478-8

April 7, 1990

OSHA
DOCKET OFFICER
DATE APR 12 1990
TIME

Docket Officer
Docket H-033-d
Occuparional Safety and Health Administration
200 Constitution Avenue, NW
Room N-2625
Washington, DC 20210

Dear Sir:

My name is mentioned and some of my work referenced in the OSHA Notice of Proposed Rulemaking on Occupational Exposure to Asbestos, Tremolite, Anthophyllite, and Actinolite (55 FR 4939, February 12, 19901. Because of possible misinterpretations I wish to elaborate on your interpretation of my work. My comments to be added to the record are my own, are done as a private citizen, and are in no way meant to reflect the opinion of NIOSH or others.

The "independent review panel" (hereafter referred to as the panel) in their evaluation of the "unpublished report by Gamble" used the draft report dated 3/20/88. There is a later and more complete draft dated April 1988. The April draft was completed after the NIOSH internal review and takes into account the reviewers comments. I am therefore enclosing this report, and is the report I will refer to in my comments.

I am also enclosing a review of the literature on the health effects of nonasbestiform amphiboles to be included in the record. It also is my own evaluation of the literature, and is not meant to reflect the opinion of NIOSH or others.

I will now comment on specific statements in the notice of proposed rulemaking.

Statement: "internal memoranda . . . disputed OSHA's regulatory treatment of nonasbestiform tremolite, anthophyllite and actinolite."

Comment: In an internal NIOSH memoranda dated 1/6/87 I reviewed the OSHA Draft Notice of Supplemental Rulemaking in Occupational Exposure to Asbestos, Tremolite, Anthophyllite and Actinolite (TAA). I argued that the evidence did not support the OSHA position that nonasbestiform TAA "presents a significant risk in the same manner and magnitude as their asbestiform counterparts and should be treated the same." In the new proposed rulemaking OSHA changes their earlier position, and is now proposing "that nonasbestiform TAA no longer be regulated in the same way as asbestos."

Another of the points I argued was that OSHA had misinterpreted the animal studies (Smith and Stanton), and that they were negative with respect to nonasbestiform tremolite and NY tremolitic talc. OSHA has also modified that earlier interpretation in the new proposed rulemaking.

The 1980 NIOSH study of NY talc workers was a crucial part of the OSHA evidence for regulating TAA as asbestos. I argued in another internal memorandum that the deficiencies in that study

(possible confounding from smoking and other exposures, and lack of exposure-response analysis) were so serious that until these questions were answered, the results could not be interpreted as either supporting or not supporting a causative association. OSHA also described the study as "inconclusive."

I further argued that mortality studies of workers exposed to other nonasbestiform amphiboles are "relevant to the issue of the carcinogenicity of nonasbestiform varieties of asbestos." OSHA in the new proposed rulemaking also discusses studies of workers exposed to nonasbestiform amphiboles and concludes that "there are .no studies which provide sufficient evidence to support the regulation of cleavage fragments as causing asbestos-related diseases to the same extent as asbestos."

Statement: "NIOSH studies of upstate NY talc miners and millers exposed to predominantly nonasbestiform tremolite and anthophyllite showed . . . a high prevalence of pleural thickening and calcification, decreased pulmonary function and lung fibrosis." One of the problems identified by NIOSH in the Stille and Tabershaw mortality study was that "the analysis did not address the prevalence of pleural thickening..."

Comment: In the morbidity study of NY talc workers there were two cases of pleural calcification in **121** talc workers **(28** with prior work experience and one case among the 93 employees working only at Vanderbilt). Pneumoconiosis (category ≥ 1) was 13% in 121 talc workers with $\geq$ 15 years talc exposure, which was **8%** less than in a comparison group of coal miners. The prevalence was 6.8% in workers employed only at Vanderbilt, **5%** more than a

comparison group of potash miners. In a separate study of Vermont talc workers, a prevalence of 21% pneumoconiosis was observed. See enclosed references Am. Rev. Resp. Dis. 119: pp. 741-753, 1979; Dusts and Disease, pp. 307-315, 1979.

A subsequent NIOSH study of talc workers in Montana, Texas and North Carolina showed no significant differences in the prevalence of pleural thickening between the talc workers in these regions and NY talc workers. A possible hypothesis suggested by these data is that talc itself is an etiologic agent in the development of pleural thickening. A separate study of Vermont talc workers showed a prevalence of 9% with pleural changes, but. the changes were not specified so comparisons are problematic. The pulmonary function among NY talc workers is comparable to that of talc workers from other regions. (Ann. Occ. Hyg, 26:841-859, 1982; Chapter 16 in Health Issues Related to Metal and Nonmetallic Mining).

Pneumoconiosis and reduced pulmonary function are not uncommon findings in mining populations. The finding of pleural changes in all the talc populations studied by NIOSH (and perhaps in Vermont talc workers) suggests an etiology unrelated to amphibole exposure. Only NY talc workers had known exposure to amphiboles.

Statement: ". . . Dr. John Gamble wrote a lengthy analysis of the NIOSH study in which he criticized the study for its lack of an exposure-effect relationship. He also attempted to attribute the excess lung cancer risk to smoking . . . he concluded that

OSHA had erred in its interpretation of the NIOSH study by Brown et al."

Comment: I criticized the study for not analyzing for an exposure-effect relationship and for not collecting smoking histories. I argued that without an exposure-response relationship, with possible bias from smoking, and without a plausible biological reason (such as negative animal studies), the evidence from this study was inadequate to support the conclusion that the nonasbestiform tremolite in the NY talc is the agent causing the excess risk of lung cancer.

I did not attribute the excess cancer risk to smoking. I said that until one can discount a smoking effect, then smoking is a viable alternative hypothesis, at least as viable as the "asbestiform tremolite and anthophyllite" hypothesis. The hypothesis that smoking caused the excess lung cancer risk has not been falsified by the 1988 NIOSH case-control study.

The NIOSH hypothesis that asbestiform tremolite and anthophyllite are the etiologic agents causing the excess risk of lung cancer is based on a false premise regarding the amphiboles in the talc. The NIOSH hypothesis has also been partially falsified by subsequent findings. These include a lack of an exposure-response relationship with tenure as the surrogate measure of exposure; confounding by smoking; a lack of evidence of tumorgenic activity in animals exposed to nonasbestiform amphiboles, antigorite,, and NY talc; and a lack of increased risk in mining populations exposed to nonasbestiform amphiboles. This evidence is documented in my enclosed review paper.

I suggested (and continue to do so now) that there are other possible interpretations of the 1980 study, and that until these other hypotheses are tested, the NIOSH hypothesis that asbestiform tremolite and anthophyllite are the agents (even prime agents) is not justified. All hypotheses should be evaluated in terms of strength of association, temporality, biologic gradient, plausibility, consistency, and lack of bias. When considered in the light of more evidence, I believe the NIOSH hypothesis to be falsified by all criteria except strength of association and temporality. The **1988** NIOSH study compared to the **1980** NIOSH study showed a reduction in the strength of association, and the lung cancer risk to be confounded by smoking. The association of increased risk with increased latency was shown to be as compatible with a smoking etiology as an occupational exposure etiology. Thus the temporality argument prominent in the **1980** study is weakened when smoking is considered.

It is of course possible that exposure to talc does result in increased risk of lung cancer, as well as an increased risk for a number of other causes of death that have elevated SMR's. But this is only speculation as appropriate analysis to evaluate this hypothesis has not been done in the latter case, and not been completed in the former case.

Statement: " . . . an unpublished report by Gamble . . [supplemented] this previous memo. The NIOSH panel . . . criticized Gamble's report for placing too much emphasis on the lack of an exposure-response relationship" as they felt the

variability of exposure intensity over time would obscure any relationship. The panel criticized the smoking analysis, "stating that smoking patterns . . . did not differ significantly from expected and thus the excess lung cancer risk . . . was not likely to be accounted for by smoking." Further, ". . . the elevated risks initially observed . . . have persisted."

Comment: I believe it is important to read the April 1988 draft report because the panel is not completely accurate in their characterization of what was said in the report and is incorrect in some of their statements. I suggest it is more appropriate for OSHA to comment on the data in the 1988 report rather than to comment on the panel's comments.

The unpublished report is not a supplement to the previously referenced memoranda. It is a draft report of a NIOSE Health Hazard Evaluation (HHE) requested by R.T. Vanderbilt and updates the original cohort studied by NIOSH. Since the data in the unpublished report has not been included in the proposed rulemaking, I will include some discussion of the findings in addition to including the latest revised version.

I will summarize the data by comparing the findings of the 1980 NIOSH study, the April 1988 draft report, and a July 12, 1988 letter sent by NIOSH to Vanderbilt. The letter is the only official report of which I am aware regarding the HHE. This letter documents "significantly ($p < .05$) elevated mortality rates" from all causes, NMRD, all malignant neoplasms and lung cancer. The two paragraph letter ends: "The analysis of this augmented mortality data set, coupled with the environmental

findings, do not provide NIOSH with the scientific basis to change its recommendations to OSHA concerning asbestos or its previous recommendations regarding exposures at your company. The full report will follow the letter in a few days."

The data reported in this letter comprise a small part of the data in the 1988 study. The NIOSH interpretation of the "augmented mortality study" is contradictory to the analysis and interpretation in the 1988 report. I believe NIOSH has impeded the scientific process relating to the collection, analysis and reporting of these data. I therefore take this occasion to briefly discuss the scientific questions addressed in the 1988 report and the OSHA rulemaking. These issues are presented in more detail in the enclosed 1988 draft report and in the 1990 literature review.

To evaluate the question addressed in this HHE (and in the OSHA rulemaking), one must look at all the evidence. As the panel indicated, the draft report of the HHE does provide additional evidence as can be seen in Table 10 (attached) which was provided to the panel during their investigation.

The panel criticized the emphasis on the lack of an exposure-response relationship, and recommended "retrospective exposure assessment which will permit estimation of cumulative exposures." To reduce possible exposure misclassification we recommended "analysis of exposure-response using as the exposure variable net tenure (actual hours each employee worked) in the case-control study and cumulative dust exposure in mppcf-years for both the cohort and case-control analyses." (pp. 41-2).

NIOSH has the retrospective exposure we estimated for every job by time period, so these analyses can be quickly and easily done.

What we said in the report about exposure-response is as follows: "Exposure-response relationships for lung cancer were estimated by least-squares regression. A line fitted to relative risks (RR) derived from the ***SMR's*** in the 20-36 year latency group was negative, with an estimated RR at 25 years tenure of 0.61." (pg. 1)

Regarding the case-control study we said: "Two sets of tenure groups were used to estimate the trend of lung cancer risk . . . The slope was negative (OR {odds ratio) increasingly less than 1 with increasing tenure) when calculated for: all cases and controls; when stratified by smoking; when excluding workers with < 1 year tenure , < 20 years latency, or < 20 years latency and < 3 months tenure." (pg. 2)

The panel stated that "smoking patterns . . . do not differ from the expected patterns in working populations. Furthermore. cases who smoked did not smoke more than controls who smoked. Smoking, therefore, is unlikely to account for the excess of lung cancer in this cohort."

The smoking patterns in the cohort are not known. The controls were not a random sample from the cohort and so do not provide "smoking patterns" for the cohort. The morbidity study was conducted in the late 1970's and does not necessarily reflect cohort smoking patterns. Certainly the smoking pattern of the cases (all smokers or former smokers) does not reflect that of a working or any other reference population.

The data suggest controls smoked on average 1.7 more cigarettes/day than the cases, and worked an average of five more years. The panel's statement that the excess risk is unlikely to account for the excess lung cancer is based on a false premise regarding smoking patterns. Further, the risk in the twenty year latency group has declined, from a 4.6 fold excess in the 1980 NIOSH study to a 2.6 fold excess in the 1988 NIOSH study.

The panel also suggests "elevated risks initially observed . . . have persisted." The risks are still in "excess," but not to the same degree. The overall risk for lung cancer decreased by 23% from 270 to 207; the lung cancer risk in the $\geq$ 20 year latency group decreased 43% from 460 to 258. The SMR for nonmalignant respiratory disease is about the same -- 277 compared to 251.

What was increased of course are the number of cases; lung cancer by 88% from 9 to 17 (and 22 in the case-control study), NMRD by 112% from 8 to 17. This is what one would expect as one increases follow-up time and length of latency.

Statement: "OSHA continues to find persuasive the rationale of the original NIOSH researchers who defended their conclusions. In addition OSHA believes that the NIOSH studies provide evidence to support the possibility that exposure to minerals at the mine is correlated to the excess mortality from NMRD and an excess of pleural thickening and lung decrements."

Comment: I suggested earlier in this discussion that the most persuasive rationale for excess pleural thickening is talc, not amphibole minerals.

I believe part of the rationale for the NIOSH conclusion was the belief that the talc contained asbestiform tremolite and anthophyllite. The data do not support this premise, nor since the **1986** rulemaking does OSHA support it.

NIOSH has criticized the Stille and Tabershaw study of the NY talc workers. These criticisms apply to all of the mortality studies of the NY talc cohort. It is instructive to apply these criticisms to the **1980** NIOSH study, to the **1988** NIOSH draft report, and to the NIOSH letter to Vanderbilt.

NIOSH criticism: small study population.

The 1988 NIOSH study and NIOSH letter have the same size study population and 17 lung cancer cases compared to 9 in the **1980** study. There would have been at least five more lung cancer cases in the cohort study if follow-up through **1985** had not been stopped by NIOSH. The case-control portion of the **1988** NIOSH study has **22** lung cancer cases.

NIOSH criticism: follow-up period relatively short.

The maximum latency is **28** years for the **1980** study and **36** years for the **1988** study and NIOSH letter. The maximum latency for the **1988** study would have been **39** years if NIOSH had not prohibited three more years of follow-up via the National Death Index.

NIOSH criticism: smoking data missing.

Smoking data are missing for the **1980** study but are complete in the **1988** study for the **88** cases and controls. These data are not mentioned in the NIOSH letter to Vanderbilt.

NIOSH criticism: possible confounding from smoking.

It was not known if smoking was a confounder in the 1980 study as smoking data were not collected. Smoking is known to be a confounder in the cohort analysis of the 1988 study and is thus a confounder in the 1980 study and in the data presented in the 1988 NIOSH letter. In the 1988 case-control analysis, smoking is shown to increase the risk of lung cancer. When the cases and controls are stratified by smoking, the risk of lung cancer decreases with increasing tenure. Smoking is not discussed in the NIOSH letter to Vanderbilt.

NIOSH criticism: possible confounding from prior exposure.

Prior exposure is unknown in the 1980 study. Prior exposure, including prior talc exposure, was not shown to increase the risk of lung cancer in the 1988 study and so is probably not a confounder. This issue is not discussed in the NIOSH letter to Vanderbilt.

NIOSH criticism: lacks exposure-response analysis.

There is no analysis by tenure or cumulative exposure in the 1980 study. There is an exposure-response analysis (exposure-tenure) in the 1988 study. In the cohort analysis no association is observed in the $\geq$ 20 year latency group. Several exposure-response analyses were evaluated in the case-control study. None showed any exposure-response association. Exposure data were collected and exposures by job and time estimated in the 1988 study. Exposure-response analyses using these data was prohibited by NIOSH, so we could only recommend the analyses be done. The lack of an exposure-response association is not mentioned in the NIOSH letter to Vanderbilt.

NIOSH criticism: need to consider criteria of strength of association, temporal relationships, biological plausibility and consistency in the interpretation of an association between environment and disease.

The **1980** study considers strength of association and temporal relationship as they relate to time since hire. Temporal relationships of time since started smoking could not be considered. Consistency is considered by comparing the mortality experience of NY talc workers with Finnish anthophyllite asbestos workers and earlier NY talc mortality studies. There is no consideration of animal studies. When these issues are discussed, the discussion is too brief to be persuasive or very informative.

The 1988 report discusses these issues on pages 16 to 31, and Tables V-2 through V-5 on pages **49-54.**

These criteria are not mentioned in the NIOSH letter to Vanderbilt, and none of the issues are discussed.

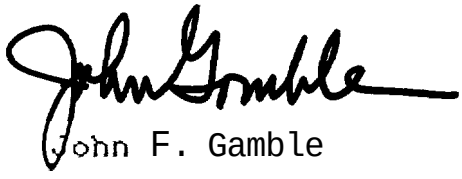
In 1986 "OSHA granted a temporary stay insofar as the standards applied to non-asbestiform tremolite, anthophyllite, and actinolite." OSHA said "it was granting the stay in part to enable the agency to review . . . the NIOSH memoranda." "The issues to be decided in this supplemental rulemaking are whether non-asbestiform tremolite, anthophyllite, and actinolite . . . should not be regulated . . . as asbestos."

I suggest the **1988** NIOSH draft report of NY talc workers provides the most complete mortality data relating to exposure to non-asbestifom tremolite. It is certainly worthy of more

consideration than the memoranda. The memoranda are based on analysis of published data as of about 1985. The 1988 study provides new data that are available nowhere else and address questions critical to this rulemaking. Relating the opinions of the NIOSH panel does not constitute an independent consideration by OSHA of the data included in the 1988 report. I therefore submit the April 1988 report for your independent consideration. Some of the issues discussed in the 1988 report are further developed in the review paper. The review paper is in essence my interpretation of the literature as it relates to the issues of this rulemaking.

The issue of this rulemaking is complicated. I hope the data I am submitting will be helpful in arriving at an objective and scientifically supportable decision.

Sincerely yours,



John F. Gamble
424 Rotary Street
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cc: Mr. Robert M. Bastress, Esq.

Table 10

Results of NIOSH Mortality Studies of Vanderbilt Talc Workers

	Brown & Wagoner (1980)		Gamble and Piacitelli (1988)		Baker (1988)
COHORT STUDIES					
	obs	SMR	obs	SKR	SMR
All Causes	74	120	161	128**	128**
Respiratory TB	3	610*	3	419	--
NMRD	8	277*	17	251**	251**
All Malignant Neoplasms	19	180*	36	145*	145*
LUNG CANCER	9	270%	17	207**	207**
≥20 y latency	6	460*	13	258**	--
≥20 y Latency & <1y tenure	--		8	357**	--
Trend uith tenure in ≥20 y latency group	--		Negative Trend		--

CASE-CONTROL STUDY - Gamble & Piacitelli, 1988

	Cases	Controls
n	22	66
% Smokers	91%	64%
% Nonsmokers	0	27%

Calculated Risks:

hoking 5.7
Nontalc Exposures No Trend
Exposure-Response Analysis - Smokers Only

		Calculated OR (95% C.I.) at 25y Tenure
Vanderbilt Talc Tenure	Negative Trend*	0.39 (.11,.67)
≥20y latency	Negative Trend*	0.47 (.19,.75)
≥20y latency, >3m tenure	Negative Trend	0.74 (.40,1.08)
Total Talc Tenure	Negative Trend*	0.54 (.21,.87)

'Statistically significant by p-value and/or 95% confidence interval.

Draft After Internal DRDS Review

478-8B

HHETA 86-012
R.T. VANDERBILT COMPANY, INC./
GOUVERNEUR TALC COMPANY
BALMAT, NEW YORK
APRIL 1988

NIOSH INVESTIGATORS
J. GAMBLE, Ph.D.
G. PIACITELLI, CXH

I. SUMMARY

On November 8, 1985, R.T. Vanderbilt requested the National Institute for Occupational Safety and Health (NIOSH) to update and re-evaluate the 1980 NIOSH study of Vanderbilt talc miners and millers. This report adds 8 more years of follow-up, an exposure-latency analysis to the cohort study, and a nested case-control study *to* control for possible confounding by smoking and other occupational exposures. All known extant environmental records were collected, and exposure by job and time period are estimated. The retrospective cohort study was based on 710 white male workers who were employed between 1947 and 1978 and whose vital status was determined as of the end of 1983. The nested case control study consisted of 22 lung cancer cases matched with 3 controls on date of birth and date of hire and who must have survived the case. In the cohort study, observed mortality compared to the U.S. white male mortality rates were significantly ($p < .05$) increased for all causes (SMR 128, 161 obs), all respiratory disease ICD 460-519 (SMR 251, 17 obs), all malignant neoplasms ICD 140-209 (SMR 145, 36 obs), and lung cancer ICD 162-3 (SMR 207, 17 obs). Lung cancer *SHRs* were statistically elevated in the 20-36 year latency group (SMR 258, 13 obs) and among workers <1 years tenure (SMR 357, 8 obs). Exposure-response relationships for lung cancer were estimated by least squares regression. A line fitted to relative risks (RR) derived from the SMRs in the 20-36 year latency group was negative, with an estimated RR at 25 years tenure of 0.61.

Information on smoking habits and non-Vanderbilt jobs were collected on all 22 cases and 66 controls. There was no apparent increased risk associated with non-Vanderbilt jobs. Twenty (91%) of the cases were smokers compared to 42 (64%) of the controls. The proportion of exsmokers in the 2 series was 9%. The odds ratios for cases who smoked was about 6 times that of combined exsmokers and nonsmokers. Two sets of tenure groups were used to estimate the trend of lung cancer risk in the equation Odds Ratios (OR) = 1 + b (tenure). The slope was negative (OR increasingly less than 1 with increasing tenure) when calculated for: all cases and controls; when stratified by smoking; when excluding workers with <1 year tenure, e20 years latency, or e20 years latency and <3 months tenure. The mean latency was 25 years from date of hire and 40 years from date started smoking. The temporal relationships are more suggestive of a smoking than an asbestos etiology.

The reasons for elevated SMR's for the several causes of death tabulated is not known, and is unusual for a working population. Although lung cancer SMR's are elevated, we could not detect an exposure-response relationship. The lack of an increased risk of lung cancer is consistent with other mining populations exposed to nonasbestiform amphibole minerals. The time occurrence of lung cancer is consistent with a smoking etiology. These findings are biologically plausible and are further supported by the lack of a carcinogenic effect of Vanderbilt talc in animal studies. Since numbers are small, recommendation for additional analyses and follow-up are presented in Section V.

Keywords: (SIC 1499) talc, amphiboles, cohort study, case-control study, mining, lung cancer.

11. INTRODUCTION

DRAFT

The National Institute for Occupational Safety and Health (NIOSH) has previously conducted studies of mortality and morbidity patterns and occupational exposures among talc miners and millers.[1-9] In February, 1980, the NIOSH Division of Surveillance, Hazard Evaluation and Field Studies (DSHEFS) and Division of Respiratory Disease Studies (DRDS) published a Technical Report entitled "Occupational Exposure to Talc Containing Asbestos"[**]) which dealt specifically with talc minerals mined by the Gouveneur Talc Company (GTC) in the Gouveneur Talc District in upper New York. This report was divided into 3 sections:

I. Environmental Study by Dement and Zumwalde;[2]

II. Cross Sectional Morbidity Study by Gamble, Fellner, and DiMeo;[3-4]

III. Retrospective Cohort Study of Xortality by Brown, Dement, and Wagoner[7]

Additionally there have been 2 other mortality studies of CTC workers.[10,11] The interpretation of these studies as well as the mineralogical composition of this talc have been a source of continuing disagreement.[12-21] Authors of the previous studies of CTC workers differ in their conclusions as to risk. Some authors[1,7] conclude there is an increased risk of lung cancer due to occupational exposure to asbestifom talc, while others[10,11] conclude there is no apparent increased risk due to exposure, and the talc does not contain asbestifom minerals.

In July of 1986, OSHA proposed regulating the nonasbestiform varieties of tremolite, anthophyllite and actinolite as asbestos on the basis of the 1980 NIOSH mortality study of the CTC employees.[22] This part of the OSHA rulemaking was subsequently stayed[22a]. Since amphiboles are present in significant amounts in many types of igneous and metamorphic rocks covering perhaps 30-40% of the U.S., regulating nonasbestiform amphiboles as asbestos is pertinent to many mining operations, much of the construction industry and its quarrying operations (for such products as concrete aggregate, dimension stone, railroad balast, and riprap) the ceramic, paint, and cement industries, as well as many other areas where silicate minerals are used.[23]

Prior to the OSHA rulemaking in 1986, R.T. Vanderbilt, Inc. requested that NIOSH conduct a follow-up mortality study of its employees at the Gouveneur Talc Company in Balmat, New York to reconsider the question: "Does occupational exposure to Couverneur talc cause an increased risk of lung cancer?" This study attempts to answer this question using retrospective cohort and nested case-control study designs in assessing exposure-response and for controlling biases. Exposure is estimated by tenure. The association of exposure and response is tested in both study designs, but potential confounding biases of smoking and non-GTC talc employment, and nontalc employment are controlled only in the case-control study.

This study builds on previous studies by: 1) updating the vital status through 1983; 2) estimating dust-exposure in the plant over time; 3) evaluating exposure-response by both tenure and latency; and 4) conducting a case-control study to control for the possible biases of smoking and other occupational exposures.

III. METHODS

Cohort definition

The study cohort is all white males hired at the GTC since its beginning of operation in 1947 through 12/31/78. The original data, obtained by DRDS from R.T. Vanderbilt, Inc., was originally collected and prepared by Tabershaw Occupational Medical Associates (TOM)[10] and updated by Lamm and Starr.[11A] Data on this tape (referred to as the "DRDS master file") were collected from plant personnel records and include GTC job histories (date of hire; age at hire; type, location and duration of each job held while working at GTC; date of termination) and date of birth.

To assure completeness of the cohort and accuracy of work history information, comparisons were made between the DRDS master file, Social Security Administration (SSA) quarterly reports (1962-1983), separate lists of employees kept by GTC (one from 1947-1962 and one from 1947-1966), and the DSHEFS master file.[1,7] Any differences in job history comparisons were resolved using company personnel records.

Vital status was determined as of 12/31/83 for all 710 white male workers in the cohort. If the vital status was not determined by the SSA or IRS; then verification was determined by phone follow-up. Death certificates were obtained on all 161 dead persons in the cohort and compared with name, SSN, and date of birth information in the DRDS master file to assure a correct match. The underlying cause of death was coded by a nosologist according to the Eighth Revision of the International Classification of Diseases.

Estimate of Exposure

Exposure is estimated by tenure (calendar time spent in all jobs betueen date of hire and termination or cutoff of study).

Cohort Study

The person-years analysis consists of a comparison of age-time-adjusted death in the study cohort with the mortality experience of U.S. white males, and lung cancer rates from white males from surrounding counties in upper Blew York State. SMR's were computed by the modified life-table technique described by Monson[24] using the OCMAP computer program.[25] Computation of expected number of deaths from the external population rates were adjusted by the OCMAP program for comparability to the Eighth revision ICD using comparability ratios developed by the National Center for Health Statistics. A statistical test to determine whether the SMR was greater than 100 was used, and the observed number of deaths was assumed to have a Poisson distribution.[26]

Person-years (PY) were calculated beginning with initial date of employment and accumulated till death or end of follow-up (12/31/83), whichever occurred first. The PYs for all workers were distributed in 5 year age groups and 5 year calendar time periods.

Exposure was estimated by tenure (years). Latency was defined as time from first employment to date of death or end of study. Also, since Doll and Peto[27] suggest that lung cancer latency is probably longer than 5 years, a lagged exposure-response analysis for lung cancer was also performed ignoring

exposure 5 years before death. In either analysis, a cause-effect relationship between talc exposure and lung cancer would be suggested if among workers with 20 or more years latency, higher SMRs are seen for the workers with higher exposure than for workers with low exposure. Studies of asbestos cohorts generally report on increased risk of lung cancer after a minimum latency of about 15-20 years.[28-30]

Lung cancer mortality risk was estimated by the trend in SMRs by tenure with the 20 or more year latency group. Following procedures outlined by Hanley and Liddel,[31,32] the relationship between tenure and lung cancer was estimated in the equation $SMR = a + b(x)$. The parameter a is the level of response when tenure is 0, b is the slope of the exposure-response curve, and x is tenure. The parameters a and b were estimated using an iterative weighted least squares regression analysis with no restriction on a. As a is often far from unity when tenure is 0, the parameter b is adjusted for the background SMR. This adjustment is the quantity $r = b/a$ (called the relative slope) and can be thought of as the risk per unit increase in tenure. It can be used to compare slopes from various studies and calculate relative risks (RR) from the equation $RR = 1 + r$ (tenure). This method includes estimation of the model, a test of the adequacy of the fit, and a 95% confidence interval for r, the ratio of the slope divided by the intercept. Reliability is expressed by confidence intervals for r, and are applicable even if the number of deaths is small.

Table III-1 provides descriptive data on the cohort. There was a total of 15,294 PY at risk. The average age at hire was 30, and the average age at death was 56.

Case-Control Study .

Two risk factors for lung cancer cannot be evaluated in the SMR analysis: smoking and non-GTC exposures. The effect of these variables were studied in a nested case-control study design. All persons with lung cancer (ICD 162-163, 8th Revision) certified as the underlying cause of death on the death certificate were defined as cases. Each case was matched with 3 controls meeting the following criteria:

1) Exclude all noneoplastic respiratory disease (ICD 460-519) and accidents (ICD E800-E949).
2) Select controls from survivors and deceased, with the closest match on date of birth and date of hire. Controls must have survived the case.

Information on each case and control concerning tobacco use and work history was obtained from interviews of the person himself (if living) or from relatives or friends. Interviews were conducted over the phone whenever possible, or by mail if not. Also, verification from other sources was done whenever possible. For example, several relatives were asked about smoking and work history. Information from GTC personnel records provided pre-GTC employment history, which was confirmed, whenever possible, by contacting the previous employer directly, as well as by questioning relatives.

To control for possible confounding due to non-talc exposure, a panel of 9 epidemiologists and industrial hygienists rated the risk of lung cancer associated with non-talc jobs as listed in the work histories of all cases and

controls. Given job titles only, each panel member independently rated each non-talc job as "probable," "possible," or "no" risk of job-associated lung cancer; each category was given a score of 3, 1, and 0 respectively. A composite score for each job was compiled from the 9 ratings. An individual's total score was the score for each job from all 9 reviewers multiplied by years in that job, and summed over all jobs. This total was calculated for each panel member and added together to get the total overall score. Total scores were arbitrarily divided into 4 categories of comparable size. Estimates of the odds ratios (OR) for each category and trend analysis were used to assess whether nontalc exposure represents a risk factor deserving control in the exposure-response analysis.

The cases and controls were divided into 2 tenure groups for analysis of exposure-response relationships. This analysis was done using GTC tenure with all cases and controls, and then repeated including only those cases and controls who were smokers at death or end of the study. Additional analysis by GTC tenure for smokers only was done with exclusion of all cases and controls with: <1 year tenure; <20 years latency; <20 years latency and <3 months tenure. The analysis for all cases and controls and smokers only was repeated using all talc tenure (GTC plus non-GTC).

Relative measures of effect in a case-control study is the odds ratio (OR). The OR is compared to the lowest exposure level, which is defined as 1. An OR less than 1 indicates a lower risk than the reference level, an OR greater than 1 indicates a greater risk than the reference level.[33] A linear trend in effect follows the equation $RR = 1 + b'x$, where RR = OR, X = exposure, and b' = the slope of the odds ratio. A positive b' means the OR

(risk) increases with exposure. A negative b' means the OR decreases with increasing exposure, or since the exposure is not thought to be protective, would indicate risk is not associated with exposure. Using a least squares approach to a weighted regression where $b' = b_1/b_0$), the slope b' was estimated from the equation $OR = b_0 + b_1x$. The slope b' describes mathematically the change in OR for each year of tenure. Using the standard error (S.E.) of b', a 95% confidence interval (C.I.) 'for b' was calculated. These methods are described by Rothman,[34] and included estimation of the model, a test of significance for whether the slope was zero or not, and a 95% confidence interval for the ratio of the slope divided by the intercept (b').

Rothman[34] argues that the estimation of the magnitude of an effect as a function of exposure is the main objective of an epidemiological analysis. To achieve this objective it is desirable to estimate a trend in effect (b' for case control analysis, r for SMR analysis). The trend analysis is preferable to point estimates (such as OR or SMR) or relying on statistical hypothesis testing for inference. Thus the estimation of slope and the range of possible values for the slope (95% C.I.) will comprise the major portion of the analysis. This type of analysis does not lose information as does estimation of effects at each exposure level, for when there is a trend infomation in bordering categories provide information about the effect in the category in between.

In addition, means of exposure were compared for cases and controls using paired and independent sample t tests as appropriate. All tests were

performed at the 0.05 significance level. Except for the comparison of exposure levels for cases and controls, all testing and confidence interval estimation may depend on the assumption of a large sample size.

IV. RESULTS

A. Cohort Study

There were 710 white males who had worked 1 day or more between 1947, the beginning construction of the mine and mill, and 1978. Vital status and cause of death was determined on the entire cohort. Complete follow-up was through 1983, at which time 161 (27%) of the cohort were dead.

Table IV-1 summarizes observed deaths from selected causes of death compared to U.S. white males. For selected causes, SMRs were significantly ($p < 0.05$) elevated above 100: all causes of death (128), as were malignant neoplasms (145), lung cancer (207), and respiratory disease (251). Table IV-2 provides the distribution by tenure and latency of lung cancer deaths, and expected deaths among U.S. white males. The lung cancer SMR for the greater than 20 year latency group was 258. Over half (8/13) of the lung cancer cases in this latency group occurred in the less than 1 year tenure group (SMR, 357). A straight line of the form $SMR = a + b(X)$, where x = tenure, was fit to the data for the 13 workers with 20 or more years tenure. The Goodness of Fit statistic was not statistically significant, indicating the linearity of the slope (b) can be accepted. The intercept (a) at 0 tenure was 2.94, the slope (b) was -0.045, the adjusted slope r was -0.015 with 95% confidence limits of -0.04 and +0.09. The point estimate of the slope indicates a reduction in

lung cancer SMR of 1.5 per year worked at GTC. Thus with 20 or more years latency and 25 years tenure, the estimated SMR from the regression model is

$$SMR = a + b(x) = 2.93 + (-.045)(25) = 1.795$$

Multiplying by 100 and the SMR = 180 (95% C.I. = 0.950.

The relative risk (RR) which adjusts for background mortality is calculated from the equation $RR = 1 + r\ (\text{tenure}) = 1 + (-0.015)(25) = 0.61\ (0,3.24)$.

Table IV-3 compares SMRs using expected lung cancer deaths from upper New York county rates and U.S. rates. While the rates of lung cancer in upper New York counties are higher than in the U.S. (resulting in slightly higher expected deaths), the difference in SMRs were relative small. For example the overall lung cancer was reduced from 207 to 199, the SMR in the 20 or more year latency group from 258 to 247, and in the <1 year tenure group with 20 or more years latency from 357 to 344. The relative SHR slope (r) was -0.013, a little less than the -0.015 using U.S. rates for expected deaths. The estimated SMR in the >20 year latency group with 25 years tenure was 188, and the RR was 0.67 (0.17, 2.82).

In Table IV-4 any employment during the last 5 years of life was not counted in the latency by tenure analysis. The person-years at risk was only slightly reduced, the expected number of deaths only slightly increased, and so latency-tenure trends were virtually unchanged from those observed in Table IV-2.

In Table IV-5 SMRs for several specific causes of mortality are presented by 5-year time periods. No deaths from lung cancer, respiratory or circulatory system disease occurred prior to 1960. Statistically significant SMRs for lung cancer were present during two 5-year time periods - 1960-64 (3 observed deaths, SMR of 568) and 1970-4 (7 observed deaths, SMR of 436) - but were much lower in the years 1975-83.

Case-Control Study

Tables IV-6 and IV-7 summarize descriptive infomation on the cases and controls. All of the 22 cases were either smokers (91%) or ex-smokers (9%) compared to controls with 42 (64%) smokers and 6 (9%) ex-smokers. Five additional cases that died after 1983 were available for analysis but did not meet the criteria for entry into the cohort study. Cases and controls who smoked were quite comparable in age, year of hire, and age at hire. Controls were heavier smokers than cases, and controls who smoked had almost twice the tenure of cases who smoked (Table IV-6).

Three potentially confounding risk factors are of primary concern: nontalc exposure, smoking, and non-GTC talc employment. Tabla IV-8 presents odds ratios for all cases and controls by estimated risk from non-talc exposure. The highest and medium low scores showed a decreased risk while the medium high score was slightly elevated. The slope of the odds ratio (b') was negative (-0.0008). At the midpoint of the high nontalc exposure group (score 377), the estimated OR from the regression model $OR = 1 + b'(\text{exposure}) = 1 + (-0.0008)(377) = 0.70$, with .95 C.I. of 0.29 and 1.09. Since there was no apparent trend for the risk of lung cancer to increase with non-talc exposure, this factor is not controlled in further analyses.

Table IV-9 presents the risk of lung cancer by smoking category and cigarettes/day. Smoking cigarettes increased the OR for lung cancer almost 6-fold compared to combined nonsmokers and ex-smokers, and 1.4 times compared to ex-smokers. There was little apparent difference in the OR for lung cancer by the number of cigarettes smoked per day. Smoking is controlled in some of the subsequent analyses by including only cases and controls who had smoked.

Table IV-10 presents the relative odds of lung cancer by 2 sets of tenure groups for all cases and controls. Odds ratios declined with increasing tenure except for 5-15 and 10-19 year tenure groups. The point estimates for the slopes of the odds ratios were negative, and the upper 95% confidence limit for the 4-tiered tenure group was also negative. At 25 years tenure the estimated OR from the regression model for the 3 tenure group analysis was 0.80 (0.55, 1.06) and for the 4-tenure group analysis was 0.32 (0.17, 0.48). (See Figure IV-10)

When only smokers were considered, odds ratios declined with increasing tenure and were all less than one except for those with 10-19 years tenure. (Table IV-11). The point estimates of both slopes and the upper 95% confidence intervals of both tenure group analyses were negative. At 25 years tenure the estimated OR for the 3 tenure group analysis was 0.39 (0.11, 0.67), and for the 4 tenure group analyoio was 0.27 (0.06, 0.49) (See Figure IV-11).

Tables IV-12 - 1\1-14 present data for smokers only and includes only cases and controls with $\geq$1 year tenure (Table IV-12); $\geq$20 years latency (Table IV-13); and $\geq$20 years latency and >3 months tenure (Table IV-14). The results are similar to those observed in Table IV-11. The OR all decline with increasing tenure.

Another possible confounder is employment at non-GTC talc mines and mills. Table IV-15 compares the risk of total talc employment (GTC plus non-GTC) for all cases and controls. For the 3 tenure categories the only change was 1 more case in the ≥15 year tenure group and 1 less case in the <5 year tenure group. The OR slope was positive, and at 25 year tenure the estimated OR was 1.03 (0.73, 1.33). When 4 tenure categories are considered the 1-9 and >20 year tenure categories had an increase in the number of cases, but only the 1-9 year category increased for controls. At 25 years tenure the estimated OR was 0.45 (0.24, 0.66).

Table IV-16 compares the risk of total talc employment stratified by smoking. It shows similar trends to those observed in Table IV-11, that is the slope and upper 95% C.I. were negative so all estimated OR were less than 1. At 25 years tenure the estimated OR from the 3 tenure group analysis was 0.54 (0.21,0.87) and for the 4 tenure group analysis was 0.37 (0.09,0.65). (See Figure IV-16).

V. Discussion

This study examined the mortality of Vanderbilt talc employees who had ever worked between 1947 and 1978. Cause-specific mortality was determined for all 710 white males in the cohort, with complete follow-up through 1983. Unlike most occupational cohorts, mortality from both all and specific causes was above expected. The increased SMRs were 2 or more times above expected for tuberculosis (419, 3 obs), all nonmalignant respiratory disease (251,17 obs), pneumonia (245, 6 obs) and lung cancer (207, 17 obs).

The primary reason for this update of previous studies was to try and determine whether talc exposure was the cause of the elevated SMRs for lung cancer, or whether the elevation might be due to smoking and/or other occupational exposures. SMRs for lung cancer were above expected (207,17 obs) for the total cohort, for the 20-36 year latency group (258, 13 obs) and for workers with 20 or more years latency and less than 1 year tenure (357, 8 obs). The lung cancer SMRs were not reduced appreciably when local rates were used for expected deaths, and when the last 5 years of employment were not included. The point estimate of the slope of the exposure-response relationship in the greater than 20 year latency group was negative, although the upper confidence limit was positive.

The nested case-control study was conducted to address the issue of possible confounding from other occupational exposure, non-GTC talc exposures, and smoking. There was no apparent confounding from other exposures as the odds ratios showed no trend to increase with increasing risk scores from nontalc employment.

As expected, smoking was a risk factor for lung cancer. The exposure-response relationship (again using tenure as the exposure variable) in the case-control analysis was similar to that observed in the cohort study, i.e. a negative slope with increasing tenure. When stratified by smoking both the slope and its upper 95% confidence limits were negative. The finding of a decreased risk ratio with lack of an increasing tenure was not materially affected by non-GTC talc exposure, and remained when cases and controls with less than 20 years latency, <1 year tenure, and less than 20 years latency and 3 months tenure were excluded.

In the early reviews of this report several issues were raised which we will briefly discuss.

One issue has to do with the inclusion of short term workers. Active workers generally have lower mortality than the population as a whole. This so-called healthy worker effect has been attributed to a variety of causes including selection, changes in lifestyle accompanying employment, and in appropriate reference populations.[35,37] The healthy worker effect was not observed in the cohort analysis for several causes of death, in fact quite the reverse. SMRs among the ≥20 year latency group are summarized::

	Tenure				
	<1	1-9	10-19	20+	Total
Total Deaths	163	93	118	126	134
All Malignant Neoplasms	197	119	145	168	167
All Disease of Circulatory System	132	87	52	92	104
AHD, Including CHD	168	67	74	120	123
All Respiratory Disease	243	206	410	260	258
Lung Cancer	357	82	446	176	258

For all lung cancer deaths, the <1 year tenure group had a SKR of 221 when U.S. rates were used and 214 using local New York rates. The increased lung cancer mortality for the <1 year tenure group with ≥20 year latency was 357; only the 10-19 year tenure group had higher mortality, but only 0.45 expected deaths. If the <1 year tenure group are excluded from analysis, the SKR in the ≥20 year latency group with >1 year tenure is 178 and the slope of the SMRs increases with increasing tenure.

On the other hand, in a NIOSH study of Vermont talc miners and millers,[8] workers with <1 year tenure were excluded. Vermont talc contains no

asbestos. The SMR for respiratory cancers was 163 (6 obs, no control on latency). The SMR in the GTC cohort for all lung cancers (≥1 year tenure, no control on latency, 9 obs deaths) was 194, only slightly larger.

