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LETTER TO THE EDITOR

Response to Drs. Churg and Green

Key words: asbestos exposure, mesothelioma, amphiboles, railroad workers, chrysotile

Drs. Churg and Green [1989] in their Letter to the Editor evidently did not have available the previously published letters that made essentially the same points and my published response to each. To avoid duplication, I should like to cite the publication and pages where the replies have been made, and to respond further to the specific statements made by Churg and Green. To facilitate matters, certain replies will be restated.

Churg and Green referred to the nature of the exposure to chrysotile and possibly other forms of asbestos and to the analysis of asbestos samples. The reply to each aspect is presented in the response to Ohlson [1989] (pp. 353, 354), as well as in the Mancuso [1988] article itself (pp. 640, 641).

Churg and Green referred to the use of amphiboles in railroads in other countries, etc. The reply is also found in response to Ohlson [1989] (p. 354).

Churg and Green referred to lung analysis and other forms of asbestos. The response to the same points by Ohlson [1989] (p. 355) was:

> The Ohlson comment [1989] "even small amounts of amphiboles would have been sufficient to explain the occurrence of the mesotheliomas due to the high durability of the amphiboles and low durability of chrysotile in the lungs" is misleading. As cited in my text, Sébastien et al. [1980] have demonstrated that chrysotile has a predilection for the pleura; in their amphibole studies this tended to be found in the lungs, and chrysotile was found in the pleura. Within this context, more recently Churg [1988, p. 237] commented on this aspect relative to the lung burden and made several points: 1) chrysotile itself does not accumulate in the lung to any great extent (it is more readily dissolved in vivo compared with amphiboles); 2) this does not mean that only amphiboles are causing disease; 3) it would be most inappropriate for anyone to conclude that just because the lung burden was considerably less, for example, among cases of asbestosis than in a matched series of mesotheliomas, that chrysotile does not cause asbestosis; 4) these data on lung burden do indicate that chrysotile is a poor marker of the amount of chrysotile exposure; and 5) it is incorrect to conclude that chrysotile plays no role in mesothelioma.

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> Indeed, Churg and his colleagues [1984] recently reported that in a consecutive series of 90 autopsies of Quebec chrysotile miners and millers, "six deaths were from pleural mesothelioma."

Churg therefore recognized that chrysotile asbestos causes mesotheliomas. Recently Case acknowledged at the Ottawa conference [1989] that he had observed 32 mesotheliomas in Canadian chrysotile operations. In reference to these observations, Mancuso [1988] (p. 649) discussed explicitly the issue of commercial chrysotile from Canada and mesotheliomas:

> In the examination of relative risks from various forms of asbestos, there is a need to put into proper perspective the references which have been made to ore contaminants, which have been identified as derived from the chrysotile mines. The epidemiological investigations of health effects that pertain to chrysotile are solely directed at the form of chrysotile that has been provided in prior decades from the Canadian chrysotile mines for commercial distribution and use in the United States and elsewhere. The chrysotile, as supplied and distributed throughout the United States, was not processed in any way to remove any ore contaminant before use and human exposure occurred. In essence, the mesotheliomas which have occurred and are the subject of the epidemiological studies relate to the form or type of chrysotile that was provided for commercial use [Mancuso, 1988].

It would be helpful if Churg and others would similarly express this clear distinction in their reference to "chrysotile alone," whether to commercial chrysotile or to some other form of uncontaminated chrysotile.

The Churg-Green basic critique is reflected in the following statements: "The validity of Dr. Mancuso's study thus hinges entirely on the question of whether exposure really was to chrysotile alone," and in the suggestion "Amphibole was likely present in the cohort studied by Mancuso and probably was largely responsible for the mesotheliomas which were observed." These rather categorical remarks imply a set of dubious assumptions about causation and these assumptions require careful scrutiny.

