REFERENCE: Harington, J., "The Carcinogenicity of Chrysotile Asbestos."

DATE: 1990

METHOD: Review of the literature.

FINDINGS: States that chrysotile is as carcinogenic as the amphiboles and causes pleural meso and lung cancer. Cites IARC Monograph of 1976 and 1987 to confirm this finding. States that animal experiments and limited epidemiological studies of human exposure prove the carcinogenic quality of chrysotile. Reviews major studies indicting chrysotile. Berry & Newhouse (1983) found one meso in exposure for only two weeks. Cites Rochdale textile factory study which showed the greatest proportion of mesos out of all chrysotile studies. Found 1 chrysotile meso among the women working in the WWII gas mask factories. But states that that study had methodological difficulties in comparing the two factories. States that all fibers carry an equal risk of causing cancerof the lung. States that tremolite exposure leads to meso. But believes that the conceptual separation of tremolite from chrysotile is merely academic. States that Morinaga (1989) may have provided proof that pure chrysotile can cause meso since only chrysotile was found in the lungs of 5 patients. States that the human population studies do not refute the findings of the animal studies that conclude that all fiber types cause lung cancer and meso.

John Harington at Collegium Ramazzini June 9 1990

THE CARCINOGENICITY OF CHRYSOTILE ASBESTOS

As chrysotile accounts for some 96% of the world's asbestos production, it becomes most important to define the carcinogenic effects of exposure to the dust produced by this material. To some extent, especially with regard to the induction of mesothelioma, the carcinogenic activity of this material has engendered quite fierce controversy and as a result, scientific objectivity has often been somewhat badly affected.

Apart from this, there is a public health policy concerning the management of the million of tons of chrysotile-containing materials currently installed, for example, in public, commercial and industrial buildings.

To what extent does this application constitute a hazard to health? Is this great enough to justify the putative health hazard and economic impact of removal during the life of the building? Clearly, these are issues of great concern, and the asseveration that serpentine asbestos does not constitute the hazard presented by the amphiboles is a fundamental consideration in the formulation of this aspect of public health policy on asbestos.

With regard to the carcinogenicity of chrysotile, and starting with the information derived from experiments on animals by many investigators, there is consistent evidence that chrysotile is at least as active as crocidolite and amosite in inducing both lung cancer and mesothelioma. It is also substantially clear from the best available evidence of studies of human experience associated with exposure to chrysotile, that this form of asbestos is carcinogenic to humans. Several studies of occupational groups for which data on dust exposure (and from this, dose-response relationships) are available, confirm the capacity of chrysotile to cause lung cancer, and to a lesser extent, mesothelioma of the pleura.

This opinion is shared by the experts advising the IARC in their Monograph on the Evaluation of Carcinogenic Risk of Chemicals to Man, of 1973 and the update of this in 1987.

There are three main classes of data from which this critical issue of the carcinogenicity of chrysotile can be evaluated:

1. Cell and tissue studies;
2. Animal experimental data, and
3. Human epidemiological investigations.

1. Cell and tissue studies, that is, in vitro studies, test the biological potency but not the biological hazards of asbestos. In test systems of hemolysis and cytotoxicity and using cells of different origin, chrysotile has been shown to be highly active in contrast to other fibers tested.

No form of mutagenicity for asbestos in general has been demonstrated by the usual gene mutation assays although chromosomal aberrations have been caused by chrysotile in rat pleural cells in culture.

Chrysotile and crocidolite induce linear dose-dependent morphological and neoplastic transformation of Syrian hamster embyro cells in culture, which is indistinguishable from the cell transformation induced by other carcinogens such as the highly-active polycyclic hydrocarbon, benzo[a]pyrene.

2. The animal experimental data concerning the carcinogenicity of chrysotile is convincing. Essentially, they confirm the human epidemiological results: all major asbestos varieties, including chrysotile, produce lung cancer and mesothelioma, with limited differences in carcinogenic potency.

