forms of asbestos, including chrysotile. The group of scientists, in addition to myself, included such noted researchers as Dr. J. C. Wagner (U.K.), Dr. I. J. Selikoff (U.S.), Professor J. Bignon (France), Dr. P. Westerholm (Sweden), Dr. G. Berry (U.K.), Professor A.M. Langer (U.S.), Dr. F. D. Pooley (U.K.), Dr. D. P. Rall (U.S.), Professor H. W. Schlipkoter (Germany), Dr. J. K. Wagoner (U.S.), and Dr. J. A. H. Waterhouse (U.K.). The Monograph concluded, "All commercial forms of asbestos tested are carcinogenic in mice, rats, hamsters and rabbits." And also "Many pleural and peritoneal mesotheliomas have been observed after occupational exposure to crocidolite, amosite and chrysotile." These conclusions, as related to humans, were based on the epidemiologic studies of various exposed cohorts.[5] The conclusions of the IARC have been echoed by every regulatory agency of the United States, including the EPA, OSHA, CDC, NIOSH, DHHS, PHS, and FDA.

The 1984 Report of the Royal Commission on Matters of Health and Safety Arising from the Use of Asbestos in Ontario concludes, "All fibre types can cause all asbestos-related diseases. . . ."[6]

The substantial body of scientific evidence that establishes that chrysotile asbestos, alone or in combination with its naturally-occurring contaminant, tremolite, an amphibole form of asbestos, is a cause of mesothelioma in human beings is revealed by the following analysis of the data according to the considerations for determining cause-and-effect relationships proposed by Hill:

1. **Strength of association** is a reflection of the strength of effect in a given study. At the outset of any evaluation of the issue of chrysotile asbestos and its risk of inducing mesothelioma, it is important to note that the medical and scientific community universally accepts the proposition that the overwhelming majority of mesotheliomas are caused by exposure to asbestos.[7,8] Moreover, it has been firmly established that the level of exposure necessary to induce mesothelioma in certain individuals is well below the level necessary to induce asbestosis or other asbestos-associated diseases.[4] Mesotheliomas have been documented not only in occupational settings but also para-occupational settings such as those occurring among family members exposed to asbestos fibers introduced into the household through the clothes of the worker, and in neighborhood settings where individuals are exposed to asbestos fibers introduced into the atmosphere by manufacturing plants.[9] The second important feature of mesothelioma that needs to be highlighted is its rarity among the population of people who have not been exposed to asbestos. While a background incidence of mesothelioma has not been firmly established, it is estimated that it occurs probably on the order of 1 case per million persons per year or less.[10] The rarity of the disease, coupled with the lack of mortality rates in the populations used as controls and problems in diagnosis and reporting, make the assessment of the actual risk for mesothelioma through the means of epidemiologic studies difficult.[4]

Despite these difficulties, numerous scientific studies of workers exposed to chrysotile asbestos have demonstrated that the risk of contracting mesothelioma after exposure to chrysotile asbestos is more than double that of individuals who have not had such exposure. While most of these studies are of cohorts of workers who were exposed to chrysotile contaminated with low levels of tremolite, an amphibole form of asbestos, several studies revealed a substantially increased risk of contracting mesothelioma from exposure to chrysotile that did not contain any tremolite contamination. In the first study, Piolatto and his associates examined a cohort of 1,094 chrysotile production workers employed at the mine and mill in Balangero, Italy, a site where no tremolite was detected in any of the samples of chrysotile.[11] Among the 427 deaths, the authors discovered two mesothelioma cases, one confirmed pathologically and one based on radiographic findings and an examination of pleural fluid. While the authors report that the fibrous silicate balangeroite was found, unlike the situation for fibrous tremolite, no data exist on its toxicity or etiologic role in mesothelioma.*

*Balangeroite was named after the Balangero serpentinite deposit at Piedmont, Italy. Balangeroite is a mineral fiber of the asbestiform variety, first discovered in 1983, with a mineral formula Mg, Fe, Fe, $Mn)_{42}Si_{16}O_{54}(OH)_{40}$, brown in color, and is found in schistose serpentinite in proximity to a large ultramafic massif associated with the Balangero serpentinite deposit. To date no data on its toxicity have been published, and definitely no record of its role in the induction of mesothelioma (sources: <www.minda.org/min-492.html>; Ministry of Energy & Mines, Government of British Columbia; <http://webmineral.com/data/Balangeroite.shtml>).

