Miller, Diane M. (CDC/NIOSH/EID)

From: Ford,William [wford@nssga.org]
Sent: Thursday, May 31, 2007 8:11 PM
To: niocindocket@cdc.gov.
Subject: FW: Docket NIOSH-099
Attachments: NSSGA Comments on NIOSH Asbestos Roadmap.doc; Table 1 Studies.doc; Mossman_In_Vitro_Effects_Asbestos_vs_Cleavage.doc; Tremolite JA Final Draft with edits c.doc; FINAL REPORT SUBMITED SEPT 1 2004 b.doc; Biology of Cleavage Fragments.pdf; Berman Report.pdf; Pictorial Presentation.pdf

-----Original Message-----
From: Ford,William
Sent: Thursday, May 31, 2007 8:10 PM
To: Dianne Miller (E-mail)
Subject: Docket NIOSH-099

Attached are comments submitted to the docket NIOSH-099 re Asbestos and Other Mineral Fivers: A Roadmap for Scientific Research.

Thank you for the opportunity to comment.

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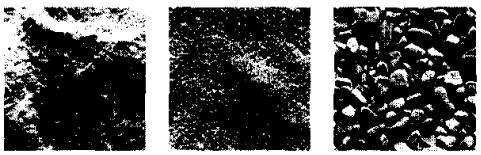

Natural building blocks for quality of life

May 31, 2007

Ms Diane Miller
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By e-mail: dmm2@cdc.gov

RE: Draft-Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research - NIOSH-099

Dear Ms. Miller:

As requested by the National Institute for Occupational Safety and Health (NIOSH), the National Stone, Sand and Gravel Association (NSSGA) is pleased to provide these comments on the above captioned document, hereafter referred to as the "Roadmap". It is hoped that these comments and the attachments will serve to inform the peer-review panel for the Roadmap as well as the NIOSH Mineral Fibers Work Group. The NSSGA also requests that its written and oral testimony and that of its experts, given at the Mine Safety Health Administration's (MSHA) public hearing on June 20, 2002 in Charlottesville, Virginia be included in the NIOSH Roadmap docket. In addition, NSSGA requests that NIOSH incorporate its (National Stone Association) testimony to the Occupational Safety and Health Administration (OSHA) 1986-1992 asbestos rulemaking into the Roadmap docket.

NSSGA, based near the nation's capital, is the world's largest mining association by product volume. Its member companies represent more than 90 percent of the crushed stone and 70 percent of the sand and gravel produced annually in the U.S. and approximately 120,000 working men and women in the aggregates industry. The vast majority of the products from our industry are utilized in public infrastructure projects.

The NSSGA has had a long history of working cooperatively with NIOSH on many occupational health issues over the years and it looks forward to active involvement on this very important issue to our many miners, our industry, its many customers and the nation. These comments are particularly focused on the NIOSH position that cleavage fragments of the asbestos minerals be treated as if they are asbestos when they meet dimensions of an analytical method's counting criteria.

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First, it must be stated that NSSGA does not believe that the Roadmap authors performed a comprehensive search or review of the scientific literature and consequently, the Roadmap rebuilds roads that have already been mapped, paved, and driven on. We are extremely concerned that much of the science involving cleavage fragments was omitted, taken out of context or improperly dismissed when it did not support NIOSH's public position of treating cleavage fragments as if they present an asbestos risk. The aggregates industry, as well as the entire mining industry, has asked NIOSH since 1986 to provide a ***single*** study (cellular, animal or epidemiological) that demonstrates that cleavage fragments (not cleavage fragments mixed with asbestos) present an asbestos-like risk. After 21 years, we are still waiting. As an example of the lack of comprehensiveness in the literature search, in 2005 the NSSGA had the scientific literature involving cleavage fragments contrasted against their asbestos analogs reviewed for cellular toxicity, animal carcinogenicity and epidemiological findings. Out of the nearly 200 papers reviewed pertinent to this subject, the Roadmap references only nine. The attached Table I lists the multitude of studies of cleavage fragments that demonstrate quite clearly that these rock particles do not pose an asbestos-like risk.

There are fourteen *in vitro* studies or reviews of the science that contrast the toxicological outcome between the asbestiform and nonasbestiform habits of the same minerals. Most of these studies involve chrysotile and its nonasbestiform counterpart, antigorite, crocidolite and its nonasbestiform counterpart, riebeckite and amosite and its nonasbestiform counterpart, cummingtonite-grunerite. These studies were conducted in a variety of species and cell types including hamster tracheal explants, hamster tracheal epithelial cells, rat lung epithelial cells, rat and hamster alveolar macrophages, rat pleural mesothelial cells, sheep red blood cells, and Chinese hamster ovary cells. All of these studies clearly show a marked toxicological difference between the nonasbestiform and asbestiform habits of the same minerals.

There are ten *in vivo* studies that also demonstrate significant differences in toxicological outcome (tumor generation) between the two mineral habits of the same mineral. Most of these studies used tremolite asbestos and nonasbestiform tremolite, ferro-actinolite asbestos and nonasbestiform actinolite under various exposure routes including inhalation, intrapleural injection, intrapleural implantation or intratracheal instillation in either rats or hamsters. As in the *in vitro* studies, clear differences are seen between the two mineral habits. Samples with the asbestiform or mixed asbestiform/nonasbestiform mineral habits caused tumors while the nonasbestiform variety of the same minerals did not demonstrate an asbestos-like risk.

There are three groups of workers who have been exposed to the nonasbestiform amphiboles cummingtonite-grunerite (Homestake Gold miners and Minnesota Taconite miners) and nonasbestiform tremolite and anthophyllite (New York Tremolitic Talc miners). Each has at least two or more separate epidemiological studies published in the literature. When these epidemiological studies are contrasted with cohorts that were exposed to either amosite asbestos (asbestiform cummingtonite-grunerite) or tremolite asbestos, the differences again are very clear. The tremolitic talc mine has 50 - 60 percent nonasbestiform tremolite in the deposit, while the Libby, Montana vermiculite mine had only 4-6 % asbestiform amphibole. The health outcomes of both are very different.

The consistency of these health findings in cellular, animal and human studies is very striking and should not be characterized as equivocal or uncertain as the Roadmap authors contend. Many of these studies were not addressed in the Roadmap. Contrasting the findings of these studies with those of their asbestiform counterparts is not difficult to do since many of the cellular and animal studies included both mineral habits to see if there was a difference in outcomes.

With the apparent selective citation of the scientific literature that supports a contentious NIOSH policy position, one has to be concerned if scientific truth is the goal of the research outlined in the Roadmap. We ask for complete transparency and public access to raw data in any research that is conducted under the Roadmap so that independent duplication of studies can be performed if deemed necessary.

The following comments are a section by section review of the Roadmap where there are issues of concern.

Section 1.1 Minerals, Mineral Fibers, and Asbestos

The Roadmap purposely uses terms such as "fibrous" that confuse the morphological distinctions between cleavage fragments and asbestos fibers. Asbestos grows in an asbestiform habit not a fibrous habit. The term asbestiform has very specific meanings (e.g. polyfilamentous growth or bundles showing splayed ends, very high aspect ratio fibers with very thin widths, fibers with parallel sides, etc.). These morphological characteristics are the hallmark properties of asbestiform minerals. NIOSH uses the term "fibrous" interchangeably with asbestiform and then uses it again to describe elongated cleavage fragments that meet an analytical counting criteria leading one to the wrong conclusion that they may indeed be similar in morphological characteristics.

NIOSH makes the following statement in this section: "Mineral fibers that grow in asbestiform habits are clearly of health concern; it remains uncertain whether particles with ***similar dimensions*** from similar minerals, but with nonasbestiform habit, represent a similar health concern" (emphasis added).

With respect to the first part of this statement, it is unknown if all asbestiform mineral fibers are a health concern. There are over 100 minerals that can form in this mineral habit and to say they are all a health concern has no scientific basis. The NSSGA has testified to MSHA that they should treat all ***asbestiform amphiboles*** as if they present an asbestos-like risk because they exist in the same dimensions as regulated amphibole asbestos and their durability is essentially equivalent, however, potency could vary.

With respect to the second part of the statement, NIOSH policy advocates that cleavage fragments with similar dimensions as asbestos fibers be treated equally with respect to risk if they are the same mineral. NIOSH now says it is uncertain, however, its policy still stands. This position/policy clearly demonstrates a lack of mineralogical understanding of the asbestiform and nonasbestiform mineral habits. The six regulated asbestos minerals are asbestiform fibers that are composed of many, many thinner fibrils. A fibril cannot be further divided and is on the order of 0.01 micron in diameter depending on the asbestos mineral. Cleavage fragments do not exist in these dimensions and are not composed of bundles of thinner and thinner cleavage fragments. When looking at the two mineral habits through an optical microscope, such as the phase contrast microscope (PCM) at 400X, all, or the vast majority, of cleavage fragments will be seen while the majority of asbestos fibers and fibrils will not be seen. When an asbestos fiber is seen under PCM, it is very likely a fiber bundle versus a single fibril and there is a real likelihood that the bundle will disaggregate once inside the lungs. In exposures to asbestos, **ALL** of these particles are inhaled not just ones that can be seen and counted under PCM. This is why the NIOSH PCM method provides only an *index of exposure*. In the case of cleavage fragments, this index accounts for nearly the 100% of the particles counted while for asbestos, the index represents a much smaller fraction of what is actually present. By understanding this mineralogical fact, cleavage fragments and asbestiform fibers can ***never*** have the same dimensions in a real exposure circumstance. There will always be a population of asbestiform fibers present that cannot be duplicated in a cleavage fragment exposure. The most recent science (Berman and Crump, 2003), points to these very thin and very long, mostly non-PCM countable fibers as being the most potent fraction of an asbestos exposure (see attached Berman Report). Under the analytical methods that are being used (PCM 7400 and PCME 7402), and this mineralogical difference between the mineral habits, a cleavage fragment exposure will be ***more severely*** regulated than an asbestos exposure.

Section 1.3 Components of Asbestos Definitions for Health Protective Regulations

Asbestos is a specific group of minerals; it does not need multiple definitions. If the asbestos that caused disease in humans is examined and its mineralogical and morphological properties are specifically described, this should be the government's definition of asbestos, not EPA's, NIOSH's ATSDR's etc. Analytical methods

should strive to analyze the minerals that closely match this definition. Asbestos that has caused human disease has been examined mineralogically and morphologically by the world's leading mineralogists. It would be prudent to use their definition.

NIOSH states that it has defined airborne asbestos for over a decade as those particles that when examined using PCM, have: (1) an aspect ratio of 3:1 or greater and a length greater than 5 microns; and (2) the mineralogical characteristics (i.e., the crystal structure and elemental composition) of the asbestos minerals both asbestiform and nonasbestiform. First, the dimensions for counting particles in an analytical method is not a definition of asbestos and the PCM cannot determine elemental composition. By this definition, an amphibole rock of one of these asbestos minerals must be no more than 2.9:1 in length to width ratio and be less than 5 microns long to not be classified as asbestos.

Section 1.2.1 Policy Components of the NIOSH Asbestos Definition

NIOSH is basically saying we don't care what asbestos actually looks like or actually is, we are going to use only our counting criteria and elemental chemistry to define asbestos. The origin of the counting criteria should give NIOSH some concern since it was not based on health factors but on attempting to obtain more reproducible counts among analysts. It was designed to measure asbestos in a known asbestos environment (actually in the asbestos textile industry) not in a mixed dust environment. As Dr. Berman has demonstrated in his report, the PCM definition counts even non-respirable particles and does not count the most potent respirable fibers. This leads to a poor or false dose-response relationship in which risk is then measured. This results in inaccurate and perhaps less protective exposure limits. This "count everything that fits a non-specific or overly broad set of dimensions" results in wrong judgments. An example of this is the Quebec chrysotile miners. Here cleavage fragments of antigorite were counted along with chrysotile asbestos and both were labeled asbestos. Since a chrysotile mine typically has only around 5 % asbestos, most of the particles being labeled as asbestos were actually antigorite. The dose-response curve for these miners differs dramatically from other chrysotile exposed workers with little or no nonasbestiform mineral component.

Section 1.2.1.2 Cleavage Fragments

This section of the Roadmap is the first time NIOSH has attempted to clarify why it recommends that cleavage fragments meeting the PCM counting criteria be regulated as asbestos. NIOSH lists four reasons:

1. "...based on experimental animal carcinogenicity studies of various minerals demonstrating that carcinogenic potential depends on particle length, diameter, and biopersistence. The testimony characterized the evidence as suggesting that neither mineralogic identity nor origin of the particle are critical factors in carcinogenic potential".

NIOSH is not clear on which animal studies it is referring to however it identifies the Davis et al. 1991 study dealing with various samples of tremolite asbestos, tremolite cleavage fragments and mixed tremolite asbestos/cleavage fragment. The Roadmap authors have clouded the distinctions between the various tremolite specimens and their tumorgenesis. In the three clearly asbestiform tremolites, the mesothelioma rates were as follows: Korean tremolite asbestos - 32 meso/33 animals; Jamestown tremolite asbestos - 36 meso/36 animals; Swansea tremolite asbestos 35meso/36 animals. In the clearly nonasbestiform tremolite the following results are reported: Shinness tremolite - 2 meso/36 animals; In the nonasbestiform tremolites with a trace subpopulation of asbestiform tremolite the following results are reported: Dornie tremolite - 4meso/33 animals and Italian tremolite - 24meso/36 after a life span nearly double that of the asbestos exposed animals. The authors of this study report that the Shinness and the Dornie tremolites are unlikely to cause cancer under the inhalation route of exposure. The differences between the asbestiform and nonasbestiform habits of the same mineral are very clear.

There are nine more animal carcinogenicity studies contrasting cleavage fragments against their asbestiform counterparts. All show no tumors above background for the cleavage fragments and nearly 100 % tumors for the asbestos exposures.

2. "...based on results of epidemiologic studies of worker populations with mixed exposures to asbestos fibers and nonasbestiform cleavage fragments or with exposures to cleavage fragments alone. The testimony characterized the evidence for excess lung cancer risk attributable to fiber-like cleavage fragment exposure as "equivocal"".

NIOSH states that it has not relied on the epidemiological studies for their current policy position since the studies only provide "scientifically inconclusive epidemiological evidence". There are three cohorts that inform NIOSH on the exposure to cleavage fragments and when contrasted against asbestos exposed workers the differences are abundantly clear. NIOSH limits its discussion to the New York Talc workers and others will address this aspect more comprehensively than NSSGA. However, there is a significant point that needs to be made. The NY Talc workers have the highest nonasbestiform amphibole (tremolite and anthophyllite) in the world. The ore is between 50 -60 % amphibole and the particles meeting NIOSH's asbestos "definition" are plentiful and have been for many years. The health outcome of the talc miners contrasted against those from Libby, Montana where the asbestiform amphibole is only 5-6% of ore is very telling. The results indicate that nonasbestiform tremolite and anthophyllite do not present an asbestos-like risk.

The two other cohorts are from Homestake Gold Miners in Lead South Dakota and the Taconite miners in Minnesota. In a NIOSH report titled: Industrial Hygiene Report: Homestake Mining Company, Lead South Dakota dated January, 1981, the reported exposure to amosite asbestos" that was actually nonasbestiform cummingtonite-grunerite longer than 5 microns ranged from 0.02 - 4.5 fibers/cc. Even with these considerable exposures to nonasbestiform amphibole, there is no asbestos-related disease reported in this very long exposed cohort. There are two additional studies of the taconite miners also showing no asbestos-related disease. When these are contrasted against amosite exposed workers the difference is hardly uninformative, inconclusive or "equivocal".

3. "The third element was that asbestiform and nonasbestiform minerals can occur in the same area. Thus, determining the location and identification of asbestiform tremolite, actinolite, and anthophyllite within deposits of their asbestiform mineral analogs ***can be difficult***, leading to inadvertent contamination of some mined/quarried commodities by tremolite asbestos, actinolite asbestos, and/or anthophyllite asbestos." (emphasis added)

It is true that whenever the asbestiform mineral habit occurs in nature, the nonasbestiform habit of that mineral is also usually present and usually in a greater concentration. This occurs because the asbestiform minerals are formed under unique circumstances of temperature, pressure and water within the nonasbestiform mineral as the host rock. The converse is not true however. Without these unique geological circumstances and stresses, the nonasbestiform minerals are just plain common rock.

A task that is difficult is not a reason to not do it especially for a research institute and especially for the ramifications of not doing it. Identifying asbestos in a deposit is performed with bulk samples from various sources collected at suspect areas (i.e. faults, folding, intrusions, etc) and either a hand lens or PLM microscope. It has been done for decades. The asbestiform habit of a mineral is readily apparent in bulk samples.

4. "...the lack of routine analytical methods for airborne exposures that can be used to accurately differentiate nonasbestiform cleavage fragments from regulated asbestos fibers ***that meet the dimensional criteria of a fiber when examined microscopically".*** (emphasis added)

This is also not too difficult with the exception that NIOSH makes it impossible because it requires that the same simplistic, all inclusive, arbitrary counting criteria be retained. Keeping the 3:1 aspect ratio and longer than 5 micron length counting criteria without supplementing it with dimensions that would alert one to a possible asbestiform exposure is less protective not more.

In summary, to paraphrase the closing remarks of Dr. Graham Gibbs, who presented at the May 4, 2007 public meeting on the draft *Asbestos Research Roadmap*, "a meeting like this provides such a superficial look at such a complex issue" that "what would be beneficial for NIOSH... would be to focus on very specific topics, "bringing together people who really have spent a lot of their time doing this in the past, so you don't reinvent the wheel." It is important for NIOSH to recognize the work that has been done in this field since it developed its currently held positions in the late 1980s and early 1990s, and move down the road to the current state of the science, and not get sidetracked on the road to nowhere.

Thank you for the opportunity to comment on this important issue.

Sincerely,

[Signed]

William C. Ford, P.E.
Senior Vice President

Attachments

Table 1

In vitro Studies

1	Mossman B. T., and Begin R. (1989). "Effects of Mineral Dusts on Cells, NATO ASI Series on Cell Biology, Springer-Verlag, Berlin, 1989.," Springer-Verlag, Berlin.
2	Woodworth C., Mossman B., and Craighead J. (1983). Induction of squamous metaplasia in organ cultures of hamster trachea by naturally occurring and synthetic fibers. *Cancer Res.* 43, 4906-4912.
3	Marsh J. P., and Mossman B. T. (1988). Mechanisms of induction of ornithine decarboxylase activity in tracheal epithelial cells by asbestiform minerals. *Cancer Res* 48, 709-14.
4	Sesko A., and Mossman B. (1989). Sensitivity of hamster tracheal epithelial cells to asbestiform minerals modulated by serum and by transforming growth factor beta 1. *Cancer Res.* 49, 2743-2749.
5	Mossman B., and Sesko A. (1990). In vitro assays to predict the pathogenicity of mineral fibers. *Toxicology* 60, 53-61.
6	Shukla A., Gulumian M., Hei T., Kamp D., Rahman Q., and Mossman B. (2003). Multiple roles of oxidants in the pathogenesis of asbestos-induced diseases. *Free Rad. Biol. Med.* 34, 1117-1129.
7	Hansen K., and Mossman B. (1987). Generation of superoxide (O2-.) from alveolar macrophages exposed to asbestiform and nonfibrous particles. *Cancer Res.* 47, 1681-6.
8	Janssen Y., Heintz N., Marsh J., Borm P., and Mossman B. (1994). Induction of c-fos and c-jun proto-oncogenes in target cells of the lung and pleura by carcinogenic fibers. *Am. J. Respir. Cell Mol. Biol.* 11, 522-530.
9	Janssen Y., Driscoll K., Howard B., Quinlan T., Treadwell M., Barchowsky A., and Mossman B. (1997). Asbestos causes translocation of p65 protein and increases NF-kappa B DNA binding activity in rat lung epithelial and pleural mesothelial cells. *Am. J. Pathol.* 151, 389-401.
10	Zanella C., Posada J., Tritton T., and Mossman B. (1996). Asbestos causes stimulation of the ERK-1 mitogen-activated protein kinase cascade after phosphorylation of the epidermal growth factor receptor. *Cancer Res.* 56, 5334-5338.
11	Zanella C., Timblin C., Cummins A., Jung M., Goldberg J., Raabe R., Tritton T., and Mossman B.T. (1999). Asbestos-induced phosphorylation of epidermal growth factor receptor is linked to c-fos expression and apoptosis. *Am. J. Physiol. (Lung Cell Mol Physiol)* 277, L684-L693.
12	Goldberg J., Zanella C., Janssen Y., Timblin C., Jimenez L., Taatjes D., and Mossman B. (1997). Novel cell imaging approaches show induction of apoptosis and proliferation in mesothelial cells by asbestos. *Am. J. Respir. Cell Mol. Biol.* 17, 265-271.
13	Wylie A., Skinner H., Marsh J., Snyder H., Garzione C., Hodkinson D., Winters R., and Mossman B. (1997). Mineralogical features associated with cytotoxic and proliferative effects of fibrous talc and asbestos on rodent tracheal epithelial and pleural mesothelial cells. *Toxicol. Appl. Pharmacol.* 147, 143-150.
14	Palekar L. D., Spooner C. M., and Coffin D. L. (1979). Influence of crystallization habit of minerals on in vitro cytotoxicity. *Ann N Y Acad Sci* 330, 673-686.

Table 1

In vivo Studies

1	Davis JMG, Addison J, Bolton RE, Donaldson K, Jones AD, Miller BG. (1985). Inhalation studies on the effects of tremolite and brucite dust in rats. Carcinogenesis. 5: 667-674.
2	Smith WE, Hubert DD, Sobel HJ, Marquet E. (1979) Biologic tests of tremolite in hamsters. In Dusts and Disease. Dement JA, and Lemen RA (eds) Pathotox Publishers, 335-339.
3	Stanton MF, Layard M, Tegeris A, Miller E, May M, Morgan E, Smith A. (1981). Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. J Natl Cancer Inst, 67: 965-975
4	Wagner JC, Chamberlain M, Brown RC, Berry G, Pooley FD, Davies R, Griffiths DM. (1982) Biological effects of tremolite. Br J Cancer 45: 352-360.
5	Davis JMG, Addison J, McIntosh C, Miller BG, Niven K. (1991). Variations in the carcinogenicity of tremolite dust samples of differing morphology. Proceedings of the Collegium Ramazzini Symposium, New York, 1990. Annals of the New York Academy of Sciences; 643; 473-490
6	Coffin, D.L., Palekar, L.D., Cook, P.M. (1983). Correlation of in vitro and in vivo methods by means of mass dose and fiber distribution for amosite and fibrous ferroactinolite. Environmental Health Perspectives, 51: 49-53.Coffin, D.L., Palekar, L.D., Cook, P.M. (1982) Tumorigenisis by a ferroactinolite mineral. Toxicology Letters, 13; 143-150.
7	Pott, F., Huth, F., Friedrichs, K.H. (1974) Tumorigenic effects of fibrous dusts in experimental animals. Environmental Health Perspectives, 9; 313-315. Pott F, Roller M, Ziem U, Reiffer F-J, Bellmann B, Rosenbruch M, Huth F. (1989) Carcinogenicity studies on natural and man-made fibers with the intraperitoneal test in rats. In Non-occupational exposure to mineral fibers, eds Bignon J, Peto J, Saracci R, IARC Scientific Publications No. 90, International Agency for Research on Cancer
8	Davis JMG, Addison J, Bolton RE, Donaldson K, Jones AD, Smith T. (1986). The pathogenicity of long versus short fiber samples of amosite asbestos administered to rats by inhalation and intraperitoneal injection. British Journal of Experimental Pathology. 67: 415-430
9	Ilgren, E. and Chatfield, E. Coalinga Fiber – A short amphibole-free chrysotile. Part 2: Evidence for lack of tumourigenic activity. Indoor Built Environ., 7:18-31.
10	Wagner JC, Chamberlain M, Brown RC, Berry G, Pooley FD, Davies R, Griffiths DM. (1982) Biological effects of tremolite. Br J Cancer 45: 352-360.

Assessment of the Pathogenic Potential of Asbestiform vs. Nonasbestiform Particulates (Cleavage Fragments) in *In Vitro* (Cell or Organ Culture) Models and Bioassays

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Peer Reviewed and Accepted for Publication in Proceedings of the *International Symposium on the Health Hazard Evaluation of Fibrous Particles Associated with Taconite and the Adjacent Duluth Complex*
St Paul, Minnesota
March 30 – April 1, 2003

Abstract

Asbestos fibers are highly fibrous silicate fibers that are distinguished by having a large aspect (length to diameter) ratio and are crystallized in an asbestiform habit that causes them to separate into very thin fibers or fibrils. These fibers are distinct from nonasbestiform cleavage fragments this may appear as thick, short fibers which break along cleavage planes without the high strength and flexibility of asbestiform fibers. Because cleavage fragments of respirable dimensions have generally proven nonpathogenic in animal studies, little data exists on assessing well-characterized preparations of cleavage fragments in *in vitro* models. The available studies show that cleavage fragments are less bioreactive and cytotoxic than asbestiform fibers.

Introduction and Definition of Asbestiform vs. Non-asbestiform Particulates

'Asbestos' is a commercial and regulatory designation for a family of naturally occurring asbestiform fibers. Asbestos fibers are recognized as human carcinogens and also cause pleural and pulmonary fibrosis, i.e., asbestosis in occupationally exposed individuals (Mossman *et al.*, 1990; Mossman & Churg, 1998; Mossman & Gee, 1989). Mineralogical and biological differences exist between various types of asbestos fibers, and much research has focused on the characteristics of fibers that are associated with the causation of lung disease. The different types of asbestos include chrysotile [$Mg_6 Si_4 O_{10} (OH)_8$] , the only asbestos in the serpentine family of minerals, and other types of asbestos classified as amphiboles. These include crocidolite [$(Na_2 (Fe^{3+})_2(Fe^{2+})_3 Si_8 O_{22} (OH)_2$], asbestiform grunerite or amosite [$(Fe,Mg)_7 Si_8 O_{22} (OH)_2$] , anthophyllite [$(Mg,Fe)_7 Si_8 O_{22} (OH)_2$], tremolite [$Ca_2 Mg_5 Si_8 O_{22} (OH)_2$], and actinolite [$(Ca_2 (Mg,Fe)_5 Si_8 O_{22} (OH)_2$]. These formulae are indeed ideal, and natural amphiboles differ to varying degrees from these as the chemical environment, pressure and temperature at the time of formation control the mineral chemistry. Other factors such as shear stresses and directed pressures determine whether or not an amphibole that crystallizes is asbestiform. Although various types of asbestos are different chemically, structurally and biologically, they are common in that they are highly fibrous silicate minerals that are crystallized in an asbestiform habit, causing them to separate into thin fibers or fibrils (Klein, 1993; Veblen & Wylie, 1993). In addition, asbestos fibers are distinguished by having large aspect (length to diameter) ratios, generally from 20:1 or higher for fibers > 5 microns in length. Smaller fibers (<0.5 microns in width) appear by microscopy as very thin fibrils as defined by the American Society of Testing Materials in 1990. In contrast, nonasbestiform cleavage fragments, although sometimes elongated with aspect ratios of >3:1 which can be defined as fibers, have widths much larger than asbestos fibers of the same length. Though the more common nonasbestiform analogs of asbestos share the same, or essentially the same chemical composition, they do not share the same crystal structure (the crystals form or grow differently).

Cleavage fragments of amphiboles lack the tensile strength of asbestos amphiboles and are traditionally regarded by mineral scientists as distinctly different from asbestos fibers, primarily based on their morphology, and lack of strength or flexibility. For example, in the report of the Committee on Nonoccupational Health Risks of Asbestiform Fibers commissioned by the

National Research Council (National Research Council, 1984), cleavage fragments were categorized as distinctive from asbestiform fibers, i.e.:

"CLEAVAGE refers to the preferential breakage of crystals along certain planes of structural weakness. Such planes of weakness are called cleavage planes. A mineral with two distinct cleavage planes will preferentially fracture along these planes and will produce ACICULAR fragments. Minerals with one cleavage plane produce PLATY fragments and those with three or more cleavage planes yield POLYHEDRAL fragments..... Cleavage cannot produce the high strength and flexibility of asbestiform fibers" (National Research Council, 1984).

These definitions were also recognized by the members of the panel of the Health Effects Research-Asbestos Research in their report on Asbestos in Public and Commercial Buildings (Health Effects Institute-Asbestos Research, 1991). Because epidemiologic and animal studies have not suggested that nonasbestiform amphiboles or cleavage fragments are pathogenic or biologically active, they have not been used in many *in vitro* models, except as negative or nonpathogenic controls for testing of asbestos fibers. Moreover, the results of numerous epidemiologic, animal, and *in vitro* studies, have led scientists to conclude that short asbestos fibers (< 5 microns in length) are inactive or much less active biologically than long, thin asbestos fibers (ATSDR, 2003; Health Effects Institute-Asbestos Research, 1991). Thus, it is unlikely that cleavage fragments of respirable dimensions (i.e., less than 3 microns in diameter) will be pathogenic or targeted extensively for *in vitro* fiber testing in the future. The results of limited work with these minerals from our laboratory and others are summarized below.

Advantages and Caveats of *In Vitro* Mineral Studies

In vitro studies have been used historically to compare the effects of different types of minerals on cells or organ (explant) cultures (Mossman & Begin, 1989). Regardless of cell type, asbestos fibers, in comparison to a variety of other nonpathogenic, synthetic or naturally occurring fibers (glass, cellulose, etc.) or particles, have been most biologically active in these models. In addition to elucidating the properties of minerals (size, fibrous morphology, surface charge, chemical composition, etc.) that are associated with toxicity (cell injury or death), DNA damage, proliferation and/or alterations in cell function that may be predictive of their pathogenic potential, *in vitro* studies have shed light on the complex features of bioreactive minerals that may be important in reactions with cells and their ability to cause disease. Cell and organ culture models are also much more inexpensive than animal testing. Thus, they have been suggested as screening tools for new synthetic fibers developed for industry.

However, there are also caveats that must be recognized in *in vitro* work with minerals. First, dependent upon the cells used in these models, cell type and species-specific responses may exist. Thus results from lab to lab working with the same mineral might be inconsistent. Although the most appropriate *in vitro* cell types to use in these models are normal cells of respiratory tract origin, i.e., epithelial or mesothelial, these are notoriously difficult to isolate and maintain in a differentiated state for prolonged periods of time. It also should be acknowledged that concentrations of minerals used in short term *in vitro* assays, where weighed amounts of fibers or particles are precipitated on cells, do not mimic normal clearance patterns and long-

term dissolution patterns after inhalation into the human lung, factors that are important in dosimetry and disease causation (Mossman *et al.*, 1990). Lastly, different minerals are generally evaluated in *in vitro* studies on an equal weight basis, which might be misleading based on the facts that different weights of dissimilar fiber types or particles may reflect vastly different total numbers of fibers and surface areas. Regardless of these caveats, however, *in vitro* studies have helped to establish mechanisms of fiber carcinogenesis and differentiated between responses to asbestos fibers and nonasbestiform particles.

Studies Using Tracheal Explants

In comparison to cell cultures, tracheal explant cultures can be maintained for weeks in a differentiated state in which the respiratory epithelium is maintained in a normal, mucociliary phenotype. We have used this model to show that crocidolite and chrysotile fibers (asbestos) and long glass fibers cause squamous metaplasia, a reversible but often premalignant lesion, and increased DNA synthesis, a signature of injury and proliferation of fibers that might be important in tumor promotion and progression and/or repair (Woodworth *et al.* 1983). In contrast, the non-fibrous mineral analogs of these asbestos types, riebeckite (similar in chemistry to crocidolite) and antigorite (similar in chemistry to chrysotile) failed to induce these changes at a range of concentrations and exposure times. Though a number of these riebeckite and antigorite particles were elongated, they were thick, short single crystal cleavage fragments. These studies highlight the importance of fibrous geometry, crystal growth and aspect ratio in bioreactivity.

Studies Using Cell Types of Lung or Pleural Origin:

The antigorite and riebeckite preparations used in the Woodworth et al. 1983 study above were also evaluated in cell cultures of hamster tracheal epithelial cells (HTE) for their ability to induce ornithine decarboxylase (ODC), an enzyme associated with cell proliferation and tumor promotion in mouse skin models of cancer, with asbestos fibers (Marsh & Mossman, 1988). These studies showed that crocidolite and chrysotile (fibers> 10 microns in length) fibers stimulated ODC, but neither of the two nonasbestiform (cleavage fragment) preparations were bioreactive. Subsequent studies revealed that both antigorite and riebeckite were less potent than crocidolite (asbestos) in stimulating survival or proliferation of HTE cells in a colony-forming assay (CFE) in which proliferation was measured directly over a 7 day period in low-serum containing medium (Sesko & Mossman, 1989). Experiments in HTE cells also revealed that antigorite and riebeckite were less cytotoxic than crocidolite or chrysotile to these cells when release of radioactive chromium, a marker of cell damage, was measured (Mossman & Sesko, 1990).

Another exciting development in our laboratory was the observation that crocidolite (asbestos) generated Reactive Oxygen Species (ROS) which have been linked to cell injury, inflammation, mutagenesis, and the development of many cancers, (Shukla *et al.* 2003). In a study in which we isolated alveolar macrophages (AMs) from rodents and measured release of the ROS, superoxide, after addition of crocidolite and riebeckite (nonasbestiform analog of crocidolite) to these cells, as well as nonasbestiform mordenite (note that all particle diameters and/or fiber

lengths were measured by scanning electron microscopy), the nonasbestiform particles were taken up, i.e., phagocytized, by cells, but were much less bioreactive than crocidolite at comparable concentrations, only causing release of superoxide at concentrations 5- to 10-fold higher than asbestos in the rat cells and never causing significantly increased release in the hamster macrophages (Hansen & Mossman 1987). It should be emphasized that lung epithelial cells, mesothelial cells and fibroblasts are target or progenitor cells of lung cancers, mesotheliomas and pulmonary fibrosis, respectively, and that alveolar macrophages are inflammatory cells that first encounter asbestos and may contribute to and/or alternatively, be important in lung defense from pathogenic minerals. This is an important question that has yet to be resolved by scientists. However, alveolar macrophages are studied because these cells accumulate in the lung at sites of deposition of inhaled particles or fibers and responses of alveolar macrophages to dusts are known to produce ROS after phagocytosis of minerals.

In recent years, we have used riebeckite and antigorite preparations as nonasbestiform control minerals to determine whether early response proto-oncogene (*fos/jun* cancer- causing genes) (Janssen *et al.* 1994) or signaling pathways leading to activation of these genes (Janssen *et al.* 1997; Zanella *et al.* 1996; Zanella *et al.* 1999) are selectively induced by asbestiform, cancer-causing fibers (crocidolite and chrysotile asbestos, erionite) in HTE cells, rat lung epithelial cells (RLE) and isolates of normal rat pleural mesothelial cells (RPM). These studies have consistently revealed that these nonasbestiform minerals are inactive, regardless of endpoint. Moreover, they are incapable, in contrast to asbestos fibers, of causing alterations in cell proliferation or death in RPM cells (Goldberg *et al.* 1997).

Comparative studies in HTE and RPM cells with well-characterized mineral samples of crocidolite and chrysotile (asbestos) and 3 mineral samples containing various proportions of fibrous talc have also been useful in illustrating fundamental differences in response to asbestos fibers and fibrous talc preparations based on various dose parameters including equal weight concentrations, equivalent surface areas and numbers of fibers > 5 microns in length (Wylie *et al.* 1997). Using the CFE assay described above to document proliferative potential (increased numbers of colonies as compared to untreated control cells) or cytotoxicity (decreased numbers of colonies as compared to untreated control cells), exposure of RPM cells to both asbestos types, but not fibrous talcs, elicited cytotoxicity in RPM cells that was more striking at higher weight concentrations of asbestos. In contrast, HTE cells proliferated in response to asbestos at nontoxic lower concentrations, but not to fibrous talcs. Since cell responses could not be correlated directly with the presence of mineral fibers > 5 microns in length or aspect ratios, mineral type rather than fiber length *per se* appeared to be a more important determinant of bioreactivity. This study suggests that while fiber morphology is important, it is not the only factor important in biologic responses. This has also been noted by critics of Stanton's famous pleural implantation studies in rats (Oehlert, 1991) (Wylie *et al.* 1987).

Studies Using *In Vitro* Models of Non-Respiratory Cells:

As detailed above, cytotoxicity testing in cells of non-respiratory origin was used decades ago to determine differences in fiber-cell interactions and the ability of asbestos fibers to induce cell

death or lysis. Since dead cells can not give rise to cancers, the extrapolation of these results, especially to mechanisms of cancer causation, is questionable. However, studies by Palekar and colleagues (Palekar *et al.* 1979) used sheep red blood cells (RBC) and Chinese Hamster Ovary (CHO) cells to test the hemolytic potential and cytotoxicity of 4 samples of cummingtonite-grunerite including amosite asbestos fibers, and 3 other samples of various crystallization habits, predominantly asbestiform cummingtonite, acicular cummingtonite ,and acicular grunerite. At the same surface areas of dose, these minerals were found to be hemolytic and cytotoxic in this same order, again showing the increased potency of amphibole asbestiform fibers.

Summary and Conclusions

The results summarized above represent a large body of work showing that nonasbestiform minerals are less potent than asbestos fibers in a number of *in vitro* bioassays. In most assays, these cleavage fragments or non-fibrous minerals are virtually inactive. These observations have been incorporated into the conclusions of several panel reports that should be recognized by regulatory agencies. For example, the HEI-Asbestos Research Panel (page 6-75, 1991) concluded:

"Good evidence exists that thick fibers (>2 to 3 microns in diameter) are less harmful than thin fibers".

"Support for the importance of fiber length in the production of biological effects has been obtained from the use of non-fibrous analogues of asbestos and other fibers. In general, these materials produce no detectable biological effects, or do so only at high dose levels"

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FINAL DRAFT

Experimental Studies of Asbestos and Non-Asbestos Tremolite.

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Experimental Studies of Asbestos and Non-Asbestos Tremolite.

Preamble

There has been a certain amount of confusion about much of the basic terminology involved with asbestos over the years so it may be appropriate to try to establish what is meant by these terms in this document.

The glossary in 'The Health Effects of Mineral Dusts' produced by The Mineralogical Society of America (Guthrie & Mossman 1993) has the following definition: 'Asbestos is a term applied to asbestiform varieties of serpentine and amphibole, particularly chrysotile, "crocidolite", "amosite", asbestiform tremolite, asbestiform actinolite, and asbestiform anthophyllite. The asbestos minerals possess asbestiform characteristics'. This must be extended now to include the asbestiform varieties of winchite, richterite and edenite (or an other asbestiform amphibole).

The glossary also describes asbestiform as: 'an adjective describing inorganic materials that possess the form and appearance of asbestos. Asbestiform is a subset of fibrous, where asbestiform implies relatively small fiber thickness and large fiber length, flexibility, easy separability, and a parallel arrangement of the fibers in native (unprocessed) samples. Often, asbestos fibers occur in bundles, i.e., they are often polyfilamentous'. From this it is clear that not all asbestiform minerals are asbestos, and that not all fibers or fibrous minerals are asbestiform.

When applied to a mineral, the term 'fibrous' is applied when it 'gives the appearance of being composed of fibers, whether the mineral actually contains separable or not' (Zoltai 1981).

The term 'fiber' has a large number of operational definitions and uses. In the general sense it is applied to a substance with an elongate morphology. The term usually implies that the smaller dimension i.e. diameter, is very thin in the sense that, for example, despite an elongate morphology, a pencil would not be described as a fiber.

A convention has developed that a fiber is any particle with an aspect ratio greater than 3:1. This stems from the fiber definition in the early UK and US fiber counting methods; it could just as easily have been 5:1 or 10:1. In using these methods, the microscopist had to make a decision to count or not count a particle depending on whether the shape and size met certain size criteria. By convention, for a fiber to be counted it has to have an aspect ratio of greater than 3:1 and a length greater than 5 microns (and in some rules a diameter less than 3 microns). The decision was more easily and consistently made for particles just higher or lower than 3:1, and much more difficult with the higher aspect ratio thresholds. Similarly the inclusion of the abundant fibers short (less than 5 microns length) in the count would have made it much less consistent or reliable. Since the aim of the fiber counting rules was to try to improve consistency for individual counters and between counters the aspect ratio and length cut-off chosen was that which produced that consistency and not the ratio or length that might have had greater toxicological significance. This 'convention' has nothing to do with a definition of asbestos per se; it was only a rule for microscopists in the fiber counting method.

Many non-asbestos particles, including nonasbestos amphiboles and other minerals can have aspect ratio greater than 3:1, but that does not make them 'asbestos' even though they are technically fibers. However, it does mean that they would be counted *as if they were an asbestos fiber* when seen in the course of a count of fibers in a membrane filter sample of airborne dust. In addition, a pure asbestos will produce asbestos dust particles that mostly have aspect ratios greater than 3:1, but it will also produce particles that have lower aspect ratio. That does not mean that these low aspect ratio particles are not asbestos, but simply that they would not be counted as asbestos in the membrane filter method. The same is true for asbestos fibers shorter than the 5 micron cut-off.

The adoption by some scientists and agencies of the 3:1 aspect ratio and 5 micron length as being in some way a definition of asbestos has no scientific basis whatsoever. It has been useful

however, in that the improved expression of the exposure in the workplace to airborne fiber dust permitted better epidemiological correlations of exposure with disease.

Introduction

The number of *in vivo* experimental studies to examine the toxicological effects of dusts derived from tremolite and tremolite asbestos is relatively limited. The study by Davies et al (1985) remains the only inhalation experiment to be carried out using tremolite asbestos. Previously, Smith et al (1979) used a variety of tremolite types in intrapleural injection into hamsters, Stanton et al (1981) used two different tremolites in intrapleural implantations in rats, and Wagner et al (1982) used three different tremolites in intrapleural injection into rats. Later, Davis et al (1991) used six tremolites of different morphology in intraperitoneal injections into rats. If the actinolite and ferro-actinolite amphiboles are included the number of studies increases slightly but is still small. Coffin et al (1978, 1981, 1983) used a fibrous ferro-actinolite in intrapleural injection and intratracheal instillation into rats. Pott et al (1974, 1988) reported results from intraperitoneal injection of a granular actinolite and (later) an asbestiform actinolite. A lifetime (including exposure to the dams and gavage during the neonatal period) oral ingestion study (1% in the diet) in rats of 'blocky' tremolite failed to show evidence of carcinogenic activity (NTP 1990).

Other studies might also be considered as contributing to the debate about the relative carcinogenicity of amphiboles and their asbestiform varieties. The inhalation and intraperitoneal injection experiments of Davies et al (1986) with long and short fiber amosite, the inhalation studies of various sized chrysotile (Ilgren and Chatfield, 1998, McConnell et al 1984, Wagner et al 1984), and the cell studies of Donaldson et al (1989, 1991) Brown et al (1991) were aimed at understanding the relative importance of fiber length in carcinogenicity and fibrogenicity. Other mechanistic studies such as those by Kane (1991), and reviews such as those by Lehnert (1991), Jaurand (1991), Oberdorster (1991) among others also have a bearing on the understanding of

the different reactions observed between asbestos particles and other particles with the same mineral chemistry but different morphology.

Mineralogy

The amphibole mineral family is characterized by a crystal structure described as a double chain of silicon oxide tetrahedra that is common to all members of the family. Within this chain structure are between 7 and 8 metal cations among which there is a wide range of permitted variation that still maintains the basic crystalline form (Deer et al 1967). This has produced the large number of named variants or species within the family (Leake et al 1997).

In addition to the chemical variability there is further variability in what is known as the 'crystal habit' of the minerals that may arise independent of chemistry (Dorling & Zussman 1987). The habit of a mineral is a description of the way that the crystals are commonly formed, and might otherwise be described as morphology.

The commonest crystal habit for any amphibole is that called prismatic; elongate prisms with a lozenge shaped cross section that grade one way into short stocky prisms and in the other way into fine needle-like crystals or ultimately fine hair-like crystals (sometimes known as byssolite). The prismatic habit is the normal form for amphiboles in igneous and metamorphic rocks and is very widespread throughout the continental crust of the planet. Some amphiboles are also found in the habit that is termed asbestiform; this means that they have crystallized as bundles or matted masses of extremely fine fibers. The appearance of these forms usually implies some sort of secondary modification such as shearing and faulting or hydrothermal alteration. These may be found in three types of geological situations; 1) cross-fiber veins where the fibers have filled planar fissures, such as in the asbestos mines of South Africa; 2) in shear planes where slip fiber has formed in the plane of movement of a fault or shear plane; or 3) as disseminated fiber formed by metasomatic alteration, such as in Libby, Montana.

The differences in the manner of the formation of asbestos amphiboles, compared to the prismatic and other forms, have led to subtle differences in the detail of the crystal structure that, while not sufficient to warrant a different mineral name, nevertheless lead to profound differences in physical properties. The commercial exploitation of the asbestos amphiboles depended upon these properties, including their capacity to be readily split into long, thin fibers with high tensile strength.

These physical differences also lead to differences in the size distributions of dusts formed when the minerals are crushed, and arguably properties which impact the pathogenic potential of the material, especially their carcinogenic properties when these dusts are inhaled.

Cleavage planes are planes of relative weakness along which certain minerals tend to fracture and are determined by the crystal lattice geometry. Mica, for example, is described as having a single perfect cleavage because it splits easily along the silicate sheet structure. Calcite has three perfect cleavages that form perfect rhomohedra when the mineral is crushed. Amphiboles have two sets of cleavage planes at 126° to each other and parallel to the long axis of the crystals (and parallel to the dominant prismatic crystal faces). In addition they also have a cleavage plane on (100).

Figure 1. Typical prismatic crystal form of amphibole showing the main cleavages and prism faces.

These are not perfect cleavages; they are not persistent across or along the crystals and tend to be more widely spaced than the separations between the fibers of the asbestos amphiboles. The prismatic amphiboles, including byssolites, have relatively low tensile strength and the thin needle-like crystals fracture easily across the length. They also fracture along cleavage planes that are parallel to the length of the crystals. When prismatic amphiboles are crushed a relatively small proportion of the fragments formed are elongate with faces determined by the cleavages along which the crystal fractures. These elongate particles will often meet the regulatory size criteria for an asbestos fiber within the asbestos legislation, but differ from the true asbestos fibers in critical ways. The cleavage fragment fibers often show the typical lozenge shape cross

section as determined by the cleavage faces, at 126° degrees to each other. The cleavage fragment fibers tend to be thicker than true asbestos fibers because of the spacing of the cleavage planes, and for any given length the cleavage fragment fibers are roughly twice as thick as asbestos fibers. Very few, if any, of the cleavage fragment fibers longer than 10 microns will have diameters less than 1 micron. With cleavage fragment fibers the width distribution is much broader and width increases with length so aspect ratios tend to be lower and of narrower distribution. In overall size distributions the asbestos fibers have a very narrow width distribution and the width of fibers is largely independent of length. As a result, the aspect ratio of fibers increases with length.

Since the cleavage fragments and asbestiform fibers tend to be morphologically defined by somewhat different crystal surfaces it is tempting to speculate that this may go some way to explaining the apparent differences in toxicological properties as described below.

Inhalation experiments

Davis et al (1985) exposed rats (SPF male Wistar) to a commercially mined tremolite asbestos form South Korea at concentrations of 10 $mg.m^{-3}$, around 1600 fml^{-1}, for 12 months. Having produced very high levels of pulmonary fibrosis as well as 16 carcinomas and two mesotheliomas (rarely found in rat inhalation experiments) among the 39 treated animals the tremolite asbestos was described by them as the most dangerous mineral ever studied at the Institute of Occupational Medicine, UK.

The Korean tremolite asbestos is the same one used later in the intraperitoneal injection experiments (Davis et al 1991) for which full size distributions of the respirable dust were given, as shown in Figure 2.

Figure 2 Size distribution of fibers in elutriated respirable dust of the Korean Tremolite Asbestos

The important feature of the size distribution of the Korean tremolite asbestos is that the vast majority of fibers are less than 0.5 □m in diameter and shorter than 5 □m in length, which is typical of asbestos amphiboles. The geometric mean diameter for Korean tremolite asbestos fibers longer than 0.4 □m was 0.24□m (SD 1.6) and the mean length was 1.97 □m (SD 2.11) which are somewhat longer and thicker than airborne fibers in crocidolite mining (GM diameter 0.076 □m, GM length 0.98 □m, Hwang & Gibbs 1981).

The high carcinogenicity of the Korean tremolite asbestos was attributed to the much higher airborne fiber concentration for fibers longer than 5 □m (1600 fml^{-1}) which was almost twice that of the UICC amphiboles at the same 10 mgm^{-3} dust mass concentration used (amosite 550 and crocidolite 860 fml^{-1}, Davis et al 1978). This also is a reflection of the finer diameter of the Korean tremolite asbestos.

Injection and Implantation Experiments

Smith et al (1979) injected a range of tremolites and tremolitic talcs intrapleurally into hamsters at doses of 10 mg and 25 mg. The samples were identified as follows:

Table 1 summary of the samples and results of the toxicological testing of Smith et al (1979)

Sample Number	Descriptor	Tumor Incidence		Composition
		25 mg dose	10 mg dose	
14	Tremolitic talc New York State,	0/35	-	50% non-asbestos tremolite
275	Tremolite selected from NY Tremolitic talc	0/31	0/34	95% non-asbestos tremolite
31	Tremolitic talc, unspecified location in W. USA	6/30	1/42	90% tremolite, possibly asbestiform
72	Asbestiform tremolite, unspecified location	5/23	3/13	95% tremolite asbestos
72N	As for 72	11/26	6/25	As for 72

The samples used by Smith et al and described as asbestos or asbestiform produced higher levels of fibrosis and numbers of mesotheliomas in the hamsters than those described as tremolite or tremolitic talc.