In experiments involving inoculation into rats, chrysotile is as carcinogenic as crocidolite or amosite. In other experiments, chrysotile has been found to be more fibrogenic and carcinogenic than crocidolite or amosite. Such inoculation experiments, notably those of Wagner, Stanton and Pott

and their colleagues, not only confirm the marked carcinogenicity of chrysotile in inducing mesotheliomas in rats, but also of much significance, they point to the importance of durability and dimension of fibers in relation to carcinogenic activity.

In the inhalation experiments of Wagner and his colleagues of 1977, designed to consider such important features as clearance, retention and dissolution of fibers, it was found that all the UICC samples of asbestos, including Canadian chrysotile, produced mesotheliomas and lung cancer, in some cases from exposures (to crocidolite and amosite) as short as one day.

3. All the human epidemiological investigations regarding exposure to chrysotile share common constraints. Foremost among many variables is the precise nature of the dust to which populations have been exposed. Although the term "chrysotile" is commonly used, the possible contribution of other associated minerals requires to be considered. Tremolite has been invoked as the confounding factor to which most of the mesotheliomas in persons exposed to chrysotile have been attributed by certain authors. While of much scientific interest, from a practical point of view this matter is of academic interest and is dealt with later in greater detail.

Another major variable in the human studies is the vexatious question of cumulative dust exposure and response (dose-response), for which some rather inconsistent information is available. There is uniform agreement that the evidence, even if it is the best available, is weak. Quantitative and qualitative definitions of dust exposure have only been determined haphazardly. Fibers found in lung burden studies can be seriously questioned in their suitability to reflect past patterns of exposure. There have been major differences too, in sampling and counting techniques and in indices

of exposure. Other significant variables are the nature of the data base, the reliability of diagnoses, the history of smoking habits, type and dimension of fiber, and the nature of specific processes in each occupation.

From the above considerations, it is clear that any conclusions about the capacity of exposure to commercial grade chrysotile to induce lung cancer and mesotheliomas in humans are limited by the few occupational studies where exposure has been ostensibly to chrysotile and to no other commercial form of asbestos, and also by the availability of reasonably-adequate dose -response data.

Such dose-response evidence exists in variable form for some six occupational categories of mining and milling in Quebec and Italy, textile production in South Carolina and in the Rochdale plant in England, and in friction product manufacture at the Ferodo brake plant, also in England. For all of these, the best available data on cumulative dust exposure and on Standardized Mortality Ratios (SMRs) for lung cancer (and for absolute numbers of mesotheliomas), were used in each study. Thus, dose-response relationships could be approximately determined for each population.

Of these six populations, however, only the chrysotile miners and millers in Quebec and the chrysotile textile workers in South Carolina have data on extensive early sampling and on particle and fiber counts.

Three other studies were also examined, although they have limitations. In one of them, of asbestos maintenance workers, there are data on dose-response relationships, but the population is one of retired men over age 65. The other studies of British gas mask assemblers in World War II reflect specific exposure to chrysotile, and separately, a mixed exposure to chrysotile and crocidolite.

1. The Quebec mining and milling studies of McDonald and associates studied the mortality of a large birth cohort from 1926 to 1975. Clear trends were found for SMRs for lung cancer to be higher, the heavier the estimated exposure to chrysotile. In general, linear relationships were shown between indices of exposure and the SMRs.

Ten mesotheliomas were found in the 4463 male deaths recorded although since there was no pathological review, the exact number is uncertain.

2. The Northern Italy mining and milling study of Rubino et al., (1979) reported a SMR for lung cancer of only 106 for the total cohort, including cases with all durations from onset of exposure. However, as latency increased during the last 5 years of observation, the SMR rose to 206.

One unconfirmed mesothelioma was reported. Again, pathology verification was not undertaken.