In any animal experiment confined solely to chrysotile by inhalation, the chrysotile causes the mesothelioma, and is recognized as the causative agent. Now, in the same experiment, if another form of asbestos exposure is applied at some point in time after the chrysotile exposure, the assumption made by Churg and Green is that the second form of asbestos *is solely* responsible for the mesothelioma, in essence, that chrysotile was no longer the cause of the mesothelioma. However, in order to establish the cause as *solely* due to the *second* asbestos carcinogen, the assumption would have to be made, that the second asbestos carcinogen can and did completely reverse and negate the entire cancer process previously initiated and established by the first asbestos carcinogen.

It is known, however, from the asbestos animal experimental data, as well as human studies, that the cancer process continues long after the exposure to the specific carcinogen has ceased. For humans, the cancer manifests itself clinically many years and decades later as has been demonstrated for mesotheliomas. This

concept of biological reversal of the cancer process of one asbestos carcinogen by the introduction of a second asbestos carcinogen would not be acceptable in animals or humans.

These considerations would also apply to the two railroad cases of pleural mesotheliomas cited in the letter to the editor by Churg and Green. In view of the underestimation by lung analysis of chrysotile demonstrated clearly by a series of investigators and acknowledged by Churg, the amounts shown for chrysotile and tremolite (representing commercial chrysotile) are very great indeed. Any assumption or premise that the presence of other forms of asbestos automatically negates the carcinogenic effect of the chrysotile in the induction of the mesothelioma is without scientific foundation. (The first case began in 1922 and had 49 years of continuous employment much beyond the cases in the Mancuso study. The second case had a different time period. For both cases, there was no information about craft, changing jobs, or nature of work exposure in different time periods, or of "any other asbestos exposure.")

The Churg lung analysis of the asbestos content in the two long-term railroad workers presents a scientific contradiction in the comparisons made within the following context. First, according to the Churg lung analysis data, "chrysotile" remarkably survives in very great quantities in the general population, in persons never occupationally exposed to it, but leaves the lungs of those who worked with it for 30 or more years and can only be found in comparatively smaller amounts. Churg provides a "background" count of 1.1 million chrysotile fibers and 1.2 million tremolite fibers, then in case No. 2 he can only find 140,000 chrysotile fibers and only 500,000 tremolite fibers in a long-time worker. Second, there is sufficient reason to question seriously the validity of the assumption of *no occupational exposure* (my italics) for those 20 male cases over age 50 selected for analysis in the general population, as provided by questionnaires to relatives [Churg and Wiggs, 1986], and the use of that data in the comparison with workers. Workers themselves were rarely informed, and have been unable to recall, even by direct intensive interrogation, the identity of the large number of different chemicals and industrial materials to which they have been exposed individually or in combination in various trade name products, each month and year, with many multiple changes of exposure for each employer, over a life work span of 40–50 years or more.

In reference to the problems of lung burden analysis, the observations of Sébastien (1980) and LeBouffant have established that lung analysis can be grossly misleading in estimating the nature and extent of prior exposure to chrysotile and other forms of asbestos [1978, 1980].

Within this context, Mancuso cited [1988] (p. 650) that a series of experiments have consistently demonstrated that chrysotile, more than any other form of asbestos, gets to the pleura and is retained in the pleura as the basis of subsequent disease.

Now, in reference to the suggestion in the Churg-Green letter "that amphibole probably was largely responsible for the mesotheliomas which were observed," even if one were to apply such an assumed estimate, an analysis of the Mancuso data [1988] would show that the higher risk of mesothelioma to commercial chrysotile remains. Churg's suggested estimate in the use of the term "largely" could mean any significant contribution or as much as 50%. If one applies (50%) to the (14) cases of mesothelioma in the cohort of railroad machinists, there still would remain seven (7) cases of pleural mesotheliomas. Even if one would apply (60%), as the Churg and

Green most severe estimate to the 14 cases of pleural mesotheliomas in the cohort, there still would be 5.6 cases, without any reference to the additional 9 cases of pleural mesotheliomas in various crafts that were observed in the study.