Campbell et al (1979) examined some of the tremolites used by Smith et al and described two of the tremolites (275 and FD72) in more detail. Even though their description is not up to modern standards in terms of the size distribution data presented, the images of the fibers clearly show FD27 to be asbestos and 275 to be a prismatic amphibole. This is reflected in the numbers of fibers of length > 10 □m and diameters less than 1 □m in the former, and their absence in the latter. Similarly 17% of all particles in the asbestos tremolite had aspect ratios greater than 20:1 while the prismatic tremolite had none.

Tremolite 14 (FD 14) was later evaluated by Wylie et al (1993) and confirmed to be a tremolitic talc with very few tremolite fibers in the size ranges longer than 5 □m and less than 1 □m diameter.

This study was criticized for being deficient in a number of ways (Federal Register, 1992). In particular, the fiber size measurements and fiber characterizations were found to be inadequate for the purposes of identification of the materials as asbestos tremolite or prismatic tremolite. The later characterizations by Campbell and by Wylie improved on the original ones and the classifications of the mineral types appears to have been sound. The higher carcinogenicity of those materials described as asbestiform compared to those of tremolitic talc or non-asbestos tremolites is without doubt.

Wagner et al (1982) used a tremolite from the California talc deposits, a prismatic tremolite from Greenland and a tremolite asbestos from Korea (probably the same one as in Davies et al 1985) for a series of intrapleural injection experiments with SPF Sprague-Dawley and Wistar rats and a range of *in vitro* tests.

The value of the Wagner et al (1982) injection experiments was impaired by the poor survival rates as a result of infection of the positive control animals injected with crocidolite. Nevertheless, the asbestos form was the only one the three tremolites that showed carcinogenic activity producing 14 (30%) tumours in 47 rats. Neither of the others produced any tumours in the 31 and 48 rats used. The fiber size data as presented are not amenable to numerical evaluation, but it is clear from the published diagrams that the asbestos tremolite contained many more fibers longer than 10 μm, and indeed the non-asbestos forms had either no fibers at all in that size range (Sample A California) or very few (Sample B, Greenland).

The similarity of the size distribution of tremolite C to that of the Davis et al (1991) tremolite asbestos is obvious.

The in vitro tests used by Wagner et al, including mouse peritoneal macrophage LDH and BGL release, cytotoxicity to V79-4 cells and giant cell stimulation with A549 cells confirmed the relative toxicity of the different tremolite morphologies in vivo. So, while the study remains flawed by the poor survival of the positive controls it is nevertheless useful in that it reproduces the general findings of Smith et al (1979).

Stanton et al (1981) described a series of 70 experiments where a wide range of different fibers were implanted at doses of 40 mg in hardened gelatin on to the left pleural surface of Osborne-Mendel rats by thoracotomy. It should be noted that in contrast to intrapleural or intraperitoneal injection, the use of the "hardened gelatin" exposure technique literally holds the fibers in contact with the target tissue (pleura) and does not allow for potential macrophage phagocytosis and clearance of the particles. Because of this, this technique is probably the most sensitive of all of the exposure methods used for assessing the potential carcinogenicity of fibers. Stanton used two tremolite asbestos samples from the same lot, described as 'in the optimal range of size for carcinogenesis' and 'distinctly smaller in diameter than the tremolite fibers used by Smith et al' (1973). As they anticipated the two tremolites produced mesotheliomas in 21 and 22 animals out of the 28 used, with a 100% tumour probability. The tremolites contained very high numbers

of fibers in the 'Stanton' size range (>8 μm L and <0.25 μm D) with $1.63.10^{8}$ and $2.76.10^{7}$ respectively in each dose for tremolites 1 and 2. In addition, the talc No 6 in the Stanton study was actually a New York State tremolitic talc (Wylie et al 1993) with 40-50% non-asbestos tremolite, in fact the same material as used by Smith et al (1979) and identified as FD 14. In contrast to the two tremolite asbestos samples this material produced no tumours.

The general relationship between the probability of developing a tumour in these experiments and the common logarithm of the number of fibers > 8 μm L and less than 0.25 μm D per microgram of implanted dust was highly significant (Figure 3).

There were however a number of problematical experiments in the Stanton series where tumours developed with no fibers in the critical size range, and where no tumours had developed even with large numbers of critical fibers present. This may be explained by the hardened gelatin technique as noted previously. Also, some of these results were attributed to large numbers of fibers with sizes close to the critical range, and others to problems of clumping and fragmentation in the fiber preparations for TEM analysis

Figures 3 and 4 show the general relationships developed by Stanton between the numbers of fibers per microgram in the dose and the probability of tumour development. The statistical relationships between the fiber numbers in the different sets and probabilities of tumour development have not been evaluated but the diagrams show that the correlation for the shorter classes of fiber is much weaker than that for the longer fibers. It is is reasonable to suggest that there must be more short fibers per microgram in the short fiber dusts than in the longer fiber dusts so the poorer correlation for short fibers is, if anything, even more indicative of their lack of importance in tumour development.

Figure 3 The probability of fiber generating a tumour compared to the log of numbers of fiber per microgram longer than 8 microns with diameter greater than or equal to 0.25 microns. This is the same data as in Stanton et al (1981).

Figure 4 Probability of fibers generating mesothelioma compared to the numbers of fibers per microgram in dose within the size range of 4 – 8microns long with diameters in the range 0.01 – 1.5 microns. Data from Stanton et al (1981)

The size distributions given in Stanton et al (1981) do not make it easy for full comparison with other size distributions of known asbestos minerals because the size classification was relatively crude and the method of exposure (hardened gelatin) was unique. The two tremolites he used do however have significant numbers of long fibers with diameters less than 0.5 μm so their identification as asbestos is reasonable. The size distributions are somewhat unusual for pure asbestos as is seen in Fig 5 which shows Tremolite 2 to have a bimodal distribution which suggests that it is actually a mixture of tremolite asbestos and prismatic tremolite. Such an occurrence in tremolite asbestos formations is not uncommon.

Figure 5 Length and diameter distribution of Tremolite 2 from the experiments of Stanton et al (1981) showing the bimodal distribution of the fibers. Based upon the Stanton data.

Wylie et al (1993) re-examined Tremolite 1 and 2 as well as Talc 6 that were used in the Stanton studies. They state that Tremolites 1 and 2 are the same material, a tremolite asbestos from California, with all the characteristics of commercial asbestos. The two size distributions given by Stanton differ somewhat but they are similar and have the appearance of a mixed asbestos – prismatic fiber assemblage.

In contrast, the size distribution of Stanton's Talc 6 shows the much thicker, shorter distribution (Figure 6) typical of a prismatic tremolite fiber population even though it consists of only 40-50% Tremolite. This talc, or tremolitic talc, was reported by Wylie et al (1993) as being identified in Stanton's laboratory notes as Nytal 300. Pure Talc is a specific mineral with a closely defined chemical composition and crystal structure. Commercial producers however

often named their products as 'talc' even Though they contained less than 50% of the mineral talc.

Figure 6 Size distribution of Talc 6 using the size data from Stanton et al (1981)

Davis et al (1991) used six tremolites of differing morphologies in a series of intraperitoneal fiber in saline injection experiments with male SPF Wistar rats. These were identified as follows:

1. Tremolite asbestos from Jamestown, California;
2. Tremolite asbestos from Korea;
3. Tremolite asbestos from National Coal Board Laboratory, Swansea
4. Tremolite, long needle-like crystals from Ala di Stura, N. Italy
5. Tremolite, short needle-like crystals from Dornie, NW Scotland
6. Tremolite, prismatic crystals from Shinness, N. Scotland

The tremolite from Korea was the same material as was used in the earlier tremolite inhalation and injection experiments by Davis et al (1991). The fiber size distributions were assessed by counting and measuring 300 fibers of all sizes in a known weight of sample deposited on to a polycarbonate filter using Scanning Electron Microscopy. At 10,000 times magnification the effective minimum diameter that is visible is 0.1 μm, so the effective minimum length of a counted fiber was 0.4 μm. This was followed by the counting and measurement of a further 100 fibers longer than 5 μm. The data were combined to calculate the numbers of fibers in a series of length and diameter classes in the 10 mg dose administered to the rats. In addition, the numbers of particles (Aspect ratio less than 3:1) were also counted and estimated for each dose.

The rats were allowed to live to their out their full life span until they showed signs of debility or tumour formation. Statistical analysis of the times at which death from mesothelioma occurred was used to calculate survival curves and these were correlated with the fiber doses received by each animal.

Table 2. Results of the Davis et al (1991) intraperitoneal injection experiments with tremolites of differing morphologies.

Tremolite Source	No of animals	No of Mesothelioma	Median survival time (days)	Relative hazard	No(*10 ^{6}) of fibers in dose injected	No(*10 ^{6}) of fibers, length >8, diameter <0.25
California	36	36	301	346939	13430	121
Swansea	36	35	365	183673	2104	8
Korea	33	32	428	51020	7791	48
Italy	36	24	755	1020	1293	1
Dornie	33	4	*	6.4	899	0
Shinness	36	2	*	1	383	0

* Insufficient animal death for calculation

Table 2 shows the relative hazard ranking, the numbers of mesotheliomas and the fiber numbers in the doses. The relative hazard was derived from Cox's proportional hazards model (Cox & Oakes 1984) and is a function of the numbers of animals developing mesothelioma and their median survival times

The values given in the table differ from those shown in Davis et al (1991) only in that the hazard is expressed arithmetically as a multiple of the lowest hazard, and the fiber numbers are expressed as those in the dose.

The main conclusions of the study were: 1) that all of the materials had some potential to cause mesothelioma by intraperitoneal injection in rats; 2) that fiber numbers alone were not sufficient to explain the differences in response, nor were the fiber numbers in the 'Stanton' fiber class able to fully explain the response; and 3) that the Dornie and Shinness material would be unlikely to pose a risk of mesothelioma to humans from inhalation of the dust. The spontaneous occurrence of peritoneal mesothelioma in male rats of this strain would probably account for the small numbers of tumors found in the animals injected with the latter two dusts.

Coffin et al (1978, 1981, 1983) confirmed that ferro-actinolite asbestos has a high potency for generating mesothelioma in rats. In each case the actinolite asbestos had large numbers of fibers in the 'Stanton' range. The papers by Coffin and his colleagues were based on experiments using intratracheal instillation and intrapleural injection of an actinolite asbestos from the Mesabi Range (USA) iron ores in comparison to UICC amosite. The results were problematical in that the response from the amosite was much lower than expected from previous experiments by others. The response to the actinolite was lower than that from the amosite in terms of the mass dose used, but the response relative to the numbers of 'Stanton' fibers was higher. The authors explained the relatively high response from the ferro-actinolite as resulting from shortening and splitting of the fibers in the lungs and on the pleural surface of the rats.

Pott et al (1988) reported more than 80% of rats with tumours two years after intraperitoneal injection of 0.3 mg of a German actinolite although the size distribution of the actinolite is not reported. In contrast, when a 'granular' actinolite was used in similar experiments (Pott et al 1974) no tumours were found.

Amosite Studies

The inhalation and intraperitoneal injection experiments of Davis et al (1986) used long and short fiber amosite asbestos. These were produced from the same bulk batch of amosite, the short form by ceramic ball milling and the long by elutriation. Importantly, TEM examination

showed no loss of crystallinity in the milled short fiber sample. In the inhalation studies rats were exposed for one year (224 days in 12 months) to 11.9 and 11.6 mgm^{-3} of respirable dust for the long and short fiber types respectively. The aerosol contained 2060 and 70 fml^{-1} for fibers longer than 5 μm, and 1110 and 12 fml^{-1} for fibers longer than 10 μm. In the injection studies two batches of rats received a doses of 10 mg and 25 mg of the respirable dust collected from the inhalation experiment chambers using a vertical elutriator.

The results showed that rats exposed to the long fiber amosite developed significantly higher levels of pulmonary fibrosis and more lung tumours than rats exposed to the short fiber amosite. In fact the animals exposed to the short fiber developed no more fibrosis than did the control animals, no pulmonary tumours and only one peritoneal mesothelioma that was considered to be unrelated to the dust exposure as the type had previously been reported in untreated rats. The animals exposed to the short fiber had significantly higher burdens of asbestos in their lungs immediately after the inhalation period, and they remained higher throughout the following six months of clearance. The injection experiments produced mesothelioma in 95% and 88% of rats treated with 25 and 10 mg respectively of the long amosite, while the short fiber amosite produced 4% (1 animal) and 0% tumours with the same respective doses (mass). The results are summarized in Table 3.

These results were taken as an indication that the short fiber amosite showed a much lower relative pathogenicity than the long fiber amosite.

Table 3. Results from Davis et al (1986) intraperitoneal injection experiments with long and short fiber amosite

Injection Experiments	Long Amosite		Short Amosite	
	25 mg	10 mg	25 mg	10 mg
Number of animals with mesothelioma	20 (95%)	21 (88%)	1 (4%)	0
Mean Tumour Induction Period	520	535	837	N/A
Fiber Number in dose>5, $*10^6$	4327	1731	150.75	60.3
Fiber Number in dose>10, $*10^6$	2330	932	25.85	10.34

Cell Studies

The cell culture studies of Donaldson et al (1989, 1991, 1992) Brown et al (1991), Hill et al (1995) have generally confirmed the impression that fibers shorter than 5 □m and indeed possibly less than 10 □m have little pathologic effect other than what might be expected from a general respirable silicate mineral dust. Tumour necrosis factor release from macrophages was shown to be dependent on fiber length as demonstrated by the long and short fiber amosite (Donaldson 1992). The same minerals showed that release of superoxide anions by macrophages differed significantly (Hill 1995). Since such factors are associated with the development of inflammation, pulmonary fibrosis, and tumour formation, this supports the view that fiber length is an important element in determining the pathogenicity of fibers.

Other relevant studies

The studies at IOM (Miller et al 1999a, Miller 1999b and Searl 1999) confirm that biopersistence was a significant factor controlling the pathogenicity in animals of a wide range of different synthetic mineral fibers, but for durable fibers the most important factor was fiber length. The

fibers used were: glass microfiber, JM 100/475; MMVF 10, 21, 22 and Refractory ceramic Fibers 1, 2, and 3, from the Thermal Insulation Manufacturers Association repository of size selected fibers; a silicon carbide whisker fiber and the long fiber amosite as used by Davis et al (1986). In the intraperitoneal injection studies the best correlation with capacity to produce mesothelioma was with the in vivo biopersistence factor (derived from measurement of fibers before and after intratracheal instillation) and the number of fibers longer than 20 μm that were thinner than 0.95 μm. In the inhalation studies with the same suite of fibers the pulmonary tumour production (lung cancer) was best predicted by a function of the dissolution rate (measured in continuous flow through with simulated physiological saline solution) and the numbers of fibers in the length range greater than 20 μm and thinner than 0.95 μm.

Discussion

The main question that has been asked of these studies is to what extent they support the hypothesis that the carcinogenicity of fibers depends upon morphology. A second question that is being debated to what extent the short mineral fibers contribute to the carcinogenicity in humans.

The early studies of Wagner et al (1982) and Smith et al (1979) were seen as flawed because of poor survival and uninformative size distribution measurements. However, both experiments showed no potential for prismatic amphibole fibers to cause tumours by inhalation or by injection. So, while the criticisms may be justified to some extent, they ought not to be seen as grounds for disregarding the results and general concepts derived from this robust set of data.

A number of other questions have been raised about the interpretation of the Davis et al (1991) study. For example, the authors suggested that the response from the Shinness fiber was no more than would be expected from control animals, and that the non-asbestos tremolites were unlikely to pose a specific mesothelioma risk to humans by inhalation. This was refuted with the suggestion that the two tumours with the Shinness dust were significant (Federal Register) since

there were no tumours among animals in many other experiments from the same laboratory (IOM). It must be pointed out therefore that the experiments referred to in the criticism were inhalation experiments with other asbestos fibers, and that, other than with the Korean tremolites, these have rarely produced mesotheliomas in rats. Furthermore, as was shown with the Stanton et al (1981) implantation data, a percentage of animals with tumours in the range of 0 to 10% may well be within the expected range for a 40 mg dose of injected mineral particles of any type.

The size distributions of the fiber types show that the asbestos tremolites, as exemplified by the Californian (Jamestown) sample, are dominated by very much thinner fibers than the prismatic tremolites, as exemplified by the Shinness sample, which contain almost no fibers longer than 8 microns and less than 1 micron diameter. While it is true that the response could be explained simply as a dose response to the numbers of Stanton fibers, yet this fails to explain all of the variance in the results between the different fiber types. It remains a possibility that, as with Stanton's experiments, the low responses from the Shinness fibers and the Dornie fibers are because they are effectively inert dust responses.

A second criticism in the interpretation of these results stems from the high tumorigenicity of the Italian (Ala di Stura) tremolite (Davis et al 1992) This was described in the paper as a spicular (the same as acicular, a sub-type of prismatic) non-asbestos variety of tremolite which would not be expected to produce tumours; so the high tumour rate has been used to suggest that acicular and byssolite amphiboles do indeed have a similar carcinogenicity to the asbestos amphiboles. It is on record however that the Italian tremolite contains a sub-set of asbestiform tremolite fibers that appear as extremely long and fine fibers but which, because of the limitations of fiber sizing, are not fully expressed in the fiber numbers as reported in the study (Fig 7).

Figure 7 Scanning Electron Microscope microphotograph of the Ala di Stura tremolite showing a large needle shape fiber cross section surrounded by thin asbestiform tremolite fibers, many with diameters less than 1 micron.

The tumour response from the Ala di Stura tremolite was unusually high compared to the number of 'Stanton' fibers in the sample, but an important factor in the response was the timing of the mesotheliomas in the life spans of the animals. Two thirds of the rats exposed to the Italian tremolite developed mesothelioma, but very late in life (median survival time was 755 days). In contrast the three true asbestos samples had much shorter median survival times ranging from 301 days to 428 days. (The Korean tremolite asbestos had a median survival time of 428 days compared to 325 days in the earlier study with a 25 mg dose). The median survival time for those animals that develop mesothelioma appears to be inversely related to dose, as seen in Davis et al (1991), so the response from this dust could be simply that which might be expected from a trace asbestos component in the dust.

It was also pointed out in the original report that the Swansea tremolite asbestos had produced a response that was much higher than expected given the number of 'Stanton Fibers' in the dose. Both the Swansea tremolite asbestos and the Korean tremolite asbestos produced the maximum response in mortality but the high Hazard Index of the Swansea asbestos, calculated in the statistical analysis, was the result of the much faster tumor induction. It was suggested that this may have been the result of a masking of the response to simple fiber numbers by the overdose of fibers in the asbestos forms, and that a dose-response experiment might produce a clearer picture of the relative potencies of these types.

The Stanton studies confirmed the high tumorigenicity of tremolite asbestos and identified the 'Stanton Fiber' range, fibers > 8 μm with diameters < 0.25 μm, for which the correlation between fiber numbers and mesothelioma generation was highly significant. Had the size classes and instillation method been different, the 'Stanton Fiber' critical size may well have been different. The authors stated that shorter and thicker size classes also correlated with mesothelioma potency, and that it should not be assumed that they had no potency. However, as can be seen in Figure 8, the numbers of fibers in the different classes are strongly correlated.

Figure 8 Numbers of 'Stanton Fibers' per microgram compared to the numbers of fibers in the size range 4 –8 microns long and 0.01 – 1.5 microns diameter showing an obvious correlation except for those samples with no 'Stanton Fibers'

So it is to be expected that if the tumorigenicity is correlated strongly with numbers in the long, thin class it will also correlate with the fiber numbers in the shorter classes. That does not necessarily imply a causal relationship, and these short fibers may indeed have insignificant tumorigenicity. Even particulates that are considered relatively innocuous, e.g. FeO, magnetite can produce tumours by injection techniques if the dose is high enough (Pott et al. 1991) -

Figure 9 Probability of producing tumour vs number of fibers longer than 4.0 microns with diameter between 0.1 and 1.5 microns (and no fibers longer than 8 microns) Data extracted from Stanton et al 1981

As can be seen in Figure 9 many of the mineral and glass fibers in the experiments had less than 10 % probability of generating mesothelioma despite having huge numbers of fibers in the administered dose in the size range of 4 –8 microns length with no fibers in the longer classes. In particular, the fibrous talc minerals (5 and 7) produced no tumours despite having large numbers of short, thin fibers. The halloysites produced only 5 and 4 tumors despite having among the highest numbers of short fibers. Halloysite has the same tubular morphology as chrysotile asbestos despite being a little thicker fundamental diameter (0.07 microns). The attapulgites (palygorskite) produced few (2/29) tumours with similarly high numbers of fibers shorter than 8 microns. However, one long fiber attapulgite has been found by Wagner (1987) to be capable of producing large numbers of mesotheliomas in rats by intraperitoneal injection.

The size distributions of the various fibers used by Stanton et al are in many cases highly unusual but a detailed discussion of all their full fiber size distributions is beyond the scope of this paper; some contained no long fibers, some contained no short fibers, some contained no fibers thinner than 0.5 microns, and others contained no fibers thicker than 0.5 microns. The tremolites

however were unusual in having bimodal distributions typical of mixtures of asbestos and prismatic tremolites.

One important factor in the Stanton studies that has implications for many other injection and implantation experiments is the range and distribution of the results found. There are a large number of dusts producing between 0 and 10% of animals with mesothelioma, even though many of these samples contained more than 100,000 fibers per microgram of implanted dust. In a 40 mg dose that means more than 4.10^{9} fibers implanted. It is reasonable to conclude that this range of tumour production may be the 'normal' background for his mineral dust implantation technique. In addition, Stanton's implantation controls had a 2.8% incidence of pleural sarcomas and all controls had an age-adjusted rate of 7.7%$\pm$4.2. Also, Pott (1991) using intraperitoneal injection stated that tumour rates of below 10% in small groups should be regarded as spontaneously occurring or induced non-specifically. The background rate of his noninjected controls is 0%, but up to 10% for saline, which is highly significant when compared to noninjected animals.

One implication of this observation would be that the testing of materials by the implantation or injection of unrealistically high doses might be too sensitive to be used as a screening test for mesothelioma potency in humans by inhalation. In addition, both routes of exposure do not allow for normal physiological removal as would be expected after inhalation (McConnell, 1995). The Stanton method is particularly problematic in this regard because the fibers are 'held in place', i.e. in contact with the mesothelium in the gelatin vehicle. For these reasons the methods may be useful for the assessment of fundamental differences between fiber types and concepts of carcinogenic activity but are not specifically useful predictors of the risk to humans from inhalation of more general dusts. Furthermore, the doses to which the animals are exposed are probably many orders of magnitude higher than would be expected from exposure of humans to airborne dust.

Conclusions

The conclusion that must be drawn from the evaluations of this fairly robust set of studies is that there is very little evidence of carcinogenicity from exposure of animals to mineral fragments or short fibers formed from normal prismatic amphibole minerals. No positive carcinogenicity has been found with any experiment using non-asbestos amphibole dust. Furthermore, when genuinely short fiber amphibole asbestos has been used in inhalation or injection experiments they have also been shown to have no carcinogenic properties. Evidence from experiments with other mineral fibers suggests that fibers in excess of 20 microns and with diameters less than 1 micron are necessary to cause cancer. This is probably because such long fibers cannot be phagocytized by resident macrophages and therefore, cannot be removed from the lung. (Lipmann et al 2000). This explains the lack of carcinogenicity of cleavage fragment fibers of amphiboles since these rarely if ever contain fibers of these critical dimensions.

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FINAL REPORT

AN EVALUATION OF THE RISKS OF LUNG CANCER AND MESOTHELIOMA FROM EXPOSURE TO AMPHIBOLE CLEAVAGE FRAGMENTS.

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AN EVALUATION OF THE RISKS OF LUNG CANCER AND MESOTHELIOMA FROM EXPOSURE TO AMPHIBOLE CLEAVAGE FRAGMENTS.

1.0 INTRODUCTION

Asbestos is a generic term applied to a group of hydrated fibrous mineral silicates. Their asbestiform habit permits them to be easily separated into long, thin, flexible, strong fibers and ultimately fibrils (single fibers). Included are the asbestiform serpentine (chrysotile) and the asbestiform amphiboles, crocidolite, anthophyllite asbestos, grunerite asbestos (amosite), tremolite asbestos and actinolite asbestos. These minerals also crystallize with non-asbestiform habits, their counterparts being lizardite or antigorite (chrysotile), riebeckite, anthophyllite, grunerite, tremolite and actinolite respectively. Crystal habit is a description of the shapes in which a certain mineral is likely to occur, both in nature and when grown synthetically. Tremolite is a mineral in the tremolite-ferro-actinolite series that has fewer than 0.5 atoms of iron, and more than 4.5 atoms of magnesium per formula unit; actinolite has between 0.5 and 2.5 atoms of iron, and 2.5 atoms of magnesium per formula unit; ferro-actinolite has more than 2.5 atoms of iron per formula unit with the balance being magnesium.

By the early 1970's, airborne concentrations of asbestos fiber were being measured using "the membrane filter phase contrast method (PCM)". In many countries, including the U.S.A., this method was adopted for the regulatory control of asbestos. Fundamental to the method was the definition of a fiber as an elongated particle having a length: breadth ratio (aspect ratio) of at least 3:1 and a minimum length of 5 micrometers (μm). Such a definition does not distinguish between asbestos fibers and non-asbestos particles. Consequently, in work environments where there are many elongated particles meeting the PCM fiber definition, they are counted as if they are "asbestos" even if they are neither asbestos minerals or even amphiboles . This results in concern by workers and health professionals about health risks and potential economic impacts for companies mining ore deposits where amphibole minerals are present. This is because the amphiboles have cleavage planes such that when they are fractured they produce elongated particles called cleavage fragments. All amphiboles exploited commercially as asbestos have non-asbestiform counterparts. Hence, workers in industries where amphibole cleavage fragments are present, but not asbestos, are often erroneously reported as being exposed to asbestos based on current regulatory practices. On the other hand, the evidence concerning the health consequences of exposure to cleavage fragments has never been clearly evaluated. Industries involving exposure to cleavage fragments should not be exempt from similar controls to the asbestos industries, if elongated particles meeting the PCM definition of fibers pose qualitatively and quantitatively the same levels of health risk as their asbestiform counterpartsHowever, if cleavage fragments pose no or a lesser risk than the asbestos minerals, they should be regulated accordingly.

The purpose of this paper is to compare, as far as possible, the cancer risks (lung cancer and mesothelioma) for workers exposed to airborne amphibole cleavage fragments with those associated with exposure to amphibole asbestos fibers. Pneumoconiosis risk will not be compared because some of the minerals associated with the amphibole cleavage fragments are recognized in their own right as causing lung fibrosis (e.g.: talc and crystalline silica). However, pneumoconiosis is sometimes used to assess whether exposure is high enough and latency long enough to detect carcinogenic risk.

2.0 METHODS

The extent to which the carcinogenic risks of exposure to cleavage fragments differ from those associated with exposure to asbestos was examined in several ways.

1. The potential of particles to cause health effects depends on the characteristics of the particles (e.g.: size, shape, respirability, solubility, toxicity, carcinogenic potential), the level and duration of exposure as well as host and other factors. It is important to determine whether amphibole cleavage fragments differ sufficiently from asbestos fibers for them to pose different levels of health risk than their asbestos counterparts. To do this requires examination of the characteristics of the particle such as dimensions, shape and density that influence fiber respirability, and fiber dimensions and biopersistence that influence carcinogenicity.

2. Mesothelioma and lung cancer are the health endpoints examined for comparison of the relative effects of nonasbestiform and asbestiform amphiboles. Mesothelioma is considered the more important indicator because it is both more specific and perhaps more sensitive than lung cancer. Mesothelioma is a rare cancer which is primarily associated with exposure to amphibole asbestos and has occurred after what appears to be exposure at quite low concentrations. Lung cancer is more subject to being caused by confounding exposures such as smoking, which is the primary cause of lung cancer. Thus while lung cancer is caused by asbestos, it is an effect that is not specific to asbestos exposure. If smoking prevalence is not known, the effects of smoking and occurrence of lung cancer cannot readily be distinguished. Secondly, mesothelioma is a more sensitive indicator of amphibole asbestos exposure in that pleural mesothelioma may occur following what are ostensibly brief exposures (Roggli, 1990). The exposure-response slope is thought to be non-linear for both mesothelioma and lung cancer. While the shapes of relationships are still subject to debate, pleural mesothelioma has been reported to increase less than linearly with cumulative dose. For peritoneal mesothelioma the risk is thought to be proportional to the square of cumulative exposure while for lung cancer the risk lies between linear and square of cumulative exposure (Hodgson and Darnton, 2000). As some mesothelioma have been reported to occur after relatively low and perhaps brief exposures one might anticipate that if amphibole cleavage fragments act like asbestos in causing mesothelioma there might be some cases even if cleavage fragment exposures were low. For mesothelioma to be attributed to amphibole cleavage particles the time since first exposure must be long and there should be no previous exposure to asbestos or other etiological factors.

3. The mortality from lung cancer and mesothelioma are compared to that expected in age- and sex-adjusted external populations. The comparison measure is the standardised observed / expected mortality ratio or Standardized Mortality Ratio (SMR). When the incidence of lung cancer and mesothelioma are compared to that expected in age- and sex-adjusted external populations, the comparison measure is the standardised observed/expected cancer incidence ratio or Standardized Incidence Ratio (SIR). External comparisons for assessing lung cancer risk have inherent limitations such as differences in smoking and lifestyle between the study population and the external referent population. It is generally not feasible to adjust for these differences. An SMR less than 1.0 (no effect level) or a statistically nonsignificant SMR is suggestive, but not conclusive, of no association. A deficit in the lung cancer SMR could be due to exposure levels below a no-effect threshold, or a few highly exposed workers diluted by many workers with low exposure, or negative confounding due to a low prevalence of smoking. A nonsignificant SMR might be due to the small size of the study population and the low power of the study to detect significant differences. Similarly, a positive finding of lung cancer could be due to differences in smoking prevalence rather than exposure to nonasbestiform amphiboles.

For mesothelioma, external comparisons using an SMR are often not possible because the expected number of cases is not known or not estimated. Therefore an internal proportional mortality ratio (PMR) is used to estimate risk of mesothelioma. PMR's have their limitations which must be taken into account when using them. For example, as PMR increases with length of follow-up of a cohort, attention must be given to the comparability of the follow-up period. Age differences in populations being compared are important as age determines the nature of diseases from which people die as well as the frequency of death. The ratio with total deaths to some extent adjusts for both differences in follow-up and age. Era of death may be important because of diagnostic trends.. Never-the-less, comparison of PMRs between nonasbestiform amphibole-exposed and asbestos-exposed populations is probably the best single measure for answering the question of whether nonasbestiform amphiboles cause cancer at the same rates as asbestiform amphiboles.

4. The actual measured risks of lung cancer and mesothelioma in persons exposed to amphibole cleavage fragments is compared to workers exposed to asbestiform amphiboles as follows:

a. The lung cancer and mesothelioma experience of workers exposed to amphibole cleavage fragments is compared with the experience of workers exposed to their asbestiform equivalents. There are three main ore bodies containing non-asbestiform amphiboles where epidemiological studies have been conducted. These are a gold mine in South Dakota (grunerite-cummingtonite exposure), taconite mines in Minnesota (grunerite and other non-asbestiform amphiboles) and a talc mine in New York State (non-asbestiform anthophyllite and tremolite and transition minerals). Their experience was compared to that of workers in amosite asbestos mines, mills and manufacturing facilities, anthophyllite asbestos mines and vermiculite mines (exposed to winchite

asbestos also known as soda tremolite asbestos). In this report, winchite asbestos from the vermiculite mine in Montana, will be referred to as "tremolite asbestos" as this has been the terminology used in the medical literature.

b. The mortality from lung cancer is examined in relation to estimated levels of exposure to "fibers" for workers exposed to asbestos and workers exposed to amphibole cleavage fragments. The existence of a positive gradient of increasing risk with increasing exposure after taking account of potential confounders would be good evidence that the cleavage fragments were posing an increased risk of lung cancer. A negative gradient is strong evidence against a causal association. The presence or absence of an exposure-response gradient is among the strongest evidence for or against a lung cancer association with cleavage fragment exposure because smoking is the major cause of lung cancer and rarely, if ever, can external comparisons be adequately adjusted for smoking.

5. The lung cancer and mesothelioma experience of workers exposed to dusts from an ore-body containing amphibole cleavage fragments is compared with that of workers exposed to dusts from a similar ore-body which does not contain amphibole cleavage fragments. This is called a negative control. If the experience of the amphibole cleavage fragment exposed workers were worse than that of the negative control (non-cleavage fragment exposed workers), this would be suggestive of an increased risk due to the presence of asbestos cleavage fragments.

In order to investigate this, the mortality for New York talc miners is compared to that of talc miners where it is claimed amphiboles were not present in the talc. Also, the mortality of iron ore miners exposed to taconite containing nonasbestiform grunerite is compared to that of miners exposed to hematite which does not contain amphiboles.

6. The biological plausibility of a difference in the potential of amphibole cleavage fragments to cause cancer compared to amphibole asbestos fibers was assessed by review of the results of toxicological studies involving asbestos and amphibole cleavage fragments. There is a clear pattern of an increased incidence of mesothelioma in animals exposed to amphibole asbestos. Observing a similar pattern for animals exposed to nonasbestiform amphiboles is evidence supporting the hypothesis that nonasbestiform amphiboles pose a carcinogenic hazard similar to asbestos. The lack of an increased incidence of mesothelioma is strong evidence against the hypothesis.

THE AMPHIBOLES

The crystallographic structure of amphiboles consists of double chains of silica tetrahedra. Their general chemistry incorporates $(Si,Al)_8O_{22}(OH)_2$. The amphibole group of minerals is made up of a number of mineral series. These series result from the substitution of different elements in the structure. For example tremolite and actinolite are part of a homologous series of minerals – tremolite-actinolite-ferro-actinolite with chemistry $Ca_2(Mg\ Fe)_5\ Si_8O_{22}(OH)_2$. Actinolite is $Ca_2(Mg_{4.5}\ Fe_{0.5})\ Si_8O_{22}(OH)_2$ -

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$Ca_2(Mg_{2.5}Fe_{2.5})Si_8O_{22}(OH)_2$. Ferro-actinolite is $Ca_2(Mg_{2.5}Fe_{2.5})Si_8O_{22}(OH)_2$ - $Ca_2Fe_5Si_8O_{22}(OH)_2$. Actinolite with less than $Mg_{0.5}$ would be tremolite.

In practice, these minerals can have a fairly wide range of composition within the broad range of substitutions possible. The mineral names are defined as minerals where the ranges of the substituted elements fall within certain arbitrary boundaries.

Grunerite is a member of the mineral series cummingtonite-grunerite with chemistry $(Mg,Fe)_7Si_8O_{22}(OH)_2$. As noted above, the asbestiform variety of grunerite is "amosite". As with the tremolite-ferro-actinolite series, the minerals in this series have a range of compositions.

Anthophyllite occurs as asbestos and in a non-fibrous form and is an end member of the anthophyllite-ferro-anthophyllite series which is chemically $(Mg\ Fe^{2+})_7Si_8O_{22}(OH)_2$. Anthophyllite is the name reserved for the orthorhombic Mg Fe amphibole where the ratio of Mg/(Mg+Fe) is greater than 0.5; a lower amount of magnesium in the same type of amphibole requires the name ferro-anthophyllite.

Non-asbestiform Riebeckite and crocidolite asbestos have the same chemistry which is $Na_2Fe_3^{2+}Fe_2^{3+}Si_8O_{22}(OH)_2$.Amphiboles exhibit prismatic cleavage, a property of nearly all samples of the amphiboles regardless of habit. There are two cleavage directions, both parallel to the length of the double-silicate chains. Cleavage across the crystal is usually poor so that the fracture of amphiboles produces long rods or prisms and repeated cleavage produces thinner rods with a rhombic outline consisting of bundles of I beams (i.e.: structural units of the amphibole) (Skinner et al., 1988). The presence of twinning or chain width errors may results in an additional direction of weakness parallel to the length, enhancing the aspect ratio of cleavage fragments.

4.0 PROPERTIES OF ASBESTIFORM AND NON-ASBESTIFORM AMPHIBOLES.

While the chemical compositions of the asbestiform and non-asbestiform amphibole minerals are identical, the characteristics resulting from their differences in crystal habit are significant. The properties of the amphibole asbestos minerals include fibrous habit with parallel fibers occurring in bundles, fiber bundles with split or splayed ends, fibers showing curvature and fibers with high tensile strength. The high tensile strength and axial nature of asbestos means the diameters of asbestos fibrils are largely unaffected by milling. On the other hand, the low tensile strength of nonasbestiform amphiboles means that milling can reduce both particle length and width. The asbestos fibers have good heat insulation qualities, low electrical conductivity, fire resistance, and suitability for weaving. All asbestos minerals separate readily into long flexible fibrils with diameters less than about 0.5 μm and with aspect ratios (length: width ratios) ranging to well over 10,000 (Ross, 1978).

In the hand specimen (that is a sample of the rock as it occurs in nature), the appearance of the non-asbestos minerals is distinctly different from that of the asbestos minerals.

This difference persists under the optical and electron microscopes where the non-asbestiform minerals appear as blocks, chunks or slightly elongated particles in contrast to the very evident fibrous nature of asbestos. The non-asbestiform counterparts tend not to grow with parallel alignment. The crystals normally fracture rather easily under pressure forming cleavage fragments, some of which may appear as acicular or needle-like crystals because of the way in which amphibole minerals cleave. These cleavage fragments have diameters which on average, are much larger than those of asbestos fibers of the same length. Some asbestiform tremolite fibers with the majority of fiber diameters exceeding 0.25 μm, tested by intra-peritoneal injection in rats were found to be highly carcinogenic (Lee 1990; Davis & Addison 1991). However, almost 70% of the fibers had aspect ratios greater than 10:1, 42% greater than 15:1 and 25% had aspect ratios more than 20:1. This contrasts with the observations that only about 6% of the aspect ratios of cleavage fragments exceed 15:1. The diameters of cleavage fragments appear to be rarely less than 0.25 μm (TABLE 1).

FIBER DIAMETERS: The aerodynamic behavior of fibers is determined mainly by their diameter (Timbrell 1982). The majority of airborne asbestos fibers have diameters less than 0.25 μm making virtually all airborne fibers, respirable. In contrast, only very small percentages of nonasbestiform cleavage fragments have diameters less than 0.25μm (TABLE 1).

For the same length distribution, counting fibers by PCM will, based on fiber diameter differences, lead to higher counts of nonasbestiform cleavage fragments than asbestos fibers, because of their visibility by PCM. On the other hand, assuming the same density for fibers as for cleavage fragments, the respirability (i.e.: ability of particles to enter the alveolar regions of the lung) of the cleavage fragments will be somewhat less that that of asbestos fibers because of their larger diameters. Thus, the PCM method as presently formulated is more stringent for cleavage fragments than for asbestos fibers.

While it has been argued that a major determinant of carcinogenic potential is decreasing fiber width (Wylie et al, 1993), the precise role of the single parameter, diameter in carcinogenesis is still not clear.

"FIBER" LENGTH: While the majority of asbestos fibers are in fact short (less than 5μm) there are airborne amphibole fibers which exceed 100 μm in length. Unfortunately, complete particle size (length vs diameter) distributions of airborne cleavage fragments and asbestos fibers are extremely limited, making it difficult to compare length distribution differences. What data are available indicate that asbestos fibers are longer. For example, Dement et al (1976) observed that the median length of "fibers" in the airborne dust in the South Dakota Homestake Gold mine was 1.10 μm long as seen under scanning electron microscopy. This is less than the median lengths of airborne amosite asbestos fibers in South Africa mines and mills which were 1.83 μm and 2.53 μm respectively (Gibbs & Hwang 1980) and of amosite from a pipe insulation operation, 4.9

μm (Dement et al 1976).

There is other evidence for a clear mineralogical difference between grunerite asbestos and grunerite. Virta et al (1983) examined airborne particles of grunerite from the Homestake gold mine in South Dakota, particles of cummingtonite, hornblende and actinolite from the Peter Mitchell iron ore mine in Minnesota and particles of grunerite asbestos samples from a shipyard and electric company. Hornblende is an amphibole that is similar to the tremolite-ferro-actinolite series but with aluminum substituted for some of the iron-magnesium as well as for some of the silicon in order to maintain the stoichiometric balance. There were two distinct particle size distributions. The nonasbestiform grunerite distributions from the mining sites were of short, wide fibers (average length x width of 4.6 μm x 1.1 μm and 5.5μm x 1.2 μm). The amosite fibers from the industrial sites were longer and narrower (average length x width = 8.2μm x 0.4μm and 15.6μm x 0.5 μm respectively). Although the populations of grunerite and grunerite asbestos are distinct, at the submicroscopic level it may be very difficult to be certain about the specific identity of an individual particle and may be extremely difficult, if not impossible to distinguish asbestos and nonasbestiform particles (Langer 1979).

The Gouverneur New York State talc deposit has been well studied for its mineralogy and presence of fibers and cleavage fragments. The mineralogy is complex. Campbell et al (1979) note that 5-10% of the earth's crust is amphiboles and therefore many mining industries have amphiboles in the tailings of the gangue minerals. There are at least 3 habits of nonasbestiform tremolite, none of which have the long, thin fibers characteristic of tremolite asbestos as shown in TABLE 2.

Long narrow fibers have been shown experimentally to be best capable of inducing mesothelioma when placed directly onto the pleura in experimental animals (Stanton et al., 1981). As there are likely to be fewer long fibers and fewer narrow diameter "fibers" in the case of exposure to amphibole cleavage fragments, compared to asbestos, it would be anticipated that cleavage fragments would pose lower carcinogenic risk.

ASPECT RATIOS: Asbestos fibers have thin diameters and do not readily break transversely. As a result, length/width ratios can be quite high. All "fibers" will by definition have aspect ratios >3:1. Around 30% of asbestos fibers will have aspect ratios >10:1 and nearly 20% greater than 20:1. There were very few cleavage fragments with aspect ratios greater than 10:1 The common blocky variety of nonasbestiform tremolite had less than 2% in the >10:1 class. The acicular and fibrous habits had more particles in the 10:1-20:1 category than did the blocky variety, but none of the nonasbestiform varieties had more than 0.5% particles in the 20:1-50:1 and none had any particles >50:1 Nearly 90% of the blocky and acicular habits did not meet the regulatory definition of a fiber. If only fibers that meet regulatory dimensions are counted, 1/100 of nonasbestiform particles have aspect ratios >20:1 while about 35/100 asbestiform tremolite particles have >20:1 aspect ratios (Table 2). A composite aspect ratio distribution reported by Bailey et al (This Monograph), showed that for nonasbestiform particles with an aspect ratio of 3:1 or greater and length greater than 5um, 6% on

average exceed an aspect ratio of 15:1 and for asbestiform particles, 80% on average exceed this 15:1.

BIOPERSISTENCE: As far as we were able to ascertain, there have been no systematic studies of the biopersistence of cleavage fragments. It is known that for long amphibole asbestos fibers, the half-life is extremely long (Berry, 1999). However, short fibers (i.e.: less than 20 μm in length) can be removed from the lung by macrophage action (Bernstein et al 1994; Allison 1973). For later phases of lung clearance, particle solubility is a key factor. In the absence of data, there is no basis for concluding that cleavage fragments will be removed any faster than asbestos fibers during that phase. However, because of their shorter lengths, cleavage fragments are much more likely to be removed more rapidly than amphibole asbestos fibers during the early lung clearance phase. This will reduce their potential for carcinogenic action.

5.0 COMPARISON OF THE RISKS OF HEALTH EFFECTS IN PERSONS EXPOSED TO ASBESTIFORM GRUNERITE AND TO NON- ASBESTIFORM GRUNERITE.

5.1 GRUNERITE OCCURRENCE

Grunerite is the mineralogically correct name for amphiboles of the cummingtonite-grunerite series in which iron is at the 50% point in the 100*Fe / (Fe+Mg)) ratio. Amosite (from the "Asbestos Mines of South Africa") is the commercial asbestiform product that was used in insulation and building materials. Grunerite asbestos is no longer mined.

The nonasbestiform variety of cummingtonite-grunerite (C-G) has no commercial use *per se* but occurs in nature in conjunction with other asbestiform and nonasbestiform amphiboles and other minerals in ore deposits mined for other purposes. In the USA, ore containing C-G has been mined in at least 2 locations. One location is the Homestake gold mine in Lead, SD, where gold has been extracted since 1876. The other location is Silver Bay, Minnesota, where taconite has been mined since the 1950's for the extraction of iron. Because of its relationship to amosite, studies were initiated to determine if these minerals had similar pathogenicity. There have been four cohort studies of Homestake gold miners (Gilliam et al, 1976; McDonald et al, 1978; Brown et al, 1986; Steenland and Brown, 1995) and two studies of taconite containing amphiboles; one of the Reserve iron deposit (Higgins et al, 1983) and the other of the Erie-Minntac mine (Cooper et al 1988, 1992).

Taconite iron ore contains actinolite and cummingtonite-grunerite (probably predominantly grunerite). In 1973, elongated grunerite particles, said to be similar to amosite, were found in the Duluth, Minnesota water supply. The source was mine tailings from the process plant serving the Peter Mitchell mine at Silver Bay, Minnesota (MN).

In a suit against the Reserve Mining Company, the US Environmental Protection Agency (EPA) claimed that some of the particles were asbestos. This finding initiated a series of studies to determine if there were effects on the Duluth residents (Cook et al, 1974; Masson et al, 1974; Levy et al, 1976; Sigurdson et al, 1981). These studies are not considered further because they are ecological studies without identification of individual exposures or responses, because the route of exposure is via ingestion and because experimental studies and the epidemiological studies described below have provided no evidence in support of any gastrointestinal cancer risk from ingestion. The other health studies are of taconite miners and millers (Clark et al, 1980; Higgins et al, 1983; Cooper et al, 1988, 1992).

A reasonably valid comparison can be made between the health risks of workers exposed to amosite asbestos in mining and manufacture and the health risks of workers involved in the production of minerals from ore bodies containing non-asbestiform grunerite.

5.2 AMOSITE ASBESTOS

Amosite is the trade name given to a mineral that was previously mined in Penge in the Transvaal area of South Africa. The mineralogical name is grunerite asbestos. In the bulk specimen the fibers can be several inches long. The colour, ranging grey to brown depends on whether the fiber was mined from a weathered or un-weathered zone. The size distribution of the airborne fibers in the mine and mill have been reported by Gibbs and Hwang (1980). In mining, 12.6% and in milling 26.6% of airborne fibers exceeded 5 μm in length when all particles with length to breadth ratios greater than 3: 1 were counted using transmission electron microscopy combined with light optical microscopy. The median lengths for mining and milling were 1.83 μm and 2.53 μm respectively. The median diameters were 0.20 to 0.26 depending on the process and there were no airborne fibers with diameters exceeding 3 μm.

5.3 AMOSITE COHORT STUDIES

The studies of cohorts of amosite-exposed workers include miners and millers in South Africa (Sluis-Cremer et al 1992) and workers engaged in amosite insulation manufacture (Acheson et al 1984; Seidman et al 1986; Levin et al 1998). Cohorts where the exposure also included crocidolite and/or chrysotile have been excluded from consideration as the ratios of the risks of mesothelioma associated with these various fiber types have been reported to be in the ratio of 500:100:1 for crocidolite, amosite and chrysotile respectively (Hodgson & Darnton 2000). For lung cancer the differences are not as great or as clear-cut. Crocidolite and amosite pose similar exposure-specific risks for lung cancer (about 5% excess per f/ml-yr), while the risk from chrysotile is estimated as 0.1-0.5% of the risk of crocidolite and amosite. Thus the risk differentials between the amphiboles (crocidolite, amosite) and chrysotile for lung cancer are about 10-50:1 (Hodgson & Darnton 2000). It should be noted that the chrysotile in these risk estimates included sources where the chrysotile contained traces of tremolite asbestos.

Only one of the cohorts with pure amosite exposure was examined for a quantitative exposure-response relationship (Seidman et al 1986). There was a clear increase in the risk of lung cancer with increasing exposure expressed in fibers/cc-years.

5.4 NON-ASBESTIFORM GRUNERITE COHORTS

Several groups of workers from Homestake gold mine and the Minnesota taconite deposits have been exposed to cleavage fragments of grunerite and studied to assess possible "asbestos-related" diseases (TABLE 3). The nonasbestiform amphiboles present in these mines generally crystallize in a prismatic habit with well-developed cleavage so breaks occur both perpendicular and parallel to particle length.

5.4.1 Taconite miners

There are several studies of workers who were exposed to cummingtonite-grunerite particles from the above deposits. These include the Reserve taconite miners (Higgins et al 1983) and the Erie-Minntac taconite miners (Cooper et al 1988, 1992). Another group of Iron ore (hematite) miners in Minnesota is included for comparison as a negative "control" since the hematite ore does not contain amphiboles (Lawler et al 1985).

Taconite is an iron-bearing rock that by 1978 was supplying nearly 90% of the iron ore used in the US iron and steel industry. More than 60% of this came from the Mesabi Range that is 110 miles long and 1-3 miles wide extending east to west from Babbitt, Minnesota to Grand Rapids, Michigan. Iron ore has been mined along the Mesabi Range since about 1892 (Langer et al, 1979). Taconite contains 20-50% quartz and 10-36% magnetite with smaller amounts of hematite, carbonates, greenalite, chamosite, minnesotaite, stilpnomelane and amphiboles which are mainly non-asbestiform minerals in the cummingtonite-grunerite series, actinolite and hornblende, (Nolan et al 1999).