3. Two separate confirmatory studies were made of the South Carolina textile plant at Charleston, where chrysotile was exclusively used. Dement in 1983 found a marked excess of lung cancer (SMR = 315) and strong exposure -response relationships. In the second study of the same plant by McDonald and others, also in 1983, a SMR of 199.5 for lung cancer was found in men 20 or more years after first exposure. A steep linear exposure-response relationship was found, some 50-fold greater at similar accumulated dust exposures than that for the Quebec miners and millers. These data point to a remarkably high level of lung cancer in the South Carolina textile workers.

Only one mesothelioma was reported, but these reports suffer the same constraints as are found in the Quebec miners and millers investigation.

4. In the Rochdale textile factory study in England, studied by Peto et al., in 1985, the principal cohort was exposed to chrysotile. A SMR of 131 for lung cancer was obtained. Studies of mortality occurring 20 or more years after first exposure show a consistent linear relationship with increasing cumulative dose and latency.

Fourteen men died of mesotheliomas, of which 3 were excluded for record purposes. This represents the greatest proportion of mesotheliomas in all the chrysotile studies reviewed here. After the mesotheliomas were found in this population, long-filed records were reviewed and it was found that small amounts of crocidolite had also been used.

5. The Ferodo brake factory in England was studied by Berry and Newhouse in 1983. For lung cancer, there was no indication of increased risk with either duration of exposure or cumulative exposure (SMR = 108 and 122).

The only evidence of excess mortality is the 11 deaths due to pleural mesotheliomas. Eight of these cases might have been exposed to crocidolite and another intermittently to the same. Again there was search of records for some use of crocidolite after the mesotheliomas were known to have occurred. In one case, there had been only two weeks of exposure to chrysotile.

6. In the Connecticut friction products study of McDonald et al. of 1984, an excess of lung cancer (SMR = 148.7), and no deaths from mesothelioma, were reported, although other sources have identified 3 mesothelioma deaths in this population.

Apart from the six principal studies already reviewed here, the investigation of maintenance service employees in the U.S. by Enterline and Henderson in 1973 should be mentioned. This population consisted of retired employees

retired employees of age 65 or over. After adjustment for cumulative dust exposure, those exposed only to chrysotile had a lung cancer mortality 2-4 times the expected (SMR = 236.4), compared to one of 5.3 times the expected (SMR = 526.3) for men exposed to chrysotile and crocidolite. The same trend was seen in other studies.

Of one mesothelioma found in an earlier study of this population, and 5 in a later one, no records were available to indicate whether exposure was to chrysotile, or to chrysotile and crocidolite. Also, for technical reasons there had been considerable under-enumeration of mesothelioma in the largest of the plants studied.

The last special studies reviewed here are those of gas mask assemblers exposed in England to asbestos during World War II. Although no data on dose-response are available, the studies serve useful comparative purposes relating to exposure to chrysotile, and to chrysotile and crocidolite.

In the first of these studies by Jones et al. (1980), of 202 female workers making filter units for gas masks and exposed to chrysotile only, none of the 10 deaths reported was due to lung cancer or mesothelioma. By contrast, of 727 female workers exposed to crocidolite only, there were 139 deaths, of which 11 were due to lung cancer and 16 to mesotheliomas. These numbers are small, however, and it is not possible to base any conclusions on the limited data available for the small number of people exposed to chrysotile for a maximum period of five months.

In the second study of two gas mask factories by Acheson et al., (1982) of 570 women exposed to chrysotile in making the filter units for the gas masks, an SMR of 145 was obtained compared to one of 241 for the crocidolite group. All but one of the 6 mesotheliomas came from the crocidolite-exposed

group. According to the authors, the most obvious difference between the two groups probably lies in the different nature of exposures in the two factories, and there may have been unknown differences in dose and exposure. Apart from this, it is difficult to compare the two factories since the one using crocidolite (Leyland) started earlier and made respirators by hand to a high standard, while at the chrysotile (Blackburn) factory, mechanized manufacture was used.