In a similar study, Cullen and Baloyi examined the records of Zimbabwean miners and millers who had been certified as having an occupational lung disease.[12,13] As in the chrysotile ore mined in Balangero, Italy, no tremolite or other amphibole mineral was detected in any of the samples, either bulk or through electron microscopic analysis. While it is now claimed anthophyllite is a contaminate of the UICC samples taken from Zimbabwe, there is no reason to doubt that no contamination was found in the study by Cullen and Baloyi or to assume that the UICC sample is representative of the exposures of the miners and millers studied. Investigations of UICC samples have found the chrysotile taken from Zimbabwe contains 2% anthophyllite as an impurity.[14] The authors estimated that 6,647 Zimbabweans had been engaged in the mining and milling operations at two mines: Shabani and Goths. Among the chosen cohort of 27 miners with sufficient documentation, the authors discovered one mesothelioma case proven by biopsy, one mesothelioma proven by postmortem examinations, and one probable mesothelioma based on radiographic findings. They also reported one case of asbestosis with probable terminal mesothelioma vs. lung cancer based on chest x-ray only as having a pleural mass five years later. Given the size of the exposed population, and even though the authors did not report a Standard Mortality Ratio (SMR), it is most likely that it would have exceeded an SMR of 2 given the rarity of the disease in a comparison population of non-exposed individuals.

Rogers and his colleagues examined 221 cases of definite and probably mesothelioma obtained from the Australian Mesothelioma Surveillance Program.[15,16] Among these cases, Rogers

> recorded a substantial number of mesothelioma patients in whom the only detectable type of asbestos was chrysotile (Table 9), with evidence of a dose–response effect as reflected in a trend to an increasing odds ratio (OR) at relatively low fibre concentration of less than 10^6 fibers per gram dry lung tissue ($\log_{10}$ = 5.5–6; OR = 8.67).

A 25-year longitudinal study of workers exposed to amphibole-free chrysotile found two confirmed cases of mesothelioma among the exposed workers.[17] The relative risk for all cancers, adjusted for smoking and age, was 4.29 (95% confidence interval [CI]: 2.17–8.46). The authors reported that analysis of four commercial samples of the asbestos used in the Chongqin chrysotile asbestos plant under study were shown to contain less the 0.001% tremolite fiber, which is less than the detection limit for amphibole contamination using x-ray diffraction analysis and the analytical transmission electron microscopy method used in this study. It has been reported that samples of Chinese chrysotile are contaminated with tremolite; however, like the findings of the Zimbabwe UICC samples contaminated with anthophyllite, the later findings from Chinese mines can not be equated to those reported by the authors from their own analysis of the samples representing those taken from their study.

In addition to the studies of exposures to uncontaminated, "pure" chrysotile, there have been several studies of populations who were exposed to chrysotile ore and processed chrysotile products, which contained trace amounts of the amphibole tremolite. In the mining context, Camus et al.[18] compared mortality among women in two chrysotile asbestos mining areas in the province of Quebec with mortality among women in 60 control areas. While focusing on lung cancer mortality, the authors discovered a statistically significant increase in mesotheliomas, as evidenced by an SMR of 7.63 with a 95% CI of 3.06–15.73. Camus et al.[19] in doing further analyses of women from both Asbestos and Thetford Mines, identified one peritoneal mesothelioma from Asbestos and ten from the Thetford Mines area, again showing the ability of fibers from both areas to produce mesothelioma. The authors explain the differences between the two areas as due to the amounts of tremolite contamination, being less in Asbestos.

With regard to processed products composed of chrysotile asbestos, Nokso-Kollvisto and Pukkala[20] examined a cohort of 8,391 members of the Finnish Locomotive Drivers' Association during the years 1953 and 1991. They found a statistically significant fourfold risk of mesothelioma [8 obs vs. 2 exp: standard incidence rate [SIR]: 4.05; 95% CI: 1.75–7.97] among men exposed to anthophyllite asbestos contaminated with tremolite and exposed to pipes, used in the locomotives, made of chrysotile. Chrysotile has been found most often together with anthophyllite.[21] While anthophyllite is exceptionally common in the lungs of the Finnish population, when compared with people in other countries, its potency in producing mesothelioma has been considered low, and mortality studies of Finnish anthophyllite miners had historically not found a causal relationship with mesothelioma[22–25]; however, Tuomi et al.[26] did report anthophyllite fibers as the major fiber type in 70% of the mesothelioma patients examined, but concluded that causality could not be established as no case was reported for anthophyllite exposure only among the mesothelioma cases. Toumi et al.[26] quoted Churg,[27] noting that saying chrysotile content in the lung is low doesn't mean that there has been no past exposure to chrysotile asbestos that could have been responsible for causing the disease. In 1994, the same year in which Nokso-Kollvisto and Pukkala reported their study results, the first epidemiologic study to suggest causation was published when Karjalainen et al.[28] identified four cases of mesothelioma, one peritoneal and three pleural, among 999 Finnish anthophyllite miners and millers, having latencies between 39 and 58 years. All four had asbestosis with

high lung fiber burdens of anthophyllite. However, the potency for anthophyllite in inducing mesothelioma is lower that that of the other fiber types of asbestos.[29]

Another study, of railroad workers predominantly exposed to chrysotile asbestos, by Dr. Thomas Mancuso, arrived at a similar conclusion.[30] Out of a cohort of 181, there were 156 deaths, 14 of which were identified as mesotheliomas, constituting 34% of all cancer deaths in the study, the incidence of mesothelioma far exceeding a doubling of the risk.