Taconite from the eastern end of the Mesabi Range contains non-asbestiform cummingtonite-grunerite (most probably grunerite) and actinolite with most elongated particles having aspect ratios greater than 3:1 and length less than 10 μm and are mostly acicular cleavage fragments. Respirable dust concentrations in the Reserve mining company ranged from about 0.02 mg/m^3 to 2.75 mg/m^3 at a crusher. The modal range in most jobs was 0.2-0.6 mg/m^3, with occasional concentrations of 1-2 mg/m^3 but mostly below 1 mg/m^3. Fiber concentrations were generally < 0.5 fibers/ml. Area samples suggest no change in concentrations between 1952-1976 and exposure estimates were based on samples collected in the period 1975-8 (Higgins et al 1983).

In the Reserve mining cohort (Higgins et al, 1983) there were no exposure-response relationships between lung cancer and cumulative exposure to silica dust or taconite (measured as mg/m3-years) and no excess lung cancer based on the SMR. There were no cases of mesothelioma. Higgins et al (1983) concluded that the lack of any increased risk of cancer is not surprising given the low silica and fiber exposure plus movement of miners to lower exposed jobs with increased seniority. The average and maximum

latencies of lung cancer were 15 and 25 years, which is relatively short for the development of either lung cancer or pneumoconiosis. The cohort was also relatively young with 5% overall mortality and the number of cases was small with 15 lung cancer cases, 8 with >15 years since hire. Exposure-response functions were estimated using cumulative total dust exposure and cumulative silica dust exposure in mg/m^3-years as the exposure metrics. The relationship with total dust exposure, which is of interest from the standpoint of cleavage fragments, was not monotonic and the SMRs were at or below 1.0 in the three highest exposure categories. Higgins et al (1983) concluded there was no suggestion of an association with lung cancer.

In the Eastern Mesabi district, west of the Reserve Mine are the Erie and Minntac operations. The Minntac ore has had a different metamorphic history and contains the lowest percentage of amphiboles. The Erie ore is a blend of the high and low amphibole ores with more amphiboles than Minntac but less than Reserve. Nolan et al (1999) reported 28-40% quartz in dust from the Erie mine and 20% quartz from the Minntac mine. Concentrations of fibrous particulates were nearly always <2 fibers/ml. These particulates were >5 μm in length and included elongated cleavage fragments.

The Erie-Minntac cohort of taconite miners (Cooper et al, 1992) showed "no evidence to support any association between low-level exposure to nonasbestiform amphibole particles or quartz" and lung cancer. The Erie-Minntac cohort is older and larger than the Reserve cohort with 31% mortality and a minimum time since hire of 30 years. There were deficits in lung cancer SMRs for miners ever working in high or medium dust areas and no trend with years worked. There was no analysis by cumulative exposure.

There was one case of mesothelioma that had been reported in the initial study (Cooper et al, 1988). In this case, exposure to taconite began 11 years before death. Previous employment included work in the railroad industry as a locomotive fireman and engineer. Nolan et al (1999) suggest it is unlikely that the mesothelioma is related to taconite because mesothelioma generally occurs after at least 25 years although latencies as short as 15 years have been reported among insulation workers where asbestos exposure can be quite high. The more likely cause is from the railroad employment where there are opportunities for amosite and crocidolite exposure. Also, the time since hire in the railroad jobs is more consistent with the long latency characteristic of mesothelioma.

Although deposits of grunerite asbestos large enough for commercial exploitation are very rare, small deposits are occasionally found as a gangue mineral in a limited area of a mine that is otherwise asbestos-free. Nolan et al (1999) described the occurrence of such a localized seam of grunerite asbestos in a small portion of an iron ore mine otherwise free of asbestos. Samples from the seam revealed three kinds of morphological types or habits. One kind was the asbestiform habit with fibers occurring as parallel fibrils and forming polyfilamentous bundles. There were two nonasbestiform habits, namely splintery fibers and massive anhedral nodules, which when crushed may form elongated cleavage fragments that resemble some asbestiform fibers. To evaluate potential asbestos exposure, 179 personal air samples were collected for all relevant jobs associated with

work on this localized seam. The mean concentration of "federal" fibers >5 μm in length was 0.05 f/ml and the highest was 0.39 f/ml. All sample results were below the Mine Safety and Health Administration (MSHA) standard of 2 f/ml but 13% were above the Occupational Safety and Health Administration (OSHA) standard of 0.1 f/ml.

Nolan et al (1999) estimated the potential lifetime risk of lung cancer and mesothelioma based on a worst case scenario. Lifetime lung cancer risks of 0.1 and 0.6 /100,000 for nonsmokers and smokers respectively were estimated using the EPA risk model and assuming a linear exposure-response relationship, age of 45 years at beginning of exposure and continuous exposure for 22 days to 0.05 asbestos fibers/ml. This was considered approximately equivalent to smoking 2 or 12 cigarettes over a lifetime.

Nolan et al (1999) also estimated risk based on grunerite asbestos fiber content in the lungs of mesothelioma cases from a British grunerite asbestos (amosite) factory (Gibbs et al, 1994). Nolan et al (1999) estimated it would take 75-265 years of daily 8-hour shifts to inhale the number of fibers found in the lungs of the mesothelioma cases, assuming no clearance. Fiber concentrations were about 45% higher in the lung cancer cases, suggesting about 100-380 years to reach similar fiber content in iron ore miner lungs.

Nolan et al (1999) suggested concentrations were a minimum of 30 fibers/ml in the Paterson, NJ amosite factory (Seidman et al, 1986). No mesothelioma cases had less than 6 months employment and 20 years latency. Assuming breathing 0.05 fibers/ml from the gangue rock in the iron ore mine, Nolan et al (1999) estimated it would take about 300 years to achieve the minimum exposures estimated by the mesothelioma cases in the Seidman et al (1986) cohort.

5.4.2 Hematite Miners as negative control

Hematite from the Mesabi Range in Minnesota is a mixture of about 83% hematite (Fe_2O_3) and limonite ($HFeO_2$). The hematite deposit differs from taconite deposits in that there is the absence of all amphiboles. Some silica (about 8%) is present plus possibly low levels of radon.

Lung cancer mortality was not associated with years worked. Mesothelioma was not mentioned. Lawler et al (1985) considered that the lack of an excess risk of respiratory disease was possibly due to strict prohibition of smoking while underground, apparent absence of significant radon daughter exposure and/or the aggressive silicosis control program. No estimates of dust exposure are available.

5.4.3 Gold Miners:

There are several studies of miners at the Homestake gold mine in South Dakota (Gilliam et al 1976; McDonald et al 1978; Brown et al 1986; Steenland & Brown 1995).

Ore containing cummingtonite-grunerite has been mined to extract gold in Lead, South Dakota, since 1876. An analysis of airborne "fibers" using electron diffraction and x-ray

spectrometry was reported to show that it contained "80-90% amphiboles" with the amphiboles being "60-70% fibrous grunerite", "1-2% fibrous cummingtonite" and "10-15% fibrous hornblende" (Gilliam et al 1976). The free silica content of the respirable airborne dust was reported to be 13.1%. Low concentrations of arsenopyrite were also reported. The NIOSH researchers identified the fibrous grunerite as amosite asbestos. Closer examination of the fiber population statistics suggests strongly that the fibrous grunerite particles are non-asbestos amphibole cleavage fragments and not asbestos. The count median length for the airborne fibers from this mine was reported to be 1.10 μm (Dement et al 1976), compared to 1.83 and 2.53 μm for amosite mining and milling operations (Gibbs & Hwang 1980). The median length of fibers in pipe insulation-pipe forming was reported to be 4.9 μm (Dement et al 1976).

Measurements of airborne concentrations of "fibers" in the mine in 1974 showed concentrations to be about 0.25 f/cc greater than 5 μm with the highest concentration being 2.8 f/cc based on 200 samples (Gilliam et al 1976). The mean total fiber concentration in the mine as determined by electron-microscopy was 4.82 (+/- 0.68) with the concentration of fibers greater than 5μm being 0.36 (+/0.08) f/cc. Approximately 94% of fibers were less than 5μm in length, the mean fiber diameter was 0.13 μm and the mean "fiber" length was 1.1 μm. The US Bureau of Mines in 1960 reported average airborne dust concentrations of 1.7 million particles per cubic foot (mppcf) (Gilliam et al, 1976). This suggests a ratio of f/cc to mppcf of about 0.25/1.7 = 0.146 f/cc per 1 mppcf.

Exposure-response relationships were developed by several of these researchers. Only the results of the latest follow-up by Steenland and Brown (1995) will be considered. However, the exposure-response developed by McDonald et al (1978) based on semi-quantitative exposure estimates is of interest because this cohort of 1321 men with 21+ years of service clearly had adequate latency to observe the occurrence of mesothelioma or increase in lung cancer. There were 17 deaths from respiratory cancer but no convincing evidence of an excess of respiratory cancer or grunerite related mesothelioma. This contrasts with the results of the earlier study by Gilliam et al (1976), which involved 440 men who had worked more than 5 years underground. They reported 10 deaths from neoplasms of the respiratory system with 2.7 deaths expected. Conclusions from the study by Gilliam et al (1976) are weakened by the fact that the study population is small and the finding that the SMR for men with latency less than 20 years (5.4) was greater than that for men with latency greater than 20 years (3.2) (McDonald et al 1978). While the reason for the high overall SMRs is not clear, selection bias is possible as the cohort was comprised of volunteers participating in a 1960 silica X-ray survey. The participation rate of workers from the mine was not reported.

The Homestake study comprises the largest and oldest cohort of workers exposed to nonasbestiform amphiboles with 47% mortality. In the Steenland and Brown (1995) study, there was a 2.6-fold excess of pneumoconiosis and a 3.5-fold excess of respiratory TB that were significantly associated with cumulative exposure and SMRs were significantly elevated in the highest exposure category for both dust-related diseases. Lung cancer was not associated with cumulative exposure in the SMR exposure-response

analysis and there was a negative trend in the nested lung cancer case-control portion of this study. There were no mesothelioma deaths.

The mesothelioma and lung cancer experience of the amosite and non-fibrous amphibole workers will be compared separately below.

5.5 COMPARISON OF MESOTHELIOMA EXPERIENCE

One method of assessing whether nonasbestiform grunerite acts similarly to amosite is to compare the proportional mortality from mesothelioma in amosite exposed workers and in nonasbestiform grunerite exposed workers. Mesothelioma is a cancer which can clearly be caused by amosite without known confounders such as smoking, although there are a small number of other potential causes. Hodgson and Darnton (2000) argue that there is unlikely to be a threshold for asbestos-related mesothelioma, but that the exposure–response function may be non-linear. As about 80% of mesotheliomas are asbestos related, mesothelioma is a more specific indicator of amphibole asbestos exposure and also more sensitive as there may be an excess mesothelioma risk in the absence of an excess lung cancer risk (Hodgson and Darnton, 2000). The measure of mesothelioma mortality is the percent of total mortality (labelled PMR in this context). To assume a work-related mesothelioma in the non-asbestiform grunerite cohorts there should be no previous asbestos exposure, no exposure to other potential etiological factors such as erionite or therapeutic radiation and the time of death should probably be 20 or more years since hire since exposure or 15+ years since hire if exposure were intense.

Although there were only 19% of persons dead in the amosite cohorts combined, there was an overall excess proportional mortality from mesothelioma of 1.2%. In contrast, 23% of persons were dead in the non-asbestiform cohorts combined and no mesothelioma linked to the exposures in the non-asbestiform cohorts (or 0.03% if the non-exposure related deaths are counted). It is well recognized that the proportion of mesothelioma increases with long follow-up as mesothelioma increases as a cubed function of the time since first exposure and so would increase as the percentage of deaths increase. Certainly on present evidence there is no increased risk of mesothelioma in non-asbestiform amphibole exposed workers at the levels of exposure encountered in these industries (TABLES 3 and 4, FIGURE 1).

In view of the fact that there was no detected increase in mesothelioma, one would not expect to see an increased risk of lung cancer, as usually the exposure necessary to produce an increased risk of lung cancer is much greater that that required to increase mesothelioma risk.

5.6 COMPARISON OF LUNG CANCER EXPERIENCE

There are statistically significant excesses of respiratory cancer in all the amosite asbestos industries (except mining). In contrast, it is very clear that, with the exception of the first

small study of Homestake gold miners (Gilliam et al 1976), there is no increased risk of lung cancer in the non-asbestiform amphibole exposed industries. The results from the study by Gilliam have not been reproduced in subsequent studies with complete ascertainment of the cohort and longer follow-up (Steenland and Brown, 1995; McDonald et al, 1978). In the taconite-exposed miners there were some statistically significant deficits of respiratory cancer. This is in spite of the fact that workers in those industries are exposed to significant silica in addition to nonasbestiform grunerite (if silica increases lung cancer risk).

Another way to examine this question is to compare the exposure-response relationships for the various studies. In TABLE 5 the exposure-response relationships for the studies by Seidman et al (1986) and by Steenland and Brown (1995) are compared. While both have limitations in their exposure estimates, there is clearly no increasing trend of lung cancer with increasing exposure to non-asbestiform grunerite (and other non-asbestiform amphiboles). The exponential increase in pneumoconiosis with increasing exposure suggests exposure produced fibrotic but not carcinogenic effects. There were 115 lung cancer cases vs 92 cases of pneumoconiosis. In contrast there is a steep and statistically significant slope for the lung cancer mortality in the amosite insulation manufacturing plant with 102 cases of lung cancer Vs 15 cases of pneumoconiosis (asbestosis) (FIGURE 2).

Acheson et al (1984) reported concentrations of 30 fibers/ml in the late 1960s in the factory using amosite asbestos. Exposures were probably much dustier before 1964 with improved conditions after 1964. However, Acheson et al (1984) did not attempt to assess exposure-response trends.

It seems clear that exposure to cleavage fragments and/or "fibers" at a concentration of 0.25 fibers/cc longer than 5 μm has not resulted in an increased lung cancer risk for workers.

5.7 OVERALL CONCLUSION CONCERNING ASBESTIFORM AND NON-ASBESTIFORM GRUNERITE.

It is evident that the "fibers" to which the non-asbestiform amphibole workers were exposed were considerably shorter than those to which the amosite workers were exposed. While both the studies of amosite and non-asbestiform grunerite (plus other non-asbestiform amphiboles) may have limitations as far as estimates of fiber exposure are concerned, the results indicate very large differences in the mortality from mesothelioma and from lung cancer from both external and internal comparisons. It seems unlikely that errors in the exposure estimates are responsible for these very large differences as the amosite factory shows a definite increase in risk of lung cancer with increasing exposure while there is no statistically valid increase in trend with non-asbestiform grunerite. The results are consistent with cleavage fragments having no apparent carcinogenic hazard for mesothelioma or lung cancer in contrast to the obvious carcinogenic hazard shown by their asbestiform counterparts.

6.0 THE EVIDENCE FROM STUDIES OF TALC AND VERMICULITE EXPOSED WORKERS

6.1 THE MINERAL TALC

The term talc is used in two ways. First, it is a term applied to a commercial or industrial product that contains finely divided mineral or rock powder that usually, but not always contains the mineral talc as its main component. Second, it can refer to the mineral talc which is a phyllosilicate mineral with the chemical formula $Mg_6Si_8O_{20}(OH)_4$. Since talc is a metamorphic mineral it is often associated with other minerals and is rarely found in its pure form. Co-exposures are specific to each site. Tremolitic talc is a commercial product that contains a high proportion of the amphibole tremolite in addition to the mineral talc; it also can contain other minerals including anthophyllite, a transitional talc/anthophyllite mineral as well as antigorite, lizardite and quartz. Cosmetic and pharmaceutical talcs have strictly controlled mineral contents; industrial talcs may contain other minerals.

Structurally, talc occurs in sheets that can be separated by slight pressure, so that when milled, talc can form cleavage fragments or elongated talc platelets (Wild et al., 2002).

6.2 THE NEW YORK AND NORWEGIAN TALC DEPOSITS (Table 6)

There are at least two talc deposits containing nonasbestiform tremolite and anthophyllite which have been studied, one in New York State and one in Norway. The best known and best characterised is the industrial talc in New York. There has been considerable discussion in the literature concerning whether the tremolite and anthophyllite present in this talc is asbestiform or nonasbestiform. However, the evidence is supportive of nonasbestiform amphiboles (Skinner et al 1988). Norwegian talc contains tremolite and anthophyllite said to be in trace amounts. However, the mineralogy of this talc is less studied and the cohort of exposed miners/millers is much smaller.

The health experience (mesothelioma and lung cancer mortality) of these two cohorts of talc workers exposed to nonasbestiform amphiboles will be compared to 1) anthophyllite asbestos miners, 2) to workers exposed to vermiculite contaminated with tremolite asbestos; and 3) to workers exposed to talc that is not contaminated with amphiboles from Vermont, Italy, France and Austria.

6.2.1 New York Talc

The Gouverneur, New York talc deposit has been well studied for its mineralogy and presence of fibers and cleavage fragments. The mineralogy is complex and there has been a long and ongoing debate about the amphiboles present in NY talc. Dement and Zumwalde (1980) concluded that bulk NY talc samples contained both amphiboles (4.5-

15% anthophyllite and 37-59% tremolite) and serpentines (10-15% lizardite and antigorite) and less than 2.6% free silica as determined by X-ray diffraction and petrographic microscope analysis. It appears that the mineral identified as anthophyllite by Dement and Zumwalde (1980), is, at least in part, a mixed phase mineral with talc evolving from the anthophyllite (Kelse and Thompson 1989). The talc also contains talc fibers. Dement and Zumwalde (1980) considered the airborne dust 'fibers' greater than 5 μm long to contain upward of 70% amphibole asbestos. Based on electron microscopy, Dement and Zumwalde reported that: "In the mine 38% of all fibers were anthophyllite. 19% were tremolite and 39% were unidentified". In the mill 45 per cent of all fibers were anthophyllite, 12 per cent were tremolite and 38 per cent were unidentified. Three percent of the fibers in the mine and 2 percent in the mill reportedly gave chrysotile electron diffraction patterns. According toThompson et al (1984) and Harvey et al (1979) all the amphibole minerals are cleavage fragments and in the non-asbestiform habit and it has now been shown that once the talc fibers are recognised, the talc does not contain asbestiform tremolite or asbestiform anthophyllite (Kelse and Thompson 1989; Dunn Geoscience Corp 1985; Langer and Nolan 1989; Virta 1985; Crane DT 1986; Wylie 1987; Wylie 1993).

A survey of the many mortality studies of workers exposed to NY talc is summarised in APPENDIX 1. Most of these have been variations of the original NIOSH cohort study (Brown et al, 1979, 1980). We will focus on the nested case-control study, which addressed three of the hypotheses raised about reasons for the increased lung cancer, namely smoking, other work exposures, and short-term workers (Gamble, 1993). Honda et al (2002) added 6 more years update and estimated quantitative cumulative exposure to talc dust to address the question of exposure-response (Oestenstad et al, 2002).

Gamble (1993) conducted a case-control study nested in the Brown et al (1990) cohort of NY talc workers. There were 22 cases and 66 controls matched on date of birth and date of hire. All cases were either smokers (91%) or exsmokers compared to 27% nonsmokers, 73% smokers or exsmokers among controls. Negative trends were consistently observed by years worked after controlling for smoking, 20 or more years latency, and exclusion of short-term workers. Lifetime work histories suggested no apparent association with non-talc exposures or non-Gouverneur talc exposures. The author concluded that "after adjustment for...smoking and the postulated role of very high exposures of short-term workers, the risk ratio for lung cancer decreases with increasing tenure." The time occurrence of lung cancer was consistent with a smoking etiology, and was not consistent with an occupational relationship.

Honda et al (2002) assessed cancer and non-cancer mortality among white male Gouverneur talc workers. The cohort analyzed for cancer endpoints consisted of 809 workers employed 1947-1989 and alive in 1950. The cohort analyzed for non-cancer endpoints consisted of 782 men employed during 1960-1989. The important additions in this study were 6 more years of follow-up (through 1989) and internal exposure-response analyses with cumulative exposure to talc dust as the exposure variable. Smoking status was not taken into account. The internal comparisons by cumulative exposure (mg/m^3-yrs) and adjusted for age and latency, showed a significant monotonic decrease in lung

cancer risk with increasing exposure with a RR of 0.5 (0.2-1.3) in the highest exposure category. Mortality from 'other NMRD' and pulmonary fibrosis showed monotonic increases in risk as exposure increase with 2-fold and 12-fold increased risks in the highest exposure categories. **(FIGURE 3)**

Honda et al (2002) concluded that talc dust was unlikely to have a carcinogenic potency similar to asbestos for several reasons. First, there were negative exposure-response trends. Second, although lung cancer mortality was increased nearly 4-fold among miners (SMR of 3.94; 95% CI 2.33-6.22, 18 observed (obs)) it was not excessive among millers (SMR of 1.28; 95% CI 0.51-2.63; 7 obs) although exposure was similar in both groups (medians of 739 mg/m3-years and 683 mg/m3-years respectively). Third, the cumulative exposure was low for lung cancer cases compared to that of other workers. For example, if median cumulative exposure is set at 1.0 for lung cancer decedents, the relative median cumulative exposure is 1.1 for ischemic heart disease, 1.5 for all decedents, 3.5 for NMRD as underlying or contributory cause of death, and 10.8 for pulmonary fibrosis.

Honda et al (2002) conclude that the lung cancer excess is unlikely to be due to talc dust *per se*. The reasons for the excess are unclear. Possible explanations for the excess include confounding by smoking or other risk factors or an unidentified constituent in the ore or mine environment that is poorly correlated with talc dust.

6.2.2 Norwegian Talc

Norwegian talc contains trace amounts of quartz, tremolite and anthophyllite; the main minerals are talc and magnesite. Small amounts of magnetite, chromite, chlorite, and antigorite are in the ore, while the surrounding rock contains small amounts of serpentine, mica, feldspar, calcite, and nonasbestiform amphiboles (hornblende, tremolite). Personal air samples were collected 1982-4. Exposures were somewhat higher in the mine with a range for total dust of 0.94-97.4 mg/m3 and peaks at drilling of 319 mg/m3. The range in the mill was 1.4-54.1 mg/m3 with peaks in the storehouse of 109 mg/m3. Fibers of tremolite, anthophyllite and talc with aspect ratios >3:1 by optical microscopy ranged from 0.2-0.9 f/cc (Wergeland et al., 1990).

The Norwegian male talc cohort consisted of 94 miners employed at least 1 year in talc-exposed jobs 1944-1972 and 295 millers employed at least 2-years 1935-1972 (Wergeland et al., 1990). In contrast to NY talc workers, this is a generally healthy work population with a significant deficit in all-cause mortality (SMR of 0.75; 0.62-0.89), which was below expected in both mine and mill. There were only 6 incident cases of lung cancer and 6.49 expected for a SIR of 0.92. There was a small positive trend with years worked because there were zero cases in the low tenure group but no significant excess (SIR) in the 2 groups with longer tenure. There were two lung cancer cases among miners (1.27 expected) and there were more expected (5.22) than observed (4) in the mill. There was no excess of NMRD cases (3 cases of pneumonia), but numbers were too small to make any conclusions. There were no cases of mesothelioma.

It is unclear why the mortality and incidence of cancer are so far below expected. There is no excess NMRD mortality and no cases of pneumoconiosis as a cause of death despite the apparently very high dust exposures. There were 3 cases of pneumoconiosis as a contributing cause of death: 2 cases with silicosis, 1 case with talcosis. In 1981, smoking histories were obtained from 63 of 94 miners. A reduced prevalence of smoking is an unlikely cause of the reduced mortality as only 8% were nonsmokers. In view of the small size of this cohort, interpretation is difficult.

6.3 NONASBESTIFIORM AMPHIBOLES IN SOUTH CAROLINA VERMICULITE

There is one small vermiculite deposit in South Carolina containing nearly 50% tremolite/actinolite but is believed to be virtually free of fibrous tremolite (McDonald et al, 1988). Mining and the first part of the milling process are carried out wet. Four types of elongated fibers were identified in air samples using EM and energy dispersive X-ray spectroscopy (EDSX): tremolite-actinolite (48%), vermiculite fragments (8%), talc/anthophyllite (5%), iron rich fibers (23%) and the rest unidentified. Mean fiber size was 1.1 μm diameter and 12.7 μm long. This mean fiber length seems to be quite large for the airborne fibrous dust cloud to be totally cleavage fragments. The mean exposure was 0.75 f/cc-yrs.

The mortality study comprises a small cohort of 194 men with 6 months or more tenure before 1971 and a minimum latency of 15 years. There were 51 total deaths and an all-cause mortality of 1.17 (0.87-1.51). There were 4 deaths from lung cancer and 3 from NMRD with SMRs of 1.21 and 1.22 respectively. There were no cases of mesothelioma and no deaths from pneumoconiosis. There was a negative exposure-response trend between cumulative fiber exposure and lung cancer **(FIGURE 4).** Three of the 4 cases were in the lowest exposure category of <1 f/cc-yr (SMR = 1.71) and the 4th case was in the medium exposure category of 1-10 f/cc-yr (SMR = 0.73). Given the low fiber exposures (mean 0.75 f/ml-yrs) and the small sample size the authors concluded there was inadequate power to detect an adverse effect in this population (McDonald et al 1988).

The health experience of workers at this mine would be of considerable interest for comparison with the miners in Montana where exposures involve asbestiform "tremolite". Unfortunately, exposure levels were so much higher in Montana and the study population is so small and exposures so low in South Carolina that at this time no valid comparisons are possible. In the longer term, the population is too small for confident conclusions concerning "no risk". Also the mineralogy of this vermiculite is poorly described, but appears to contain trace amounts of asbestiform amphiboles in addition of nonasbestiform amphiboles.

Although the actual percentage of "non-asbestiform" anthophyllite in the airborne dust is not clear in these studies, for the purposes of this report, it will be considered that the airborne dust contains a proportion of non-asbestiform anthophyllite and non-asbestiform tremolite. In view of this, comparison of the risk of mesothelioma and lung cancer in the

NY and Norwegian talc mining industry will be compared with other talc studies (negative control) and with asbestos-exposed workers in anthophyllite mining and workers exposed to vermiculite contaminated with tremolite asbestos(positive comparison). South Carolina vermiculite will be compared with Libby, Montana vermiculite.

7.0 OTHER TALC DEPOSITS

There are several mortality studies of talc where amphibole minerals are reported to be absent and the talc is relatively "pure" talc. These include studies of workers in the Vermont talc mines (Selevan et al, 1979), Italian talc mines (Coggiola et al., 2003), French and Austrian talc mines (Wild et al, 2002) (Table 6). According to Wild et al (2002) "no asbestos contamination has ever been clearly documented in the talc deposits, at least not in the European sites."

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7.1 LUNG CANCER IN NEW YORK AND VERMONT TALC MINERS AND MILLERS

In contrast to the high levels of amphibole cleavage fragments in the New York Gouverneur talc deposit, geological studies conducted since the early1900's have shown no "asbestos" and little quartz in Vermont talc deposits (Boundy et al, 1979). Analyses of bulk samples collected in 1975/1976 from mines and mills of the three major Vermont talc companies showed talc and magnesite as major components (20-100%) and chlorite and/or dolomite as minor constituents (5-20%). There were trace amounts (<5%) of dolomite, calcite, quartz, biotite, ankerite, chromite, phlogopite and oligoclase and no asbestos.

Sampling surveys conducted in summer/winter of 1975/1976 at the 3 talc mines/mills resulted in respirable geometric mean concentrations in the mines ranging from 0.5-5.1 mg/m^3 (median = 0.9) and in the mills from 0.5-2.9 mg/m^3 (median = 1.0). Two methods were used to count "fibers" with aspect ratios >3:1 and a "maximum width and minimum length" of 5 μm. Counts using phase contrast microscopy at a magnification of 437x ranged from 0-60 fibers/cc (median = 4.1). Parallel fibers counted by SEM at a magnification of 5000x ranged from 0-0.8 fibers/cc (median = 0). Cumulative exposures were not estimated, but past exposure levels commonly exceeded the MSHA and OSHA standards of 20 mppcf. (Selevan et al 1979).

The Vermont talc study provides the best comparison with the New York talc because the original studies were conducted during the same time period using the same methods and investigators, and the mines were in adjacent US States only a few miles apart (although different ore bodies).

The cohort comprised 392 men who had had a chest radiograph administered by the Vermont Health Department since 1937 and had been employed for more than 1 year in the Vermont talc industry between January 1, 1940 and December 31, 1969. Workers were followed through December 31, 1975. As the inclusion of workers in the cohort required a radiographic examination, it was thought that long-term workers were more likely to have participated than short-term workers. In the 1960's the Health Department reported that 70% of those missing from their radiographic surveys had less than 1-year employment. While the overall effect is not known, the original authors concluded that selection bias could not explain the observed excess mortality.

There were a total of 90 deaths with an overall SMR of 1.16. Mortality from NMRD (excluding influenza and pneumonia) was the only cause of death in statistically significant excess and was primarily among millers (SMR=7.87 using the USA comparison or 5.26 using Vermont as the comparison group). Radiographic evidence of pneumoconiosis (80% >2/1) taken as part of the annual radiographic surveillance program of active workers, suggested to the authors that Vermont talc exposure was the causal agent. There was a non-significant 2-fold excess of lung cancer, which was significant among the miners (SMR = 4.35 using USA rates, or SMR = 4.1 using Vermont referent rates) but not millers. There were no cases of mesothelioma (Selevan et al, 1979).

Overall, lung cancer, mesothelioma and NMRD were similar in the NY and Vermont talc cohorts. In the Vermont mills the mortality from NMRD was twice that in the mines, while in the New York deposit the mortality from NMRD was similar for mine and mill workers (Honda et al, 2002). However, the lung cancer mortality was similar in the two cohorts with 4.6- and 3.9-fold excess lung cancer in both Vermont and NY talc miners and no excess among millers in either cohort. (TABLE 6)

Selevan et al (1979) concluded that for NMRD, "additional etiologic agent(s) either alone or in combination with talc dust affect mine workers" because exposures were higher in the mill than in the mines yet mortality was higher in the mines. If this same reasoning is used for lung cancer, one would also conclude that other etiological agents were involved since SMRs for lung cancer were near the null among millers in both cohorts.

A clear limitation of the Vermont study is the small number of deaths and fact that there were only 6 lung cancer deaths and 11 deaths from NMRD. Nevertheless, the increased risk of lung cancer in talc miners in Vermont where there is no evidence of exposure to asbestos or amphibole cleavage fragments is consistent with a conclusion that amphibole cleavage fragments are not responsible for the increased risk of lung cancer in the New York Talc miners. On the other hand the increased risk of Non-Malignant Respiratory Disease (Pneumoconiosis) appears to be related to the talc dust exposure.

Unfortunately the reason for the increased risks of lung cancer in the New York and Vermont mining areas still remains speculation. This includes exposure to radon as levels

were apparently elevated in the Vermont Mines. The possibility that miners worked in areas of high asbestiform tremolite in the past cannot be totally excluded on present evidence as in one closed mine in Vermont "cobblestones of serpentine rock which were "highly tremolitic" have been reported, although workers in the Vermont cohort were considered unlikely to have had such exposure (Selevan et al 1979). Whether this was asbestiform tremolite is not described although this appears to be inferred.

7.2 ITALIAN TALC

Italian talc is very pure and is used in the pharmaceutical and cosmetic industries. Miners and millers in this industry were studied for mortality (Rubino et al 1976, 1979; Coggiola et al 2003). Miners were analyzed separately from millers because of silica exposure in the mine. The silica content of airborne dust in the mines was as high as 18% in drilling operations from footwall contact rocks, rock type inclusions, carbonate, calcite and magnesite inclusions. The quartz content of the rock strata was inconsistent, ranging from 10-45%. Other minerals in the inclusions included muscovite, chlorite, garnet, and some carbonate material. A small amount of (nonasbestiform?) tremolite was detected in the inclusions but not in the talc samples. Talc samples were commonly contaminated with chlorite. From 1920-1950 there was dry drilling and no forced ventilation so exposures were over 10 times the TLV (which appears to have been about 25 mppcf at that time) in the mines and a little over the TLV in the mills. Wet drilling and forced ventilation were introduced in about 1950 and dust concentrations dropped precipitously to about 1 mppcf and well below the TLV. Concentrations in the mills were reduced slightly and slowly and after about 1960 were higher than in the mines (Rubino et al, 1976).

Coggiola et al (2003) updated the earlier talc studies by Rubino et al (1976, 1979). The updated cohort comprised 1,795 men with at least 1 year of employment 1946-1995 and national rates were used for comparisons. There were 880 observed deaths with an overall SMR of 1.20 (1.12-1.28). There were slight deficits in observed lung cancer and total cancer and there were no mesotheliomas.

The SMR for lung cancer was 1.07 (0.73-1.50) for miners, while there was a deficit of lung cancer with an SMR of 0.69 (0.34-1.23) in millers. There was a 2-fold excess of NMRD due mainly to silicosis with the excess occurring among miners with a significant SMR of 3.05 (2.50-3.70) compared to 1.04 (0.65-1.57) among millers. Exposure-response was examined using duration of exposure. This showed that for miners the only lung cancer excess was in the <10-year exposure group while for NMRD the exposure-response trends were flat with all categories of duration of exposure showing about a 2-fold excess mortality.

The authors concluded there was no association between lung cancer or mesothelioma and exposure to talc containing no asbestos fibers. But there was an association in miners between NMRD (primarily silicosis) and talc containing quartz.

7.3 FRENCH AND AUSTRIAN TALCS

Wild et al (2002) conducted cohort studies of talc workers in France and Austria with nested case-control studies of lung cancer and NMRD. The French ore was a talc chlorite mixture with quartz contamination ranging from undetectable to less than 3%. In Austria, three mines were studied. At one site the ore was a talc-chlorite mixture with 0.5-4% quartz. Dead rock inclusions of about 25% gneiss were not milled. A talc-dolomite mixture of 25% medium talc and <1% quartz in the final product was the product at the second mine. The ore at the third site did not contain talc but was mixture of approximately equal proportions of quartz, chlorite and mica. Workers were stratified into semi-quantitative exposure categories. The non-exposed group consisted of office workers not exposed to talc and personal dust samples averaged 0.2 mg/m3. The low exposure group was for workers with no direct contact to talc, such as maintenance workers, and concentrations were less than 5 mg/m3. The medium exposure category included workers exposed to concentrations between 5-30 mg/m3 for dustier areas such as bagging or milling and onsite maintenance. Quartz exposures occurred mostly in underground mining, tunneling and barrage building and milling products at site D. The highest exposure category was reserved for past production jobs (all before 1980) where concentrations were >30 mg/m3. Some samples produced concentrations >50 mg/m3 and higher. Three samples taken on workers wearing personal protective equipment were 73, 82 and 159 mg/m3. To calculate cumulative exposures, values of 2.5, 10 and 40 mg/m3 were assigned to the low, medium and high exposure jobs.

The French cohort consisted of 1070 men with more than one year tenure between 1945 and 1995, with vital status follow-up through 1996. The Austrian cohort consisted of 542 men with >1-year tenure between 1972 through 1995 and vital status follow-up during this same period. Three controls per each case of NMRD and lung cancer from both the French and Austrian cohorts were matched on age and calendar year of employment.

Overall mortality was below expected. There were 294 deaths in the French cohort in the period 1968-1996 for an SMR of 0.93 (0.82-1.04). The Austrian cohort was smaller with 67 deaths and an SMR of 0.75 (0.58-0.95). In the French cohort SMRs were only slightly elevated for NMRD and lung cancer (1.06 and 1.23 respectively) but were increased over five-fold (SMR = 5.56; 1.12-16.2) for the 3 cases with pneumoconiosis. There were zero mesotheliomas.

The case-control studies combined the French and Austrian cohorts. There were 40 combined deaths from NMRD: 10 from pneumoconiosis (including silicotuberculosis), 10 from chronic obstructive pulmonary disease (COPD, restricted to chronic bronchitis and airway obstruction), and 20 deaths from pneumonia and other diseases. When analyzed by exposure categories, the exposure-response trend for NMRD was not monotonic, with no apparent increased mortality below 400 mg/m^3-yrs and 2-fold and 2.5-fold increased risks in the 2 highest exposure categories respectively. When analyzed by conditional logistic regression there was a significant exposure-response trend with an

8% increased risk per 100 mg/m^3-yrs exposure. The slope was even higher for pneumoconiosis, 1.17 for pneumoconiosis Vs 1.08 for NMRD. The slope was only 1.02 for COPD. Adjustments for covariates in the regression analyses had little effect on these trends. Smoking prevalences were similar between cases and controls with about 40% nonsmokers. (FIGURE 5)

There were 30 combined lung cancer cases. There was a negative exposure-response trend with odds ratios of 0.6 and 0.73 in the two highest exposure categories. The trend was unchanged when adjustments were made for smoking, quartz, working underground or when lagging the exposure estimates. Also, there were no trends when analyzed by maximum dose, latency, or duration of exposure (data not shown). About 40% of the controls were nonsmokers compared to about 8% (1/19) among cases although smoking classification was unknown on about half of the cases.

Wild et al (2002) concluded that the small excess of lung cancer was not due to talc, despite follow-up of over 50 years, high exposures and mean duration of exposure >20 years.

The pattern of mortality of workers exposed to cleavage fragments in the New York talc mines and mills (FIGURE 3) is very similar to that of workers in the French and Austrian mines and mills where there was no exposure to cleavage fragments (FIGURE 5). The latter shows the French-Austrian exposure-response trends for lung cancer and NMRD (categorical analyses by exposure group) and for pneumoconiosis (continual analysis by conditional logistic analyses) from the case control studies. A major problem is the very large differences in the cumulative exposures of workers in these two studies. If they are comparable, the dust to which the New York miners and millers are exposed is considerably more potent than that in the French and Austrian mines and mills from the standpoint of increasing lung fibrosis/pneumoconiosis. On the other hand, this "apparently highly potent pneumoconiosis producing dust" does not increase lung cancer risk.

These studies show that "pure" talc does not increase lung cancer risk. This is consistent with the observations for the New York millers, exposed to talc as there was no excess lung cancer in talc millers.

8.0 ASBESTOS-EXPOSED COHORTS FOR COMPARISON WITH NEW YORK TALC WORKERS.

There are 2 ore deposits containing tremolite asbestos or anthophyllite asbestos potentially suitable for comparison with the talc cohorts exposed to nonasbestiform tremolite and asbestos. One site is the vermiculite mine located in Libby, Montana with

significant contamination from tremolite asbestos. The other is an anthophyllite asbestos mine in Finland.

8.1 LIBBY, MONTANA VERMICULITE MINE CONTAMINATED WITH ASBESTIFORM TREMOLITE

Ore fed to the mill in Libby, Montana contains 4-6% asbestiform amphiboles in the tremolitic series. The health concern is the asbestiform amphibole contamination in these ores and not the vermiculite.

The raw ore and vermiculite concentrate from the Libby mine contains both asbestiform and non-asbestiform tremolite-actinolite and non-fibrous anthophyllite. Atkinson et al (1982) found 21-26% fibrous tremolite-actinolite in the raw ore and 2-6% in the concentrate. Company data taken several years later indicated 3.5-6.4% at the head feed of the mill and 0.4-1% in the concentrate (Amandus et al, 1987a). After removal of coarse rock the ore contained about 20% vermiculite, 21-26% fibrous tremolite-actinolite and the rest augite, biotite, calcite, diopside, hornblende, magnetite, quartz, sphene, and non-fibrous tremolite-actinolite (McDonald et al, 1986).

Eight airborne samples from the mill and screening plant examined by phase contrast light microscopy indicate the asbestiform nature of the particles: 96% had aspect ratios >10, 67% >20 and 16% >50. In addition, 73% of the fibers were longer than 10 μm, 36% >20 μm and 11% >40 μm and width was < 2.5 μm in all instances (Amandus et al, (1987a).

Two independent mortality studies of the Montana vermiculite have been conducted. McDonald et al (1986) conducted a cohort and nested case-control study of 406 persons employed for at least a year prior to 1963 with follow-up until 1983. This was later updated with follow-up to 1999 (McDonald et al, 2002; 2004). We will primarily focus on the up-dated analysis. Exposure was estimated from first exposure (1945) to 1982 when work histories were no longer available. By this date most of the cohort was no longer employed and fiber concentrations were about 0.1 f/ml. The plant closed in 1990. Before wet milling processes were installed, fiber concentrations were very high (estimates of >100 f/ml). A wet mill was installed in 1954 and an entirely wet process replaced both wet and dry mills in 1970 so by 1980 nearly all concentrations were <1 f/ml. Exposure-response was estimated by both categorical and linear E-R Poisson regression models and excluding those with <10 years latency. Average and cumulative exposure metrics showed similar relationships with mortality.
In the Libby cohort, the overall all cause SMR was 1.27 (1.13-1.43). SMRs for lung cancer and NMRD were 2.40 (1.74-3.22) and 3.09 (2.30-4.06) respectively; the PMR for mesothelioma was 4.2%. Exposure-response trends were not linear, as risks of lung cancer, NMRD and mesothelioma increased steeply in the second quartile exposure category and showed less steep slopes in the third and fourth exposure quartiles. **(FIGURE 4, TABLE 8)**.

The other Libby cohort study was by NIOSH and published in 3 sections that included exposure estimates (Amandus et al., 1987a), cohort mortality study (Amandus et al (1987b) and a cross-sectional radiographic study (Amandus et al (1987c). Amandus et al

(1987b) also reported positive exposure-response trends for lung cancer with an almost 7-fold increased SMR in the high exposure category with more than 20-years latency. The PMR for mesothelioma was 2.2% considering only those with 20 years or more latency.

These results are a marked contrast to the decreasing trend of lung cancer with increasing exposure seen in the New York talc miners. There is little doubt that the mesothelioma experience of the Montana work force is considerably worse than that of the talc miners. This is in spite of the fact that the New York Talc ore workers are reported to have been exposed to dusts containing a very high percentage of talc fibers (Kelse and Thompson, 1989).

The amphiboles in NY talc are nonasbestiform while they are asbestos in the Libby deposit (Kelse and Thompson, 1989; Langer and Nolan, 1989; Thompson et al, 1984; Dement and Zumwalde, 1980).

While not on the same scale as exposures for the New York Talc Miners it can be seen from FIGURE 4 that there are clear increases in deaths from both pneumoconiosis and lung cancer which relate to cumulative fiber exposure when workers are exposed to asbestiform tremolite. There are certainly no such exposure-related increases in lung cancer risk for New York talc miners and miners (FIGURE 3).

8.2 FINNISH ANTHOPHYLLITE ASBESTOS MINERS/MILLERS

Dement and Zumwalde (1980) mentioned the study of Finnish miners by Meurman et al, (1974) in the belief that both the NY talc and Finnish anthophyllite asbestos cohorts were exposed to asbestiform anthophyllite. They recommended that the risk of mesothelioma should be further studied by further follow-up of the NY talc workers. Both the NY talc (Honda et al, 2002) and anthophyllite asbestos cohorts have had further follow-up so the maximum latency in Finland is now about 40 years (Karjalainen et al., 1994; Meurman et al, 1994).

In the updated Finnish study there was a significant 2.9-fold excess incidence of lung cancer overall with a somewhat higher risk in the heavily exposed males (SIR 3.15) than in moderately exposed (SIR 2.35). There were four mesothelioma cases for a significant 46-fold increased SIR (95% CI = 12.2-115) overall All of the cases were in the heavy exposure group where there was a 67-fold excess (95% CI = 18.3-172) and all four had asbestosis. Asbestosis was mentioned on 20% of all death certificates (Karjalainen et al, 1994; Meurman et al, 1994).

8.3 MESOTHELIOMA COMPARISONS

In the NY talc cohort, Honda et al (2002) reported 2 deaths from mesothelioma. One was coded as benign neoplasm of the respiratory system and the other as malignant neoplasm of the lung and bronchus, unspecified. One man worked for 15 years and died 15 years after starting work at the talc facility. He had been a carpenter and millwright for 16 years, 8 years as a lead miner and 5 years as a repairman in a milk plant. The other man worked briefly at the facility as a draftsman during mill construction. He would have had minimal talc exposure. He had been employed on the construction of a previous talc mine, and then installed oil burning heating systems. Honda et al (2002) concluded it is unlikely that either of these cases occurred as a result of talc exposure in the mine or mill that they were studying. In essence, there are no mesothelioma cases that are plausibly related to the cohort of Gouverneur talc workers.

Vianna et al (1981) reported a mesothelioma rate in Jefferson County twice that of New York State based on an incidence study of histologically confirmed mesothelioma cases. A total of six cases, four male and two female cases diagnosed between 1973 and 1978 were reported to have occurred in talc miners. Enterline and Henderson (1987) reported an excess mesothelioma incidence in Jefferson County from 1968 to 1981 with 4 female (0.6 expected) cases and 7 male (1.4 expected) cases for risk ratios of 6.7 and 5.0 respectively. These latter rates were the second and sixth highest in the USA.

Hull et al (2002) drew attention to these elevated rates, added "five new mesothelioma cases," and concluded New York talc exposure was associated with increased risk of mesothelioma. This conclusion is inconsistent with the limited available data as outlined in the following bullet points.

- The entire work history of the "talc miners" with mesothelioma is apparently not known. Exposure to asbestos in other jobs is likely given the diagnosis of asbestosis and the smaller widths of the fibers in lung tissue.

- Hull et al. [2002] attempt to interpret the results of their tissue analyses of only two mesothelioma cases. This sample is too limited to reach any reliable conclusions. What data is available does not support a talc etiology.

- Fiber dimensions are consistent with asbestos exposure as the mean fiber widths in the 2 mesothelioma cases examined are less than 0.25 μm, which are the dimensions characteristic of asbestos.

- The source of the fibers in the lungs is unlikely to be NY talc mines. The average width of the fibers in the mesothelioma lungs was 0.15 μm, which is considerably less than the average width of 1.3 μm of anthophyllite and tremolite in milled talc

samples (Siegrist and Wylie, 1980). Kelse and Thompson (1989) reported 0% fibers in NY talc samples had widths less than 0.25 μum.

- Asbestos-related employment occurs among residents of the two talc-mining counties. Fitzgerald et al (1991) reported that 39% of workers with radiographic abnormalities of parenchyma and pleura had been employed for a year or more in asbestos-related industries (e.g., shipyard, construction, pipe and furnace insulation).

- Two of the five cases had worked only four years and two years in occupations likely to be linked to the mining industry. One of these persons died at age 72 and the other at age 53. There was no information concerning their employment during the rest of their lives.

- A non-talc etiology for mesothelioma is plausible. As noted above, females in the talc mining counties have a greater risk of mesothelioma than males (Enterline and Henderson, 1987). On the other hand, the cohort data on talc workers is based on men because less than 5% of those hired in the talc industry were women (Honda et al, 2002; Brown et al, 1990; Lamm et al, 1988).

- In the cohorts, the worker populations and exposures are well defined and no association is observed between talc or nonasbestiform amphibole exposure and mesothelioma in the absence of possible asbestos exposure. The cohort studies provide a more reliable estimate of risk than a small case series with limited information on exposure.

Comment [GG1]: •

Comment [GG2]:

- In the Libby cohort there were twelve mesothelioma cases. The PMR was 4.2 %. Exposure to tremolite asbestos in the Libby vermiculite clearly increased the risk of mesothelioma (McDonald et al 2004). These comparisons show a clear excess incidence of mesothelioma for workers exposed to asbestiform tremolite and anthophyllite, but no mesothelioma attributable to exposure to nonasbestiform tremolite/actinolite or anthophyllite.These comparisons are graphically displayed in FIGURE 6.

8.4 LUNG CANCER COMPARISONS

There was an overall 2-fold increased rate of lung cancer in the New York Gouverneur talc miners and millers compared to the surrounding counties in which the mine was located. This excess of lung cancer was concentrated in miners with an SMR of 3.94 (CI= 3.33-6.22) while millers had only a small increased risk with an SMR= 1.28 (CI 0.51-2.63). In contrast, non-malignant respiratory disease mortality was increased in both miners (SMR= 2.41, CI =1.16-4.44) and in millers (SMR =2.27 CI= 1.13-4.07) to almost the same extent. When exposure-response relationships were examined, the rate ratio for the highest respirable dust exposed workers to the lowest respirable dust exposed workers was 0.5 (0.2-1.3) for lung cancer and 11.8 (3.1-44.9) for pulmonary fibrosis. **(FIGURE**

3) One would expect that a respirable dust exposure index would reflect the respirable fractions of dust regardless of composition. Thus, the results indicate that the lung cancer excess in this industry is unlikely to be the result of exposure to the respirable fraction of dust (which would include talc and cleavage fragments of the various amphibole minerals). On the other hand the data suggest that the respirable dust did increase the risk of fibrosis.

In asbestos producing or using industries where midget impinger measurements were used as a basis for exposure estimates (Liddell et al 1997), the risk of lung cancer increased with increasing levels of exposure. This illustrates the validity of exposure indices based on midget impinger measurements for assessing fibre-related risks, at least when exposures are high. However, in this talc mine, exposure estimates derived from midget impinger measurements (Oestenstad et al 2002), showed no such relationship. If cleavage fragments were responsible for the lung cancer excess, an exposure-response relationship would have been anticipated.

Unfortunately, to date a satisfactory explanation for the observation of an overall excess of lung cancer and for the concentration of the excess in miners rather than millers has not been found for workers exposed to either NY or Vermont talc, although at least part of the excess among NY talc workers is due to smoking (Gamble, 1993; Honda et al, 2002). If the airborne dust contained over 70% amphibole asbestos fibers as reported by Dement and Zumwalde (1980), there should an overall increased risk of lung cancer, which there is, but there should also be a logical increasing risk of lung cancer with increasing dust exposure, with a very high risk of lung cancer in highly exposed workers. This is clearly not the case.

