

WRG 000663

RESEARCH GRANT APPLICATION

TO

W.R. GRACE & CO., CAMBRIDGE, MA

FOR

Epidemiological studies of the health effects of
exposure to tremolite in mining operations at Libby, Montana

by

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PLAINTIFF'S
EXHIBIT
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EXHIBIT

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1. Background

Vermiculite, a micaceous mineral which expands on heat treatment has many uses in construction industries, agriculture and packaging. The largest known vermiculite deposit, at Libby, Montana, has been commercially mined since 1923. At first it was on a very small scale but, after 1939, when two companies merged to form the Zonolite Company, production increased: 20,000 tons were shipped in 1940, 150,000 tons in 1950 and about 200,000 tons annually, since 1972.

The Libby deposit is mined using the open pit mining technique incorporating rubber-tired loaders and trucks for both ore and waste removal. Waste is discharged at the perimeter of the mined area while the ore is hauled to a transfer point for blending and wet beneficiation. During early years of the operation, all functions of mining and milling were performed in a dry state, resulting in very dusty conditions. A series of process improvements resulted in present mine personnel operating from within enclosed air controlled cabs and a totally wet beneficiation process for the mill by 1974. Upon completion of the wet beneficiation process, vermiculite concentrate is graded into five size fractions before shipment.

It has been known that heavy contamination with tremolite is present, averaging 4-5% of the ore mined. Tremolite, which has no commercial use, is a fibrous mineral of the amphibole series. Other members of the amphibole family include crocidolite and amosite which are known to cause pulmonary fibrosis and malignant disease.

Few observations on the health effects of tremolite in man have been made. Cohort-mortality studies of a tremolite-containing talc mine in New York State showed an excess of pulmonary disease and lung cancer and two cases of malignant mesothelioma (1). In 99 cases of malignant mesothelioma with matched controls, four cases with more than 10 million fibres of tremolite per g dried lung were observed compared with one control. The comparable figures, in cases and controls, for other asbestos fibres were as follows:- chrysotile 39:33, amosite 12:1, crocidolite 9:0, anthophyllite 2:0. (2). In lung tissue from chrysotile miners and millers the quantity of tremolite has on average been found to be similar to that of chrysotile although only a minute fraction of the asbestos fibre mined (3-4). Satisfactory explanations for this observation are not yet forthcoming but it may be noted that the risk of malignant mesothelioma is low in the production and manufacturing of chrysotile but high with crocidolite and amosite (5). Experimental studies in animals have demonstrated that the carcinogenic potential of tremolite is similar to that of other fibrous amphiboles (6).

Some pulmonary disease was first noted among Libby employees in 1959 and, after W.R. Grace acquired the company in 1963, annual X-ray of employees was started. In the 1970's, pulmonary function tests were introduced and later a respiratory disease questionnaire. Efforts made by the company to investigate pulmonary disease among workers included the search for death certificates for all known deceased employees. Individual exposures in terms of duration and dust concentration were also estimated. Intensive efforts to further reduce exposures were made and a vigorous anti-smoking campaign was instituted to attempt to reduce the risk. It was recently observed that there was an apparent excess of

respiratory cancer: 16 lung cancer deaths and 2 from malignant mesotheliomas in a total of 109 deaths. This information was reported by the Company to EPA on March 24, 1983.

In 1981, NIOSH expressed the wish to investigate the health of employees in the industry and the company offered their collaboration. Protocols were developed by NIOSH for:

- 1) morbidity studies using available x-rays, lung function tests and symptom questionnaires.
- 2) a mortality study of all persons employed one year or more, 1940-1969.

This proposal was presented in February 1982 and it was then agreed that the company might also undertake their own studies but that all information should be shared. ~~More recently, NIOSH~~ has indicated their intention to include all persons ~~ever~~ employed in their mortality studies. They do not expect to complete the work before the end of 1984.

2. Objectives

The purpose of the research program described below is to complement the NIOSH studies in four ways:-

- a) by obtaining a more rapid indication of the extent of any occupationally related mortality, in particular of lung cancer, mesothelioma or pulmonary fibrosis, with estimated exposure-response relationships.
- b) by checking that the findings in exposure-response obtained from the extensive radiological study by NIOSH, based on selected routine X-rays from current workers, are borne out by films of good quality taken by a well standardized modern technique from both current workers and a defined sample of ex-employees.
- c) by studying the relationship between past exposure and measurements of tremolite in lung tissue at autopsy, at the same time confirming that there are no significant amounts of other minerals present -- particularly in cases of mesothelioma.
- d) by evaluating the use of ferruginous body counts in sputum as an objective measure of accumulated past exposure to amphibole fibre (in this case, tremolite). If proved valid, this test could have wide application in pre employment screening, in epidemiological studies and in assessing attributability.