Whether the number of mesotheliomas remaining is (7) out of the cohort of 181 railroad machinists, representing one case in every 26 machinists or (5.6) representing one case for every 32 machinists in comparison with the observations of the American Cancer Society [Selikoff et al., 1965], of one pleural mesothelioma for every 10,000 deaths (three cases occurred among 31,652), either number would establish that the relative risk for the induction of mesotheliomas by chrysotile asbestos is significantly high.

LITERATURE CONSIDERATIONS

The in vivo experimental evidence, as recorded in the literature, does not support in any way the concept that the relative risk for the induction of mesotheliomas by chrysotile is lower than other forms of asbestos. This was demonstrated by Wagner and cited by Mancuso [1988] (p. 650):

> Wagner et al. [1980] conducted extensive experimental studies on animals with all types of asbestos, by intrapleural inoculation and by inhalation. Wagner observed in summary: "These experiments produced some surprising results, in particular, although the crocidolite sample had produced more mesotheliomas than did the chrysotile after intrapleural injection, after inhalation, the sample of chrysotile from Canada produced as many mesotheliomas as did crocidolite; this was in spite of the fact that the retention of chrysotile dust in the lungs was very much less than that of crocidolite. This experiment has cast some doubt on the epidemiological evidence that crocidolite is much more hazardous than chrysotile as far as mesotheliomas are concerned.

In view of the strong carcinogenic potential as demonstrated by Wagner for chrysotile asbestos from Canada in the induction of mesotheliomas, and the similarly strong carcinogenic potential of chrysotile asbestos in the induction of lung cancers, as demonstrated in both experimental and human studies, it is reasonable to conclude that the limitations of the prior epidemiological mesothelioma studies on chrysotile asbestos have been understated.

Within this context, in reference to the literature, as expressed by Churg, and also expressed by McDonald [1989] as "other evidence," the Mancuso reply to McDonald was as follows:

> In reference to the comment about "other evidence," it would be helpful if McDonald would publish for each of his cohort studies, the same data as provided by the Mancuso study; by year of hire, sex, race, number hired that year, age at hire, age at death, year of death, for all cases of mesotheliomas, as well as lung cancer and other forms of cancer, together with the number dead, and those not found or traced.

The absence of such essential data in the McDonald epidemiological studies, as well as in others, has made it extremely difficult to evaluate properly the statement of

lower risk for the induction of mesotheliomas by chrysotile asbestos that has been quoted.

Nevertheless, for one of the two chrysotile cohort studies in the United States that formed the basis for the McDonald statements on relative risk, there is some information derived from a separate study of the Connecticut Tumor Registry that provides another perspective.

Teta et al. [1983] noted an important observation on mesotheliomas that occurred among the women employees, acknowledged by McDonald as part of the total cohort study of the Connecticut plant. This was cited by Mancuso [1988] (p. 654).

The Teta et al. [1983, 1986] observations emphasized that cohort studies directed at rare cancer sites, such as mesotheliomas, based on death certificate alone, can and have provided false-negative findings.

Similarly, for the McDonald second basic chrysotile cohort study (South Carolina), microscopic reviews of various cancer sites over a span of years would have significantly assisted in the identification of mesotheliomas that were not recognized on the death certificates.

It has been clearly established, as already expressed, that chrysotile has a predilection for the pleura and that chrysotile is more likely and more frequently the cause of pleural mesothelioma than any other form of asbestos.

In the Mancuso railroad cohort study of machinists [1988], pleural mesotheliomas occurred in the 14 cases observed and in the 9 other cases of workers employed in the crafts at the same railroad facility. Further, the pleural mesotheliomas were observed sequentially, by individual year of hire from 1920 to 1929, and within specific years (1922, 1923, 1925, 1927), at comparable age at hire, two and three cases of pleural mesotheliomas were consistently identified. This consistency, the replication, sequentially over time, for pleural mesotheliomas and the relationship to chrysotile asbestos raise serious questions about the appropriateness of the assumptions that have been previously made on relative risk. The reality is that commercial chrysotile asbestos has caused mesotheliomas and that the relative risk for the induction of mesotheliomas is significantly higher than previously asserted.

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