In Finland where the incidence of cancer has been studied in anthophyllite miners, it was found that among heavily exposed male workers, the standardized incidence ratio (SIR) for lung cancer was 5.54 (CI= 3.90-7.63) and among moderately exposed workers it was 1.63 (0.20-5.89). The heavily exposed were those who worked in the mine or mill and the moderately exposed included all other personnel (Meurman et al 1994). This exposure-response pattern is quite the opposite of that in the New York talc mines and mills.

There were consistent positive exposure-response trends for lung cancer risk as winchite (soda tremolite) asbestos exposure increased in the Libby cohort. The slope of the exposure-response curve was steeper for lung cancer than for pneumoconiosis and for mesothelioma (FIGURE 4).

The clear exposure-response trends for lung cancer to increase with increasing exposure to asbestiform tremolite and anthophyllite is in marked contrast to the negative exposure-response trend for lung cancer risk to decrease with increasing exposure to nonasbestiform tremolite and anthophyllite present in industrial talc. The pattern of increasing risk of fibrosis is consistent with the tremolite asbestos pattern.

These lung cancer comparisons are graphically displayed in FIGURE 6.

9.0 BIOLOGICAL PLAUSIBILITY

Biological plausibility is not a necessary prerequisite to establishing a causal association. However, in this case, it is quite useful to consider whether or not the experimental evidence supports the hypothesis that cleavage fragments are less carcinogenic than asbestos fibers as there have been studies to assess the harmful effects of asbestiform and non-asbestiform varieties of amphiboles. These issues have been independently evaluated by Addison and McConnell and by Mossman, elsewhere in this monograph.

Experimental studies have the potential advantage of precisely defining the characteristics of the minerals and amount of exposure. However there are also difficulties that affect the studies and their interpretation. Hence it is important to examine the overall pattern of biological responses to asbestos fibers and cleavage fragments rather than the results of single studies. Feeding studies will not be considered.

Many experiments in animals have been used to assess the potential of fibers to produce mesothelioma-type neoplasms. For example, Stanton et al (1981) counted as a positive response, pleural sarcomas that resembled the mesenchymal mesothelioma of man. The observed response is a measure of potential hazard rather than risk. Nevertheless such studies have been helpful in suggesting the morphological characteristics of particles in relation to "mesothelioma" producing potency. "Index particles" have been derived from these experiments. For example, based on the work of Stanton and colleagues the index particle is >8 μm long and <0.25 μm wide and is the best predictor of tumors without regard to the chemical composition of the particle. As far as we were able to ascertain, few if any cleavage fragments have the combination of diameter less than 0.25 μm and length greater than 8 μm. This would suggest that cleavage fragments are not the most potent particles for the production of mesothelioma.

Different exposure techniques have been used, but most have not involved the inhalation route of exposure applicable to humans. Most experiments have involved placing fibers onto the pleural or into the peritoneal cavity or injections intratracheally, routes of exposure which are artificial. The incidence of tumors is therefore higher and the tests are likely to be more sensitive than by inhalation. However, these experiments ignore the factors which limit fiber passage to these sites and also the alterations to the particles during their passage to these sites if they get there at all. Nevertheless, these data are useful in hazard assessment, as the absence of "mesothelioma" occurrence when fibers are placed directly on the pleura or peritoneum in sufficient numbers, is strong evidence that human inhalation exposure is unlikely to be hazardous.

Samples used in experimental studies are not always related to the minerals to which workers are exposed. For example, no experimental studies of the Homestake gold ore were found. On the other hand, there are several studies of tremolitic talc samples from the Gouverneur Talc Company (GTC) mine in New York State (talc samples 6 and 7 used by Stanton et al, (1981); FD-14 and FD-275 used by Smith et al, (1979) and FD-275 by McConnell et al (1983)) in feeding studies. Wylie et al, (1997) used in-vitro cell

studies to compare the effects of asbestos fibers to talc fibers and transitional fibers in NY talc.

FIGURE 7 shows the results of rat injection studies of asbestiform and nonasbestiform varieties of amphiboles, primarily tremolite. These data show a consistent pattern of high incidence of mesothelioma tumors with exposure to tremolite asbestos from South Korea, California, Swansea and Italy (Davis et al, 1985; Wagner et al, 1969, 1982; Stanton et al, 1981). The mesothelioma incidence of both controls and samples was around 10%. The two Scottish tremolites studied contained relatively few asbestiform fibers and there was little difference between the control and exposed rats irrespective of whether the tremolite was asbestiform or not. Davis et al (1991) noted that the intraperitoneal injection test used in their experiments is extremely sensitive so that any dust that produces fewer than 10% tumors is unlikely to show evidence of carcinogenicity by inhalation. Thus the nonasbestiform Scottish tremolite from Shinness was considered to pose no hazard. The Scottish tremolite from Dornie was considered to be probably harmless as well. The latter sample was described as containing mostly cleavage fragments but also some very long, thin fibers, with a possible small asbestiform subpopulation. These results should be contrasted with those of asbestiform tremolite from Italy, California, Swansea and South Korea, which showed incidences of 70-100%. The Italian tremolite was described as a needle-like (byssolite) tremolite fiber but later shown to have an asbestiform component. For this fiber, the induction of tumors was much later than for the three asbestos types from California, Swansea and Korea. This is a normal response to a small dose of amphibole asbestos. Incidence was reduced to near zero for samples of nonasbestiform tremolitic talc (Wagner et al, 1982; Stanton et al, 1981).

Smith et al (1979) assessed the incidence of tumors after injection of NY tremolitic talc and tremolite asbestos at two different doses. There were clear exposure-response trends for the asbestiform tremolite but no effect of nonasbestiform tremolite at either 10 or 25 mg exposures **(FIGURE 8).**

9.1 STATISTICAL ANALYSIS OF POTENCY BY SIZE, SHAPE AND MINERALOGY

Berman et al (1995) conducted a statistical reanalysis of inhalation studies using data from studies of AF/HAN rats exposed to different types of asbestos to identify the exposure metrics that best predicted the incidence of lung cancer or mesothelioma. New exposure metrics were first generated from samples of the original dust because of limitations in the original characterizations. This analysis provided more detailed information on mineralogy (i.e., chrysotile, amosite, crocidolite, tremolite), type of structure (i.e., fiber, bundle, cluster, matrix), size (length, width) and complexity (i.e., number of identifiable components). In particular, transmission electron microscopy (TEM) was added to the descriptions so that asbestos structures less than 0.2 μm could be detected and identified and use in the statistical analysis of size distributions to evaluate combined effects of length and width.

Implantation and injection studies generally indicate long, thin fibers are most likely to induce mesothelioma. However, Berman et al (1995) considered inhalation studies more relevant for assessing human risk because lung retention and transport from the lungs are likely to be important variables in potency but are bypassed in the implantation/injection studies. Also the exposure metrics from these studies are unable to satisfactorily predict tumor incidence (for example see Oehlert, 1991).

The analysis by Berman et al (1995) indicated that particles contributing to lung tumor risk are long (>5 μm) thin (<0.4 μm) fibers or bundles with the potency increasing as length increases. For example, thin fibers longer than 40 μm are about 500 times more potent than thin fibers 5-40 μm in length. Long and very thick particles (>5 μm) may pose some risk, but these appear to be complex structures rather than fibers. It is hypothesized that these fat structures may break down and release additional long thin fibers or bundles. Short particles less than 5 μm in length do not appear to pose any lung cancer risk in this database. Thus in rats a particle length of 5 μm or less (or as Berman et al suggest, 5-10 μm or less) appears to have zero potency. There was no apparent difference in potency to cause lung cancer between serpentine asbestos (chrysotile) and amphiboles (crocidolite, amosite, and tremolite asbestos).

Amphiboles appeared to be about 3.4 times more potent than chrysotile for inducing mesothelioma in rats assuming the potency by size is similar for mesothelioma and lung cancer, which in humans is not the case. This is probably because chrysotile is relatively soluble and its biopersistence much less than that of the amphiboles.

The only other available data set for quantitatively assessing particle size is that of Stanton et al (1981). The Berman et al (1995) data set is considered more relevant because

1) It is based on an inhalation rather than implantation route of exposure;
2) It includes a range of representative samples of both asbestos types and particle sizes;
3) There is a more detailed characterization of long particles and complex structures than any other experimental study; and
4) The statistical analysis is more appropriate.

The analysis by Berman et al (1995) is more appropriate as logarithms were not used, which avoided the problem of zero exposures in some size ranges and 0 tumors at some exposures. Also, an optimum exposure index was determined that provides a statistically adequate fit to the data. The models used by Stanton et al (1981) do not fit the data well and therefore do not adequately describe the ranking of particle size potency.

In a statistical reanalysis of the Stanton et al (1981) data, Oehlert (1991) confirmed the Stanton hypothesis that the primary ability of mineral particles to cause tumors are their dimensional properties, namely index particles that are long and thin (> 8 μm long and <0.25 um wide). Using improved models that fit the data better, Oehlert (1991) reinforced the idea that very long, very thin particles were the best predictors for tumors and that particles with dimensions outside the index class did not contribute to

carcinogenicity. This is also in agreement with Berman et al (1995) that non-index particles have essentially zero potency.

Oehlert (1991) disagreed with the Stanton hypothesis that dimensions alone determine carcinogenic potency. Model fit was significantly improved by assessing each mineral type separately, which indicates mineral type is also important. This disagreement was unfounded, as in fact, Stanton, himself noted that the solubility of the fiber was also important, a parameter that would be incorporated in any analysis by considering fiber type. Dimensions are necessary but are not alone sufficient to classify a substance as capable of inducing tumors. It is now well established that factors such as particle solubility and perhaps surface properties are also important. For example, fibrous talc from the Gouverneur talc deposit in New York is not equivalent to amosite in tumor producing potential although the dimensions are similar.

In sum, the Oehlert (1991) reanalysis of the Stanton et al (1981) data is consistent with Berman et al (1995) that particles of certain dimensions are important predictors of tumor incidence. Long and thin particles are the significant dimensions. Also, the minerals comprising sufficient particles in these size ranges to produce tumors included asbestos (crocidolite, amosite, and tremolite asbestos) but not the nonasbestiform amphibole mineral (tremolitic talc).

Given the importance of width and length from these experimental data, it is useful to summarize available data on dimensions of amphiboles in the epidemiological studies summarized in previous sections [TABLE 8].

This analysis indicates low amounts or the absence of long, thin particles in the size ranges that predict lung tumors or mesothelioma in the three ore bodies containing nonasbestiform amphiboles (NY talc, taconite and Homestake). A primary interest in studying these workers is the fact that they were exposed to nonasbestiform amphiboles. Steenland and Brown (1995) expressed the interest as follows: "Nonasbestiform amphibole fibers have not been shown to cause lung cancer, **but are suspect because of their similarity to asbestiform fibers** (emphasis added)." The data in TABLE 8 and noted above suggest that the similarity is applicable only to chemistry since there is no similarity in the occurrence of index particles. The long thin elongated particles (fibers) capable of inducing tumors are common in asbestiform amphiboles and absent in nonasbestiform amphiboles.

The absence of long thin particles in the size ranges identified by Stanton (1981) and by Berman (95) as responsible or lung cancer and mesothelioma experimentally from ores containing nonasbestiform amphiboles detracts from the hypothesis that nonasbestiform particles have a carcinogenic potency similar to asbestos fibers. The other parameter which is now recognized as being important is biopersistence. As the cleavage fragments are in general shorter than the asbestos fibers they are likely to be more readily removed by macrophages than the asbestos. On the other hand, the solubility difference between cleavage fragments and fibers is not known and is assumed to be the same. However, it is possible that fibers, because they could split apart, would have greater surface areas and

might be more soluble than cleavage fragments of the same dimensions. This would mean that they would have greater lung biopersistence than fibers. On this basis, long cleavage fragments would have the potential to pose a lung cancer/mesothelioma risk if cleavage fragments had the same biological potency as asbestos fibers of the same length.

In fact this is not a real problem because the biopersistence of the amphibole fibers is known to be very high. Even if there were long cleavage fragments, their large diameters would reduce the risk compared to asbestos and their retention would be highly unlikely to render them more hazardous than the asbestos fibers. In this regard, it should be noted that the sample FD14 from the NY deposit did contain elongated particles that ranged up to 50 um in length [Griegner G and Walter C. McCrone Associates analysis of tremolitic talc FD-14, April 5, 1972] and did not produce mesothelioma.

Conclusions about cleavage fragments from some of the other experiments are somewhat limited because, for example, the sample of Greenland non-asbestiform tremolite studied by Wagner et al [1982] had no fibers greater than 10 um in length and less than 0.25 um in width. The sample FD 275-1 did not contain any particles longer than 10um in length and no particles with a width less than 1 um. Stanton (1973) showed that crocidolite, pulverized to the state where 80% of the mass of fibres was in the size range less than 10 μm in length, produced a "negligible incidence" of mesotheliomas in pleural implantation studies.

While it is reassuring that none of the samples of non-asbestiform tremolite have produced elevated rates of mesothelioma in experimental animals, it is unfortunate that systematic studies have not been done to determine whether cleavage fragments of the same lengths as asbestos fibers produce the same risks as doses have generally been measured on a mass basis and not on the basis of number of fibers or cleavage fragments of particular lengths. An obvious problem with cleavage fragment studies is that in order to achieve similar numbers of long thin fibers to the tremolite asbestos in the dose, there would have had to be a very much larger mass of cleavage fragments injected, and that alone would have produced difficulties in animal survival. There do not appear to be cleavage fragment-related increases in lung cancer or mesothelioma risk in the studies. The lack of risk may be related to the fact that workers in those industries are not exposed to high concentrations of long cleavage fragments and the fact that because of their diameters such fragments would carry a much lower carcinogenic potency than their equivalent asbestiform mineral.

Our limited review of the experimental literature did not reveal any findings which would indicate that cleavage fragments have the same or greater carcinogenic potential than asbestos. In fact, they indicated that amphibole cleavage fragments have a much lower carcinogenic potential than their asbestiform counterparts. In conclusion, there are still many unanswered questions relating to the extent to which the asbestiform habit of a mineral influences its biological behavior relative to that of a cleavage fragment (size for size). But the experimental data do provide strong support for the epidemiological findings that the risks of lung cancer and mesothelioma are considerably less [or absent]

for persons exposed to amphibole cleavage fragments when compared to persons exposed to amphibole asbestos fibers.

10.0 OTHER AMPHIBOLES AND OTHER MINERALS

A search of the literature for studies containing both health outcomes and descriptions of exposure to cleavage fragments failed to identify additional studies that would be of immediate assistance in examining the health risks associated with cleavage fragments. The review did identify studies such as that in Finland where the percentages of asbestiform tremolite and cleavage fragments and fibrous wollastonite and cleavage fragments of wollastonite were characterised in metamorphic limestone and dolomite mines (Junttila et al 1996). However, epidemiological studies to relate to the environmental studies do not appear to be available. The exposure to "Federal fibers" in quarrying industries and coal mines with their large workforces would be would be interest. There were experimental studies and health evaluations of arfvedsonite in Russia (Pylev and Iankova 1975, Kogan et al 1970). There were well described studies of crocidolite-exposed populations, but no health studies of workers exposed to non-asbestiform riebeckite have been identified.

There are potentially other populations of workers exposed to the hundreds of other minerals (e.g., erionite; fluoroedenite), which can occur with a fibrous morphology. In some instances there is some information on mesothelioma risks for some of these minerals. But no studies were found of populations exposed to the non-asbestiform forms of these same minerals.

While the gaps in knowledge concerning the US studies need to be filled, a broader base of information would be helpful. In the absence of well defined occupational groups exposed to well characterised cleavage fragments with well studied health outcomes, it may be useful to consider non-occupational settings. In some of these areas, there are definite concentrations of pleural calcification and definite areas of elevated rates of malignant mesothelioma. Perhaps mapping the geographical distribution of mesothelioma in various countries such as Southern Europe, New Caledonia and the Mediterranean region might identify clusters of cases which might be investigated for asbestiform amphibole exposure and non-asbestiform amphibole exposure in for example, case-comparison studies.

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TABLE 1

The diameters of asbestiform and non-asbestiform amphiboles

"FIBRE"	REFERENCE	PERCENT DIAMETER > 0.25 μm
Amosite	Gibbs & Hwang [1980]	28% - 42% (> 0.3μm)
All amphiboles [Homestake Gold mine]	Virta et al [1983].	100%
Taconite – Grunerite & Actinolite [East Mesabi Range]	Wylie [1988]	100%
Asbestiform Tremolite [Swansea]	Lee [1990]	76%
Nonasbestiform tremolite, [Alada Stura, Italy]	Lee [1990]	98%
Nonasbestiform tremolite [Greenland]	Wagner & Berry [1969]	100%
All amphiboles [N.Y. State]	Kelse and Thompson [1989]	100%

Table 2

Proportion of tremolite particles longer than 10 μm and narrower than 3 μm from milled blocky (prismatic), acicular, fibrous, and tremolite asbestos stratified by aspect ratio using petrographic microscope (modified from Table 2 of Campbell et al, 1979).

Aspect Ratio	% <3:1 Non-regulatory	% 3:1 to 5:1	% >5:1 to 10:1	% >10:1 to 20:1	% >20:1 to 50:1	% >50:1
Nonasbestiform tremolite particles (cleavage fragments)						
Blocky	87	6.5	5	1	0.5	0
Acicular	87	4	6	3	0.5	0
Fibrous	57	18.5	18.5	5.5	0.5	0
Asbestiform Tremolite						
Asbestos1	48.5	6.5	13	13.5	13.5	5
Asbestos2	53.5	3.5	14.5	12	13	4.5

Non-regulatory designates particles that do not meet the length >5 um, width <3 um, and aspect ratio >3 criteria

TABLE 3

MESOTHELIOMA/LUNG CANCER EXPERIENCE – NON-ASBESTIFORM GRUNERITE**** WORKERS AND NEGATIVE NON-AMPHIBOLE CONTROL.

STUDY POPULATION	FOLLOW-UP PERIOD	Cohort N (% dead)	N mesothelioma / N DEATHS PMR)	Lung cancer: O/E = SMR (95% CI)
Nonasbestiform Grunerite Cohorts (latest follow-up)				
Homestake Gold Miners (Steenland & Brown 1995)	Follow-up 1977-1990	3328 (46.6%)	0 / 1551= 0 7***	115/101.8 = 1.13 (0.94-1.36)
Reserve Taconite Miners (Higgins et al 1983)	More than 1 year in period 1952-1976	5751 (5.2%)	0 / 298	15 /17.9=0.84(0.47-1.38)
Erie Mining of taconite (Cooper et al 1992)	> 3 months <1959, Erie-Minntac mine, 1947-1959	3431 (30.8%)	1** 0 / 1058 = 0	62/92.2 = 0.67(0.52-0.86)
TOTAL		12510 (23.2%)	0/2907=0	192/211.9 = 0.91
Negative Comparison: Hematite Iron Ore without amphiboles				
Hematite mining in Minnesota [Lawler et al 1985].	> 1 year employment before 1966. Follow-up 1937-79.	Ugd 4708 (55%) Surface 5695 (36%)	0 / 2642 = 0 0 / 2057 = 0	117/117.6=1.00(0.83-1.20) 95/108 = 0.88(0.71-1.08)

** Exposure began only 11 years before death making it unlikely that this mesothelioma is related to work in the taconite mine. He was previously a locomotive fireman and engineer.

*** There were seven cases [4 cancers of the peritoneum and 3other respiratory cancers] in categories that might include mesothelioma but no mention of mesothelioma on the death certificate or other evidence to support diagnoses of mesothelioma. No mention of mesothelioma was found in a review of deaths from lung cancer or other non-specified cancer, "categories which at time include mesothelioma" [Steenland & Brown 1996].

**** It is recognised that these workers were also exposed to non-asbestiform hornblende and actinolite.

TABLE 4

MESOTHELIOMA /LUNG CANCER EXPERIENCE – AMOSITE ASBESTOS EXPOSED WORKERS

STUDY POPULATION	FOLLOW-UP PERIOD	No. IN COHORT (% mortality)	No. meso / No. DEATHS = PMR	Lung Cancer: Obs/exp = SMR (95% CI)
Amosite mining [Sluis-Cremer et al 1992]	Miners 1945-1955. Follow-up to 1986	3212 (20.2%)	4 / 648 = 0.6%	26/18.8 = 1.38 (0.97-1.91)
Amosite Insulation manufacturing [Acheson et al 1984]	1945-78: Follow-up to 1980.	4820 (6.9%)	5/333 =1.5%	61/29.1 = 2.10 (1.62-2.71)
Amosite insulation manufacturing [Seidman et al 1986]	1941-1945; more than 5 year latency; follow-up to 1983	820 (72%)	6/593=1.01% (death certificates) 17/593=2.9% (Best evidence)	102 / 20.51 =4.97 (4.08-6.1)
Amosite insulation manufacturing [Levin et al 1998]	1954-1972, >10 years latency; follow-up to 1994	755 (29.4%)	6/222=2.7%	35/12.6=2.77 (1.93-3.85)
TOTAL		9607 (18.7 %)	21/1796=1.2%	224/81=2.77

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TABLE 5

SMRs by cumulative exposure expressed as fibre/cc-yrs for non-asbestiform grunerite [Steenland & Brown 1995] and asbestiform grunerite exposures [Seidman et al 1986].

Non-asbestiform Grunerite [Steenland & Brown 1995]								
MPPCF-yrs *	<33.3	33.3 – 133.3	133.3 – 200	>200	-	--	--	--
Fibre/cc-yrs **	< 4.8	4.8 – 19.5	19.5 - 29.2	>29.2				
SMR	1.17	1.01	0.97	1.31				
Asbestiform Grunerite [Seidman et al 1986]								
Fibre/cc-yrs **	<6	6-11.9	12-24.9	25-49.9	50-99.9	100-149.9	150-249.9	250+
SMR	14/5.31 = 2.64	12/2.89 = 4.15	15/3.39 = 4.42	12/2.78 = 4.32	17/2.38 = 7.14	9/1.49 = 6.04	12/1.32 = 9.09	11/.94 = 11.7

*** Dust days in table II of the paper by Steenland and Brown 1995 (i.e.: 1 day at 1 mppcf was converted to dust years by dividing by 240 days per year [i.e. 48 weeks x 5 day week).**

** MPPCF-yrs converted to f/cc-yrs using a factor of 1mppcf = 0.146 f/cc. The conversion is based on the average concentration of "fibers" greater than 5μm and particles measured by the midget impinger and reported by Gilliam et al (1976) i.e.: 0.25f/cc divided by 1.7mppcf

TABLE 6.
Lung cancer and nonmalignant respiratory (NMRD) mortality (SMR) among talc workers.

AUTHOR	YEARS	Lung Cancer SMR	Lung Cancer Mine SMR	Lung Cancer Mill SMR	NMRD Overall SMR	NMRD Mine SMR	NMRD Mill SMR
NY Lamm et al (1988)	1947-78 >1-year 14.8% mortality	6/3.1=1.93 (0.71-4.20)			7 / 2.5 = 2.78 (1.11-5.72)		
NY Honda et al (2002)	>1 day 1948-1989	31/13=2.32 (1.57-3.29)	18/46=3.94 (2.33-6.22)	7/5.5=1.28 (0.51-2.63)	28/13=2.21 (1.47-3.20)	10/4.2=2.41 (1.16-4.44)	11/48=2.27 (1.13-4.07) (1.13-4.07
NY Brown et al (1990)	1947-1978; >1-yr; follow-up 1983; 23% mortality	17 / 8.2 = 2.07 (1.20-3.31)			17 / 6.8 = 2.50 (1.46-4.01)		
Vermont Selevan et al(1979)	1940-1975; >1-yr; 23% mortality	6/3.69= 1.63 (0.60-3.54)	5/1.15=4.35	2/1.96=1.02	11/3.67=3.0 (1.50-5.36)	2/1.23= 1.63	7/1.72=4.07
Italy Coggaiola et al (2003)	>1 yr, 1946-1995 49% mortality	44 / 46.9 = 0.94 (0.68-1.26)	33 / 30.9 = 1.07 (0.73-1.50)	11/ 16 = 0.69 (0.34-1.23)	127 / 55.7 = 2.28 (1.9-2.72)	105 / 34.4 = 3.05 (2.5-3.7)	22 / 21.3 = 1..04 (0.65-1.57)
France Wild et al (2002)	1945-1995, >1- yr; 27.5% mortality	21/17=1.23 (0.76-1.89)			26/24.6= 1.06 (0.69-1.55) Pneumoconiosis 3/0.5=5.56 (1.12-16.2);		
Austria Wild et al (2002)	1972-1996, >1-yr; 12.4% mortality	7/6.6=1.06 (0.43-2.19)			1/3.7=0.27 (0.01-1.52)		
Norway Wergeland et al (1990)	>1-yr: miners 1944 –1972; 28.7% mortality >2-yrs millers 1935-1972; 30.5% mortality.	SIR: 6/6.49 = 0.92 (0.34-2.01)	SIR: 2 / 1.27 = 1.57	SIR: 4 / 5.22 = 0.77	Diseases of Respiratory System SMR: 3/10.9 = 0.28	SMR: 1 2.5 = 0.40	SMR: 2 8.5 = 0.24

TABLE 7

MESOTHELIOMA/LUNG CANCER EXPERIENCE –
NON-ASBESTIFORM ANTHOPHYLLITE AND
ANTHOPHYLLITE MINERS AND TREMOLITE ASBESTOS

STUDY POPULATION	FOLLOW-UP PERIOD	N in COHORT (% deaths)	PMR)Mesothelioma / total deaths)	Lung Cancer SMR (95% confidence intervals)
Talc workers, NY State. [Honda et al 2002]	White men actively employed >1 day between 1948 and 1989 and alive in or after 1950. Follow-up 1950 thru 1989	809 (27%) Mill = 377 Mine = 311	2/209= 0.96%*	31/13=2.32 (1.57-3.29) Mill: 7/5.5=1.28 (0.51-2.63) Mine: 18/4.6=3.94 (2.33-6.22)
Norwegian talc workers (Wergeland et al, 1990)	Miners >1 yr 1944-1972; Millers >2 yrs 1935-1972; Follow-up 1953-1987	Total (M) 389 (30.1%) 94 miners (28.7%) 295 millers (30.5%)	0/117=0% 0/27=0% 0/90=0%	Incidence (SIR): 6/6.49=0.92(0.34-2.01) 2/1.27=1.57 4/5.22=0.77
Finnish anthophyllite miners ## Karjalainen et al 1994] #Meurman et al (1994)	# > 3 mos 1953-1967; Follow-up 1953-1991	999 (59.4%) M = 736 (68.3%) F = 167 (53.9%)	4 / 593 (0.7%) M = 4/503 (0.8%) F=0/90 (0%)	Incidence: SIR M: 76/26.4 = 2.88(2.27-3.6) Heavy Exp: 3.15(2.37-4.09) Mod Exp: 2.35(1.45-3.58)
Vermiculite miners, Libby, MN. [McDonald et al 2004]	> 1-year before 1963, followed to 1999	406 70.2% mortality	12 / 285 = 4.2%	44 / 18.3 = 2.40 (1.74-3.22)
South Carolina Vermiculite McDonald et al (1988)	<6 months 1971-1986, followed to 1986	194 51/194 = 27.8% (>15 yrs latency	0 / 51 = 0%	4/3.31 = 1.21 (0.33-3.09)

* See text. Cases were not considered to have resulted from work at the talc mine. One case had latency of 15 years and one was a draftsman during construction only.

TABLE 8

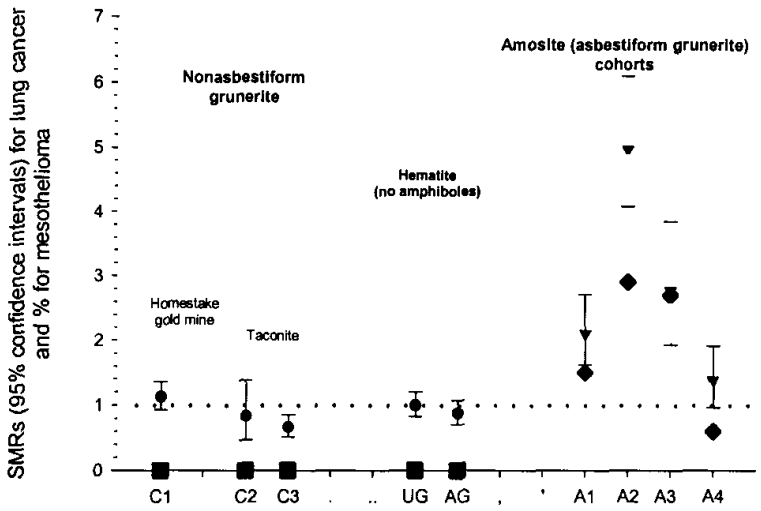
Dimensions of elongated particles associated with various amphibole exposure industries studied experimentally and/or epidemiologically.

Cohort	Width (μm)	Length(μm)	Reference
Libby vermiculite; tremolite asbestos	46% <0.25	62% >5	Langer et al (1974)
Homestake gold mine (CG = cummingtonite-grunerite) (TA = tremolite-actinolite) (GM = geometric mean)	69% CG: GM= 0.43 15% TA: GM = 0.27 0% <0.25 minimum 0.3 mean 1.1	34% >5 32% >5 Mean 4.6 Max 17.5	Brown et al (1986) Virta et al (1983)
Taconite	0% < 0.25 min 0.25 mean 1.2	Mean 5.5 Max 32.4	Wylie (1988)
Vanderbilt tremolitic talc	0% <0.25		Kelse and Thompson (1989)
Experimental Studies			
Korean tremolite asbestos >5 um L	44.7% <0.25	11.8%>5 [1.9]	Addison (2004) Davis et al (1985)
Californian white tremolite asbestos (Davis and Addison,1981)	50%<0.25	14.9%>5 [3.2]	Addison(2004)
Swansea tremolite asbestos (Davis et al , 1991)	8.2%<0.25	33.6%>5 [1.0]	Addison(2004)
Italian tremolite (Davis et al , 1991)	13.3%<0.25	9.7% >5 [0.27]	Addison (2004)
Greenland tremolite (Wagner, 1982)	0% <0.25	100% <10	Wagner and Berry (1969, 1982).
Dornie,Scotland tremolite Davis(1991)	13.7% <0.25	22.5% >5 [0.1]	Addison (2004)
Shinness tremolite, Davis (1991)	13.8%<0.25	10.6% >5 [0]	Addison (2004)
Ferro-actinolite asbestos	Median: 0.24 Range: 0.03-5.2	Median: 1.50 Range:0.3-52.5	Coffin et al (1982)
UICC Amosite	Median: 0.22 Range: 0.02-4.1	Median: 1.8 Range:0.15-378	Coffin et al (1982)

Figures in [] = % >5μm and less than 0.25μm.Addison(2004) provided figures from Davis et al (1991), calculated from the fiber numbers in the doses used in the experiments by Davis et al.

FIGURE 1

Lung cancer and mesothelioma mortality in cohorts of workers exposed to Nonasbestiform amphiboles (Homestake gold ore, taconite), Hematite (no amphiboles, negative controls), and Amosite asbestos cohorts (positive controls)



C1 = Steenland and Brown (1996)
C2 = Higgins et al (1983)
C3 = Cooper et al (1992)

UG, AG = underground and aboveground Hematite (Lawler et al (1985)

A1 = Acheson et al (1984, amosite insulation mfg
A2 = Seidman et al (1986) amosite insulation factory
A3 = Levin et al (1998) amosite insulation pipe mfg plant
A4 = Sluis-Cremer et al (1992) chrysotile/amosite insulation

- ● lung cancer SMRs
- ■ % meso (n cases/total deaths = PMR)
- • • • No effect level for lung cancer (SMR=1)
- ◆ % mesothelioma, asbestos cohorts
- ▼ lung cancer SMRs, Asbestos cohorts

FIGURE 2

Lung cancer SMRs by cumulative exposure (fibers/cc-years)
and pneumoconiosis for non-asbestiform grunerite
(Steenland and Brown, 1995)
and grunerite asbestos (Seidman et al, 1986)

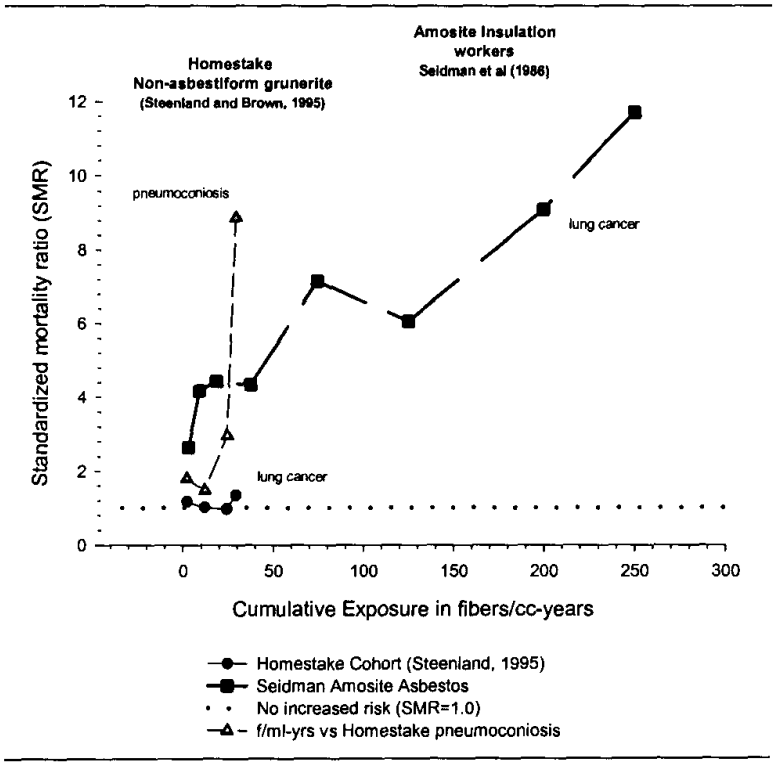


FIGURE 3

Exposure-response of lung cancer, other non-malignant respiratory Disease (other NMRD) and lung fibrosis by Cumulative exposure (mg/m3-years) Honda et al (2002)

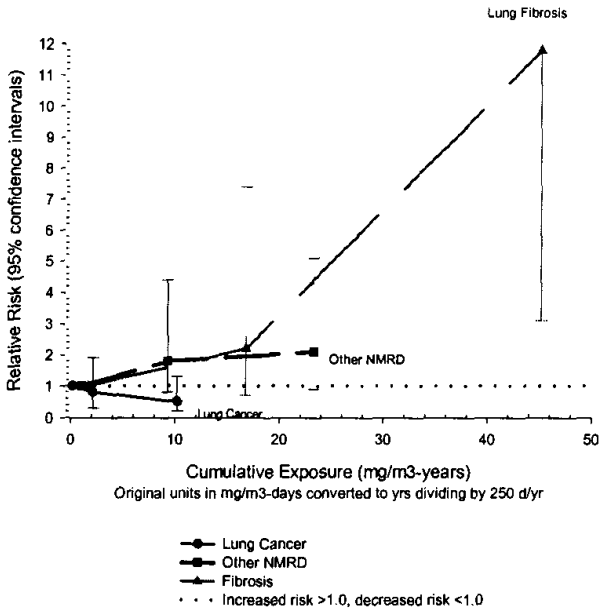


FIGURE 4

Exposure-response trends for lung cancer, mesothelioma and Pneumoconiosis among Vermiculite workers exposed to Vermiculite Ore contaminated with Tremolite asbestos In Libby, Montana (McDonald et al, 1986) Vermiculite with nonasbestiform amphiboles in South Carolina (McDonald et al, 1988)

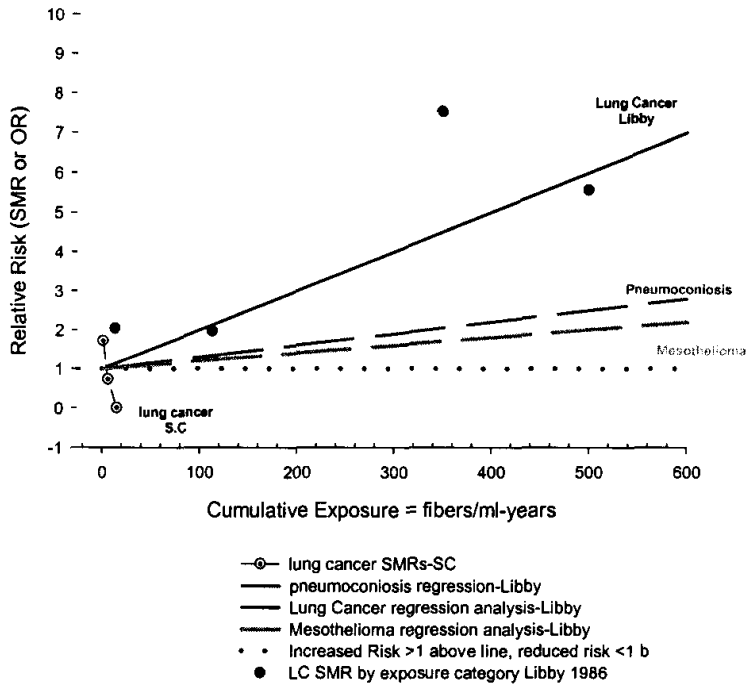


FIGURE 5

Exposure-response trends for lung cancer
Non-malignant respiratory disease (NMRD) and
Pneumoconiosis by cumulative exposure (mg/m3-years)
To Talc not containing amphiboles
Among French/Austrian Talc Workers
Wild et al (2002)

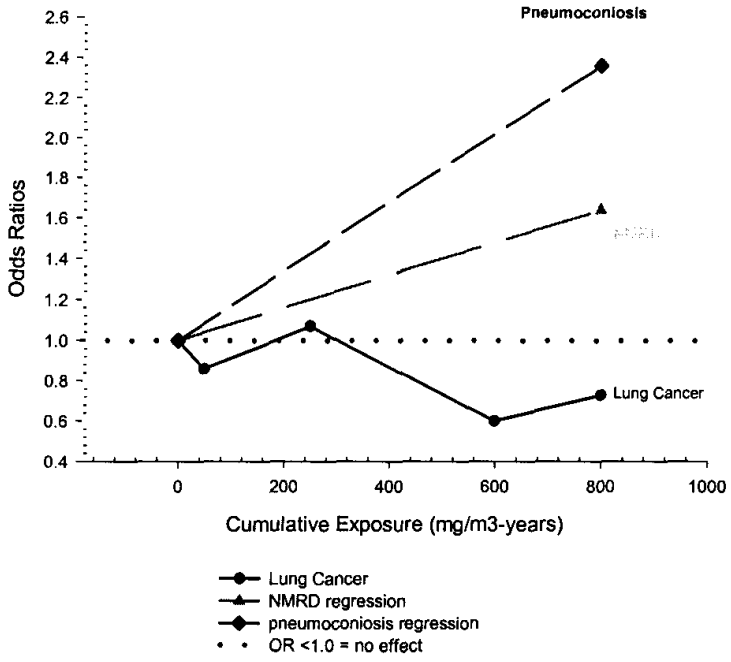


FIGURE 6

Lung cancer and mesothelioma mortality in workers exposed to
Talc containing nonasbestiform amphiboles in New York and Norway
(Honda et al, 2002; Wergeland et al (1990)
Talc without amphiboles (Vermont, Italy, France/Austria)
Selevan et al (1979), Coggiola et al (2003), Wild et al, (2002)
and
Vermiculite containing tremolite asbestos (McDonald et al (1986
Anthophyllite Asbestos (Karjalainen et al, 1994;Meurman et al, 1994)

Formatted: Spanish (Spain-Modern Sort)

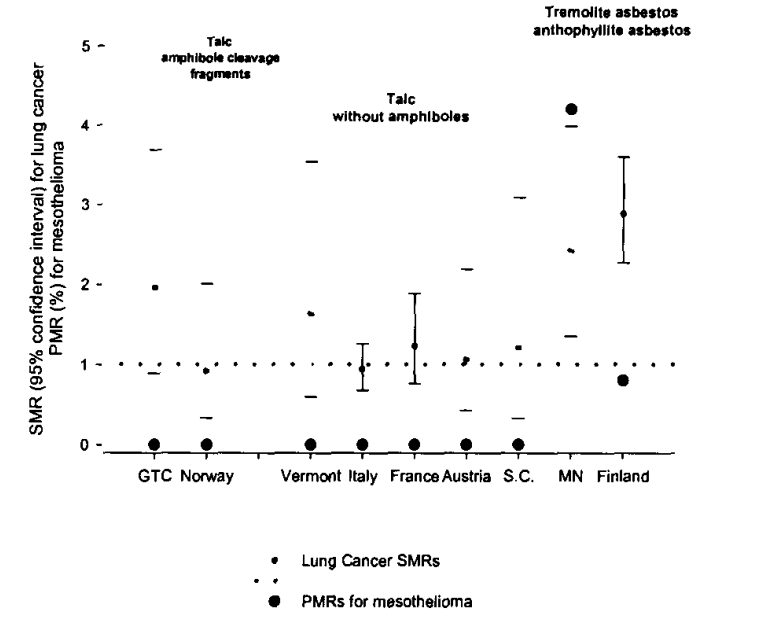


Figure 7

Experimental studies of injections into rats
Of asbestiform amphiboles and
Nonasbestiform amphiboles

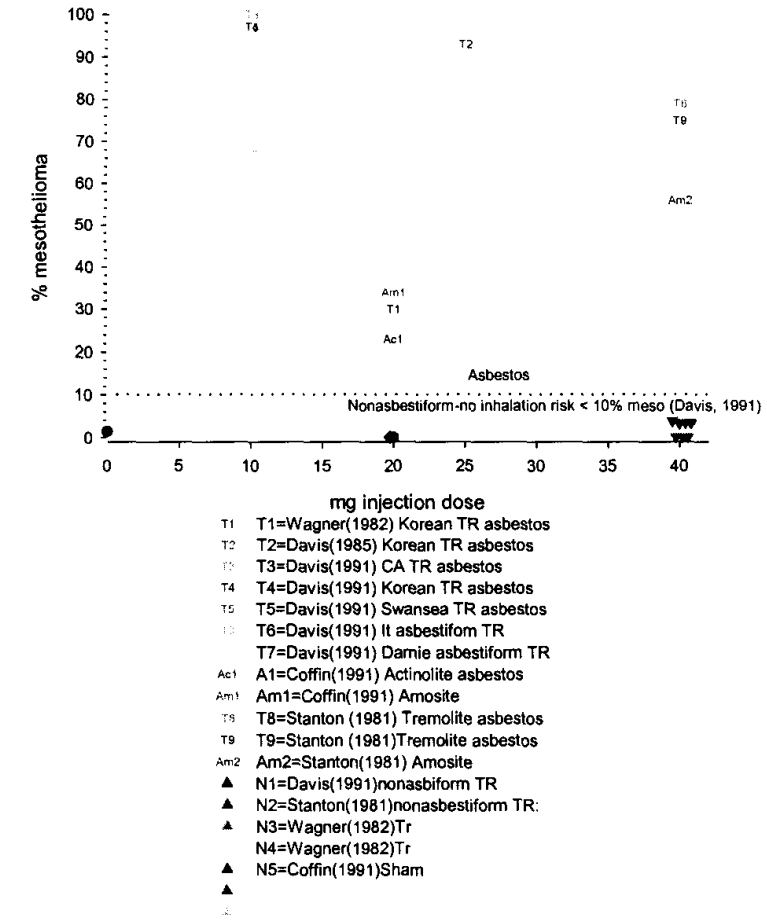
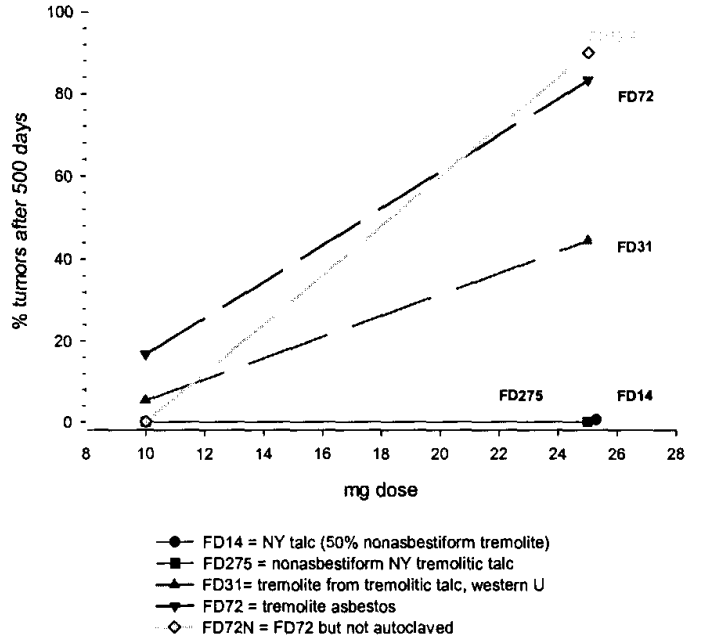


Figure 8

Mesotheliomas in hamsters after intrapleural injection
Of tremolite asbestos and talc containing nonasbestiform tremolite
Smith (1979)



APPENDIX .

There is some overlap between this appendix and the main text in order to maintain the historical development of knowledge concerning the NY Talc deposit.

NEW YORK STATE TALC

Early NY Talc Studies

Kleinfeld et al (1967) conducted a PMR mortality study among 220 talc miners/millers with 15 or more years exposure in 1940, with follow-up to 1965. There were 28 deaths (31%) attributed to pneumoconiosis and complications and a PMR of 3.44 for 9 deaths from lung cancer and 1 from fibrosarcoma of the pleura. Kleinfeld et al (1967) also reported that in a small group of asbestos insulation workers with similar years of exposure, the asbestos workers had about twice the proportion of lung cancer deaths (11% Vs 24%) and the significant excess was in both the 40-59 and 60-79 year age groups. This is "at variance" with the talc workers where the excess was only in the 60-79 year age group (PMR = 4.36) and a deficit (PMR = 0.96) in the 40-59 year age group. Overall, lung cancer mortality among the asbestos insulators was 2.5 times higher than among the talc workers, 8.43 Vs 3.44.

Kleinfeld et al (1974) added 4 more years of follow-up (to 1969), 40 more workers in the cohort (for total of 260), 17 more total deaths (for a total of 108) and 3 more respiratory cancers (for a total of 13). Similar results to the 1967 study were obtained with the only significant excess of respiratory cancers in the 60-79 age range (PMR = 4.61) and not in the 40-59 year age group (PMR = 1.63). The authors thought it was noteworthy that the significant excess respiratory cancer mortality was in the years 1945-1959 (PMR = 3.37) and not in the years 1960-69 (PMR = 1.35) when dust counts were appreciably reduced but fiber counts (fibers/ml >5 um) remained high. Ten of the 13 respiratory cancer deaths occurred in workers exposed 15-24 years (and about the same latency). The authors suggested a more susceptible group develops cancer between 15-24 years leaving a less susceptible group in spite of more years of exposure. The size of the cohort is too small to confirm this hypothesis. There was one case of peritoneal mesothelioma but no information regarding latency or other work exposures.

Exposure was characterized as predominantly talc admixed with silicates such as serpentine, tremolite, carbonates and a small amount of free silica. Exposures were quite high before 1945 when both pneumoconiosis and lung cancer cases began working. Wet drilling began after 1945, which reduced mine levels from 818 to 5 mppcf. Exposures were lower in the mill than the mine prior to 1945, but after 1945 were not reduced as much as in the mine and were now 5 times or more higher than in the mine. Workers with lung disease had initial exposures prior to 1945 before wet drilling began and when average dust counts in the mine were 818 (83-2800) mppcf for drilling and 120 (2-475) for mucking. In the mill, averages were 180, 69, 92 and 151 mppcf for crushing,

screening, milling and bagging. After 1945 (1946-1965) average dust counts were reduced to about 5 mppcf in these jobs in the mine and in the mill averages were generally below 50 mppcf.

Kleinfeld et al (1973) studied 39 workers exposed to commercial talc dust where tremolite and anthophyllite were the major fibrous components. They also examined 16 talc samples from different mining and milling operations as well as finished products from NY State. Analyses included polarized LM, TEM with selected area diffraction, X-ray diffraction and electron microprobe analysis. No data are provided on distribution by fiber sizes. The point is made that there was no correlation between fiber count (fibers > 5 um) and mean dust counts (mppcf). Particles observed included "true talc, talc fibers, serpentine minerals and after fragments, and amphibole fibers and fragments." Fiber counts "may not provide a true picture of exposure to asbestiform minerals because the fiber counts include talc fibers but exclude many small asbestos fibers and 'aggregate fibers' which may contain substantial amounts of asbestiform minerals." The electron micrographs of amphibole fibers present in talc suggested amphibole cleavage fragments.

Gouverneur NY Talc

Mineralogy of NY tremolitic talc

Brown et al (1980) reported the dimensions of fibers determined by electron microscopy. Only 3% of tremolite fibers and 8-10% of anthophyllite fibers were longer than 5 μm; median lengths were about 1.5 μm. Median aspect ratios of 7.5 and 9.5 were reported for all fiber lengths of tremolite and anthophyllite. Data were not provided on aspect ratios for fibers > 5 um counted using the phase contrast microscope.

There then began a series of mortality studies of workers at one mine and mill in NY state variously called Gouveneur talc (GTC) or Vanderbilt talc (Brown et al, 1979, 1980, 1990; Stille and Tabershaw, 1982; Lamm et al., 1988; Gamble, 1993; Honda et al., 2002; Oestenstad et al, 2002). The extensive literature on GTC talc centers on three major issues that started with the first NIOSH mortality and industrial hygiene study of GTC workers.