McDonald et al. found SMRs for short-term workers above 100 for Conneticut friction products workers[36] and South Carolina textile workers, and below 100 for Pennsylvania textile workers.[37] They considered a lack of comparability with the reference population or work in other hazardous jobs as possible explanations, and suggested a more appropriate comparison would be to calculate relative risks (RR) from SMRs at zero exposure derived from the adjusted slope. This would be the r and the RR calculated from the SMRs.

The other method they utilizied [36,37] was to calculate RR from a case-control study, i.e. using reference group from the same population. We also did this, utilizing: all cases and controls; smokers only, smokers only with >1 year tenure; smokers only with ≥20 years latency; and smokers only with >20 year latency and >3 months tenure. The RR from both the case-control and SMR analysis are summarized.

	Tenure			
	<1	1-9	10-19	20+
RR from SMR (>20 year latency)	1.0	0.92	0.77	0.55
RR from Case-control				
All Cases and Controls	1.0	0.86	0.59	0.21
Smokers Only	1.0	0.85	0.56	0.16
>1 year tenure	--	1.0		
>20 year latency	1.0			
>20 year latency, >3m tenure	1.0			

The results are similar between SUR and case-control analysis; in the case-control comparisons the exclusion of short-term workers does not change the results.

A second concern was control for latency in the case-control analysis. Among the smokers, there were 3 cases and 1 control with <20 year latency, and the OR slope remains negative when the analysis excludes cases and controls with <20 years latency.

A third concern was the use of the estimation of the slope of the exposure-response curve. Some reasons for this analysis are briefly discussed in the methods section. The analysis of dose-response is a time-honored method in experimental studies. By analogy epidemiologists have often quantified dose-response relationships, as the existence of such a relationship is strong evidence of a causal association. "If a factor is of causal importance in a disease, then the risk of developing the disease should be related to the degree of exposure to the factor; that is, a dose-response relationship should exist... An observed dose-resonse relationship makes a causal hypothesis more plausible."[38] Quantification of trends have been extensively used in analysis of asbestos chorts.[31,32,36,37,39] Liddell and Hanley[32] point out that formal methods of curve-fitting for cohort studies were apparently first used in 1982, and document its use by distinguished epidemiologists.

Rothman[34] argues that data analysis based on statistical hypothesis testing (p values) is inappropriate. The main objective of an epidemiologic analysis is to estimate the magnitude of effect...as a function of exposure status" (p. 330). The extent to which the data indicate a trend in effect, or the absence of such a trend, over various levels of exposure can provide insight into the biology of the relation under study and guidance for any public health intervention" (p. 327).

Before discussing the individual criteria for assessing causality, the previous mortality studies of this cohort and earlier cohorts of New York talc workers should be summarized (Table V-1). The earliest report was a proportional mortality study of talc workers in the northern part of New York state, presumably in the Couverneur talc district.[40,41] The talc contained amphibole and serpentine minerals.[42] The major "fibrous components" were tremolite and anthophyllite as determined using polarized light microscopy (PLM), transmission electron microscopy (TEM), x-ray diffraction and electron microanalysis.[42] It is not clear from the description that the "fibers" were asbestifom by a definition using an aspect ratio greater than say 15:1 or 20:1. In this cohort of workers with at least 15 years tenure and a maximum of about 44 years latency, the proportionate mortality ratio (PMR) for lung cancer was about 3 times expected.[40] The authors pointed out that the excess occurred among the 60-79 year age group, which is at variance with what they observed among asbestos insulators, where the excesses were in the age group 40-79. They suggested that tremolite and anthophyllite mixed with talc might be "less carcinogenic than chrysotile dust to which the asbestos insulators were exposed." Secondly, they suggested that the talc workers might have had less exposure. No smoking information was available. Dust levels were substantially reduced about 1945, and the PMRs were somewhat reduced in 1960-69 compared to 1945-60.

The remaining SMR studies[1,7,10,11] involved essentially the same cohort as in this study, i.e. white male employees who ever worked at CTC since it began operations. The results were somewhat consistent with each other in that both overall mortality and lung cancer mortality were elevated (1.2-1.4 and 2-3

times respectively). When evaluated by latency, the SMR for lung cancer in the 20 or more year latency group was about twice that expected.[1,11] Lamm et al.[11] found that the lung cancer SMR was 2.4 times greater for short-term (<1 year) than long-term (>1 year) employees. We found that the <1 year tenure group had 62% of the lung cancer cases and the SMR was twice that of the ≥1 year tenure group. Despite the 5-8 years longer latency and tenure in our study than these previous studies, the SMRs were as much as 25% less for all lung cancers, and almost 50% less in the ≥20 year latency group (Table V-1).

In this study we are concerned about the relationships between lung cancer and GTC talc exposure, and specifically exposure to amphibole minerals. The questions can be stated more explicitly in the null hypothesis: "In comparison with individuals who remain free of lung cancer, individuals who develop lung cancer have had no greater exposure to GTC talc, cigarette smoke, or other hazardous job exposures." The alternative hypotheses are: 1) "In comparison with individuals who remain free of lung cancer, GTC workers who develop lung cancer will have an increasing risk with increasing exposure"; 2) "In comparison with individuals who remain free of lung cancer, GTC workers who develop lung cancer will have an increased exposure to cigarette smoke and/or other hazardous occupations." The denial of the null hypothesis for example, implies that the OR slope = 0.[43]

At least 2 presumptions are important in the interpretation of these hypotheses. One relates to whether or not GTC talc contains asbestos. By its

title, the original NIOSH study suggests the presence of asbestos in the talc. To the contrary, there is compelling evidence from NIOSH,[20] OSHA[22], BOM[17-19] and others [44,45] that the "federal fibers", are nonasbestiform.

The second presumption follows from the first. If GTC talc contains asbestifom amphiboles that cause lung cancer, then one would expect the risk of lung cancer among GTC workers to be similar to asbestos exposed populations, and the talc to have toxic properties similar to asbestos. If GTC talc contains nonasbestiform amphiboles, one would expect the risk of lung cancer for GTC workers to more nearly resemble that of other populations exposed to nonasbestiform amphiboles, and the toxicity of the talc to resemble that of nonasbestiform amphiboles.

Because of the inherent limitations of a single epidemiological study in determining causation, the considerations of several aspects of the evidence has become an accepted procedure in epidemiology.[33,34,46,47] Authors of the original NIOSH Study[12,13] pointed to the need to consider Hill's [46] -criteria such as dose-response, strength of association, temporal relationships, biological plausability, and consistency in the interpretation of an association between environment and disease. These and other criteria (including control for confounding) have widespread popularity in helping to make causal inferences in epidemiology. Except for the temporality of an association, none of these viewpoints provide indisputable evidence for or against the cause-and-effect hypothesis, but are meant to assist us in making an inference on the basis of existing information.[34]

We will now summarize the evidence using these epidemiologic guideposts as a Framework for the organization of our discussion.

Strength of association refers to the magnitude of the ratio of rates for lung cancer between the exposed and reference populations. A moderate (1.5-3) to strong (3-10) association is more likely to be causal than is a weak association which can more easily be explained by bias.[48]

Using Monson's classification of risk,[48] all of the cohort mortality studies of New York talc workers show moderate degrees of association for all lung cancers (2.1-2.7 excess). The strength of association is increased in the high latency group (2.6-5.7 excess). In this study the SMR remains moderate (<3) for lung cancer except for the <1 year tenure group (SMR=357; 95% CI, 154,704) and 10-19 year tenure group (SMR=446, 95% CI 54,1611). The group with highest exposure and latency has a moderato association (SMR 176), but small numbers of observed and expected (95% CI, 21,636).

Temporality is the only standard that may provide indisputable evidence that an association is not causal.[34] The "cause" must precede the effect, or it cannot be considered a cause. A period of 20 or more years is a commonly used period between first exposure and the induction of lung cancer.[28,29] Since death often occurs fairly shortly after diagnosis of the disease, we are using the time between date of hire (or date started smoking) and date of death as the latency period. Rothman[49] points out there is both an induction period (between causal action and disease initiation) and latent period (between disease initiation and detection). He calls the entire interval between causal action and disease detection the empirical

induction period. We are adding to the empirical induction period the unknown interval between initial exposure and causal action and a variable but likely relatively short interval from date of disease to date of death. The date of first exposure to date of death then, is called the latent period in this report.

What kind of latency might we expect from asbestos exposure, amphibole exposure, and smoking exposure? Table V-2 summarizes estimates of mean latency for lung cancer in several cohort studies.

The range of latency for asbestos workers at highest risk (textiles, insulation) and with long exposure is about 28-34 years.[52,53,29] Chrysotile miners and millers, regardless of smoking habits or asbestos exposure, have a mean latency of about 40 years.[54] For a cohort exposed to high levels of amosite for short time periods, the mean latency is lower (21 y),[51] as it is for vermiculite and asbestos cement workers.[28,55,56]

For the mining cohorts exposed to nonasbestifonn amphiboles (and for which there is no apparent exposure-response or causative relationships) the mean latency ranges from 22 to 32 years.[58-60] Smokers have a latency of about 40 years.[54,61]

Nicholson et al.[30] compared the latency for lung cancer among 3 cohorts of asbestos workers with 20 or more years employment. These cohorts corresponded closely in terms of exposure and periods of observation, and showed shorter

latent periods with increasing hazard. These results are summarized:

Latency

	20-29 (%)	30-39 (%)	40+ (%)	OBS Deaths (n)	Estimated Mean Latency (years)
Chrysotile Miners & Millers	0	25	75	28	41
Factory Workers	12	70	18	33	36
Insulation Workers	36	39	24	450	34

The chrysotile miner cohort,[30] the smoking cohort,[61] and occupational cohorts with smoking history[54] suggest that the latency for lung cancer is similar and about 40 years. When exposure is more hazardous (asbestos factory workers,[51] vermiculite miners and millers,[56,57] textile workers)[39,37] and the exposure response curve steeper, the latency appears to be shorter. Workers exposed to nonasbestifonn amphiboles (including GTC workers) show mean latencies of 22-32 years, which is shorter than for most of the high risk asbestos cohorts. The latency for GTC lung cancer cases is about the same as the hospital-based cohort of lung cancer cases who smoked, about 40 years.[61]

Biological gradient refers to the presence of an exposure-response curve. While some causal associations may not show an apparent trend with exposure, etiologic agents (including asbestos) relating to lung cancers have generally

shown an effect that increases with exposure. Using tenure as a surrogate measure of exposure, we have calculated for the 20 or more year latency group the relationships between lung cancer and tenure in the cohort study.[31,32] In the case-control study we have calculated the slope and 95% C.I. of the OR[34] using two difference ways to categorize tenure, and several qualifications for cases and controls including all cases and controls, smokers only, smokers with >_20 years latency, smokers with 20 years latency and 3 months or more tenure. The point estimates for the slope of the exposure-response curves are negative; that is the risk ratio decreases as tenure increases. The slope is more negative when stratified by smoking in the case-control analysis. This negative slope of the exposure-response curve is opposite to the effect one would expect if talc exposure increased the risk of lung cancer.

Consistency is the repeated observation of an association under different conditions of study. A consistent association (or lack of it) strengthens (or weakens) a causal hypothesis in that it is unlikely that confounding or bias or some other factors would consistently be present in several populations or consistently bias results toward the same conclusion. Similar studies with diverse results weaken a causal interpretation.

The Kleinfeld mortality studies of New York talc workers[40-42] are most similar to the GTC cohort. Both talcs contained amphiboles, and both cohorts of talc workers showed an excess lung cancer risk among workers exposed 20 or more years. Exposure was much higher in the earlier years (at least prior to 1945). This study did not include an exposure-response analysis, control on latency or smoking.

Do the amphiboles in GTC talc have a risk for lung cancer similar to the risk of lung cancer in populations exposed to nonasbestiform amphibole minerals? There are four retrospective cohort studies of U.S. mining populations with some exposure to nonasbestiform amphiboles.[58-60,62-64] Table V-3 and Figure V-3 summarize the results of these cohort studies and includes this study for comparison. The adjusted slopes (r) of the "dose-response". curves for the 20 or more year latency group are negative or nearly horizontal. The number of deaths in the high tenure, long latency group of each study is small. Exposure to amphiboles may be low because of low amphibole content, or as in the instance of the crushed stone cohort, some operations may not contain amphiboles.

Taconite in the eastern Mesabi range contains the nonasbestiform amphiboles, notably cummingtonite, grunerite, actinolite and hornblende. These amphiboles have generally been shown to not be asbestifom, but the cleavage fragments do meet the regulatory definition (>5 μm length, >3:1 aspect ratio) for fibers.[60,62,66,67] The SMRs for lung cancer and nonmalignant respiratory disease were similar to hematite iron miners in the same area, but with no exposure to amphiboles.[68] There were no environmental data on which to estimate past taconite exposure although jobs were ranked by relative dustiness. Analysis by level and type of past exposure showed no evidence of excess risk of lung cancer associated with past taconite exposure.[60]

The cohort of gold miners was initially studied by NIOSH to examine the hypothesis that exposure to amphibole mineral is associated with asbestos-related diseases. The nonasbestiform amphiboles found in the ore include cummingtonite-grunerite (~69%), with lesser amounts of

tremolite-actinolite (~15%) and fibrous hornblende (~16%). Average airborne "federal fiber" exposure (>5 μm long, >3:1 aspect ratio) to miners was 0.44 f/cc. There was no apparent association of lung cancer with tenure, total dust, or latency.[58]

The cohort mortality study of crushed stone workers was initiated in large part because of the potential for "asbestos" (>5μm long, >3:1 aspect ratio) exposure in the mining and milling of stone. Sampling at the 9 limestone, 5 granite and 5 traprock quarries in the cohort demonstrated no fibers at any of the limestone quarries; one traprock quarry had fibrous serpentine and tremolite. Cleavage fragments were observed in 3 traprock and 1 granite quarry. Counts of "federal fibers" ranged from below the limit of detection to 1 f/cc.[59] SMR's for lung cancer were elevated in this cohort of quarry workers: the excess was greatest in the middle tenure group (10-25 years). However, the adjusted slope (r) was negative. Bailey[69] reports that "federal fibers" in concentrations greater than 0.1 f/cc were found in 86% of personal samples taken at 21 granite quarries. In 289 samples taken by MSHA at 107 stone quarries, 55% were greater than 0.1 f/cc (51 or 48% of the operations). The apparent lack of a exposure-response relationship in these mining cohorts might be attributable to "fiber" exposure below MSHA standard of 2 f/cc, and often below the OSHA PEL of 0.2 f/cc. The low exposure to "federal fibers" and the absence of amphiboles in a large part of this cohort suggests the elevated sites for lung cancer are not caused by amphibole exposure.

In the GTC cohort low exposure to "federal fibers" level would not appear to be a reason for no apparent exposure-response relationship. Dement and

Zumwalde[2] reported "federal fiber".exposures to range from 0.8 to 9.8 f/cc in the mine and 0.2 to 16 f/cc in the mill. Exposures in 9 of 24 job categories sampled were in excess of the ceiling values of 10 f/cc.

Do the amphiboles in GTC talc pose a risk for lung cancer similar to the risk of lung cancer in populations exposed to asbestos? Table V-4 and Figure V-4 summarize the results of retrospective cohort mortality studies of asbestos miners,[50,70] asbestos textile workers,[37,39] amosite factory workers, insulation workers,[51] asbestos cement workers,[71,72] friction products workers,[36] and vermiculite workers exposed to tremolite-actinolite asbestos.[56,57] All of the studies except asbestos cement workers in Sweden[72] and Plant 1 in Louisiana,[71] and workers making friction products[36] show a positive slope, i.e., the risk of lung cancer increases with increasing tenure.

The cohort of amosite asbestos factory workers[51] was mostly white males who worked for only a short time during 1941-5. Exposure was quite high, as was the risk of lung cancer; within 15 years for longer term workers (>2 years) and 25 years or more for workers with shorter tenure. Dose-response patterns were similar whether asbestos exposure was estimated by tenure or f/cc.

Hobbs et al.[70] suggest that crocidolite exposure accounted for nearly 30% of the respiratory cancer deaths, assuming no contribution from medium/light exposure groups with <3 months tenure, or to deaths with less than 10 years latency.

The cohort study of chrysotile miners in Quebec showed linear relationships betueen cumulative exposure (mppcf x tenure) and lung cancer. There was no apparent excess relative risk of lung cancer except in workers with 20 or more years tenure in high exposure groups (33.8 mppcf or about 100 f/mL).[50]

McDonald et al. reported on 3 cohort studies constituted in the same way: two chrysotile textile mills[37,39] and a friction products plant.[36] The two textile cohorts had similar linear exposure-response relationships whether exposure was tenure (Table V-3A and Figure V-3A) or mppcf. Exposure averaged 2.3 mppcf in the Pennsylvania cohort[37] and 1.8 mppcf in the South Carolina cohort.[39] The <1 year tenure groups in both studies had fewer observed than expected deaths. In the lowest cumulative exposure group (<10 mpcf.y), the SMR was elevated in S.C. (116) but not in Pennsylvania.[70] Because of this apparent lack of comparability of reference populations, they suggested that relative risks calculated from the fitted regression on SMRs (r) or RR calculated from the case control analysis (b') were the appropriate comparisons.

The friction products cohort[36] had exposures similar to the South Carolina textile plant: an average of 1.84 mpcf compared to 1.8 mpcf. The only group showing excess risk of lung cancer were short-term workers (<1 yr). A similar decrease in risk of lung cancer with increasing exposure was observed in both the SMR and case-control analysis. A slight increase in lung cancer risk with increasing exposure was observed in the case-control analysis (but not SUR analysis) when the low exposure group was omitted. The findings from the study of friction product workers are in some ways similar to those from this study. The only subcohort with SMRs clearly above expectation are the men

with <1 year tenure, and this pplies to all causes and virtually all diagnostic categories. For the asbestos workers the use of state or national rates made no difference (and for GTC workers made no difference for lung cancer). HcDonald et al.[36] considered the possibility (as did we) of work in other hazardous industries. Neither they nor we found this to be an explanation for the increased risk. The findings suggested a selective process could have resulted in the employment of men with relatively poor health or healthhabits(such as heavy smokers perhaps) in low exposure jobs in which they remained only a short time. If the low exposure group of friction product workers was excluded the fitted regression suggested adverse health effects of employment were small, and similar to Quebec chrysotile miners and millers. (If low tenure group is excluded the slope is essentially zero). In the GTC cohort the SMR slope would be positive if workers with <1 year tenure were excluded, and abou the same if workrs with <3 months tenure were excluded. Another approach is to indirectly adjust the SMRs.[73] If we assume 1) 100% confounding in the 0-1 year tenure group (all smokers, 2) no confounding in the >1 year tenure group (same proportion of smokrs in study and reference populations), 3) 69% of white male populations were smokers, and 4) RR of lung cancer due to smoking was 15, then the adjusted SMR in the 0-1 tenure group would be 253. The SMR slope would still not be positive. If we exclude low tenure workers in the case-control analysis the slopes remain negative.

There are 2 cohorts of asbestos cement workers that provide latency by tenure data, one in Louisiana[71] and one in Sweden.[72] In the Swedish study[72] exposure prior to 1970 was estimated at 2 f/cc and 1 f/cc after 1970. Short-term employees (<2 years) had higher mortality than long term (>5

years) employees from virtually all causes but especially lung cancer. However there was only 1 case among workers with more than 5 years tenure. In the Louisiana cohort there are 2 plants. Both have elevated SMRs for lung cancer in the short tenure groups. In plant 1 there is no apparent increased risk with tenure, and with or without short-term workers. In plant 2 there is an increasing risk.

The vermiculite workers[56,57] are exposed to high levels of tremolite-actinolite asbestos. For example, estimated dust exposure was 42 mppcf (in 1950-64) and 9-7.5 mppcf (65 f/cc) in 1967-8. In working areas of the dry mill estimated exposures were 168 f/cc prior to 1964 and 33 f/cc from 1964-71. After 1971 exposures declined and appeared to be less than 1 f/cc after 1977. That the vermiculite is asbestos is indicated by the distribution of aspect ratio of airborne fibers >5μm long: 96% had aspect ratios >10:1, and 67% > 20:1.[74] The exposure-response slope was positive whether workers with <1 year tenure were included or not. The SMR for the <1 year tenure group was 100 using U.S. rates, but 123 using state rate and 121 using local county rates for expected deaths.[57]

The asbestos cohorts generally show increasing risk of lung cancer with increasing tenure as indicated by the positive SMR slopes. One exception was the friction products cohort,[36] in part due to increased risk among workers with <1 tenure, perhaps because of selection of men with poor health or health habits (e.g. heavy smokers). Only when short-term workers are excluded is there an exposure-response relationship. Risk of lung cancer for workers in the asbestos cement cohorts is more similar to chrysotile miners and millers than textile workers. Short-term workers tended to have the

higher SMR. Retaining or excluding these workers inthe analysis did not change the exposure-response relationships.

It is clear from Figures V-3 and V-4 which of the cohorts the GTC workers approximate.

The interpretation of a cause-and-effect association should have coherence and biological plausibility. That is, it should not seriously conflict with our knowledge of the natural history and biology of the disease, and it is helpful if it conforms to biological knowledge. Much of this type of information comes from animal studies.

If GTC talc causes lung cancer in animals, then the probability that the talc is causing the increased lung cancer in workers is made more believable. We will examine the evidence in order of increasing complexity, starting with in vitro models, implantation or injection in the pleura or peritoneum, and then inhalation. The implantation or injection studies bypass deposition, clearance, and aerodynamic considerations and apply to mesothelioma rather than lung cancer. However these type of experiments have been important in the development of the hypothesis that in the pleura of the rat, "durable fibers < 3μm in diameter and >20μm in length are far more carcinogenic than either fibers of various lengths with diameters >3μm or fibers with diameter <3μm and lengths <20μm."[75]

Frank et al.[76] compared the in vitro cytotoxicity of serpentine asbestos (chrysotile) and platy serpentine (antigorite, lizardite) from a Rockville quarry. The nonfibrous platy material caused no damage to a macrophage-like

cell line, while the chrysotile was cytotoxic and inhibited cell growth.

Hyperplastic and metaplastic lesions occur in the airways of rats following asbestos exposure.[77,78] Woodworth et al.[79] used cultures of hamster trachea to assess the ability of asbestos and nonasbestiform analogues to induce metaplastic changes. Crocidolite and chrysotile asbestos induced metaplasia over all dose ranges, while their nonasbestiform analogues riebeckite and antigorite did not.

Implantation or injection of fibers in the peritoneum and pleural space (usually of rats) yield sarcomas that are similar to the mesotheliomas induced by asbestos in man. Evidence from this kind of experiment in animals has resulted in the Stanton hypothesis, which states that durable fibers within an approximate range of <1.5 μm in diameter and greater than 8 μm in length cause cancer.[80] A number of investigators have used intrapleural injections of both asbestos and nonasbestiform materials to assess biological activity (Table V-5). Asbestos (chrysotile, crocidolite, amosite, actinolite asbestos, and tremolite asbestos) have all induced tumors by these methods. Anthophyllite asbestos does not appear to increase tumor probability above control levels. None of the talcs (including 4 experiments using Vanderbilt talcs, or the nonasbestiform analogues of asbestos (tremolite, actinolite, antigorite) have induced tumors above the control rates. The tumor rates were 0% in the 4 experiments where Vanderbilt talc was used.[82,83,85]

From these kind of data was formulated the well-known Stanton hypothesis that durable fibers with well-defined ranges of diameter and length can cause cancer irrespective of whether they are asbestos or not. The size ranges

suggested by Stanton[85] were fibers with an approximate size of ≤ 1.5μm diameter and >8μm in length. One should be cautious in extrapolating from these animal experiments to the risk of mesothelioma in man because of the artificial nature of administration that bypasses aerodynamics, deposition, and clearance, as well as the high doses used (40 mg in the Stanton studies). As Stanton himself observed,[91] "direct application of the results to the problems in man would be unwise." Further, the results should apply to mesothelioma, as no judgment is possible regarding asbestos and lung cancer in animals or man.

The pleural or peritoneum assay is more sensitive than inhalation studies, and the cautions are relevant when tumors are produced. That is, this type of study may be an indicator of biologic activity, and as Harington[80] has suggested, could be thought of as a prescreen for inhalation studies. (These and other comments on the technique are discussed further in reference 78,80,91,92). By this criteria none of the talcs or nonasbestifonn amphiboles would be tested by inhalation.

There is only one inhalation study of talc, and that is of Vermont talc. This is a cosmetic talc that produced no lung tumors.[93] There are no inhalation studies of nonasbestiform tremolite or tremolitic talc.

Inhalation of asbestifom amphiboles do produce lung tumors in animals. Davis et al.[90] exposed rats to 10 mg/m^3 tremolite asbestos. This asbestos produced more fibrosis and pulmonary tumors (41% carcinomas, 5% mesothelioma) than chrysotile, which previously had been the most carcinogenic dust they had tested. The tremolite asbestos fibers were thin (<1% were >0.5μm wide) and

long (~8% > 10 μm); the proportion of tremolite fibers longer than 5μm and 10μm was about double that found for UICC crocidolite and amosite. Using the light microscope, close to 20% of the tremolite asbestos fibers were greater than 20μm long.

Animal studies can provide further insight into the fiber dimension relevant to fibrosis, lung cancer, and mesothelioma. Davis et al.[89] report on an injection and inhalation study of long and short amosite asbestos. This study is significant because, for perhaps the first time, the short fiber dust contained very few long fibers. So it is a partial test of the long fiber theory of carcinogenesis.

The results are summarized:

n	Short Fiber	Long Fiber	Control
Intraperitoneal injection - % tumors			
25 mg (control - UICC amosite)	4%	95%	94%
10 mg	0%	88%	
Inhalation - 10 mg/m^3			
Pulmonary fibrosis	0.15%	11%	~0.15%
Pulmonary tumors	0	20%	1.6%
Pleural mesothelioma	0	5%	0
Length dimension of the dust			
% > 5μm	1%	30%	--
% ≥10μm	0.1%	11%	--

This study demonstrates little or no tumorigenic or fibrogenic effect of amosite asbestos containing few fibers greater than 5μm in length. UICC amosite with a particle size distribution intermediate to the long and short fibers had intermediate effects on fibrosis. Intrapleural injection of UICC amosite produced

mesotheliomas similar to the long fiber amosite.[94] From these results Davis et al.[89] conclude that "while very short fibers exhibit little carcinogenicity to either lung or mesothelial tissues at the doses examined, mesotheliomas can be produced by dust preparations consisting of shorter fibers than are needed to produce pulmonary tumors".

What about deposition and clearance of fibers? The respirability of fibers is a function of diameter more than length, and the maximum diameter of respirable fibers is 3-3.5μm (when length is >5μm). Fibers with a width greater than this will deposit on the mucocilary blanket and normally be cleared in 24 hours. Fibers with a smaller diameter are deposited in the alveoli, engulfed by macrophages (if not too long) and transported to the mucociliary escalator, to the lymph nodes, or to subpleural foci.[92,95,96]

Short fibers (<5 μm) deposited in the alveoli are readily and completely taken up by phagocytes. Macrophages are 17-20 μm in diameter (~12μm rats) and cannot engulf fibers which exceed a critical length greater than the diameter of the macrophage. Fibers 5-20μm long are sometimes completely ingested and sometimes not, while fibers >20μm long are never completely engulfed. These findings were demonstrated by exposing rats to anthophyllite asbestos and measuring clearance.[97] Rats were exposed for 3 days to 35 mg/m^3 of anthophyllite asbestos. Clearance was followed serially for 205 days. The half-life for retention was about 76 days. Fiber uptake by macrophages was essentially complete within a few hours, and the average fiber content of lung macrophages was reduced by 1/2 about every 45 days due to clearance of fiber-containins cells and replacement with fiber-free cells. Fiber < 5μm were removed more rapidly than fibers >5μm.

On the basis of these kind of data, Wagner,[98] hypothesized that asbestos fibers <0.5μm in diameter and 5-30μm in length are responsible for mesotheliomas, and fibers < 2μm in diameter and 10-50μm long cause asbestosis and lung cancer.

What are the dimensions of the particles in CTC talc? Dement and Zumwalde[2] reported over 90% of airborne particles at the CTC mine and mill were <5μm long, and less than 2% were longer than 10μm. This leaves ~5-7% between 5-10μm long. In bulk samples of CTC Campbell et al.[18] reported mean widths of 5.2μm for particles > 10μm long (making most of them nonrespirable); particles 5-10μm long were about 2.5μm wide. Dement and Harris[99] estimate that deposition in pulmonary spaces of straight rods 5μm long and 1.9μm in diameter is 12%, and for straight rods 10μm long and 2.95μm in diameter is 2%. Thus pulmonary deposition of particles in GTC talc >10μm long is essentially 0%, and is between about 2-12% for particles 5-10μm long. Dement and Harris[99] also estimated the fraction of airborne particles that met Stanton's size criteria of $\leq$ 1.5μm diameter and $\geq$ 5μm length ("relaxed" from 8μm long), and the fraction of these fibers deposited in the pulmonary spaces. For airborne tremolite in GTC talc, 4% were <1.5μm wide and >5μm in length; 15% of these were estimated to deposit in the pulmonary spaces. The percentages for anthophyllite were 11-12% and 14% respectively.

Churg[100] recently reviewed the literature to determine the role of chrysotile and tremolite in malignant mesothelioma. He suggested that the few data available are consistent with the idea that short length, low aspect ratio tremolite found in chrysotile ore "appears to be a very low-grade mesothelial carcinogen", and that extremely high exposures are required to produce an appreciable incidence of

mesothelial tumors. Tremolite asbestos such as that found in some vermiculite[56] and some areas in Greece is a much more potent inducer of mesothelioma. "New York State talc miners, who are...exposed to a short, low aspect ratio fiber, have a low or nonexistent mesothelioma death rate". There is only 1 known mesothelioma death in this cohort, and the death has not been attributed to talc because of short latency and previous exposure to asbestos.[1,7,100]

If the Wagner hypothesis[98] is correct, it is more plausible that CTC talc causes mesothelioma than lung cancer because of the dimensions of particles in talc. There would appear to be virtually no respirable particle >10μm which is the size fiber hypothesized to cause lung cancer. Of Fibers 5-10μm, less than about 1 fiber out of 100 (all lengths) will be deposited in the lung; these are the size fibers hypothesized to cause mesothelioma.

In conclusion, how do we answer the question of whether exposure to Vanderbilt talc causes increased risk of lung cancer?

In the analysis we have used tenure as the measure of exposure. Mean exposure to talc was slightly less in cases than controls, and there was no evidence of an increased risk as tenure increased. That is, the slope of the exposure-response curves were negative, and remained negative when stratified by smoking, excluding short-term workers, and controlling for latency. The proportion of nonsmokers was 30% higher among cases than controls. Nontalc occupations did not appear to increase the risk of lung cancer. The latency for lung cancer from smoking is about 40 years. GTC workers mean length of time from date of hire was 25 years; the length of time since starting smoking was 40 years. Thus the criterion of time

suggests smoking rather than talc exposure is the more likely risk factor for lung cancer.

Consistent findings among different exposed workers of an excess risk of lung cancer is a difficult criterion in this instance. There is only one group of workers exposed to GTC talc, although there is an earlier PMR study of workers exposed to a New York talc containing amphiboles. A 3-fold increased risk vas observed in that study. A study of Vermont talc (nonasbestiform) workers had an SMR of 163 for respiratory cancer, compared to 194 for a similarly constituted group of GTC workers.

Other mining cohorts exposed to nonasbestiform amphobole have negative or nearly horizontal slopes of the exposure-response curves. The relative slopes and relative risks calculated from the SMRs for workers with ≥20 year latency and 25 years tenure are summarized:

Cohort	slope r (x100)	RR at 25 years tenure, ≥20 year latency (RR = 1 at 0 years tenure)
Vermiculite Workers	+10.68	3.67
Textile Workers		
South Carolina	+8.38	3.10
Pennsylvania	+6.53	2.63
Amosite Factory Workers	+18.5	5.63
Crocidolite Miners (>15 year latency)	+6.72	2.68
Quebec Chrysotile Miners	+2.38	1.60
Friction Products Workers	+0. 70	0.83
Asbestos Cement -		
Sweden	-4.55	0
Louisiana - Plant 1	+0.77	1.19
- Plant 2	+6.21	2.55
Talc (w/o low tenure workers)	-1.55	0.61
Taconite miners	0.77	1.19
Gold miners	-1.42	0.65
Crushed Stone	-0.82	0.80

The short low aspect ratio particles in GTC are unlikely agents to cause lung cancer according to present thinking on deposition, clearance, and biological activity of fibers

In summary there is no pattern suggesting exposure to GTC talc increases the risk of lung cancer. The pattern as just summarized suggests that the elevated SMR for lung cancer is not a causal association. However, the numbers of cases is small, and background mortality is high, and so additional analyses and further follow-up are recommended.

Recommendations

1) Analysis of exposure-response is in our opinion an important element in the assessment of causality in this study. Misclassification of exposure was a concern expressed repeatedly in the reviews of the protocol of this study. The use of tenure as a surrogate estimate of exposure will not result in misclassification if subjects have the same exposure over time.(101) If exposure is not the same over time then it may be difficult to show a dose-response relation, or even observe decreased risk with increased tenure. In Part 2 we show that exposures in the mill have changed over time. We have matched for the time period of exposure in the case-control study, but this may not control for changes in exposure over time. To reduce the possibility of exposure misclassification we recommend analysis of exposure-response using as the exposure variables net tenure (actual hours each employee worked) in the case-control study and cumulative

dust exposure in mppcf-years for both the cohort and case-control analyses. Time in the cumulative exposure estimates should be tenure for both study designs (and net tenure as well in the case-control dose-response analysis).

2) Follow-up through the National Death Index should be initiated immediately, death certificates obtained and nosologized, and information on cases and control obtained. The analysis should then be repeated using the updated information. This update will add at least 5 lung cancer deaths in the >20 year latency category for the cohort analysis.

Surveillance of the cohort in this manner should continue at least every 4 or 5 years. Approximately 2 lung cancer deaths/year are expected to occur in the >20 year latency group. The expected number of cases and the 95% confidence interval at SMRs of 1.5 and 2 for the >20 year latency group are calculated[102] for a follow-up through 1990:

Follow-up Through	Approximate Number of Expected Cases	95% C.I. at SMR of 1.5	95% C.I. at SMR of 2.0
1983	1.42		
1985	5	(.64, 3.00)	(.96), 3.66)
1987	7	(.78, 2.1)	(1.14, 3.38)
1990	10	(.84, 2.47)	(1.22, 3.08)

An internal comparison using the total cohort should also be included in subsequent analysis.[103,104]

3. Another way to perhaps increase the cohort size is to include talc workers from other talc mines that had operated in the Gouveneur Talc District. Some potential problems with this approach are the increased difficulty in contacting relatives of cases dying in the 1950's and 1960's, the relative lack of environmental data and knowledge of the mineralogy of the talc. The talc at these other companies may differ considerably from GTC talc.[12a] Since these companies are no longer operating, procurement of records may not be possible. However, the feasibility of this approach could be explored.

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Age

<20
20-
30-
40-
50-
60-
70-
≥80

Tota

Aver

Table IV - 2

Lung Cancer Mortality by Latency and Ten
using U.S. white male death rates, 1947-1

R.T. Vanderbilt Company, Inc./Gouveneur Talc
KHETA 86-012

Years since date of hire		Tenure-Years 0-<1	1-9	10-19	2
0-<10	O/E	0/.54	1/.65	0/0	
	SMR	--	152.8	--	
	PY	3612	3274	0	
10-19	O/E	0/.82	2/.54	1/.64	
	SMR	--	372.8	157.4	
	PY	2229	1203	1247	
+20-36	O/E	8/2.24++	1/1.22	2/.45	
	SMR	357.2**	81.9	445.9	
	PY	1870	821	289	
Total	O/E	8/3.6	4/2.41	3/1.08	
	SUR	222.1	165.9	276.8	
	PY	7711	5297	1536	

* p < .05
** p < .01

Mean latency: 22.9 (5.5-34.3)
Mean tenure: 6.3 (.003-23.5)

\+ For the 20-36 year latency group
SMR = a + b (tenure)
a = 2.936
b = -0.0454
r = b/a = adjusted slope = -0.01546
95% confidence interval for r = -0.0411, + 0.0895
Calculated relative risk (RR) at 25 years
tenure = 1 + (-0.01546)(25) = .61 (0,3.24)

++ Observed/expected deaths and SMRs when divided in to 0-
months tenure are as follows:

	0-3m	3-12m
O/E	6/1.64	2/0.60
SMR	366.3*	332.5

Cause

All Causes
Tuberculosis
Diseases of Ci
Arteriosclerot
Disease, inc
All Respirat
All Pneumoni
Emphysema
All Malignant
Digestive Org
Peritoneum
Stomach
Lung
Accidents
Unknown Causes

* p < .05
** p < .01

Table IV-3

Lung Cancer Mortality Using U.S. and upper NY county rates for Expected Deaths

R.T. Vanderbilt Company, Inc./Gouveneur Talc Company
MHETA 86-012

	Tenure-Years				
	0-<1	1-9	10-19	20-36	Total
Observed deaths 20-36 year latency	8	1	2	2	13
U.S. Rates					
Expected	2.24	1.22	0.45	1.14	5.04
SMR	357.2**	81.9	445.9	176.0	257.7*
95% C.I.	154.2,703.9	2.0,456.5	54.0,1611.0	21.3,635.7	137.2,440.6
NY County Rates					
Expected	2.33	1.28	0.48	1.19	5.27
SMR	344.0**	77.9	418.9	168.4	246.5*
95% C.I.	148.5,677.7	1.9,434.3	50.7,1513.3	20.4.608.4	131.2,421.5
Total Observed	8	4	3	2	17
U.S. rates					
Expected	3.6	2.41	1.08	1.14	8.23
SMR	221.1	165.9	276.8	176.0	206.5**
95% C.I.	95.9,437.5	95.2,424.7	57.1,808.8	21.3,635.7	120.3.330.6
NY County Rate					
Expected	3.74	2.49	1.14	1.19	8.55
SMR	213.8	161.0	262.9	168.4	198.7*
95% C.I.	92.3,421.4	43.9,412.2	54.2,768.2	20.4,608.4	115.8,318.2

* p < .05
** p < .01

+For the 20-36 year latency group using N.Y. rates.

a = 2.7942
b = -0.036648
r = b/a = -0.013116
95% C.I. for = -0.03326. +0.07277
Calculated RR at 25 years = 1 + (-0.0131)(25) = 0.67 (0.17,2.82)

Table IV -4

Lung Cancer Mortality by Latency and Tenure,
but not counting employment incurred during
the last 5 years of life;
U.S. white male death rates

R.T. Vanderbilt Company, Inc./Gouveneur Talc Company
MHETA 86-012

Time Since Hire		Tenure-Years (-5 years) 0-<1	1-9	10-19	20-36	Total
0-<10	O/E	1/.55	0/.063	0/0	0/0	1/1.18
	SMR	180.7	--	--	--	84.6
	PY	3616	3229	0	0	6846
10-19	O/E	0/.87	2/.60	11.62	0/0	3/2.09
	SMR	--	332.1	161.5	--	143.3
	PY	2230	1265	1185	0	4680
≥20	O/E	8/2.33	1/1.29	2/.SO	2/1.16	13/5.27
	SMR	344.0**	77.7	403.1	171.7	246.5**
	PY	1870	823	313	724	3729
Total	O/E	9/3.75	3/2.52	3/1.12	2/1.16	17/8·55
	SMR	239.9*	119.2	269.0	171.7	198.8*
	PY	7716	5317	1498	724	15256

*p < .05
**p < .0i

Table IV-5

Mortality by Time Period
Compared to U.S. White Males

R.T. Vanderbilt Company, Inc./Gouveneur Talc company
MHETA 86-012

	Time Period'					
Lung Cancer	1960-64	1965-69	1970-74	1975-79	1980-83	Total
O/E	3/0.53	0/.96	711.60	4/2.36	3/2.34	1718.23
SMR	568*	--	436.2**	170	128	207**
All Causes						
O/E	26111.5	17116.9	28122.7	41129.8	34129.7	1011125
SMR	226*	101	123	137	115	128**
Circulatory System						
O/E	14/5.4	7/8.2	9111.0	16114.6	14/15.3	68160.7
SMR	258**	86	82	110	92	112
All Respiratory Disease						
O/E	21.52	11.84	3/1.24	7/1.74	4/1.87	17/6.78
SMR	383	119	242	403**	213	251**

*p < .05
**p < .01

Table IV-6

Characteristic of Lung Cancer Cases **and** Controls

R.T. Vanderbilt Company, Inc./Gouveneur Talc company
MHETA 86-012

	Cases	Controls	
n	**22**	***66***	
Mean year of first employment	1949.7	1949.5	
Men age at first employment	**34.6**	**34.1**	
Mean year of birth	1915	1915	
Mean years worked - Wean **(S.D.)**	**6.6** (8.6)	**9.2 (11.1)**	**(p=.08)**
- Range	(.003-23.5)	**(.003-35.3)**	
Wean years worked all talc	7.7 (9.2)	**9.9(12.1)**	**(p=.12)**
Exsmokers - n(%)	2(9)	6(9)	
mean cig/day (S.D.)	20 (0)	48.3(13.3)	
mean pack years (S.D.)	29.5(9.2)	87.5(35.0)	
year of hire	1953.5	1950.0	
age at hire	37.5 (9.2)	32.5 (8.7)	
year of birth	1915.5	1916.8	
years worked - mean (S.D.)			
GTC	18.3(2.3)	4.6(9.8)	(p=.11)
all talc	18.3 (2.3)	4.9(9.6)	**(p=.11)**
Smokers - n(%)	20(91)	42(64)	
mean cig/day	25.7 (12.0)	27.4 (12.7)	
mean pack years	53(31.9)	61.9 (34.1)	
mean age began smoking	18.0 **(3.7)**	16.7 **(3.5)**	
year of hire	1949.3	1949.2	
age at **hire**	34.3 (8.5)	32.7 (7.02)	
year of birth	1914.7	1916.3	
years worked - mean (S.D.)			
GTC	5.4 (8.1)	**10.4 (11.4)**	**(p=.08)**
all talc	6.6 (8.9)	**11.5 (12.8)**	**(p=.13)**
Non-Smokers - n(%)	**0(-)**	18(27)	