In a study of workers employed between 1940 and 1967 in an asbestos textile, friction, and packing manufacturing facility that utilized 99% chrysotile asbestos, Robinson et al.[31] observed 17 mesotheliomas, representing 4.3% of the deaths. The authors concluded that the study demonstrated an excess risk of mesothelioma to the men and women studied.

Finally, a review of 843 cases of mesothelioma recorded in the German Federal State of Saxony–Anhalt betweeen 1960 and 1990 found 67 cases, representing 14% of the total, were directly attributable to a sole exposure to chrysotile asbestos.[32]

2. **Temporality** requires that the cause precede the effect. This consideration is satisfied because in all of the studies examining the carcinogenic potential of chrysotile, the exposures to chrysotile preceded the development of mesothelioma.

3. **Biologic gradient** is the existence of a dose–response relationship for the proposed cause–effect combination. Research has shown that the association between exposure to chrysotile asbestos and the development of mesothelioma is a dose–response relationship. In their epidemiologic study, Rogers et al. found a significant trend of an increasing risk of mesothelioma with increasing fiber concentrations, as shown by an odds ratio of 15.7 for chrysotile fibers less than 10 μm long.[15] A similar dose–response relationship for all asbestos types was recently documented by Rodelsperger et al.[33] and Iwatsubo et al.[34]: "A significant excess of mesothelioma was observed far below the limits adopted in most industrial countries during the 1980s."

Every United States government agency that has dealt with this issue; the World Health Organization; and the World Trade Organization have all determined that this dose–response relationship has no threshold, that is, any exposure to chrysotile raises one's risk of developing mesothelioma.

4. **Consistency** requires that a proposed effect be observed repeatedly under different circumstances. A review of the medical literature reveals that this consideration has been amply demonstrated with regard to chrysotile exposure and mesothelioma. Cases of mesothelioma have been observed in: chrysotile miners in Canada,[35] Italy,[11] and Zimbabwe, South Africa[12,13]; in workers manufacturing chrysotile asbestos cement in Louisiana,[36] textiles containing chrysotile asbestos in North Carolina[31,37] and Somerset, New Jersey[38]; workers manufacturing chrysotile asbestos friction products in Connecticut,[39] England,[40] and Germany[41]; wives of workers who manufactured chrysotile textiles and friction products in New York State[42]; mechanics who installed chrysotile asbestos brake linings in Australia,[43] Canada,[44] the United States,[45–47] England,[48] and Denmark[49]; railroad workers using chrysotile insulation on locomotives in the United States,[30] Italy,[50] Finland,[20] and Switzerland[51]; an Italian worker in the wine filter industry[52]; and individuals who simply lived in close proximity to a chrysotile asbestos textile and friction products plant.[53,54]

5. **Specificity** requires that each cause have a single effect. This is rarely a useful criterion when dealing with environmental carcinogens because most of them cause more than one type of cancer.[55] Chrysotile, like the other forms of asbestos; amosite, anthophyllite, crocidolite, and tremolite, causes asbestosis, lung cancer, and gastro-intestinal cancer in addition to pleural and peritoneal mesothelioma.[4,5,23,24]

6. **Biologic plausibility** seeks to determine whether the theory of causation fits known mechanisms of injury causation. While it is impossible to have a complete understanding of the mechanisms of cancer causation, the biologic facts known about the various asbestos fibers and how they cause disease are consistent with the postulate that chrysotile asbestos fibers are capable of producing mesotheliomas. First, it has long been known that it is not the chemical composition alone of the various asbestos fibers that is important in their ability to produce disease, the health effects of asbestos are related primarily to fiber morphology and size. Many researchers contend that the potency of crocidolite is related to its thin diameter.[56,57] Similarly, inhaled chrysotile fibers have a tendency to split longitudinally and partially dissolve, creating short fibrils of the thin fibers in the lung.