3.1 Cohort study

The cohort will comprise all male employees with a record of employment for one year or more who were hired before January 1st, 1963. There are 419 men who meet these criteria, 11 of whom were first employed before 1940. Four of these men left in 1940-45; the remaining 7 were long-term employees. Using company records all jobs in which the subjects were employed will be identified. For each job exposure estimates will be made year by year. This work will be undertaken by Dr Sébastien (see 3.5 below).

The vital status of each member of the cohort, on July 1st 1983, will be sought. Excluding those for whom death certificates have already been obtained, enquiries will be made through other employees, friends and relatives. These inquiries will be made mainly by Earl Lovick who will state that the company is assembling statistics about all past employees. In addition, names and dates of birth will be submitted to drivers' licence bureaus in states where the subjects may be living. Other possible sources of information are electoral lists, local taxation files and the U.S. Post Office. For those reported to be alive, place of residence with address or telephone number will be sought. If no certain information is available, the subject will be contacted personally by telephone or mail. For those reported as dead, the place and date of death is required.

When other methods of tracing have failed, cases will be submitted to Equifax, a company which provides credit information and also offers tracing services.

Upon being informed of a death, data will be submitted to State Vital Statistics Departments and a copy of the death certificate sought. If the death was not registered in the state of last residence, or the death occurred after 1978, the certificates will be obtained from the National Center for Health Statistics. Failing this, the cause of death will be sought from the hospital where the death occurred. Finally, the causes of death will be coded by a qualified nosologist using the 8th revision of the ICD.

The data will be compiled on magnetic tape in three files including:

- 1) date of birth, work history (by numbered jobs), vital status and date and cause of death, for all cohort members.
- 2) exposure estimates by year and numbered job.
- 3) death rates for white males by cause, age and quinquennium for (a) Montana and (b) USA.

In line with our usual practice, the statistical analyses will be of two kinds. First, a man-years life-table analysis will be made in which observed numbers of deaths by cause are compared with those expected from (a) Montana and (b) US rates. From this SMRs will be calculated for the main diagnostic categories in relation to estimated exposure in terms of duration and dust or fibre concentration (see 3.5 below). A case-control 'internal' analysis will follow in which relative risks by exposure group are estimated from the overall experience of the cohort. To the extent that smoking histories are available, we shall also try to assess separately the contribution of smoking and tremolite exposure on the occurrence of lung cancer.

3.2 Studies of mineral fibres in lung tissue

Material for study will be gathered from two main sources:-

1. Cohort deaths to July 1983

In all cases in which an autopsy was reported on the death certificate we shall communicate with the head of the department of pathology and request some lung tissue if available. For studies of lung tissue our order of preference is as follows:
1) whole lung 2) sagittal section of lung (about 1 cm thick)
3) pieces of lung tissue 4) paraffin blocks of tissue. For cases where the question of autopsy was not clear or in which a thoracotomy had been performed an enquiry about lung tissue will be made.

2. Non-cohort deaths to July 1983.

Systematic efforts will be made to obtain lung tissue from autopsy or surgery from any other deceased ex-employees. After July 1983, continued efforts will be made with the collaboration from pathologists at Kalispell and Spokane to encourage appropriate consent to autopsy in ex-employees to obtain whole lung or sagittal sections.

Electron microscopic studies on the samples collected will be made by Dr Sébastien to quantify mineral fibres by type, size and topographical area of lung in relation to estimated exposure.

3.3 Radiologic study

To obtain reliable results with reasonable economy the radiological study (and related analyses) must be based on a

relatively small but well defined group of subjects. Current employees are X-rayed annually at Libby Hospital and it is important that the resulting films should be of good and even quality. The radiologist, Dr. Tyler Gill, has new equipment and we shall discuss with him the use of some widely accepted and well standardized technique for survey radiography such as that recommended to the International Labour Office (7). This will enable all films for our purposes to be taken at Libby at least extra cost. Subjects for study should then comprise a) all current male employees and b) all living members of the mortality cohort resident within say 3 hours travel time from Libby Hospital - about 300 in all. We suggest that arrangements be made by Grace to have the films taken at company expense, if possible by the end of 1983. The nature and purpose of the study should be made clear and, so far as this research is concerned, participation is voluntary. The current employee sample will provide information mainly on the effects of the relatively low exposure of the last 10 years and will provide a basis both for comparisons with persons more heavily exposed in the past and for future observations. The ex-employee sample will show the nature of long term effects across a wide range of exposures and help provide a total picture of the health of the cohort. We do not believe that the imposition of a geographical (travel time) limit in selecting the sample will introduce important bias.