Table IV-7

Case Review of Lung Cancer Deaths Among Talc Miners and Hillers

R.T. Vanderbilt Company, Inc./Gouveneur Talc Company
MHETA 86-012

	Age at Death	Smoking Status	Age Started	Latency	Cig/ day	Pack Years	Work History Age at Hire	GTC Latency	GTC	Tenure Yrs all talc
1.	79	S	17*		20	62	57	22	0.02	0.02
2.	77	S	17	60	40	120	42	35	0.20	0.20
3.	63	S	18	45	40	90	42	21	0.05	0.05
4.	75	S	17*		20	55	41	34	23.5	23.5
5.	52	S	19	33	3	5	47	5	5.31	5.31
6.	55	S	29	26	10	8	39	16	2.83	2.83
7.	62	Ex	17	45	20	36	44	18	16.7	16.7
8.	68	S	12	56	20	56	35	33	0.35	3.35
9.	58	S	17*		20	41	34	24	0.64	1.06
10.	64	S	25	39	20	38	34	30	1.49	2.02
11.	59	S	14	45	30	56	36	23	11.78	23.5
12.	62	S	20	42	40	84	32	30	22.51	23.5
13.	63	S	17*		20	46	31	32	0.003	0.003
14.	53	S	17*		20	36	31	22	0.15	0.15
15.	65	EX	17*		20	23	31	34	20.0	20.0
16.	63	S	15	48	50	120	30	33	16.67	16.67
17.	54	S	19	35	20	33	30	24	2.51	9.59
18.	39	S	14	25	20	25	27	12	2.58	2.58
19.	53	S	17*		20	36	26	27	0.21	0.21
20.	45	S	20	25	40	50	24	21	0.15	0.15
21.	49	S	17	32	20	23	25	24	17.38	17.38
22.	56	S	18	38	40	76	23	33	0.16	0.16

*estimated

Table IV-7 (continued)

Case Review of Lung Cancer Deaths Among Talc Miners and Millers

R.T. vanderbilt Company, Inc./Gouveneur Talc Company
MHETA 86-012

	GTC Jobs	Non GTC Jobs (yrs worked)
1.	Carpenter	Construction Carpenter (37); Lumber Camp (2); Iron Mine (1)
2.	Painter	Painter (35); Purchasing Clk (Iron, St. Joes) (16)
3.	Millwright	Welder (Steel Mill) (10); Paper Hill (5)
4.	Miller; Oiler; Forklift Op.	Driller (16)
5.	Laborer; Oiler	Miner (>9); Foundry (molder) (12); Construction Carpenter (2
6.	Blacksmith and Welder	Road Construction (5); Mine Blacksmith and Welder (6); Car Mechanic (3); Welder (10)
7.	Miner	Dairy Fanner (35)
8.	Mucker; Machine Man	Driller (talc, coal, zinc) (18), St. Laurence Seaway (5)
9.	Wucker and Driller	St. Joe Lead (2); Paper Co. (2); Int. Talc (1); Farm (5); Army (4); Unk (13)
10.	Mucker and Driller	Military (7); Int. Talc (1); Mfg (?) (18); Truck Driver (17)
11.	Trammer; Electrician; Driller; Eimco Op; Scaper Op; Uucker	Paper Mill (1); Hosiery Hill (3); Loomis Talc (Driller, Foreman) (12); Construction (1); TV Repair (10)
12.	Mucker; Eimco Op; Driller; Hoistman; Trammer	Hucker, Driller (St. Joe Lead) (2); Packer (Talc) (1) Farm (3); Sinking Shafts (1)
13.	Hucker	Driller (Iron) (2); Dairy Farm (3); carpenter (1) construction (31)
14.	Uucker	Army (4); ALCOA (5); Driller (6m); Sawmill; Unk (3); Const. Driller (3); Farm (11)
15.	Mucker, Scraper Op.; Eimco Op; Shaft Hucker; Driller	Farm; Feed Hill (1); Operator (Aluminum Comp) (1)
16.	Miner	Farm (23); Zinc miner (3); Heavy Equip Op (5); Zn mill (5)
17.	Uucker; Driller	Farm; Mucker/Driller (Talc) (7); Blaster (Iron Mine)(19)
18.	Mucker; Eimco Op.	Mucker (1); ALCOA (3m); Military (1); Mfg bowling pins (1); Unk (7)
19.	Wucker	Army (7); Mfg (1); Miner (3m); Farm (4m); Sawmill (1); Radio repair; TV repair (5)
20.	Blacksmith	Quarry (>1); ALCOA (5); Driller (Iron) (4m); Roofer (hot tar) (2); Machinist (5); Foundry (1)
21.	Labor; Hiller; Cal Process Op; Wheeler Hill; Process Air Op; Car Liner	Paper Hill (9); Stock Clk (7)
22.	Laborer	Road Crew (3m); St. Joes Mineral (1); Iron Mine (6m); Foundry (molder) (4m); Construction (1m); Navy (3); Custodian (22)

Table IV-8

Case-Control Study of Lung Cancer by Non-Talc Exposure
(Panel Score x years worked) - All cases and controls

R.T. Vanderbilt Company, Inc./Gouveneur Talc Company
MHETA 86-012

Score (Panel Score x years employed)	Cases	Controls	Odds Ratio
221-533	3	13	0.55
121-220	6	13	1.10
51-120	5	21	0.57
0-50	a	19	1.00
Total	22	66	

Slope of odds ratios b' (S.E.) = -0.0008(.0005); $b' = b_1/b_0$;
95% C.I. of b' -0.002, + 0.0002
b_0 = 0.823
b_1 = -0.00067
Estimated OR at mid point of high exposure group (score = 377)
= 1 + b' (score) = 1 + (-0.0008)(377) = 0.70;
95% C.I.: 1 + (-0.002)(377) = 0.25 (lower)
1 + (+0.0002)(377) = 1.08 (upper)
X^2 = 0.266 (NS)

Table IV-9

Case-Control Study of Lung Cancer by Smoking Status and Cigarettes Smoked/day - All cases and controls (Smokers compared to (1) exsmokers and nonsmokers and (2) exsmokers only)

R.T. Vanderbilt Company, Inc./Gouveneur Talc Company
MHETA 86-012'

	Cases	Controls	Odds Ratio (95% C.I.)	
Smoker	20	42	5.71(0.36,7.81)	1.43 (0.31,9.07)
Exsmoker	2	6	1.0 (exsmoker and nonsmoker)	1.00 (exsmoker only)
Nonsmoker	0	18		
Total	22	66		

Cigarettes/day	Cases	Controls	Odds Ratio	
>40	6	11	6.55	1.64
20-39	12	27	5.33	1.33
1-19	2	4	6.0	1.5
Exsmokers and	2	6		1.00 (exsmoker only)
Nonsmokers	0	18	1.00 (exsmoker and nonsmoker)	
Total	22	66		

Slope of odds ratio when reference group = exsmokers and nonsmokers;
b'(S.E.) = +0.1211 (0.0083)
95% C.I. = 0.1048, 0.1374
b_0 = 1.087
b_1 = 0.1317
Estimated OR for 20 cig/d smoker = 1 + (0.12)(20) = 3.42 (3.10, 3.75)
X^2 = 4.68

Table IV-10

Case-Control Study of Lung Cancer by
Tenure at GTC - All
Cases and Controls

R.T. Vanderbilt Company, Inc./Gouveneur Talc Company
KHETA 86-012

Tenure-years	Cases	Controls	Odds Ratio
15-36	6	21	0.816
5-15	2	5	1.14
<5	14	40	1.00
Total	22	66	

Slope of odds ratios b' (S.E.) = - 0.0079(0.0033); $b' = b_1/b_o$;
95% C.I.of b' = -0.018,+0.0025
b_o = 1.026
b_1 = -0.0081
Estimated OR (95% C.I.) at 25 year tenure = 1 + (-0.008)(25) = 0.80 (0.55, 1.06)
X^2 = 0.13 (NS)

Tenure-years	Cases	Controls	Odds Ratio
20-36	2	20	0.24
10-19	5	2	6.0
1-9	5	20	0.60
<1	10	24	1.00
Total	22	66	

Slope of odds ratios b' (S.E.) = - 0.0271(0.0032); $b' = b_1/b_o$;
95% C.I. = -0.0334,-0.0208
b_o = 0.870
b_1 = -0.0236
Estimated OR (95% C.I.) at 25 year tenure = 1 + (-0.03)(25) = 0.32 (0.17,0.48)
X^2 = 1.36 (N.S.)

Table IV-11

Case-Control Study of Lung Cancer by Tenure at GTC - Smokers Only

R.T. Vanderbilt Company, Inc./Gouveneur Talc company
MHETA 86-012

Tenure-years	Cases	Controls	Odds Ratio
15-36	4	15	0.42
5-15	2	5	0.63
<5	14	22	1.00
Total	20	42	

Slope of odds ratios b' (S.E.) = - 0.0243(0.0057)
95% C.I. = -0.0354,-0.0131
b_0 = 1.045
b_1 = -0.0254
Estimated OR at 25 y tenure = 1 + (-0.02)(25) = 0.39 (0.11),0.67)
X^2 = 1.78 (N.S.)

Tenure-years	Cases	Controls	Odds Ratio
20-36	2	15	0.19
10-19	3	1	4.2
1-9	5	12	0.58
<1	10	14	1.00
Total	20	42	

Slope of odds ratios b' (S.E.) = - 0.0291(0.0044)
95% C.I. = -0.03177,-0.0204
b_0 = 0.861
b_1 = -0.0250
Estimated OR at 25 year tenure = 1 + (-0.03)(25) = 0.27(0.06),0.49)
X^2 = 2.93 (N.S.)

Table IV-12

Case-Control Study of Lung Cancer by Tenure at GTC
Smokers Only - ≥ 1 y tenure

	Cases	Controls	Odds Ratio
15-36	4	15	0.53
5-15	2	5	0.80
1-5	a	8	1.0
	10	28	

Slope of odds ratio b' (S.E.) = -0.0193(0.00666)
95% C.I. = (-0.0324, -0.0063)
b_0 = 1.0420
b_1 = -0.0201
Estimated OR at 25 years tenure = 1 + (-0.019)(25) = 0.52 (0.19,0.84)
X^2 = 0.577

	Cases	Controls	Odds Ratio
20-36	2	1s	0.32
10-19	3	1	7.2
1-9	5	12	1.0
	10	28	1.0

Slope of odds ratio b' (S.E.) = -0.02579 (0.0033)
95% C.I. = (-0.03228, -0.01930)
b_0 = 1.158
b_1 = -0.0299
Estimated OR at 25 years tenure = 1 + (-0.0258)(25) = 0.36 (0.19,0.52)
X^2 = 1.641

Table IV-13

Case-Control Study of Lung Cancer by Tenure at GTC
Smokers Only With ≥ 20 years latency

Tenure-years	Cases	Controls	Odds Ratio
15-36	4	15	0.49
5-15	1	4	0.46
<5	12	22	1.0
Total	17	41	

Slope of odds ratio b' (S.E.) = -0.021185 *(0.0057)*
95% C.I. = (-0.0324, -0.00996)
b_0 = 1.011
b_1 = -0.0214
Estimated OR at 25 years tenure = 1 + (0.0212)(25) = 0.47 (0.19,0.75)
X^2 = 1.152

Tenure-years	Cases	Controls	Odds Ratio	
20-36	2	15	0.19	
10-19	3	*0*	--	
1-9	2	12	0.23	0.58
<1	10	14	1.0	
Total	17	41		

Slope of odds ratio b' (S.E.) (tenure <1, 1-19, ≥20) = -0.028772 (0.00386)
95% C.I. = -0.0363, -0.0212
b_0 = 0.0938
b_1 = -0.0270
Estimated OR at 25 years tenure = 1 + (0.029)(25) = 0.28 (.09,.47)
X^2 = 4.199

Table IV-14

Case-Control Study of Lung Cancer by Tenure at GTC
Smokers Only With ≥ 20 years latency and >3 months tenure

Tenure-years	Cases	Controls	Odds Ratio
15-36	4	15	0.73
5-15	1	4	0.69
3m-Sy	4	11	1.0
Total	9	30	

Slope of odds ratio b' (S.E.) = -0.01038 (0.00698)
95% C.I. = (-0.0241, +0.0033)
b_0 = 0.978
b_1 = -0.01015
Estimated OR at 25 years tenure = 1 + (-0.0104)(25) = 0.74 (0.40,1.08)
X^2 = 0.120

Tenure-years	Cases	Controls	Odds Ratio	
20-36	2	15	0.20	
10-19	3	0	--	
1-9	2	12	0.25	0.63
3m-ly	2	3	1.0	
Total	9	30		

Slope of odds ratio b' (S.E.) (tenure 3m-ly, 1-19, ≥20) = -0.02777 (0.0043)
95% C.I. = (-0.0362, -0.0193)
b_0 =0.892
b_1 = -0.02478
Estimated OR at 25 years tenure = 1 + (-0.028)(25) = 0.31 (0.10,0.52)
X^2 = 2.352

Table IV-15

Case-Control Study of Lung Cancer by Total Talc Tenure - All Cases and Controls

R.T. Vanderbilt Company, Inc./Gouveneur Talc Company
MHETA 86-012

Total Talc Tenure-years	Cases	Controls	Odds Ratio
15-41.7	7	21	1.026
5-15	2	5	1.23
<5 13	~~10~~ 13	~~1.0~~ 40	1.0
Total	22	66	

Slope of odds ratios b' (S.E.) = + 0.0013(0.0061)
95% C.I.: -0.0107,+0.0134
b_0 = 1.0275
b_1 = 0.0013
Estimated OR at 25 year tenure = 1 + (0.001)(25) = 1.03 (0.73,1.33)
X^2 = 0.002 (N.S.)

Total Talc Tenure-years	Cases	Controls	Odds Ratio
20-41.7	3	20	0.356
10-19	4	2	4.75
1-9	7	25	0.665
<1 8	~~19~~ 8	~~1.0~~ 19	1.0
Total	22	66	

Slope of odds ratios b' (S.E.) = - 0.0220(0.0042)
95% C.I.: -0.0303,-0.0138
b_0 = 0.862
b_1 = -0.0190
Estimated OR at 25 year tenure = 1 + (-0.02)(25) = 0.45 (0.24, 0.66)
X^2 = 0.92 (N.S.)

Table IV-16

Case-Control Study of Cases and Controls by Total Talc Tenure - Smokers Only

R.T. Vanderbilt Company, Inc./Gouveneur Talc Company
MHETA 86-012

Total Talc Tenure-years	Cases	Controls	Odds Ratio
15-41.7	5	15	0.564
5-15	2	5	0.6769
<5 ~~12~~	~~22~~ 13	~~2.0~~ 22	1.0
Total	20	42	

Slope of odds ratios b' (S.E.) = - 0.0185(0.0067)
95% C.I.: -0.0317, -0.0053
b_0 = 1.0294
b_1 = -0.0191
Estimated OR at 25 year tenure = 1 + (-0.019)(25) = 0.54 (0.21, *0.87*)
X^2 = 0.84 (N.S.)

Total Talc Tenure-years	Cases	Controls	Odds Ratio
20-41.7	3	15	0.275
10-19	2	1	2.75
1-9	7	15	0.642
<1 8	~~18~~		1.0
Total	20	42	

Slope of odds ratios b' (S.E.) = - 0.0252(0.0058)
95% C.I. = -0.0365, -0.0139
b_0 = 0.846
b_1 = -0.0213
Estimated OR at 25 year tenure = 1 + (-0.025)(25) = 0.37 (0.09,0.65)
X^2 = 2.18 (N.S.)

Table V-1

Summary of Hortality Study of New York Talc Workers

R.T. Vanderbilt Company, Inc./Gouveneur Talc Company
MHETA 86-012

DRAFT

Ref	Eligibility tenure period of employment	Follow-up	n in Cohort (PY)	Results: All Causes OBS	All Causes RR	Lung Cancer: All O-RR OBS	All O-RR RR	>20 yr latency: All OBS	All RR	<1y OBS	<1y RR	≥1y OBS	≥1y RR
40	≥15y tenure employed 1940-1969	1969	260	108	--	13	324	--	--	--	--	--	--
1	1/1/47-12/31/59	6/30/75	398	74	121	9	273*	6	462**	--	--	--	
10	1/1/48-12/31/77	12/12/78	655	113	106	10	157	--	--	--	--	--	--
11b	1947-12/31/77	12/31/78	705 (11,704)	118	141*	12 11	240* 220*	-- 8	-- 574	-- 6	-- 667	-- 2	-- 283
This Study	1947-1978	12/31/83	710 (15,294)	161	128	17	207**	13	258*	8	357**	5	178

* p < .05
** p < .01

+Includes 1 fibrosarcoma

Table V-2

Summary of Mean Latency (Interval Between Date of Hire or First Exposure and Date of Death) for Lung Cancer Cases

R.T. Vanderbilt Company, Inc./Gouveneur Talc Company
MHETA 86-012

Reference	Cohort	n	Estimated Mean Latency-years
50	Asbestos Insulation Workers	429	32.1
51	Amosite Asbestos Factory Workers - Short-term Exposure	131	21.4
52	Asbestos Textile Workers > 20 year tenure	18	34.2
53	Chrysotile Textile Workers, ≥ 3m tenure	35	28.1
54	Quebec Chrysotile Miners and Millers, >1m Tenure		
	Nonsmokers	20	42.1
	Exsmokers, light smokers	100	39.7
	Smokers, 15-50 cig/d	124	39.2
56	Vermiculite Workers (tremolite/actinolite asbestos)		
5756	>1y tenure)	20	21.8
	1m-<1y, >20-y latency	4	28.9
58	Homestake Gold Miners, >1y tenure	43	31.9
59	Crushed Stone Workers, >1y tenure	52	23.5
60	Taconite Mining and Milling	41	22.3
This Study	Vanderbilt Talc Workers	22	25.1
	Smokers Only (from date first Started smoking)	14	39.2
61	Smokers	478	41.4

*Except for references 50,54,56-7 and this study, latency was estimated by taking the midpoint of each latency interval, multiplying by the number lung cancer cases in each interval, and dividing by the number of lung cancer

Table V-3

Consistency of Results for Risk of Lung Cancer Among
Retrospective Cohort Studies of Nonasbestiform
Amphibole Exposed Populations: Exposure-Response Relationships
Among ≥20 Year Latency Croups Only

R.T. Vanderbilt Company, Inc./Gouveneur Talc Company
MHETA 86-012

Ref.	Cohort	Airborne Amphiboles Present (% > 20:1 aspect ratio > 5μm long)	Tenure	Exposure-Response+ OBS	SMR	a,b	r (95% CI)
58,63,64	Gold Miners++	Cummingtonite-grunerite, tremolite-actinolite fibrous hornblende (0-4% from Ref. 65)	1-9 10-19 20-34	11 6 1	84 140 35	a:1.034 b: -0.0146	r: -0.0142 (-0.1005,+0.2241
60.62	Taconite miners*	cummingtonite-grunerite hornblende, actinolite (0% from Ref. 65)	3m-<1y 1-<5 5-<10 10-36	8 7 2 13	50 65 32 62	e: 0.514 b: +0.0040	r: +0.0077 (-0.1089, +0.0913)
59	Crushed Stone (limestone. granite. traprock quarry workers)	Some tremolite & hornblende	1-10 10-25 25-40	13 15 6	145 221 105	a: 1.835 b: -0.0151	r: -0.0082 (-0.0247,+0.0588)
This Study	Vanderbilt Talc	tremolite (4% in bulk, 0% in airborne, from 18,45)	<1 1-9 10-19 20-36	8 1 2 2	351 02 446 116	a: 2.936 b: -0.0454	r: -0.0109 r:-0.0155

*Report by Higgins et al.(62) omitted as no comparable latency by tenure analysis included.
+SMR = a t (b.x) where x = tenure; a = intercept at 0 tenure; b = slope of SMR regression;
r = b/a = adjusted slope with 95% confidence interval for r (after[31,32])
To calculate RR from SMRs: RR = 1 t r.x.
++ Only the data from Ref. 58 are discussed.

Table V-4

Consistency of Results for Risk of Lung Cancer Among
Retrospective Cohort Studies Asbestos Exposed Populations:
Exposure-response Relationships Among ≥20 Year Latency Groups Only

Ref.	Cohort (Exposure)	Asbestos	Tenure years	OBS	SMR (x100)	Exposure-Response a,b	r (95% C.I.)
			<1		100		
56,57	Vermiculite Miners[a]	(Tremolite-actinolite, asbeetos)	<1	4	100		
			1-5	3	103	a: 0.980	r: t0.1068
			5-10	4	400	b: +0.1046	
			10-19	0	--		
			20-47	5	500		
50	Miners, Quebec (Chrysotile)	Chrysotile, Quebec	1m-<1y	47	97	a: 0.923	r: t0.0238
			1-5	29	83	b: t0.0220	(0.0076, 0.0482
			5-20	50	137		
			20-46	104	161		
71	Cement Workers. LA[b]	Chrysotile, some crocidolite (LA rates)					
		Plant 1	1m-6m	26	139	a: 1.214	
			1m-1y	6	113	b: -0.0111	
			1-5	6	75	r: -0.0092	
			5-15	4	115	(-0.0367), +0.0500)	
			15-	6	105		
		Plant 2	1m-3m	34	140	a: 1.212	
			4m-1y	21	99	b: 0.0531	
			1-5	20	139	r: t0.0443	
			5-15	8	224	(0.0034, 0.1113)	
			15-	24	220		
12	Cement Workers, Sweden Sweden	Chrysotile <1% crocidolite	3m-2y	5	278	a: 2.841	r: -0.0455
			2-5	3	231	b: -0.12965	(-0.1023,-0.00066)
			5-33	1	39		

Table V-4 (continued)

Consistency of Results for Risk of Lung Cancer Among
Retrospective Cohort Studies Asbestos Exposed Populations:
Exposure-response Relationships Among ≥20 Year Latency Groups Only

Ref.	Cohort	Asbestos	Exposure-Response Tenure years	OBS	SMR (x100)	a,b	r (95% C.I.)
			<1		100		
36	Friction Products, Conn,	Chrysotile	1m-1y	24	180	a: 1.628	r: -0.0070
			1-5	19	149	b: -0.0114	(-0.0195,+0.0154)
			5-20	9	123		
			20->40	21	133		
37	Textile Workers, PA	Chrysotile	1m-1y	9	70	a: 0.562	r: 0.0653
			1-5	3	33	b: 0.0367	(0.0110,0.2238)
			5-20	14	129		
			20->40	27	159		
39	Textile Workers, SC	Chrysotile	1m-1y	8	78	a: 1.032	r: 0.0838
			1-5	10	164	b: 0.0865	(0.0206,0.2626)
			5-20	15	304		
			20->40	26	317		
70	Miners, W. Australia	Crocidolite (>15 y. latency)	<3m	6	87	a: 1.257	r: 0.0672,
			3m-1y	13	167	b: 0.0845	(-0.0052,+0.2299)
			1-28	19	246		
51	Factory Workers	Amosite Insulation for ships	<1m	6	324	a: 4.260	r: +0.1853
			1-2m	3	180	b: +10.7910	(0.0372,0.4754)
			2-3m	7	583		
			3-5a	11	485		
			6-11m	9	508		
			1-2y	16	829		
			2-14	24	976		

a: If Vermiculite workers with 1m-1y tenure are included the fitted regressions are: a: 0.961
b: +0.1058
c: +0.1102 (0.0002, 0.8609)

b: If the low tenure groups of asbestos cement workers are not included, the fitted regressions are:

	Plant 1	Plant 2
a:	0.922	1.052
b:	0.0071	0.0653
r:	0.00113	0.0621
95% C.I.:	(-0.1464, -0.1612)	(0.00765, 0.1754)

Table V-5

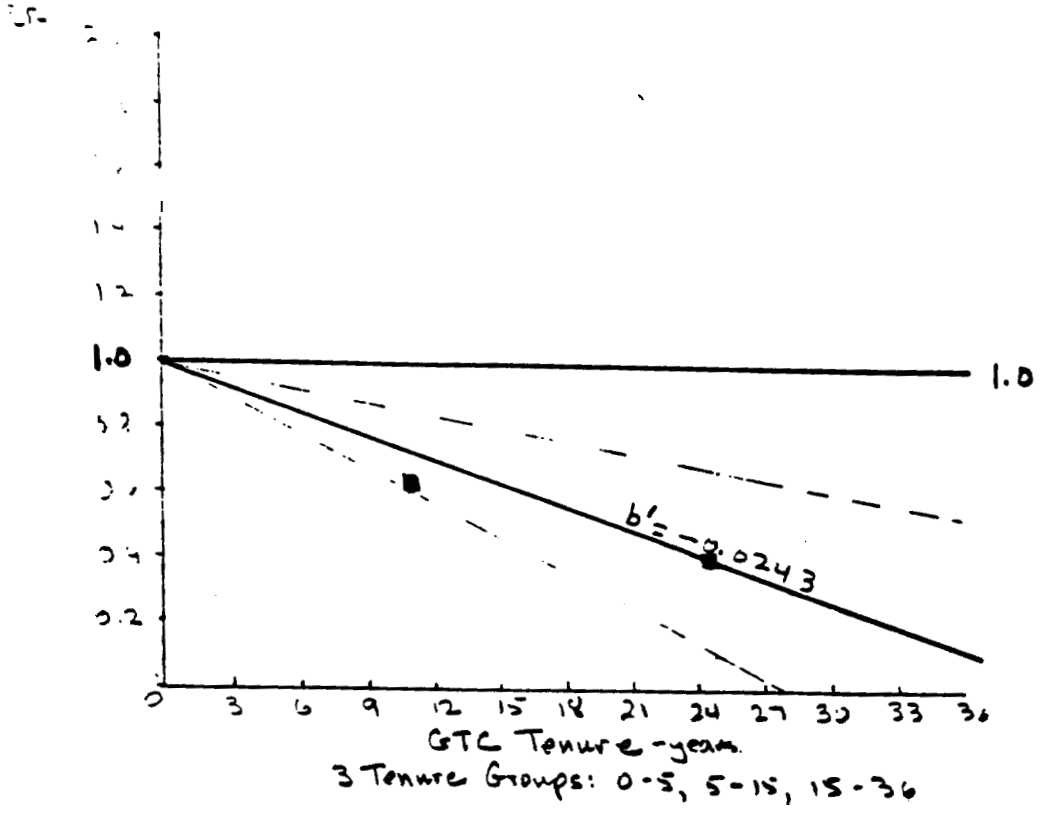
Summary of Tumor Incidence (Sarcomas) in Animals
with Fibrous and Nonfibrous Materials Implanted
or Injected in the pleural or peritoneum

R.T. Vanderbilt Company. Inc./Gouveneur Talc Company
MHETA 86-012

Reference (animal)	Mineral and Dose	% Tumors	Comments
81 (rat)	Crocidolite (2 mg)	39	100% < 5μmL
	Chrysotile milled (4 x 25 mg)	32	no fibers
	Talc (4 x 25 mg)	2.8	no fibers
	Actinolite (4 x 25 mg)	--	no fibers
82.83 (hamster)	Chrysotile (25 mg)	16	EM 6.9μm L. 0.1μm *D*
	Chrysotile milled (25 mg)	0	0.9μm L, 0.03μm *D*
	Crocidolite (10 mg)	20	
	Amosite (10 mg)	6	
	Anthophyllite Asbestos (10 mg)	6	
	Tremolite asbestos (10 mg)	23	many >20μm L; 0.4μm D
	Tremolitic talc (western U.S\)		
	(25 mg)	21	mean width 0.5μm
	(10 mg)	2	
	New Yotk talc		
	95% tremolite (25 mg)	0	
	50% tremolite. 10 mg)		
	antigorite (25 mg)	0	Fibers 2.5-16.5~L (5.7) 1-10μm D (1.6)
84 (rat)	Chrysotile (20 mg)	62	
	Tremolite asbestos (20 mg)	*30*	56.100 >8μm L <1.5μm D
	Tremolite from Calif. talc (20 mg)	0	1700 > 8μm L < 1.5μm D
85 (rat)	Tremolite asbestos (Calif)	100	2 exp'ts % > 8μm L < 1.5μmD
	Crocidolite	0-63	5 exp'ts
	Talc[1] (Montana)	7	
	Talc[2] (Vermont. cosmetic)	4	
All 40 mg *doses*	Talc[3] (Montana)	4	
	Talc[4]	3	
	Talc[5] (Montana)	0	
	Talc[6] (Nytal 300, Vanderbilt)	0	
	Talc[7] (Asbestine, Vanderbilt)	0	
	Antigorite (control)	<7	nonfibrous analogue of chrysotile
86 (rat)	Italian cosmetic talc (20 mg)	0	
87,88 (rat)	Ferroactinolite asbestos (20 mg)	23	0.3-53μm L (3.2) 0.03-5.2μm D (0.41) 3-130 aspect ratio (9)
	Amosite (20 mg)	34	.2-378μm L (3.4) .02-4.1μm D (0.29) 3-287 Aspect ratio (11.8)
89 (rat)	Long fiber amosite (10 mg)	88	11% > 10μm L. 3% > 25μm L
	Short fiber amosite (25 mg)	4	<<1% >10μm L
	(10 mg)	*0*	
90 (rat)	Tremolite asbestos (25 mg)	93	μ25% > 5μm L, 8% > 10μm

Figure IV-11 (from Table IV-11)

Relative Risks (Slope (b') and 95% Confidence Intervals) from Odds Ratios by Tenure at GTC €or Smokers Only



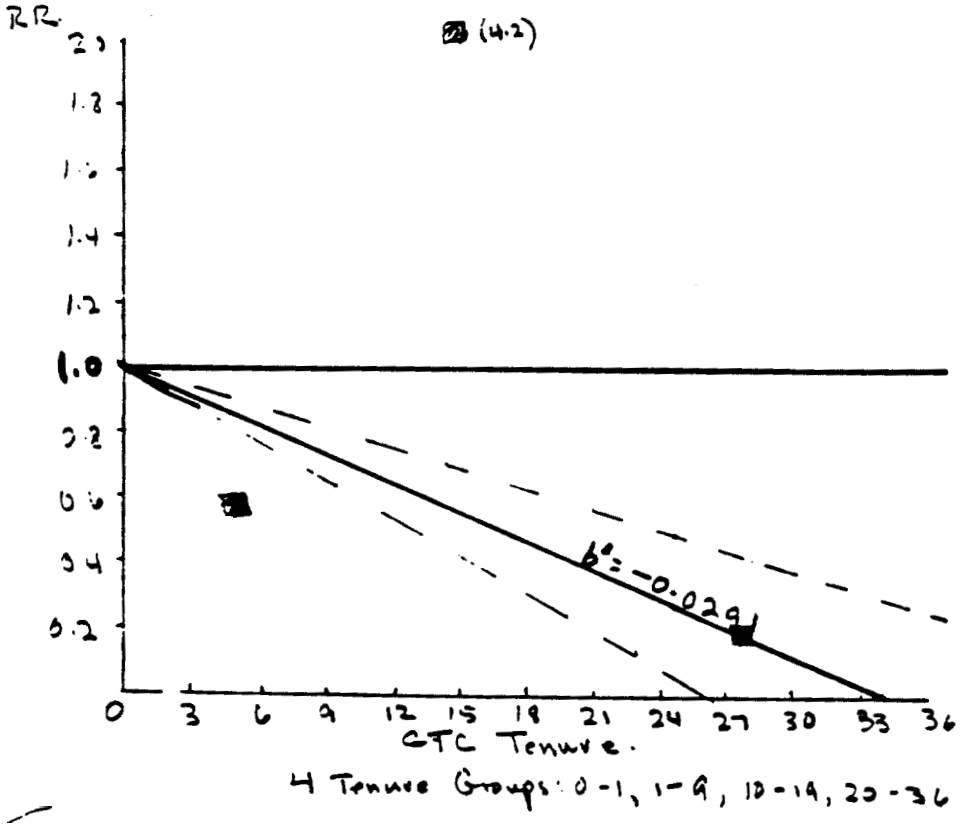
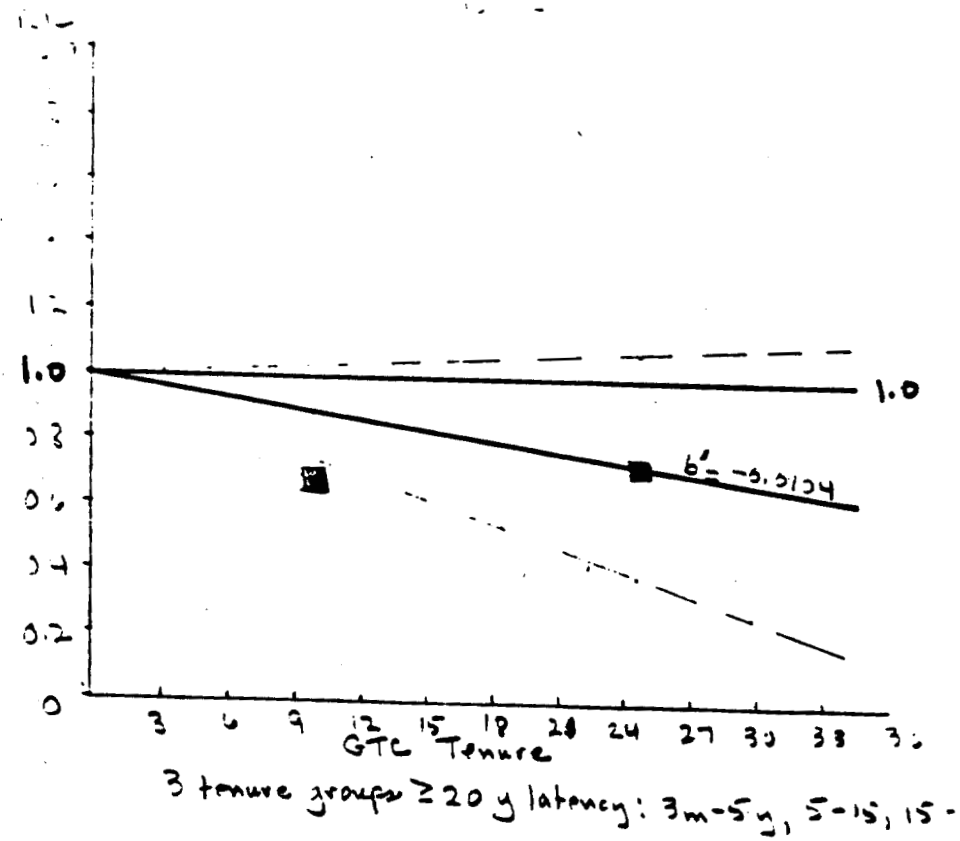
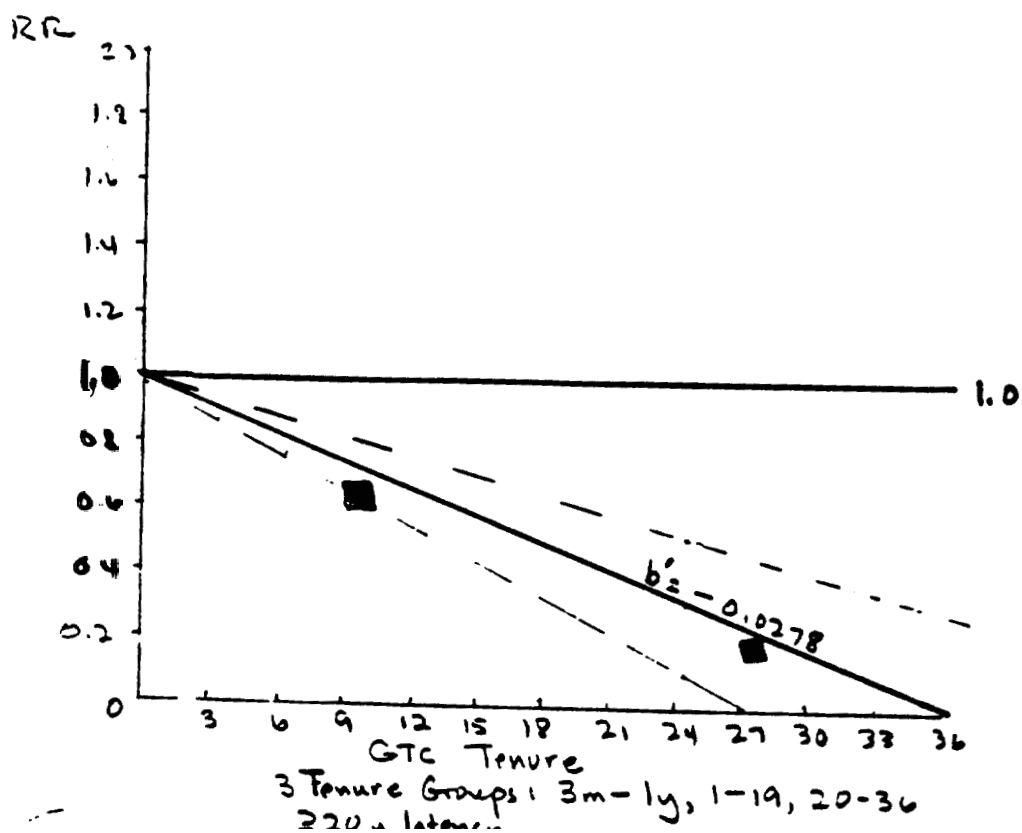


Figure IV-14 (from Table IV-14)

Relative Risks. (Slope (b') and 95% Confidence Intervals) from **Odds Ratios by Total Talc (GTC and non GTC) tenure for smokers only**





478-8C

Nonasbestiform Analogues of Asbestos: Are They Carcinogenic? A Review

by

John Gamble

January 1990

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Running Head: Nonasbestiform Minerals -- Carcinogens? A Review.

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Abstract

The mineralogical distinction between asbestos and nonasbestiform minerals has been blurred by the regulatory definition which utilizes a 3:1 aspect ratio of length to width. Although similar by regulatory definition, it is shown that there are clear differences between fiber populations derived from asbestiform and nonasbestiform habits. When characterized by aspect ratio and fibrosity index (log width/log length). Fibers from a nonasbestiform habit are primarily short and thick (high fibrosity index, few fibers with aspect ratio >20:1), while fibers from an asbestiform habit have larger numbers of long, thin fibers (low fibrosity index) and a substantial proportion of fibers with aspect ratios >20:1). Is there a similar distinction in the carcinogenicity of fibers from asbestiform and nonasbestiform habits? In comparing lung cancer mortality of cohorts exposed to fibers from asbestiform and nonasbestiform habits, the asbestos exposed cohorts tend to show a higher risk of lung cancer than the workers not exposed to nonasbestiform minerals. Asbestos exposed workers generally show an increased risk with increasing exposure, while workers exposed to fibers with a nonasbestiform habit do not show an exposure-response gradient. .Biological activity as measured in animal exposures consistently shows tumorigenic activity of asbestiform fibers but not nonasbestiform fibers. Current hypotheses regarding fiber pathogenicity suggest it is plausible for nonasbestiform mineral fibers to cause fibrosis, but implausible that exposure to nonasbestiform mineral fibers causes either lung cancer or mesothelioma.

Introduction

Asbestos and other minerals can be found in both asbestiform and nonasbestiform habits. A commonly used regulatory definition defines asbestos as a fiber longer than 5um with an aspect ratio greater than 3:1. Evidence is reviewed showing that this definition does not distinguish between the asbestiforrn and nonasbestiform habits of mineral fibers.

Using relatively simple dimensional criteria for identification, it is possible to distinguish between asbestiform and nonasbestiform habits of mineral species. Since dimensions of fibers are thought to play a major role in causing adverse health effects, a more precise definition of asbestos would help avoid misclassification of exposure which can occur now when minerals with a nonasbestiform habit are classified as asbestos. Different morphological indices will be presented that support the contention of mineralogists that the particle-size distribution of minerals with an asbestiform and nonasbestiform habit are dissimilar. These indices will also be used in classifying exposure to asbestiform and nonasbestiform minerals in the epidemiology and experimental studies.

A fibrosity index shows that in minerals with an asbestiform habit, width is relatively constant and independent of length. In minerals from an asbestiform habit, the fibrosity index is high, that is, as iength of the fiber increases the width also increases.

Particles longer than 5um and from a nonasbestiform habit generally have less than 5% fibers with aspect ratios >20:1. Minerals with asbestiform habit

generally have over *50%* of fibers with aspect ratios >20:1. *(See* Tables 4 and 5)

In simplified terms, evidence will be reviewed showing that the bulk of fibers from nonasbestiform habit are short and thick, with few long, thin fioers. Fibers from an asbestiform habit are generally longer and thinner, and there are a considerable number of long, thin fibers.

Does this difference in particle size distribution produce a different risk for respiratory cancer? Epidemiologic studies of populations exposed to fibers from asbestiform and nonasbestiform habits are compared for consistency in exposure-response relationships and strength of association. Comparability between studies is increased by including only workers with 20 or more years since first known exposure. This also reduces the likelihood of including cancer cases who have not had adequate time to develop respiratory cancer due to fiber exposure.

Relationships of particle morphology and habit with respiratory cancer are also evaluated in lifetime animal studies. Iypotneses regarding the mechanisms of fiber toxicity are reviewed for the biological plausibility of asbestiform and nonasbestiform fibers causing respiratory cancer.

The first part of this paper will characterize the fiber sizes of asbestiform and nonasbestiform minerals. In the second part data related to the question of whether this is an important distinction to make from the standpoint of risk of respiratory cancer will be discussed.

Asbestos Definitions

Asbestos belongs to two mineral families, ampniboie and serpentine. an4 each mineral has members with both asbestiform and nonasbestiform habits. (Table **1)** The asbestiform serpentine mineral, chrysotile, includes nonasbestiform serpentines antigorite and lizardite. Each of the asbestiform amphiboles have analogues with a similar composition and crystal structure, but a different habit or growth form ranging from nonfibrous (blocky) to fibrous (acicular or needlelike). The nonasbestiform amphiboles and other rockforming silicates possess prismatic cleavage. When these rocks are pulverized, microscopic fragments with parallel edges are formed. Since asbestos fibers also have parallel edges, the distinction between asbestiform and nonasbestiform amphiboles that is visible on the macroscopic level is not always clear at the microscopic level. (Campbell et al, 1977).

The nonasbestiform analogues are quite common. For example, about 30% of rocks in the continental U.S. contain amphiboles. Using a regulatory definition that defines asbestos as a particle having a >3:1 aspect ratio, most hard rock mines contain fibers that would be classified as "asbestos". Minerals containing such fibers include ore deposits of gold, iron, talc, and crushed stone. Such minerals are found in many water supplies, soils and sediments, certain sand and gravel deposits, drilling muds, portland cement, and ceramic materials. (Ross, 1984).