DISCUSSION

Lung Cancer in Human Populations

In discussing the human evidence, Doll noted in 1988 that there is no evidence to suggest that chrysotile carries a smaller risk of lung cancer than amphibole asbestos, though the risk has been notably low in miners and millers and in friction product workers, compared to the very high levels found in the textile workers of South Carolina. It may be concluded that all types of asbestos carry an equal risk of cancer of the lung.

The marked differences of risk within the six main occupational groups studied here is noteworthy. For each of these studies, the best available data for cumulative dust exposure and mortality were used, and the variation seen may be due in part to the factors discussed earlier: the nature of the data base, the history of smoking habits, the type and dimension of fiber, the nature of specific processes in each occupation and to the all-important variable of cumulative dust exposure and response relationships. Degree of latency is yet another profound variable.

Mesothelioma in Human Populations

In contrast to the capacity of chrysotile to commonly cause lung cancer

in occupationally-exposed populations, this form of asbestos appears to cause fewer mesotheliomas than either crocidolite or amosite under conditions of exposures that have been studied.

It has been proposed that in at least some occupational exposures ascribed purely to chrysotile, mesothelioma induction may be due to contamination of the chrysotile by the amphibole, tremolite, which occurs during the geomorphogenesis of chrysotile. As a result, small amounts of tremolite, sometimes of the order of 1%, may be found in the chrysotile ore body and from this, in the commercially-produced and processed chrysotile fiber. There is evidence from Turkey, Greece and Cypress that exposure to tremolite may cause mesotheliomas. Reports of lung burden studies of mesothelioma cases exposed to commercial chrysotile show the presence of tremolite, and several workers have suggested that the mesotheliomas ascribed to chrysotile exposure may in fact, be due to the contaminating tremolite.

However, the matter is none too simple, especially since nothing is known of specific mechanisms of action for any kind of fiber nor of the possibility of any co-carcinogenic action of chrysotile and tremolite when present together. It seems correct to agree with Doll and Peto (1985) that any distinction between the effects of chrysotile and tremolite in inducing mesothelioma is academic unless the tremolite can be removed from the chrysotile or samples can be obtained that are tremolite-free.

From a practical point of view, as long as any tremolite is <u>not</u> removed in industrial processing, and as long as chrysotile remains to the overwhelming extent of some 99% the bulk carrier of this tremolite, the issue of tremolite-contamination of chrysotile does indeed seem to be of academic concern.

Useful evidence that mesotheliomas may be induced by pure chrysotile are the data presented by Kerinaga <u>et al</u>., (1989) from Osaka, Japan. Here,

5 pleural and one peritoneal mesotheliomas (6 of 19 found) were reported to have chrysotile only in the lung tissue. No tremolite or other amphiboles were detected by transmission electron microscopy and X-ray analysis.

Other Asbestos-Related Cancers

Of the several population groups reviewed here, a substantial excess of gastrointestinal cancers was found in men most heavily-exposed to chrysotile in mining and milling operations in Quebec. An excess was also seen in some of the heavily-exposed men in the South Carolina textile plant. No excess risk, however, was found in studies of mining and milling in Italy, in Rochdale textiles, in friction products (in the UK and the US) nor in U.S. maintenance service employees.

Doll and Peto (1985) and McDonald and McDonald (1987) argue that many of the excess cancers attributed to gastrointestinal cancers could be misdiagnosed lung cancers but present no data for this assertion. They also point to the lack of available animal experimental data relating to the induction of this cancer.

CONCLUSION

Carefully-designed experimental cell and animal studies confirm the carcinogenicity of chrysotile. In *in vitro* test systems, chrysotile is markedly toxic and is capable of inducing morphological and neoplastic transformation.

The human population studies do not refute the experimental studies. Chrysotile asbestos is carcinogenic to humans, especially for the induction of lung cancer and mesotheliomas in exposed populations. For cancers of other sites, the evidence for all forms of asbestos is inadequate for evaluation.

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