Is the reported excess SMR for lung cancer due to the alleged asbestiform amphiboles in the talc or due to confounding? Confounding factors could include other work exposure (primarily in the surrounding mines/mills), from life-style factors such as smoking or short-term employees.

Is the tremolite and anthophyllite content of the talc non-asbestiform cleavage fragments or is the talc contaminated with tremolite asbestos and anthophyllite asbestos?

Is there biological plausibility that the tremolitic talc acts like asbestos producing asbestos-like effects in animal studies?

Epidemiology of health effects of GTC talc

Brown et al (1979, 1980) studied 398 white males first employed 1947-1959 with vital status determined as of 1975. There was a 2.73-fold excess risk of lung cancer. Risk increased with increasing latency with SMRs of 2.00 and 4.62 at 10-19 and 20-28-yrs latency, which was said to be "consistent with an occupational etiology." There was no analysis by years worked although 4 / 9 cases had worked less than 1 year. Smoking was considered unlikely to account for all the increased risk by Brown et al. Exposures in surrounding mines and mills were higher but all were said to involve exposures to "asbestiform amphiboles." Exposures to "asbestiform tremolite and anthophyllite stand out as the prime etiologic factors associated with the observed increase in bronchogenic cancer."

Stille and Tabershaw (1982) studied 655 white males employed 1948-1977 with vital status determined at the end of 1978. Lung cancer was not significantly elevated except among employees with any history of prior employment. There was no analysis by years worked and latency was not taken into account.

Because of these conflicting findings, Lamm et al (1988) reanalyzed these data. They studied 725 male talc workers who had ever worked at Vanderbilt since the plant opened in 1947 through the end of 1977 with follow-up through 1978. Previous employment obtained from job applications were classified as posing a prior risk, no prior risk or unclassifiable (no indication of prior work history) with regard to risk of lung cancer. Among those with more than 1-year employment the SMRs for lung cancer and non-infectious, non-neoplastic respiratory diseases were 1.93 and 3.70 respectively, compared to 3.00 and 0 for those with less than 1-year duration. Adding prior exposure history to the analysis showed that lung cancer risk appeared to be related to prior jobs. The SMRs were similar for all job risk categories, although the number of cases was too small to be definitive. Mean latency was 20.8 years (12-25) and all those with less than 20 years latency since being hired at GTC had worked elsewhere. Five of the 12 cases had 3 months or less employment. The authors conclude the increased risk of lung cancer in this cohort of talc workers is concentrated in short-term workers, probably due to prior employment, smoking or other differences in behavioral characteristics.

At the request of Vanderbilt, NIOSH conducted a health hazard evaluation (HHE) of the GTC cohort. Eight years of follow-up (through 1983) and an analysis by latency and tenure were added to the retrospective cohort study (Brown et al, 1990). Nearly a third (27%) of the cohort had died, with 161 total deaths and 17 lung cancer deaths with an overall SMR of 2.07. About 50% of the cohort had worked less than 1 year. Among the 13 lung cancer cases with 20 or more years latency, there was a 3.6-fold excess in the 8 cases with less than a year tenure vs a nonsignificant SMR of 1.79 among the 5 cases with >1-year tenure. There were also 17 NMRD deaths with an overall SMR of 2.50 (1.46-4.01). Six of the cases had worked for less than 1 year with an SMR of 1.94 (0.72-4.28). There was a 3-fold excess (SMR 2.89; 1.45-5.18) among those with more than 1-year tenure. This pattern is "more consistently associated with an occupational exposure at GTC." Principal limitations in this study were small size (especially those with long tenure), inability to precisely characterize past occupational exposures at GTC or elsewhere, and lack of reliable smoking history. The authors concluded it is unlikely these potential confounders alone could account for the observed excess risks.

Gamble (1993) conducted a case control nested in the Brown et al (1990) cohort. Information was collected on smoking, time exposed to talc plus a risk ranking on non-talc exposure. There were 22 cases and 66 controls matched on date of birth and date of hire. There were zero nonsmokers among the cases (91% smokers, 9% exsmokers) compared to 27% nonsmokers, 73% smokers or ex-smokers among controls. Inverse trends were consistently observed by years worked; e.g., all cases and controls, smokers only, those with >20-years latency, total talc years. The author concluded that "after adjustment for...smoking and the postulated role of very high exposures of short-term workers, the risk ratio for lung cancer decreases with increasing tenure." The time occurrence of lung cancer was consistent with a smoking etiology, and was not consistent with an occupational relationship.

Finally, Honda et al (2002) assessed cancer and non-cancer mortality among white male GTC talc workers. The cohort analyzed for cancer mortality consisted of 809 workers employed 1947-1989 and alive in 1950. The cohort analyzed for non-cancer mortality consisted of 782 men employed during 1960-1989. The important additions in this study were 6 more years of follow-up (through 1989) and internal exposure-response analyses with cumulative exposure to talc dust as the exposure variable. Overall mortality continued to remain elevated at 1.31 ((209/160) due largely to 2.32-fold excess from lung cancer (31/13) and 2.21-fold excess in NMRD (28/13). The patterns are consistent with previous results, in particular with the inverse lung cancer trends from the nested case-control study (Gamble, 1993) and the inverse relationships for NMRD and lung cancer reported by Lamm et al (1988). Honda et al (2002) reported that among workers with >20-years latency, there was a 3.3-fold excess lung cancer for <5-years tenure and 1. 9-fold excess for >-5 years tenure. For other NMRD (COPD + pneumoconiosis and excluding pneumonia, influenza, asthma, emphysema and bronchitis) the SMRs were 2.71 and 3.02 respectively. The internal comparisons by cumulative exposure (mg/m3-yrs) and adjusted for age and latency, showed a significant monotonic decrease in lung cancer risk with increasing exposure with a RR of 0.5 (0.2-1.3) in the highest exposure category. Mortality from 'other NMRD' and pulmonary fibrosis showed monotonic increases in risk as exposure increase with 2-fold and 12-fold increased risks in the highest exposure categories. (Figure 1)

There were 2 cases of mesothelioma, but because of too short latency in one case and minimal exposure for a short time, Honda et al (2002) considered it unlikely that exposure to talc ore was the cause.

Because of too short latency, Honda et al (2002) concluded that the cause of the increased lung cancer mortality in the cohort is unclear, but speculated that it could be due in part to smoking or "other unidentified risk factors." They suggest it is unlikely to be related to talc ore dust per se. Other NMRD (and in particular fibrosis) were considered causally related to talc ore dust, other dusts in other work environments and smoking. This conclusion is supported by the differences in years worked and median cumulative exposures among decedents with these three causes of death and the inverse E-R trend for lung cancer (Table 1).

Table 1. Exposure differences between cases of lung cancer, Other NMRD and Fibrosis in NY talc workers (Honda, 2002)

	Lung Cancer	Other NMRD	Fibrosis
Median Yrs worked	1.0	8.3	11.8
Median Cumulative Exposure (mg/m3-days)	347	1199	3759

These results are not at all consistent with the dust causing fibrosis being responsible for the lung cancer excess.

3.1.2.3 Summary of Results from studies of NY Talc Workers (TABLE 2)

In this Appendix the talc mines in New York are identified as GTC, Vanderbilt, Gouverneur which are essentially synonymous.

The authors of the two NIOSH studies of GTC talc (Brown et al, 1979, 1980, 1990) concluded that the tremolite and anthophyllite were the most likely etiological agents based on the follow logic.

The excess risk of lung cancer and NMRD were consistent with the findings of Kleinfeld et al (1967, 1973) among NY talc workers and Meurmann et al (1974, 1979) among anthophyllite asbestos miners.

The etiological agents were considered to be "asbestiform tremolite and anthophyllite," which were said to be in both talc ores at concentrations well above standards. Smoking could not account for the excess lung cancer risk. Short-term workers may have had "very high exposures, especially in the early years of the mining operation," which might account for their excess risk (Brown et al, 1990). There was an increased risk of developing pleural changes (including pleural thickening and pleural calcification), and the prevalence is higher when there is exposure to anthophyllite (Dement et al, 1980).

The lack of an association with years worked could be due to a combination of factors above plus work in other talc operations and/or other work-related exposure to lung carcinogens.

Many of these arguments have been contradicted by further analyses.

Kleinfeld et al (1967) compared lung cancer risk patterns of talc workers with (apparently) their own data for a similar group of asbestos insulation workers. The asbestos PMRs were 2-3 times higher among the asbestos workers for lung cancer and GI cancers. Kleinfeld et al. commented that a major difference was the increased risk of lung cancer in age groups of 40-59 and 60-79 among asbestos workers, but excesses for talc workers were among only the 60-79 age group. In addition, longevity was longer than the national average. Age at death among the talc lung cancer cases was 3-years greater than the average of all deaths and 10-years greater than the U.S. average. The talc lung cancer

cases occurred in persons exposed before wet drilling was introduced. Wet drilling reduced mean exposures 164-fold from an average of 818 mppcf to 5. Kleinfeld et al (1967) suggested part of the reason for the earlier deaths of asbestos cases compared to talc cases "may be partly due to the greater carcinogenicity of asbestos dust or to an increased level of exposure to asbestos or both."

There was excess mortality among the NY talc workers, but considerably less than the risk of asbestos workers exposed in the same time period. It is not possible to directly compare risks from the Kleinfeld et al (1974) cohort with that of the GTC cohort. The Kleinfeld et al cohort et al is older, had worked decades earlier than the GTC cohort, and consisted of workers with more than 15-years tenure and 40+ years tenure. Vanderbilt workers included many short-term workers, the 26-years was the maximum possible years worked and there was no analysis by years-worked (Brown et al, 1979, 1980). In addition, overall mortality was over twice as great in the Kleinfeld et al cohort, i.e., 42% vs 19%.

Smoking. Further updates of the Vanderbilt cohort revealed that all of the lung cancer cases were or had smoked cigarettes, while only 73% of controls had ever smoked. Also, smoking latencies for Vanderbilt cases was consistent with latency from studies of smokers. Talc latencies were too short to attribute lung cancer etiology to talc exposure or work (Gamble, 1993). This is particularly true for short-term workers where the risk of lung cancer was highest and talc exposure (or most any work exposure including asbestos) too short to be plausible. Risk among workers with more than 1-year exposure was increased about 2-fold compared to the US population. This degree of increased risk is in large part plausibly attributable to smoking.

High Exposure of Short-term workers. Gamble (1993) matched on date of hire in the nested case control study of lung cancer. Thus, cases and controls had equivalent opportunities for very high exposures. Six of the lung cancer cases had less than 3-months tenure, several with only a few days, so there were very few opportunities for excessive cumulative exposure. Honda et al (2002) showed that lung cancer cases had lower exposures than other subgroups. For example, median cumulative exposure of lung cancer decedents was 347 mg/m3-days, which was less than all decedents (520), ischaemic heart disease decedents (376), all NMRD decedents (888), other NMRD decedents, pulmonary fibrosis decedents (3759). Thus there is no evidence to support the speculation that excessively high exposure in short-term workers could explain their increased risk.

Pleural Changes. Gamble et al (1979, 1985) showed that the prevalence of pleural changes in GTC talc workers was essentially the same among other workers exposed to talc containing no measurable quantities of amphiboles. Thus it would appear that the pleural thickening observed in NY talc workers and other talc workers is likely due to factors other than exposure to amphiboles.

Exposure-response (E-R): The inverse exposure-response trends with duration of exposure were present when adjustments were made for other talc exposures and potential exposure to other work-related carcinogens (Gamble, 1993). The inverse E-R

trends for lung cancer and cumulative exposure are strong arguments against attributing increased risk of lung cancer to talc exposure. This argument is further strengthened by the very strong exposure-response relationship between fibrosis and cumulative talc exposure as well as the higher exposure of NMRD and fibrosis cases compared to lung cancer cases (Honda et al, 2003).

TABLE 2

Summary of results for Lung Cancer and Mesothelioma from studies of NY Talc workers. All but two of the studies (Kleinfeld et al, 1967, 1974) were the same cohort of GTC workers.

Reference	Study Characteristics	Lung Cancer	Mesothelioma
Kleinfeld et al (1967)	220 NY Talc Miners ≥ 15 yrs tenure in 1940; 1965 follow-up, 91 total deaths, PMR	PMR=3.44 (1.65-6.3) (11 deaths)	1 peritoneal mesothelioma (1.1%)
Kleinfeld et al (1974)	260 NY Talc Workers ≥ 15 yrs in 1940 or between 1940-1969; 108 total deaths, PMR, follow-up of Kleinfeld et al (1967)	PMR resp cancer =3.24 (1.72-5.54) (12 lung cancer, 1 fibrosarcoma of pleura)	1 peritoneal mesothelioma (0.93%)
Brown et al (1979,, 1980)	398 WM employed Vanderbilt 1947-1959, follow-up 1975; 18% < 1month, 24% 1mos-6 mos, 50% < 1 yr; 44% <1950;	9/3.3 = 2.73 (1.25-5.18) (p<0.05); 4 <1-yr tenure	1/74 = 1.4% (16-y talc tenure, 11 yrs construction)
Stille & Tabershaw 1982)	655 WM employed Vanderbilt 1948-1978, vital status 1978;	10/6.4 = 1.57 (10 obs) Prior employment=2.14 (8 obs)) No prior work = 0.76 (2 obs))	
Lamm et al (1988)	705 men employed Vanderbilt 1947-end 1977, vital status 1978	12/5=2.40(1.24-4.19) ≥1 yr 6/3.1=1.93(0.71-4.20) prior risk = 3.08(6/2) ≤1 yr 6/1.9=3.160.16-6.88) prior risk=3.33 (3/0.9)	1 electrician 15-yr latency; 20-yrs prior as miner, miller, construction
Brown et al (1990)	710 WM employed at Vanderbilt 1947-1978 with vital status 1983;	17/8.2=2.07(1.20-3.31) ≥20-yrs latency <1-yr = 3.64(1.54-7.04) 1-9-yrs = 0.83(0.02-4.57) 10-19-yrs = 4.0(0.54-16.1) 20-36-yrs = 1.820.21-6.36)	Not reported,
Gamble (1993)	22 lung cancer cases at Vanderbilt 1947-1978 matched 3:1 on data of birth and date of hire.	Tenure < 5 yr 5-15 yrs 15-36 yrs	OR lung cancer Smokers >20-y latency 1.0 0.63 0.42
Honda et al (2002)	809 WM talc workers employed GTC 1948-89 follow-up Cancer: 1950-1989 Non-cancer mortality = 1960-1989	mg/m3-d RR (n) <95 1.0 (11) <987 0.8 (9) 987 + 0.5(9) Hired : < 1955 SMR 2.86 (0.9-4.1) Hired >1955 SMR:0. (0.2-2.4)	2 cases not considered causal due to short latency, Case 1 & very low exposure, Case 2 (3.7%)

Pn = pneumoconiosis

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The Biology of Cleavage Fragments: A Brief Synthesis and Analysis of Current Knowledge

E.B. Ilgren

Bryn Mawr, Penna

Key Words

Amphibole • Chrysotile • Cleavage fragment • Biopersistence • Animal studies • *In vitro* studies

Abstract

Asbestos is a commercial term referring to 6 fibrous minerals from 2 mineralogical classes: serpentine and amphibole. Chrysotile, or white asbestos, is the only serpentine mineral. The asbestiform habit of amphibole asbestos is far more toxic than chrysotile. However, most amphibole minerals are found in the "non-asbestiform" state that pose few, if any, health risks. Comminution, whether deliberate during crushing or grinding, or incidental in usage may produce structures known as "cleavage fragments" from a wide variety of sources. A considerable body of evidence, gathered over the last 30 years, demonstrates that amphibole cleavage fragments do not show the same toxicity as their asbestiform analogues. Since there still continues to be confusion and controversy on this point, this review is aimed at resolving a major portion of this controversy. It has done so by bringing together the supporting mineralogical, animal and human evidence from many sources. These observations demonstrate that cleavage fragments and amphibole asbestos fibers have fundamentally different properties and these differences are biologically relevant. Indeed, the toxicity of respirable cleavage fragments is so much less than that of the fibrous amphiboles that by any reasonable measure they are not biologically harmful.

Introduction

Asbestos is a commercial term referring to 6 fibrous minerals from 2 mineralogical classes: serpentine and amphibole. Chrysotile, or white asbestos, is the only serpentine mineral. As fibrous asbestiform minerals amphiboles are far more toxic than chrysotile (see Ilgren and Chatfield for review) [1]. However, most amphibole minerals are found in the "non-asbestiform" (non-fibrous) state that pose few, if any, health risks [2]. Amphiboles may be associated with a variety of very common industrial minerals such as serpentine, talc, vermiculite and certain marbles [3,4], and may also be a component of many rocks used as aggregate, road stone, or building materials [5]. Comminution, whether deliberate during crushing or grinding, or incidental in usage may produce structures known as "cleavage fragments". Some elongated cleavage fragments are difficult to distinguish from amphibole asbestos fibers using counting criteria routinely employed for regulatory purposes. It is very

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important to distinguish whether the amphibole in a sample is, or is not, asbestiform not only for regulatory reasons but also because, without this knowledge, it would be impossible to assess properly any health risks associated with exposure to respirable particles released from the materials being used. A considerable body of evidence, gathered over the last 30 years, demonstrates that amphibole cleavage fragments do not show the same toxicity as their asbestiform analogues. The evidence in support of this was summarized previously in the voluminous hearings that led up to the OSHA regulations [6]. In spite of much evidence to support the lack of toxicity of cleavage fragments, there continues to be confusion and controversy both in the USA [6–10] and Europe, see [5] as cited by Chisholm, on this point.

This review is thus aimed at resolving a major portion of this controversy. To do so, it has brought together evidence from a wide variety of sources. These demonstrate that the toxicity of respirable cleavage fragments is so much less than that of the fibrous amphiboles that by any reasonable measure they are not biologically harmful.

Cleavage Fragments and Amphibole Asbestos Fibers have Fundamentally Different Properties

Amphibole minerals make up as much as 6% of the earth's crust and are major constituents of approximately 30% of the rocks in the continental United States [11,12]. Tremolite is a particularly common form of non-commercial amphibole. Thus, given their ubiquity, tremolite cleavage fragments are, not surprisingly, "the most commonly encountered amphibole in the lungs of urban dwellers in North America" [3,9,13]. Indeed, the vast majority of amphiboles in nature are "non-asbestiform" [11,14] (also frequently called 'massive') a term that refers to an amphibole's growth habit.[1] The precise determinants of the growth habit of a mineral are not known (Zussman, 2000 pers comm) but, very specific conditions of temperature and pressure are required to form asbestos fibers (Addison, 2003 unpub.) [15]. "[T]he appearance of [asbestiform fibers] usually implies some sort of secondary modification such as shearing, faulting, or hydrothermal alteration" (Addison, 2003 unpub.). Such conditions rarely occur in nature and, thus, the asbestiform habit is very rare [16,17]. Non-asbestiform amphiboles may also be found in areas where asbestos occurs. The rocks around Libby, Montana provide a good example of this since a large percentage of the dust aerosols from this area is composed of cleavage fragments [18]. Cleavage fragments have also been found, for example, in the ore from the Libby vermiculite mines [19].

Non-asbestiform and asbestiform amphiboles are chemically indistinguishable.[2] The "classification of minerals in the amphibole group is based on the general formula A0–1B2C5T8O22 (OH,F)2 in which A=Na, K; B=Na, Ca, Fe(II), Mg, Mn; C=Fe(II), Mg, Al, Fe(III), Mn; and T=Si, Al" [21]. The main difference between them is their morphology.[3] However, "Subtle differences in their crystal structure can lead to profound differences in physical properties" (Addison, 2003 unpub.).

Geology governs morphology [25].[4] The asbestiform and non-asbestiform habits thus reflect vastly different modes of origin. The asbestiform habit arises through unidirectional crystalline growth which produces exceedingly long, thin fibrils [26]. Each fibril is a single crystal "the structure [of which] consists of SiO_4 tetrahedra linked into double chains or ribbons with a strip of cations sandwiched between pairs of double chains" [4,5]. Individual asbestiform amphibole fibers, in turn, contain fibrils that run parallel to one another. Asbestiform minerals are thus highly fibrous and fibrillar.

"Only specimens which occur as bundles of fibres (commonly having splayed ends) which readily split into still finer sub-microscopic units (fibrils), are referred to and are classed as asbestos" [16]. Thus, "fiber bundles are the hallmark of asbestos" [25]. Non-asbestiform amphiboles are not naturally fibrous. They are not composed of fibers or fibrils. Their crystalline growth is not unidirectional; instead, it occurs along two or three planes. This most commonly gives rise to tiny "prisms" or irregularly shaped crystals by prismatic or acicular growth [16] (Addison, 2003 unpub.).[5]

"The way a mineral sample breaks is determined by its crystal structure and geological history" [27]. Breakage generally occurs along cleavage planes. These are "planes of relative weakness along which certain minerals tend to fracture and are determined by their crystal lattice geometry" (Addison, 2003 unpub.). Since such planes are pre-determined, "you cannot make fibers out of non-fibrous material by mechanical manipulation" [27]. The US Agency for Toxic Substances and Disease Registry (ATSDR) [9] thus wrongly contends that "tremolite asbestos can cleave into short, squatty cleavage fragments". Asbestiform minerals never form cleavage fragments. Conversely, non-asbestiform (massive) amphibole minerals never separate into fibers or fibrils.

Instead, when non-asbestiform amphiboles are crushed, fragments are cleaved or "torn" away from the main rock mass and structures called "cleavage fragments" may be formed. Such "cleavage fragments were thus once part of a larger (non-fibrous) crystalline lattice split apart due to the application of force". Cleavage fragments attain their shape by breakage, not by fibrous growth [25]

Non-asbestiform and asbestiform amphiboles have fundamentally different physical properties [14,16,26,28, 29]. Even though they are inter-related, these properties can be discussed in terms of those that relate primarily to a fiber's "surface structure" or to its "internal structure".

Surface Properties

Surface properties are probably the most important factor distinguishing asbestiform from non-asbestiform amphibole fibers and reflect "differences in their origins" [14]. The geological forces that produce the asbestiform habit make the outer surfaces of asbestos fibers largely smooth[6] and defect free [4,14,16,26,29,30]. Asbestiform fibrils have smooth surfaces with "relatively well satisfied chemical bonds" [29]. The surface of a cleavage fragment is created by external force, and consequently, is not expected to be as stable as an asbestos fiber, since "the stresses have created a high density of surface defects" [14], "steps, and cracks" [29]. "A strong surface structure, with relatively few defects, can only develop when a crystal grows in one direction" [26] as is characteristic of asbestiform fibers. Since the surfaces of asbestos fibers are "growth faces", not mechanical breakage planes, their surfaces are therefore radically different from those of cleavage fragments. Macroscopically, "many asbestos fibers have the shiny luster indicative of a surface structure that is relatively free of defects" [26]. This is not the case for cleavage fragment-derived materials.

At least 3 pieces of evidence suggest that the outer surface of an asbestiform fiber is stronger than its inner surface (and that the opposite is true for non-asbestiform cleavage fragments). These include studies of tensile strength, grinding and acid dissolution.

Tensile Strength

Tensile strength is "the most important and most commonly quoted physical property of an asbestos fiber" [31]. It provides flexibility, the hallmark of an asbestos fiber [14,26,28]. Such properties have enabled asbestos fibers to be exploited widely for the many commercial purposes they are uniquely suited to. The lack of defects in the outer surface of an asbestos fiber largely accounts for its great strength since it allows the integral "linear silicon–oxygen structures" to continue uninterrupted [31] throughout the length of the fibril. Moreover, the outer surface needs to be stronger than its internal structure for a fiber to be flexible [14]. Thus, as each fiber is made up of a discrete number of fibrillar units, the greater outer surface strength of the fiber enables the fibrils within to "slide" past one another without causing the fiber to disintegrate. Their ability to slide past one another within the fiber enables the fiber to bend and therefore serves as the basis of its unique flexibility. Such sliding is also known as interplanar "parting" or "slip" and this occurs at sites called twinning planes [4,14,25,32]. Twin planes,[7] common in amphibole asbestos fibers, are rare in non-asbestiform amphiboles and may be an important microstructural feature in differentiating the one from the other [5,16,25,32,33,34; Seshan and Wenk, 1976, op. cit. 5; Chisholm, 1995; Whittaker, 2000 pers comm]. A high frequency of partings across multiple twinning planes {100} and possibly multiple chain disorders {010} within the crystals and fiber bundles may thus lead to the development of extreme fibrosity (Addison, 2003 unpub.). By contrast, a high frequency of dislocation networks and sub-grain boundaries in prismatic crystal forms (but not in asbestos) may reduce tensile strength (Addison, 2003 unpub.). In fact, "The frequency of {100} twin boundaries (high in amphibole asbestos, very low in prismatic amphiboles) seems to offer the most reliable means of distinguishing the two types [5]"[8]

By contrast, non–asbestiform cleavage fragments are weak, brittle and inflexible largely because their outer "surfaces are weaker than their internal structure" [26,28] (also Addison, 2003 unpub.). Cleavage fragments "cannot be bent more than a few degrees" [26,35] which makes them more susceptible to physical stress than the asbestiform varieties of the same mineral" [26]. Numerous defects and cracks make cleavage fragments inherently weak and brittle, "the density of these defects [Griffith cracks] being inversely proportional to [the fiber's] tensile strength" [4]. "Surface defects also propagate brittle fracture" enabling physical and chemical forces to proceed internally to cause secondary structural faults and failure zones that can weaken the already brittle cleavage fragment even further [4].

Direct measurements of tensile strength demonstrate that cleavage fragments are much weaker and less flexible than asbestos fibers of the same size [36]. The tensile strength of amphibole asbestiform fibers is between 20 to 115 times stronger than non-asbestiform varieties of the same amphibole mineral [26,28,29,31]. The difference in strength between asbestos fibers and cleavage fragments

becomes greater as they get progressively thinner [4,26,28,29,31]. The difference is therefore probably greatest for fibers and fragments thin enough to meet the minimal width (<0.5 μm) and length (>5 μm) criteria of a biologically relevant structure (see below). Asbestos fibers are therefore unique in displaying diameter-dependent strength. Thus, as an asbestos fiber becomes thinner, it gets stronger [26,28,29]. By contrast, as a cleavage fragment gets thinner, it gets weaker [28,36].

Grinding Studies

Simple grinding studies provide additional evidence to support the proposition that the outer surface of a cleavage fragment is weaker than its inner surface. Such studies demonstrate that cleavage fragments can be easily reduced to a powder by hand grinding [17,26] to yield short equant fragments [16,32,37] (Addison, 2003 unpub.). Simple manipulation of asbestos can cause large numbers of very long, thin fibers and fibrils to separate [16,17,32]. By contrast, whilst the simple manipulation of asbestos fibers may cause them to split into large numbers of very long thin fibrils [16,17,32], bundles of asbestiform amphibole fibers can only be ground with great difficulty often causing the asbestos fibers to mat in the mortar [16,17,26].[9] The greater resistance of an asbestos fiber's surface to such physical stress reflects the greater surface strength of the asbestiform over the non-asbestiform habit. Paoletti et al. [39] have also demonstrated that the response of fibrous and non-fibrous tremolite to comminution is very different.

Dissolution Studies

Dissolution studies provide further evidence to support the notion that a cleavage fragment's surface is weaker than its internal structure. Indeed, the unique ability of amphibole asbestos fibers to survive the harshest forms of chemical attack has formed the basis of many vital industries Thus, the defect-free outer surface of an amphibole asbestos fiber is highly acid resistant [28,29]. By contrast, the numerous cracks and defects on the surface of a cleavage fragment serve as "etch pits" that can allow acid to penetrate into the interior of the structure [21,26,28,29] (also Zoltai, 2000 pers comm). In such cases, grunerite (known as amosite when in a fibrous form) cleavage fragments will begin to dissolve on all surfaces when soaked in acid. By contrast, asbestiform grunerite fibers start to dissolve at the ends of the fibers and also require a stronger acid to commence the dissolution process [26,29]. As dissolution proceeds, solid asbestiform fibers become partially hollow cylinders long before their surfaces have dissolved. By this time, many cleavage fragments have undergone complete dissolution [26,28,29]. Surface defects are thus "preferred sites for chemical attack" [29] through which fractures may be propagated. If this occurs, a cleavage fragment may be weakened along its length so reducing its resistance to fracture even further [4] (Wylie, 2000 pers comm). Additional experimental data from chemical "weathering" studies [40,41,42] further demonstrate that surface defects cause massive non-asbestiform amphiboles to dissolve more readily than asbestiform amphiboles.

Surface Charge Studies

The surface charges of asbestiform and non-asbestiform amphiboles may also differ [14,43,44]. Such differences may be biologically important since surface charge has been shown to be related to cationic exchange and particle absorption [29] as well as fibrogenic and tumorigenic potential [45] (also see [30,46,47]).

Internal Micro-Structural Features

A detailed discussion of the internal micro-structural features that differentiate cleavage fragments from amphibole asbestos fibers is beyond the scope of this review but has been detailed by others [5,16,21]. By TEM, prismatic non-asbestiform specimens have been found to contain "extensive sub-grain boundaries and dislocation networks". "Fine multiple twinning" has been observed in asbestos but is less common in non-asbestiform amphiboles. Microscopically, the "crystallographic orientation to an electron beam of an asbestos fiber differs markedly from that of a cleavage fragment" [32]. "The behaviour of cleavage fragments of amphibole should be different as their most strongly developed faces are {110}" [5]. This is reflected in differing polarizing, x-ray diffractometric and infrared spectrophotometric patterns due to preferred orientation and preferential alignment of the crystals [5] (Addison, 2003 pers comm; also see [37]).

The Differences in the Properties of Cleavage Fragments and Amphibole asbestos Fibers are Biologically Relevant

Cleavage Fragments Do Not Possess the Extreme Dimensions of asbestos Fibers

Because non-asbestiform amphiboles are brittle they typically fracture "horizontally" across their length rather

than along it and in so doing produce shorter fragments. These are, for the most part, much thicker, for the same length, than their asbestiform analogues [16] (Addison, 2003 pers comm). Asbestiform amphiboles, however, don't typically break horizontally to produce short fibers when crushed. Instead, they tend to separate into fibrils of their original length [16]. The typical manner in which cleavage fragments fracture is unable to generate uniform long, thin fibrils and fibers (also see [5]; Addison, 2003 pers comm). The extremely high percentage of "short fibers" in dusts generated by those working with ores contaminated with massive amphibole (e.g. Homestake Gold and Minnesota Taconite miners) noted by the ATSDR [9] strongly supports this idea. Only a very small proportion of cleavage fragments conform to the dimensions of asbestiform fibers.[10] An even smaller percentage ever resembles a biologically relevant structure longer than 5 μm and less than 0.5 μm in width.

Therefore, the fiber dimensional distributions of equivalent numbers of cleavage fragments and their asbestiform analogues differ greatly [5] (Addison, 2003 pers comm). The dimensional differences are so great that Chisholm [5] concluded that "A criterion based on particle dimensions is left as the only quick and simple option for a routine method of quantitative analysis" and that "it should be possible to set criteria such that there is very little risk of failing to count an asbestos fibre through wrong identification as a cleavage fragment". Furthermore, "there is relatively little overlap between the width and aspect ratio distributions for the two particles types" [11] so "good quality size distribution data should provide a satisfactory basis for distinguishing between asbestos particles and cleavage fragments" [5].[11] Indeed

> "The distinction between asbestos particles and mineral fragments emerges most clearly in their width: virtually no cleavage fragments are <0.25 μm in width and almost none are <0.5 μm (if >5 μm in length) [49,52]. In examining a single fibre <0.5 μm wide, or a small population of such narrow particles, it is reasonable to conclude that they are asbestos" [5] (see Table 1).[12]

This is related to the fact that, as cleavage fragments get longer, their widths increase, so that nearly all cleavage fragments that are longer than 5 μm are also greater than 0.3 μm in width (Chatfield, pers comm. also see [5]). By contrast, as asbestos fibers get longer, they remain uniformly thin [53] so significant quantities of asbestiform fibers longer than 5 μm and thinner than 0.25 μm are commonplace. Cleavage fragmentation *cannot* therefore generate appreciable quantities of extremely long, thin structures so the majority of airborne cleavage fragments are not biologically relevant (see above).

Cleavage fragments thinner than 0.3 μm and longer than 15–20 μm are very rare, if they exist at all [5,9–11]. Amongst asbestos fibers thinner than 0.3 μm, those longer than 40 μm are 500 times more potent than those shorter than 40 μm [54]. Cleavage fragments of these dimensions do not exist. Fibers less than 5 μm have little or no potency [9,10] and those in the 5–10 μm range have a mesothelioma potency 1/300th of fibers longer than 10 μm [10]. Cleavage fragments greater than 10 μm long are, in fact, very uncommon [5].

Regarding width, cleavage fragments >5 μm long are generally too thick to be respired (they would need to be *c.* <1.5 μm) [10], too wide to penetrate into the deep lung (they would need to be *c.* <0.6 μm) [10], or too thick to comport with a pathogenic width (*c.* <0.15–0.3 μm) [55,56]. Various researchers have demonstrated width

Table 1. SEM characterization of bulk samples of asbestos and cleavage fragments

Asbestos	(a) % >5 μm	% of (a) with Widths <0.5 μm	% of (a) with Aspect Ratio >3:1	% of (a) with Aspect Ratio >10:1	% of (a) with Aspect Ratio >15:1	% of (a) with Aspect Ratio >20:1
Fibers						
Croc, SA	48	85	100	99	95	89
Amosite, SA	73	50	100	98	84	75
Cleavage fragments						
Tremolite, NY	30	1	47	3	2	2
Riebeckite, Calif.	50	5	78	35	21	12

From [38] as cited by [5], Table 2.

cut-offs for mesothelioma formation on the basis of animal studies [57]; also see criticisms in [10] where this [57] was refuted in discussion, and human observations in relation to attendant fiber size measurements made in air, ore, and lung tissue, e.g. [50,58–63] (Karjalainenen, 1997 pers comm and Wagner, 1999 pers comm). Therefore, cleavage fragments cannot have the same mesothelioma-inducing potential as asbestos fibers since the vast majority do not conform to the physical dimensions that pose a mesothelioma risk (also see [10]).

Biopersistence Strongly Determines Carcinogenicity and Cleavage Fragments are Far Less Bio-persistent than Asbestos Fibers

Biopersistence strongly determines carcinogenicity [64]. This is largely a macrophage-mediated phenomenon. Macrophages can physically clear a fiber depending on its length and/or dissolve it depending largely upon its durability and surface strength.

The Ability of the Macrophage to Clear and/or Dissolve Asbestos Fibers and Non-asbestiform Cleavage Fragments from the Lung is Very Different

Long, thin durable asbestiform amphibole fibers are extremely difficult for the lungs to clear and can 'biopersist' long enough to produce severe adverse biological effects. The critical length for fiber clearance approximates the diameter of an alveolar macrophage [63]. This is species-dependent with the critical length cut-off being significantly longer for humans than rodents (rat: 10–15 μm [63]; 5–10 μm [54]; 8 μm [65,66]: humans: 10–15 μm [54]; 24 μm [65,66]; 17 μm [67,68]; 18–20 μm [9]). Human alveolar macrophages are also better able to clear fibers than those of rodents due to their vastly greater surface areas and because the number of macrophages per alveolus in humans is much greater than in rodents; a 600-fold difference [66]. Since risk assessments generally ignore such comparative clearance considerations, animal data usually overestimate human risk.

Any long, thin cleavage fragments that exist are almost certainly brittle and weak and "cannot bend more than a few degrees" [26]; also see [44]. Physical stresses may cause them to break as they enter, remain within, and/or leave the body. The forces experienced during alveolar collapse and expansion may impose bending forces on cleavage fragments causing them to break. After phagocytosis, the muscular strands of a macrophage's cytoskeleton (that enable it to change shape and size dramatically so it can enter lymphatic vessels or squeeze through tiny pores between epithelial cells), may impose forces on the phagocytosed cleavage fragments that cause them to break. By contrast, asbestos fibers are extremely strong and flexible. Thus, "The relatively high flexibility of asbestiform fibers enables them to bend without breaking and may facilitate their passage through the respiratory tract" [26].

Fibers thin enough to reach the deep alveolar lung may be engulfed by phagocytic cells such as macrophages and neutrophils. Although phagocytes cannot "digest" mineral particulates as they might, say, bacteria, the acid milieu produced by release of intracellular acidic enzymes does cause some mineral dissolution. Dissolution is greatest within surface defects [69]. The exceedingly strong, defect-free surface of an amphibole asbestos fiber enables it to resist acid attack better than a cleavage fragment [26,28,29]. If fibers are too long to be completely engulfed, the cell will eventually die in an attempt to clear it. Repeated attempts by cells to engulf a long fiber result in deposits of glycoprotein/hemosiderin along its length giving it an appearance, under the microscope, of a beaded 'drumstick'. This is known as an 'asbestos body'. Asbestos body formation takes place primarily on long amphibole structures. Partial dissolution of the fiber can eventually weaken the asbestos body so that its breaks at "internodal" points along its length. This disintegration continues until the fragments are short enough to be phagocytosed and can then be cleared from the body.

The difference in biopersistence between cleavage fragments and asbestos fibers may be most pronounced for the very small proportion of cleavage fragments with 'biologically relevant' dimensions, i.e. those longer than 5 μm and thinner than 0.5 μm. As discussed above, cleavage fragments become weaker as they become thinner which follows in part from the inverse relationship between diameter and surface area. As the surface of an asbestos fiber is largely defect free, this increase in surface area with decreasing diameter does not particularly increase defect frequency. The converse is true for cleavage fragments; the thinner they are, the greater their surface area, and the greater the number of surface defects [28]. This would make thin cleavage fragments far more susceptible to the effects of macrophage attack than amphibole asbestos fibers of the same width.

Animal Studies Demonstrate Cleavage Fragments are not Carcinogenic

The effects of asbestos fibers and non-asbestiform cleavage fragments on animals have been assessed in the same

studies to compare their carcinogenic potential.[13] Indeed, some of the "most compelling evidence that their effects are very different comes from animal studies" [5]. All such studies have used either intrapleural injection, intrapleural implantation, or intraperitoneal injection. Each delivers massive doses directly to the mesothelium. This can only be accomplished by artificial exposure methods that bypass host defense mechanisms that normally prevent all but a small fraction of fibers from reaching the mesothelium following inhalation. Despite the extreme sensitivity of these injection test methods and the massive doses employed, cleavage fragments still fail to produce any tumors or a tumor response exceeding background [70–72]. This concept is ignored by some such as the Final Report [10]. By contrast, asbestos fibers in these injection studies produce high tumor rates not infrequently reaching 100%. The negative carcinogenic responses noted with cleavage fragments therefore provide very strong evidence that cleavage fragments are not carcinogenic to humans, particularly when the sensitivity of the assay and the large doses used are taken into consideration. OSHA [6] concluded that "virtually all participants agreed" that the animal studies clearly demonstrate qualitative differences in the carcinogenic potential of asbestos and cleavage fragments.

The following summarizes the most relevant studies.

Wagner et al. [62], Stanton et al. [57] and Smith et al. [73] intrapleurally injected rodents with large [10–40 mg] doses probably containing up to 80 million cleavage fragments longer than 5 μm and less than 0.5 μm wide (also see [74,75]). The rats either failed to develop mesotheliomas or the resultant tumor rates did not exceed background [70–72].

Davis et al. [76] intraperitoneally injected rats with 10 mg doses [49 million cleavage fragments longer than 5 μm; 2 million longer than 5 μm and thinner than 0.5 μm] of two tremolite cleavage fragment samples. The Shinness tremolite sample, "almost exclusively composed of very brittle cleavage fragments" [76], (Addison, 2000 pers comm) and not a "mix" as suggested by Lockey (cited in [10]), produced mesotheliomas in only 5.6% (2/36) of rats, an incidence well below background [76–78]. The same number of asbestos fibers of similar dimensions would have produced a very high incidence of mesotheliomas (see Table 2) [77]. Davis et al. [77,78] said that asbestos fibers longer than 8 μm were the most carcinogenic in intraperitoneal injection studies. He stated further that "tumours may be expected regularly at dose levels of between 150,000 and 200,000 fibres (>8 μm) and will develop in at least 25% of animals if more than about 600,000 fibers are injected". However, the intraperitoneal injection of 17 million cleavage fragments longer than 8 μm [77] failed to produce mesothelioma rates above background (Table 3). By contrast, much smaller numbers of asbestos fibers produced mesothelioma rates up to 95% [77]. The second cleavage fragment sample from Dornie, Scotland contained 24 million fibers longer than 5 μm and this also failed to produce tumor rates greater than background (data not shown). Davis et al. [76] concluded that human exposure to materials such as those obtained from Shinness or Dornie, Scotland, whether as a pure mineral dust or as a contaminant of other products, "will almost certainly produce no hazard".

In Vitro Studies

In vitro studies have also demonstrated that non-asbestiform tremolite [61,79], grunerite [43,80] and riebeckite [81–83]; also see [84], cleavage fragments are far less biologically active than asbestiform amphibole fibers tested in the same study as measured by a great variety of cellular endpoints.

Table 2. Comparison of Shinness tremolite "fibers" (>5 μm) and asbestos fibers (>5 μm)

Type	Mass Dose (mg)	No. Fibers >5 μm Length	Meso. Incidence	Above Background?	Study
Shinness Tremolite (cleavage fragments)	10	49,000,000	5.6%	No	Davis et al. [76]
Amosite	0.05	1,700,000	25%	Yes	Davis et al. [78]
Crocidolite	0.05	2,075,000	25%	Yes	Davis et al. [78]
Actinolite	0.01	4,000,000	23%	Yes	Pott [137]
Actinolite	0.05	20,000,000	42%	Yes	Pott [137]

Table 3. Comparison of Shiness tremolite "fibers" > 8 μm and asbestos fibers > 8 μm

Type	Mass Dose (mg)	No. Fibers >8 μm Length	Meso. Incidence	Above Background?	Study
Shinness Tremolite (cleavage fragments)	10	17,000,000	5.6%	No	Davis et al. [76]
Amosite	2.5	153,000	60%	Yes	Davis et al. [138,139]
Amosite	0.05	305,000	28%	Yes	Davis et al. [138,139]
Amosite	5.0	305,000	78%	Yes	Davis et al. [138,139]
Crocidolite	0.05	420,000	25%	Yes	Davis [140]
Amosite	7.5	458,000	65%	Yes	Davis et al. [138,139]
Amosite	10	610,000	72%	Yes	Davis [141]
Crocidolite	0.05	745,000	25%	Yes	Davis et al. [78]
Amosite	0.05	765,000	25%	Yes	Davis et al. [78]
Amosite	15	915,000	76%	Yes	Davis et al. [138,139]
Crocidolite	0.5	4,200,000	31.3%	Yes	Davis [140]
Amosite	10	6,100,000	88%	Yes	Davis [140]
Amosite	25	1,525,000	95%	Yes	Davis [138,139]

Epidemiological Studies Show No Association Between Exposure to Amphibole Cleavage Fragments and Asbestos-Related Disease

Homestake Gold Miners

Steenland and Brown [85] performed the most recent study of the Homestake gold miners (n=3,328). Although these workers were exposed to significantly elevated levels [86] of grunerite and tremolite cleavage fragments, there were no deaths due to mesothelioma. The one "mediastinal" mesothelioma was "unconfirmed" [9,87,88] and there was no lung cancer excess (SMR 1.13) (also interpreted as "negative" by the ATS [7], Chisholm [5] and the ATSDR [9]).

Ontario Gold and Nickel Miners

Kusiak et al. [89] conducted the most recent study of the Ontario gold and nickel miners (n=54,128) exposed to non-asbestiform amphibole fibers. A lung cancer excess was thought to be related to arsenic and radon, not to cleavage fragments (also see [90, 91] (Kusiak, 2003 pers comm). Two cases of mesothelioma occurred in gold miners but neither case "was known to be exposed to the komatiite rocks that sometimes contain fibrous amphiboles" [89].

Minnesota Taconite Miners

Higgins et al. [92] studied the Reserve Mining Company taconite miners and millers (n=5,751). These workers were exposed to elevated levels of grunerite cleavage fragments but displayed no attributable asbestos-related disease.

Cooper et al. [93] conducted the latest update of the Erie and Minntac Company taconite miners and millers (n=3,444) exposed to elevated levels of grunerite cleavage fragments (as estimated from Higgins et al. [92]). One mesothelioma was found but it was not thought to be attributable due to insufficient latency and significant alternative exposure, i.e. from long-term work with boiler insulation on locomotives [93]. A recent mesothelioma case control study by the Minnesota Department of Health [94] also failed to find any attributable cases. There was no lung cancer excess (SMR<100) (interpreted as "negative" by others [5,9]).

New York State Gouverneur Talc Company [GTC] Talc Miners

Honda et al. [95] conducted the most recent study of the GTC talc miners and millers (n=818) exposed to significant levels of tremolite cleavage fragments [49,96]. A lung cancer excess was observed. However, this was not felt to be attributable due to a lack of dose response, smoking (see [5,90,91,97–104] and pers comm from Delzell, 2003 and Beall 2003) and alternate causation (e.g. see data for individual lung cancer cases in [103–106]). Two mesotheliomas noted by Honda et al. [95] and Delzell et al. [105] were not thought to be attributable on the basis of insufficient latency, inadequate exposure and/or alternative causation. Hull et al. [107] claimed that there were at least 8 mesotheliomas, citing their own work and that of others [108–110]. Again most, if not all, of those cases did not appear to be attributable on diagnostic and/or causation grounds. A radiographic survey of the counties surrounding the GTC mines failed to find attributable asbestos-related disease [111].

US Paint Plant Production Workers Exposed to GTC Talc

Morgan [112] did the only study of paint and coating production workers ($n=16{,}000$) from 32 plants in the United States and these workers, in particular sub-cohort 2 (pigment) (Sides, 2003 pers comm) had a very high, ongoing use of and presumed exposure to GTC talc. No lung cancer excess was found (also see [103,104,113]). No mesotheliomas were reported.

UK Ceramics Pottery Workers

Thomas and Stewart [114] noted that pottery workers exposed to tremolitic talc displayed no lung cancer excess (also see [7,103, 104]

Norwegian Talc Miners and Millers

Wergeland et al. [115] studied Norwegian talc miners and millers probably exposed to trace amounts of tremolite cleavage fragments (see [115], p. 506). No lung cancer excess was found. No mesotheliomas were recorded.

Italian Talc Miners and Millers

Rubino et al. [116] studied Italian talc miners and millers probably exposed to trace amounts of tremolite cleavage fragments [7,117–119], and see the Pooley Report cited by [116]. No attributable cancer excess was found.

Vermont Talc Miners and Millers

Wegman et al. [120] and Selevan et al. [121] performed the latest studies of the Vermont talc miners and millers probably exposed to trace amounts of tremolite cleavage fragments [121]. No cancer excess was found.

Swedish Dolomite Limestone Miners and Millers

Selden et al. [122] studied Swedish dolomite limestone miners exposed to low concentrations of tremolite cleavage fragments. No cancer excess was found.

Enoree Vermiculite Miners and Millers

McDonald et al. [123] studied the Enoree South Carolina vermiculite workers ($n=194$) exposed to "trace" amounts of cleavage fragments [124]. There were no attributable deaths due to lung cancer, pneumoconiosis or mesothelioma.

New York Hard Rock Tunnel Diggers

Selikoff [125] studied 932 tunnel workers in New York City exposed from 1955 to 1972 to cleavage fragments from the massive, non-asbestiform amphibole, known as hornblende. There were 294 deaths but no evidence of asbestos-related disease [126].

Kennicott Copper Miners

The Kennicott Copper mine is one of the largest mining operations in the world. Workers have been exposed to cummingterite–tremolite–actinolite cleavage fragments for many years [4] with no suggestion of attributable asbestos-related disease (Kennicott management, 2000 pers comm).

The "Central European Arc of Pleural Pathology"

Endemic pleural plaques, not associated with any occupational exposure, occur from Finland in the north southwards through the former Soviet Union, Czechoslovakia, Austria, Yugoslavia, Bulgaria and Greece [127]. The plaque excess has been attributed to exposure to soils naturally contaminated with "coarse" (>1 μm in diameter) tremolite (or anthophyllite) fibers [62,127] that are probably cleavage fragments. Such asbestos-related plaques are thought to be due to largely non-fibrous, "blocky" [128], thick [55] amphibole [129,130].

Sparta Marble Quarry Workers and Residents

The Sparta New Jersey marble quarry has been in operation for almost 100 years and the workings are associated with very low exposures to tremolite cleavage fragments. There is no evidence to indicate that these exposures are associated with an attributable risk of asbestos-related disease in either the workforce or the residents of the town of Sparta several miles from the quarry.

Nephrite Jade Workers

Nephrite jade is a form of massive tremolite–actinolite amphibole (see, for example, [16]) mined in various parts of the world. One of the world's largest deposits is in British Columbia and the removal, wedging and slicing of nephrite boulders can be a source of dust exposure (Ward, 2003 pers comm). Whilst formal epidemiological studies of the Canadian nephrite jade miners have not been performed, mesotheliomas do not appear to have occurred in these workers (Ward, 2003 pers comm). Canadian nephrite is also purchased by the Chinese who work the stone on a lathe. This can be a source of considerable dust exposure (Ward, 2003, pers comm.). To date, there do not appear to have been formal studies of the health of the Chinese jade factory workers.