Asbestiform and nonasbestiform habits of serpentine and amphibole mineral samples can be differentiated by the naked eye. When these samples are milled, crushed or pulverized, both will form fibers that are >5um **Long,** <3um

wide, and with aspect ratios >3:1. The nonasbestiform amphibole particles, called cleavage fragments, meet the 3:1 aspect ratio definition for asbestos, However they lack the unique physical and crystallographic properties of the asbestiform fibers. These properties of asbestiform minerals generally include the following: (Campbell et al., 1979)

1. Aspect ratios from 20:1 to 100:1 or higher.
2. Very thin fibrils, generally <0.5um in width, and
3. Two or more of the following attributes:
    a. parallel fibers occurring in bundles;
    b. fibers dispiaying splayed ends;
    c. fibers displaying thin needles:
    d. matted masses of individual fibers;
    e. fibers showing curvature.

Prior to the 3:1 aspect ratio being used to define an asbestos fiber, asbestos referred to minerals with an asbestiform habit that possessed these characteristics. (Zoltai, 1978). That terminology will be used in this paper, i.e. asbestos and asbestiform are considered as synonymous terms.

The Bureau of Mines several years ago began studying the question of how to discriminate between amphibole cleavage fragments and amphibole asbestos fibers. Using morphological or dimensional criteria only, they demonstrated that asbestiform and nonasbestiform minerals comprise two different populations of particles when characterized by fibrosity index and aspect ratio ≥20:1. These indices will now be discussed.

Fibrosity Index

It has been shown in both bulk and airborne samples that the regression line relating log width to log length distinguishes populations of fibers from nonasbestiform and asbestiform habits:

Log10 width = F(log10length) + b, where

F = slope of the regression line= fibrosity index, a measure of the dependence of width on length,

b = intercept on the log width axis.

The fibrosity index is a measure of the dependency of width on length (Wylie, 1979). Larger values of F suggest less fibrosity (lower aspect ratios and variable widths that increase with increased length). Small values of F are characteristic of greater fibrosity (high aspect ratios and constant width which is independent of length).

The fibrosity index of minerals from asbestiform and nonasbestiform habits is presented in Table 2. After grinding, samples from nonasbestiform habits show that particle width varied as a function of particle length. For particles from asbestiform habits, width was small and approximately constant and showed little or no relationship to particle length. Similar results were observed for the nonamphibole fibrous mineral wollastonite, where different methods and degrees of grinding had only minor effects on the fibrosity index (Wylie and Schweitzer, 1982). Wollastonite is from a nonasbestiform habit but does possess prismatic cleavage and many particles are elongated ($\geq$3:1 aspect ratio). It is sold as a fiber, and might be expected to be affected by grinding. Both nonasbestiform amphiboles and wollastonite form fibers $\geq$5um

long and with aspect ratios >3:1. As defined by the fibrosity index, neither form fibers characteristic of minerals from asbestiform habits.

There are fewer data on the fibrosity indices of airborne samples, but what are available show similar results to those of bulk samples. The larger values for b and F in the mining populations indicate greater fiber width and a dependence of width on length, a feature Characteristic of cleavage fragments (Table 3).

In the data so far availabie, the fibrosity indices of particles from asbestiform habits and nonasbestiform habits do not overlap for either bulk or airborne samples as summarized from Tables 2 and 3:

	Asbestos	Nonasbestiform Minerals
F		
Airborne samples	0.21 to 0.24	0.68 to 0.78
Bulk samples	0.02 to 0.48	0.50 to 0.85
b		
Airborne samples	-0.61 to -0.64	-0.43 to -0.52
Bulk samples	-0.40 to -1.23	-0.13 to -1.02

Aspect Ratio Distribution of Fibers

The aspect ratio distribution of fibers from bulk and airborne samples of minerals from asbestiform and nonasbestiform habits is summarized in Tables 4 and 5. These data suggest that the 3:1 aspect ratio criterion does not distinguish between asbestiform fibers and cleavage fragments. The use of a

20:1 aspect ratio appears to completely separate populations of particle from asbestiform and nonasbestiform habits. The highest proportion of nonasbestiform fibers with an aspect ratio > 20:1 was 29% (for acicular mordenite, a fibrous zeolite); the lowest proportion in the asbestiform mineral group was 32% (FD72 tremolite asbestos). For airborne samples the gap is wider: 4% for cleavage fragments and 40% for asbestos fibers.

It is legitimate to wonder what relationship there might be between aspect ratio and tumor production. At least two points are relevant; neither have been fully analyzed. For asbestos fibers longer than 5um, as length increases, so does the aspect ratio. Second, Friedricks (1979) snowed that in animals exposed to different fibrous dusts (glass, mineral wool, chrysotile, nemalite, crocidolite, gypsum), the tumor rate increased with aspect ratio when the length/width ratio was about 15 or greater.

One point seems obvious. Incorrect descriptions of nature can cause errors in interpretation. Tyron Edwards said that "accuracy of statement is one of the first elements of truth. A large part of the discussion of disputants come from the want of accurate definition " (Edwards, 1955). In the instance of mineral fibers, it seems possible and advisable to more precisely characterize and label fibers from asbestiform and nonasbestiform habits so that in the discussion of their effects we are on common ground,

Effects on Health

Whatever definition of a fiber is used, the question remains: Do mineral fibers from nonasbestiform habits cause adverse health effects? Respiratory cancer, and primarily lung cancer, is the health outcome to be addressed in this paper. Lee (1981) suggests major differences of opinion are about the following questions.

1) "Is a 3:1 aspect ratio an appropriate medical or physical lower limit for the definition of an asbestos fiber?"
2) "Are asbestos fibers shorter than some arbitrary length (5um) as hazardous as longer fibers?"
3) "Is the mineralogical distinction between asbestos and nonasbestos minerals medically significant?"

Method of Review

The evaluation of causation is a difficult problem in epidemiology as it is not possible to make conclusive inferences that one event causes another. In this review the basis for making inferences about cause and effect will include criteria of temporality, biological gradient, strength of association, consistency, plausibility and coherence (Hill, 1965). There is only one rule that must be met. The cause must precede the effect. Otherwise there is no formal method for weighing one criterion relative to another, nor is there any rule to precisely determine the extent to which the evidence conforms to these criteria (Rothman, 1986)

Thus, the answer to the question of whether nonasbestiform fibers cause lung cancer must be an informal rather than a rigorous judgment. The approach taken in this review is outlined in Figure 1. Since the issue is respiratory cancer, the only epidemiological studies considered will be mortality studies. Temporality and comparability between different cohorts is controlled by evaluating only workers with 20-40 years since first exposure. Biological gradient and strength of association are summarized for all known cohorts of exposed populations meeting minimum methodological requirements. These requirements include over 90% follow-up and exposure well enough characterized so it can be classified as a mineral with an asbestos or nonasbestiform habit. To increase comparability, each study should be in sufficient detail that a $\geq$20 year latency group can be separated to estimate strength of association and calculate an exposure-response trend. A exposure response slope that

takes into account background mortality is calculated using the method described by Hanley and Liddell (1985).

Consistency is the repeated observation of an association under different conditions of study. A consistent association (or lack of it) strengthens (or weakens) a causal hypothesis in that it is unlikely that confounding or bias or an inappropriate comparison group would consistently bias results toward the same conclusion. What is of interest is tne consistency of results in the ≥20 year latency group with regard to 1) the strength of association and 2) the slope of the exposure-response curve. Consistency of results is judged within the nonasbestiform exposed cohorts and compared to results from "positive" controls (asbestos-exposed) and "negative" controls (noncoal mining cohorts exposed to neither amphibole nor serpentine minerals, and without other known confounding exposures). This comparison is somewhat analogous to the use of negative and positive controls in animal experiments.

Tenure is the surrogate measure of exposure for all of the studies. Some studies also had estimates of mppcf-years as a measure of exposure. The exposure-response relationships were similar when both estimates of exposure were used: only the tenure data will be shown in this review. The finding of a biological gradient is considered strong evidence of a causal association. An increased prevalence of smoking in a cohort will usually result in an increase in the strength of association (overall SMR) but is considered less likely to confound an exposure-response relationship. In this review SMR's and exposure-response results are computed for the ≥20 year latency group. The slope of the exposure-response gradient is adjusted to background

mortality; i.e. SMRs are set at 100 at 0 years tenure and can therefore be compared directly (Hanley and Liddell, 1985).

Since twenty years is a generally accepted time period for the development of lung cancer, the issue of temporality (cause must precede the effect) and comparabiltiy between studies is taken into account by including only workers with >20 years latency. Strength of association refers to the magnitude of the ratio of rates for lung cancer between the exposed and comparison populations. A moderate (SMR 1.5-3) to strong SMR (3-10) association is more likely to be causal than a weak association(SMR < 1.5) which is more easily explained by bias (Monson, 1980).

Plausibility and coherence are similar concepts. Coherence is in large part derived from animal studies of tumor production, and experimental and pathological studies of deposition, clearance, and retention. Plausibility refers to whether theory conforms to an observed association.

Review of Nonasbestiform Amphibole Exposed Cohorts

There are a total of 3 cohort mortality studies of nonasbestiform amphibole exposed populations that meet the requirements for inclusion in this review. No study of workers exposed to nonasbestiform serpentine minerals was found. The populations are gold miners (Brown et al., 1986), iron (taconite) miners (Cooper et al., 1988), and tremolitic talc miners and millers (Gamble and Piacitelli, 1988). Both gold and taconite contain primarily cummingtonite' grunerite (the nonasbestiform analogue of amosite). The talc contains 37-59% nonasbestiform tremolite. Results are summarized in Table 6 and Figure 2.

GOLD MINERS.

The cohort of gold miners was initially studied to examine the hypothesis that exposure to amphibole minerals is associated with asbestos-related disease. The amphiboles have been characterized by both fibrosity index ana aspect ratio as nonasbestiform (Virta et al., 1983; Wylie, 1988), and include cummingtonite-grunerite (~69%), with lesser amounts of tremolite-actinolite (~15%) and fibrous hornblende ('16%). Average airborne fiber (>5um long, >3:1 aspect ratio) exposure was **0.44** f/cc.

This study does not include workers with <1 years tenure, and there was only one lung cancer case in the ≥20 year tenure group. There was a 95% probability the SMR was between 53 and **142.** The point estimate of the exposure-response slope was slightly negative. At **20** years tenure there was a 95% probability the SMR is between 0 and **548,** with a point estimate of **72.** The point estimate of the slope was also negative when exposure was mppcf-years. The authors concluded there was no association of lung cancer with tenure, total dust, or latency (Brown et al., 1986).

TACONITE MINERS.

Taconite in the eastern Mesabi range of Minnesota contains nonasbestiform amphiboles, notably cummingtonite, grunerite, actinolite, and hornblende. These amphiboles are nonasbestiform using the fibrosity index and aspect ratio criteria, but the cleavage fragments meet the regulatory definition of >5um length and >3:1 aspect ratio (Cooper et al., 1988; Virta et al., 1983). Fiber exposure generally was <0.5 f/ml, but occasionally as high as **2** f/ml.

This is the largest cohort of workers exposed to nonasbestiform amphiboles, with 25 lung cancer cases in the ≥20 year latency group. There was 95% probability the SMR was between 37 and 84. The point estimate of the exposure-response slope was slightly positive. At 20 years tenure there was a 95% probability the SMR was between 0 and 282, with a point estimate of 116. The authors concluded there was no evidence of excess risk of respiratory cancer associated with past taconite exposure (Cooper et al., 1988). The SMRs for lung cancer and nonmalignant respiratory disease were similar to hematite iron miners in the same area, but hematite does not contain amphiboles (Lawler et al., 1985, Table 8). Higgins et al. (1983) reported similar results in their study of a different cohort of taconite miners. However latency was generally less than 20 years, and so was not included.

TALC MINERS.

Yortality of tremolitic talc miners and millers have been previously reported (Brown and Wagoner, 1980; Stille and Tabershaw, 1982; Lamm et al., 1988). These studies are not included in this review as they did not meet the criterion for inclusion, and included workers at the same mine and mill as reported by Gamble & Piacitelli (1988). The latter study however had more lung cancer cases, longer latency, and an exposure-response analysis by tenure and latency. It is the only study included in this review that controlled for confounding from smoking, and analyzed for potential confounding from other occupational exposures.

The habit of the amphiboles in the talc has been called asbestiform (Brown and Wagoner, 1980; Dement and Zumwalde, 1979). However this New 'fork tremolitic talc meets the nonasbestiform criteria for fibrosity index in bulk samples

(Siegrist and Wylie, 1980), and the aspect ratio criterion for both bulk (Campbell et al., 1980, 1979; Wylie, 1988) and airborne samples (Kelse and Thompson, 1988). It is therefore included in the nonasbestiform exposure category both here and in the animal studies.

This cohort study (Gamble and Piacitelli, 1988) included all workers irrespective of how short their tenure; over 50% of the workers were short-term (<1 year tenure). Only two cases of lung cancer were in the ?-20 year tenure group. There was a 95% probability the SMR was between 137 and 441 with a point estimate of 258. The point estimate of the exposure-response slope was slightly negative and about the same as in the gold miner study. At 20 years tenure there was 95% probability the SMR was between 20 and 280 with a point estimate of 78.

The study of talc miners and millers also included a nested case control design, with 22 lung cancer cases and 3 controls/case matched on date of birth and date of hire. All of the cases were either smokers (91%) or exsmokers (9%) while 64% of the controls were smokers and 9% exsmokers. There was no apparent association between nontalc work and risk of lung cancer. The slope of the exposure-response relationship was negative for the 17 lung cancer cases and 41 controls who smoked and also had ≥20 years latency. At 20 years tenure, there was a 95% probability the odds ratio was between 0.36 and 0.8 with a point estimate of 0.58.

The authors concluded there was no apparent causal association between lung cancer and talc exposure. They point out, however, that background mortality

is high, the number of cases small, and there is no analysis using mppcf-years as the exposure parameter,

In two of the three studies of amphibole exposed populations the SMR was at the null value, In the talc cohort there was less precision in the estimate of the SMR, and it was considerably higher than is generally seen in working populations. The case control study suggested little likelihood of confounding nontalc exposures, but showed considerable confounding from smoking. Using tenure (and mppcf-years for the goldminers) as the exposure variables, the point estimate of the exposure-response slopes were at the null value, suggesting no biologic gradient. However, the precision of the estimate was low for all three cohort studies, and particularly the study of gold miners. When smoking was controlled in the exposure-response analysis of lung cancer risk among the talc workers, the confidence interval was narrow and the limits below the null value.

The apparent lack of an exposure-response relationship in the mining cohorts might be attributable to "fiber" exposure below MSHA standard of 2 f/cc, and often below the OSHA PEL of 0.2 f/cc. In the taconite cohort some exposures above 2 f/cc were reported. Dement and Zumwalde (1979) reported exposures ranging from 0.8 to 9.8 f/cc in the talc mine and 0.2 to 16 f/cc in the mill. Exposures in 9 of 24 job categories sampled were in excess of 10 f/cc. In all the cohort studies it is possible if not likely that exposures in earlier years were higher.

Review of Asbestos Exposed Cohorts

Does exposure to nonasbestiform amphiboles pose a risk for lung cancer similar to the risk of lung cancer in populations exposed to asbestos? This comparison is analogous to a positive control in an experimental study. Table 7 and Figure 3 summarize the results of retrospective cohort mortality studies of asbestos miners (McDonald et al., 1980; Hobbs et al., 1980) asbestos textile workers, (McDonald et al., 1983, 1983a), amosite factory workers (Seidman et al., 1986), asbestos cement workers, (Hughes, et al., 1987; Ohlson and Hoystedt, 1985), friction products workers, (McDonald et al., 1984b), and vermiculite workers exposed to tremolite-actinolite asbestos, (Amandus and Wheeler, 1987, Amandus, 1988). Most of these cohorts (six) were exposed primarily or exclusively to chrysotile. Crocidolite, amosite and tremolite-actinolite asbestos exposed cohorts are each represented once. Only three of the studies are mining cohorts

The cohort of amosite asbestos factory workers (Seidman et al., 1986) comprised mostly white maies who worked for only a short time during 1941-5. Exposure was quite high, and the risk of lung cancer was increased for all tenure groups. The overall SMR was 452 and the exposure-response trend was the highest of any of the cohorts.

Hobbs et al., (1980) suggested that crocidolite exposure accounted for nearly 30% of the respiratory cancer deaths among Australian miners. They assumed no crocidolite-caused cancer deaths among the medium/light exposure groups with <3 months tenure, or miners with less than 10 years latency, Exposures were

quite high (up to 100 f/ml in bagging). All workers were included, and only at tenures greater than 3 months was the SMR elevated. Latency in this study was >15 years, and 50% of the cohort had >1 year tenure. The distribution of workers by tenure group is similar to the Seidman et al.. (1986) cohort in that tenure was short. In both of these studies the exposure-response slope might be even higher if the highest tenure group were categorized into smaller units (say 20-28 years instead of 1-28 years). Using three exposure categories (two include workers with <1 year tenure), these data show a 95% probability that at 20 years tenure the SMR was between 90 and 560 with a point estimate of 234.

The research group in Canada has reported four major cohort studies of asbestos exposed workers (McDonald et al., 1980, 1983, 1983a, 1984b). Similar methods are used in each study. Only workers with ≥20 years latency and ≥1 months tenure are included. Both tenure and mppcf-years were exposure variables and showed a similar exposure-response relationship. An internal case-control log rank procedure analysis showed a similar pattern of relative risk to that of the man-years life table cohort analysis. Only the latter results are presented.

The cohort study of chrysotile miners in Quebec (McDonald et al., 1980) showed a slightly increased slope with both cumulative exposure (mppcf-years) and tenure. At 20 years tenure there was 95% probability the SMR was between 116 and 196. The authors suggested there was no apparent excess relative risk of lung cancer except in workers with 20 or more years tenure in high exposure groups (33.8 mppcf or about 100 f/mL). This is the largest cohort of any asbestos-exposed workers.

McDonald et al. also reported on two chrysotile textile mills (McDonald et al., 1983, 1983a) and a friction products plant (McDonald et al., 1984b). The two textile cohorts were of similar size and showed similar positive exposure-response slopes whether exposure was tenure or mppcf-years. Exposure averaged 2.3 mppcf in the Pennsylvania cohort (McDonald et al., 1983) and 1.8 mppcf in the South Carolina cohort (McDonald et al., 1983a). The plant with lower exposures (S.C.) had an SMR of 200 (95%CI 152,253). The Pennsylvania textile plant had an overall SMR of 106 (95%CI 79,139). Nevertheless the exposure-response trends were similar for both tenure and cumulative exposure (mppcf-yrs) in the two textile plants. The point estimates of the slopes were .08 and .07 for S.C. and Pennsylvania respectively, and much steeper than the slope of .02 for the chrysotile miners.

These data point up the unexplained variability sometimes observed in the strength of association criteria. The authors (McDonald et al., 1983a) suggested the low SMR in the Pennsylvania textile plant might be due to the large number of nonsmoking Mennonites in the cohort. The S.C. textile plant is the same plant reported by Dement et al. (1983). The McDonald et al. (1983) study was used because of the larger number of cases, analysis of the $\geq$20 year latency group was provided, and the methodology was the same as the two other McDonald et al. studies (1983, 1984b).

The friction products cohort of asbestos exposed workers (McDonald, 1984b) had average dust concentration (1.84 mppcf) similar to the South Carolina textile plant (1.80 mppcf), but lower than the Pennsylvania plant (2.32 mppcf). The point estimate of the exposure-response slope was negative using both tenure

and mppcf-years as exposure variables. The SMR was 50% above expected however, with a 95% confidence interval of 116, 186, The short-term workers (<1 year) had the highest SMR.

Work in other hazardous industries did not appear to be an explanation for the increased risk in either the friction products or S.C. textile plant cohorts. McDonald et al. (1984b) suggested that in the friction products cohort a selective process could have resulted in the employment of men with relatively poor health or health habits (such as heavy smokers perhaps) in low exposure jobs in which they remained only a short time. When they excluded the low exposure group of friction product workers, the fitted regression suggested adverse health effects of employment were small, and similar to Quebec chrysotile miners and millers.

There are two cohorts of asbestos cement workers. In the Swedish study (Ohlson and Hoystedt, 1985), exposure was estimated at 2 f/cc prior to 1970 and 1 f/cc after 1970. Short-term employees (<2 years) had higher mortality than long term employees (>5 years) from virtually all causes, but especially lung cancer. The exposure-response slope was negative, and the overall SMR was 159. However there was only 1 case among workers with more than 5 years tenure and 9 cases overall.

The Louisiana cohort of asbestos cement workers comprised two plants analyzed separately (Hughes et al., 1987). Plant 2 appears to have had slightly higher exposure than plant 1 with a 50% increase in the SMR and a positive exposure-response slope for both tenure and mppcf-years. Plant 1 showed no apparent exposure-response relationship with either exposure parameter. There was 95%

probability the SMR was between 85 and 154. Exposure was also reported in mppcf, and was 10 mppcf or less. The lack of an exposure-response trend observed in Plant 1 was also observed in the low to medium exposure groups of chrysotile miners (McDonald et al., 1980) where average exposure was also <10 mppcf, and was absent even when tenure exceeded 20 years.

The vermiculite miners and millers (Amandus and Wheeler, 1987; Amandus, 1988) were exposed to high levels of tremolite-actinolite asbestos. For example, estimated dust exposure in the dry mill was 42 mppcf from 1950-64 and 8.4 mppcf from 1965-9. After 1971 exposures declined, and after 1977 appeared to be less than 1 f/cc. That the vermiculite was contaminated with asbestos is indicated by the distribution of airborne fibers >5um long: 96% had aspect ratios >10:1, and 67% > 20:1 (Amandus, 1988). The exposure-response slopes were positive whether workers with <1 year tenure were included or not and were similar to the slopes of the textile cohorts. The SMR of workers with 5-10 years and >20 years tenure was among the highest of any of the cohorts.

The asbestos cohorts roughly fall into two groups. One group showed steep exposure- response curves, and for four of the seven conorts the SMRs were >150. In rank order they are listed according to the exposure response slope:

	Slope (x100)	SMR
Amosite Insulation Workers	+18.5	**452**
Vermiculite Miners	+10.7	**165**
Textile Workers-S.C.	**+ 8.4**	**200**
Crocidolite Miners	**+ 6.7**	**170**
Textile Workers-PA.	**+ 6.5**	**106**
Asbestos Cement-Plant **2**	**+ 4.4**	**144**
Canadian Chrysotile Miners	**+ 2.4**	**125**

A second group had exposure-response curves near the null:

Friction Products-Conn.	-0.7	148
Asbestos Cement-Plant 1	-0.9	116
Asbesto Cement-Sweden	-4.6	159

Review of Cohorts Not Exposed to Amphibole Minerals

Do mining populations not exposed to amphibole minerals (or other possible carcinogens such as radon) experience a risk of lung cancer that is less than that of nonamphibole-exposed mining populations? This comparison is analogous to a negative control in an experimental study. Table 8 summarizes lung cancer risk among nonamphibole mining populations.

The studies of Canadian nickel miners (Roberts and Julian, 1983, Shannon et al., 1984) and U.S. attapulgite miners and millers (Waxweiller, 1988) provided

only a dichotomous analysis of exposure-response, making interpretation difficult.

Attapulgite is a fibrous clay containing short fibers less than 2.5um long. The lung cancer risk was paradoxical in that whites had a 3-fold increased risk overall, and a 4-fold increased risk in the >5 year tenure group. Nonwhites had SMRs $\leq$ 100. While the number of lung cancer deaths is quite small, it is interesting to note that the attapulgite cohort had among the highest and lowest SMRs for lung cancer of any study surveyed.

The two studies of nickel miners were in the same area of Canada and used the same methodology, The Study of Falconbridge workers (Shannon et al., 1984) generally had higher SMRs than Inco workers (Roberts and Julian, 1983), with the largest SMRs occurring in the workers with lower tenures. The number of lung cancer deaths with $\geq$20 years latency was small (20 miners and 9 service workers), and SMRs were about 50% above expected. The Inco study was quite large, and SMRs for UG and all workers were slightly above 100. No environmental data were available for either study, but amphiboles are not reported to be present. In both cohorts the underground and surface miners had similar SMRs.

The iron ore miners cohort (Lawler et al., 1985) is from the same region as taconite miners (Cooper et al., 1988); only hematite miners without exposure to taconite were included. There was no apparent excess risk of lung cancer as all SMRs were at or below 100 for both UG and surface miners, and there was no trend for SMRs to increase with tenure. However there was no stratification by latency in the exposure-response analysis.

Muller et al. (1986) reported no association of lung cancer risk and total years underground among Ontario gold miners. Dust levels were quite high prior to the mid 1940's. Miners starting work prior to 1945 showed a higher risk of lung cancer, and a trend for risk to increase with the number of years worked prior to 1945 (SMRs increased from 116 with 0 years to 202 for those with >20 years employment prior to 1945). There was no stratification by latency. The authors concluded it was the high dust levels prior to 1945 that was responsible for the overall increased SMR for lung cancer. No amphiboles are present in this ore.

This group of mining cohorts does not provide a lot of information for comparison. There are generally no exposure data, two were not stratified by latency, and two provided only dichotomous tenure-response data. In the two studies with adequate exposure-response data, there was no apparent slope. The white attapulgite miners had a three-fold excess SMR for lung cancer (95% CI of 110, 653). This is similar to the excess observed among miners exposed to tremolitic talc. Nonwhite workers at the some plant and often in the higher exposed jobs had an SMR of 70 with a 95% CI of 19 to 180. There were however only six whites and four nonwhites with lung cancer in this cohort.

Summary of Epidemiologic Studies

There were three eligible mortality studies of nonasbestiform amphibole exposed cohorts. Two of the three studies had SMRs below 100, and all three had exposure-response slopes at or below the null. One (talc) had a 2.6 fold increased SMR, but when smoking was controlled in the case-control analysis,

there was clearly no increased risk with increased tenure. Since 100% of the lung cancer cases were smokers or exsmokers, at least part of the elevated SMR could be due to confounding from smoking.

There were ten eligible mortality studies of asbestos exposed conorts. One (asbestos cement workers) had two plants that were analyzed separately and so constitutes two studies. There were no SMRS below 100, five between 100 and 150, four between 150 and 300, and one >300. Seven of the ten had positive relative siopes, and the other three had exposure-response slopes suggesting little or no increased risk of lung cancer with increasing tenure. Except for the elevated SMR of the talc cohort, the nonasbestiform exposed cohorts resembles this second group of asbestos cohorts rather than the first group where there was a substantial risk of lung cancer.

Reports on five mortality studies of mining cohorts not exposed to either amphiboles, asbestos or known confounders were found in the literature. This type of negative control was chosen because of their similarity to the amphible reposed cohorts in their occupation, and may therefore have similar risks in ways other than amphibole exposure. Unfortunately few studies were found. Three of these separated the analysis by race (attapulgite) or undergrounds is surface (hematite, nickel). Only 2 of the cohorts (hematite, gold) had multiple tenure categories. Two of the five underground cohorts had SMRs <100, two were between 100 and 150, and one was 300. Wone had exposure information other than tenure. There was no apparent biological gradient in the hematite or gold miner cohorts, although SMRs ranged from 135 to 150 among the Ontario gold miners. There were no obvious differences between the

cohorts exposed to nonasbestiform amphiboles and these so-called negative controls.

The cohorts exposed to nonasbestiform amphiboles were consistent in not showing an exposure-response gradient. In this respect they were aissimilar to the majority of asbestos exposed cohorts, and similar to the nonasbestos exposed mining cohorts. Strength of association did not provide a clear or consistent pattern that distinguished exposure effects. The few studies of cohorts not exposed to asbestiform minerals were generally small in size and used tenure as the surrogate measure of exposure. Exposure-response trends in the asbestos (and gold miner) cohorts were similar when both tenure and mppcf-years were the exposure variables, thereby increasing confidence in tenure as a useful exposure variable.

The criteria of biological gradient and consistency do not implicate nonasbestiform amphiboles as posing an increased carcinogenic risk. Strength of association did not provide an indication of any clear difference among the three groups although the asbestos cohorts tended to show a higher risk than the nonasbestiform amphibole cohorts and the nonamphibole exposed mining cohorts. Except for the moderately increased SMR in the tremolitic talc cohort, there was no apparent evidence of any association consistent with a causation.

Review of Experimental Studies and Plausibility

A second type of evaluation to assist in the interpretation of a cause-and-effect-association is biological plausibility. That is, a causal association

should not seriously conflict with our knowledge of the natural history and biology of the disease, and it is helpful if it conforms to biological knowledge. Are there animal studies that provide information on tumor production? What are the current theories regarding the carcinogenic properties of fibers? Do the nonasbestiform amphiboles possess these properties?

Experimental Studies

If fibers from nonasbestiform habits do not produce tumors in animals while fibers from asbestiform habits do, then the probability that nonasbestiform fibers are not carcinogenic is made more believable. I will examine the evidence in order of increasing complexity, starting with in vitro.. models, implantation or injection in the pleura or peritoneum, and then inhalation. The implantation or injection studies bypass deposition, clearance, and aerodynamic considerations and apply to mesothelioma rather than lung cancer. However this type of experiment has been important in the development of the hypothesis that long, thin, durable fibers cause cancers (Harrington, 1981). Since morphology is considered the major factor relating to fiber carcinogenicity, the main focus will 'be on this variable, and on experiments utilizing fibers from both asbestiform and nonasbestiform habits.

In Vitro Studies

Frank et al. (1979) compared the in vitro cytotoxicity of serpentine asbestos (chrysotile) and platy (non-asbestiform) serpentine (antigorite, lizardite) from a Rockville quarry. The nonfibrous platy material caused no damage to a

macrophage-like cell line, while the chrysotile was cytotoxic and inhibited cell growth. Woodworth et al. (1983) used cultures of hamster trachea to assess the ability of asbestos and nonasbestiform analogues to induce metaplasic changes. Crocidolite and chrysotile asbestos induced metaplasia over all dose ranges, while their nonasbestiform analogues riebeckite and antigorite did not.

In Vivo Studies (Inoculation)

Implantation or injection of fibers in the peritoneum or pleural space yield sarcomas that are similar to the mesotheliomas induced by asbestos in man. A number of investigators have used this method to assess biological activity of both asbestos and nonasbestiform materials. Dose is generally quite high with many studies using doses of 20 mg, 40 mg and 100 mg (Table 9).

Chrysotile, crocidolite, amosite, actinolite asbestos, anthophyllite asbestos and tremolite asbestos have all induced tumors and reduced survival time by these methods. Nonasbestos fibers with the morphology of asbestos fibers (e.g. brucite, fibrous zeolites, long length attapulgites, palygorscite) also increased tumor rates. The minerals'with nonasbestiform habits did not increase tumor rates or decrease survival. These included: 1) Asbestos treated to practically eliminate long fibers; 2) nonfibrous minerals (e.g. talc, .hematite, kaolin), 3) fibrous minerals (some attapulgites, wollastonite) and 4) serpentine and amphibole fibers from nonasbestiform habits (tremolite, actinolite, antigorite, tremolitic talcs).

The animal studies are completely negative with regard to tumor activity of nonasbestiform amphibole and serpentine minerals, but are positive with regard to the asbestiform minerals.

These studies of minerals with an asbestiform habit also demonstrate a dose-response effect. As the dose is decreased (or the number of long fibers decreases) the incidence of tumors decreases, till there is no discernible tumor production at very low doses.

Two studies provided some quantitative data on the number of fibers by particle size for minerals with and without an asbestiform habit. Stantan et al. (1981) observed correlations of .45, .68, .63, and .80 for particle with dimension of $\leq$0.25um-1.5um width and >4-8um length, $\geq$0.25-1.5um width and >8um length respectively. Wollastonite, attapulgite and some of the talcs contained fibers >4-8um long in numbers similar to those of tremolite and amosite asbestos. There were considerably fewer fibers >8um in length (and especially so for the thin fibers $\leq$0.25um in diameter) compared to the asbestos minerals. The tumor rates for the asbestiform minerals were about 100%. For the nonasbestiform minerals the tumor rates were not distinguishable from controls, and often no tumors were found.

This study also provides a direct comparison of tumor activity in asbestiform and nonasbestiform varieties of tremolite. The tumor rates and fiber numbers were as follows:

		tumorrat-e	fibers/mg			
	width	≥.25	≥.25	≥.25	≥.25
	length	>4–8	8–64	>4–8	8-64
tremolite asbestos 1	100%	9698	9698	4135	4135
2	100%	9185	7930	2399	692
tremolite (nonasbestiform)	0%	5326	5326	3548	1778
	0%	9355	4677	4677	--

The fiber content was similar for all fibers ≥.25um, and for the thin relatively short fibers (>4-8um). There were no thin, long fibers (8-64um) in the one tremolite sample, but the other tremolite sample contained more than tremolite asbestos 2. The data from Table 2 on the tremolite sample suggests that the fibers in the long thin category will have a length nearer to 8um, whereas for asbestos there will be more fibers toward the 64um length. However, this is just a hypothesize that concurs with plausibility, and requires further documentation on particle size distribution to be more definitive concerning the reason for the differences in tumor rate.

Wagner et al. (1982) performed three experiments injecting 20 mg of the amphibole tremolite into rat pleura. The tremolite asbestos from South Korea contained 56,100 fibers/mg that were >8um x <0.25um and produced a 30% tumor rate. The two samples of nonasbestiform tremolite produced no tumors. One

sample was from Greenland and contained no fibers of these dimensions. The other sample was >95% tremolite from California talc and contained 1700 fibers/mg of these dimensions. These experiments suggest that exposure to high concentrations of nonasbestiform tremolite does not produce tumors, whereas exposure to tremolite asbestos does.

From these kinds of data was formulated the well-known Stanton hypothesis that durable fibers with well-defined ranges of diameter and length can cause cancer irrespective of whether they are asbestos or not. The size ranges suggested by Stanton et al. (1981) were fibers with an approximate size of ≤1.5um diameter and >8um in length. Stanton suggested caution, however, in extrapolating from these animal experiments to the risk of mesothelioma in man because of the high doses often used and the artificial nature of administration that bypasses consideration of aerodynamics, deposition, and clearance. As Stanton and Wrench (1972) observed, "direct application of the results to the problems in man would be unwise." However the tumorigenic action of the asbestos minerals in general appears to correspond to the epidemiologic findings, although there are no epidemiologic studies of anthophyllite asbestos workers that met the criteria for inclusion in this review.

In Vivo Studies: Inhalation:

There are no inhalation studies of amphibole and serpentines with a nonasbestiform habit. Inhalation of asbestiform serpentines and amphiboles produce lung tumors and mesotheliomas in rats if exposure is high enough. There is no increased tumor production if the proportion of fiber >20 um is

less than about 3-5% as demonstrated by special preparations of short fiber amosite and the dusting of animals with minerals containing primarily short fibers (brucite, some attapulgites) (Table 10).

In the study by Davis et al. (1978), the proportion of fibers >20um long was quite different between asbestos species. No bronchial carcinomas and almost no fibrosis were produced by asbestos containing <72 f/mL longer than 20um.

Animal studies can provide further insight into the fiber dimensions relevant to fibrosis, lung cancer, and mesothelioma. Davis et al. (1986b) report on an injection and inhalation study of long and short amosite asbestos. This study is significant because, for perhaps the first time, the short fiber dust contained very few long fibers. *So* it is a partial test of the long fiber theory of carcinogenesis. The results are summarized:

	Short Fiber	Long Fiber	(UICC Amosite)
Intraperitoneal injection-% tumors			
25 mg	4%	95%	94%
10 mg	0%	88%	--
Inhalation - 10 mg/m3			
% Pulmonary fibrosis	0.15%	11%	-
% Pulmonary tumors	0	20%	0
% Pleural mesothelioma	0	5%	0
Length dimension of the dust			
% > 5um	1%	30%	--
% ≥ 10um	0.1%	11%	--

This study demonstrates little or no tumorigenic or fibrogenic effect of amosite asbestos containing 1% or less of fibers greater than 5um in length. UICC amosite had a particle size distribution intermediate to the long and short fibers although proportions were not provided. While intrapleural injection of UICC amosite produced a similar incidence of mesotheliomas to

that produced by the long fiber amosite, no lung tumors or mesotheliomas were produced by UICC amosite when inhaled. From these results Davis et al. (1986b) concluded that "very snort fibers [of amosite] exhibit little carcinogenicity to either lung or mesothelial tissues at the doses examined."

Biological Plausibility

Do the deposition and clearance characteristics of fibers affect their ability to produce tumors? The respirability of fibers is a function of diameter more than length, and the maximum diameter of respirable fibers is 3-3.5um (when length is >5um). Fibers with a width greater than this will deposit on the mucociliary blanket and normally be cleared from the lung in 24 hours. Fibers with a smaller diameter are deposited in the alveoli, engulfed by macrophages (if not too long) and transported to the mucociliary escalator, to the lymph nodes, or to subpleural foci (Timbrell, 1965, *Gross,* 1981). Timbrell (1983) estimates 100% retention of fibers over 20um long, about 70% retention of fibers lOum long, and about 30% retention for fibers 5um Long.

Short fibers (<5um) deposited in the alveoli are readily and completely taken up by phagocytes and are more rapidly cleared than longer fibers (Morgan et al., 1978; Roggli et al., 1987). Macrophages are 17-20um in diameter (~12um in rats) and cannot engulf fibers which exceed a critical length greater than the diameter of the macrophage. Fibers 5-20um long are sometimes completely ingested and sometimes not, while fibers >30um long are never completely engulfed (Allison, 1977).

Fibers can also interact with chromosomes and with cellular membranes. The consequences are a loss of hydrolytic enzymes and a promotion of prooxidant states, producing increased concentrations of active oxygen and organic peroxides and radicals that promote neoplastic growth (Allison, 1977; Wang et al., 1987; Cerutti, 1985; Moalli et al., 1987).

For over 30 years the idea that the toxicity of asbestos is due to long, thin fibers has been gaining more evidence (see Table 11). The hypothesis has become more precise, with current hypotheses suggesting that particular fiber sizes are more likely to induce a particular effect. The most recent hypothesis is that of Lippman (1988). Based on the type of data reviewed in this paper, he suggests fibers between about 5 and 10 um long and <0.1 um width are the critical lengths for inducing mesotheliomas. While large numbers of these size fibers may presumably produce lung cancer, the risk is particularly associated with substantial numbers >10um long and between 0.3 and 0.8um widths (Table 11).

There are relatively few data from the workplace on particle size distributions and no consistent or standardized way to describe size characteristics of fibrous dusts. Some data and methods are described in the first part of this review. Can the physical dimensions of fibrous but nonasbestiform minerals be more precisely described so their potential effect on health can be predicted on the basis of current hypotheses?

In Table 12 are calculated from the fibrosity index the width for different lengths of selected asbestos and fibrous minerals. Included is the range of widths for about 95% of the particles with that length. Using the Lippmann

(1988) criteria of fiber size (Table 11), only asbestos minerals have more than **5%** of the fibers meeting the criterion for mesothelioma and lung cancer:

	Fibrosis	Mesothelioma	Lung Cancer
Dimensions (LxW)	(>2 x 0.15-2)	(5-10 x <0.1)	(>10 x 0.3-0.8)
Nonasbestiform fibrous minerals	generally meet width criteria for fibers 2-10 um long	<<5% of fibers are this size	<<5% of fibers are this size
Asbestos Minerals	All lengths have some fibers that meet width criteria	All types of asbestos have some fibers that meet these criteria	All types of asbestos have substantial proportions of fibers in this size category

By these criteria, it is plausible that exposure to fibrous minerals could result in fibrosis, but these calculations suggest that even massive exposures of nonasbestiform minerals contain few fibers of the hypothesized dimensions considered critical for the induction of lung or mesothelial tumors.

Summary and Conclusion

Yineralogists have distinct meanings for terms such as fiber, fibrous, asbestiform, and asbestos. A more recent definition uses a 3:1 aspect ratio for fibers longer than 5um to define asbestos. This definition does not distinguish between fibrous and asbestiform habits, and "endangers the success of coordinated interdisciplinary studies aimed at the understanding and the solution of the health hazards created by asbestos pollution." (Zoltai, 1978).

The size of particles in asbestiform and fibrous minerals have a different distribution when characterized by fibrosity index and by percent of fibers with an aspect ratio greater than 20:1. It thus appears feasible to distinguish between populations of fibrous minerals and asbestiform minerals while still using criteria such as length, width, and aspect ratio. These criteria have been used in this review to distinguish between exposure to nonasbestiform amphibole and asbestos in studies of both humans and animals. The fibrous index has also been used to estimate fiber dimensions in minerals with an asbestiform and nonasbestiform habits to evaluate the plausibility of carcinogenicity according to current theories.

Are there differences in health effects between fibrous and asbestiform minerals? In particular, do fibrous, but nonasbestiform minerals cause respiratory cancer? The rules of evidence used in epidemiology for determining causality were applied to this question.

Epidemiological studies of cohorts exposed to asbestos, fibrous minerals and nonfibrous dusts were selected for comparison if they met procedural requirements including adequate follow-up and stratification by exposure and latency. Exposure-response relationships and strength of association were calculated for subgroups with ≥20 years latency. The asbestos cohorts tended to be at greatest risk of lung cancer and the risk of lung cancer generally increased with both tenure and fiber exposure. The cohorts exposed to nonasbestiform amphiboles showed little or no evidence of a exposure-response gradient. The tremolitic talc cohort had an elevated SMR for lung cancer, but all cases were smokers or former smokers, and when confounding by smoking was controlled there was no increase in risk with increased tenure.

Based on the results of epidemiological studies, animal experiments investigating tumor production, particle deposition, clearance, and retention, and aerodynamic considerations, a current hypothesis regarding critical fiber dimensions has emerged. The fiber dimensions of nonasbestiform minerals are such that there appear to be few fibers of critical dimensions to make biologically plausible a causative relationship for respiratory cancer. Animal experiments consistently shows no increased risk of respiratory cancer from exposure to nonasbestiform minerals in contrast to the consistently increased risk for asbestiform minerals. The tabular summary of the evidence suggests the probability of nonasbestiform analogues of asbestos causing respiratory cancer is low.