Second, it is universally accepted that chrysotile asbestos is carcinogenic and capable of causing or contributing to the development of lung cancer.[55] Third, mesotheliomas develop in the pleura, peritoneum, and other mesothelial cells that form a monolayer mesothelium lining the serosal cavities and the organs contained within these cavities.[60] Chrysotile is a cause of cancer in the lung and migrates to the mesothelial linings of the body.[61–64] Since chrysotile is carcinogenic and is present in high concentrations in the mesothelial linings where the mesothelioma is induced, it is biologically plausible that it causes or contributes to causing mesothelioma. Fiber penetration can rearrange the cytoskeletal apparatus of the cell and this could indicate an interaction between the chrysotile fibers and the normal mitotic process, since giant multinucleated cells are formed.

These studies indicate that chrysotile penetrates the cell, enters the nucleus, and induces abnormal chromosome formations in dividing cells.[65] Some of these abnormalities include the deletion of the P53 gene growth.[66]

7. **Coherence** asks whether the causal theory is not inconsistent with what is already known of the injury or disease. There is no biologic argument that explains why chrysotile is incapable of causing mesothelioma.

8. **Experimental evidence** can consist of laboratory studies, animal studies, controlled clinical trials, or observational pathology studies. The results from animal bioassays present a strong case that there is no safe form of asbestos. Studies have shown that commercial-grade Canadian chrysotile can induce mesotheliomas when injected intrapleurally into rats, and induce primary lung neoplasms when the animals are exposed by inhalation. The inhalation studies that produced mesotheliomas among animals inhaling the superfine asbestos (SFA), where the majority particle size was less than 5 μm, found the most mesotheliomas occurring after injection of the SFA, which was found to be the most carcinogenic overall.[67] It appears that chrysotile is not only as potent as crocidolite and the other amphiboles in inducing mesotheliomas after intrapleural injections,[68] but also equally potent in inducing pulmonary neoplasms after inhalation exposures. In terms of degree of response related to the quantity of dust deposited and retained in the lungs of rats, chrysotile appears to be much more fibrogenic and carcinogenic than the amphiboles.[69] Another study found mesotheliomas developing in rats six to 23 months after peritoneal introduction of chrysotile asbestos, and the tumors were strikingly similar to those occurring in man with regard to both histologic features and growth patterns.[70] Epidemiologic evidence and animal data support the role that all fiber types, including chrysotile, have in the causation of lung cancer and mesothelioma as well as other cancers. Several different animal species that have inhaled or been injected with pure chrysotile fibers have developed mesothelioma.[71,72]

9. **Analogy** asks whether epidemiologic and other studies have established that an environmental exposure analogous to the exposure being considered may cause diseases similar to those reported for the exposure being considered. All other morphologically similar asbestos fibers cause mesothelioma in both the pleura and the peritoneum.[4,5] The presence of tremolite in chrysotile and the acceptance of the ability of tremolite alone to cause mesothelioma satisfy this consideration.[73,74]

CONCLUSIONS

The above-mentioned scientific data that are in accordance with the Hill causation model support the conclusion that chrysotile per se can induce mesothelioma even when tremolite or other amphiboles are not detected. These findings along with the results of the experimental studies leave no doubt that the scientific evidence supports the carcinogenicity of chrysotile alone in the induction of mesothelioma.[75,76] The debate, as it applies to human exposure to pure-chrysotile-containing products, is academic, at best, as there appear to be few if any pure chrysotile deposits unequivocally identified or reported in the scientific literature; nor has any product purported to contain only chrysotile been conclusively shown to contain uncontaminated pure chrysotile. However, if and when such deposits or products are identified, the fact remains that chrysotile alone can cause mesothelioma, as demonstrated in this paper, when fitting the existing scientific knowledge into the parameters of the Hill causation model. The exact potency of chrysotile, per dose needed to cause mesothelioma, when compared with the amphiboles, remains controversial and has been discussed elsewhere.[4,77–79] However, even when potency, on a dose-by-dose basis, is considered, the fact remains that chrysotile is capable of causing mesothelioma and that no safe dose has been identified below which a risk of developing mesothelioma no longer exists.

While the Hill causation model has served a very useful purpose, its relevance to today's multi-chemical environment may have its limitations. Further, no epidemiologic study has ever been done to validate such models for causation. In fact, the sum total of reliance upon any causation model has been to resolve policy decisions. Dr. Hill indicated he did not believe all nine of his factors of causal evidence were clearly necessary to establish causation. Dr. Hill was concerned with "How do we determine what are physical, chemical and psychological hazards of occupation, and in particular those that are rare and not easily recognized." He was also concerned "However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the result of that research." He further states that to determine causation "No formal tests of significance can answer that question. Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that they contribute nothing to the 'proof' of our hypothesis." Finally, Hill states "The evidence is there to be judged on its merits and the judgment (in that sense) should be utterly independent of what hangs upon it—or who hangs because of it."

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