Quebec Chrysotile Miners and Millers

The Quebec chrysotile miners and millers have almost certainly been exposed to considerable airborne concentrations of tremolite cleavage fragments since a substantial proportion of the tremolite contaminating the ore is non-asbestiform [15]. However, detailed review of the Quebec chrysotile miner and miller lung burden studies for which relevant data are available failed to provide evidence that the predominant form of tremolite retained in these lung tissues is non-asbestiform.[14] In fact, the only study that appears to have addressed this issue [131] concluded that most of the tremolite was asbestiform. This observation would provide further support that non-asbestiform tremolite amphiboles are, for the most part, short enough to be cleared or, if initially longer than the macrophage, fragile enough to be rapidly broken down in the body and thus readily removed. Case [3] remarked "on the long tremolite fibers in miners and millers with asbestosis" and suggested that these could "produce increased levels of shorter fibers due to fiber breakage into shorter fragments" and thus contribute to a "possible increasing composition of the tremolite mass by cleavage fragments". This could only happen if the long tremolite fibers were actually long tremolite cleavage fragments since asbestiform fibers cannot produce non-asbestiform structures. Moreover, Dufresne et al. [131] did not find increased numbers of cleavage fragments making it very unlikely that cleavage fragments, contributed to the pathology found in the Quebec chrysotile miners and millers.

Conclusions

Cleavage fragments are not asbestos ("non-asbestiform"). There are fundamental differences in the properties of cleavage fragments and asbestos fibers. Cleavage fragments lack the strength, durability, flexibility and acid resistance of asbestos. They are therefore unable to persist in the body largely because they are short and are readily cleared. They also fail to persist since the few that are long break into short fragments due to their lack of strength, durability, flexibility and acid resistance. Moreover, those that would be long enough to thwart the macrophage are almost always too wide to be inhaled. Therefore, physical properties related to respirability and clearance and, probably to a lesser extent, chemical characteristics related to dissolution directly and clearance indirectly, account for their observed differences in carcinogenic potential.

OSHA [6] determined that the scientific evidence was insufficient to regulate cleavage fragments. Nonetheless, the California Geological Survey [134] still does not recognize the difference between asbestiform fibers and cleavage fragments saying there is "no general consensus on the health effects of cleavage fragments in the scientific community". This conclusion is contradictory since the California Geological Survey has said that "cleavage cannot produce the high strength and flexibility of asbestiform fibers" and that acicular crystals, "special types of prismatic (non-asbestiform) crystals", do not have the "strength, flexibility, or the other properties of asbestiform fibers" [134].

The scientific evidence that demonstrates that cleavage fragments are non-carcinogenic in animals and humans is robust. The methods used to assess tumor production in these animal studies are extremely sensitive and discriminatory even when the doses employed are vastly greater than humans would ever encounter even under worst-case scenario exposure conditions. This is particularly relevant to allegations of low dose risk where the levels of exposure are exponentially lower than those employed in such animal studies. The fact that cleavage fragments are non-carcinogenic in such animal tests demonstrates that cleavage fragments, even at extremely high doses, do not pose a carcinogenic risk to humans. Epidemiological studies of many tens of thousands of workers in various primary and secondary industries exposed to cleavage fragments fail to reveal evidence of an attributable cancer excess.[15] Moreover, amphiboles are ubiquitous throughout the earth's crust and clearly permeate numerous mineral deposits of potentially high commercial value, e.g. gold, silver [135], nickel [89], copper [4], sulphide [136], talc [95], vermiculite [123], marble [4], crushed stone, and a variety of gemstones such as jade (Ward 2003, pers comm). Many thousands of workers exposed to dusts containing cleavage fragment do not appear to display an attributable excess of mesothelioma. Similarly, the permeation of numerous residential areas by non-fibrous amphiboles has not resulted in a "pandemic" of mesotheliomas which again attests to the inability of cleavage fragments to produce asbestos-related disease.

Notes

1 The most common habit for an amphibole is an elongated prism, lozenge-shaped in cross section, ranging from short stocky prisms to fine needle-like crystals or ultimately fine hair-like crystals (sometimes known as byssolites). The prismatic habit is the normal form of igneous and metamorphic rocks and is very widespread throughout the continental crust of the earth (Addison, 2003 unpub.).

2 Very subtle chemical differences may influence growth habit. For example, the presence or absence of traces of aluminum may determine whether an asbestiform or a non-asbestiform habit exists. [16,17,20]. Since a fiber is composed of highly aligned and oriented chemical units, there is no room to accommodate larger atoms such as aluminum. [4]. Substitution of aluminum for silicon will lead to structural distortions that cause the development of prismatic crystals rather than asbestos fibers. [4]. This substitution also increases the Z–O bond distance and therefore reduces the strength of bonding within, and parallel to, the length of the amphibole chain. Although substitution is thought to occur mostly with aluminum, other metals have been proposed such as calcium [4], manganese [4], iron [4], titanium [16] and chromium [16] (and also see [5,17]) to be important substituents.

3 Elongated amphibole structures known as "transitional fibers" also exist but these are very rare [6]. They are thought to display features of both the asbestiform and the non-asbestiform condition. Their rarity puts them beyond the scope of this review (but see [22] for discussion) and they cannot materially affect the overall conclusions reached herein. Some [23] incorrectly claim that it is very difficult to distinguish between asbestiform and non-asbestiform amphiboles inferring that "transitional structures" are actually commonplace. Such claims do not comport with their data and may be related to a certain degree of "litigation bias" [24].

4 This might be reflected for asbestos in geological environments that favor "relatively rapid multi-nucleation and growth in a low temperature stress free environment", "the opposite conditions applying to most prismatic specimens" [16].

5 Some problems exist in distinguishing asbestos particles from cleavage fragments. The main difficulties arise from uncertainty over the features used to define asbestos, from the effect which processing has on those characteristic features and from the limited applicability of the defining characteristics to the small particles observed in the TEM [5].

6 Dorling and Zussman [16] refer to the surface of a cleavage fragment as "smooth" but "broken up by steps in the {110} cleavage plane" and the surfaces of growth faces [of asbestos fibers] as "usually roughened and striated due to the presence of vicinal faces" and small irregularities". The use of the term "smooth" in this review denotes the large scale absence of steps, dislocations, and large irregularities from asbestos fibers. Vicinal faces are also probably "metastable" disappearing as growth continues [16].

7 A "twinning plane [may also be regarded] as a stacking fault: the Si_4O_{11} double chains of the structure lie in planes parallel to {100} and are displaced relative to each other by approximately $\pm c/3$ along the chain axis in order to provide octahedral co-ordination for the cations between the double chains". ... twinning planes are points of weakness in the crystal structure and fracture is likely to occur along the {100} planes as a result, producing bladed or lath-like particles. This process may contribute to the observed morphology of asbestos particles and their tendency to have {100} faces as well as or in preference to {110} [5]

8 Chisholm [5] describes the many problems encountered in developing a reliable quantitative method and these include selection of the correct microscopic method, the degree of overlap between the size and aspect ratio ranges for the two types of particle; the lack of reliable, independent, systematically derived data in the literature; the use of potentially atypical reference samples; and the availability of data from different measuring techniques. Chisholm [5] also discusses the limitations of using diffraction to differentiate cleavage fragments from amphibole asbestos fibers. Also, "The frequency of {100} twin boundaries may offer the most reliable means of distinguishing the two types" on a quantitative basis but it "may not be easily determinable for all particles."

9 The main dimensional characteristics of the material are retained unless the grinding is extremely severe [38]. Grinding opens the asbestos fibers, i.e. separates them into their component fibrils, whose cross-section dimensions are established during their formation. The width of cleavage fragments will depend more on the degree of grinding. The width distribution does however depend on whether the measurements are made using TEM or SEM (see above): TEM tends to 'see' the smaller fibers better compared to SEM. So comparisons between width distributions should ideally be made using the same type of instrument. TEM gives by far the most accurate size data for thin fibers [5].

10 The NIOSH definition covered particles >5 μm long with an aspect ratio >3:1; the limit on the aspect ratio was intended to exclude non-fibrous mineral fragments but was otherwise arbitrary. It subsequently emerged that many particles derived from non-asbestiform amphiboles nevertheless came within the scope of this definition. Measurements on the particle dimensions of asbestiform and non-asbestiform amphiboles have shown that the 3:1 aspect ratio criterion bears little relation to the differences between the two. Many proposals have been made to change the definition of a fiber but the original definition still stands [11,48–51]:

> "the definition of a 'fibre' usually adopted for optical microscopy, i.e. a particle >5 μm in length and with aspect ratio >3:1, is not a satisfactory criterion for distinguishing asbestos particles from cleavage fragments. Alternatives have been proposed (length >5 μm and aspect ratio >20:1, [11=]; length >5 μm and width <1 μm, [50] which are certainly more realistic."
>
> "A distinction based on size and aspect ratio is the only practical way of [classifying a fibre or a fragment] whatever uncertainties it may introduce. To set up a quantitative method whose results have some practical meaning will require great care in setting the size and aspect ratio criteria which define asbestos fibres and cleavage fragments ... it should be possible to set criteria such that there is very little risk of failing to count an asbestos fibre through wrong identification as a cleavage fragment. However, the overlap of the size and aspect ratio distributions is such that there will always be some risk of wrongly counting a cleavage fragment as an asbestos fibre. The key to a successful quantitative method lies in minimising this latter risk by careful setting of the defining criteria for an asbestos fibre" [5].

11 Whilst Chisholm [5] said "no conclusion on a fibre-by-fibre basis can be drawn for particles >0.5 μm wide unless their aspect ratio is <3:1 in which case they lie outside the conventional definition of asbestos fibres and would be taken to be cleavage fragments", the data he provides "for particles >0.25 μm wide, >5 μm long and with aspect ratio >3:1" clearly demonstrate that "the greater the aspect ratio, the more likely the particle is to be an asbestos fibre". This is evident from the percentage of particles with aspect ratios >10:1, >15:1 and >20:1" (cf: Fig. 8 from [5]). Therefore, whilst "the possibility that one particular particle is an unusually long cleavage fragment can never be completely eliminated", "The aspect ratios of a small population of particles >0.25 μm wide may give a valid indication of their type" [5].

12 Some have suggested that the potencies of equi-dimensional tremolite fibers or cleavage fragments from different sources, e.g. vermiculite, marble, chrysotile, talc, may differ and that such differences may be biologically important, thus lowering the comparability of some of the animal studies. These differences, however, do appear to be minor (Zussman, 2003 pers comm), e.g. see cell parameter and chemical microprobe results for Gouvenour Talc, Shiness, Jamestown, Korean, and Ala d' Stura tremolites [16,17]. The observed chemical and morphological variations have also been described as "slight" (Zussman, 2003 pers comm).

13 Some panelists of the Final Report [10] "cautioned against inferring too much from this animal study" since they said it was not peer reviewed, the fiber measurements were difficult to reproduce, and the mesotheliomas could have reflected the use of the intraperitoneal injection model". However, the study was peer reviewed (by Case according to Addison, 2003 pers comm); there was no problem with fiber measurement reproducibility (Addison, 200 0 pers comm); and the model, as indicated above, could be used reliably to interpret such data.

14 The ATSDR report [9] states that the tremolite found in the lungs of the Quebec chrysotile workers is "relatively short, low aspect ratio" which seems to contradict the findings of Dufresne et al. [131]. However, the geometric mean (GM) of these fibers is 8:1–10:1. Since this is based on all fiber lengths, it could still include large numbers of high aspect ratio asbestos fibers. Moreover, according to the ATSDR [9] citing both the ATS [7] and Case (unpublished), the GM AR of fibers longer than 5 μm is said to be greater than 20:1. This may certainly contain significant numbers of fibers with much higher aspect ratios and thus be compatible with the findings of Dufresne et al. [131] (also see Langer's testimony in [6]). Thus, there is little evidence to support the ATSDR's [9] view that "high concentrations" of "lower" aspect ratio tremolite (i.e. cleavage fragments) can cause mesothelioma". Magee et al. [132] is often cited to support this notion, e.g. [7] but this paper is simply a case report and the data have been misinterpreted (e.g. by the ATSDR [9]). Wagner et al.

[62] says that "there are irregular deposits of a coarse fibered tremolite in the massive chrysotile ore bodies in Quebec" [which are] "found in the lungs of miners with pulmonary fibrosis and pleural plaques" [133]. Nonetheless, Pooley [133] actually fails to provide diameter distribution and aspect ratio data for these tremolite fibers. Only the pictures of the tremolite fibers in the lungs are given and, whilst these suggest that some may be "thick" or "coarse" in nature [133], they obviously cannot substitute for actual data.

15 Some may criticize cross comparison of studies based on exposures to different types of amphibole fiber, i.e. those derived from grunerite, taconite or cummingtonite. However, as the Final Report [10] states: "The potency of regulated and unregulated amphibole fibers should be considered equal based upon the reasoning that similar durability and dimension would be expected to result in similar pathogenicity." Uncertainties are also expressed about some of the conclusions reached by the ATS [7] panel (e.g. Lockey, 2003) but these are surely overridden by the fact that OSHA [6] concluded that there was not enough evidence to say that cleavage fragments posed a risk to workers. The Final Report [10] also said it was "prudent to assume an equivalent potency for cancer" (for cleavage fragments and fibers) despite that fact that most panelists acknowledged that the epidemiology and animal studies were negative.

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EVALUATION OF THE APPROACH RECENTLY PROPOSED FOR ASSESSING ASBESTOS-RELATED RISK IN EL DORADO COUNTY, CALIFORNIA

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1 EXECUTIVE SUMMARY

The U.S. Environmental Protection Agency (EPA) recently conducted a multi-media assessment of exposure to naturally occurring asbestos (NOA) in El Dorado County (Ladd 2005). In this study, exposure to asbestos was evaluated by monitoring airborne concentrations obtained both under ambient conditions and while various recreational activities were simulated at locations selected because the soil was believed to contain NOA. An approach was also proposed in this study for assessing the risks associated with the observed exposures.

The merits of the approach proposed by the U.S. Environmental Protection Agency (EPA) for assessing asbestos-related risk in El Dorado County were evaluated. The approach involves assessing asbestos exposures by determining the concentration of airborne structures satisfying a particular set of dimensions defined in what is termed the phase contrast microscopy equivalent (PCMe) metric and combining these with the current EPA-recommended risk factor (IRIS Current) to assess risk.

The evaluation was conducted by considering:

- the current status of science and the limitations of the PCMe metric;
- the historical consistency with which the PCMe metric has been applied;
- the general limitations of the Ladd (2005) study;
- implications from the literature concerning structure sizes and types;
- precedents set by approaches used for assessing risk at other government-lead sites;
- the relative degree of peer and regulatory review for the various steps of the proposed approach and an alternate approach also considered (the approach for assessing asbestos-related risks proposed by Berman and Crump); and
- the degree of overall health protectiveness afforded by the approach proposed for El Dorado County relative to that afforded by the approach proposed by Berman and Crump.

Conclusions

The conclusions from this evaluation are that:

- it appears that the proposed approach satisfies neither of two criteria that are critical for assuring that risk assessments are reliable. First, due to substantial differences in character, exposure concentrations determined in terms of the PCMe metric in El

Dorado County (Ladd 2005) are not directly comparable to the PCM-based exposures evaluated in the epidemiology studies used to derive the risk factor in IRIS (Current). Second, the PCMe exposure metric itself has been shown not to remain reasonably proportional to risk across exposure environments. Given these findings, applying the IRIS risk factor to exposures measured in El Dorado County will not provide reliable estimates of risk;

- the Ladd (2005) study appears to suffer from quality control (QC) problems that will need to be resolved before any attempt is made to interpret the data. Even after the QC issues are resolved, however, it may prove difficult to extrapolate findings that may be gleaned from the study more broadly than to the specific locations at which airborne measurements were collected. This is because no relationship between bulk concentrations and airborne exposure measurements was established in the Ladd study;

- until the quality control issues are resolved and an appropriate statistical analysis of the data is conducted, a proper assessment of risk cannot be completed from the Ladd (2005) data. Thus, it is not possible to tell at this time whether risks estimated using either protocol structures (another exposure metric considered in this report) or PCMe structures will prove to be acceptable for the areas represented by the Ladd study environment. However, assuming that the ratios of concentrations are approximately correct, it appears that the IRIS approach for assessing risk yields a higher risk estimate than the Berman and Crump approach (another approach considered in this report) for the specific locations that were studied;

- as the above observation (should it hold up) is highly unusual, compared to findings based on broad experience at other sites, it reinforces the finding that conditions at these specific locations in El Dorado County are very different from conditions found at most sites where asbestos is a hazard (potentially including other parts of El Dorado County);

- if applied uniformly at sites across the nation (and other parts of El Dorado County), the approach proposed for assessing risk by EPA will be less health protective than if such risks are assessed using the approach proposed by Berman and Crump. This is based on a growing body of experience at multiple, varied sites;

- whatever the relative risks that might be estimated for El Dorado County based, respectively, on the approach proposed by EPA and the approach recommended by Berman and Crump (2001), it appears that the proposed EPA approach is no better supported by precedent; and

- given that (based on discussions with multiple geologists) about 30% of the soil and near-surface rock in the nation may contain amphibole, if the agency intends to apply their asbestos regulations consistently to all areas where amphibole may be present, then it is in everyone's interest to employ an approach that will adequately

distinguish situations that are potentially risky from those that are not. Otherwise, there is a potential either to miss those sites in which true risks exist or, conversely, to *unnecessarily* wreak economic havoc. Neither result is in the public interest, although the first kind of error is clearly the more important to avoid.

2 INTRODUCTION

The U.S. Environmental Protection Agency (EPA) recently conducted a multi-media assessment of exposure to naturally occurring asbestos (NOA) in El Dorado County (Ladd 2005). In this study, exposure to asbestos was evaluated by monitoring airborne concentrations obtained both under ambient conditions and while various recreational activities were simulated at locations selected because the soil was believed to contain NOA. An approach was also proposed in this study for assessing the risks associated with the observed exposures.

The approach that the EPA proposed to assess risk in El Dorado County, if it is to be applied uniformly, may not be generally protective of public health. Given the status of the science, it also appears that the approach may not be as well established by precedent as the approaches that the Agency commonly employs for other hazardous materials.

When evaluating the risks associated with exposure to asbestos, it is important to recognize that the situation with asbestos is particularly complex. Following a brief background discussion highlighting the complexity of the issues involving asbestos sampling, analysis, exposure assessment, and risk assessment as well as conditions in El Dorado County, the remaining sections of this report address:

- scientific considerations concerning the validity and reliability of the proposed approach;
- an overview of relevant precedent;
- implications for health protectiveness;
- conclusions; and
- references.

Note, a sub-section on quality control was also added to highlight what appear to be serious quality control (QC) issues with the data set generated during the recent El Dorado County study (Ladd 2005). When the quality of data can be questioned, it is in everyone's interest to address the problem. Thus, conducting whatever corrective actions might be necessary to examine and address the problems appear to be appropriate.

Importantly, based on the available information, it is possible that the QC problems with the Ladd (2005) study are primarily related to documentation errors. Thus, these problems may be easily correctable. Nevertheless, it is not possible to determine this at this time. Therefore, before anyone should consider the data from this study to be reliable, the QC issues need to be formally addressed. To assist in initiating this effort, a discussion is provided below that is intended to better define the quality control issues that appear to be associated with these data.

3 BACKGROUND

A brief overview of asbestos terminology, the characteristics of asbestos dusts, asbestos measurement methods and their corresponding exposure metrics, and the nature of conditions in El Dorado County is provided in this section.

3.1 Terminology

Asbestos is a term traditionally used to describe a particular fibrous form (asbestiform crystalline habit) of a set of minerals from the serpentine and amphibole mineral groups. The most widely accepted (traditional) definition of asbestos includes the asbestiform habits of six of these minerals (IARC 1977). The most common type of asbestos is chrysotile, which belongs to the serpentine mineral group. Chrysotile is a magnesium silicate. The other five asbestos minerals are all amphiboles (i.e., all partially hydrolyzed, mixed-metal silicates). These are: asbestiform riebeckite (crocidolite), asbestiform grunerite (amosite), anthophyllite asbestos, tremolite asbestos, and actinolite asbestos.

All six of the minerals whose asbestiform varieties are termed asbestos occur most commonly in nonfibrous, massive crystalline habits. While unique names have been assigned to the asbestiform varieties of three of the six minerals (chrysotile and the two amphiboles noted parenthetically above) to distinguish them from their massive forms, such nomenclature has not been developed for anthophyllite, tremolite, or actinolite. Therefore, when discussing these latter three minerals, it is important to specify whether a massive habit of the mineral or the asbestiform habit is intended.

Among the difficulties associated with any discussion of asbestos risk is that the terminology developed for asbestos was designed to address the macroscopic properties of commercially useful materials. However, it is the properties of the microscopic structures that are released from bulk asbestos (when it is disturbed) and their subsequent inhalation that ultimately determine the potential for disease. Thus, the available terminology is limited and can lead to ambiguities if not carefully applied.

Among other things, for example, it has been proposed that the term asbestos be expanded to include the asbestiform habits of a broader range of amphibole minerals (see, for example IRIS Current) and the documents from the Libby, Montana Site (e.g. EPA 2003). This was also recommended by Berman and Crump (2001, 2003). The

reason for this change has been driven by increasing evidence that the asbestiform habits of all amphiboles contribute to the induction of asbestos-related diseases. It should also be noted, however, that the scientific justification for specifically applying the current procedures for assessing asbestos-related risk (e.g. IRIS Current) to these additional minerals has not been formally evaluated or reviewed heretofore.

Another important, but less obvious issue related to the definition of asbestos is the question of the size range of structures that determine biological activity, which is clearly what needs to be regulated. This affects both the measurement of asbestos and the assessment of risk, in addition to the application of regulations. This issue is addressed further in Section 2.3.

To facilitate clarity, definitions for several critical terms used in the remainder of this report are provided below.

Asbestiform means the particular crystalline habit of a mineral that exhibits the common characteristics of asbestos (e.g. highly fibrous, polyfilamentous – existing in bundles, flexible, high tensile strength, and good chemical and thermal resistance). Geologically, the dimensions of fibers formed in this habit are defined by the growth of the crystals (in contrast to cleavage fragments).

Asbestos Minerals means the suite of serpentinite and amphibole minerals currently included in the definition of asbestos when they occur in *any* of their crystalline habits.

Cleavage Fragment means a structure that is formed by physical separation from a larger crystal. Thus, the dimensions of such a structure are defined by the orientation of the weakest cleavage planes in the parent crystal, which is in contrast to the manner in which dimensions are determined for asbestiform structures.

Exposure Metric means the set of sizes, shapes, and morphological types of structures (e.g. fibers, bundles, clusters, or matrices) that are included in the determination of concentration. Sometimes, a particular exposure metric also includes mineralogical constraints (i.e. only structures identified as specific mineralogical types are included). Therefore, exposure metrics for a particular analysis are defined as a function of both the rules of the specific analytical method applied to determine concentration and the limitations of the particular instrumentation employed during the analysis.

Fiber is a relative term that has come to mean any elongated particle that satisfies specific dimensional constraints. The term is relative because the dimensional constraints placed on the definition of the term fiber are specific to the analytical method/exposure metric by which fiber concentrations are determined for a particular application.

Fibril means a single fiber of asbestos (i.e. from an asbestiform population). Single asbestiform fibers cannot be further reduced in width without altering their properties.

Fibrous is a relative term that is used to denote a material composed primarily of fibers. The term is relative because the term for fiber is relative (see above). Note, for example, a dust composed primarily of elongated particles that nevertheless satisfy the dimensional definitions for fibers from a particular application could therefore be defined as fibrous.

Fibrous structure is a collective term used to mean any fiber, bundle, cluster, or matrix. These latter terms for specific types of structures are discussed further in Section 3.2 and concisely defined in ISO (1995).

3.2 The Characteristics of Asbestos Dusts

Structures comprising the dusts from asbestiform minerals come in a variety of shapes and sizes. Not only do single, isolated fibrils vary in length and somewhat in thickness, but such fibrils may be found combined with other fibrils to form bundles (aggregates of closely packed fibrils arranged in parallel), which represent the actual structure of all large "fibers" in an asbestiform population. In turn, fibers may form clusters (aggregates of randomly oriented fibers) or (may be combined with equant particles to form matrices (asbestos fibers embedded in non-asbestos materials). Consequently, asbestiform dusts (even of one mineral variety) are complex mixtures of structures. For precise definitions of the types of fibrous structures typically found in asbestos dusts, see ISO (1995).

In addition to the above, which describes the asbestiform component of a dust, dusts created from asbestos will also contain particles from any material with which the asbestos may be associated. Thus, for example, dusts at mining and milling sites may include particles (including elongated particles that may pass as fibers) that are rock fragments (cleavage fragments) from host minerals. If the mineral being mined is the asbestos itself, likely the host mineral would simply be the massive crystalline habit of the same mineral type as the embedded asbestos.

In environments in which an asbestos dust is derived from an asbestos product (either during manufacture, as a consequence of use, or associated with disposal), the dust may also contain particles (including elongated particles that may pass as fibers) composed of any of the various other component materials of the asbestos product.

Detailed descriptions of the characteristics of dusts typically encountered at environmental and occupational asbestos sites have been reported in the literature and the following summary is based on a previously published review (Berman and Chatfield 1990). Typically, the major components of the dust observed in most environments are non-fibrous, isometric particles. A notable exception to this general observation are the dusts from asbestos textile manufacturing, which is highly fibrous.

The likely reason these dusts are fibrous is that the only major source of dust in such an environment is refined, nearly pure, asbestiform fiber (Walton 1982). However, for asbestos dusts in general, fibrous structures consistently represent only a minor fraction of the total dust. In addition, fibrous structures composed of asbestos minerals typically represent only a subset of the total number of fibrous structures that may be observed in such environments.

The magnitude of the fraction of total dust represented by fibers and the fraction of fibers composed of asbestos minerals vary from site to site. However, the fraction of asbestos in total dusts has been quantified only in a very limited number of occupational and environmental settings (see, for example, Cherrie et al. 1987 or Lynch et al. 1970).

Importantly, as the definition of the term fiber is relative (Section 3.1), the fractional concentration of fibers observed in a particular environment will vary as a function of the analytical methodology employed to determine their concentration. Historically, fibrous structures have been arbitrarily defined as structures exhibiting aspect ratios (the ratio of length to width) greater than 3:1 to distinguish them from isometric particles (Walton 1982). However, alternate definitions for fibers have also been proposed, which are believed to better relate to biological activity (see, for example, Berman et al. 1995 or Wylie et al. 1993).

The gross features of structure size distributions appear to be similar among asbestos dusts characterized to date (Berman and Chatfield 1990). The major asbestos fraction of all such dusts are small fibrous structures less than 5 μm (micrometers) in length. Length distributions generally exhibit a mode (maximum) between 0.8 and 1.5 μm with longer fibers occurring with decreasing frequency. Fibrous structures longer than 5 μm constitute no more than approximately 25% of total asbestos structures in any particular dust and generally constitute less than 10%.

In some environments, the diameters of asbestiform structures (e.g. fibers and bundles) exhibit a narrow distribution that is largely independent of length. In other environments, diameters appear to exhibit a narrow distribution about a mean for each specific length. In the latter case, both the mean and the spread of the diameter distribution increases somewhat as the length of the structures increase. Among asbestiform materials, this increase appears to be due to contributions from bundles. Thus, for example, the increase in diameter with length appears to be more pronounced for chrysotile than for the amphiboles, presumably due to an increase in the fraction of chrysotile bundles contributing to the overall distribution as length increases. This is likely true since a single chrysotile fibril exhibits the thinnest diameter of all asbestiform structures.

Only a few studies have been published that indicate the number of complex structures in asbestos size distributions. The limited data available indicate that complex structures may constitute a substantial fraction (up to one third) of total structures, at least for chrysotile dusts (see, for example, Sebastien et al. 1984). Similar results were

also obtained during a re-analysis of dusts generated from the asbestos samples evaluated in the animal inhalation studies conducted by Davis et al. (Berman et al., in preparation). This is the same re-analysis used to support a study to identify asbestos characteristics that promote biological activity (Berman et al. 1995), which is discussed further in Berman and Crump (2003).

The degree to which fibers are combined within complex structures in a particular dust may also affect the biological activity of the dust (Berman et al. 1995). Therefore, proper characterization of asbestos exposure requires that the relative contributions from each of many components of exposure be simultaneously considered. Factors that need to be addressed include the distribution of structure sizes, shapes, and mineralogy in addition to the absolute concentration of structures. Such considerations are addressed further in Berman and Crump (2003). Thus, unlike the majority of other chemicals frequently monitored at hazardous wastes sites, asbestos exposures cannot be adequately characterized by a single concentration variable.

3.3 Asbestos Measurement Methods and Their Corresponding Exposure Metrics

Exposure to asbestos primarily involves inhalation of asbestos dust and evidence indicates it is primarily the size and shape of the fibrous structures in the dust that determine potency (in addition to their absolute concentrations). As a result, estimates of asbestos exposure concentrations vary radically as a function of both the particular type of instrumentation employed for analysis and the specific method applied during the analysis (see, for example, Berman and Crump 2003). Consequently, the ability to establish the relationship between asbestos exposure and disease has been confounded by use of multiple exposure metrics and by the fact that the relationships between exposure metrics *do not remain proportional to each other* from one environment to the next.

A variety of exposure metrics have been (and are being) used for the determination of asbestos concentrations. Those most important to the discussion in this report include "PCM", "PCMe", and "protocol structures" and each of these are briefly described below. Other potentially relevant exposure metrics are also introduced and briefly described in a table at the end of this section.

PCM is the size range of particles *traditionally* included for the determination of asbestos concentrations when analyzed by phase contrast microscopy (an optical microscopy technique). These are defined as "fibers" longer than 5 µm with an aspect (length-to-width) ratio equal to or greater than 3 and exhibiting largely parallel sides. At the magnification at which this type of asbestos analysis is typically conducted (~400x), PCM fibers are also typically limited to those thicker than approximately 0.25 µm because thinner fibers cannot be seen by the microscopist. Actually, this lower limit on width also varies somewhat as a function of the condition and quality of the microscope,

the visual acuity and training of the analyst, and the type of mineral.[1] Further, because there is no mechanism for distinguishing among mineral types when conducting analysis by PCM, all particles that are observed to satisfy the defined dimensional criteria are counted. Depending on environment, these may include, for example, cellulose and other organic fibers as well as a much broader range of inorganic fibers than have traditionally been included in the definition of asbestos (see last section).

It also needs to be understood that, due to limitations in the resolution of the microscope, the internal details of the structures that are observed by PCM cannot be distinguished. Thus, what may appear to be a simple and solid fiber by PCM may in fact be a complex structure composed of finer components. A fiber visible by PCM may alternately be a component of a larger structure whose other components are too fine to resolve. In fact, it is sometimes due to these differences (as opposed simply to mineralogy) that PCM and PCMe (defined below) concentrations determined for the same sample do not coincide. This complicates the relationship between PCM and PCMe in different environments.

An account of the history of the development of the PCM exposure metric was published by Walton (1982), which traces the origin to its definition back to meetings of a group of asbestos industry personnel in Britain (The Asbestos Research Council) in 1958. Methods suitable for determining concentrations in terms of this metric have been adopted in several countries, including the United States, and the World Health Organization. One version of the method in broad use in the United States is NIOSH Method 7400 (NIOSH 1985, 1994).

PCMe or "phase contrast microscopy *equivalent*" represents a range of particles nominally exhibiting the same range of sizes and shapes as PCM fibers, except that they are adjusted to exclude contributions from any countable particles not composed of the defined set of minerals included in the definition of asbestos[2]. As indicated above, however, mineralogy may not be the only reason for differences in concentrations estimated, respectively, by PCM and PCMe.

Originally, determining a PCMe concentration formally involved use of two, complimentary analytical techniques: phase contrast microscopy (PCM) and transmission electron microscopy (TEM) with the manner in which PCMe

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1 The ability to observe a structure using a phase contrast microscope is also a function of the contrast between the structure and the base on which it resides. If the contrast is limited, the structure will be invisible. Contrast in turn is a function of the relative refractive index of the structure and the base, which is therefore a function of the mineralogy (chemical composition) of the structure (Kenny et al. 1987).

2 As evidence of their ability to cause asbestos-related diseases has increased, the range of minerals proposed for inclusion in the definition of asbestos has been broadened in recent years from what was originally defined in IARC (1977) and even what is defined in the current version of NIOSH Method 7402 (1994) to include virtually all amphiboles.

concentrations are determined described in NIOSH Method 7402 (NIOSH 1986,1994). By this method, asbestos concentrations are determined by analyzing sample filters using both analytical techniques and the concentration estimated by PCM is then modified by a factor derived by TEM to determine a final (adjusted) asbestos concentration expressed in terms of PCMe.

Over the years, some have adapted Method 7402 by using only the TEM component to determine an absolute concentration for PCMe (rather than using it to determine an adjustment factor for the PCM component). Other modifications to the PCMe metric (such as changes to size restrictions) have also been developed over time. In 1995, for example, ISO Method 10312 (ISO 1995) incorporated a definition for PCMe that includes an upper limit of 3.0 µm on the width of a countable particle[3] and also reduces the minimum width to 0.20 µm (from 0.25 µm)[4]. Other modifications to the definition of PCMe have also been proposed in other documents.

Table 1 presents a summary of definitions for PCMe that are provided in several Federal and California sources. In descending rows, the table provides:

- the (current) year of revision for each reference cited;
- the original year that the reference was published;
- the minimum length of structures included in the definition;
- the minimum width;
- the maximum width;
- the aspect (length-to-width) ratio; and
- relevant comments.

As can be seen in Table 1, the size definitions for PCMe vary across the different documents cited. Of these, for example, ISO 10312 incorporates a maximum width. As indicated by the comments, it is also noteworthy that an entirely different procedure is employed for deriving PCMe estimates when evaluating hazards under either California Proposition 65 (COEHHA 2006) or the California Air Resources Board's background document (CARB 1986) for their Asbestos Air Toxics Control Measure (ATCM). By CARB's rules, PCMe is determined by counting total TEM structures (of "all sizes") and dividing the count by between 100 and 1,000 (depending on whether an estimate in the low or high end of their risk range is desired). In fact, another California document that is labeled as "not to be cited or quoted" suggests an intermediate value of 320. Similarly, ATSDR (2001) defines PCMe concentrations as approximately equivalent to the concentration of total TEM structures (of all sizes longer than 0.5 µm) divided by 60.

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[3] This is also consistent with the definition originally proposed for PCM (see Walton 1982).

[4] While this latter change may appear minor, as shown later, even minor changes in the minimum width for PCMe actually represent critical changes because asbestos structures tend to be particularly numerous in this range of widths and they also tend to be particularly potent (see, for example, Berman and Crump 2003).

It is also interesting that the minimum width defined for PCMe structures in EPA's IRIS is twice the minimum width defined by ISO and IRIS further indicates that the correlation between PCM and TEM fiber counts is "highly uncertain." Note that EPA has applied the ISO rules to determine PCMe concentrations in El Dorado County (Ladd 2005), which suggests inconsistency with IRIS (among other things).

Overall, the information presented in Table 1 suggests a procedure that has been subject to some modification over the years (which may appear minor but can be important)[5]. Given these distinctions, it appears that PCMe concentration estimates for asbestos may not have been derived entirely consistently over time by various parties generating such estimates.

In fact, the variability in PCMe definitions and determinations described in Table 1, does not represent the full range of variability in the manner that PCMe has been defined and applied over the last 20 years. In some studies, for example, PCMe has also been informally defined simply as "all TEM fibers longer than 5 µm", with no minimum width defined. Moreover, the concentration of TEM fibers used to estimate PCMe has sometimes been obtained using methods requiring magnifications of 10,000 and greater, which could result either in the counting of substantially greater numbers of structures or somewhat smaller numbers of structures than what can be seen at the PCM magnification of approximately 400. This depends on whether more "solid" structures become visible at the greater magnification or more structures that appear solid at the lower magnification appear to be non-countable complexes of smaller structures at the higher magnification. Thus, it does not appear that determination of PCM/PCMe ratios for use in risk assessment over the last 20 years has been entirely uniform. Nor is it clear whether any of these approaches have been subjected to formal peer-review at EPA. Thus, it does not appear that an established precedent currently exists.

Protocol Structures represent a size range of asbestos structures that is expected to better correspond to those that contribute to the induction of cancer than PCM structures.[6] Implications regarding the relationship between various exposure metrics and disease induction are addressed further below. A detailed presentation of the

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[5] For example, Hwang and Gibbs (1981) suggest that the median fiber diameter for amosite asbestos observed in mining environments lies at approximately 0.35 µm (for fibers longer than 2.5 µm and remains approximately constant for longer fibers). This suggests that the fraction of such fibers that would be alternately included or excluded in an analysis may vary radically as the minimum width to be included changes between 0.2 and 0.4 µm. Thus, the ratio between PCM and PCMe may also vary radically, depending on which cutoff is selected for PCMe.

[6] Importantly, the defining dimensions of protocol structures were also somewhat constrained by limitations in the published size distributions available for applying this exposure metric in the meta analysis used to evaluate its utility (Berman and Crump 2001).

rationale for the definition of protocol structures is also available (see Berman and Crump (2001).

Protocol structures are defined as a weighted average of two size ranges of structures, whose concentrations are separately determined and then combined using the following equation:

$$C_{\text{protocol structures}} = 0.003*C_{\text{size A}} + 0.997*C_{\text{size B}} \qquad \text{(Equation 1)}$$

where:

$C_{\text{protocol structures}}$ is the concentration of protocol structures;

$C_{\text{size A}}$ is the concentration of structures between 5 and 10 μm in length with widths less than 0.5 μm; and

$C_{\text{size B}}$ is the concentration of structures longer than 10 μm with widths less than 0.5 μm.

The concentration of protocol structures is typically determined by analyzing a sample by TEM using ISO Method 10312 (ISO 1995) and incorporating a modification to include only structures of the above-indicated sizes in the structure count. Importantly, the rigorous procedures defined in the ISO Method for considering contributions from both simple structures (i.e. fibers and bundles) and complex structures (i.e. clusters and matrices) and their components are incorporated into the determination of the concentration of protocol structures.

Note that including instructions for detailed characterization of complex structures contrasts with the determination of PCMe, which involves only consideration of fibers and bundles. Such lack of detailed instructions for handling the analysis of complex structures represents a further means by which inconsistency may have been introduced into determinations of PCMe.

Other exposure metrics are also considered in this report in a variety of contexts. A summary of the characteristics of all of these exposure metrics is presented in Table 2.

In Table 2, successive rows provide the following information for each exposure metric:

- the structure dimensions defining each exposure metric;
- the associated instrumentation and method required for sampling and analysis;
- the origin of the metric;
- the theoretical basis linking the metric to risk;
- other evidence supporting/refuting the relationship between the metric and risk;
- the original (design) intent of the metric;
- pre-requisites for applying the metric to assess risk; and
- the strength of evidence supporting application of the metric to environments in which asbestos may be naturally occurring.

Note that the last row is provided to indicate the degree to which the metric might be considered to be applicable to assess risks in places such as El Dorado County.

3.4 Issues Associated with Estimating Risk Attributable to Asbestos Exposure

As with any hazardous material, asbestos-related risks are typically estimated by multiplying exposure concentrations determined in a site study (such as the study conducted in El Dorado County) with an exposure/response (risk) factor that is derived from one or more control studies (such as an epidemiology study)[7]. However, asbestos is unlike other hazardous materials because the exposure metrics employed for determining and reporting its concentration are necessarily complex.

For most hazardous materials, concentrations are expressed by a single exposure metric (e.g. mass per unit volume) incorporating a single parameter: mass. In contrast, there are multiple exposure metrics for asbestos and they each necessarily incorporate multiple parameters (i.e. dimensional limitations on a range of structures). Moreover, risk can only be reasonably estimated for asbestos when the particular exposure metric used to estimate concentrations is properly matched to the exposure metric in which the corresponding risk factor is expressed. This is because concentrations estimated in each of the multiple exposure metrics that have been used for asbestos may vary by orders of magnitude for the same sample (see, for example, Berman and Crump 2003).

Choice of the particular exposure metric is also critical to the proper estimation of risk. This is because asbestos exposure metrics do not remain proportional to one another from one environment to the next. Of course, this is simply another way of saying that the size distribution of airborne structures in an asbestos dust do not remain proportional from one environment to the next (Section 3.2).

Importantly, to successfully extrapolate risk from control studies (in which potency is determined) to a site study (in which risk must be ascertained), the metric chosen to characterize exposure must satisfy *both* of two criteria:

(1) asbestos must be measured in a comparable manner in the two environments; *and*

(2) such measurements must remain reasonably proportional to the characteristics of exposure that contribute to risk.

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[7] Actually, the manner in which risk is evaluated for asbestos is somewhat more complicated than for other materials in that the relationship between exposure and risk involves a complex function of time as well as exposure level so that, strictly, risk factors and exposure concentrations may not be simply multiplied together (see, for example, Berman and Crump 2003). However, the details of such complexities are not directly relevant to the issues at hand. Thus, they will not be addressed further in this discussion.

These requirements derive from common sense (as illustrated below) and are universal. Moreover, the importance of satisfying these criteria was clearly demonstrated in a mathematical model developed by Chesson et al. (1990). If they are not satisfied, risks estimated in the traditional manner (described above) are not valid.

Satisfying the above criteria is trivial for most chemical toxins because their effects remain proportional to mass in all environments. Thus, this single exposure metric supports valid risk assessment for these toxins. Not so for asbestos. This is a direct consequence of the nature of asbestos exposure metrics (Section 3.3) and the characteristics of asbestos dusts (Section 3.2).

To illustrate how the first of the above two criteria needs to be addressed for asbestos, consider that one would clearly not apply a risk factor for nickel (derived from dose-response studies in which exposure concentrations are determined explicitly for nickel) to assess the risks from exposure concentrations measured for chromium. That is because the two exposure metrics are not comparable. Similarly, risk factors derived for one particular exposure metric (incorporating a specific size range of asbestos structures) should not be applied to exposure concentrations determined using a different exposure metric (incorporating a different size range of structures).

To illustrate how the second of the above two criteria needs to be addressed for asbestos, consider that measuring the concentrations of nickel in various study environments (each containing dusts of mixed metals) tells one nothing of the relative concentrations of chromium in those environments; there is clearly no reason to expect that the concentrations of nickel and chromium will remain proportional from one environment to the next. Thus, it would be absurd to attempt to assess chromium-related risks based on measurements of nickel. This is true even though the relationship between the risk factors for nickel and chromium is known. It is not the relative potency, but the unknown relationship between exposure concentrations that prevents extrapolation in this case.

Similarly, because different exposure metrics for asbestos do not remain proportional from one environment to the next, unless risk is assessed using an exposure metric that specifically remains proportional to biological activity, one cannot reliably assess risk. This is because, if a particular exposure metric does not remain proportional to biological activity, the relationship between this metric and the truly biologically active fraction of an asbestos dust will vary in an undefined manner between control and study environments. Thus, a risk factor defined for such a metric in a control environment will not relate in the same manner to an exposure concentration determined for that same metric in a study environment. Therefore, it would not be valid to apply such a risk factor to the exposure determined in that study environment.

Given the above, to assess asbestos-related risk, it is therefore critical that exposures determined in terms of a particular exposure metric be combined *only* with a risk factor

that is properly matched to that particular exposure metric *and* the two must be appropriate for the environments in which they are applied.

3.5 The Nature of Conditions in El Dorado County

Conditions in El Dorado County have raised concern for years. It is an established fact that asbestiform amphibole is present in the soil and rocks of El Dorado County. The real question is whether it is ubiquitous or "patchy." Thus, there are areas of El Dorado County where various kinds of activity restrictions are prudent, but there are likely other areas where they may not be required. Thus, a reliable procedure is needed to distinguish among such areas. It is also important to consider the need to be able to distinguish "clean" fill (which might be brought in from elsewhere) from either asbestos-containing fill or local, asbestos-containing soil. In fact, these needs are common to every area of the nation in which the presence of asbestos is a concern.

4 EVALUATING THE PROPOSED EPA APPROACH IN EL DORADO COUNTY

It appears that the EPA is planning to assess risk in El Dorado County primarily by applying the current EPA slope factor for asbestos (IRIS current) to estimates of PCMe exposure derived from the Ladd (2005) study. Assuming that the QC issues that are discussed in 4.1.2 are first resolved, there still appear to be several potential problems with this approach so that the Agency needs to consider:

- the state of the science informing the validity and reliability of the proposed approach, especially as applied in El Dorado County and including considerations concerning QC;
- the degree with which the proposed approach appears to be supported by precedent; and
- the associated implications concerning the general health protectiveness of the proposed approach.

4.1 The State of the Science

Relevant issues that need to be considered to address the potential validity and reliability of the proposed approach for El Dorado County are:

- the limitations of the PCMe metric;
- more general limitations of the Ladd (2005) study; and
- implications from the literature concerning cleavage fragments.

4.1.1 The limitations of the PCMe metric

The limitations of the PCMe exposure metric are reasonably well documented and include:

- that the metric does not appear to satisfy the second of the two criteria identified in Section 3.4 that are required to support reliable risk assessment (i.e. it does not remain reasonably proportional to risk across environments of interest); and

- at least when applied at sites exhibiting the specific characteristics of the areas studied by Ladd (2005), the metric may not satisfy the first of the two criteria articulated in Section 3.4 (i.e. it is not comparable to the concentrations determined in the control studies evaluated to develop the IRIS risk factor).

Regarding the first of the above, evidence that PCMe does not remain adequately proportional to risk across environments comes from a diverse variety of sources. First (and perhaps simplest), one should consider that PCMe is intended to mimic the dimensional range of structures counted by PCM. However, the dimensional range counted by PCM was never designed or intended to reflect the characteristics of asbestos that contribute to disease. Rather it was simply designed as an arbitrary index of exposure.

A history of the development of the PCM exposure metric, at least up to the time of its publication by Walton (1982), clearly indicates that the dimensions chosen for defining PCM (by a British Council in 1958) were *arbitrary* and designed primarily to facilitate analysis. Moreover, while the minimum length may have been selected with some thought for the range of structures believed to contribute to disease (although the primary motivation was to promote analytical reproducibility), the minimum width was entirely arbitrary, as it was an artifact of the choice of magnification and the type of microscope.

Further evidence that PCMe may not adequately track the characteristics of asbestos that contribute to risk also comes from a study of animal inhalation experiments (Berman et al. 1995). In that study, the ability of various exposure metrics to predict risk (including PCM/PCMe) was formally tested. In that study, PCM/PCMe was shown to provide a *statistically significant lack of fit*.

Perhaps the most compelling evidence comes from the meta analysis reported in Berman and Crump (2003). In this study, the range of variation in risk factors reported across available epidemiology studies is compared with exposure expressed, respectively, in terms of PCM (which is considered to be equivalent to PCMe in this case) and expressed in terms of long protocol structures (defined in Section 3.3 above). The results of this comparison are illustrated in Figure 1.

In Figure 1, the ratios of the maximum to the minimum values of the risk factors derived from the set of available epidemiology studies (excluding a single, negative study) are presented. The ratios for lung cancer are presented on the left and mesothelioma on the right. The ratios labeled "PCM" are derived using the PCM exposure metric and preserves the current EPA policy of a common risk factor for chrysotile and the amphiboles. The ratios labeled "protocol" are derived using long protocol structures as the exposure metric and incorporate distinct risk factors for chrysotile and the amphiboles (which is recommended in the Berman and Crump protocol).

As can be seen in Figure 1, when exposure is expressed in terms of PCM/PCMe, risk factors derived from the available epidemiology studies range over almost two orders of magnitude (by a factor of 90) for lung cancer and over more than three orders of magnitude (by a factor of 1100) for mesothelioma. With such variability across the known studies, the confidence that can be placed in extrapolating risk estimates derived from these control studies to new environments is limited.

In contrast, when the risk factors from the same set of studies is adjusted to reflect exposure in terms of the long protocol structures metric, the range of lung cancer factors drops to about 60x (a modest improvement) and the range for mesothelioma factors drops to about 30x (a substantial improvement). Thus, the confidence that risk factors derived in terms of long protocol structures can be extrapolated to new environments is substantially improved. Note, that a more formal statistical analysis (conducted without omitting the one negative study) is also presented in Berman and Crump (2003) and the results are similar.

To address whether the PCMe exposure metric satisfies the first of the two criteria needed to assure reliable risk assessment (Section 3.4), one needs to consider two issues. The first is the relationship between PCMe and the various metrics employed to assess exposure in the original epidemiology studies and the second is the relationship between the characteristics of the dusts studied in those control environments and the character of the dusts observed in El Dorado County (or at least the specific sites in El Dorado County studied by Ladd).

Table 3 presents a comprehensive list of the quantitative epidemiological studies used to support development of the slope factor for asbestos that is currently recommended by EPA (IRIS Current). In Table 3, the eight columns respectively indicate:

- the type of asbestos: chrysotile, amosite, or mixed;
- the type of operation studied;
- the specific cohort studied;
- the potency factor for lung cancer;
- the potency factor for mesothelioma;
- the majority of the types of measurements relied on to estimate exposure;
- the study reference; and
- relevant comments.

As can be seen in the sixth column of Table 3, concentrations were initially determined based on three different methods of measurement, which resulted in three different exposure metrics among these studies. These include:

- MI or midget impinger, which is a device used to determine concentrations of total respirable particles in the air;

- PCM; or

- TP or thermal precipitator, which is another device used to determine concentrations of total respirable particles in the air. Note that MI and TP measurements are not entirely comparable (Walton 1982).

The fourth designation in the sixth column of Table 3, "NS" means non-specific. To derive a dose/response factor from the Selikoff et al. (1979) study, Nicholson simply assumed that exposures to the entire cohort could be considered equal to the average exposure concentration estimated for the entire industry at the time.

As can be seen in this same column of the Table, of the 13 available risk factors for lung cancer that were considered, nine (70%) were derived primarily by measurements other than PCM and thus had to be converted. Moreover, of these, five (60%) used factors to convert the measurements to PCM that were non-study specific.