	Asbestos	Nonasbestiform Minerals
Epidemiology:		
Strength of Association	Some to strong	Some to moderate
Exposure-Response	Mostly yes	NO
Experimental Studies:		
Mesotheliomas in animals from:		
Pleural Inoculation	Yes	No
Inhalation	Yes	NO
Lung Cancer on Inhalation	Yes	So (but limited data)
Plausibility:		
Fibrosis	Yes	Yes
Mesothelioma	Yes	No
Lung Cancer	Yes	NO

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Figure 1. Flow Sheet for Evaluating Causation

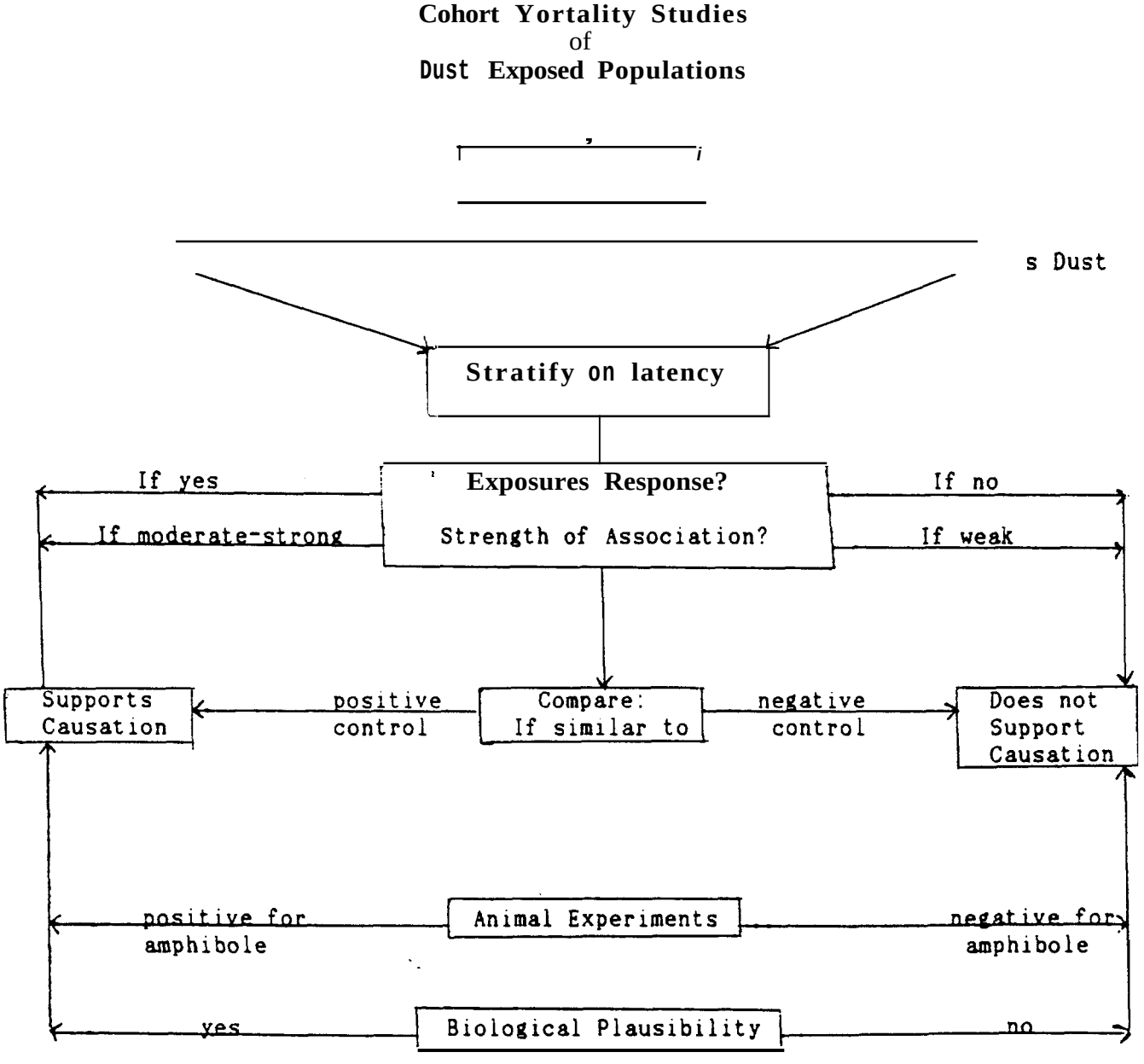


Figure 2. Relationships between exposure (tenure) and lung cancer SMRs among workers with 20 or more years latency and exposed to nonasbestiform amphiboles from Table 6; Calculation of relative slope (r) from Hanley and Liddell, 1985).

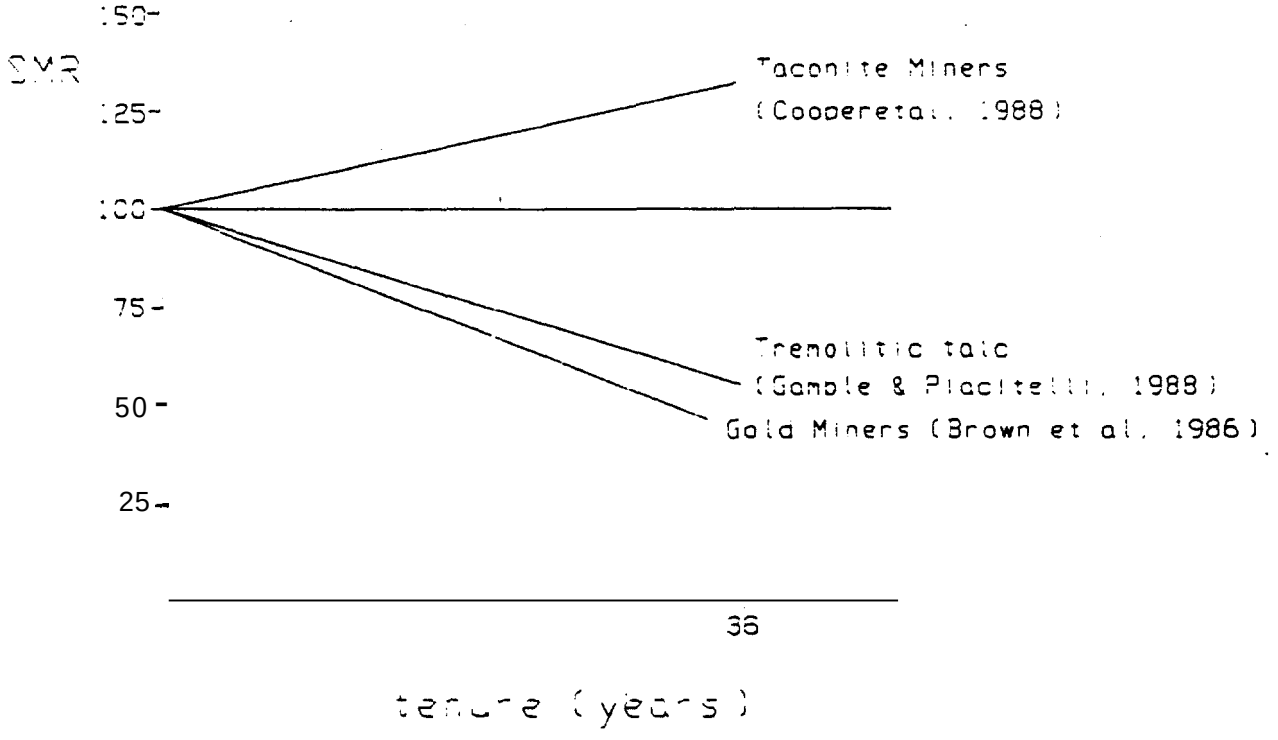
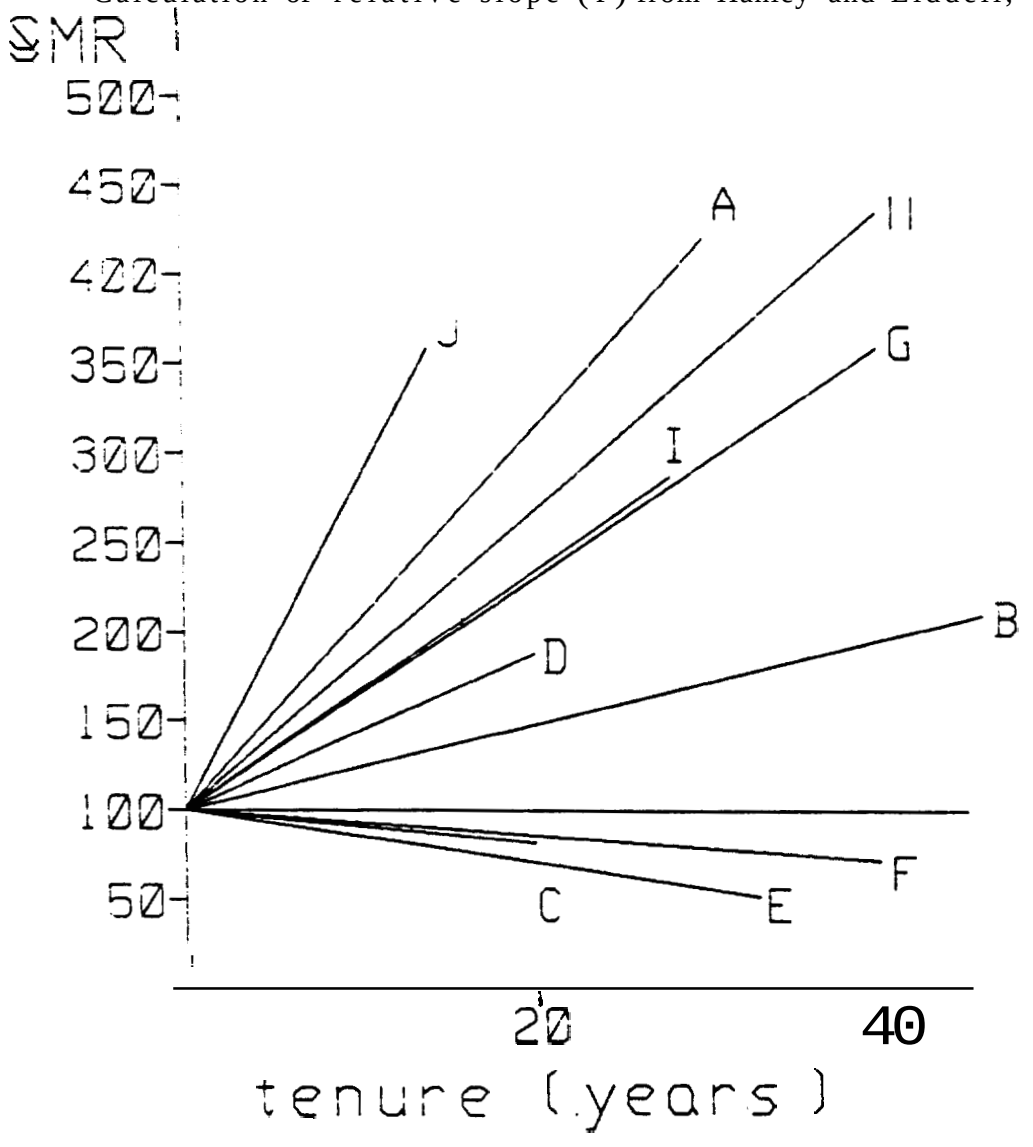


Figure 3 Relationships between exposure (tenure) and lung cancer **SHRs** among asbestos workers with **20** or **more** years latency from Table **7**; Calculation of relative slope (r) from Hanley and Liddell, 1985).



A Vermiculite Hiners (Amandus, 1988)
B Chrysotile Hiners (McDonald et al., 1980)
C Asbestos Cement - Plant **1** (Hughes et al., 1987)
D Asbestos Cement - Plant **2** (Hughes et al., 1987)
E Asbestos Cement - Sweden (Ohlson and Hoystedt, 1985)
F Friction Products (HcDonald **et** al., 1984b)
G Textile Workers - **PA** (McDonald et al., 1983)
H Textile Workers - S.C.(McDonald et ai., 1983a)
I Crocidulite Hiners (Hobbs et al., 1980)
J Amosite Factory (Seidman **et** al., 1986)

Table 1

Some Common Asbestos Hinerals and Their Nonasbestifora Counterparts

	Habit	
Mineral Group	Asbestiform	Nonasbestiform
Serpentine	Chrysotile	Antigorite-1izardite
Amphibole	Crocidolite	Riebeckite
	Grunerite Asbestos (Amosite)	Cumminptonite-Grunerite
	Anthophyllite Asbestos	Anthophyllite
	Tremolite Asbestos	Tremo1ite
	Actinolite Asbestos	Tremolite-actinolite, actinolite

Tabla 2

Linear Least-squares Regression Analysis (Log width = F log length + b) of Bulk Samples of Fibers from Asbestiform and Nonasbestiforn Habits

Ref.	Asbestos	e	b	S.E.*
Siegrist & Wylie (1980)	Short-fiber Chrysotile (SEM)	0.14	-0.97	0.25
	Short-fiber Chrysotile (TEH)	0.24	-1.23	0.22
	Long fiber Chrysotile(NIEHS tst mat.	0.02	-0.82	0.18
	Amosite - (NIEHS test material)	0.18	-0.56	0.20
	Crocidolite - (NIEHS test material)	0.14	-0.71	0.19
Shedd (1985)	Crocidolite - (Transvaal Province)	0.48	-0.91	0.31
	Crocidolite - (Bolivia)	0.41	-0.89	0.30
	Crocidolite - (Western Australia)	0.29	-1.05	0.21
	Crocidolite - (Cape Province)	0.33	-1.12	0.21
Wylie & Schweitzer (1982)	Actinolite Asbestos; (S. Africa)	0.16	-0.56	0.24
	Tremolite Asbestos (India)	0.34	-0.40	0.27
	Actinolite Mountain Leather	0.24	-0.64	0.17
Shedd et al. (1986)	**Wooly Erionite	0.07	-1.53	0.18
	Nonasbestiform Amphiboles			
Siegrist and Wylie (1980)	TREHOLITE (N.Y. talc; NIEHS test material).	0.67	-0.19	0.18
	TALC-SERPENTINE (N.Y. talc; NIEHS test material.	0.75	-0.13	0.17
	Riebeckite - CA.	0.56	-0.34	0.34
	Nonamphibole Fibrous Minerals (nonasbestiform habit)			
Wylie and Schweitzer (1982)	Wollastonite St. Lawrence County, NY	0.69	-0.41	0.24
Shedd et al. (1982)	Mordenite (acicular)			
	25407	0.64	-0.88	0.19
	25409	0.62	-0.78	0.20
	25418	0.50	-1.02	0.22
	Erionite (fibrous habit)			
	25214	0.86	-0.77	0.22
	25219	0.85	-0.74	0.20
	25220	0.83	-0.74	0.22

* S.E. - standard deviation of the log width around the computed regression line; about 95% of the fiber widths should be within ± 2 S.E. of the regression line

** Rare zeolite with asbestiform habit.

tlinerals in capital art noaasbestiforn amphibole from mine in epidemiologic studies (Gamble & Piacitelli, 1988)

Table 3

Fibrosity Indices* for Airborne Amphiboles (Virta et al., 1983)

Sample	F	b	S.E.
Asbestos			
Shipyard-cummingtonite-grunerite (CG)	0.24	-0.64	0.26
Electric Company -CG	0.21	-0.61	0.26
Nonasbestiform Amphiboles			
GOLDMINE-Cummingtonite	0.68	-0.43	0.17
TACONITE-Cummingtonite, hornblende, actinolite	0.76	-0.52	0.18
Stone Quarry-actinolite	0.78	-0.46	0.20

* See Table 2 for definitions.
Minerals in capital are same as minerals in mortality studies of (Brown et al, 198
Cooper et al, 1988)

Table 4

Aspect Ratio Distribution of Bulk Samples of Fibers from Asbestiform and Nonasbestifora Habits

Reference	Sample	Fibers >5μm long. >3:1 % with Aspect Ratios 3:1 - 10:1	≥20:1
	Asbestos		
Campbell et al., 1979	Tremolite Asbestos (FD72 used by Smith, 1979)	44	32
Campbell et al., 1979	Tremolite Asbestos - (CA)	37	35
Campbell et al., 1979	Tremolite Asbestos - (India)	20	**55**
Campbell et al., 1979	UICC Amosite	19	47
Campbell et al., 1980	Amosite (NIEHS test material)	2	**75**
Campbell et al., 1980	Crocidolite (NIEHS test material)	1	89
Campbell et al., 1980	CERYSOTILE-Quebec; (NIEHS test material)	0	96
Campbell et al., 1980	Chrysotile (CA)	1	94
Wylie, 1988	Actinolite Asbestos	14	**52**
Uylie, 1988	Actinolite Asbestos, mountain leather	8	63
Shedd et al., 1982	*Wooly Erionite	0	100
	Nonasbestiform Analogs		
Campbell et al., 1979	Prismatic Tremolite, (NY)	89	**2**
Campbell et al., 1979	Acicular tremolite	77	15
Campbell et al., 1979	Fibrous tremolite (serpentine Quarry)	89	0
Campbell et al., 1980	TREMOLITE from NY Talc, NIEHS test material)	44	2
Campbell et al., 1979	NY TREMOLITIC TALC (FD275) used by Smith et al. (1979).	80	0
Wylie, 1988	NY SERPENTIVE-TALC (NIEHS test material)	28	**0**
Uylie, 1988	Riebeckite (CA)	43	12
	Nonamphibole Fibrous Mineral (nonasbestiform habit)		
Wylie, 1988	Wollastonite (NY)	**62**	**4**
Shedd, et al. (1982)	Mordenite	29	**29**
	Erionite	**66**	**9**

* Rare zeolite with asbestiform habit
Minerals in capital is talc from mine reported in Gamble & Piacitelli, 1988, and asbestos cohort (HcDonald et al., 1980)

Table 5

Aspect Ratio Distribution of Airborne Samples of Fibers from Asbestiform and Nonasbestiform Minerals

Reference	Sample	Fibers >5mm long, >3:1 % with Aspect Ratios 3:1 - 10:1	≥20:1
	Asbestos		
Wylie, 1988 (from Gibbs & Hwang, 1980)	Crocidolite - South Africa mining	0	93
	bagging	0	96
Wylie, 1988 (from Pooley & Clark, 1980)	Crocidolite Mining (South Africa)	0	89
Wylie, 1988 (from Gibbs & Hwang 1980	Amosite (South Africa) mining	0	70
	bagging	0	73
Wylie, 1988 (from Pooley & Clark, 1980)	Amosite Mining (South Africa)	0	75
Wylie, 1988 (from Gibbs & Hwang, 1980)	CHRYSOTILE (Canada) Hining	0	62
	Bagging	0	79
Pinherton et al. (1983)	CHRYSOTILE (Jeffrey Mine, Canada	0	92
(Exp't. Study in Chamber)	Chrysotile (Coalinga Mine; Canada; Short Fiber	24	40
	UICC B Chrysotile	2	82
Amandus et al. (1987)	TREMOLITE-ACTINOLITE ASBESTOS (LM) (Vermiculite, Montana)	4	67
	Nonasbestiform Amphiboles		
Wylie, 1988	CUMMINGTONITE (SD Gold Mine)	75	0
Wylie, 1988	CUMMINGTONITE (SD Gold Mine)	51	4
Wylie, 1988	CUMMINGTONITE (SD Gold Mine)	18	1
Wylie, 1988	Actinolite (VA Stone Quarry)	64	2
Wylie, 1988	TACONITE (Hinn)	11	0
Kelse and Thompson, 1988	TREHOLITE (NY Talc)	8	0

Hinerals in capital are thought to be from mines in mortality studies of nonasbestifora amphiboles (Brown et al., 1986; Cooper et al., 1988; Gamble & Piacitelli, 1988) and asbestos (McDonald et al., 1980; Amandus, 1988).

Table 6

Conoistency of Results for Risk of Lung Cancer Among
Retrospective Cohort Studies of Nonasbestiform
Amphibole Exposed Populations: Exposure-Response Relationships
Among ≥20 Year Latency Groups Only

Reference	Cohort (f/mL > 5um)	Airborne Amphiboles Present (% > 20:1 aspect ratio >5um long)	Exposure-Response Tenure years	OBS	SMR (x100) (95%CI)	a,b,r+ (95%CI)
Brown, et al., 1986	Gold Miners Gm (range) Hiners 0.44 (.Os-4) UG Hiners 0.24 (.02-2.6) Crushing 1.2 (.12-5)	Cummingtonite-grunerite, tremolite-actinolite fibrous hornblende (0-4%)	1-9 10-19 20-34 Total	11 6 1 18	84 140 35 89 (53,142)	a: 1.034 b: -0.0146 r: -0.014 (-0.101, +0.224)
Cooper et al., 1988 (Higgins et al., 1983)	Taconite Hiners (occasionally >0.5, but <2)	Cummingtonite-grunerite hornblende, actinolite (0%)	3m-<1y 1-<5 5-<10 10-36 Total	3 7 2 13 25	50 65 32 62 57 (37,84)	a : 0.614 b: +0.0040 r: +0.008 (-0.109,+0.091)
Gamble & Piacitelli (1988) (Dement & Zumwalde, 1979)	New York Talc Mine: 4.5 (.8-10) Hill: 5 (.2-16)	Tremolite (4% in bulk, 0% in airborne)	<1 1-9 10-19 20-36 Total	8 1 2 2 13	367 82 446 176 258 (137,441)	a: 2.936 b: -0.0454 r: -0.011 (-0.041,+0.090)

Table 6 (Continued)

Consistency of Results for Risk of Lung Cancer Among
Retrospective Cohort Studies of Nonasbestiform
Amphibole Exposed Populations: Exposure-Response Relationships
Among ≥20 Year Latency Groups Only

Reference	Cohort (f/mL > 5um)	Airborne Amphiboles Present (% > 20:1 aspect ratio >5um long)	Exposure - Response Tenure years	CASES	CONTROLS	Odds Ratio	Slope (95% CI)
Gamble & Piacitelli (1988) Case-Control Study ++			<5	12	22	1.0	-0.021
			5-16	1	4	0.46	(-0.032,-0.010)
			16-36	4	15	0.49	

t SMR = a t (b*x) where x = tenure; a = intercept at 0 year tenure; b= slope of SMR regression;
r=b/a = adjusted slope with 95% confidence intervals. (Hanley & Liddell, 1985).
SMR after x years tenure = 100[1+(r)(x)].

++Case-control study includes only cases with ≥20 years latency. Calculation of exposure-response slope'& 95% C.I. after. Rothman, 1986.

Table 7

Consistency of Results for Risk of Lung Cancer Among
Retrospective Cohort Studies Asbestos Exposed Populations:
Exposure-response Relationships Among ≥20 Year Latency Groups Only

Reference	Cohort (f/mL > 5um)	Type of Asbestos	Exposure-Response Tenure years	OBS	SMR (x100) (95% CI)	a, b, r+ (95% CI)
Amandus & Wheeler, 1987 Amandus, 1988	Vermiculite Hiners & Hillers [1967-74 Mean: 22.3 (11-65)]	Tremolite-actinolite asbestos	<1	4	100	
			1-5	3	103	a: 0.98
			5-10	4	400	b: +0.105
			10-19	0	--	r: +0.107
			20+	5	500	
			Total	16	165 (94,268)	
McDonald et al, 1980	Hiners, Quebec [f/mL not reported; Mean mppcf by exposure: low 2.6-4.2 med 4.3-9.4 high 14-24 very high 47-83	Chrysotile	1m-<1y	47	97	a: 0.92
			1-5	29	83	b: +0.22
			5-20	50	137	r: +0.024
			20-46	104	161	(+0.008, +0.048)
			Total	230	126 (109,142)	
Hughes et al. 1987	Cement Workers, LA f/mL not reported; mppcf by plant and year 1 2 1940-9 10 8 1950-9 7.2 9.1 1960-9 1.3 3.9 (Expected deaths from LA rates)	Chrysotile, some crocidolite	Plant 1			
			1m-6m	26	139	a: 1.21
			7m-1y	6	113	b: -0.011
			1-5	6	75	r: -0.009
			5-15	4	115	(-0.037, +0.050)
			16+	6	105	
			Total	48	116 (85,154)	
			Plant 2			
			1m-3m	34	140	a: 1.21
			4m-1y	21	99	b: 0,064
			1-5	20	139	r: +0.044
			5-15	8	224	(+0.003, +0.111)
			15+	24	220	
			Total	107	144	

Table 7 (continued)

Consistency of Results for Risk of Lung Cancer Among
Retrospective Cohort Studies Asbestos Exposed Populations:
Exposure-response Relationships Among ≥20 Year Latency Groups Only

Reference	Cohort (f/mL > 5um)	Type of Asbestos	Tenure years	Exposure-Response OBS	SMR (x100) —(95% CI)	a,b,r+ (95% CI)
Ohlson & Hoystedt, 1986	Cement Workers, Sweden (1970-6, Avg=1; <1970 est '2 max 8]	Chrysotile <1% crocidolite	3m-2y	5	278	a: 2.85
			2-5	3	231	b: -0.130
			5-33	1	39	r: -0.016
			Total	9	159 (72,302)	(-0,102,-0.001)
McDonald et al., 1984b	Friction Products, Conn. (f/mL not reported; Avg mppcf 1.84)	Chrysotile	lm-ly	24	180	a: 1.63
			1-5	19	149	b: -0.011
			5-20	9	123	r: -0.007
			20->40	21	133	(-0.020,+0.015)
			Total	73	148 (116,186)	
McDonald et al, 1983	Textile Workers, PA (f/mL not reported; Avg mppcf 2.3)	Chrysotile	lm-ly	9	70	a: 0.562
			1-5	3	33	b: 0.0367
			6-20	14	129	r: +0.065
			20->40	27	159	(+0.011,+0.224)
			Total	53	106 (79,139)	
McDonald et al., 1983a	Textile Workers, SC (f/mL not reported; Avg appcf 1.8)	Chrysotile	lm-ly	8	78	a: 1.031
			1-6	10	164	b: 0.08
			5-20	16	304	r: +0.084
			20->40	26	317	(+0.021,+0.263)
			Total	59	200 (152,253)	

Table 7 (continued)

Consistency of Results for Risk of Lung Cancer Among
Retrospective Cohort Studies Asbestos Exposed Populations:
Exposure-response Relationships Among ≥20 Year Latency Groups Only

Reference	Cohort (f/mL > 5um)	Type of Asbestos	Exposure-Response Tenure years	OBS	SMR (x100) (95% CI)	a,b,r+ (95% CI)
Hobbs, et al., 1980	Hiners, W. Australia	Crocidolite (>15 y. latency)	<3m	6	87	a: 1.26
			3m-1y	13	167	b: 0.08
(Armstrong et al. 1988)	[20 (certain parts of mine) to 100 (bagging)]		1-28	19	246	r: +0.067
			Total	38	170 (120,233)	(-0.005,+0.230)
Seidman et al., 1986	Factory Workers (NA from study plant. f/mL = 5-120 in similar plant from same company)	Amosite Insulation for ships	<1m	6	324	a: 4.27
			1-2m	3	180	b: +10.79
			2-3m	7	583	r: +0.185
			3-5m	11	485	(+0.037,+0.475)
			6-11m	9	508	
			1-2y	16	829	
			2-14	24	976	
			Total	76	452 (356,566)	

+ See Table 6 for meaning of a, b, r.

Table 8

Consistency of Results for Risk of Lung Cancer Among cohorts of Miner Populations Not Exposed to Amphiboles: Exposure-response Among ≥20 Year Latency Groups unless otherwise noted.

Reference	Cohort	Exposure	Tenure	OBS	SMRx10 (95% CI
			White		
			UG		
Roberts and Julian (1983)	Canadian Nickel Hiners (Inco) (≥15y latency)	Nickel sulfide Cu/Fe sulfide, FeS	6m-5y	28	91
			≥5	96	109
			Total	124	105 (87,126)
			All Sudbury (not sinter plant)		
			6m-5y	25	114
			>5	197	108
			Total	222	108 (94,124)
Shannon, Julian and Robers (1984)	Canadian Nickel Mines (Falconbridge)		Miners		
			6m-5y	6	180
			≥5Y	14	148
			Total	20	156 (95,241)
			Service Workers		
			6m-5y	5	268
			≥5Y	4	92
			Total	9	145 (66,275)
Lawler et al. (1985)	Iron Ore Miners (not stratified by latency)	Hematite	UG		
			0-9	18	84
			10-19	19	102
			20-29	22	92
			30-39	36	106
			Total	95	97 (79,119)
			Above around		
			0-9	51	107
			10-19	22	96
			20-29	12	59
			30-39	9	73
			Total	94	91 (74,110)

Table 8 (continued)

Consistency of Results for Risk of Lung Cancer Among cohorts of Miners Population Sot Exposed to Amphiboles: Exposure-response Among >20 Year Latency **Groups**

Reference	Cohort	Exposure	Tenure	OBS	SMRx10 (95%.CI
Muller et al. (1986)	Ontario Gold Miners (not stratified by latency)	So asbestiform like material	<10	23	144
			11-2	43	136
			21-3	54	135
			31+	45	150
			Total	165	140
					(119,163)
Waxweiler, et al. (1988)	Attapulgite Miners and Millers	Airborne fibers 0.1-2.5mm long	Whites		
			1m-4y	3	250
			≥5y	3	429
			Total	6	300
					(110,653)
		(High and intermittent exposure jobs)	Nonwhite		
			1m-4y	2	54
			≥5y	2	100
			Total	4	70
					(19,180)

Table 9

Summary of Tumor Incidence (Sarcomas) in Lifetime Studies of Animals
Implanted or injected Intrapleural or intraperitoneal
With Selected Asbestiform and Nonasbestiform Minerals

Reference	Mineral	Dose (mg)	Tumors (%)	Mean Induction or survival (days)	Particle Size % > 5m	% 2-5um
Hunter and Thompson (1973) (rat) interpleural injection	Chrysotile asbestos	25	48	NA	28.5	71.5 (<5um)
	Vermiculite	25	0	NA	6.9	55.8
	Saline Control	0.2mL	0	NA	--	--
Wagner et al. (1973) (rat) intrapleural injection	UICC Amosite	20	38	716		
	UICC Anthophyllite	20	25	761		
	UICC Chrysotile (Canada)	20	31	747		
	UICC Crocidolite	20	59	682		
	Brucite	20	56	680	Contained some chrysotile; long coarse fibers >50cm.	
	Barium Sulphate (control)	20	3	783		
	Saline Control	20	0	818		
Pott et al. (1974) (rat) intraperitoneal injection	Chrysotile	6	67.5	343	6.1	21.3
		25	65	276		
		4 x 25	37.5	270		
	Chrysotile (milled)	4 x 25	30	400	0.2	2.6
	Nemalite (fibrous brucite)	4 x 25	62.5	249	3.6	8.5
	Palygorscite	3 x 25	65	257	30	62.5
	*Actinolite	4 x 25	0	--	--	--
	Hematite	4 x 25	0	--	--	--
	Talcum	4 x 25	2.5	587	--	--

Table 9 (continued)

Summary of Tumor Incidence (Sarcomas) in Lifetime Studies of Animals
Implanted or Injected Intrapleural or Intraperitoneal
With Selected Asbestiform and Nonasbestiform Hinerals

Reference	Mineral	Dose (mg)	Tumors (%)	Mean Induction or survival (days)	Particle Size % > 5m	% 2-5um
Pott et al. (1976)	UICC Chrysotile A	2	16	468	6.4% > 5um	
		6.25	77	490		
		25	81	407		
		4 x 25	55	347		
	UICC Chrysotile A (milled)	4 x 25	32	512	0.2%	
	Palygorscite	3 x 25	77	327	30%	
	Fibrous Gypsum	4 x 25	6	587	large dia fibers; 25% >5um	
	Fibrous Nemalite	4 x 25	74	299	3.6%	
	*Actinolite	4 x 25	--	613	--	
	Biotite	4 x 25	--	627	--	
	Hematite (precipitated)	4 x 25	--	588	--	
	Hematite (mineral)	4 x 25	--	547	--	
	Pectolite	4 x 25	3	592	Fibrous Silicate that loses fibrous	

Table 9 (continued)

Summary of Tumor Incidence (Sarcomas) in Lifetime Studies of Animals
Implanted or Injected Intrapleural or Intraperitoneal
With Selected Asbestiform and Nonasbestiform Minerals

Reference	Mineral	Dose (mg)	Tumors (%)	Mean Induction or survival (days)	Particle Size % > 5m	Particle Size % 2-5um
Smith et al. (1979)	Chrysotile	25	18	NA	Mean L:W (EM) 6:0.18	
		10	8	NA		
		1	0	NA		
Smith (1974) (hamster) interpleural injection	Milled Chrysotile	25	0	NA	Mean L:W (EM) 0.9:0.03	
	Amosite	10	6	NA	NA	
		1	0	NA		
	Anthophyllite Asbestos	10	6	NA	NA	
	Crocidolite	10	20	NA	NA	
		1	4	NA		
	Tremolite Asbestos (FD72)	25	25	NA	Many > 20um long, 0.4umW	
		10	23	NA		
	*Tremolite (FD31); from. western U.S. tremolitic talc	25	21	NA	Many long, thin fibers;	
		10	2	NA	0.5um W; probably not true asbestos, but a short fibrous amphibole, probably byssolite	
	*Fibrous tremolite from NY (FD14)	25	0		5.7 (2.5-16.5):1.6 (1-5)	50% tremolite, 10% antigorite
	*Fibrous tremolite from NY talc (FD275)	25	0	NA	Similar to FD14	
Wagner et al. (1977) intrapleural	Italian Cosmetic Talc	20	0	655	Mean particle size=25um; 92% talc	
	Superfine (SFA) Chrysotile	20	38	598	NA	
	Saline Controls	20	0	691	--	

Table 9 (continued)

Summary of Tumor Incidence (Sarcomas) in Lifetime Studies of Animals Implanted or Injected Intrapleural or Intraperitoneal With Selected Asbestiform and Nonasbestiform Minerals

Reference	Mineral	Dose (mg)	Tumors (%)	Mean Induction or survival (days)	Particle Size-fiber/mg width	>.25 >4-8	>.25 >8	>.25 >4-8	>.25 >8
Stanton et al. (1981) (rat) pleural implantation	Tremolite asbestos 1	40	**100**	NA	9698	9698	4135	4135	
	Tremolite asbestos 2	40	**100**	NA	7185	7930	2399	692	
	Amosite	40	93	NA	5922	9123	3113	3359	
	Wollastonite 1	40	31	NA	1541	**389**	**257**	--	
	Wollastonite 2	40	12	NA	912	--	**302**	--	
	Wollastonite 3	40	19	NA	3075	--	--	--	
	Wollastonite 4	40	0	NA	107	**81**	--	--	
	U.S. Attapulgite 1	40	3	NA	4365	--	**87096**	--	
	U.S. Attapulgite 2	40	11	--	--	--	--	--	
	Talc 1	40	7	NA	6874	**1230**	**617**	--	
	Talc 2 (Vermont)	40	4	NA	282	**95**	--	--	
	Talc 3 (Montana)	40	4	NA	--	--	--	--	
	Talc 4 (Montana)	40	3	NA	7213	--	--	--	
	Talc 5 (Montana)	40	0	NA	--	--	--	--	
	Talc 6 *(NY Tremolitic)	40	0	NA	(30-50% nonasbestiform tremolite)				
					5326	5326	3548	1778	
	Talc 7 *(NY Tremolitic)	40	0	NA	9355	4677	4677	--	
	**Control (Antigorite)	--	2.8		% tumors =7.7% by life-table; must exceed 30% in Exp'ts. to be sig. > controls				

Table 9 (continued)

Summary of Tumor Incidence (Sarcomas) in Lifetime Studies of Animals
Implanted or Injected Intrapleural or Intraperitoneal
With Selected Asbestiform and Nonasbestiform Minerals

Reference	Mineral	Dose (mg)	Tumors (%)	Mean Induction or survival (days)	Particle Size % > 5m	Particle Size % 2-5um
	Experiment 1				Fibers/ug > 8um x <0.25um (EM)	
Wagner et al. (1982) (rat) intrapleural injection	*A: >95% tremolite from CA talc	20	0	644	1700 (most <6um X <0.8um)	
	Chrysotile (pos. control)	20	62	612	NA	
	saline control	20	0	717	--	
	Experiment 2					
	*B: Tremolite rock from Greenland	20	0	549	0 (most <3um x <1.2um	
	C: Tremolite asbestos, S. Korea	20	30	541	56,100 (max L 140um; most <0.6um W)	
	UICC Crocidolite (pos. control)	20	6	557	64,000 (46% tumors in previous expts, low tumor rate due to infection)	
	Saline Control	20	0	552	--	
					Fibers/ug >8um <0.25um (L;W;aspect ratio)	
Coffin et al. (1982) (rat) intrapleural injection	Ferroactinolite Asbestos	20	23	NA	90 [3.2 (.3-63);0.4;9 (3-130)]	
	Amosite	20	34	NA	830 [3.4(.2-378);0.3;12(3-2825)]	
	Sham	--	1.5	NA	--	
	No Treatment	--	0	NA	--	
Davis et al. (1985) (rats) intraperitoneal injection	Tremolite asbestos (Korea)	25	93	352	8% >10umL; 12% < 0.5um W (SEM)	
	Brucite	25	96	418	5% >10umL;17% < 0.5um W (SEM)	

Table 9 (continued)

Summary of Tumor Incidence (Sarcomas) in Lifetime Studies of Animals Implanted or Injected Intrapleural or Intraperitoneal With Selected Asbestiform and Nonasbestiform Minerals

Reference	Mineral	Dose (mg)	Tumors (%)	Mean Induction or survival (days)	Particle Size % > 5m	% 2-5um
					% > 8um x <0.2um W	
Wagner et al. (1985) intrapleural injection	Oregon Erionite	20	100	390	7.4 (12.5% > 10umL)	
	Karain, Turkey Rock Fi re	20	95	440	0.9 (1.4% > 10umL)	
	Nonfibrous Zeolite	20	5	780	NA	
	Chrysotile	20	48	659	NA	
	Saline	20	2.5	721	--	
Davis et al (1986b) (rats) intraperitoneal injection	Amosite-short fibers	25	4	837	[illegible] fibers >10umL; <0.[illegible]um W (SEM) 0.1%;85%	
	Amosite-long fibers	10	0	NA		
		25	95	520		
		10	88	535	11%;70%	
	UICC Amosite (pos. control)	25	94	505	10%;NA	
Jaurand et al. (1987) (rat) intrapleural injections	UICC Amosite	20	57	615	% > 8um x <0.25um (Mean L:W:AR 2.7 (3.9:0.3:13.4)	
	UICC Chrysotile	20	48	591	7.3 (3.2:0.06:61.5)	
	UICC Crocidolite	20	56	671	4.5 (3.1:0.15:21)	
	Attapulgite	20	0	788	0(0.77:0.06:12.6)	
	Saline Control	20	0	809	--	

Table 9 (continued)

Summary of Tumor Incidence (Sarcomas) in Lifetime Studies of Animals
Implanted or Injected Intrapleural or Intraperitoneal
With Selected Asbestiform and Nonasbestiform Minerals

Reference	Mineral	Dose (mg)	Tumors (%)	Mean Induction or survival (days)	Particle Size % > 5m	Particle Size % 2-5um
					Number (%) fibers/mg >6um x <0.5um	
Wagner et al. (1987) (rat) intrapleural injection	Spanish Attapulgite (Lebrija)	NA	5	NA	100% <2umL	
	Spanish Attapulgite (Torrejan)	NA	35	NA	85000 (0.5%); 2% 6-8um x <0.02um	
	Spanish Attapulgite (Madrid)	NA	<1	NA	0(0);1.9% 6-8um x <0.2um	
	Palygorskite (UK)		75	NA	3,650,000 (20%); 9% 8-25um x <0.02um	
	UICC Crocidolite (pos. control)	NA	85	NA	NA	
	Chrysotile B (pos. control)	NA	48	NA	NA	
	Kaolin (neg. control)	NA	0	NA		
	Saline	NA	2.5	NA	-	
	Fibrous marl	NA	0	NA	100% < lum L	
					f/mg >5um (Median L;W;AR)(TEM)	
Rodelsperger et al. (1987) (rats) intrapleural injections	U.S. Attapulgite Georgia 1	40	No	NA	610000 (0.8:0.04:20)	
	Georgia 2	40	NO	NA	410000 (0.9:0.05:16)	
	Attapulgite - Mormoiron	40	No	NA	60000 (0.7:0.07:11)	
	Attapulgite - Lebrija	40	No	NA	340000 (0.5:0.07:7)	
	Attapulgite - Caceres	40	Yes	NA	240000000 (1.3:0.07:19)	
	Attapulgite - Torregjon	40	Yes	NA	99000000 (1.9:0.04:46)	
	Oregon Erionite	40	Yes	NA	64000000 (2.0:0.2:9)	
	UICC Crocidolite	40	Yes	NA	13000000 (1.2:0.16:7)	

Table 9 (continued)

Summary of Tumor Incidence (Sarcomas) in Lifetime Studies of Animals
Implanted or Injected Intrapleural or Intraperitoneal
With Selected Asbestiform and Nonasbestiform Minerals

Reference	Mineral	Dose (mg)	Tumors (%)	Mean Induction or survival (days)	Particle Size % > 5m	Particle Size % 2-5um
Keast et al. (1988) (rat) intrapleural injection	Respirable iron ore containing fibrous pseudomorphs of kaolinite	50	0	--	5-11% > lumL; avg fiber 2.5um, max 6.5um	
	Crocidolite	20	25	NA	NA	
	Saline Control	--	--	--	--	
(mice)	Respirable iron ore	20	0	--	5-11% >lumL	
	Saline Control	--	0	--	--	
Addison and Davis (1988) (rat) intraperitoneal injection	Tremolite asbestos (Korea)	10	high	NA	Experiment is not yet complete (18 mos since injections), but show clear difference between asbestos and nonasbestiform analogues,	
	Tremolite asbestos (CA)	10	high	NA		
	Tremolite asbestos (UK)	10	high	NA		
	*Fibrous tremolite (Italy)	10	0	0		
	*Fibrous tremolite (Scotland)	10	0	0		
	*Prismatic tremolite (Scotland)	10	0	0	--	

NA = not available
* = nonasbestiform amphibole
** = nonasbestiform serpentine

Table 10

Summary of Lifetime Inhalation Studies

Fiber Parameters

Reference (species)	Mineral	Respirable Dust conc. mg/m3	# f/mL >5um	# f/mL >20um	Width % <0.5um	Length % > 10um	Length % > 20um	% tumors lung	% tumors mesothelioma	Interstitial Fibrosis
Wagner et al. (1977) (rat)	Italian Cosmetic Talc	11	N20	NA	NA	NA	NA	2	--	4.6
	SFA Chrysotile	11	500	NA	NA	NA	NA	0	--	4.2
	Controls	--	--	--	--	--	--	0	--	1.9
	(fibrous scale: 1=nil, 2=minimal, 4=slight, 6=moderate)									
	(talc fiber dia generally >lum, whereas asbestos fibers dia <lum)									
Davis et al. (1978) (rat	Chrysotile	9.9	1950	360	70	18	7	20	0	9.2
		2.0	390	72				4.8	2.4	3.9
	Crocidolite	10	860	34	79	4	0.5	0	0	1.4
		4.9	430	17				0	0	0.8
	Amosite	10	556	6	75	2	0.2	0	0	2.6
	Control	--	--	--	--	--	--	0	0	--
Davis et al. (1980) (rat)	UICC Chrysotile	10	NA	NA	75	15	5	19	0	9.2
	Factory Chrysotile	10	NA	NA	70	19	7	7	0	7.7
	UICC Amosite	10	NA	NA	80	3	0.5	0	0	2.6
	Factory Amosite	10	NA	NA	40	9	3	0	0	8.5
Wagner et al. (1985) (rat)	Oregon Erionite	10	354	NA	85	16	0.8	0	96	NA
	Crocidolite (pos. control)	10	1630	NA	96	11	0.5	4	0	NA
	Synthetic Non-fibrous Erionite	10	NA	NA	NA	NA	NA	4	4	NA
	Control	--	--	--	--	--	--	0	0	NA

Table 10 (continued)

Summary of Lifetime Inhalation Studies

Fiber Parameters

Reference (species)	Mineral	Respirable Dust conc, mg/m3	# f/mL >5um	# f/mL >20um	Width % <0.5um	Length % > 10um	Length % > 20um	% tumors lung	% tumors mesothelioma	Interstitial Fibrosis
Davis et al. (1985) (rat)	Tremolite asbestos (Korea)	10	1600		88	8	<1	41	5	14.5
	Brucite (contained 10% chrysotile by weight and probably >10% of total fiber count)	10	230		82	4	<1	5	0	2.9
	Control	--	--		--	--	--	0	0	NA
Davis et al (1986) (rat)	Wet dispersed chrysotile (WDC)	3.6	679	NA	91	12	3.5	32	0	12.8
	Factory HDC	3.6	468	NA	94	4	0.8	23	0	12.1
	Chrysotile yarn	3.6	428	NA	97	2.5	<0.5	31	2	8.8
	Exp't WDC	4.4	108	NA	85	35	25	23	9	9.6
	Exp't WDC (reversed daylight)	4.7	111	NA	85	35	25	32	3	10.8
	Controls (1 & 2)	--	--	--	--	--	--	2	0	<1
				(>10um)						
Davis et al (1986b) (rat)	Short fiber Amosite	10	70	12	88	0.15	0	0	2	0.15
	Long fiber Amosite	10	2060	1110	72	10	5	20	8	11
	Controls	--	--	--	--	--	--	1.6	0	0.2

Table 10 (continued)

Summary of Lifetime Inhalation Studies

Fiber Parameters

Reference (species)	Mineral	Respirable Dust conc. mg/m3	# f/mL >5um	# f/mL >20um	Width % <0.5um	Length % > 10um	Length % > 20um	% tumors lung	% tumors mesothelioma	Interstitial Fibrosis
Wagner et al. (1987) (rat)	Spanish Attapulgite (Lebrija)	10	0	--	NA	0	0	2.5	2.5	3.2
	Spanish Sepiolite (Madrid)	10	0	NA	100	0	0	5	0	3.1
	Polygorskite (UK)	10	20	NA	100	1.4	NA	2.5	7.5	NA
	UICC Crocidolite	10	NA	NA	NA	NA	NA	2.5	0	3.8
	Kaolin	10	Nonfibrous		--	--	--	0	0	2.1
	Unexposed	--	--	--	--	--	--	0	0	1.2
	(5% lung tumors and/or 2.5% mesotheliomas are in expected range)									
Keest et al. (1987) (rats and mice)	Iron ore containing fibrous pseudomorphs of Kaolinite	6-12	NA	0 -	NA	0	0	0	0	NA
	Control	--	--	--	--	--	--	0	0	NA
	(High levels of interstitial pneumonia in all animals)									

+ Fibrosis scale: 1=normal; 2=dust in macrophages; 3=early interstitial reaction; 4=first sign of fibrosis); 8=severe fibrosis)

++ TEM for fibers/mg > 6um x <0.5um

Table 11

Summary of Hypotheses Concerning Fibers and Asbestosis, Lung Cancer and Mesothelioma

Voruald et al. (1951)	"Long asbestos fibers are essential in the production of ...fibrosis; short fibers are incapable of producing the reaction." The minimum required length is between 20 and 50um, or an exposure of <1 mppcf of fibers > 10um.
Wagner et al. (1973)	The risk of developing mesotheliomata are approximately proportional to the number of significant fibers (>10um long x <0.5um wide). Finer fibers are more carcinogenic and more likely to penetrate to the periphery of the lung.
Pott et al. (1974)	"...we are inclined to believe that even short fibers less than 10um in length, can induce tumors...[and] do not believe that the carcinogenic effect can be limited to fibers with a diameter less than 0.5um."
Pott et al. (1976)	Factors affecting fiber carcinogenicity include the number of fibers with biological relevant dimensions (length, width, aspect ratio), deposition, clearance, and retention, and durability. A diameter of one um or less may be more active, with decreasing activity as diameter increases. The minimum length of a fiber for carcinogenic activity may be <5um.
Stanton et al. (1977)	"...the carcinogenicity of fibers depends on dimensions and durability rather than physicochemical properties..." Implantation studies suggest that highest carcinogenicity was from fibers >8um long and ≤1.5um wide, and activity increases with increasing length for fibers with diameter <1.5um."
Pott (1978)	"Either carcinogenic fiber sizes and 'fibrogenic fibre sizes' are not identical, or a lesser number of fibres are sufficient for tumor induction. A carcinogenicity potency of 50% or more is hypothesized for fibers with diameters <0.5um, lengths of 10um or more.
Davis (1979)	Dust clouds with almost no fibers >20um long produce no bronchial carcinoma and almost no fibrosis, Long fibers may be more dangerous than short fibers because short fibers can be completely encapsulated in a single phagocyte, while long fibers can be only partially edclosed. Partial enclosure allows lysomal enzymes to leak out, and could account for the increased fibrogenic effect.
Wagner (1980)	Fibers 5-30um long and less than 0.5um width tend to induce mesothelioma, Fibers 10-50um long and less than 2um wide tend to induce carcinomas.