~~Assessment of the films will be wholly the responsibility~~ of the McGill team. For this purpose about 50 chest radiographs of similar quality and appearance will be added to the series from unexposed persons working in and around Libby. The complete set of about 350 films will be arranged in random order, labelled to obscure identification and allocated a serial number in preparation for classification into the 1980 ILO International system by

three experienced survey readers. We would propose to invite Dr John Gilson (formerly director of the MRC Pneumoconiosis Unit, Cardiff), Dr Robert Jones (Tulane University) and another radiologist of international standing, to attend a 3-day reading session probably at McGill in February/March 1984 for this purpose. ~~The assessments will be made independently and the scores then averaged.~~

The data analysis, again focusing on exposure-response, will examine the prevalence of radiographic changes - pleural and parenchymal - in relation to accumulated exposure (see 3.5 below) with allowance so far as possible for age, time since first exposure duration of exposure and smoking habit.

Secondary analyses. The results from the most recent routine pulmonary function tests and respiratory symptom questionnaires will be analysed in relation to the radiographic readings, age and smoking habit for degree of correlation. These findings will help the Company to evaluate its present health monitoring procedures at Libby.

3.4 Sputum study

This investigation will be confined to current workers. During Dr Sébastien's visit to Libby in October, 1983 (see 3.5) ~~he will arrange to see all male employees and explain the purpose~~ of the study. He will provide each of them with three small plastic containers containing some preservative fluid and instruct them on how to collect their sputum at home on three consecutive days. So far as possible, all employees will be persuaded to participate but they will be quite free not to if they so wish. When all specimens are collected they will be brought back to McGill by Dr Sébastien or by some other secure means.

In the laboratory the three samples from each man will be pooled and the volume measured. After homogenization slides will be prepared for analysis by Dr. Bruce Case for the presence or absence of true sputum and for cellularity but not for evidence of malignancy. Half of each sample will then be digested and an estimation made of ferruginous body (FB) content by optical microscopy. A proportion of the remaining half samples will be further analysed by electron microscopy for fibre identification. It is expected that almost all the FBs will have a tremolite core; if this is not so, the electron microscopic work will be extended as necessary.

Statistical analysis of the laboratory test results will aim to determine the relationship between the tremolite FB count, standardized for volume and cellularity, and work history, taking note of time since past exposure and accumulated exposure in fibre years.

3.5 Exposure estimates

A limited quantity of information is available on the past exposure of workers at Libby mine. Environmental measurements using a midjet impinger were made by Montana Health Department on a number of occasions during the period 1941 through 1963. In 1968, MESA carried out midjet impinger and membrane filter measurements side by side. Since then, regular personal and frequent stationary membrane filter measurements have been made.

In 1956, impinger counts of up to 80 mpcf were reported. There was then a gradual reduction in dust levels which became dramatic with the introduction of wet milling. Further engineering improvements have since brought down average fibre counts to just below 0.5 f/ml.

In order to estimate individual exposures all jobs listed in employee work records will be identified and the best estimates possible made for the period 1937-1963. For this, use will be made of information assembled by the company, measurements made by Montana State Health Dept, MESA, and measurements newly made by Dr Sébastien together with his best evaluation of data available. Having regard for the fact that the most significant exposure took place at a time when only dust counts were taken and very few at that, our primary analyses may well be made in relation to dust. However, we shall then repeat the analyses using the best estimates we can on conversion ratios.

4. Personnel

The project will be under the general direction of Dr J.C. McDonald, in collaboration with Dr A.D. McDonald and Dr P. Sébastien. Dr A.D. McDonald will be responsible for the cohort study of mortality and for the identification and collection of autopsy material, Dr Sébastien for all environmental and laboratory work, and Dr B. Armstrong (who joins the School staff this month) for statistical analysis. The assistance of Dr J. Birke is required for specific aspects of the mortality and radiologic studies and Dr B. Case (Assistant Professor of Pathology of McGill) for cytological analysis of sputum samples.