As indicated in Walton (1982), La Ville de Thetford Mines (1994), and Smith, G.W. (1968), as well as based on general commercial considerations regarding the need for pure product material, the processes that were used to separate and isolate fiber product from the ore in asbestos mills was very efficient. Thus, the fraction of host rock fragment remaining in most commercial asbestos fiber product was extremely small. This is particularly true of the textile grade material, although it is possible that slightly greater amounts of grit and dirt (left over from mining and milling) might remain with the lower grade fiber products (especially the lowest grade fiber primarily used in the manufacture of friction products).

Given the above, the last column of Table 3 indicates the potential for rock fragments (i.e. non-asbestiform cleavage fragments) composed of asbestos minerals to be present in the various control environments studied. As can be seen in the table, the only environment in which a substantial fraction of any such fragments (primarily serpentinite fragments in this case) could potentially be present is in the Quebec mine and mill environment. Yet this environment was in fact excluded from the analysis conducted to derive the recommended EPA slope factor (EPA 1986, IRIS Current).

It should also be noted from the table that most of the control environments (other than for textiles or mining/milling) potentially contain some kind of non-asbestiform fragments, but these are generally expected to be composed of materials not related to the asbestos minerals. In such environments, therefore, the potential relationship

between PCM and PCMe will be very different than what is observed in places where large numbers of amphibole rock fragments exist (such as in El Dorado County). Further evidence for this is provided by Lynch et al. (1970). Also, see Section 3.3.

Given the above and because no study of any amphibole mining or milling operation was available at the time that the analysis was conducted (EPA 1986), there are no control environments among those studied to support development of the current EPA risk factor in which amphibole rock fragments were more than a very minor component of dust exposures. Therefore, given the radically contrasting conditions in the specific locations of El Dorado County studied by Ladd (in which amphibole rock fragments appear to be plentiful), PCMe does not satisfy the first of the criteria listed in Section 3.4 when applied to environments such as that found at these specific sites.

In contrast, the exposure metric recommended by Berman and Crump should be considered applicable to the environment in El Dorado County for two reasons. First, the Quebec mining studies (e.g. Liddell et al. 1997) were not excluded from the analysis used to evaluate the metric (Berman and Crump 2003). Second, and perhaps more importantly, the more recent studies of crocidolite (amphibole asbestos) miners in Wittenoom, Australia (de Klerk et al. 1994) and the Vermiculite miners in Libby (e.g. Amandus and Wheeler 1987) were also included. Note that the vermiculite mined in Libby is contaminated with amphiboles that include both rock fragments and what appears to be particularly hazardous forms of asbestiform amphiboles (most likely due to size).

In fact, there is direct evidence of the kinds of differences in the various environments that are described in the previous paragraphs. It comes from the examination of data from every environment characterized in a set of readily available studies in which PCMe and protocol structures were simultaneously determined (including airborne dusts from asbestos products, dusts at sites in which the source of asbestos is known to be debris from commercial asbestos products, and dusts at sites in which the source of asbestos was a minor, natural contaminant of a matrix composed of a non-asbestos mineral). In virtually all of these environments, protocol structure concentrations were comparable to or greater than that of PCMe concentrations. Among other things, the above confirms that asbestiform structures are almost exclusively thin, as the thinnest structures are included in the protocol structure metric but excluded from the PCMe metric.

In contrast, the data from the Ladd (2005) study show samples in which the concentration of PCMe fibers is *two orders of magnitude* greater than the concentration of protocol structures. Based on the size distributions reported by RJ Lee for the data from Ladd (2005), only 4% of the structures longer than 5 μm are protocol structures while 96% are PCMe (although only 25% of these are respirable). Even if one assumes a greater width cutoff than the respirable limit (such as the 1.5 μm proposed by the peer review committee of the Berman and Crump protocol, ERG 2003), almost 50% of the PCMe fibers would still be excluded. Clearly, something is very different about these

samples relative to samples that have been collected in environments known to be contaminated with asbestos.

4.1.2 General limitations of the Ladd (2005) study

There appear to be two important limitations that need to be addressed before the data from the Ladd (2005) study can be properly interpreted. These are:

- QC-related issues; and
- the extent to which the results of the study can be considered generally applicable to conditions within El Dorado County (i.e. beyond the specific locations studied).

These are each addressed below.

Quality Control Issues. Based on interpretation of the data reported from the analysis of QC samples from the Ladd study, there appear to be potentially serious laboratory quality control issues.

It appears that a number of QC analyses have been performed in which either the same analyst has re-analyzed a sample by examining the same set of grid openings twice (replicate analysis) or two different analysts have independently examined the same set of grid openings from the same sample (duplicate analysis). In several cases, such analyses were also conducted in triplicate for the same sample.

Although the EPA analyses were not conducted in a fashion allowing interpretation using the formal rules of verified counting (see, for example, Turner and Steel 1994; Steel and Small 1985; and Turner and Steel 1991), their results can still be evaluated to test whether the same sets of structures were observed over the same area scanned during each analysis. If one is to have faith that analyses have been properly conducted and documented, it is critical that one be able to show that analysts see the same structures when scanning the same areas of a sample.

Importantly, the QC evaluation discussed here is based simply on an independent interpretation of the results reported in Ladd (2005) for the analyses of QC samples. This is not a case in which an independent microscopist is working to verify specific results. Thus, direct access to the samples is not required. Rather, the role being filled here is simply one of a data analyst evaluating the performance that is to be expected when data become available from multiple analyses of the same set of grid openings on the same sample.

The procedure by which the QC results are evaluated here represents a *less* severe test of the comparability of the analyses than are typically performed for verified counting. Therefore, the degree of agreement one should expect should be at least as good as what is commonly achieved during verified counting. This means that false

positives (i.e. observation of a structure by one analyst that cannot be verified by another) should represent no more than 5% of the total number of structures reported and true positives (i.e. observations of the same structure by each analyst) should represent no less than 85% of the total number of structures reported[8,9]. Yet, across the five sets of replicate or duplicate analyses that were examined, substantially worse agreement was observed.

The evaluation was conducted simply by comparing the number of primary structures that each analyst reported for each specific grid opening. If the numbers disagreed, it would be concluded that there was an error in counts on that grid opening. Since whether one value reported by a particular analyst was higher or lower than the other was not considered in this evaluation, each observed error could be due either to a false positive or a false negative. Thus, this represents the total error that might occur on a particular grid opening and the total error should be less than 20% = (1 - 85%) + 5% where the number of false negatives is assumed to be the total number minus the number of true positives (see Turner and Steel 1994).

Clearly, this is the most general possible comparison, as it entirely ignores comparisons involving specific features of any of the structures (such as type, mineralogy, or dimension). Even multiple count errors were ignored (i.e. errors in counts from particular grid openings that differ by more than one unit were still counted as a single error).

Results for the set of five samples evaluated are presented in Table 4. Note that, when the same grid openings were analyzed by three (rather than two analysts), the error rate for each analyst is reported as the number of grid openings for which a disparate number was recorded against the average of the other two analysts.

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[8] Importantly, comparing results of analyses across the same areas of a scanned surface is qualitatively different than simply comparing structure counts across multiple analyses (or independent preparations) of the same sample when each analyst analyzes unique areas of the scanned surface (i.e. different grid openings). In the latter case, at best, one can expect agreement across analyses to be no better than what is predicted based on Poisson statistics. This is because the distribution of asbestos structures on a filter are random so that the chance of encountering a certain number of structures on any particular area of the filter exhibits a statistical distribution. In contrast, however, if multiple analysts scan the same area of a sample (i.e. the same grid openings), they should observe the same, unique set of structures that were deposited on that particular area. Thus, ideally, their counts and observations should be identical.

[9] Based on the performance shown to be achievable for verified counting in general (Steel and Small 1985 and Turner and Steel 1991), the targets defined above appear reasonable for analysts counting structures in support of the Ladd study and this is especially true given the extremely favorable manner in which performance is evaluated (see main body of text).

In Table 4:

- the first column provides the Sample Identification Number;
- the second column indicates the number of analyses conducted on the specific set of grid openings from the indicated sample;
- the third column indicates the total number of grid openings analyzed;
- the fourth column indicates the number of differences in counts observed between the indicated analysis and the other analyses of the sample;
- the fifth column indicates the total error rate; and
- last column indicates whether the counts are consistent (i.e. whether they exceed the total error rate).

As can be seen in Table 4, analyses from four of the five samples that were evaluated are inconsistent. That there are problems with four of these five samples, indicates that further investigation is warranted. Moreover, although the remaining 18 QC analyses conducted on the same grid openings that were reported by Ladd are not further evaluated here, the findings reported by RJ Lee (RJ Lee 2005) concerning these remaining samples suggests that the same kind of QC problems are more prevalent than what has been reported here.

Table 5 is provided both to illustrate how the estimates in counts of differences were derived for Table 4 and to illustrate the strength of the evidence that QC problems may be even worse than what is indicated by the data in Table 4.

Table 5 displays the sets of structures observed over the same set of 15 grid openings during each of three analyses conducted for sample SRA-R05-110604. Note that the data are presented in such a manner so as to line up corresponding structures in the same rows, to the extent possible. When not possible, however, a series of arrows between the columns representing each analysis are also displayed to connect structures in different rows that, however unlikely due to clear differences in character, were assumed to be equivalent. Thus, each analyst was given every possible benefit of the doubt in the evaluation described above.

For each analysis presented in Table 5, the 10 columns respectively present:

- the grid specimen number (typically, analyses are spread across grid openings from each of two grid specimens);
- the sequential number of each grid opening scanned;
- the code identifying the particular grid opening scanned;
- the code representing the manner in which the mineralogy of a particular structure was identified (see ISO 1995);
- the sequential number of each primary (isolated) structure encountered;
- the sequential number of the total number of structures encountered (including structures embedded in larger, complex structures);
- the class (type) of each structure encountered (i.e. fiber, bundle, cluster, matrix, matrix-fiber, etc., see ISO 1995);
- the length of the structure (μm);

- the width of the structure (μm); and
- the aspect ratio of the structure.

To determine the number of primary structures reported on a particular grid opening by a particular analyst (in support of the evaluation reported in Table 4), the number of primary structures (denoted by having a numerical entry in Column 5 of Table 5) for each unique grid address (denoted by the combination of grid specimen in Column 1 and the specific grid opening location in Column 3) were simply counted. These values were then compared across analysts and the total number of grid openings for which a disagreement was observed was summed (with the results presented in Column 5 of Table 4). This sum was then divided by the total number of grid openings included in each analysis to derive the fraction (percentage) of total errors that are reported in Column 6 of Table 4.

Also in Table 5, rows representing missed structures in a particular analysis (false negatives) are highlighted in pink and rows representing an unconfirmed structure (false positives) are highlighted in green. Mismatches between dimensions or structure types are highlighted in blue. Note that, although *none* of this information was used in the evaluation of performance conducted as described above (and reported in Table 4), the degree of color observable in the table suggests substantially greater problems than what is reported in Table 4. For example, as indicated at the bottom of Table 5:

- for the Original Analysis reported on the left, of the 11 structures observed during this analysis:
  - four (Nos. 3, 8, 9, and 11) are unconfirmed during either of the other analyses (rows highlighted in green);
  - two (Nos. 1 and 7) are disputed (identified during only one of the two other analyses);
  - 6 structures identified during the other analyses were entirely missed during this analysis (rows highlighted in pink); and
  - although these structures were nominally matched with other structures, the character and/or dimensions of four structures (Nos. 1, 6, a component of 6, and 7) reported in this analysis do not even reasonably match the character and/or dimensions reported for these structures during the other analyses. These discrepancies are highlighted in blue;

- for QC Analysis No. 1 (in the middle of Table 5), of the 14 structures observed during this analysis:
  - three (Nos. 3, 7, and 9) are unconfirmed during either of the other analyses (rows highlighted in green);
  - seven (Nos. 1, 2, 4, 11, 12, and 13) are disputed (identified during only one of the two other analyses);
  - 1 structures identified during the other analyses were entirely missed during this analysis (rows highlighted in pink); and

- although these structures were nominally matched with other structures, the character and/or dimensions of 12 structures (Nos. 2, 4, a component of 4, 6, 8, 10, a component of 10, 11, a component of 11, 12, 13, and 14) reported in this analysis do not even reasonably match the character and/or dimensions reported for these structures during the other analyses. These discrepancies are highlighted in blue; and

- for QC Analysis No. 2, of the 19 structures observed during this analysis:
  - 12 (Nos. 1, 4, 5, 6, 7, 8, 9, 12, 14, 15, 17, and 18) are unconfirmed during either of the other analyses (rows highlighted in green);
  - three (Nos. 2, 3, and 16) are disputed (identified during only one of the two other analyses);
  - 2 structures identified during the other analyses were entirely missed during this analysis (rows highlighted in pink); and
  - although these structures were nominally matched with other structures, the character and/or dimensions of 12 structures (Nos. 3, a component of 3, 10, 11, 13, a component of 13, a component of 15, 16, a component of 16, a component of 17, a component of 18, and 19) reported in this analysis do not even reasonably match the character and/or dimensions reported for these structures during the other analyses. These discrepancies are highlighted in blue.

The source of the errors indicated in Table 4 is not immediately apparent. However, an evaluation of all of the 57 paired analyses reported in the Ladd (2005) data set show statistical agreement among pairs. This suggests that the errors may be associated with reporting and documentation, rather than the actual performance of the analysts. Nevertheless, these problems are still serious. One cannot consider data reliable until one has confidence not only that analyses are correct, but that the results have been properly documented. Therefore, until these problems are addressed through some appropriate corrective action, one cannot place confidence in the concentrations reported in the Ladd (2005) study. This is simply because there is otherwise no independent means of confirming whether the analysts in fact saw what they reported.

The general applicability of the Ladd study. Exposures linked to a small number of specific areas within El Dorado County were studied by Ladd (2005). These include, for example, specific school yards and a nature trail (among other places). If broader conclusions concerning asbestos exposure in El Dorado County (beyond those linked exclusively to the specific areas studied) are to be derived from this study, however, the degree with which the specific locations studied reflect broader conditions in El Dorado County needs to be characterized.

It is expected that conditions in El Dorado County will vary substantially from one location to the next. This is likely true both in terms of the concentrations of serpentinite and amphibole minerals in local soils and rock as well as the fraction of such minerals

that are truly asbestiform.[10] For example, despite evidence that the fraction of true asbestiform amphibole is small in soils in the areas specifically studied by Ladd (Sections 4.1.1, 4.2.1, and 4.3), it is known that asbestiform amphibole exists in at least some parts of the county (see, for example, Davis et al. 1991).

Given the above, without tying exposure estimates from the Ladd (2005) study to bulk determinations of asbestos in the soil (e.g. through some type of appropriate modeling validated with field confirmation from a robust and properly designed study), any results derived from the Ladd study cannot be extrapolated beyond the bounds of the specific areas within which the study was actually conducted. Moreover, without developing some type of general approach to link airborne measurements to bulk measurements, it will prove impractical to conduct simulations in every area of concern around El Dorado County (let alone the nation) in which the presence of amphibole or serpentinite minerals may suggest concern with regard to the presence of asbestos.

4.1.3 Implications from the literature concerning cleavage fragments

A wealth of studies have been published that potentially provide information distinguishing the relative potencies of amphibole cleavage fragments and true asbestiform structures. These include, for example, the studies cited by Ilgren (2004)[11] and those included in the docket supporting the OSHA final rule (OSHA 1992). However, the interpretation of these studies remains controversial.

It is true that many of these studies suffer from the various kinds of limitations that commonly plague similar studies typically associated with true asbestos, including primarily the inadequate manner in which the relevant exposures have been characterized in many studies. Also, individual studies exist that "appear" to contradict the impressions gleaned from the majority of these studies. However, the apparent contradictions simply suggest a robust database that may actually provide an opportunity to evaluate and identify exposure models capable of reconciling these disparate results (see below). It is expected that a single unified model can ultimately be developed that adequately predicts the risk associated with exposure to elongated particles of serpentine and amphibole, whether asbestiform or not.

In fact, it appears that the protocol developed by Berman and Crump (2003), perhaps with minor modifications, may be close to achieving the goal of reconciling this set of literature studies. However, further study is clearly required to test this possibility.

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[10] This will also radically affect overall size distributions and thus the relationships between various exposure metrics. Thus, exposure and risk estimates will be affected, no matter how one chooses to assess risk.

[11] Importantly, it is primarily the citations reported in Ilgren (2004), rather than the specific findings reported by Ilgren that should be the focus here.

Taken as a whole, the evidence from the available literature is strongly suggestive either that cleavage fragments (structure for structure) are less potent than true asbestiform structures or that populations composed primarily of cleavage fragments contain fewer structures within the size range that induces biological activity than populations containing substantial fractions of asbestiform material.

In fact, this general impression is consistent with the findings by OSHA. In their final rule, OSHA (1992) concluded that the evidence from these studies was insufficient to regulate cleavage fragments as asbestos. Nevertheless, controversies persist and these need to be thoroughly explored and reconciled.

In fact, the best interpretation of the literature may be that controversies concerning the distinction between the hazards associated with cleavage fragments and true asbestiform structures are driven primarily by use of an inappropriate metric for characterizing asbestos-related exposures. There is ample evidence that the size range represented by "regulatory fibers" (i.e. those included in the PCM/PCMe metrics) does not adequately reflect the size range of asbestos structures that predict risk (Section 4.1.1).

That the controversies surrounding cleavage fragments are largely a function of size and the associated need to employ an appropriate exposure metric when evaluating asbestos risk is directly supported by the findings of both the American Thoracic Society (ATS 1990) and the expert panel that contributed to the peer consultation workshop on the Berman and Crump protocol (ERG 2003). Both of these groups explicitly question the appropriateness of "regulatory fibers" as an exposure metric for asbestos. Moreover, given such comments, it is clear that neither the ATS nor the expert panel explicitly supports the approach proposed by EPA for assessing risks in El Dorado County.

Many studies (including the extensive work documented by Berman and Crump) point to longer and thinner structures (thinner than PCMe fibers) as the ones that contribute most to disease. Thus, once an appropriate exposure metric (which focuses on these structures) can be fully evaluated and optimized:

(1) the disparate results of the existing epidemiology studies will be fully reconciled by a unified model of exposure and risk; and

(2) the need to distinguish true fibers from cleavage fragments will be unimportant in this model. Thus, the entire controversy surrounding the differences between true fibers and cleavage fragments may simply disappear.

The exposure metric proposed by Berman and Crump (2003), even though not fully optimized (due to the limitations of the data available for supporting such optimization) already provides substantial improvement toward reconciliation of the disparate epidemiology studies (relative to that observed when exposure response factors from

these studies are expressed in terms of the regulatory fiber metric). In fact, the improvement is statistically significant for mesothelioma (Section 4.1.1).

Although it is recognized that the data set recently studied by a team from NIOSH (Kuempel et al. 2006) has limited power to evaluate such questions, the results that they report support the findings of Berman et al. (1995) and the overall direction for optimization proposed by Berman and Crump. This direction is ultimately to consider exposure metrics focusing on even longer structures than currently considered. Kuempel et al. (2006) also proposed better evaluating the cutoff for width, once an adequate data set can be found for supporting such an evaluation. Unfortunately, the available exposure characterizations are insufficient to adequately evaluate the effects of width across the published epidemiology studies (Berman and Crump 2003).

It should also be pointed out that (absent the ability to identify or manufacture study environments in which exposures are known to be pure) the best and most definitive way to resolve the controversies involving cleavage fragments would be by:

(1) reconstructing the characteristics of the historical exposures in the available epidemiology studies conducted in the complete set of environments in which exposure is known to have been almost exclusively composed of pure asbestiform structures (i.e. in the various asbestos product factories studied historically), in environments in which exposures have been demonstrably mixed (i.e. the various mining environments studied historically), and in environments in which exposures appear to have been primarily (but not necessarily exclusively) to non-asbestiform amphiboles; and

(2) conducting a meta analysis over this entire suite of studies incorporating the data derived from (1) that provides an improved characterization of the associated exposures.

If, as expected, the result of such a study would be the identification of a single exposure metric (with multiple risk factors) that would explain the observed variation in dose-response across all three sets of studies, this would provide reasonable confidence that the studies had been adequately reconciled so that risks for all of these types of sites can be adequately predicted by a single model.

4.2 Considering Precedent

To evaluate the degree with which the approach proposed by EPA for evaluating asbestos-related risk in El Dorado County is supported by precedent, it is important to consider:

- the overall consistency of approaches used to evaluate asbestos exposure and risk at government-lead sites; and

- a comparison of the relative degree of review of the proposed approach and the Berman and Crump approach.

4.2.1 Approaches used at other government-lead sites

Table 6 presents information about a set of government-lead studies in which the EPA played a major role. In fact, EPA was the lead agency on all of the projects listed except the Southdown Project for which the lead was shared with the New Jersey Department of Environmental Protection (NJDEP). These studies were selected primarily to indicate the diversity of approaches that EPA has recently taken to assess asbestos-related risk[12].

In Table 6, the studies are presented in chronological order (based on the date of the respective reports from which the information about each project was derived). Successive rows of the upper portion of the table respectively indicate:

- the year that the study was reported;
- the source of asbestos at the studied site (e.g. natural or commercial products);
- the nature of the surrounding matrix in which the asbestos is found;
- the type of asbestos;
- the types of microscopic structures associated with each matrix;
- the specific versions of the definition(s) employed for the PCMe exposure metric;
- the analytical method(s) employed to determine the concentrations of asbestos structures in the samples collected from the site; and
- the approach(es) employed to assess asbestos-related risks.

The middle portion of Table 6 provides information on the relative magnitude of risks estimated using each of the various approaches adopted in each study. This, in turn, provides a general indication of the relative degree of health protectiveness afforded by the various approaches. Rows in this section of the table respectively indicate:

- whether the ratios of risk presented in this section were observed or estimated. Risk ratios were considered to be observed if they were derived directly from risks reported in the study indicated for each of the exposure metrics considered. Risk ratios were considered to be estimated if the relevant risk estimates were not reported directly but the ratios could be extrapolated from information on the distribution of structure sizes observed in the analyses conducted to support each study;

- the ratio of risks estimated by combining PCMe concentrations with the risk factor in IRIS to risks estimated for a selected, baseline case. Because this approach also

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[12] Importantly, while the set of studies presented in Table 6 are neither comprehensive nor statistically representative of the broader range of studies conducted by EPA over the years, their review is nevertheless instructive. Moreover, the findings presented in this section requires neither comprehensiveness nor representativeness for validity.

(approximately) represents the baseline case, all the ratios in this row are reported as one;[13]

- the ratio of risks estimated by combining PCMe (as defined by COEHHA) with the risk factors recommended by COEHHA to risks estimated for the baseline case. The COEHHA definition of PCMe is provided in Table 1 under the heading: "CA Proposition 65." Note that the COEHHA definition of PCMe was only considered in the first study listed in the table (i.e. Diamond XX);

- the ratio of risks estimated using the approach recommended by Berman and Crump (2001) to the risks estimated for the baseline case; and

- based on the ratios presented in the previous rows, whether risks derived using Berman and Crump (2001) or those derived using IRIS would be expected to be larger and thus drive risk management decisions. The procedure providing the greatest estimates of risk would generally be expected to drive these decisions.

It should be noted that the ratios presented in this section of the table for El Dorado County (the last column of Table 6) are all listed in parentheses to highlight the fact that they are especially uncertain due to a need to resolve QC issues associated with the data from this study as well as the need to address other study limitations (Section 4.1.2).

The lower portion of Table 6 provides information on the risk levels equivalent to an AHERA benchmark criterion that was used in some studies to support risk management decisions. Details concerning the manner in which this benchmark was established for the various sites in which it was applied (i.e. Libby and the World Trade Center) are provided in the respective studies cited in the table for those sites.

Depending on the availability of data from a particular study, the level of risk that would be equivalent to the concentration represented by the AHERA benchmark were derived using both the risk approach employing the IRIS risk factor and for the approach

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[13] In fact, the baseline case is intended to be one in which PCMe concentrations with dimensions *matching* those indicated in IRIS would be combined with the IRIS risk factor (see Table 1). In contrast, PCMe concentrations derived in the studies presented in Table 6 actually represent PCMe structures with the dimensions defined either by NIOSH or by ATSDR, which include thinner structures than those included in the IRIS definition (see Table 1). This makes the exposure concentrations slightly larger than what would have been determined in the strict manner defined in IRIS. Thus, the ratios presented in the "IRIS (Current)" row of the table should all be somewhat smaller than one. Unfortunately, however, without access to the raw data from each study (and the time required to conduct the requisite calculations), it is not possible to determine the exact value of this ratio. Thus, they are all presented as "one" in the table, with footnotes indicating the problem.

recommended in Berman and Crump (2001)[14]. For the former, the concentration of PCMe structures equivalent to the AHERA benchmark (given the characteristics of the asbestos structures at each particular site) was first determined from the data and this was then multiplied by the risk factor in IRIS. Similarly for the Berman and Crump approach, the concentration of protocol structures (and the fraction of long protocol structures) equivalent to the concentration represented by the benchmark were first determined from the site data and the protocol structure concentration was then multiplied by a risk factor appropriate for the type and size distribution of asbestos, as described in Berman and Crump (2001). IRIS-based risk estimates and Berman and Crump-based risk estimates are presented, respectively, in the last two rows of Table 6.

A number of findings can be gleaned from the information presented in Table 6. It is apparent, for example, that the EPA has been applying the Berman and Crump protocol (or a forerunner to the protocol) to assess asbestos-related risks at least at some sites as far back as 1994. Interestingly, the Diamond XX study was also the first of several studies of asbestos roads commissioned by the EPA in which highly robust and statistically significant results were obtained (ICF Technology 1994).

It is also interesting to note that, at least at the Southdown site, the EPA supported distinguishing contributions to risk from true asbestiform structures and cleavage fragments. Thus, it appears that this issue has received past attention.

The information presented in the middle portion of Table 6 indicates that, except for the El Dorado County Study, risks estimated using the Berman and Crump protocol are equivalent to or higher than those estimated using IRIS. In fact, for sites in which amphibole asbestos is present, the Berman and Crump protocol provides risk estimates that are substantially higher than those estimated using IRIS. This observation is further supported from observations at virtually all other sites in which both approaches have been applied to assess risk. These include both sites at which asbestos is naturally occurring and sites at which the source of asbestos is debris from asbestos-containing construction materials.

That the above contrasts sharply with what is observed for the El Dorado County Study (i.e. that risks estimated using the Berman and Crump protocol are substantially lower than those estimated using IRIS) reinforces the notion that something may be radically different about the nature of exposures in the *specific* locations in which this study was conducted than for the exposures characterized at most other asbestos sites. This and related considerations are addressed further in Section 4.3, below.

The information provided in the lower portion of Table 6 reinforces the findings obtained from the middle portion. It also suggests that use of the AHERA benchmark to

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[14] Note that in all cases here, estimated risks were derived assuming lifetime-continuous exposure, which may or may not be appropriate for specific situations. Thus, such considerations need to be more carefully explored before drawing definitive conclusions.

delineate potentially hazardous exposures to asbestos may not be particularly health protective. As can be seen in the second to last row of the table, the risk equivalent to the AHERA benchmark (using IRIS) is near or at the upper end of the range of risks potentially considered acceptable by EPA (i.e. $1x10^{-6}$ to $1x10^{-4}$) for both the Libby and the World Trade Center sites. Moreover, based on the characteristics of the exposures at Libby, the risk equivalent to the AHERA benchmark estimated using the Berman and Crump approach is substantially above the range of risks potentially considered acceptable by EPA.

Unfortunately, the available data were not sufficient to estimate a risk equivalent to the AHERA benchmark using the Berman and Crump protocol at the World Trade Center site. If it is true, however, that virtually all of the asbestos observed is chrysotile (and that is not entirely clear), then the Berman and Crump protocol would not necessarily be expected to produce a risk estimate that is substantially higher.

4.2.2 A comparison of the status of review of the proposed approach with the Berman and Crump approach

Table 7 is a side-by-side comparison of the steps required to assess asbestos-related risk using, respectively, the approach proposed by EPA for El Dorado County and the Berman and Crump protocol. It also indicates what appears to be the current (review) status of each of the steps, based on a brief review of relevant documents.

In Table 7, the first column lists the major phases required for assessing risk (from acquisition of data through applying a risk factor to exposures estimated using a particular metric). Obviously, the steps of these phases had to be streamlined for brevity, although an effort was made to capture all steps in which distinctions are potentially important.

The remaining columns of Table 7 respectively indicate:

- the steps employed by EPA to develop the current risk factor for asbestos (IRIS Current) and to apply it using the approach proposed for El Dorado County;
- comments highlighting important considerations for some of these steps;
- the steps employed to develop the risk factors proposed by Berman and Crump (2001, 2003) and to apply it to El Dorado County; and
- comments highlighting important considerations for some of these steps.

As can be seen in Table 7, the Berman and Crump approach has substantially benefitted from the advantage of 14 additional years of research over development of the risk factor currently listed in IRIS. Among other things, this means that control environments potentially relevant to environments in which asbestos is naturally

occurring (and may therefore coexist with substantial contributions from massive forms of the same mineral) were considered.

It is also acknowledged in the table that the current IRIS risk factor enjoys the precedent of having been subjected to the entire, formal EPA review process needed for establishing such values. In contrast, the Berman and Crump protocol has only been subjected to an initial peer-review consultation (by a panel of 11 experts) heretofore. At the same time, even EPA staff acknowledge that the IRIS risk factor is out of date and needs to be revised (Fed Reg 2006).

What may be more important to the issues at hand, however, is the status of the steps listed in Table 7 that are subsequent to the establishment of risk factors. As can be seen in the table, because one is applying "apples directly to apples," and because the exposure metric recommended in the Berman and Crump protocol has already been converted to a TEM-dependent exposure metric (during development of the risk factor itself), no further assumptions are required (or need review) when applying the factor to assess risks at particular sites.

In contrast, as has been shown in previous sections of this report, determination of PCMe-based concentrations may not have been conducted entirely consistently heretofore. Moreover, the manner in which PCMe relates to risk in an environment such as observed in El Dorado County are entirely different than the kinds of environments studied by epidemiologists in the control studies used to derive the current risk factor in IRIS. In addition, it does not appear that either of these critical considerations have been subjected to any kind of formal agency review at this point in time.

The comment from the Peer Review Committee concerning the idea that the minimum diameter of the size range for protocol structures needs to be increased to 1.5 μm also needs to be addressed. It is important to understand that, currently, this is only a recommendation from the group of reviewers. It is *not* a finding from a formal analysis of any kind. This contrasts with the current size range limit, which has been formally evaluated as part of a meta analysis of the human epidemiology studies and extrapolated from a formal analysis of animal inhalation studies. Moreover, it is unlikely that members of the peer-review committee would suggest that such a change should be applied for exposure determination without first defining an appropriately matching risk factor (which would require that a formal meta analysis be completed using appropriate exposure data)[15].

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[15] Unfortunately, the database of existing size distributions is not sufficiently rich to adequately evaluate the effects of length or width further than what has already been done (Berman and Crump 2003). It is important to remember, for example, that the effects of length and width are confounded so that the unfortunate length truncation of the existing database (i.e. that no information is available for the distribution of lengths beyond 10 μm) prevents more detailed consideration of either width or length using the

In fact, it is not even known whether such a change would result in risk estimates increasing or decreasing in specific environments. This is because the result of the meta analysis (which would need to be conducted to develop properly matched risk factors) would be to spread the "fixed" risk from the mortality observed in the epidemiology studies across a larger number of structures than is the case for the exposure metric currently recommended by Berman and Crump. The relative magnitude of the risk estimated using the new, thicker structures (versus current protocol structures) would then depend on the relative ratios of the two sets of structures in control studies vs. site studies.

To illustrate the above consideration, if the ratio of the new exposure metric (incorporating the thicker structures) to protocol structures is greater in the control environments (studied by epidemiologists) than in environments of interest at specific sites (where risks are assessed), then risks estimated using the new metric will be lower than risks estimated using the current (Berman and Crump) metric. Thus, it is possible that even this approach could potentially be "less health protective," although an appropriate meta analysis might (or might not) show that it is more reliable.

4.3 Considering Health Protectiveness

It is instructive to evaluate the relative degree of health protectiveness potentially afforded by the various approaches for assessing asbestos-related risk that are considered in this report. The information provided in the middle and lower sections of Table 6 can be used for this purpose.

Based on the factors presented in the row of Table 6 labeled: "Berman and Crump (2001)" and confirmed in the row labeled: "Risk Driver," it appears that the Berman and Crump protocol provides a more sensitive measure of asbestos-related risk than the approach using IRIS. Moreover, for sites in which asbestiform amphiboles are the primary contributors to exposure, risks estimated using the Berman and Crump protocol tend to be an order of magnitude or more greater than those estimated using IRIS. Such observations are further confirmed by studies at other sites (including sites at which amphibole asbestos is naturally occurring and sites at which it is derived from manufactured asbestos product debris). At virtually all such sites in which data are available for comparing the two approaches for assessing risk, the Berman and Crump protocol yields risk estimates that are substantially higher than those estimated using IRIS.

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human epidemiology data.

It should also be noted that the results reported by NIOSH at a recent conference (Kuempel et al. 2006) tend to support the direction of the Berman and Crump work (i.e. toward very long and very thin fibers as the cause of disease), it is also important to recognize that the single environment available to the authors in this analysis is not sufficiently robust to adequately examine these kinds of questions.

The information in Table 6 also highlights the fact that the set of sites exhibiting elevated risks and the rank order of such risks varies as a consequence of the choice of the exposure metric used to assess risk. This helps to inform the question of which approaches, if applied consistently, are likely to best reflect what is known about the incidence of asbestos-related disease.

Use of the Berman and Crump protocol focuses attention on sites where long, thin, asbestiform amphiboles contribute substantially to exposure. These include (for example) sites such as Libby, where asbestos-related diseases have actually been observed among the exposed population.

In contrast, the approach proposed by EPA for use in El Dorado County (i.e. estimating exposure using the PCMe metric and combining such results with the IRIS risk factor) tends to focus attention on sites where local soils and rock contain high concentrations of non-asbestiform amphiboles (or serpentinite). Thus, locations such as the specific areas of El Dorado County studied by Ladd are emphasized. However, given that surface soils and rock over approximately 30% of the nation apparently contain substantial concentrations of non-asbestiform amphiboles with no current evidence of elevated disease in these areas, it is not clear how helpful such emphasis may be.

At the same time, the approach proposed by EPA may "miss" elevated risks at sites in which asbestiform amphiboles are present at low concentrations, but the host rock does not otherwise contain substantial concentrations of other (non-asbestiform) amphiboles. Thus, there may be situations in which "diluted" versions of Libby may be missed by this approach. Given such possibilities, it appears that the proposed EPA approach, if applied consistently, may miss potentially risky situations in various parts of the nation or even other parts of El Dorado County.

It should also be emphasized that, based on the information provided in the last two rows of Table 6, use of the AHERA benchmark as a screen for distinguishing potentially risky situations from those that are relatively safe, may not be as effective as desired (see Section 4.2.1).

One final note is also relevant here. As further work will inevitably be conducted to refine exposure metrics for assessing asbestos-related risk, it is important to debunk one widely held misconception. As it is a requirement of sound science for assessing risk, exposure concentrations estimated using any particular exposure metric should only be combined with risk factors that are properly matched to that particular exposure metric. Assuming this is the case, it is *not* true that an exposure metric resulting in greater numbers of structures being counted to determine concentration will necessarily result in greater estimates of risk than those derived using other exposure metrics.

To derive a risk factor matched to a particular exposure metric, it is first necessary to convert estimates of exposures relevant to the control studies (epidemiology studies) to the particular exposure metric. The manner in which this is accomplished is described

in detail in Berman and Crump (2003). However, the consequence of this step is that the risk factor derived from control studies will decrease as the number of structures included in exposure concentration estimates increase in these studies.

Given the above, whether risk estimated using a particular exposure metric will increase or decrease relative to a baseline case is a function of the ratio of the concentrations estimated for the particular exposure metric at the study site to the concentrations estimated at sites evaluated in the control studies. If more of the particular kinds of structures (defined by the exposure metric) are present in control study exposures than observed at a study site (relative to the baseline case), the risk estimated using the particular exposure metric will be *lower* than the baseline case for the study site in question.

5 CONCLUSIONS

Based on the evaluation presented above, it appears that the approach proposed by EPA to assess risk in El Dorado County satisfies neither of two criteria that are critical for assuring that risk assessments are reliable. First, due to substantial differences in character, exposure concentrations determined in terms of the PCMe metric in El Dorado County (Ladd 2005) are not directly comparable to the PCM-based exposures evaluated in the epidemiology studies used to derive the risk factor in IRIS (Current). Second, the PCMe exposure metric itself has been shown not to remain reasonably proportional to risk across exposure environments.

Given these findings, applying the IRIS risk factor to the exposures measured by Ladd will not provide a reliable estimate of risk. In contrast, use of the protocol structure metric combined with the appropriately matched risk factors recommended by Berman and Crump (2001)[16] can potentially provide a reliable estimate of risk for the locations studied by Ladd, subject to the additional considerations discussed below.

The Ladd (2005) study appears to suffer from quality control (QC) problems that will need to be resolved before any attempt is made to interpret the data. Even after the QC issues are resolved, however, it may prove difficult to extrapolate findings that may be gleaned from the study more broadly than to the specific locations at which airborne measurements were collected. This is because no relationship between bulk concentrations and airborne exposure measurements was established in the Ladd study.

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[16] The analyses conducted to generate the data reported in Ladd (2005) were not explicitly designed to determine concentrations of long structures (longer than 10 μm) with sufficient sensitivity and precision to support risk assessment exclusively using these longer structures. Therefore, if there is ultimately a desire to apply the Berman and Crump protocol to these data, the 2001 version of the protocol should be applied rather than the 2003 version.

Until the quality control issues are resolved and an appropriate statistical analysis of the data is conducted, a proper assessment of risk cannot be completed from the Ladd (2005) data. Thus, it is not possible to tell at this time whether risks estimated using either protocol structures or PCMe structures will prove to be acceptable for the areas represented by the Ladd study environment. However, assuming that the ratios of concentrations are approximately correct, it appears that the IRIS approach for assessing risk yields a higher risk estimate than the Berman and Crump approach for the specific locations that were studied.

As the above observation (should it hold up) is highly unusual, compared to findings based on broad experience at other sites, it reinforces the finding that conditions at these specific locations in El Dorado County are very different from conditions found at most sites where asbestos is a hazard (potentially including other parts of El Dorado County).

If applied uniformly at sites across the nation, the approach proposed for assessing risk in El Dorado County will be less health protective than if such risks are assessed using the approach proposed by Berman and Crump. This is based on a growing body of experience at multiple, varied sites.

Whatever the relative risks that might be estimated for El Dorado County based, respectively, on the approach proposed by EPA and the approach recommended by Berman and Crump (2001), it appears that the proposed EPA approach is no better supported by precedent.

Given that (based on discussions with multiple geologists) about 30% of the soil and near-surface rock in the nation may contain amphibole, if the agency intends to apply their asbestos regulations consistently to all areas where amphibole may be present, then it is in everyone's interest to employ an approach that will adequately distinguish situations that are potentially risky from those that are not. Otherwise, there is a potential either to miss those sites in which true risks exist or, conversely, to *unnecessarily* wreak economic havoc. Neither result is in the public interest, although the first kind of error is clearly the more important to avoid.

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TABLE 1:
DEFINITIONS FOR PCM EQUIVALENT FROM VARIOUS SOURCES[a]

Source:	IRIS	NIOSH 7402[b]	ISO 10312	CARB Staff Report	CARB Method 427	CA Proposition 65	ATSDR
Year:							
Referenced	Current	1994	1995	1986	1988	2002	2001
Original	1988	1989	1995	1986	1988	1987	2001
TEM Criteria:							
Min Length (µm)	5	5	5	ND	5	ND	5
Min Width (µm):	0.4	0.25	0.2	ND	0.2 *or* 0.3	ND	0.3
Max Width (µm):	ND	ND	3	ND	ND	ND	3
AR:	≥3	≥3	≥3	≥3	≥3	≥3	≥3
Comments:	Indicates that correlation between TEM and PCM fiber counts are "very uncertain."	Count those structures that "would have been counted by PCM"		Defined as total TEM structures (no minimum length or width defined) divided by either 100 or 1000.		Defined as total TEM structures (no minimum length or width defined) divided by either 100 or 1000.	Defined as total TEM structures longer than 0.5 µm divided by 60
		Indicates that potential interferences include non-asbestos amphibole particles with AR ≥ 3:1 and some non amphiboles with similar diffraction patterns to amphiboles	Indicates that the method cannot distinguish between the asbestiform varieties of amphibole minerals and their non-asbestos analogs.				

NOTES:

ND means: "not defined in the method"

[a] To the extent possible, the most recent version of each of the above documents are presented, based on the results of a search of the appropriate agency websites. If there are newer versions, they are not easily located.

[b] This method was not designed to provide concentrations of asbestos fibers directly. Rather, it was designed to provide a factor that would be used to "adjust" a concentration measurement derived by PCM.

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TABLE 2:
COMPARISON OF STATUS OF VARIOUS EXPOSURE METRICS FOR EVALUATING ASBESTOS RISKS

	EXPOSURE METRIC						
	Total Respirable Particles	**PCM**	**PCMe**	**Total Protocol Structures**	**Long Protocol Structures**	**Long Protocol Structures Further Optimized**	**Long Protocol Structures Extended to Address Mouth Breathing**
Dimensions	AED < 10 µm	Length > 5 µm Width > ~0.25 µm Aspect Ratio ≥ 3	Length > 5 µm Width > ~0.25 µm Aspect Ratio ≥ 3	Length > 5 µm 0.5 µm > Width	Length > 10 µm 0.4 µm > Width	Dimensional criteria would be optimized based on new meta analysis	Length > 5 µm 1.5 µm > Width
Sampling and Analysis	Midget Impinger with Analysis by Optical Microscopy[a]	Membrane Filter with Analysis by Optical Microscopy[a]	Membrane Filter with Tandem Analysis by both Optical and Transmission Electron Microscope[a]	Membrane Filter with Analysis by Transmission Electron Microscopy[a]	Membrane Filter with Analysis by Transmission Electron Microscopy[a]	Membrane Filter with Analysis by Transmission Electron Microscopy[a]	Membrane Filter with Analysis by Transmission Electron Microscopy[a]
Magnification	~400	~400	500-1,000	10,000	10,000	10,000	10,000
Origin		Asbestos Research Council (ARC)[a]	NIOSH[a]	Berman and Crump[f]	Berman and Crump[g]	Hypothesis proposed by Berman[h]	Peer Review Committee[i]
Year		1958	1989	2001	2003	2001	2003
Theoretical Basis for Linking to Risk	None. In common use for particulate matter at the time.[a]	Ad hoc.[a] Developed primarily for analytical convenience with general recognition of need to distinguish fibers from particles.[a]	Based informally on presumption that measuring same size range as PCM (but adding mineral confirmation) would allow link to epidemiology study results.	Size rationally extrapolated from findings in Berman et al. 1995 with a modification required by the published size data available for application to the epidemiology studies.[f,g]	Modified from 2001 protocol based on *formal hypothesis test* of effect of length on ability to reduce variability across existing epidemiology studies.[g] Width interval reduced to match that indicated in Berman et al. (1995) per recommendation of the peer review committee.[g,j]	Proposed for testing based on implications from the literature that even longer structures are the major contributors to risk. Would also have optimized width dimensions based on a new analysis using new data	Proposed for consideration based on general idea that this range of structures includes all structures that potentially contribute to risk. Importantly, this metric may not automatically prove more health protective than others.[i]
Other Evidence	Recognized as inadequate for asbestos when extrapolating across environments[a]	(1) Recognized as inadequate for asbestos when extrapolating across environments.[a,f,g] (2) Shown not to adequately predict risk in animal inhalation studies.[b]	As PCM has not been shown to reasonably predict risk, utility for extrapolating across exposure environments is questionable.	In a formal meta analysis, shown to substantially reduce variability across existing epidemiology studies compared to use of PCMe.[f]	Shown to provide some improvement over 2001 protocol, based on limited hypothesis testing involving effects of length.[g]	Proposed for testing by completing a new meta analysis as soon as data from now cancelled study would have become available.[h]	The peer review committee proposed this metric for consideration as part of further meta-analysis, which is required to define matching dose-response factors for the metric.[i]
Intent	Designed originally for general application to toxins inhaled as particulate matter.[a]	Designed originally for evaluating exposure to commercial asbestos. NOT initially designed for application to other environments.[a]	Based on interferences listed in the method, it appears to have been designed originally for evaluating exposure to commercial asbestos.[a]	Designed originally for general application to asbestos in any environment.[f]	Designed originally for general application to asbestos in any environment.[g]	Proposed for consideration for application to asbestos in any environment.	Proposed for consideration for application to asbestos in any environment.
Pre-requisites for Implementation for Linking to Risk	No Longer Applied	None for most environments involving exposure to commercial asbestos, although direct link to risk is questionable.[a,b] Shown to be NOT applicable in natural environments due to presence of extensive interfering materials.[a,c,e]	NONE for environments involving exposure to commercial asbestos (but subject to some of the same limitations as PCM).[a,b] Applicability to natural environments still not demonstrated (and this is the current controversy).	NONE Already shown to provide substantial improvement over PCMe.[f]	NONE Already shown to provide some improvement over Total Protocol Structures.[g] ***Can be further optimized with data from now-cancelled study***	Need to evaluate in a formal meta-analysis both: (1) to develop appropriately matched dose-response factors and (2) to compare against the performance of Long Protocol Structures.	Need to evaluate in a formal meta-analysis both: (1) to develop appropriately matched dose-response factors and (2) to compare against the performance of Long Protocol Structures.
Strength of Evidence for Supporting Extrapolation to Natural Environments	No longer Applied and clearly not applicable	Shown not to be applicable in natural environments.[a,k,m]	Applicability to natural environments still not demonstrated (and this is the current controversy).[n]	Based on a growing track record, expected not to under-estimate asbestos risk relative to PCMe.	Expected not to under-estimate asbestos risk relative to PCMe.	Unknown. Will require validation with a meta analysis incorporating appropriately relevant control environments.	Unknown. Will require validation with a meta analysis incorporating appropriately relevant control environments.[i]

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TABLE 2 (cont.):
COMPARISON OF STATUS OF VARIOUS EXPOSURE METRICS USED FOR EVALUATING ASBESTOS RISKS

Notes:

AED means aerodynamic equivalent diameter.

[a] TBP

[b] NIOSH Method 7400 (1989). The history of the development of precursor methods predating the NIOSH Method is provided in Walton (1982).

[c] NIOSH Method 7402 (1994).

[d] ISO Method 10312 (1995), with modifications incorporated to focus on the indicated size range of structures. Note that complex structures (bundles, clusters, and matrices) are also incorporated into the counting rules.

[e] Walton (1982).

[f] Berman and Crump (2001).

[g] Berman and Crump (2003).

[h] Until February of this year, I was conducting a study to generate improved characterizations of the historical exposures relevant to critical epidemiology studies, which would have been used to support a revised meta analysis. The study was terminated.

[i] ERM (2003)

[j] As noted in the table, the potency assigned to structures representing any particular exposure metric needs to be determined by a formal meta analysis. If the concentrations of structures representing a particular exposure metric are more plentiful in the exposure environments of the original epidemiology studies (i.e. the control environments) than in the test environments (e.g. El Dorado County), than risks estimated in such environments will be lower than if such risks are estimated using an exposure metric in which such a difference is not as extreme (or the ratios are even reversed).

[k] Berman et al. (1995).

[l] Cheme et al. (1989).

[m] Berman (no date) Unpublished data from the Oakland Hills Fire Project.

[n] At a minimum, an appropriately matching slope factor should be redeveloped for this exposure metric from a meta analysis that appropriately incorporates considerations of environments in which cleavage fragments predominate such as the Homestake Mine in South Dakota and the Taconite Mines in Minnesota. The slope factor currently being employed with this metric was derived from an analysis in which cleavage fragments were at most a miniscule component of the dusts in the environments studied (see text).

[o] The existing database of size distributions is not sufficiently rich to evaluate effects of diameter among the human epidemiology data with adequate statistical power. Among other things, for example, the existing database is truncated for length so that, due to the confounding effects of length and width, hypothesis testing using this truncated data set may not provide reliable determinations beyond what has already been reported by Berman and Crump. The study described in Footnote h was designed to provide the needed, additional data.