Table 11 (continued)

Summary of Hypotheses Concerning Fibers and Asbestosis, Lung Cancer and Hesothelioma

Stanton et al. (1981)	"...carcinogenicity correlates best with increasing numbers of fibers having both diameters of 0.25um or less and lengths of more than 8um and that the correlation diminishes with fibers of greater diameter or lesser length." Short fibers and large diameter fibers are inactivated by phagocytosis, but "negligible phagocytosis of long thin fibers occurred."
Harington (1981)	Durable fibers with appropriate dimensions cause cancer irrespective of their physicochemical nature, simply because they are fibers. Aerodynamic and inoculation studies suggest fibers considered significant in producing mesotheliomas in rats are lOum long and <0.5um diameter, and the carcinogenicity decreases as the number of these fibers decreases. Mesothelioma incidence in human populations suggest a reasonable number for fiber diameter is <0.05um, and 8um length is too long. "The probability that very short fibers are carcinogenic is very low, but the probability increases with increasing fiber lengths being significant even at 5um."
Wagner and Pooley (1986)	"...we can now conclude [on the basis of aerodynamic considerations and animal experiments] that the fibres responsible for mesotheliomas have a diameter of less than 0.25um and probably a length greater than 5um. Fibres of up to 3.0um in diameter that are inhaled and retained in the peripheral airways are associated with pulmonary fibrosis;" an effective length of lOum has been suggested, but the maximum length associated with disease is not known. "...fibres of the correct size other than asbestos could cause mesotheliomas."
Davis et al. (1986)	"...fibre dimensions are the major factor in disease production..." Short asbestos fibers have relatively low pathogenicity for either lung or mesothelial tissue. Hesotheliomas can be produced by shorter fibers than pulmonary tumors. "Fibres >25um in length are unlikely to be transported through lung tissues to reach the pleural or peritoneal mesothelioma. If this length were necessary to transform mesothelial cells then mesotheliomas might not occur at all even in heavily exposed individuals. Medium length fibres (8-15um) probably represent a size that is difficult but not impossible to move. After a long period of time enough of these may reach mesothelial tissue to produce mesotheliomas in a feu individuals, Short fibres (shorter than 5um) are relatively easily moved but do not appear to be very carcinogenic."

Table 11 (continued)

Summary of Hypotheses Concerning Fibers and Asbestosis, Lung Cancer and Mesothelioma

Gerde & Scholsnder (1987)	"...asbestos exposure multiplies the already high risk that smokers run of contracting lung cancer... One hypothesis...is that the asbestos fibres somehow acts as a 'carrier' for carcinogens in the smoke...into their target cells... The most plausible location for an interaction between inhaled fibres and tobacco smoke is the bronchial lining layer (BLL). It is here that both agents have their densest deposition at inhalation and most lung cancers connected with smoking and asbestos exposure are of bronchial origin." The authors propose a lipid-link mechanism to account for the synergism of smoking and asbestos exposure for the induction of bronchial cancer, "Dimensions (of fibers] are important. The fibre must be long enough to traverse the BLL and it probably has to retain this position for a longer period of time. This suggests a fibre length of at least 5um and preferably much longer. The probability that a fibre...is traversing the BLL will...increase with length. Furthermore...long fibres have a prolonged retention in the lung" Fibre diameters have to be small for the fibres to reach into the tracheo-bronchial region, and to often less mechanical resistance to clearance by the mucus blanket.
Lippman (1988)	"...fibrosis is most closely related to the surface area of fibers with diameters between 0.15 and 2um, and lengths greater than 2um...the critical fibers for mesothelioma induction have lengths between 5 and 10um [and diameters <0.lum]...fibers shorter than 5um appear to be ineffective, while an appreciable fraction longer than lOum appears to be unnecessary...the risk of lung cancer is associated with long fibers, especially those with diameters between N0.3 and 0.8um, and that substantial numbers of fibers >10um in length are needed... ...short fibers may be less damaging...[because] they can be fully ingested by macrophages, and can therefore be more rapidly cleared from the lung. The fibrogenic response to long fibers could result from the release of tissue digesting enzymes from alveolar macrophages...short fibers will have a low order of toxicity within the lung, comparable to that of nonfibrous silicate minerals...the critical fiber length would most likely be on the order of the diameter of an alveolar macrophage, i.e., about 10 to 15um...if there is negligible potential for exposure to fibers no longer than 5um, there would be virtually no risk or either mesothelioma or lung cancer...If there were appreciable concentrations of fibers >5um in length, but with essentially all having fiber diameters larger than 0.lum, there would be virtually no risk of mesothelioma-"

Table 12

Estimated Widths of Asbestos and Fibrous Yinerals for Given Fiber Lengths. Range of Fiber Widths will Encompass about 95% of the Fibers of that Length (Calculated from Fibrosity Indices in Tables 2 and 3)

	Fiber Length (um)			
	2 Width (+25.D) (+25.D.)	5 Width (+25.D) (+ 25.D.)	10 Width (+25.D) (+ 25.D.)	20 Width (+25.D) (+. 25.D.
Fibrous Minerals				
Airborne Samples				
Cummingtonite (Homestake)	0.60 (0.26,0.94)	1.11 (0.77,1.45)	1.78 (1.44,2.12)	2.85 (2.51,3.19)
Taconite (iron ore)	0.51 (0.15,0.87)	1.03 (0.67,1.39)	1.74 (1.38,2.1)	2.94 (2.58,3.30)
Actinolite (stone quarry)	0.60 (0.20,1.0)	1.22 (0.82,1.62)	2.09 (1.69,2.50)	3.59 (3.19,3.99)
Bulk Samples				
Tremolitic Talc	1.03 (0.67,1.38)	1.90 (1.54,2.26)	3.02 (2.66,3.38)	4.80 (4.44,5.16)
Talc-serpentine	1.25 (0.91,1.59)	2.48 (2.14,2.82)	4.17 (3.83,4.51)	7.01 (6.67,7.35)
Riebeckite	0.67 (--,1.35)	1.13 (0.45,1.81)	4.17 (0.98,2.34)	7.01 (1.77,3.13)
Wollastonite	0.63 (0.15,1.11)	1.18 (0.70,1.66)	1.91 (1.43,2.39)	3.07 (2.59,3.55)
Asbestos				
Airborne Samples				
Cummingtonite (Shipyard)	0.27 (--,0.79)	0.34 (--,0.86)	0.40 (--,0.92)	0.47 (--,0.99)
Bulk Samples				
Chrysotile (NIEHS)	0.15 (--,0.51)	0.16 (--,0.34)	0.16 (--,0.34)	0.16 (--,0.34)
Amosite	0.31 (--,0.71)	0.37 (--,0.77)	0.42 (0.02,0.82)	0.47 (0.07,0.87)
Crocidolite (Cape Province)	0.10 (--,0.52)	0.13 (--,0.55)	0.16 (--,0.58)	0.20 (--,0.62)
Crocidolite (Transvaal)	0.17 (--,0.79)	0.27 (--,0.89)	0.37 (--,0.99)	0.52) (--,1.14)

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AN EPIDEMIOLOGICAL–INDUSTRIAL HYGIENE STUDY OF TALC WORKERS

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Abstract—Two-hundred and ninety-nine (299) miners and millers exposed to talc from Montana, Texas and North Carolina were examined in a cross-sectional study of respiratory systems, lung function and chest X-rays. Work histories were taken from personnel records. Personal respirable dust samples were collected for all jobs. Cumulative exposure was calculated by summing the products of the estimated exposure for each job and the length of time worked in that job. The average time worked was 7, 6, and 10 yr and the average exposure (cumulative exposure/total time worked) was 1.2, 2.6, and 0.3 mg m^{-3} in Montana, Texas, and North Carolina respectively. Free silica content of bulk samples was low (below the limit of detection in Montana, 1.5% in North Carolina, and 2.2% in Texas). No fibres were observed under the light microscope. Under the transmission electron microscope, tremolite and antigorite fibres (0.5–3 μm length) were observed on the Texas talc, acicular particles (aspect ratios 5–100 to 1 and some diameters less than 0.1 μm) in North Carolina talc. and no fibres in the Montana talc. The differences in age-corrected symptom prevalences (cough, phlegm. and dyspnea) between regions, when compared by both smoking categories and exposure groups were not statistically significant. None of the symptoms showed any consistent association with years worked or cumulative exposure. Symptom prevalence was not elevated compared with blue collar workers and potash miners. There were *two cases* (less than 1%) of grade 1 small rounded opacities. The prevalence of bilateral pleural thickening among workers 40 yr or older was 7, 16, and 14% in Montana, Texas, and North Carolina, and 0, 0, and 10% in those less than 40 yr of age. No non-smoker had bilateral pleural thickening and there was a slight tendency for the prevalence to increase with exposure. Workers with bilateral pleural thickening had lung function 10–20% below workers with no pleural thickening. They had also worked twice as long (13 yr) and an average of 13 yr between beginning exposure to talc and the time of the X-ray. The prevalence of bilateral pleural thickening was elevated in workers 40 yr or older compared with blue collar workers and potash miners There also were no demonstrated differences in prevalence when the subjects in this study were compared with workers exposed to New York talc which contains tremolite and anthophyllite. For the entire study population no association of reduced lung function with exposure was demonstrated. After adjustments for age, height, and smoking, FEV_1 and FVC were not detectably different compared with potash miners and blue collar workers; however, flow rates at low lung volumes were reduced 4–19%. There was little difference among these three populations in age coefficients for FEV_1, FVC, and flow rates by smoking category. Predicted pulmonary function of the study population was elevated compared with New York talc workers.

There were no significant increases in symptoms or pneumoconiosis among the study group of talc workers nor significant reductions in lung function; however, the average amount of time worked by the study group was short. Bilateral pleural thickening was significantly increased and was associated with decreased pulmonary function. The prognostic significance of the pleural thickening awaits prospective evaluation.

INTRODUCTION

TALC is a mineral with a wide variety of uses in paint, paper, ceramics, cosmetics, roofing products, textile material, rubber, lubricants, corrosion proofing compositions, fire extinguishing powders, cereal polishing, water filtration, insecticides, to name a few. Pure talc is a hydrated magnesium silicate, but the talc found in nature has a quite variable chemical composition. The mineral contaminant in talc of most concern is

asbestos. Such contaminated talc can produce a clinical condition resembling that seen on exposure to asbestos. The hazard from exposure to 'pure' talc free of asbestos contamination is less well documented. The purpose of this study was to ascertain the effects on the respiratory system (symptoms, lung function, radiographic) of exposure to talc dust thought to contain no asbestos.

Talc workers in seven mines and eight mills in Montana, Texas and North Carolina were studied in this cross-sectional study. The mines in Montana and Texas were typical open pit operations, while the underground mine in North Carolina employed square set timbers and stopes. In each mine examined, typical mucking techniques were employed. ANFO (ammonium nitrate and fuel oil) was the most common type of explosive used.

Following extraction of the ore, the talc was hand sorted to remove extraneous material, as in Montana, or went directly from the mine to the primary crusher. Froth flotation and heavy metal separation techniques were not used in any facility examined. Following initial crushing, the talc might be calcined, as in the case of ceramic grade talcs, before being ground using dry grinding methods into the final product. Once the talc was ground to the appropriate mesh size, it was sterilized as in the case of pharmaceutical grade talc and then shipped in bags or bulk.

The specific questions being addressed in this paper are: (1) What is the prevalence of symptoms and abnormal radiographic findings by exposure categories within each region? What is the association of exposure with reduced lung function? (2) After adjustment for confounding variables, how does the study population compare with other mining and non-mining populations in the prevalence of symptoms, abnormal radiographic findings and mean lung function?

METHODS

The study of population consisted of workers who mined and milled talc from three regions of the United States: Montana, Texas and North Carolina. Although several different companies may be involved, the results for each region were combined and analysed. Since there were no demonstrated differences among the regions by age, smoking and exposure groups, the combined results of all regions are presented in this paper. Over 90% of the workers participated in the study.

The industrial hygiene portion of the study took place in every facility in which the morbidity data were collected. Personal respirable breathing zone samples were collected utilizing a Model G MSA* pump and a 10 mm nylon cyclone. These samples were analysed for respirable dust and percent quartz and cristobalite. The quartz and cristobalite analysis was done by X-ray diffraction (NIOSH, 1977). Time weighted averages (TWA) were obtained for each job classification at each facility. General area dust samples were collected on open face cellulose acetate filters and were analysed by atomic absorption for iron, manganese, calcium, aluminium, zinc and nickel (NIOSH, 1977).

From each ore body airborne dust samples were collected on open face cellulose acetate filters and analysed by phase contrast microscopy for the presence of fibres

* Mention of brand names does not constitute endorsement by the USPHS.

(NIOSH). Analysis for fibrous tremolite and anthophyllite was done on bulk and airborne dust samples utilizing analytical electron microscopy (NIOSH, undated). Bulk samples from each ore body were analysed for calcite and dolomite by X-ray diffraction (NIOSH, 1977).

All workers were administered either a Spanish or English version of the British Medical Research Council respiratory questionnaire by trained interviewers. Non-talc work histories were obtained in the interviews; work experiences at the talc facility were obtained from company records. Standard postero-anterior chest radiograms were read by three 'B' readers using the ILO U/C 1971 scheme. The films were read independently without knowledge of age, occupation or smoking history. The median of the three readings (i.e. the middle number) was used for analysis. Flow volume curves from a minimum of five forced expiratory manoeuvres were obtained and recorded on magnetic tape using an Ohio 800* rolling seal spirometer. Values from the maximum envelope were used for analysis. Sputums were collected on workers ≥ 35 yr of age. Personal environmental samples were collected on day shift workers and were used to estimate talc dust exposure for each job. This estimate was then used to calculate cumulative talc dust exposure by multiplying job exposure by time and adding the results. The association of lung function and exposure (cumulative exposure and years worked) was analysed by multiple regression. Years worked was divided into <5, 5–9, and ≥ 10 yr worked categories for analysis of symptoms and pleural thickening. Cumulative exposure was the estimate of total exposure to respirable particulate over all years employed and was divided into low (<2 mg m^{-3} x years), medium (2–6 mg m^{-3} x years) and high (>6 mg m^{-3} x years) exposure groups for analysis of symptoms and pleural thickening. Differences by region and department (classified according to whether the majority of work was done in the mine, mill, crayon plant or other) were also estimated.

The prevalences of selected symptoms and pleural thickening were compared with mining and non-mining populations after indirect adjustment for smoking and using the age distribution of all populations (Fleiss, 1973). Prediction equations were calculated for each smoking category of the comparison populations. The observed lung function of each worker from the study population was compared with the predicted of the appropriate smoking category of the comparison population. The percent predicted lung function from all smoking categories and regions were then combined. Female prediction equations were available for only the blue collar comparison populations. Percent predicted lung function comparisons with the mining populations are therefore for males only.

RESULTS

Environmental results

Respirable dust exposure was highest in Texas and lowest in North Carolina, and mill dust levels were higher than mine dust levels in all regions (Table 1).

Montana talc had the lowest concentrations of trace metals of the three regions examined. Concentrations were slightly higher in North Carolina. Texas talc differed

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TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE TALC WORKER POPULATIONS BY REGION

		Montana	Texas	North Carolina
n		177	71	51
Age	(SD)	34.9 (11.5)	38.0 (13.7)	43.1 (12.6)
Height (cm)	(SD)	175.5 (8.8)	173.0 (6.9)	172.5 (8.3)
Years worked	(SD)	6.6 (6.3)	5.5 (5.7)	10.1 (8.6)
Cumulative exposure [(mg m^{-3}) x years]	(SD)	5.9 (7.6)	11.3 (45.1)	3.0 (4.8)
Average exposure (mg m^{-3})	(SD)	1.21 (0.94)	2.64 (7.12)	0.28 (0.33)
Geometric mean of current respirable dust samples (mg m^{-3})	(GSD)	0.86 (0.77)	1.08 (0.72)	0.21 (0.86)
Mine (95% CI)		0.66 (0.85–1.41)	0.45 (0.18–0.75)	0.14 (0.07–0.31)
Mill (95% CI)		1.1 (0.47–0.92)	1.56 (0.96–2.54)	0.26 (0.13–0.51)
Non-smokers	(%)	33	20	21
Ex-smokers	(%)	21'	27	17
pack years	(SD)	15.7 (17.9)	13.3 (20.7)	18.2 (16.5)
cigarettes/day	(SD)	23.0 (15.0)	12.0 (14.0)	21.4 (15.7)
Smokers	(%)	45	54	62
pack years	(SD)	17.9 (16.9)	14.3 (19.7)	23.7 (21.8)
cigarettes/day	(SD)	20.4 (11.0)	14.5 (11.1)	20.4 (10.0)

most significantly from the other regions by its extremely large concentration of calcium, as indicated by a much larger percentage of dolomite (13 compared with 3 and 1%) and a slightly larger percentage of calcite (1 compared with < 1 and 0%) than the other two regions. Silica content of bulk samples of Montana talc was below the limit of detection (< 0.8%), 1.45% in North Carolina and 2.23% in Texas. Respirable dust samples revealed the silica content in Montana and North Carolina to be generally below the limit of detection (0.04 mg m^{-3}). The Texas talc had slightly higher levels of respirable silica (0.09 mg m^{-3}) (Table 2).

No fibres were detected in any of the regions by light microscopy utilizing phase contrast techniques. Analysis of bulk samples from each region utilizing analytical transmission electron microscopy revealed no fibres in any samples of Montana talc. Two fibrous minerals were identified in the Texas talc: tremolite and antigorite. Antigorite, a serpentine mineral, was the main constituent. The fibres of both minerals ranged from 0.5 to 3.0 μm in dia. and 4 to 30 μm in length. The morphology of the North Carolina talc was identified as acicular. The acicular particles had aspect ratios ranging from 5–1 to 100–1, with some dia. < 0.1 μm, and may have resulted from mechanical destruction of talc plates.

Demographic characteristics

All Texas talc workers were male, while about 20% of the Montana and North Carolina workers were female. The North Carolina population had the highest proportion of smokers (62%) and lowest proportion of ex-smokers (17%). The highest proportion of non-smokers (33%) and lowest proportion of smokers (46%) were in Montana. Pack years ranged from 13 to 24 and cigarettes smoked/day from 12 to 23 in the three regions. Montana workers were on average 8 yr younger, 3 cm taller, had worked 3.5 yr less and had 2.9 mg m^{-3} yr more cumulative exposure than the workers

TABLE 2. METAL AND MINERAL COMPOSITION OF BULK SAMPLES BY REGION

	Montana	Texas	North Carolina
mg m^{-3}			
Iron	0.05	0.5	0.05
LOD*	0.01	0.1	0.02
Manganese	<0.01	<0.08	<0.02
LOD	0.01	0.08	0.02
Calcium	0.05	8.0	0.05
LOD	0.03	0.2	0.02
Aluminium	0.2	0.4	0.2
LOD	0.1	0.2	0.04
Zinc	<0.01	0.03	<0.02
LOD	0.01	0.08	0.02
Nickel	<0.01	<0.08	<0.02
LOD	0.01	0.08	0.02
Percent			
Calcite	<1	1	0
(range)	(0–0.8)	(0–3)	0
Dolomite	1	13	3
(range)	(0–3)	(7–20)	(1–4)

* LOD = Limit of Detection.

in North Carolina. Mean values for these parameters in Texas were not demonstrably different from those for Montana and North Carolina. Average exposure (cumulative exposure divided by years worked) was less in North Carolina than in the other two regions (Table 1).

There was one case each in Texas and Montana of grade 1 small rounded opacities. This number is too small to analyse further. There were no other radiographic interpretations of pneumoconiosis. Cytology on sputums collected from workers 35 yr of age or older were read as follows: 20% unsatisfactory, 60% normal cytology or regular metaplastic cells, 20% atypical.

Symptoms and radiography (internal comparisons)

Tables 3-6 summarize the prevalence of cough, phlegm, shortness of breath and pleural thickening by age, smoking and exposure. Regions were combined for presentation of these results as there were generally no statistically significant differences among the regions. If differences were observed they are noted in the text.

The overall prevalence of cough was 19%. The prevalence tended to increase with age and smoking (only the difference between non-smokers and smokers was significant). There was no apparent association with either exposure variable (Table 3).

The overall prevalence of phlegm was 23%. There was no consistent increase with age. Overall, smokers had a higher prevalence of phlegm than non-smokers. There was no apparent association with exposure (Table 4).

The overall prevalence of dyspnea was 5%. Prevalence increased with age in all regions and smoking categories, but the increase with age was significant for only the total population. There was no apparent association with smoking or exposure (Table 5).

TABLE 3. PREVALENCE (%) OF COUGH* AMONG ALL TALC WORKERS BY AGE, SMOKING AND EXPOSURE (ALL REGIONS COMBINED)

	Age		
	<40 % (95% CI)	≥40 % (95% CI)	Total % (95% CI)
Non-smoker	7 (2–16)	15 (5–32)	10 (5–20)
Ex-smoker	7 (1–21)	19 (9–34)	13 (6–24)
Smoker	26 (18–35)	30 (18–45)	27 (20–35)
Total	21 (15–29)	23 (15–32)	19
Yrs worked			
<5			19 (14–25)
5–9			19 (10–31)
≥10			21 (10–36)
Cumulative exposure			
Low			14 (8–23)
Medium			25 (17–35)
High			16 (9–26)

Summary: (i) No demonstration difference among regions by age. smoking or exposure. (ii) Tendency to increase with age except among smokers. (iii) Higher prevalence in smokers. (iv) No demonstrated association with exposure.

* Cough = Answering yes to the question: 'Do you usually cough on most days for as much as 3 months each year?'

TABLE 4. PREVALENCE (%) OF PHLEGM* AMONG ALL TALC WORKERS BY AGE, SMOKING AND EXPOSURE

	Age		
	<40 % (95% CI)	≥40 % (95% CI)	Total % (95% CI)
Non-smoker	12 (5–24)	7 (1–22)	11 (5–20)†
Ex-smoker	13 (5–29)	27 (14–43)	21 (12–33)
Smoker	33 (24–43)	26 (15–40)	31 (24–39)†
Total	23 (16–30)	22 (15–31)	23
Years worked			
<5			19 (14–25)
5–9			16 (8–26)
≥10			25 (14–39)
Cumulative exposure			
Low			13 (7–21)
Medium			24 (16–34)
High			19 (11–30)

Summary: (i) No demonstrated difference among regions by age, smoking or exposure. (ii) Smokers had highest prevalence. (iii) No demonstrated association with age or exposure.

* Phlegm—Answering yes to the question: 'Do you usually bring up phlegm from your chest for as much as 3 months each year?'

†95% CI do not overlap.

TABLE 5. PREVALENCE OF DYSPNEA* AMONG ALL TALC WORKERS BY AGE, SMOKING AND EXPOSURE

	Age		
	≤40 % (95% CI)	≥40 % (95% CI)	Total % (95% CI)
Non-smoker	4 (1-13)	11 (3-27)	6 (2-14)
Ex-smoker	3 (0-16)	16 (1-18)	10 (4–20)
Smoker	1 (0–5)	6 (0-13)	3 (1-7)
Total	2 (0–5)†	10 (5–18)†	5
Years worked			
≤ 5			6 (3-10)
5–9			0 (0–6)
≥10			8 (2-20)
Cumulative exposure			
Low			5 (2–11)
Medium			3 (1–8)
High			1(2-14)

Summary: (i) No demonstration differences among regions by age, smoking or exposure. (ii) Increased prevalence with increased age. (iii) No demonstrated association with smoking or exposure.

* Dyspnea = Answering yes to the question: 'Do you get short of breath walking with people your own age on level ground?'

† 95% CI do not overlap.

TABLE 6. PREVALENCE OF BILATERAL PLEURAL THICKENING AMONG ALL TALC WORKERS BY AGE, SMOKING AND EXPOSURE

	Age		
	<40 % (95% CI)	≥40 % (95% CI)	Total % (95% CI)
Non-smoker	0 (0–7)	0 (0-11)	0 (0–6)
Ex-smoker	6 (0–24)	3 (0–15)	4 (0-14)
Smoker	2 (0–7)*	22 (11–36)*	9 (5-15)
Total	2 (0–6)	11 (5–18)	5
Years worked			
<5			2 (0–5)‡
5–9			3 (0–10)*
≥10			23 (12–38)*‡
Cumulative exposure			
Low			4 (1–10)†
Medium			5 (1-12)
High			8 (3–17)†

Summary: (i) No demonstrated differences among regions by age, smoking or exposure, except medium cumulative exposure group in North Carolina had higher prevalence than in Montana (ii) Tendency to increase with age (significant among smokers). (iii) No bilateral pleural thickening among non-smokers. (iv) Increasing prevalence with increasing years worked. (v) No demonstrated association with cumulative exposure.

*‡ 95% Confidence intervals do not overlap.

† 1 with extent 2 pleural thickening.

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were reduced compared with those without pleural thickening. Those with unilateral pleural thickening generally had intermediate lung function values. The prevalences of cough and phlegm were not statistically significant and were not adjusted for age and smoking.

Symptoms and radiography (external comparisons)

Table 8 summarizes the characteristics of the comparison populations. The potash mines were part of the MSHA/NIOSH epidemiologicalindustrial hygiene study of metal and non-metal underground miners (ATTFIELD, 1979; SUTTON *et al.*, 1979). White male miners from six potash mines were used for comparison. All of the potash mines used diesel engines and had high dust exposures. The New York talc miners and millers were exposed to tremolite and anthophyllite (GAMBLE *et al.*, 1979a; DEMENT and ZUMWALDE, 1979; DEMENT *et al.*, 1980). The blue collar comparison population was part of a NIOSH blue collar control study and included male and female workers from North Carolina in such industries as electronics, synthetic textiles, bakeries and bottling plants (PETERSEN, personal communication). The workers in the comparison populations had generally worked longer in their current industry than had the Montana and Texas talc populations. The mining populations generally were heavier smokers than the study populations and the blue collar workers. The mining comparison groups had occupational exposuresin the form of diesel fumes and 'potash' (primarily sylvite, a mixture of KCl and NaCl, and langbeinite or $K_2Mg_2(SO_4)_3$) and talc containing asbestifom fibres.

Table 9 summarizes the age and smoking adjusted prevalence of cough, phlegm, dyspnea and pleural thickening of the study and comparison populations. There was no demonstrated difference in the prevalence of cough between the study population and the potash or blue collar workers. New York talc workers had an elevated

TABLE 8. CHARACTERISTICS OF COMPARISON POPULATIONS

	New York talc	Blue collar‡ Male	Blue collar‡ Female	Potash
n	121	843	597	875
Age (SD)	39 (12)	38 (14)	40 (13)	41 (13)
Height (cm) (SD)	176 (6)	173 (7)	162 (6)	176 (6)
Years worked (SD)	11 (9)	12 (12)	11 (10)	16 (13)
Non-smokers (%)	21	25	49	20
Ex-smokers (%)	31	23	10	28
Mean pack years (SD)	26 (28)	21 (23)	9 (10)	23 (20)
Mean cigarettes/day (SD)	28 (19)	23 (15)	16 (12)	25 (14)
Smokers (%)	48	54	42	52
Mean pack years (SD)	26 (17)	23 (19)	17 (13)	28 (23)
Mean cigarettes/day (SD)	27 (11)	23 (11)	19 (9)	25 (12)
Current dust levels ($mg\,m^{-3}$)	*0.77 (Mine) *0.87 (Mill)	NA	NA	†3.45
Fibres $> 5\,\mu m\ cc^{-1}$	*5.40 (Mine) *4.80 (Mill)	NA	NA	NA

NA = Not Available.
* Personal samples of respirable dust and light microscope fibre counts from DEMENT et *al.* (1980).
† Personal samples of total dust from ATTFIELD (1979) and SUTTON et *al.* (1979).
‡ Unpublished data from Martin Petersen.

TABLE 9. COMPARATIVE RATES OF COUGH, PHLEGM, DYSPNEA AND BILATERAL PLEURAL THICKENING AMONG ALL TALC WORKERS COMPARED WITH NEW YORK TALC WORKERS, BLUE COLLAR WORKERS AND POTASH MINERS (INDIRECTLY ADJUSTED FOR AGE AND SMOKING)

	Study population (combined) % (95% CI)	Comparison group: New York talc % (95% CI)	Comparison group: Potash miners % (95% CI)	Comparison group: Blue collar workers % (95% CI)
Cough	20.3 (16-25)	36.1 (28–45)	24.1 (20-27)	16.7 (14-20)
Phlegm	20.3 (16-25)	35.5 (27–45)	29.5 (27-34)	17.3 (14–21)
Dyspnea	5.8 (4-10)	12.3 (7-19)	8.4 (6–11)	7.5 (6–10)
Bilateral pleural thickening	6.3 (3–9)	7.9 (4–15)	0.2 (0–0.5)	0.4 (0–1)

Summary: (i) Cough: Study population less than New York talc, no different from potash and blue collar. (ii) Phlegm: Study population less than New York talc and potash, no different from blue collar workers. (iii) Dyspnea: No difference among study and comparison populations. (iv) Bilateral Pleural Thickening: Study population and New York talc workers greater than potash and blue collar workers. (Difference indicated by non-overlap of confidence intervals)

prevalence of cough compared with other populations. There was no apparent difference in the prevalence of phlegm among the study population and blue collar workers, and the prevalence in both these populations was less than the potash and New York populations. There were no demonstrated differences in the prevalence of dyspnea among the study and comparison populations. The prevalence of bilateral pleural thickening was higher in both talc (study and New York) populations compared with the potash and blue collar populations.

Pulmonary function

Table 10 summarizes the results of multiple regression models of pulmonary function with the predictor variables race, sex, age, height, smoking status. Region, department, years worked and cumulative exposure were tested for association with lung function. Age and height were significant for all parameters. Race, department, years worked and cumulative exposure were not significant for any of the lung function tests. Sex was not significant for FEF_{50} and FEF_{75}. FVC was reduced in Texas compared with Montana and North Carolina. The effect of smoking was generally as expected.

Table 11 summarizes the mean percent predicted pulmonary function of the study population compared with potash, blue collar workers (male and female) and New York talc workers. Flow rates (peak flow, FEF_{25}, FEF_{75}) of the talc workers were reduced compared with the potash and blue collar workers, but there were no significant differences in FEV, and FVC. Compared with New York talc workers, all pulmonary function parameters were elevated except percent predicted peak flow.

TABLE 10. SUMMARY OF MULTIPLE REGRESSION MODEL* FOR LUNG FUNCTION AND SELECTED MEANS ADJUSTED FOR SEX, AGE, HEIGHT, SMOKING STATUS REGION AND EXPOSURE

	Lung function parameter				
	FEV,	FVC	Peak flow	FEF_{50}	FEF_{75}
Department	NS	NS	NS	NS	NS
Years exposure	NS	NS	NS	NS	NS
Cumulative exposure	NS	NS	NS	NS	NS
Region	NS	†	NS	NS	NS
Montana	3.58 (0.06)	4.65 (0.06)	8.51 (0.16)	4.07 (0.13)	1.41 (0.06)
Texas	3.51 (0.10)	4.39 (0.11)	8.46 (0.27)	4.63 (0.23)	1.48 (0.10)
North Carolina	3.71 (0.10)	4.62 (0.11)	7.87 (0.28)	4.48 (0.24)	1.55 (0.11)
Smoking status	†	NS	‡	†	†
Non-smokers	3.71 (0.08)	4.62 (0.09)	8.31 (0.23)	4.55 (0.19)	1.63 (0.09)
Ex-smokers	3.58 (0.09)	4.51 (0.10)	8.60 (0.25)	4.52 (0.21)	1.44 (0.10)
Smokers	3.51 (0.07)	4.53 (0.08)	7.93 (0.20)	4.12 (0.17)	1.37 (0.08)

* Regression model: Lung function $= \alpha + \beta_1$ (race) $+ \beta_2$ (sex) $+ \beta_3$ (age) $+ \beta_4$ (height) $+ \beta_5$ (smoking status) $+ \beta_6$ (region) $+ \beta_7$ (department) $+ \beta_8$ (years exposure) $+ \beta_9$ (cumulative exposure).

NS $= P > 0.05$.

† $P < 0.05 > 0.01$.

‡ $P < 0.01$.

Summary: (i) Age and height were always significant; sex was significant for FEV,. FVC and Peak Flow. (ii) No exposure variable was significant. Region was significant for FVC (Texas was reduced). (iii) Cumulative exposure was significant for FVC ($P = 0.02$) in model lung function $= \alpha + \beta_1$ (sex) $+ \beta_2$ (age) $+ \beta_3$ (height) $+ \beta_4$ (weight) $+ \beta_5$ (smoking status) $+ \beta_6$ (cumulative exposure) $\beta_6 = -4(4)$.

Comparison of age coefficients by smoking categories showed little difference among the four populations. The New York and blue collar populations showed a greater effect of age than did the study and potash populations. (Table 12).

DISCUSSION

Interpretation of the data from this study has the inherent problems of all cross-sectional prevalence studies. The workers examined in this study comprise only those currently working. While there are few studies that have examined ex-workers to determine the effects of selection, significant disease has been observed among older ex-hemp workers (BOUHUYS et *al.*, 1969) and progressive massive fibrosis among ex-workers in two silica flour mills (BANKS et *al.*, 1981). In both of these studies there was significant disease among the currently employed workers. The consequences of not examining ex-workers in this study are unknown.

The reasons for using several comparison populations are that no comparison population is ideal, and several may help in interpretation of the data. Factors that may affect the morbidity of a study population (in addition to work exposure) but are not measured include region, socio-economic status and type of employment (for example, mining). These may affect morbidity by selection of particular kinds of individuals, but it is unlikely that all the comparison populations will have biases in the same direction relative to the study population (although the biases in the study group still cannot be estimated).

The length of the study group's working history is a relatively short time for the development of occupationally related symptoms, radiographic changes and impaired

TABLE 1I. MEAN PERCENT PREDICTED PULMONARY FUNCTION OF ALL TALC WORKERS COMPARED WITH POTASH MINERS AND BLUE COLLAR WORKERS AND ADJUSTED FOR AGE, HEIGHT AND SMOKING.

Percent predicted pulmonary function (SE)	New York talc (males only) $n = 119$	Potash miners [males only) $n = 251$	Blue collar workers (males and females) n=292
FEV,	106.3 (1.3)‡	98.9 (1.0)	99.7 (1.0)
FVC	105.7 (1.1)‡	99.6 (0.8)	101.0 (0.8)
Peak Flow	95.2 (1.1)	93.2 (1.0)†	97.9 (1.0)
FEF_{50}	161.1 (39.8)	95.6 (2.1)†	94.1 (2.0)†
FEF_{75}	130.5 (4.7)‡	88.2 (3.1)†	84.5 (2.4)†

• Percent predicted pulmonary function = Σ(observed/expected) x 100.
† = > 2 SE less than 100.
‡ = > 2 SE greater than 100.

Summary: (i) FEV, and FVC were not demonstrably different from comparison potash and bluecollar populations, but elevated compared with New York talc values. (ii) FEF_{50} and FEF_{75} reduced compared with potash and blue collar populations, but elevated compared with New York populations.

TABLE 12. AGE COEFFICIENTS OF MALE STUDY AND COMPARISON POPULATIONS (WITH SE)

	Study population	New York talc	Potash	Blue collar
FEV, (ml)				
Non-smokers	−24 (5)	−52 (9)	−28 (3)	−30 (3)
Ex-smokers	−35 (5)	−36 (11)	−32 (3)	−36 (3)
Smokers	−41 (5)	−54 (6)	−40 (2)	−39 (2)
FVC (ml)				
Non-smokers	−6 (5)	−55 (12)	−23 (3)	−24 (3)
Ex-smokers	−32 (6)	−42 (13)	−26 (4)	−25 (3)
Smokers	−27 (6)	−50 (8)	−32 (3)	−25 (2)
FEF_{25} ($ml\,s^{-1}$)				
Non-smokers	−51 (11)	−66 (29)	−36 (7)	−43 (6)
Ex-smokers	−49 (15)	−21 (24)	−44 (8)	−58 (8)
Smokers	−73 (11)	−80 (14)	−63 (5)	−71 (5)
FEF_{75} ($ml\,s^{-1}$)				
Non-smokers	−43 (7)	−40 (11)	−32 (4)	−38 (4)
Ex-smokers	−2 (10)	−22 (7)	−28 (3)	−40 (3)
Smokers	−44 (5)	−38 (5)	−41 (2)	−50 (2)
n				
Non-smokers	67	25	178	207
Ex-smokers	56	36	244	193
Smokers	128	58	451	442

lung function that might be caused by exposure to a mineral dust. Significant changes in FEV_1 and FVC due to exposure to respiratory irritants (such as cigarette smoke, for example) may not become noticeable until after 20–30 yr of smoking. Essentially the same time interval may be required for the development of pneumoconiosis (CHERNIACK and MCCARTHY, *1979*). The mean ages of the study populations were

around 40, and mean exposure to talc dust was less than 10 yr. Therefore, if talc dust was to adversely affect FEV, and FVC, the lung function results might not reflect that effect because of the short exposure times.