The project has been discussed with Mr. Robert Glenn, Director of the NIOSH laboratories in Morgantown and it was agreed that an 'observer' from his staff would be appointed to our research group, to maintain close contact between their studies and our own. A reciprocal arrangement will also be made.

5. Timetable

We propose that the project begin formally on September 1st, 1983 (or as soon as approved) and that the data collection and basic analysis be completed if possible in one calendar year. We shall make every effort to achieve this target but cannot guarantee to do so since we could be delayed by factors beyond our control. Progress might be usefully reviewed at about 4 monthly intervals. Concise progress reports will be prepared at these times sufficient to permit full discussion if necessary. An approximate timetable is set out below showing the deadlines for each main component of the proposal.

		<u>Cohort</u>	<u>Autopsy</u>	<u>Radiology</u>	<u>Sputum</u>	<u>Environmental</u>
<u>1983</u>	Jul	cohort defined				
	Aug					
	Sep				collect samples	review data
	Oct					
	Nov	tracing complete				
	Dec			x-rays completed		
<u>1984</u>	Jan	certificates obtained				exposures estimated
	Feb					
	Mar		specimens collected			
	Apr	analysis		x-rays read	lab work completed	
	May					
	Jun				analysis	
	Jul		analysis	analysis		
	Aug et seq.		Preparation of reports for publication			

6. Budget (in US\$)

All figures are estimates

6.1 Salaries

a) Technician	(1 year full-time)	16,000
b) Clerk	(1 year full-time)	12,000
c) Statistical clerk/programmer	(1 year half-time)	8,000
		36,000
d) Fringe benefits 16%		5,760

Sub-total (a-d) 41,760

6.2 Honoraria for x-ray readers

3,000

6.3 Laboratory expensesincl. tissue analysis, sputum analysis
and cytology

8,400

6.4 Office expensesincl. phone, photocopying, typing, etc.
and conduct of x-ray reading session

4,200

6.5 Travel and subsistence expensesincl. visits to Libby, Cambridge,
Morgantown, etc. and travel costs for
x-ray readers

11,000

6.6 Miscellaneous fees and expensesincl. Equifax services, tracing expenses,
fees to state departments of vital statistics

2,000

6.7 Statistical analysis

incl. coding, computing, programming, etc.	4,000
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6.8 Equipment grant

toward cost of new EM equipment	24,000
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6.9 McGill indirect costs

2% on item 6.5	-	220
50% on rest (excluding 6.8)	31,680	

sub-total	31,900
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Estimated total:	130,260
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Please note:

- 1) that the budget does not include the cost of the X-rays and related expense for current and past employees,
- 2) that all figures are estimates and freedom to transfer expenditure from one heading to another is required.

7. General conditions

This application is subject to certain conditions:-

- 1) that, as required by a duly constituted ethics committee at McGill, both management and employees shall receive an account of the overall findings and each person examined (or his physician) a confidential report on the results of the chest X-ray. Should any finding of clinical relevance be discovered by sputum analysis, this will also be reported to the subject or his doctor.
- 2) that the protocol is formally approved by the local trades union representing employees at Libby. The Union President, Mr. R. Wilkins, agreed to the proposal at our meeting on May 16th but we would require written confirmation.
- 3) that we have the right to publish the findings from this research in (an) appropriate scientific journal(s), having given the Company reasonable time (at least 90 days) to comment.

8. References

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2. McDonald AD, McDonald JC, Pooley FD (1982). Mineral content of lung in mesothelial tumours in North America - Ann Occup Hyg. 26: 417-422.
3. Pooley FD (1976). An examination of the fibrous mineral content of asbestos in lung tissue from the Canadian chrysotile mining industry, Environ Research, 12: 281-298.
4. Rowlands N, Gibbs GW, McDonald AD (1982). Asbestos fibres in the lungs of chrysotile miners and millers, a preliminary report. Ann Occup Hyg, 26: 411-415.
5. McDonald JC (1983). Exposure response, fibre type and industrial process. Proceedings of World Symposium on Asbestos, Canadian Asbestos Information Centre, Montreal, pp 29-48.
6. Wagner JC, Chamberlain M, Brown RC, Berry G, Pooley FD, Davies R, Griffiths DM (1982). Biological effects of tremolite. Brit J Cancer 45: 352-360.
7. Guidelines for the use of ILO Classification of radiographs of pneumoconioses. Revised edition (1980) Appendix A. Occupational Safety and Health Series No 22, ILO, Geneva, pp 21-25.