Estimating past exposure was a problem in this as in other studies where there was no environmental surveillance. Although dust levels were assumed not to have changed substantially with time, past exposures were probably higher than the calculated estimates and could obscure a true dose–response relation if it existed. Years worked is an exact time period, but it may be a less accurate measure of overall exposure than the calculated estimate of cumulative exposure. Often, years worked and exposure are highly correlated. This was not as true for Texas, but there was an association of years worked and cumulative exposure in Montana and North Carolina. Age was also correlated with exposure (years worked and cumulative exposure).

In this report, both internal comparisons (dose–response relations) and external comparisons were made with another talc population, another mining population and a 'non-exposed' blue collar population. For symptoms and pleural thickening the two comparisons supported each other. That is, for symptoms of cough, phlegm and dyspnea there was no dose–response relationship and no excess prevalence in the external comparison. For bilateral pleural thickening there was a dose–response relationship (association with years worked) and the prevalence was increased compared with both non-talc populations.

For pulmonary function there was also substantial agreement in the internal and external comparisons. Mean percent predicted pulmonary function after adjustment for age, height and smoking, and the age coefficients by smoking status taken from prediction equations were used for the external comparisons. Age coefficients are thought to be less subject to bias than predicted values (HANCOCK and ATTFIELD, 1980). The two methods were consistent in showing a tendency for the study population to have an elevated pulmonary function compared with New York talc workers, with no detectable differences in FEV, and FVC in the other comparisons. Mean flow rates were reduced in the study population compared with potash and blue collar workers, but the age coefficients did not reflect this deficiency.

Flow rates at low lung volumes (FEF_{50} and FEF_{75}) were slightly reduced compared with two of the control populations. FEF,, was better than 90% predicted, while FEF,, was between 80 and 90%. Air flow at low lung volumes is considered to be measuring changes occurring primarily in the small airways (HYATT et al., 1979; MEAD, 1979). A current hypothesis of the pathophysiology of chronic air flow obstruction is that changes in the lung function seen in disease such as emphysema start in the region of the small airways (BECKLAKE and PERMUTT, 1979; MACKLEM, 1972). Tests such as FEF_{50} and FEF_{75} are of interest, because it is difficult to detect pathophysiological changes in the small airways that may be occurring for unknown time periods before they become evident in more routine tests such as FEF_1 and FVC. While existing data (such as the ability of FEF,, and FEF,, to detect differences in the young smokers and non-smokers) are compatible with the idea that air flow obstruction begins in the small airways, there are no available prospective data to prove it. Therefore, the significance of these reductions is only suggestive. Thus, the prognostic significance of reduced flow rates at low lung volumes is not proven and the evidence for reductions in the study population is not convincing.

Peak flow was reduced in the study population compared with potash and New

York talc workers but was no different from blue collar workers. Peak flow is most sensitive to changes in large airways, but is also most subject to technician differences and subject effort. The prognostic significance of reduced peak flow is also not known.

The most important finding in this study was the increased prevalence of pleural thickening. Asbestos (particularly anthophyllite) from either occupational or community exposure is believed to cause an increased prevalence of pleural thickening (SARGENT *et al.*, 1977) and in some instances, pleural changes have been more common than parenchymal changes (HURWITZ, 1961). Talc contaminated with asbestos (tremolite and anthophyllite) seen under the light and electron microscope has also been associated with an increased prevalence of pleural thickening (GAMBLE *et al.*, 1979b). But studies of workers exposed to talc without significant asbestos content have reported higher prevalence of pneumoconiosis than pleural changes (RUBINO *et al.*, 1977; DELAUDE, 1977; MESSITE *et al.*, 1959; FINE *et al.*, 1976; WEGMAN *et al.*, unpublished) and excessive mortality due to non-malignant respiratory disease (SELEVAN *et al.*, 1979). Radiographic evidence from these Vermont talc millers showed pneumoconiosis on 9 of 11 available chest roentgenograms. Although exposures were high, the talc was free of asbestos and free silica (BOUNDY *et al.*, 1979). Pneumoconiosis, however, was not significant in this study. Pleural abnormalities (unspecified) were found in 9% of Vermont talc workers (WEGMAN *et al.*, unpublished), compared with 9% with small irregular opacities and 12% with small rounded opacities. This is in contrast to this study where pleural thickening was observed in 9% of the population, but less than 1% had any signs of pneumoconiosis.

Pleural thickening is generally considered to take many years to develop. In a study of a Swedish population, mean latency for the development of bilateral pleural plaques after first exposure to asbestos was estimated at about 30 yr, which was consistent with other studies. Pleural plaques were rare before age 40 (HILLERDAHL, 1978). However, OCHS and SMITH (1976) reported on at least one case where as little a time interval of 1 yr was necessary for the appearance of bilateral pleural thickening in an individual without occupational asbestos exposure. In the study reported here, latency (time between first known talc exposure and date of the study) was 13 yr for workers with bilateral thickening and 4.5 yr in those with unilateral pleural thickening, a much shorter time than generally associated with pleural thickening from asbestos exposure. North Carolina also had an increased prevalence in workers less than 40 yr of age.

The association of pleural thickening and asbestos exposure may vary considerably in different populations. In a Swedish study about 1% of the men over 40 and less than 0.1% of men less than 40 had bilateral pleural plaques (HILLERDAHL, 1978). Almost 80% were current ex-smokers and had had some exposure to asbestos. Fibrosis was rare (4% of those with pleural thickening). Another community type study in Birmingham, England (BTTA and MRCPU, 1972) found that about 7% of those attending chest clinics had pleural plaques (10% of these were calcified). Unilateral obliteration of the costophrenic angle (not considered to be caused by asbestos) was observed in 36% of those with pleural plaques and there was a definite history of asbestos exposure in no more than 11% of the cases. Much of the pleural thickening was considered to be due to pleural disease (e.g., emphysema, severe chest wall injury, pleurisy). In the study of talc workers reported here, there was no apparent difference between those with and without pleural thickening in the exposure to asbestos or in chest disease.

In these two community studies the association of pleural thickening and asbestos exposure was quite different. The association of pleural thickening with asbestos may be coincidental, as the prevalence of pleural thickening is quite different in asbestos exposed workers. For example, prevalences of 17.5 and 35% have been reported in asbestos manufacturing plants and shipyard joiners (WEISS and THEODOS, 1978; FLETCHER, 1971). Two other studies of shipyard and dockyard workers reported prevalences of pleural thickening of around 5% (FLETCHER, 1972; reported in WEISS and THEODOS, 1978). It is possible that factors other than asbestos may account for these differences (e.g., age distribution, method of reading X-rays, oblique X-rays in addition to PA, differentexposures and exposure times, smoking habits, readers, etc). Some of these factors could possibly account for the differences between study and comparison populations seen in this study.

Exposure to other dusts have also been associated with pleural abnormalities. SMITH (1952) reported finding a pleural calcification among 302 men making mica insulators, 6.3% among miners and millers of tremolitic talc, but zero among 261 asbestos workers. The common feature of exposure of all four groups was said to be exposure to talc/or mica.

No asbestos was seen in the NIOSH samples of Montana and North Carolina talc. MCCRONE (1975) analysed two samples from North Carolina and found 0.1–5% tremolite-actinolite by polarized light microscopy in one of the samples. Tremolite and actinolite have been reported in the Murphy talc deposits although the quantities were small (VAN HORN, 1948). GREXA and PARMENTIER (1979) report 0–5% anthophyllite in 'North Carolina' talc and no asbestos in Montana talc. Seven samples from Montana revealed no asbestos (MCCRONE, 1975) and antigorite was observed in some of the Texas samples (MCCRONE, 1975). While analysis of the talc from these three regions revealed little or no asbestos, the presence of asbestos as an impurity often occurs. It is not known whether very low levels of exposure to asbestos for short periods of time is sufficient to cause pleural thickening.

Thus, while pleural thickening is generally considered to be a signpost of asbestos exposure (SARGENT *et al.*, 1977), the possibility of other agents causing pleural thickening should be considered. The conclusion of MEURMAN (1966) that factors other than asbestos were either contributory or the sole cause of calcified plaques seems applicable to pleural thickening. The results of this study suggest that talc itself may produce pleural changes.

The clinical significance of pleural thickening, pleural plaques and pleural calcification as a result of asbestos exposure remains unclear, but is of concern because the pleural changes were considered to represent a significant exposure to asbestos and may be related to mesothelioma. However, there may be no association of mesotheliomas and pleural plaques even in the presence of asbestos, as no mesotheliomas associated with anthophyllite asbestos exposure have been observed in Finland (MEURMAN *et al.*, 1974). The suggestion that talc is carconogenic (BLUER and ARLON, 1973) may be due to asbestos contamination of the talc. The characteristics of talc have been poorly reported in the past. Talc free of asbestos contamination does not appear to increase the risk of cancer, and mesothelioma has not been associated with talc exposure (KLEINFELD *et al.*, 1974; RUBINO *et al.*, 1976; WAGNER *et al.*, 1977; RCBTA and MRCPU, 1979; SELEVAN *et al.*, 1979). Risk of cancer in this study cannot be determined. Among those with bilateral pleural thickening, lung function was

significantly reduced. The prognostic significance of these observations is unknown and deserves prospective evaluation.

CONCLUSIONS

In this cross-sectional study of 299 talc workers from Montana, Texas and North Carolina, there was no demonstrated association of symptoms (cough, phlegm, dyspnea) or reduced lung function with exposure. The prevalence of symptoms was not elevated and there was no demonstrable reduction in FEV, and FVC compared with the control populations. Thus, both internal and external comparisons were consistent in confirming the lack of association between morbidity and exposure variables. While there were no demonstrated differences in the symptom prevalences among the three talc regions (despite differences in exposure and talc composition), there were differences in the prevalence of cough and phlegm between the study population and the workers exposed to talc containing tremolite and anthophyllite.

The only significant effect observed in this study was related to the increased prevalence of bilateral pleural thickening. The excess was considerable in relation to the non-talc comparison populations, but the dose–response relationship was somewhat confounded with age. The comparable results among the talc populations, the lack of a consistent association of pleural thickening with asbestos exposure, and the lack of parenchymal changes in the talc exposed workers suggest talc as an etiological agent in the development of bilateral pleural thickening. While those with bilateral pleural thickening had reductions in lung function and a possible increase in symptoms, the long-term significance is unclear.

At least two warnings must be acknowledged. The mean number of years worked is relatively short. Therefore, more time may be needed to see exposure effects. The suggestion of reduced flow rates at low lung volumes supports this caution, as they may be early indicators of airways disease. The association of talc exposure with bilateral pleural thickening was relatively weak. However, latency was shorter than is commonly found in other studies and the excess is considerable compared with non-talc populations. A prospective study is necessary to answer the questions concerning prognostic significance.

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DISCUSSION*

J. C. MCDONALD: In addition to the pleural thickening you observed, was there any evidence of pleural calcification?

J. A. MERCHANT: May I answer that? I reviewed all the films with pleural thickening and there were no cases at all of pleural calcification. Most of the pleural thickening was grade 1, but there was one case where the thickening was considered grade 2. Two of the cases of pleural thickening were extent 2; the remainder extent 1.

J. WILLEMS: Do you have full information on the size-distribution of your talc dust particles?

Dr DEMENT: We do have some information that is not presented in this report. Of course, the respirable dust sampling attempted to simulate those particles which have the possibility of deep lung penetration. In general, the Montana talc had by far the largest particle size with much larger plates. In North Carolina there is a combination of the platy and acicular particles which were identified by electron diffraction and micro-chemical analysis as being talc with a rather unusual morphology.

S. F. MCCULLAGH: In this study (and several others) use is made of the standard respiratory questionnaire. Among other questions. workmen are asked if they get more short of breath walking on the level than other men of their own age. I have asked this question of thousands of workmen in Australia and at least half answer, 'Gee, Doc, I wouldn't know'. In the present study were the men forced to a decision, do you have a 'don't know' category or are American workers a great deal more intelligent than Australians?

Dr DEMENT: We try to administer the same questions to both our exposed and non-exposed populations and hope the level of intelligence is similar and better. The questionnaires are difficult to answer off-the-cuff, but we employ trained interviewers who are familiar with answering the questions and try to seek the answer in a polite manner. Very seldom does a worker answer, 'I don't know'. A very high percentage answer 'Yes' or 'No' and, if the answer is equivocal, the question is repeated with the admonition to answer 'Yes' or 'No'.

M. JACOBSEN: May I comment on Dr McCullagh's question. Whilst it is true that there are often ambiguous answers and strict protocols have to be used in order to maintain properly recorded answers useful for epidemiological studies, there is evidence from our studies that, if this is done rigorously and conscientiously, then the data obtained may be used sensibly for epidemiological purposes. Coal miners who have been asked these questions are no more or less intelligent than Dr McCullagh's patients. Their responses indicate very clearly that their mortality risk, particularly to the respiratory diseases, can be related to those responses to the questions particularly those relating to breathlessness and to cough and phlegm.

M. L. NEWHOUSE: I am surprised at the high prevalence of pleural thickening that you report. In a survey of 30-40 pharmaceutical workers exposed to a carefully specified, non-fibrous talc, we observed no more than one or two pleural thickenings.

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* The paper was presented, and questions taken, by Dr J. M. DEMENT.

Dr DEMENT: There are several possible reasons for the difference. I think the possibility of contamination cannot be ruled out until we look at the talc composition in these facilities over a number of years. The possibility that pockets of fibre contamination exist in these operations also cannot be excluded.

F. D. K. LIDDELL: Tables 3-5 present the prevalence of cough, of phlegm and of dyspnea by years worked and by cumulative exposure, but for all three States combined. On the other hand, Table 1 reveals important associations between age, duration of employment and dust concentration in the three States. To what extent are the 'negative' findings of Tables 3-5 a masking of positive associations. within at least one State, by the interactions shown in Table I?

Dr DEMENT: All the regions analysed were looked at separately. Admittedly the numbers were small within each region, but the only really significant finding in each of the regions was the pleural thickening.

J. C. GILSON: I would like to make two comments. The first concerns the recording of pleural thickening. The classification does provide a means of measuring the extent of this as well as the width, and I think it is important to make use of this information in order to deal with the kind of question that Dr Newhouse has raised.

My second point relates to the respiratory questionnaire. This questionnaire, as many of you know, was originally started here in S Wales by my colleague Dr Fletcher and, of course, it was applied to coal miners. Now coal miners do, by virtue of their job, have to walk together often underground under very adverse conditions. Also. in this particular area, the coal mines are in relatively steep valleys so miners were constantly walking with their colleagues. I have always thought the questions were particularly applicable in these circumstances and that they might well be inapplicable where people were walking on the level. If we had originally had coal mines in Norfolk this particular questionnaire would never have been developed.

J. C. MCDONALD: In our studies of Quebec asbestos workers, we found a very much higher prevalence of pleural thickening in one region than in the other, even allowing for exposure and other factors. This suggested to us that there might be something other than the asbestos involved, but we found no evidence for this. The same went for calcification.

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Table XU. Prevalence of Unilateral and Bilateral Pleural Thickening by Smoking, Years Worked and Region Among Talc Populations

	Prevalence, %				
	n	Obmed	Expected	Ratio: Observed/ Expected x 100	Comment
Total	400	9.5			
Age					p < 0.0005
<40	233	2.1	8.6	24	Expected values adjusted
>40	167	19.8	10.7	185	by smoking status.
Smoking					p < 0.025
Nonsmokers	102	2.9	7.6	38	Expected values adjusted
Ex-smokers	98	15.3	13.2	116	by age.
Smokers	200	10.0	8.7	115	
Years Worked					p < 0.01
<5	196	4.1	5.7	72	Expected values adjusted
6-14	131	9.2	10.4	88	by age and smoking.
>15	73	24.7	18.1	136	
Region					p < 0.01
New York	121	11.6	12.1	96	Expected values adjusted
Montana	161	3.7	6.9	54	by age, smoking and years
Texas	69	13.0	8.3	157	worked.
North Carolina	49	18.4	13.4	137	

was entered in the model. Within each region, the most consistent predictors of Pulmonary function were sex, age and height. There was no consistent association with smoking and exposure.

The effect of the independent variables (sex, age, height, smoking, region and tenure) can be seen more easily in the model, where all regions are combined (Table XV).

The smoking effect was analyzed using smoking categories (nonsmoker, ex-smoker, smoker) or the continuous measures of pack-years and cigarettes smoked per day. Discussion will be limited to the model using smoking categories, unless stated otherwise.

Weight was not a significant predictor for any of the pulmonary function parameters. Tenure was only a significant predictor for FVC and FEV_1. Smoking was significantly associated with reductions in FEV_1, FEF_{50} and FEF_{75}. While smoking status was not a significant predictor of FVC, pack-years and cigarettes smoked per day were significant predictors. The age coefficient of FVC for all nonsmokers was about half that for smokers

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RESPIRATORY MORBIDITY AMONG MINERS AND MILLERS OF ASBESTIFORM TALC

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Talc mining in New York state began in 1878. It is one of the leading states in terms of tonnage of talc produced. The commercial use is largely paint and ceramics, but New York talc is also used in rubber, insecticides, foundry facings and plastics. The mineral composition varies widely, with tremolite, anthophyllite, talc, or serpentine predominating. Quartz, carbonates, diopside, manganese and iron oxides, and gypsum may occur as minor impurities.

Airborne dust levels in the New York mine and mill of this study showed 38-45% of anthophyllite, and 12-19% tremolite fibers by electron microscopy. More than 90% of the airborne fibers were < 5 μm in length. No free silica exposures *exceeded* 50 $\mu g/m^3$ (*see* paper by John Dement in this volume.)

Lung disease associated with talc exposure was first described in 1896. Individuals exposed to various talcs report symptoms of cough and dyspnea, physical findings of crepitance, clubbing, and wheezing, changes in pulmonary function (reduced Forced Expiratory Volume in one second (FEV,), Forced Vial Capacity (FVC), transfer factor, increased residual volume to total lung capacity ratios, x-ray and autopsy findings of fibrosis and calcification) (Kleinfeld *et al.*, 1965; Kleinfeld et *al.*, 1964; Kleinfeld et *al.*, 1963; Morgan and Seaton, 1975; Parkes, 1974). Several kinds of "talcosis" have been described in the literature, and are thought to be descriptive for the causative agents. They are talcosis similar to asbestosis, talcosis similar to silicosis, mixed, and "pure" talcosis (Kleinfeld, et *al.*, 1963, 1964; Leophante, et *al.*, 1975; Morgan and Seaton, 1975; Parkes, 1974).

A cross-sectional morbidity study was initiated at the plant under study to answer the following questions:

(1) Is there an increased prevalence of respiratory symptoms, impaired lung function, and/or radiographic abnormalities?
(2) If there are detrimental effects on health, are they related to exposure to talc?

MATERIALS AND METHODS

Each worker was administered a Medical Research Council respiratory questionnaire (which included questions on employment history), two chest

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x-rays (PA and lateral), and five forced expirations. X-rays were read by three readers using the ILO/UC scheme. Maximum pulmonary function values were selected from acceptable flow volume curves (FEV and FVC within 5%, and peak flow within 15% of maximum).

The results obtained from the examination of talc workers were compared to 9,347 coal miners examined by the National Institute for Occupational Safety and Health (NIOSH) in the second round of the National Coal Study. Some comparisons are made with 1,095 potash miners also studied by NIOSH. Both studies used the same equipment and methodology. In the comparisons, adjustments for age, height, smoking and years worked are made by direct standardization for rates. For lung function values, ratios of actual to predicted x100 are used, except for FEV% (FEV/FVC) which is expressed as (observed–expected) + 100. Cumulative exposure was calculated by multiplying a x b where (a) equals the average exposure to fiber and particulate in each job and (b) equals the time spent in each job. All the scores were then added together ($\Sigma(a \times b)$) and expressed as fiber-yrs/cc for asbestiform fibers and mg-yrs/cc for particulates. Average exposure levels are those reported by Dement in these proceedings.

RESULTS AND DISCUSSION

121 (78%) of the currently employed male miners and millers participated. The average number of years worked is 10.2. Ninety-three of those participating had worked only at the facility studied, 28 at other talc mines and mills. The results are presented for the 121 workers, although there is no *apparent* difference between the two groups.

Figure 1 summarizes exposure by age. Years worked, fiber exposure, and particulate exposure increase proportionally in all age groups except the oldest. The high correlation of these three variables *make* it impossible to analytically disentangle their separate effects.

Figure 2 summarizes symptoms and radiographic findings in talc workers compared to *coal* miners. In the group working less than 15 years, talc workers have a 33% prevalence of cough, and a 38% prevalence of phlegm, which are significantly higher than the coal miners. The rates for hemoptysis and dyspnea are the same as those for the coal miners. In the talc group working more than 15 years, dyspnea increases from 13 to 23%, but the increase to 39% in coal miners is significantly greater. The prevalence of hemoptysis, phlegm, and cough is reduced slightly, or remains the same, in the talc group working more than 15 years, while the prevalence increases in the comparison group of coal miners. The prevalence of phlegm is significantly higher in this group of coal miners compared to talc workers.

The reduction in symptom prevalence between those working less than 15 years, and those working 15 or more years, points out the problems of natural selection in cross-sectional studies. If those in the younger age group with the higher prevalence of hemoptysis and phlegm had continued to work, would the prevalence of these symptoms have been reduced in the greater than 15 year group? Other survey6 show no consistent relationship between the symptoms of cough and phlegm and age, although in most *studies* shortness of breath increases with age (Higgins, 1974). A major determinant for cough and phlegm is smoking. Most of the smokers in this study are in the less than 15 years worked category, and this is probably the reason for the higher rates in this group. The lower prevalence of phlegm and dyspnea in the talc workers with greater than 15 years worked, when compared to coal miners, could be due to a difference in selection (more coal miners

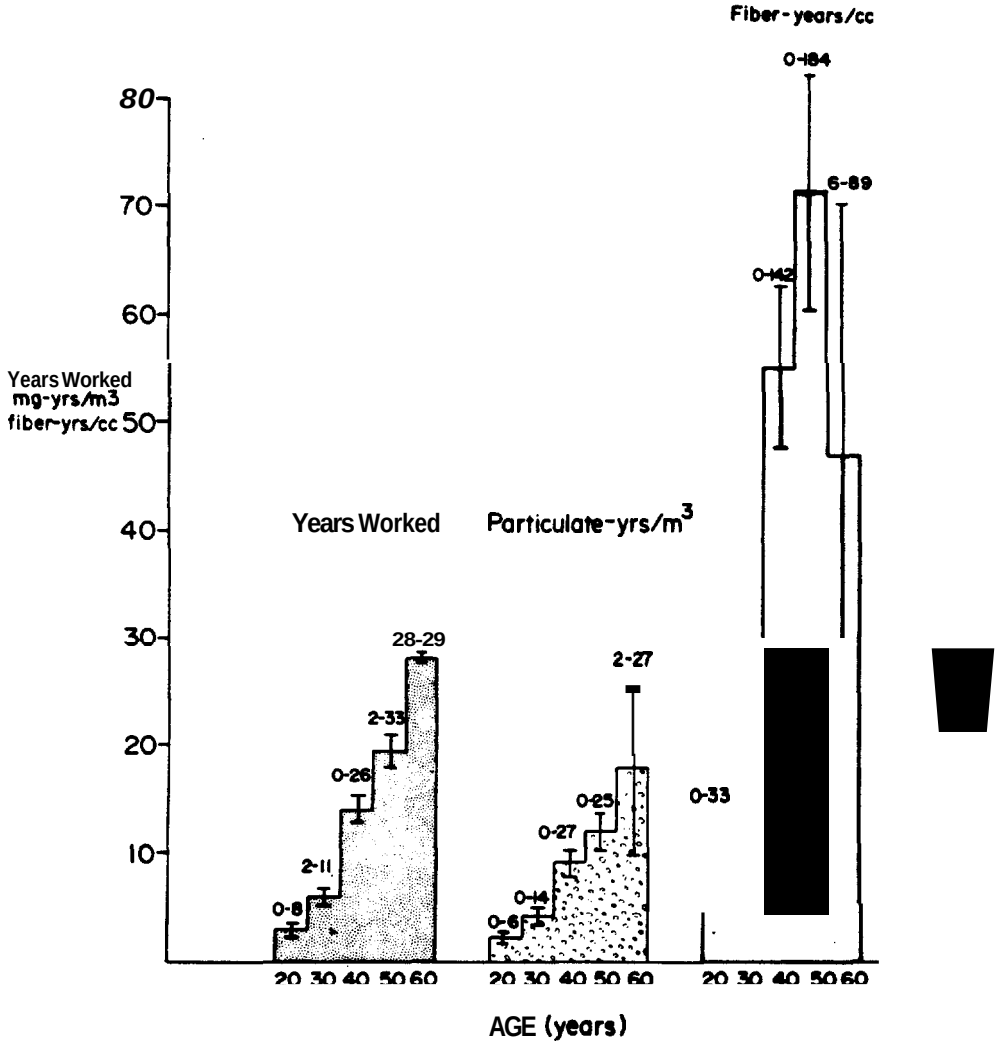

FIGURE 1. Age/Exposure Characteristics of Study Population with Standard Error. Exposure is expressed as years worked. mg-yrs/m 3 (particulate exposure) and fiber-yrs/cc (asbestiform fiber exposure).

remain in the industry despite symptoms). It should be noted that in the greater than 15 years worked group, dyspnea is 2.5 times more prevalent, and cough 1.7 times more prevalent in talc workers than in potash miners. but there is no difference in the prevalence of phlegm. With respect to symptoms, then, in the younger age groups the talc workers, in general, have more symptoms than coal and potash miners. In the older age groups, the prevalence of symptoms in talc workers is greater than in potash miners, but is less than in coal miners.

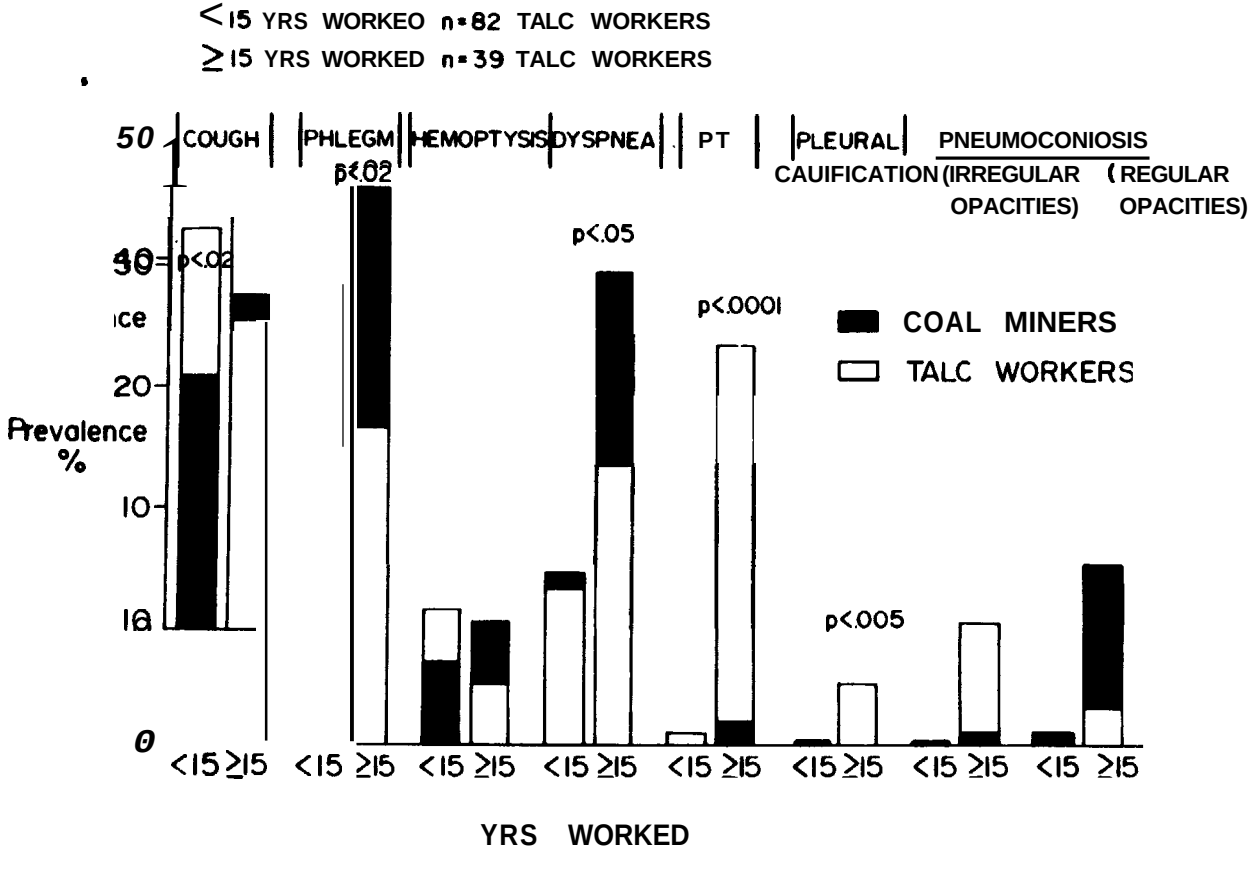

FIGURE 2. Symptoms and Radiographic Findings by Years Worked in Talc Workers Compared to Coal Miners and Adjusted for Age. Height, and Smoking.

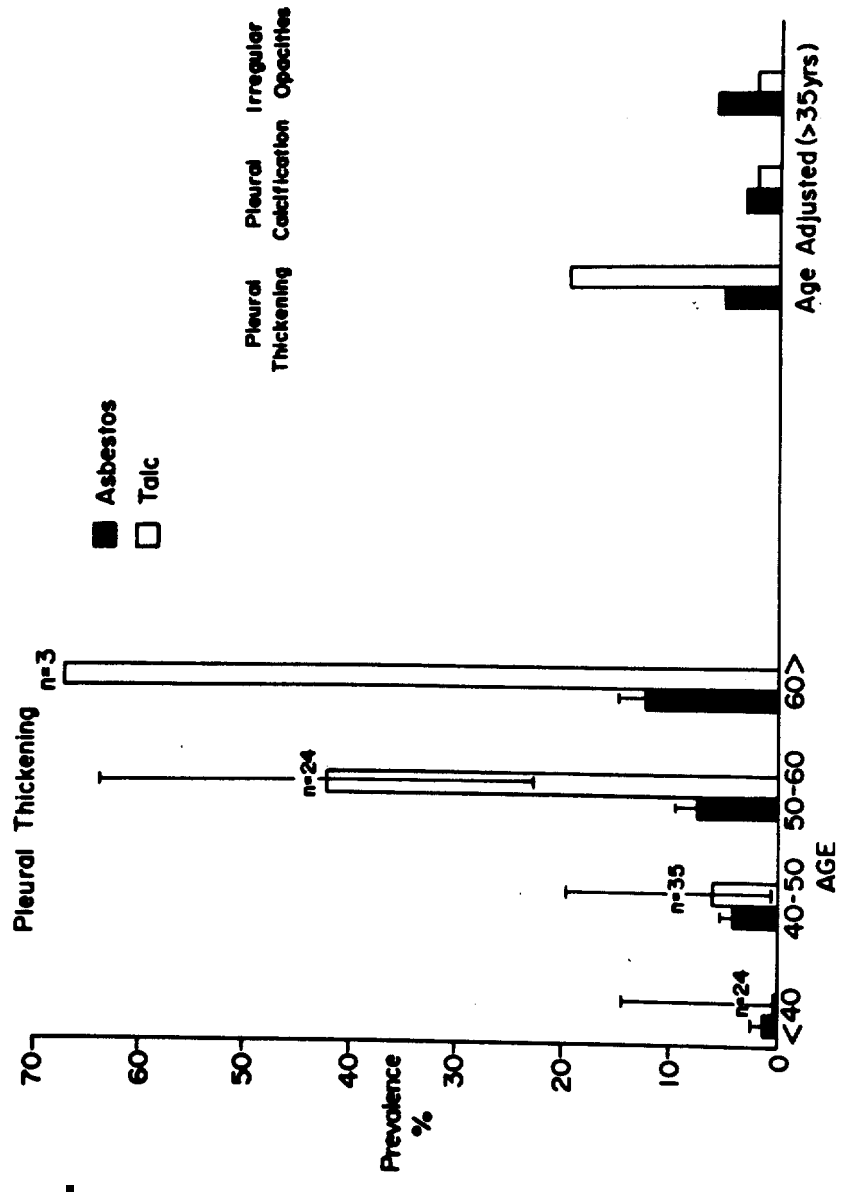

FIGURE 3. Prevalence of Radiographic Findings by Age in Talc and Chrysotile Asbestos Workers (95% Confidence Interval).

The prevalence of radiographic findings is below 2% in talc and coal workers with less than 15 years worked. In those working more than 15 years, the prevalence in coal miners of regular and irregular opacities is 15% and 6% respectively, and 3% and 10% in talc workers; these differences are not statistically significant. The prevelance of pleural calcification and pleural thickening does not change with increasing years worked in coal miners, but increases to 5% and 33% respectively in talc workers. The prevalence of pleural changes in talc workers with more than 15 years worked is highly significantly increased compared to coal miners. In addition, the prevalence of pleural thickening, but not other x-ray changes, is significantly higher in these talc workers than in chrysotile asbestos workers in Canada (Figure 3).

Pleural thickening and fibrosis are very much related to age and years worked as seen below and in Figure 4.

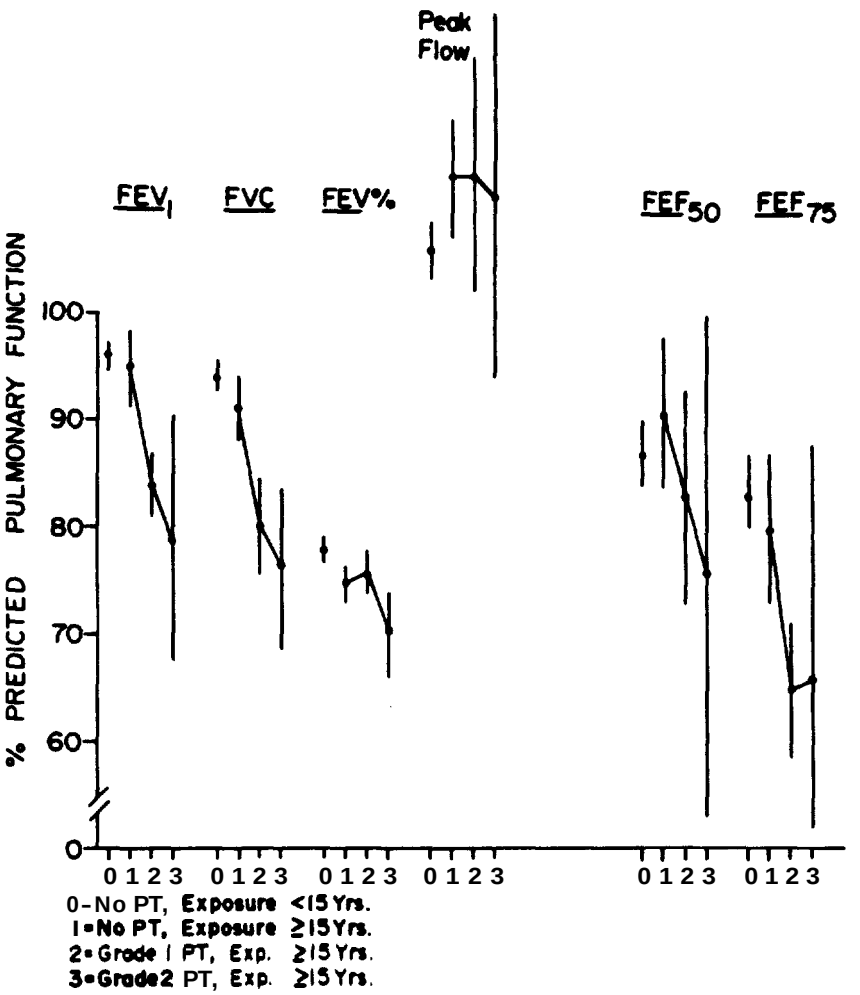

FIGURE 4. Effect of Pleural Thickening on Lung Function of Talc Workers. Lung Function (with standard error) of Talc Workers Compared to Coal Miners and Adjusted for Age, Height, and Smoking.

	Years Worked						
Prevalence (%)	0	5	10	15	20	25	30
Pleural Thickening	0	5%	0	10%	40%	38%	100%
Irregular Opacities	0	0	0	0	7%	15%	100%

In talc workers with either pleural thickening or irregular opacities, all but one are over 40 years of age and have worked more than 15 years. The long period required for the development of these conditions is consistent with studies in asbestos workers, where the mean length of exposure before the x-ray appearance of pleural or pulmonary changes is greater than 20 years (Soutar et *al.*, 1974; Selikoff, 1965). However, fibrosis and pleural changes can occur sooner in some individuals (Fletcher and Edge, 1970; Harries, 1972; Sheers and Templeton, 1968). Historically, fibrosis has been frequently associated with asbestosis, with little or no mention of pleural changes (Selikoff, 1965). In more recent years, however, pleural changes in asbestos workers are frequently described (Fletcher and Edge, 1970; Harries et *al.*, 1972; Selikoff, 1965; Sheers and Templeton, 1968; Soutar et *al.*, 1974), and may be more common even than the fibrotic changes (Hurwitz, 1961; Sheers and Templeton, 1968; Solomon, 1970). Pleural thickening is considered an early indicator of asbestos exposure (Fletcher and Edge, 1970; Harries et *al.*, 1972; Sheers and Templeton, 1968; Solomon, 1970). Pleural calcification has been suggested as a sequel to pleural thickening (Hourihane et *al.*, 1966; Hurwitz, 1961; Kiviluoto, 1965; Solomon, 1970).

What is the significance of the findings of increased prevalence of pleural thickening in the talc workers? As discussed above, pleural thickening is an early indicator of asbestos exposure, if not asbestosis. The higher prevalence of pleural thickening, compared to fibrosis, in currently employed asbestos workers may indicate a lower exposure to asbestos than workers experienced earlier in this century (Selikoff, 1965). At lower exposure levels, fibrotic changes develop more slowly, and are not as disabling (Selikoff, 1965; Sheers and Templeton, 1968). Fibrosis is inadequate as an early indicator of asbestosis, as early changes are an exaggeration of normal lung markings, are readily simulated by underexposed films, and are very subjective (Fletcher and Edge, 1970). It is not known if pleural changes precede malignancy, although this has been observed in at least one *case* (Sheers and Templeton, 1968). Figure 5 shows that those with pleural thickening compared to those without have reduced FEV, FVC, and flow rates at low lung volumes. FEV% is reduced only in those with grade 2 pleural thickening. The interstitial fibrosis associated with asbestosis is generally considered to be associated with a restrictive pattern of pulmonary function, i.e., decreased FVC, no change in FEV% (Becklake, 1976; Langlands et *al.*, 1971; Thomson et *al.*, 1965). In older age groups particularty, an obstructive pattern of pulmonary function may be equally prominent (Fournier-Massey and Becklake, 1975). No significant differences in FEV,, FVC, peak flow, and Total Lung Capacity (TLC) were observed in men 40 to 59 years old with, and without, pleural abnormalities (pleural fibrosis and/or calcification). If younger age groups of these asbestos exposed insulation workers are analyzed, however, FEV%, N C , and peak flow are reduced in those with pleural abnormalities, compared to men with a normal x-ray (Langlands et *al.*, 1971). Muldoon and Tumer-Warwick found a normal or greater than normal specific conductance and low TLC (restrictive pattern) in 6 of 8 asbestos workers with pleural shadows only (1972). Becklake, et *al.*, in a larger series of chrysotile asbestos workers in Canada,

found mild, but consistent, reductions in lung function (FVC, FEV, MMEF - but not FEV%) in workers with pleural thickening (1970). These findings of an association of reduced lung function with pleural changes on the x-ray are consistent with those observed in the talc workers in this study.

Figure 5 summarizes mean pulmonary function values of talc workers compared to coal miners, and the association of pulmonary function with exposure. All

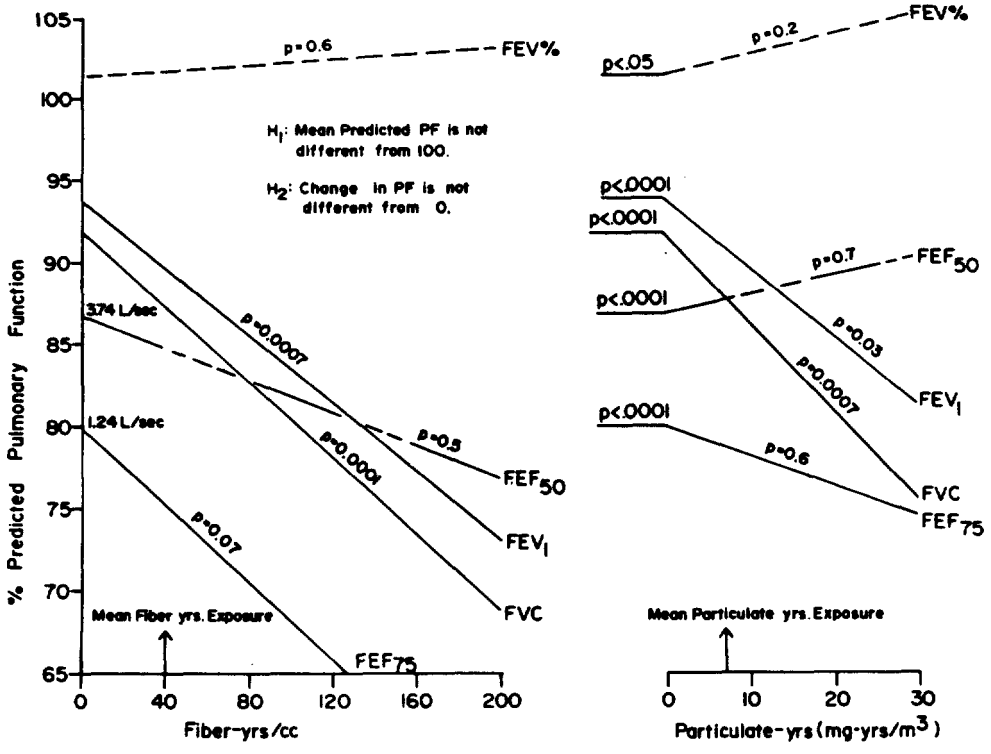

FIGURE 5. Mean Percent Predicted Lung Function of Talc Workers and Change in predicted Lung Function by Exposure to Fibers (fiber-yrs/cc) and Particulates (mg-yrs/m^3). Talc Workers are Compared to Coal Miners and Adjusted for Age, Height, Smoking, and Years Worked.

pulmonary function values are below expected (except FEV% and peak flow, which are slightly elevated). Volumes and flow rates generally decline with particulate and fiber exposure, but the reductions are statistically significant only for FEV, and FVC. This reduction in lung function is thought to be the result of occupational exposure, since in the comparison of talc and coal workers pulmonary function adjustments are made for years worked, age, height and smoking.

SUMMARY AND CONCLUSIONS

An increased prevalence of abnormal health effects is observed in the talc workers in this study. The talc workers with less than 15 years worked have an increased prevalence of cough and dyspnea compared to coal and potash workers. The talc workers with greater than 15 years worked have an increased prevalence of pleural calcification compared to coal and potash workers, and an increase of pleural thickening compared to coal, potash, and chrysotile asbestos workers. Workers with pleural thickening have a greater reduction in lung function than those without pleural thickening. Mean FEV_1, FVC, FEF_{50}, and FEF_{75} of talc workers is reduced compared to coal and potash workers.

Radiographic findings occur primarily in those working more than 15 years. There are no radiographic abnormalities in those less than 40 years old. FEV, and FVC reductions are significantly associated with particulate and fiber exposre, and years worked. Because of the high correlation of exposure, age, and years worked, and because current exposure levels do not reflect past exposures, it is not possible to determine dose-response relations. A prospective study is required to determine the effects on health of present exposure to this talc.

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An Epidemiologic Study of a Group of Talc Workers'

JOHN F. GAMBLE, WILLIAM FELLNER, and MICHAEL J. DIMEO

SUMMARY

Chest roentgenograms, pulmonary function assessment by spirometry, respiratory symptoms. smoking history, and occupational history by questionnaire were obtained from 121 male talc miners and millers exposed to talc containing tremolite and anthophyllite asbestiform fibers. Ninety-three of the employees had worked in talc only at the plant under study. Symptoms were only slightly more prevalent in talc workers when compared to potash miners. Mean pulmonary function (forced expiratory volume in one sec, forced vital capacity, and maximal expiratory flow at 50 and 75 per cent of vital capacity) of talc workers was significantly decreased in comparison to that of potash miners. The prevalence of pleural calcification and pneumoconiosis in talc workers with 15 or more years of employment was higher than in potash miners. The prevalence of pleural thickening was 31 per cent in those who worked more than 15 years and was significantly increased as compared to that in potash miners. Workers with pleural thickening had decreased pulmonary function in comparison to those who did not. Decreased one-sec forced expiratory volume and forced vital capacity were associated with exposure to respirable particulate and asbestiform fibers

Introduction

Talc is a heterogenous group of hydrated magnesium silicates commonly found in deposits that contain varying amounts of other minerals including carbonates, quartz, and the main asbestos-forming minerals, the amphiboles and serpentines. Talc is used in the ceramic industry, the rubber industry, as a filtering agent in the chemical industry, in cosmetic powders and pharmaceuticals, and as a filler in paint, paper, soaps, and roofing materials (1).

The United States produces approximately 30 per cent of the worlds talc, with New York, California, Vermont. Texas. and Montana accounting for three fourths of the U.S. production (2). and there is considerable variability in composition among the different talc deposits. Talc in the Death Valley area of California is commonly a mixture that includes tremolite, quartz, dolomite. and calcite in addition to the talc. The best California talc is approximately 60 per cent pure and is used for cosmetic and pharmaceutical applications, with synthetic minerals and pigments, and in paper. plastics, paint, and ceramic tile. Texas talcs are darker because of carbon and dolomite impurities. Although the carbon volatilizes at temperatures below that used in production of ceramic wall tiles, most of the Texas talc is used for less demanding applications such as roofing and rubber dusting materials. Montana talcs are of high purity, the principal impurity being a dark dolomite that is removed by hand sorting (3). This steatite platy talc is generally ground into ultrafine particles and used in pitch control In pulp and paper manufacture and in the reinforcement of synthetic rubber. Vermont talc characteristically has low fiber and silica content. The New York State deposits in St. Lawrence County are associated with tremolite and anthophyllite.

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1 From the National Institute of Occupational Safety and Health (NIOSH). Appalachian Laboratory for Occupational Safety and Health, Morgantown, W.V., E. I. duPont de Nemours and Company, Wilmington, Del., and the Veterans Administration Hospital, San Francisco, Calif.

Talc miners and millers who work these deposits are the subject of this report.

Lung disease associated with exposure to talc was first described in 1896. Since then, several studies have suggested an association between exposure to talc and respiratory symptoms (dyspnea, cough, wheezing), lung dysfunction (decreased forced vital capacity [FVC], one-sec forced expiratory volume [FEV_1], and pulmonary diffusing capacity for CO [DLCO]), and lung abnormalities seen on chest roentgenogram (infiltration, pericardial and pleural calcification, and pleural thickening) (4–20). Talc is both the name of a specific mineral [$Mg_3Si_4O_{10}(OH)_2$] and a commercial term for a mixture of minerals in which the mineral talc may be a minor constituent. Because talc may contain silica and asbestifom fiben, 3 forms of talc pneumoconiosis have been described: talco-silicosis, talco-asbestosis, and pure talcosis (18). Epidemiologic studies of the prevalence of talc pneumoconiosis have been confined primarily to workers exposed to talc containing asbestiform minerals but with a low silica content (4–6, 8–10).

A cross-sectional morbidity study was initiated to examine all presently employed workers in a talc mine and mill where 38 to 45 per cent of airborne fibers were anthophyllite asbestos and 12 to 19 per cent were tremolite asbestos (determined by electron microscopy). More than 90 per cent of all airborne fibers were shorter than 5 μm. All free silica exposures were less than 50 μg per m^3. This study was designed to answer the following questions concerning the effects of chronic exposure: (1) Is there an increased prevalence of abnormal health effects (respiratory symptoms, radiographic abnormalities, and impaired pulmonary function) in workers exposed to talc containing anthophyllite and tremolite fibers when compared to a population of potash miners? and (2) If there are detrimental effects of exposure, what are the dose-response relationships?

Materials and Methods

The work force consisted of 156 male millers and miners. One hundred twenty-one workers (78 per cent) participated. The average duration of exposure to talc was 10.2 years for the study population and 10.5 years for the nonparticipants. The participation rate among the different work areas was similar. Thirty-five of the 121 participants had worked at other talc-mines in the region. Reporting on the effects of exposure is confined to the 93 men who worked only at the mine and mill under study, although results were similar when all 121 workers were included in the analysls. For both the talc workers and the comparison population of potash workers. a Medical Research Council respiratory questionnaire containing questions on total work and smoking history was administered by trained interviewers. Standard posteroanterior chest roentgenograms were read by 3 "B" readers using the ILO U/C 1971 scheme. The films were read Independently without knowledge of age, occupation, and smoking history. The median of the 3 readings was used for analysis. Flow-volume curves from a minimum of 5 forced maneuvers were obtained and recorded on magnetic tape wing an Ohia 800 rolling seal spirometer,* with maximal values used for analysis. Blood samples were collected from talc workers and were analyzed for antinuclear antibodies and rheumatoid factor.

Personal air samples were collected from miners and millers to determine time-weighted average (TWA) exposure to respirable dust, free silica, and asbestos fibers. Samples for respirable dust and free silica were collected on polyvinyl chloride filters preceded by 10-mm nylon cyclone separators.

Samples for fiber analysis were collected on open-faced, 36-mm diameter Millipore Type AA filters (0.8-μm pore size) and were analyzed using the NIOSH phase contrast counting technique (21). A random sample was analyzed by electron microscopy using selected area electron diffraction and energy dispersive. roentgenographic analysis for fiber identification.

Lung function and the prevalence of symptoms and radiographic findings in this population were compared to those in 1,077 potash miners recently examined by NIOSH (22). The Mine Enforcement and Safety Administration in collaboration with NIOSH and as part of the Metal/Nonmetal Miner Study, conducted environmental surveys of the 6 dieselized potash mines in which the comparison population worked. Personal total dust samples were collected on membrane filters and were analyzed gravimetrically for total dust and by roentgenographic diffraction for per cent of free silica. Personal NO, measurements were taken, NO_2, being collected on a gel-coated grid and analyzed by means of a spectrophotometer. Area samples for total respirable particulate and fibers were collected. The average proportion of respirable to total particulate from area samples in each potash mine was used to estimate personal exposure to respirable particulate. The mean and range of the mine averages were as follows:

* Mention of brand names does not constitute endorsement by the U.S. Public Health Service.

	Mean of Mine Average	Range of Mine Averages
Total particulate, mg per m^3	10.62	6.67–15.84
Free silica, %	0.89	0.17–2.4
NO_2, ppm	0.90	0.04–3.22
Respirable particulate (estimated), mg par rn3	3.44	2.17–8.32
Fibers per ml > 6 μm (area)	1.28	0–3.77

For comparison of symptoms and radiographic findings. persons in cach population were grouped into categories by similar age (15-year intervals). hcfght (1.5-cm intervals), smoking (nonsmokers, ex-smokers, and smokers), and duration of employment in mining (less than 15 years, 15 years or more). The expected number in potash workers was calculated by laking the rate in each category of the comparison potash population and multiplying by the number of persons in the same category of the talc population. The number of potash workers in *each* category—age, height, smoking status, and duration of employment—was added together. giving a calculated expected number for each symptom and radiographic finding. Because the observed/expected comparisons are expressed as rates. the observed and *expected* number of workers with each aymptom and radiographic abnormality was divided by the total number. in the study and comparison population. This standardization for age, height, smoking status. and number of years of employment is analogous to the age-standardization calculation of a standard mortality ratio.

For pulmonary function results, predictive equations taking into account the effects of age and height were calculated for each smoking and duration of employment category of potash miners. Every talc worker's pulmonary function was then compared *to* the appropriate category in the comparison population. Comparison of each talc worker's actual pulmonary function with expected pulmonary function in the appropriate category of the potash population was averaged and multiplied by 100 to give mean per cent of predicted pulmonary function. For FEV_1/FVC × 100 (FEV_1%), the difference between observed and expected values +100 was used.

Years of exposure is the number of years worked at the plant under study. Cumulative exposure was calculated by multiplying (*a*) present exposure in each job as determined by personal sampling (fibers per ml, mg per ma) by *(b)* the time (years) spent performing that job, and then adding all the exposure x times scores; i.e., $\Sigma (a_i \times 6_i)$. The results for each individual are expressed as fibers per ml × years for cumulative fiber exposure and mg per m^3 x years for respirable particulate. Although some sampling was done in the past, previous environmental exposures for each job are not well defined because little particulate and no fiber sampling was done before 1970. Very few samples were taken in any one year, and the representativeness of these samples is unknown. Comparison of current and previous degrees of exposure suggests that in some jobs exposures were greater in the past than at present (23). Therefore, the estimates of cumulative exposure are probably lower than actual cumulative exposures.

Results

The highest observed TWA exposure to free silica was *0.04* mg pet m^3. Most workers sampled bad TWA exposures to free silica of less than *0.02* mg per m^3. Mean TWA exposures to respirable particulate in the mine ranged from 0.23 to 1.20 mg per m^3, and in the mill from 0.25 to 2.96 mg per m^3. Airborne fibers collected in the mine were identified as 38 per cent anthophyllite, 19 per cent tremolite, and 3 per cent chrysotile; 39 per cent were unidentified. In the mill, 45 per cent of the airborne fibers were anthophyllite, 12 per cent were tremolite, 2 per cent were chrysotile, and 38 per cent remained unidentified *ps).* Median fiber diameters of 0.19 and 0.13 μm were observed for tremolite and anthophyllite: in the mine, median fiber lengths were 1.6 and 1.5 μm for tremolite and anthophyllite, respectively, and were 0.1 μm

TABLE 1

AGE-SMOKING COMPOSITION OF TALC WORKERS

	Age (years)											
	20–29		30–39		40–49		50–59		> 60		Total	
Smoking Status	(no.)	(%)	(no.)	(%)	(no.)	(%)	(no.)	(%)	(no.)	(%)	(no.)	(%)
Nonsmoker	12	(41)*	2	(11)	3	(11)	2	(12)	0	(0)	19	(20)
Ex-smoker	3	(10)	3	(17)	13	(48)	8	(47)	1	(50)	28	(30)
Smoker	14	(48)	13	(72)	11	(41)	7	(41)	1	(50)	46	(49)
Total	29	(31)	18	(19)	27	(29)	17	(18)	2	(2)	93	

*Cells are column percentages; marginals are percentages of the total.

TABLE 2
AGE-EXPOSURE COMPOSITION OF TALC WORKERS

	Age (years)				
	20–29	30–39	40–49	50–59	>60
Subjects, no.	29	16	27	17	2
Years of employment, no.	27 (0.3)*	6.9 (0.8)	13.9 (1.4)	19.5 (2.0)	28.0 (0.0)
Particulate exposure, mg/m³ X years	2.0 (0.3)	4.8 (1.0)	8.6 (1.3)	11.3 (2.0)	13.7 (11.7)
Fiber oxporuro, fibers/ml X years	10.4 (1.6)	16.7 (3.3)	52.7 (7.6)	68.8 (13.1)	47.4 (41.4)

*Numbers in parentheses indicate SE.

shorter for each in the mill. TWA exposure to more than 5 fibers > 5 μm pet ml was observed for 3 different jobs in the mine and 6 different jobs in the mill. Exposures exceeding 2 fibers > 5 μm per ml occurred in 17 of 24 job categories, and exposure for all jobs exceeded 0.5 fibers > 5 μm per ml.

The age-smoking distribution of the 93 talc workers whose exposure to talc was limited to the mine and mill being studied is shown in table 1. Almost one-half were smokers, with slightly more ex-smokers than nonsmokers. Almost two-thirds of the nonsmokers were less than 30 years of age, and more than three-fourths of the ex-smokers were 40 years of age or older. Smokers were more evenly distributed in all age groups. although the pcrcentagc of smokers was highest in the SO- to 39-year age group.

Shown in table 2 is the distribution of duration of employment in talc and estimated cumulative particulate and fiber exposures by age. Except for the group of Subjects more than 60 years of age, in which there were only 2 persons, there was a consistent and approximately equal increase in years of employment and exposure to particulate with increasing age.

The distribution of symptoms and radiographic findings by smoking status are summarized in table 3. Smokers had a higher prevalence of cough, phlegm, hemoptysis, and shortness of breath, with symptoms markedly lower among nonsmokers. The differences were significant for cough and phlegm. Smoking showed no apparent association with pleural thickening. There was one case each of calcification and regular and irregular opacities, which were too few to analyze for dose-response relations.

Summarized in table 4 is the association of age with symptoms and radiographic findings. Age (and implicitly, long-term exposure) showed no discernible association with symptoms. The higher prevalence of cough and phlegm in the SO- to 39-year age group is probably a reflection of the large proportion of smokers in that category. Similarly, the slightly higher prevalence of dyspnea in the 30- to 39-year and

TABLE 3
PREVALENCE (%) OF SYMPTOMS AND RADIOGRAPHIC FINDINGS BY SMOKING STATUS"

	Smoking Status				
	Nonrmokor	Ex-smoker	Smoker	Total	P
Subjects, no.	19	28	46	93	
Cough	0	21.4	52.2	32.3	0.0001
Phlegm	10.5	14.3	50.0	31.2	0.0005
Hemoptysis	0	3.6	13.0	7.6	0.12
Dyspnea (≥ grade 2)	0	14.3	19.6	14.0	0.12
Pleural thickening (≥ extent 1)	10.6	14.3	8.7	10.8	0.76
Pleural calcification	6.3	0	0	1.1	0.14
Irregular opacities (≥ grade 1)	0	0	2.2	1.1	0.60
Rounded opacities	0	0	2.2	1.1	0.60

*Hypothesis: thoro is no difference in rates among thr 3 smoking categories.

TABLE 4

PREVALENCE (%) Ot' SYMPTOMS AND RADIOGRAPHIC FINDINGS BY AGE*

	Age (years)						
	20-29	30-39	40-49	50-59	≥ 60	Total	P
Subjects, no.	29	18	27	17	2	93	
Cough	17.2	55 6	22.2	41.2	100.0	32.3	0.009
Phlegm	20.7	44.4	29.6	29.4	100.0	31.2	0.11
Hemoptysis	6.9	11.1	11.1	0.0	0.0	7.6	0.66
Dyspnea (≥ grade 2)	10.3	16.7	11.1	17.7	50.0	14.0	0.56
Pleural thickening (≥ extent 1)	0	0	7.4	41.2	50.0	10.8	0.0001
Pleural calcification	0	0	3	6.9	0	11	0.34
Irregular opacities (≥ grade 1)	0	0	0	5.9	0	11	0.34
Rounded opacities	0	0	3.7	0	0	1.1	0.65

*Hypothesis: there is no difference in rates among the 5 age groups.

> 50-year age groups is also probably due to the proportion of smokers and ex-smokers in those ages. Pleural thickening, on the other hand, was not found in the age groups less than 40 years (mean exposure of 14 years), and was highest in the 50- to 59-year (mean exposure of 20 years), and more than 60 year {mean exposure of 28 years) age groups.

Demographic information on the talc and potash workers by smoking status and years of employment is provided in table 5. The populations were comparable with the following exceptions: in the group with less than 15 years of employment. talc workers who did not smoke were slightly younger than potash worken: talc workers who did smoke were slightly taller and on the average smoked approximately 5 cigarettes per day more than potash workers who smoked. In tlie category of 15 years or more of employment, tlie potash nonsmokers and ex-

TABLE 5

DEMOGRAPHIC INFORMATION ON POTASH AND TALC WORKERS BY SMOKING STATUS AND NUMBER OF YEARS WORKED

	Years Worked							
	< 15				≥ 15			
Variable/Group	Talc		Potash		Talc		Potash	
Subjects, no.								
Nonsmokers	16		179		3		62	
Ex-rmokorr	11		171		17		117	
Smokers	37		399		9		149	
Age. years								
Nonsmokers	26.8	(1.8)*	30.7	(0.8)	60.0	(1.2)	63.7	(0.8)
Ex-smokers	38.1	(3.3)	36.6	(0.8)	48.8	(1.4)	53.9	(0.6)
Smokers	33.3	(1.5)	32.9	(0.5)	61.7	(1.7)	52.0	(0.6)
Height, cm								
Nonsmokers	176.6	(1.6)	173.4	(1.1)	179.0	(5.6)	176.6	(0.7)
Ex-smokers	177.0	(1.9)	174.0	(1.1)	177.4	(2.0)	174.9	(0.5)
Smokers	176.1	(0.9)	174.7	(0.5)	173.8	(1.4)	174.6	(0.5)
Years underground, no.								
Nonsmokers	4.4	(0.9)	4.5	(0.3)	24.0	(1.2)	24.6	(0.7)
Ex-rmokers	4.0	(1.2)	6.1	(0.3)	21.3	(1.0)	23.6	(0.5)
Smokers	6.2	(0.6)	6.1	(0.2)	22.6	(1.4)	23.3	(0.6)
Cigarettes/day, no.								
Ex-rmokorr	24.6	(5.7)	21.7	(1.1)	34.1	(4.7)	25.9	(1.3)
Smokers	27.9	(1.6)	22.7	(0.7)	16.9	(2.5)	22.3	(0.9)
Packs/year, no.								
Ex-smokers	13.6	(2.7)	14.0	(1.1)	36.7	(7.8)	29.7	(2.0)
Smokers	24.1	(3.0)	19.1	(0.9)	30.6	(3.8)	38.0	(1.8)

*Numbers in parentheses indicate SE.

TABLE 6

PREVALENCE (%) OF SYMPTOMS AND RADIOGRAPHIC FINDINGS IN TALC WORKERS COMPARED TO POTASH WORKERS, ADJUSTED FOR AGE, HEIGHT, AND SMOKING STATUS*

	Years Worked			
	< 15		≥ 15	
	Talc	Potash	Talc	Potash
Subjects, no.	64	669	29	414
Cough	31.3	23.2	34.5	25.6
Phlegm	34.4	27.2	24.1	23.7
Hemoptysis	10.9	6.4	0.0	6.7
Dyspnea (≥ grade 2)	12.6	6.3	17.2	11.3
Pleural thickening (≥ extent 1)	1.6	0.6	31.0†	4.4
Pleural calcification	0.0	0.0	3.4	0.0
Irregular opacities (≥ grade 1)	0.0	0.0	3.4	0.7
Rounded opacities (≥ grade 1)	0.0**	0.0	3.4	1.1

*Hypothesis: there is no difference in rates between the talc and potash populations.
†$P < 0.005$.
**Expected values were not large enough for chi-square test.

smokers were slightly older than the talc workers. On the average, potash workers who were ex-smokers had worked approximately 2 more years than the talc ex-smokers. In the smoking category, talc workers reported smoking approximately one-half the number of cigarettes per day, but had more pack-years of smoking when compared to the potash workers.

In table 6, the prevalence of symptoms and radiographic findings in talc workers are compared with those of potash workers by indirect standardization. after adjustment for age, height, and smoking differences and stratification by number of years of employment. In the group with more than 15 years of employment, there was no significant difference in prevalence of

TABLE 7

PULMONARY FUNCTION REGRESSION EQUATIONS FOR TALC AND POTASH WORKERS BY SMOKING STATUS

	Talc Workers					Potash Workers				
Variable	No.	Intercept	Age	Height (cm)	(SE)	No.	Intercept	Age	Height (cm)	(SE)
FEV_1										
Nonsmokers	19	-0.243	-0.043:	0.033	(0.127)	241	3.34	−0.026*	0.010.	(0.037)
Ex-smokers	28	-3.51	-0.031	0.047.	(0.079)	286	3.22	-0.034	0.012	(0.037)
Smokers	46	-4.71	-0.052'	0.058*	(0.067)	546	2.60	−0.041*	0.016	(0.025)
FVC										
Nonsmokers	19	-2.63	−0.044*	0.052*	(0.162)	241	2.78	-0.021*	0.018	(0.045)
Ex-smokers	28	-6.73	-0.035:	0.073.	(0.098)	286	2.93	-0.027.	0.018	(0.044)
Smokers	46	−1.94	-0.051	0.049*	(0.087)	546	1.60	*-0.032.*	0.027.	(0.031)
FEV_1 %										
Nonsmokers	19	118.29	-0176	-0.183	(1.63)	241	97.6	-0.282	-0.047	(0.448)
Ex-smokers	28	103.03	-0.124	-0.122	(1.17)	286	101.6	-0.186*	-0.088	(0.488)
Smokers	46	12.07	−0.282*	-0.424.	(0.99)	646	103.0	−0.364*	−0.076*	(0.340)
$\dot{V}max_{50}$										
Nonsmokers	19	-0.900	-0.014	0.040	(0.281)	241	6.91	-0.034.	0.002	(0.090)
Ex-smakors	27	-1.32	-0.016	0.032	(0.264)	286	6.98	−0.059*	0.007	(0.091)
Smokers	44	-11.61	*-0.062'*	0.010	(0.167)	646	6.69	-0.068*	0.008	(0.068)
$\dot{V}max_{75}$										
Nonsmokers	19	2.73	-0.043'	0.002	(0.143)	241	3.05	−0.029.	−0.001	(0.043)
Ex-smokers	27	0.473	-0.028:	0.010'	(0.088)	286	2.90	*-0.033**	0.000	(0.037)
Smokers	44	2.60	-0.041	0.031	(0.067)	646	2.68	−0.044'	*0.003*	(0.026)

Definitions of abbreviations: FEV_1 = one-sec forced expiratory volume; FVC = forced vital capacity; $\dot{V}max_{50}$ and $\dot{V}max_{75}$ = maximal expiratory flow at 50 and 75 Par cant. respectively, of the vital capacity.
*$P < 0.06$.

symptoms. The prevalence of radiographic abnormalities was less than 2 per cent in all groups with less tlran 15 years of employment. The rates were higher in the groups with more than 15 years of employment, but there was little difference in the prevalence of irregular and rounded small opacities. Among the talc workers, pleural calcification was nonexistent in those with less than 15 years of employment and occurred in 5.4 per cent of those with more than 15 years of employment (one case): pleural thickening was 1.6 and 31 per cent, respectively. This compares to rates of 0.5 and 4.4 per cent in potash miners. There was no pleural calcification in the potash population.

Pulmonary function regressions for the talc and potash workers are provided in table 7. Age and height were generally significant in both populations for FEV_1 and FVC. Height was usually not significant for maximal expiratory flow at 50 and 75 per cent of vital capacity ($\dot{V}max_{50}$, $\dot{V}max_{75}$), and usually neither height nor age was significant for $FEV_1\%$ for nonsmokers and ex-smokers. Among the talc workers, ex-smokers had the smallest decrease and smokers had (except for $\dot{V}max_{75}$) the largest decrease in pulmonary function with age. Among the potash population, decreased pulmonary function with age was intermediate in ex-smokers (except for $FEV_1\%$); smokers had the largest decreases.

Mean per cent of predicted pulmonary function and changes in predicted pulmonary function as they relate to estimated cumulative particulate and fiber exposure are summarized in table 8. Average volumes (FEV_1 and FVC) and flows ($\dot{V}max_{50}$ and $\dot{V}max_{75}$) were significantly decreased as compared to potash workers.

When predicted pulmonary function of workers with different estimates of exposure are compared, there is a significant association between estimated exposure (as measured by respirable particulate and asbestifom fibers) and decreased volumes (FEV_1 and FVC), but not to $FEV_1\%$ and flow rates. For example. if a talc worker's average exposure to respirable particulate during one year. was 2 mg per m^3, on the average he experienced a 1.5 percentage point decrease per year in the ratio of observed to predicted FEV_1. Shown in table 8 is a calculated decrease of 7.5 in per cent of predicted FEV_1 for 10 mg per m^3 × years of exposure. If the exposure is 2 mg per m^3 for one year, then the change in per cent of predicted $FEV_1 = -7.5/5 = -1.5$ percentage points. If a talc worker's average exposure to fiber during one year were 5 fibers per ml, the calculated decrease in per cent of predicted FEV_1 would be −13.7/100 fibers per ml × year (table 8), or −0.14/fiber per ml × year. Assuming exposure for one year of 5 fibers per ml, the decrease in per cent of pre-

TABLE 8

OBSERVED PULMONARY FUNCTION OF TALC WORKERS COMPARED TO PULMONARY FUNCTION OF POTASH WORKERS AFTER ADJUSTMENT FOR DIFFERENCES IN AGE, HEIGHT. SMOKING STATUS, AND YEARS OF EMPLOYMENT

	Function				
	FEV_1	FVC	$FEV_1\%$	$\dot{V}max_{50}$	$\dot{V}max_{75}$
Subjects. ne.	93	93	93	89	89
Talc workers, mean % of predicted*	94.5†	94.7†	99.8	85.3†	83.7†
	(1.4)**	(1.3)	(0.7)	(3.2)	(3.3)
Change per 100 fibers/ ml X years††	−13.7†	−12.7***	−0.7	−7.6	−13.8
	(3.4)	(3.3)	(1.8)	(7.9)	(8.3)
Change per 10 mg/m^3 X years††	−7.5***	−6.7†††	−0.6	−4.8	−7.9
	(2.2)	(2.1)	(1.1)	(4.9)	(5.1)

For definitions of abbreviations, see table 7. Per cent predicted FEV_1, FVC, $Vmax_{50}$, end $\dot{V}max_{75}$ = Σ (observed talc value/observed potash value) X 100; per cent predicted $FEV_1\%$ = 100 + (observed $FEV_1\%$ − predicted $FEV_1\%$).

*Hypothesis: moan per cent of predicted pulmonary function is not different from 100.

†$P < 0.0001$.

**Values in parentheses indicate ± SE.

††Hypothesis: change in Per cent of predicted pulmonary function is not different from 0.

***$P < 0.001$.

†††$P < 0.005$.

dicted FEV, is then −0.14 × 5 = −0.69 percentage points per year. The average yearly exposure to particulate was 0.64 mg per m³ and to fibers was 3.14 fibers per ml (table 2). If one assumes these exposure values, the calculated deaease in per cent of predicted FEV, related to particulate and fiber exposure is −0.48 and −0.43 percentage points, respectively, and for FVC the calculated decrease is −0.43 and −0.40 percentage points. Similar decreases occur if years of employment are substituted for fiber and particulate exposure. Talc workers empirically "age" faster (experience a more rapid decrease in FEV, and FVC) than do potash workers.

To assess the significance of pleural thickening. symptoms and pulmonary function of all talc workers with pleural thickening and/or 15 or more years of employment are summarized in table 9. Those with pleural thickening were slightly older than those without it, but only those with extent 2 pleural thickening had worked longer. Workers with extent 2 pleural thickening had significantly increased rates of cough and phlegm, but those with extent 1 pleural thickening had rates lower than the comparable age group without pleural thickening. The prevalence of hemoptysis and dyspnea increased with increasing extent of pleural thickening, but the differences were not large. Mean ratios of observed to predicted FEV_1 and FVC for those with extent 1 and extent 2 pleural thickening were 11 and 15, and 10 and 14 percentage points, respectively, less than those ratios for the group without pleural thickening. Mean FEV_1% was decreased only in those subjects with extent 2 pleural thickening.

Discussion

Any cross-sectional epidemiologic study is beset by the problem of selective survival. This study population consists only of workers presently employed, and there is no information on the health status or work history of ex-workers. Nonrespondents present a similar problem. For example, if all of the workers who did not participate in the study had had no cough or phlegm and had participated, the prevalence of cough would have been decreased from 32 to 24 per cent. Similarly, if all such workers had reported cough and phlegm, the rate would have increased from 32 to 49 per cent.

Several methodologic issues are important in interpreting the data. Even if there had been 100 per cent participation instead of 78 per cent, the size of the population is still relatively small to estimate chronic effects and dose-response relationships. To evaluate the significance of

TABLE 9

SYMPTOM PREVALENCE AND PULMONARY FUNCTION BY PLEURAL THICKENING IN ALL TALC WORKERS WITH 16 YEARS OR MORE OF EMPLOYMENT. PER CENT OF PREDICTED PULMONARY FUNCTION OF TALC WORKERS COMPARED TO THAT OF POTASH WORKERS WITH 15 YEARS OR MORE OF EMPLOYMENT AND AOJUSTED FOR AGE, HEIGHT, AND SMOKING STATUS*

	Extent of Pleural Thickening					
	0		1		2	
Subjects, no.	24		8		6	
Years worked, no. (SE)	21.8	(0.8)	21.6	(2.1)	24.7	(2.7)
Age, years (SE)	48.9	(1.0)	60.9	(1.1)	65.2	(2.0)
Prevalence of rymptomr (95% confidence intervals), % (range)						
Cough	34.6	(18–55)	12.6	(0–50)	88.3	(40–100)
Phlegm	23.1	(9–43)	12.5	(0–50)	66.7	(25–95)
Hemoptysis	0.0	(0–13)	12.5	(0–50)	33.3	(4–75)
Dyspnea (≥ grade 2)	19.2	(7–39)	25.0	(3–65)	33.3	(4–75)
Pulmonary function, mean % predicted (SE)						
FEV_1	91.5	(3.5)	80.9	(3.6)	76.6	(11.1)
FVC	90.4	(3.1)	79.5	(3.7)	75.8	(7.7)
FEV_1/FVC % (actual)	75.3	(1.3)	76.0	(1.7)	70.2	(4.1)
$\dot{V}max_{50}$	86.2	(7.0)	78.1	(10.7)	70.9	(20.0)
$\dot{V}max_{75}$	82.2	(7.5)	66.4	(5.1)	66.7	(19.9)

For definitions of abbreviations, see table 7.
* All talc workers (except one with extent 1 pleural thickening) had 15 years or more af employment.

the health findings and to adjust for confounding variables of age, height, and smoking status in estimating dose-response relationships, potash miners were selected as a comparison group. No control group is perfect, and using these potash miners as a comparison population can be justified in several ways.

First, the measurement of lung function is an unstandardized procedure with respect to equipment, training and proficiency of technicians, number of breaths, and calculation of lung function measurements. These errors of measurement are decreased because the procedures, equipment, and personnel were virtually the same in the control and study populations. The same is true for the roentgenograms and questionnaires. All roentgenogram interpretations were read by certified "B" readers in the same calendar year. Two of the readers for the talc population also read approximately 20 per cent of the potash roentgenograms. The remaining 6 readers read either only talc (one reader) or only potash (5 readers) roentgenograms.

Second, published prediction equations of different smoking categories is either nonexistent or based on small numbers, thereby making smoking adjustments impossible or of questionable validity. Because among our primary interests are the effects of exposure to talc on pulmonary function, adjustments for smoking status, age, and height are necessary. Because smokers' pulmonary function often decreases more rapidly than that of ex-smokers and nonsmokers (table 7), comparing smokers with nonsmokers may produce an apparent association of exposure with age, which in fact may be a smoking-age interaction *(24)*. We therefore compared the pulmonary function of talc workers with the same category of potash workers. Thus, the analysis of the effects of exposure should not be confounded by the effects of smoking. Similarly. we compared respiratory symptoms and radiographic findings of talc and potash workers of similar age, height, smoking status, and years of employment.

Third, talc and potash workers are both from mining populations and are likely to be similar with respect to many potentially confounding variables (e.g., physique, socioeconomic characteristics, education) that could affect the conclusions, but are unrelated to the effect of work exposure. Using a mining comparison group is probably better, lor example, than comparisons with salaried workers in the same company. In the comparison with salaried workers there may be major discrepancies in pay, education, smoking status, nutrition, and ocher socioeconomic factors that by themselves could result in differences in health status.

The potash mines are in the southwestern United States, whereas the talc mine is in the northeastern United States. Although the former are called potash mines, it is not potassium carbonate that is being mined. The potassium ores in the U.S. mines include sylvite, (KCl), carnallite ($MgCl_2 \cdot KCl \cdot 6H_2O$), langbeinite ($K_2SO_4 \cdot 2MgSO_4$), and polyhalite ($K_2SO_4 \cdot MgSO_4 \cdot 2CaSO_4 \cdot 2H_2O$). The most common potash ore is sylvite, which contains approximately 43 per cent KCl and 57 per cent NaCl.

A recent mortality study of potash miners does not indicate increased mortality from respiratory disease in potash workers (25). This finding is not unexpected considering that potash ores, being soluble in water, are deposited largely in the upper respiratoty tract. A morbidity survey of 2 potash mines in Canada revealed a prevalcnce of 4.5 per cent and 3.2 per cent nasal septum perforation in 448 and 63 miners, respectively (26). Other associated symptoms included nose bleeds, soreness, and discharge. Because the potash mines in this study use diesel equipment, there is a potentially hazardous exposure to diesel particulate and nitrogen oxides. Thus, the potash workers are clearly an exposed population.

Therefore. if the "health" of talc workers is worse than that of potash workers, the differences indicate the toxicity of this talc compared to the environmental exposure in potash miners. Conversely, if the effects of this talc arc less toxic than those of potash, one should not assume that there is no risk, but only that talc workers are "better off" (e.g., have fewer symptoms, radiographic abnormalities, etc.) than potash workers. In this instance, these talc workers may still be less "healthy" than if they were not exposed at all.

Many of the epidemiologic studies of persons exposed to talc have been done in the same region as this study (1, 5, 9, 10, 27–30). In the earlier studies, talc workers reported increased complaints of cough and dyspnea. and spirometry measures were consistent with restrictive disease (decreased FVC, normal $FEV_1\%$). Radiographic changes included fibrosis and pneumoconiosis, primarily reported as reticulonodular infiltrates. The presence of pleural plaques and

densities was variably reported (4, 14). The pleura of men exposed to talc were often found on autopsy to have dense fibrotic thickening (13–16). Pericardial calcification was also observed (12).

The prevalence of respiratory symptoms in this study was high for any "healthy" population. Most of the subjects with symptoms were either smokers or ex-smokers, and many populations in the dusty trades report high symptom rates. As discussed previously, the potash comparison group is not an unexposed population, and the symptom rates are more obvious when tlie talc workers are compared to a nonmining, blue-collar population of synthetic textile workers with no known respiratory exposure (table 10) (31).

In specifically comparing the respiratory symptom rates of talc and potash populations, talc workers had higher symptom rates both among those who had worked for less than 15 years and among those with 15 years or more of employment (except for phlegm and hemoptysis in the group that had worked 15 years or more). The comparatively high rates of cough and phlegm in the group working 15 years or more, as compared to the group that had worked for less than 15 years, may have been due to the higher rates of cough and phlegm in the 30- to 39-year age group and probably reflects the higher proportion of smokers in that age group.

Parenchymal fibrotic changes are categorized as small or large opacities (there were no large opacities in this study]. Small, rounded opacities are typically associated with coalworker's pneumoconiosis and silicosis, and small irregular opacities are associated with exposure to asbestos. However, small, rounded opacities with or without irregular opacities may also result from exposure to asbestos (32). Small, irregular opacities also increase with age and cigarette smoking in the absence of exposure to asbestos (33). After adjustments were made for age and smoking status, the talc workers who had worked 15 years or more had a slightly higher prevalence of both rounded and irregular opacities than did potash workers with 15 or more years of work experience.

The greatest difference between the talc and potash workers was the increased prevalence of pleural thickening in the talc workers, among whom nearly one of every 3 workers who had worked 15 years or more had pleural thickening. Pleural thickening can be nonoccupational in origin (e.g., hemothorax, tuberculosis, empyema, broken or fractured ribs), in which case the thickening is usually unilateral (34, 35). Bilateral pleural thickening is generally considered an indication of exposure to asbestos and may be the most common radiographic abnormality (36, 37). The highest prevalence is associated with exposure to anthophyllite and tremolite (35, 38-40). Both of these fiber types were present in the talc of this study. Pleural thickening has been observed both in the presence and absence of parenchymal fibrosis (40–42). Normal pulmonary function tests are expected in persons with pleural thickening (32), although several studies (including this one) have shown an association between decreased FEV, and FVC and pleural thickening (43–46).

A concern about pleural thickening is its possible association with cancer. Bronchial carcinoma is more frequent in men with pleural plaques (47); shipyard workers with pleural tliickcning are at incrcascd risk of developing mesothelioma (47), and there is a case report in which pleural thickening may have been premalignant (48). On the other hand, an association of neoplasia and pleural thickening has not been seen when the exposure is to anthophyllite (49), because tlie incidence of pulmonary and pleural neoplasms is rare in compari-

TABLE 10

COMPARISON OF SYMPTOM RATES IN TALC WORKERS AND SYNTHETIC TEXTILE WORKERS BY AGE AND SMOKING STATUS

Symptom	Status: Non-rmokor (%)	Ex-rmokor (%)	Smoker (%)
Phlegm			
Talc Workorr, age In years			
20–39	18	17	45
40–65	20	11	60
Synthetic textile workers. age in years			
16–39	6	0	12
40–70	9	6	22
Shortness of breath (≥ grade 2)			
Talc workers. age In years			
20–39	e	17	14
40–66	0	14	20
Synthetic textile workers			
15–39	6	5	6
40–70	4	7	9

son to the high incidence of pleural thickening (39).

Except for $FEV_1\%$, mean per cent of predicted pulmonary function was significantly decreased as compared to that of potash miners: these decreases remained after controlling for age, height, smoking, and number of years of employment, and are therefore believed to be the result of occupational exposure. The decreases in pulmonary function associated with exposure to respirable particulate and fibers were significant only for FEV, and FVC. Although $\dot{V}max_{50}$ and $\dot{V}max_{75}$ were also decreased, the variation was quite large.

Despite tlie association of decreased pulmonary function with fiber and particulate exposure and number of years worked, interpretation is difficult. The cumulative exposure is only an index, not a measure of actual exposure. Previous environmental measurements have suggested that in certain jobs, particularly those in the mill, exposure has decreased over the years. Exposure in the mine appears to be more constant. Therefore, estimates of over-all exposure are probably lower than actual exposure.

The prevalence of cough, phlegm, hemoptysis, and grade 2 or grcatcr dyspnea in the 93 talc workers was 32, 31, 8, and 14 per cent, respectively. All of these symptoms were most prevalent in smokers and least prevalent in nonsmokers; none of tlie symptoms showed any tendency to increase with age. The prevalence of these symptoms (except for hemoptysis in tlie group that lrad worked 15 years or more) was higher in the talc workers than in the comparison potash miner population after adjustments were made for age, height, and smoking status. These symptom rates are high for potash workers, because they are exposed to a substance that causes ulceration in the upper respiratory tract. There was one case each of rounded opacities, irregular opacities, and pleural calcification. The overall prevalence of pleural thickening was 11 per cent, but in the age group of 40 years or more, the prevalence was 24 per cent, Among talc workers who had worked 15 years or more, the prevalence was 31 per cent, 7 times higher than in potash workers. Pleural thickening *is* commonly a sign of exposure to asbestos, particularly to anthophyllite asbestos. Those subjects with extent 2 pleural thickening had increased symptoms; per cent of predicted FEV, and FVC wax decreased in those with pleural thickening of extent 1 or greater, as compared to talc workers without pleural thickening. Mean values for FEV, and FVC in talc workers were *95* per cent of those in potash workers after adjustments were made for age, height, smoking status, and numbers of years worked. Flows at *50* and *75* per cent of FVC were *85* per cent of those observed in potash workers. Decreased FEV, and FVC were related to dose; i.e., after adjustments were made for the effects of age, height, and smoking. workers with higher respirable particulate and fiber exposure had a larger deficit in FEV, and FVC than did workers with less exposure.

These findings clearly show increased respiratory symptoms, radiographic abnormalities, and decreased pulmonary function among these talc miners and millers. with some findings related to dose and duration of exposure. Therefore, it is important to follow this population for cause-specific mortality and respiratory morbidity and to determine whether the observed effects continue under improved environmental conditions.

Appendix

Definitions

Cough—Yes to the question. "Do you cough like this on most days for as much as three months each year?"

Phlegm—Yes to the question. "Do you bring up phlegm like this on most days for as much as three months each year?"

Hemoptysis—Yes to the question. "Have you ever coughed up blood?"

Dyspnea—Yes to the question, "Do you get short of breath walking with other people your own age on level ground?"

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