TABLE 3:
CHARACTER OF EXPOSURES IN ENVIRONMENTS INCLUDED IN THE 1986 HEALTH EFFECTS ASSESSMENT UPDATE REVIEW OF ASBESTOS EPIDEMIOLOGY STUDIES AND REPORTED IN IRIS 1988 AS THE BASIS FOR ESTABLISHING THE CURRENT UNIT RISK FACTOR

Fiber Type	Operation	Cohort	Lung Cancer K_L x 100	Mesothelioma K_M x 100	Exposure Metric[a]	Reference	Comments
							All samples contain asbestiform fiber. The indicated samples contain fiber with:
Chrysotile	Mining and Milling	Quebec mines and mills	***Not Used***[b]		MI	(1)	serpentinite and trace amphibole cleavage fragments[b]
			Not Used[b]		MI	(2)	serpentinite and trace amphibole cleavage fragments[b]
	Friction Products	Connecticut plant	0.01		MI*	(3)	*at most*, small amounts of serpentinite cleavage fragments[c]
	Textiles	South Carolina plant	2.8		PCM	(4)	*at most*, trace serpentinite cleavage fragments
			2.5		PCM	(5)	*at most*, trace serpentinite cleavage fragments
Amosite	Insulation Manufacture	Patterson, NJ factory	4.3		PCM**	(6)	*at most*, trace amphibole cleavage fragments[d]
				1.00E-06		(7)	
Mixed	Friction Products	British factory	0.058		PCM	(8)	*at most*, trace amphibole cleavage fragments[c,d]
	Cement Manufacture	Ontario factory	6.7	1.20E-05	MI*	(9)	*at most*, trace serpentinite and amphibole cleavage fragments[e]
		New Orleans plants	0.53		MI	(10)	*at most*, trace serpentinite and amphibole cleavage fragments[e]
	Factory workers	U.S. retirees	0.49		MI*	(11)	*at most*, trace serpentinite and amphibole cleavage fragments
	Insulation Application	U.S. insulation workers	0.75	1.50E-06	NS	(12), (13)	*at most*, trace serpentinite and amphibole cleavage fragments[d]
	Textiles	Pennsylvania plant	1.4		MI*	(14)	*at most*, trace serpentinite and amphibole cleavage fragments
		Rochedale plant	1.1	3.20E-06	TP*	(15), (16)	*at most*, trace serpentinite and amphibole cleavage fragments

NOTES:

[a] Symbols in this column indicate the primary metric by which exposure was monitored in the indicated study. "MI" means midget impinger with a study specific factor applied to convert to PCM. "MI*" means midget impinger with a non-study specific conversion factor. "PCM" means phase contrast microscopy. "PCM**" means PCM, but with measurements determined at a different plant from the one where mortality was monitored. "TP*" means that the initial measurements were collected by thermal precipitator and a non study specific conversion factor was applied. "NS" means non-specific; exposures were estimated for the Selikoff et al. (1979) simply as the average concentration reportec for the overall insulation industry.

[b] Although these are the only environments in which serpentinite or amphibole cleavage fragments might be present at greater than very small amounts (due to the presence of the parent rock in which the asbestos is embedded), these studies were excluded from the EPA analysis used to derive the EPA recommended unit risk factor for asbestos.

[c] Although cleavage fragments are potentially present (at most in small amounts) in friction product environments (because the lowest grade asbestos fiber used to manufacture these materials may not have been as well purified as higher grade fiber (Walton 1982), these environments also exhibit among the lowest dose-response factors.

[d] In these environments, it is possible that particles composed of organic materials or other non-serpentinite and non-amphibole inorganic materials may be present (which are distinct from serpentinite or amphibole cleavage fragments). However, it is not clear whether any of these materials have been shown to cause cancer in other environments where asbestos was not used. Certainly, up to this point, EPA has not applied the asbestos regulations to environments where particles of these other materials might be present without asbestos also being present.

[e] In these environments, particles composed of the cementitious binders and fillers used in cement manufacture may be present (which are distinct from serpentinite or amphibole cleavage fragments). However, whether any of these materials have been found to be carcinogenic in other environments in the absence of asbestos is not relevant here. Certainly, up to this point, EPA has not applied the asbestos regulations to environments where these types of cementitious binders and fillers are present without asbestos

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TABLE 3 (cont.)

CHARACTER OF EXPOSURES IN ENVIRONMENTS INCLUDED IN THE 1986 HEALTH EFFECTS ASSESSMENT UPDATE REVIEW OF ASBESTOS EPIDEMIOLOGY STUDIES AND REPORTED IN IRIS 1988 AS THE BASIS FOR ESTABLISHING THE CURRENT UNIT RISK FACTOR

REFERENCES

(1) McDonald et al., (1980)
(2) Nicholson et al., (1979)
(3) McDonald et al., (1984)
(4) Dement et al., (1983)
(5) McDonald et al., (1983a)
(6) Seidman (1984)
(7) Seidman (1979)
(8) Berry and Newhouse (1983)
(9) Finkelstein (1983)
(10) Weill et al., (1979)
(11) Henderson and Enterline (1979)
(12) Selikoff et al., (1979)
(13) Peto et al. (1982)
(14) McDonald et al., (1983b)
(15) Peto (1980)
(16) Peto et al. (1982)

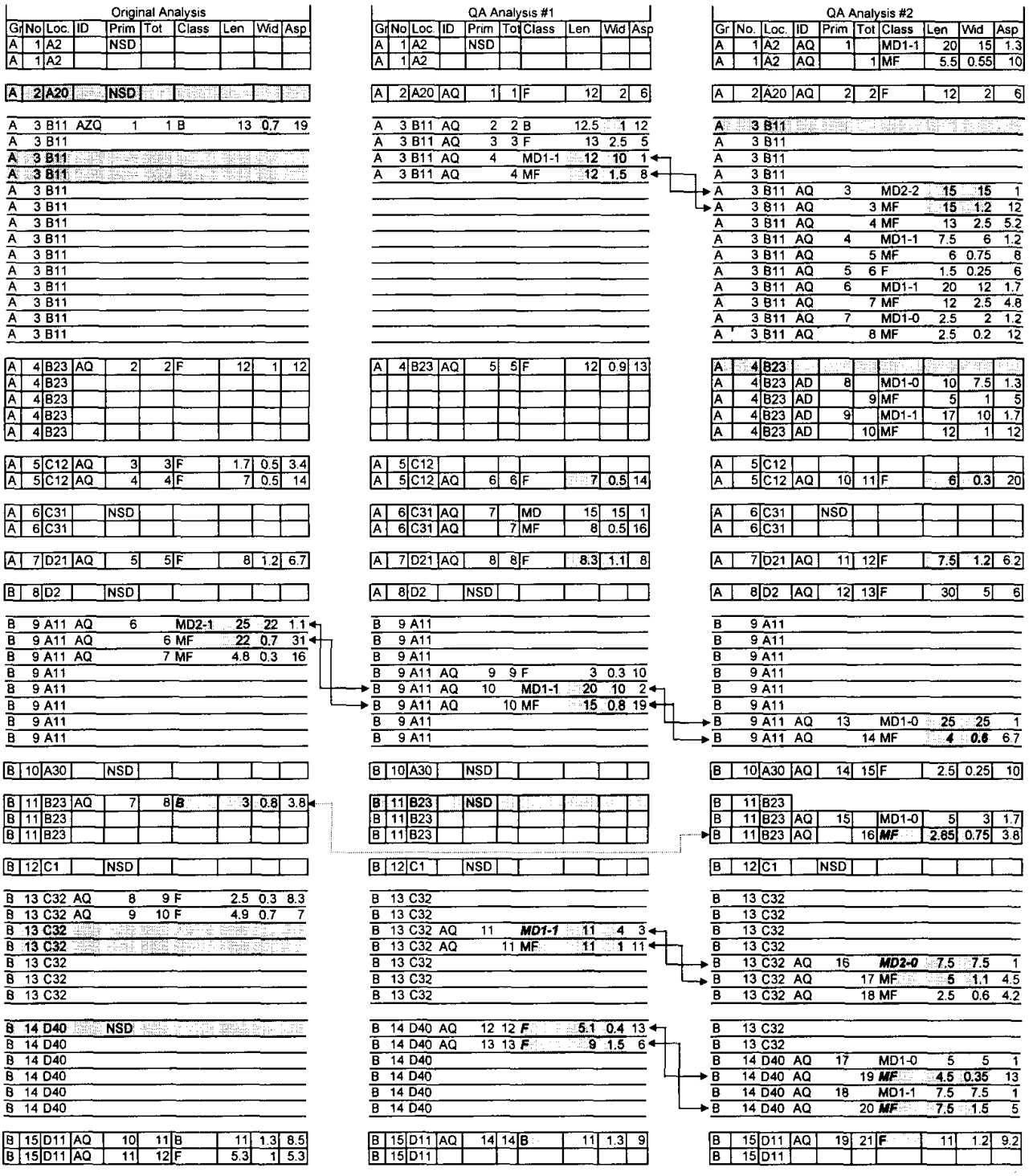
TABLE 4:
COMPARISON OF REPORTED NUMBERS OF STRUCTURES BY DIFFERENT ANALYSTS IN COMMON GRID OPENINGS

Sample Identification	Number of Analyses	Analysis Identification	Number of Grid Openings Compared	Number of Differences in Counts	Total Error Rate	Consistent?[a]
SRA-R05-110604	3	Original	15	6	40%	**NO**
		QC Analysis 1	15	4	27%	**NO**
		QC Analysis 2	15	5	33%	**NO**
SRA-R02-100604	2		14	7	50%	**NO**
NRA-02-101104	3	Original	17	2	12%	YES
		QC Analysis 1	17	1	6%	YES
		QC Analysis 2	17	2	12%	YES
NRA-R03-101104	2		16	9	56%	**NO**
SFBC-H2-1FD-10064	2		22	8	36%	**NO**

NOTES:

[a] Analyses were considered consistent if the total error rate was less than 20% (see text).

TABLE 5:
COMPARISON OF REPLICATE EXAMINATIONS OF THE SAME GRID OPENINGS ACROSS GRID SPECIMENS PREPARED FROM SAMPLE SRA-R05-110604



Original Analysis									
Gr	No	Loc.	ID	Prim	Tot	Class	Len	Wid	Asp
A	1	A2		NSD					
A	1	A2							
A	2	A20		NSD					
A	3	B11	AZQ	1	1	B	13	0.7	19
A	3	B11							
A	3	B11							
A	3	B11							
A	3	B11							
A	3	B11							
A	3	B11							
A	3	B11							
A	3	B11							
A	3	B11							
A	3	B11							
A	4	B23	AQ	2	2	F	12	1	12
A	4	B23							
A	4	B23							
A	4	B23							
A	4	B23							
A	5	C12	AQ	3	3	F	1.7	0.5	3.4
A	5	C12	AQ	4	4	F	7	0.5	14
A	6	C31		NSD					
A	6	C31							
A	7	D21	AQ	5	5	F	8	1.2	6.7
B	8	D2		NSD					
B	9	A11	AQ	6		MD2-1	25	22	1.1
B	9	A11	AQ		6	MF	22	0.7	31
B	9	A11	AQ		7	MF	4.8	0.3	16
B	9	A11							
B	9	A11							
B	9	A11							
B	9	A11							
B	9	A11							
B	10	A30		NSD					
B	11	B23	AQ	7	8	B	3	0.8	3.8
B	11	B23							
B	11	B23							
B	12	C1		NSD					
B	13	C32	AQ	8	9	F	2.5	0.3	8.3
B	13	C32	AQ	9	10	F	4.9	0.7	7
B	13	C32							
B	13	C32							
B	13	C32							
B	13	C32							
B	13	C32							
B	14	D40		NSD					
B	14	D40							
B	14	D40							
B	14	D40							
B	14	D40							
B	14	D40							
B	15	D11	AQ	10	11	B	11	1.3	8.5
B	15	D11	AQ	11	12	F	5.3	1	5.3

QA Analysis #1									
Gr	No	Loc.	ID	Prim	Tot	Class	Len	Wid	Asp
A	1	A2		NSD					
A	1	A2							
A	2	A20	AQ	1	1	F	12	2	6
A	3	B11	AQ	2	2	B	12.5	1	12
A	3	B11	AQ	3	3	F	13	2.5	5
A	3	B11	AQ	4		MD1-1	12	10	1
A	3	B11	AQ		4	MF	12	1.5	8
A	4	B23	AQ	5	5	F	12	0.9	13
A	5	C12							
A	5	C12	AQ	6	6	F	7	0.5	14
A	6	C31	AQ	7		MD	15	15	1
A	6	C31	AQ		7	MF	8	0.5	16
A	7	D21	AQ	8	8	F	8.3	1.1	8
A	8	D2		NSD					
B	9	A11							
B	9	A11							
B	9	A11							
B	9	A11	AQ	9	9	F	3	0.3	10
B	9	A11	AQ	10		MD1-1	20	10	2
B	9	A11	AQ		10	MF	15	0.8	19
B	9	A11							
B	9	A11							
B	10	A30		NSD					
B	11	B23		NSD					
B	11	B23							
B	11	B23							
B	12	C1		NSD					
B	13	C32							
B	13	C32							
B	13	C32	AQ	11		MD1-1	11	4	3
B	13	C32	AQ		11	MF	11	1	11
B	13	C32							
B	13	C32							
B	13	C32							
B	14	D40	AQ	12	12	F	5.1	0.4	13
B	14	D40	AQ	13	13	F	9	1.5	6
B	14	D40							
B	14	D40							
B	14	D40							
B	14	D40							
B	15	D11	AQ	14	14	B	11	1.3	9
B	15	D11							

QA Analysis #2									
Gr	No.	Loc.	ID	Prim	Tot	Class	Len	Wid	Asp
A	1	A2	AQ	1		MD1-1	20	15	1.3
A	1	A2	AQ		1	MF	5.5	0.55	10
A	2	A20	AQ	2	2	F	12	2	6
A	3	B11							
A	3	B11							
A	3	B11							
A	3	B11							
A	3	B11	AQ	3		MD2-2	15	15	1
A	3	B11	AQ		3	MF	15	1.2	12
A	3	B11	AQ		4	MF	13	2.5	5.2
A	3	B11	AQ	4		MD1-1	7.5	6	1.2
A	3	B11	AQ		5	MF	6	0.75	8
A	3	B11	AQ	5	6	F	1.5	0.25	6
A	3	B11	AQ	6		MD1-1	20	12	1.7
A	3	B11	AQ		7	MF	12	2.5	4.8
A	3	B11	AQ	7		MD1-0	2.5	2	1.2
A	3	B11	AQ		8	MF	2.5	0.2	12
A	4	B23							
A	4	B23	AD	8		MD1-0	10	7.5	1.3
A	4	B23	AD		9	MF	5	1	5
A	4	B23	AD	9		MD1-1	17	10	1.7
A	4	B23	AD		10	MF	12	1	12
A	5	C12							
A	5	C12	AQ	10	11	F	6	0.3	20
A	6	C31		NSD					
A	6	C31							
A	7	D21	AQ	11	12	F	7.5	1.2	6.2
A	8	D2	AQ	12	13	F	30	5	6
B	9	A11							
B	9	A11							
B	9	A11							
B	9	A11							
B	9	A11							
B	9	A11							
B	9	A11	AQ	13		MD1-0	25	25	1
B	9	A11	AQ		14	MF	4	0.6	6.7
B	10	A30	AQ	14	15	F	2.5	0.25	10
B	11	B23							
B	11	B23	AQ	15		MD1-0	5	3	1.7
B	11	B23	AQ		16	MF	2.65	0.75	3.8
B	12	C1		NSD					
B	13	C32							
B	13	C32							
B	13	C32							
B	13	C32							
B	13	C32	AQ	16		MD2-0	7.5	7.5	1
B	13	C32	AQ		17	MF	5	1.1	4.5
B	13	C32	AQ		18	MF	2.5	0.6	4.2
B	13	C32							
B	13	C32							
B	14	D40	AQ	17		MD1-0	5	5	1
B	14	D40	AQ		19	MF	4.5	0.35	13
B	14	D40	AQ	18		MD1-1	7.5	7.5	1
B	14	D40	AQ		20	MF	7.5	1.5	5
B	15	D11	AQ	19	21	F	11	1.2	9.2
B	15	D11							

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Key:

- Structure Missed on this G.O.
- Phantom Structure on this G.O.
- Disagreement in Structure Dimensions Between Analysts on this G.O.

Findings:

Original Analysis
of 11 structures observed, 4 are unconfirmed and 2 are disputed. Also, there are 6 missing

QC Analysis #1
of 14 structures observed, 3 are unconfirmed and 7 are disputed. Also there is 1 missing

QC Analysis #2
of 19 structures observed: 12 are unconfirmed and 3 are disputed. Also, 2 are missing.

NOTES:
Comparisons were performed using rules that are most favorable to finding agreement among the analysts. The colors in the table highlight the descrepencies noted.

TABLE 6:
COMPARISON OF APPROACHES FOR EVALUATING ASBESTOS-RELATED RISKS APPLIED AT SELECTED GOVERNMENT-LEAD SITES

	Diamond XX [a]	World Trade Center [b]	Southdown [c]	Libby [d]	El Dorado [e]
Year of Study	1994	2002	2003	2003	2005
Source of Asbestos	Natural	Construction Products	Natural	Natural	Natural
Surrounding Matrix	Serpentinite road aggregate	Varied construction materials	Marble with massive amphibole	Soil with vermiculite and massive amphibole	Serpentinite soil with massive amphibole
Type of Asbestos	Chrysotile	Primarily Chrysotile	Amphibole Asbestos	Amphibole Asbestos	Chrysotile and Amphibole Asbestos
Type of structures	Chrysotile with serpentinite rock fragments	Pure, milled asbestos with fragments of other construction debris	Mixed massive and asbestiform amphibole with other rock fragments	Mixed massive and asbestiform amphibole with other rock fragments	Mixed massive and asbestiform serpentinite[f] and amphibole with other rock fragments
PCMe Definition[g]	(1) NIOSH; and (2) COEHHA	ATSDR	NIOSH	NIOSH	NIOSH
Analytical Method for PCMe Determination[h]	ISO (1993)	AHERA	ISO 10312	(1) ISO 10312; and (2) AHERA	ISO 10312
Risk Assessment Approach	(1) Combined $PCMe_{NIOSH}$ with IRIS URF (2) Early version of Berman and Crump Protocol	Used standards rather than risk analysis: (1) PCM < 0.1 f/ml for workers (2) $PCMe_{ATSDR}$ < 0.0003 f/ml (converted from 70 s/mm^2) for residents	(1) Combined $PCMe_{NIOSH}$ with IRIS URF (2) Berman and Crump Protocol In both cases, separately evaluated "total structures" and the asbestiform component	Combined $PCMe_{NIOSH}$ with IRIS URF	Not Yet Completed: Requires attention to QC issues
Relative Risk[i] (Relative to IRIS)					
Observed or Estimated[i]	Observed	Estimated	Observed	Estimated	Estimated
IRIS (Current)	1[j]	1[j]	1[j]	1[j]	(1[j])[k]
COEHHA PCMe (1986)	0.3x - 2x	NA[l]	NA[l]	NA[l]	NA[l]
Berman and Crump (2001)	1.2x[m]	DNA[n]	15x - 90x	5.9x - 7.5x	(0.04)[k]
Risk Driver[o]	Berman and Crump Protocol	DNA[n]	Berman and Crump Protocol	Berman and Crump Protocol	IRIS
Risk Equivalent for AHERA Benchmark[p]					
Compared to IRIS	NA[l]	8.E-05	NA[l]	1.E-04	NA[l]
Compared to B and C protocol	NA[l]	DNA[n]	NA[l]	6.E-04	NA[l]

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TABLE 6 (cont.)
COMPARISON OF APPROACHES FOR EVALUATING ASBESTOS-RELATED RISKS APPLIED AT SELECTED EPA-LEAD SITES

NOTES:

[a] ICF Technology 1994

[b] NCEA 2002

[c] Berman, 2003

[d] EPA 2003

[e] Ladd 2005

[f] Asbesiform serpentinite is just a synonym for chrysotile.

[g] The PCMe definitions that are referenced in this table vary by the specific dimensions (primarily the minimum width) of the structures included when counting to determine PCMe concentrations. Thus, "NIOSH" means PCMe as defined in NIOSH 7402 (NIOSH 1994); COEHHA means PCMe as defined in COEHHA 2006; and ATSDR means PCMe as defined in ATSDR 2001. For further information about these various definitions, see Table 1.

[h] The specific analytical methods employed for determination of asbestos concentrations in each cited study (from which PCMe concentrations were estimated) are defined in this row. In this row, ISO (1993) is a draft version of ISO Method 10312 (ISO 1995) and that "AHERA" refers to the analytical method defined in the Asbestos Hazard Emergency Response Act (EPA 1987). Interestingly, for some studies, there is a mismatch in the size range defined for PCMe structures actually recorded in various studies (i.e. NIOSH) and the size range defined in the specific analytical method employed to determine PCMe concentrations (i.e. ISO 10312). For details, see Table 1.

[i] The ratios of the levels of risk estimated using the indicated approach for assessing risk to the risk estimated based on the approach recommended in IIRIS (Current) are provided in this section of the Table. When these ratios are listed as "observed" for a particular study, it means that risk estimates derived in the study itself were directly compared to derive the indicated ratios. When listed as "estimated" it means that the ratios were derived indirectly from information concerning the distribution of asbestos structure sizes reported for the site studied. Note that, when the ratios indicated for a particular approach are greater than one, it means that risks estimated using that approach would be *more* health protective than the approach recommended in IRIS *for the particular environment studied.*

[j] This footnote was added to the specific cases in which there is actually a mis-match in the size range of PCMe structures counted to determine exposure concentrations and the size range indicated in IRIS (Current). For details, see Table 1.

[k] The ratios estimated for the El Dorado County study are shown in parentheses because they are highly uncertain due to a combination of QC questions that remain to be addressed for this study and the fact that the analytical methods employed in the study may not have been optimized to adequately determine protocol structure concentrations.

[l] In this table, "NA" means not applied in the study indicated.

[m] For this one study, an earlier draft of the Berman and Crump protocol was applied, as the study was conducted 7 years prior to completing the 2001 version of the protocol.

[n] In this table, "DNA" means dimensions not analyzed (or, at least, the data are not readily available).. Thus, it was not possible to estimate relative concentrations for the exposure metric indicated.

[o] The approach for risk assessment that produced the greatest risk estimate (between the Berman and Crump protocol and IRIS) is indicated in this row for each of the site studies presented in the table. This is based simply on whether the ratios of relative risks indicated in the previous row are less than or greater than 1.

[p] The level of risk that would be equivalent to the benchmark health criteria employed in each indicated study is presented in this portion of the table. In the row labeled, "compared to IRIS," the level of risk equivalent to the health criterion is determined based on the approach in IRIS. In the row labeled, "compared to B and C protocol," the level of risk equivalent to the health criterion is determined based on the Berman and Crump protocol.

TABLE 7:
COMPARISON OF STEPS USED TO ASSESS RISK BY THE BERMAN AND CRUMP PROTOCOL AND THE CURRENT IRIS APPROACH, RESPECTIVELY, ALONG WITH THEIR RELATIVE REVIEW STATUS

Steps in Assessing Risk Current IRIS Approach	Comments	Berman and Crump Approach	Comments
Assemble Database of Control Studies			
Used 1986 database of 13 studies, rejected two studies	The studies rejected were the two available mining studies: McDonald et al. (1980) and Nicholson et al. (1979).	Used 2000 database of 19 studies	
Contains no amphibole mining studies		Includes an amphibole mining study	de Klerk et al. (1994)
Contains no amphibole contaminated mining studies		Includes 2 amphibole contaminated mining studies	Liddell et al. (1997) and Amandus and Wheeler (1987).
Derivation of Risk Factors in Control Studies			
1 Mortality Evaluated		1 Mortality Evaluated	
2 Exposure Evaluated		2 Exposure Evaluated	
3 Exposure Converted to PCM		3 Exposure Converted to PCM	
		3a Exposure Converted to Protocol Structures based on published TEM size distributions matched to each respective control study.	
4 Informally "averaged" exposure/response factors generated for PCM metric from existing studies excluding mining studies.		4 Optimized risk factors across all studies by fitting data as part of a meta analysis.	Resulting agreement across control studies is substantially improved over agreement observed using the current EPA approach (see Figure 1)
Status of Review Process for Derivation of Risk Factors			
Completed full, formal EPA review process	EPA has recognized the need to update this document and is in the process of doing so. Also, see comment on Berman and Crump approach to the right.[a]	Completed initial peer-review consultation (by a panel of 11 experts)	Review comments suggesting changes to dimensions for protocol structures are not based on formal analysis and the comment would apply equally to IRIS approach in any case.
Derivation of Exposure Estimates from Site Studies			
Determine PCMe concentrations by direct measurement using TEM		Determine protocol structure concentrations by direct measurement using TEM	
Evaluate Site-Specific Risk			
Combine risk factors derived for PCM metric to exposure estimates derived in PCMe metric	Requires consistency in manner that PCMe is determined and equivalence in risk/PCMe relationship across environments. Evidence suggests neither. Process has not been subjected to formal agency review.	Combine risk factors matched to protocol structure metric with exposure estimates derived in matching metric	No assumptions required
Considerations for Application to Amphibole Contaminated Soil and Rock			
Risk factors not derived from potentially relevant control studies	Mining studies were excluded from the analysis used to derive the current IRIS risk factor.	Risk factors derived from potentially relevant control studies	The mining studies are most relevant to environments with naturally occurring asbestos

NOTES:

[a] Federal Register 2006

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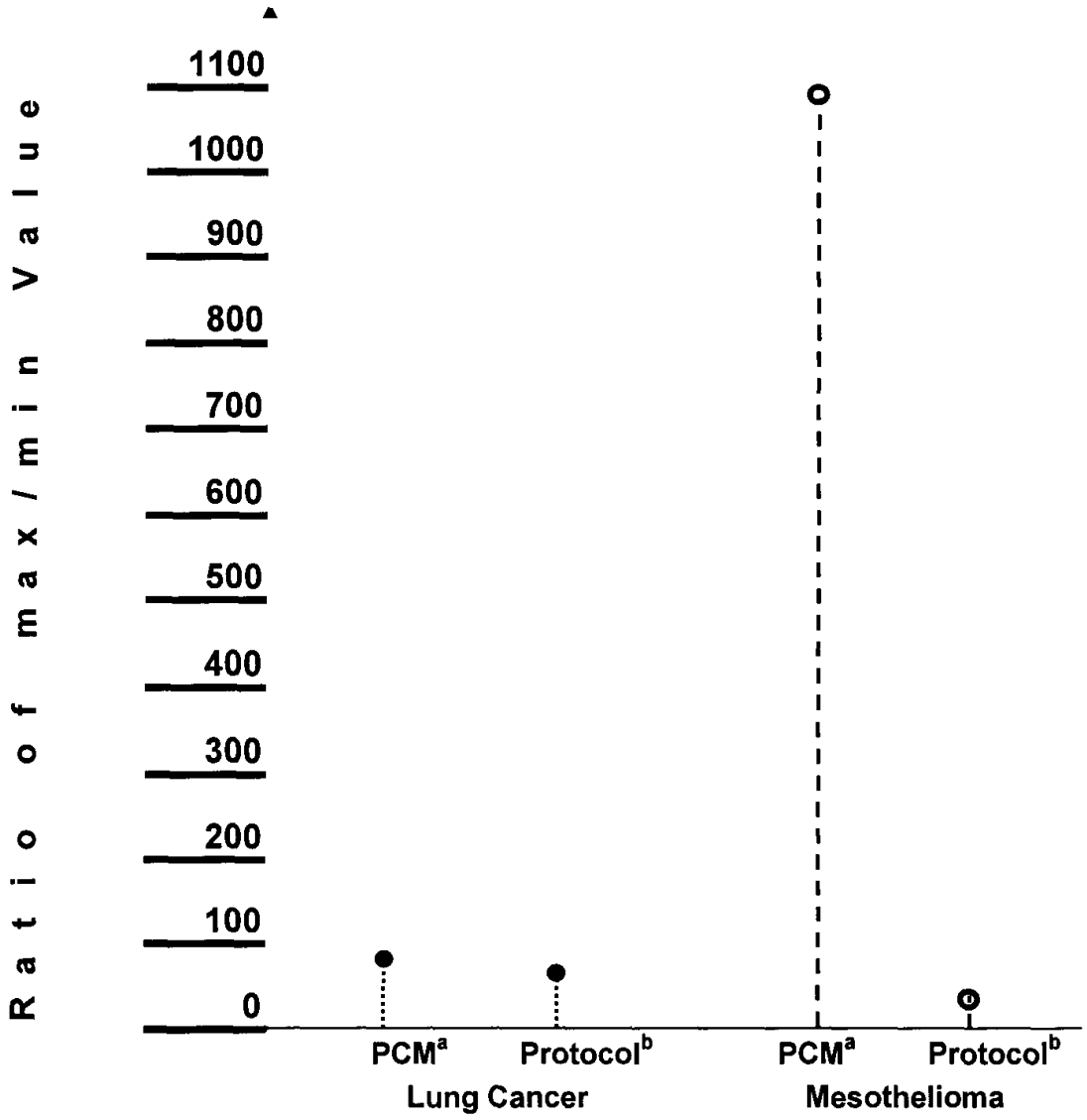
FIGURE 1:
RELATIVE RANGE OF POTENCY ESTIMATES FOR LUNG CANCER AND MESOTHELIOMA BASED ON EXISTING MODELS



Notes:

In all cases, ranges are evaluated using the studies available in 2000 with one negative study excluded.

[a] PCM with common potency for chrysotile and amphibole, as is current EPA policy.

[b] Long Protocol Structures with differing potency for chrysotile and amphibole, as in Berman and Crump (2003).

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THE ASBESTIFORM AND NONASBESTIFORM MINERAL GROWTH HABIT AND THEIR RELATIONSHIP TO CANCER STUDIES

A PICTORIAL PRESENTATION

April, 2003

The Asbestiform and Nonasbestiform Mineral Growth Habit and Their Relationship to Cancer Studies

Kelly F. Bailey, CIH
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President
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The recognition and regulation of asbestiform and nonasbestiform minerals is of critical concern to the entire mining and aggregates industry, to individuals exposed to these materials and to the economic vitality of the United States.

CONTENTS

INTRODUCTION

It has long been recognized that the inhalation of excessive asbestos fibers, over time, is associated with significant pulmonary disease in humans. The link between asbestos, lung cancer and mesothelioma is well established. Asbestos is perhaps the most feared mineral risk and certainly is among the most publicized, litigated and studied.

Despite this attention, a clear understanding of what asbestos actually is remains a source of confusion to many. This is often demonstrated when commercial asbestos is not known "a priori" to exist in a dust exposure. Nowhere is this problem better demonstrated than the decades old confusion over the difference between asbestiform and nonasbestiform crystal growth.

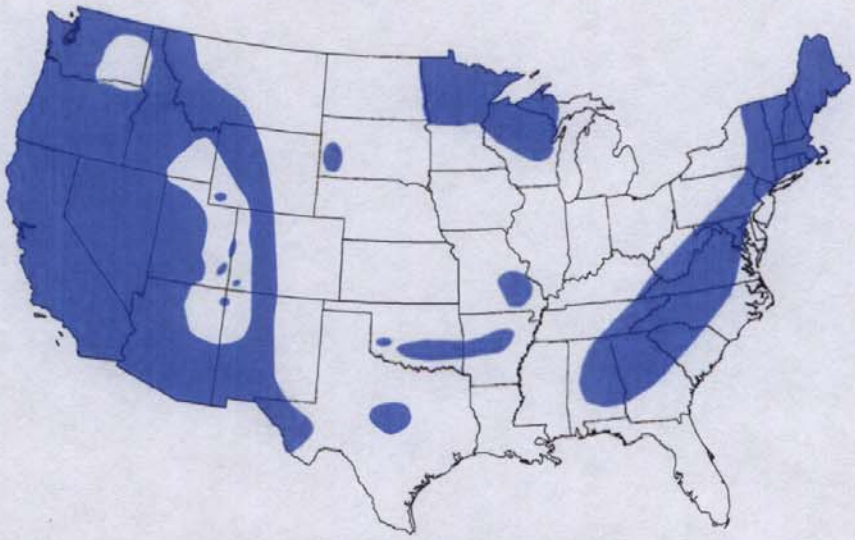
No federal regulatory agency treats elongated nonasbestiform mineral particulates as asbestos, yet some in the regulatory and health community believe that they should. These individuals mistakenly believe that the essential difference between nonasbestiform minerals and asbestos is not significant from both a mineralogic and biologic perspective.

This pictorial presentation demonstrates that important mineralogic and health differences do, in fact, exist. Health researchers who fail to understand these differences can assign and have attributed the carcinogenic effects of asbestos exposure to nonasbestiform minerals. Because these common, nonasbestiform rock-forming minerals make up so much of the earth's crust, it is important that this error be avoided.

WHY IS THIS DISTINCTION IMPORTANT?

The nonasbestiform minerals are common hard rock forming minerals found throughout the earth's crust. Unlike asbestos, they are not at all rare.

The map below shows the general areas in the continental United States where igneous and metamorphic rocks are likely to be found on or near the surface. Amphiboles and serpentine, the two mineral groups that contain mineral species that may form asbestos, are restricted in their occurrence to these types of rock. When amphiboles and serpentine form part of the bedrock, they may also be found in the overlying soil. All the rock and soil in the shaded areas, however, do not contain amphibole and serpentine, and the occurrence of the asbestiform habits of these minerals in the shaded areas is even more restricted. The shaded areas do not mean that every rock or soil mass in that area contains these minerals, but it does mean that they are often present in these areas.



igneous or metamorphic rocks (1)

The composition of the rock also affects the likelihood of finding asbestos. Asbestos is more likely to form during the metamorphism of limestone, mafic and ultramafic rocks and alkali igneous rocks than during the metamorphism of other common rocks such as granite and sandstone. Furthermore, many of the amphiboles, particularly those that contain a significant amount of aluminum, never form asbestiform fibers. Therefore, while the nonasbestiform habits of amphibole and serpentine are common throughout the shaded areas, asbestos occurrences are localized and uncommon.

The U.S. Bureau of Mines reports that the regulation of nonasbestiform minerals as asbestos would significantly impact the mining of important mineral commodities such as gold, copper, iron, crushed stone, sand, gravel and talc. Downstream users of these mineral commodities such as construction, refractories, smelters, ceramics and paint manufacturers, would be affected as well (2).

Therefore, it is important that these nonasbestiform minerals be properly assessed with respect to their health risk.

The goal of this document is to clearly and succinctly demonstrate that mineralogical and biological differences exist between asbestos and common nonasbestiform minerals. To accomplish this objective, this presentation:

- **DESCRIBES THE MINERALOGICAL DIFFERENCES BETWEEN ASBESTIFORM AND NONASBESTIFORM MINERALS.**

- **CLARIFIES THE MINERAL EXPOSURES CITED IN KEY HEALTH STUDIES.**

- **SUMMARIZES THE OUTCOME OF THIS COMPARISON.**

REFERENCE EXHIBIT 1

What is Asbestos?

In the *Glossary of Geology*, asbestos is defined as. . .

"A commercial term applied to a group of highly fibrous silicate minerals that readily separate into *long, thin, strong* fibers of sufficient flexibility to be woven. . ." (3).

This definition has been further expanded based on mineral-crystallographic studies over the last decade or so:

A. ASBESTOS - A collective mineralogic term that describes a variety of certain silicates belonging to the serpentine and amphibole mineral groups, which have crystallized in the asbestiform habit causing them to be easily separated into long, thin, flexible, strong fibers when crushed or processed. Included in the definition are: chrysotile, crocidolite, asbestiform grunerite (amosite), anthophyllite asbestos, tremolite asbestos and actinolite asbestos. The nomenclature and composition of amphibole minerals should conform with International Mineralogical Association recommendations (Leake, B.E., *Nomenclature of Amphiboles.* American Mineralogist. Vol. 82, 1019 - 1037, 1997).

B. ASBESTOS FIBERS - Asbestiform mineral fiber populations generally have the following characteristics when viewed by light microscopy:

1. Mean aspect ratios ranging from 20:1 to 100:1 or higher for fibers longer than 5 µm,
2. Very thin fibrils, usually less than 0.5 µm in width,
3. Parallel fibers occurring in bundles, and
4. One or more of the following:
   a) Fiber bundles displaying splayed ends,
   b) Matted masses of individual fibers,
   c) Fibers showing curvature

This definition represents the consensus of a group of mineral scientists, several of whom have published extensively in this area (see Appendix I).

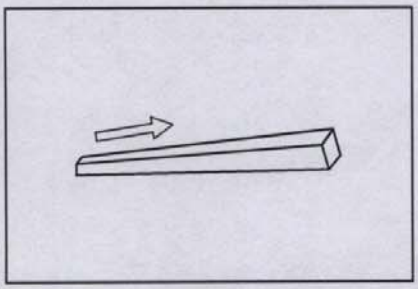
Morphological properties are difficult to apply to single particles when classifying them as a cleavage fragment or a fiber. Distinctions on morphology are most reliably made on populations. Furthermore, in air and water samples, in which particles are often less than 5 μm in length, the presence of asbestos should be verified in bulk material at the source before identification of particles as asbestos can be reliably made. Bulk materials display the full range of distinctive morphological characteristics, but in fibers collected from air and water, the range of morphological properties is more limited.

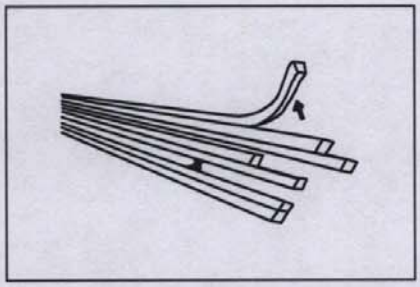
Asbestiform fibers normally exhibit anomalous optical properties that are distinctive. For example, under polarized light microscopy, asbestiform fibers may display parallel extinction in all orientations, they may display oblique extinction in some orientations at angles that are less than those characteristic of ordinary amphibole fragments in the same crystallographic orientation, they may have only two principal indices of refraction (as opposed to the expected three), or they may display orthorhombic optical properties when monoclinic optical properties are expected (79).

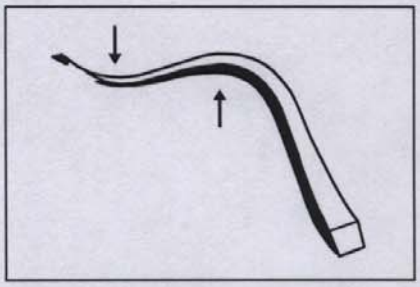
When asbestiform fibers are found in nature, there may be other habits of the same mineral intergrown such as the brittle, fibrous nonasbestiform habit byssolite and fragments of the enclosing rock (cleavage fragments). Byssolite is characterized by wide, single glassy crystals usually > 1 μm in width. While asbestos is characterized by high tensile strength which results in difficulty on grinding with a mortar and pestle, byssolite and cleavage fragments will easily reduce to powder under the same circumstances (see page 16, Reference Exhibit #5).

Although asbestiform crystal growth is very rare in nature, under the right geologic conditions approximately 100 minerals may be formed in this manner - not just the six minerals we refer to as asbestos (76). Evidence on the carcinogenicity of asbestiform minerals that are not asbestos is mixed, but there is no compelling evidence that all asbestiform minerals are carcinogenic. Different minerals have different biodurabilities, surface chemistries, friabilities in vivo, and bioavailability differences that influence their biological activities (77). Asbestiform richterite, winchite and erionite are examples of fibers that appear to pose a risk similar to that of asbestos (74,78). In contrast, asbestiform talc (72) and minerals such as xonotlite (commonly found in an asbestiform habit but is water soluble) do not appear to pose the same risk.

ASBESTIFORM







In the asbestiform habit, fibers grow almost exclusively in one direction and exhibit narrow width (on the order of 0.1 µm). Fibers that are visible to the eye are bundles of individual crystal fibers known as "fibrils". In some deposits, there is a range in fibril width, sometimes extending up to as much as 0.5 µm. Asbestiform fibers wider than 1.0 µm are always bundles of fibrils. Asbestiform minerals have fibrils that are easily separated, although variability exists. In populations of asbestiform fibers, the distribution of particle widths will reflect single fibrils as well as bundles of fibrils. Under the light microscope, this "polyfilamentous" characteristic of fibers is evident, and **is the single most important morphological characteristic of the asbestiform habit**. Asbestiform fibers are flexible and exhibit high tensile strength. The flexibility may be accounted for by the very narrow widths of fibrils and perhaps by the ability of fibrils to slide past one another on bending.

Six minerals have been regulated as asbestos. These are listed below:

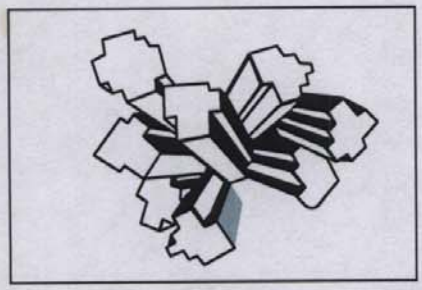
ASBESTIFORM VARIETY (Asbestos, CAS No. 1332-21-4*)	
SERPENTINE GROUP	
chrysotile	(CAS No. 12001-29-5)
AMPHIBOLE GROUP	
crocidolite	(CAS No. 12001-28-4)
grunerite asbestos (amosite)	(CAS No. 12172-73-5*)
anthophyllite asbestos	(CAS No. 77536-67-5*)
tremolite asbestos	(CAS No. 77536-68-6*)
actinolite asbestos	(CAS No. 77536-66-4*)

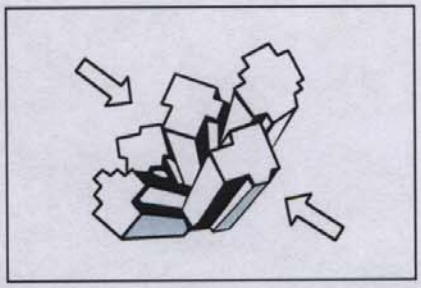
The presence of an asterisk (*) following a CAS Registry Number indicates that the registration is for a substance which CAS does not treat in its regular CA index processing as a unique chemical entity.

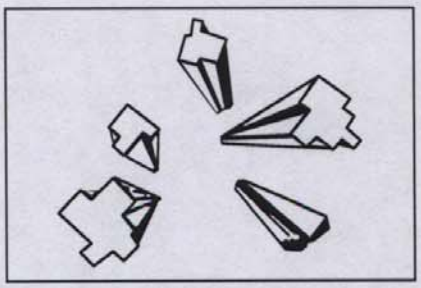
For asbestiform fibers to grow, there must be mineral rich fluids that are either associated with regional metamorphism or contact metamorphism around crystallizing igneous bodies. The vast majority of the occurrences of asbestos are small because, in addition to metamorphic fluids, there must be open spaces into which the fibers can grow, a condition restricted to the upper portions of the earth's crust in structurally specific environments such as faults, joints, the axes of folds, etc. Only rarely are large portions of a rock composed of asbestos.

The most common occurrence of asbestos is in cross-fiber or slip fiber veins. In the former, the fiber axes are perpendicular to the walls of narrow openings in the host rock; in the latter, they are parallel. Asbestos rarely occurs as mass fiber bundles in which fibrillar growth is in many directions. This growth pattern is not clearly related to planar structural features of the rock.

NONASBESTIFORM







In the nonasbestiform variety, mineral crystal growth tend not to grow with parallel alignment, but form multi-directional growth patterns instead. When pressure is applied, the crystals fracture easily, fragmenting into prismatic particles called cleavage fragments. Some particles or cleavage fragments are acicular or needle-shaped as a result of the tendency of amphibole minerals to cleave along two dimensions but not along the third. Stair-step cleavage along the edges of some particulates is common. Serpentines have a single cleavage direction and single crystals would form sheets when crushed. Serpentine rock, when crushed, will produce some elongated fragments.

Comminution of nonasbestiform amphibole produces particles that, although generally elongated, have widths larger than asbestos fibers of the same length. These wide widths are characteristic of all amphibole cleavage fragments, even those that have developed higher aspect ratios due to well-developed parting. Byssollite, the most acicular, needle-like nonasbestiform amphibole, will break perpendicular to the fiber axis during comminution because it is brittle, thereby producing particulates with low aspect ratios (See Reference Exhibit 5).

NON-ASBESTIFORM VARIETY

SERPENTINE GROUP	
antigorite	(CAS No. 12135-86-3)
AMPHIBOLE GROUP	
riebeckite	(CAS No. 17787-87-0)
grunerite	(CAS No. 14567-61-4)
anthophyllite	(CAS No. 17068-78-9)
tremolite	(CAS No. 14567-73-8)
actinolite	(CAS No. 13768-00-8)

REFERENCE EXHIBIT 2

Macroscopic Raw Ore Comparisons

Each of these six minerals included in OSHA's asbestos standard occurs in both an asbestiform and a nonasbestiform variety.

Three of the six minerals have been given a different name for each of their two forms. *Chrysotile* is the asbestiform variety of the serpentine minerals group. In this group *antigorite* is a common nonasbestiform mineral. In the amphibole group, *crocidolite* is the asbestiform variety of *riebeckite*; *amosite* is the asbestiform variety of "cummingtonite"-grunerite.

Asbestiform

Nonasbestiform

a. 
chrysotile

b. 
antigorite

c. 
crocidolite

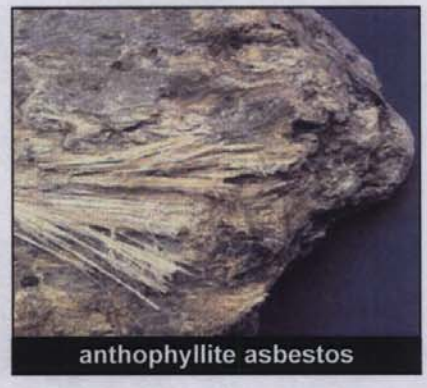
d. 
riebeckite

e. 
amosite

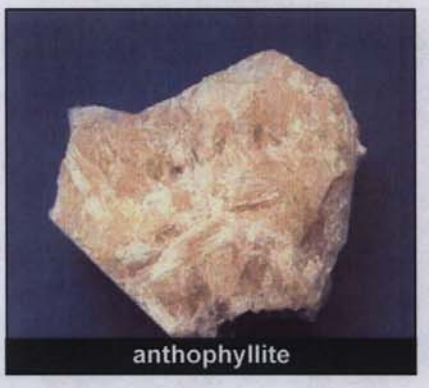
f. 
cummingtonite-grunerite

Macroscopic Raw Ore Comparisons

Asbestiform

g. 
anthophyllite asbestos

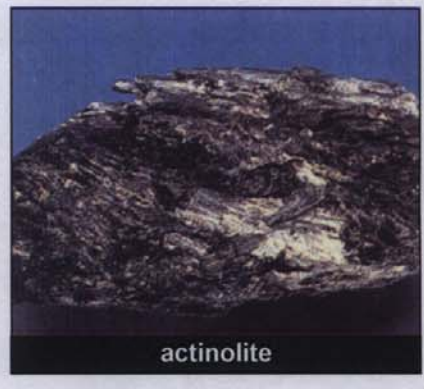
Nonasbestiform

h. 
anthophyllite

i. 
tremolite asbestos

j. 
tremolite

k. 
actinolite asbestos

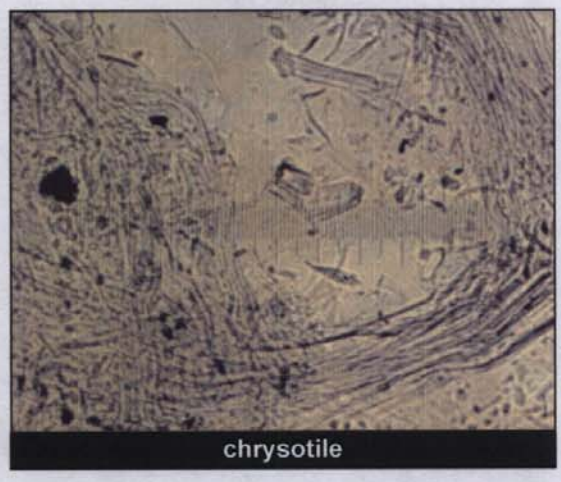
l. 
actinolite

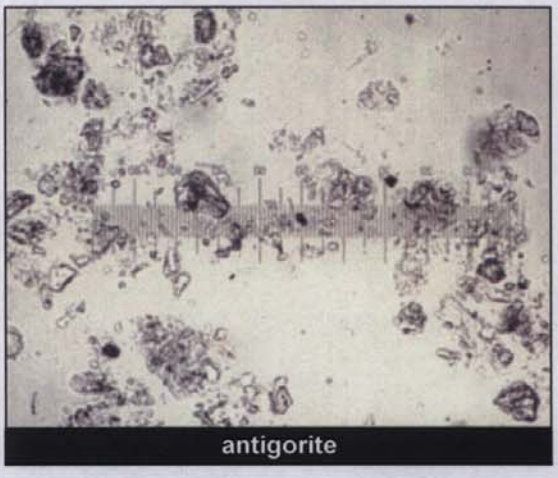
REFERENCE EXHIBIT 3

Light Microscopic Comparisons

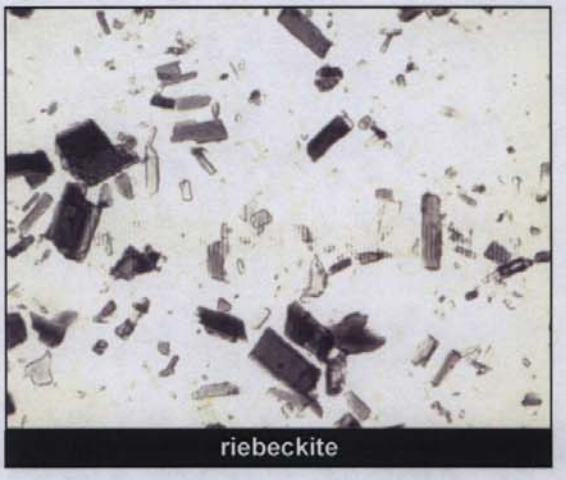
(2.75 µm/divisions)

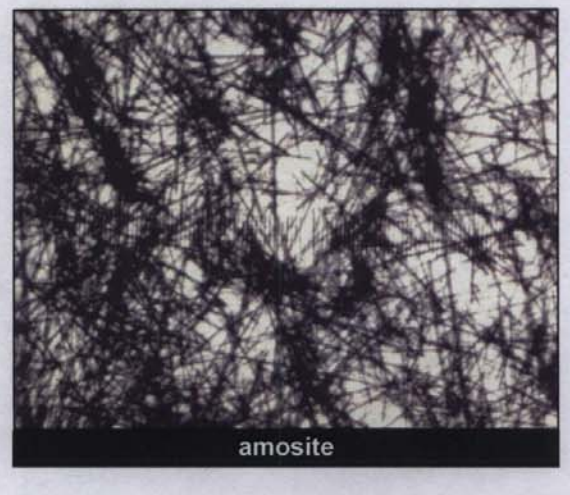
Asbestiform | **Nonasbestiform**

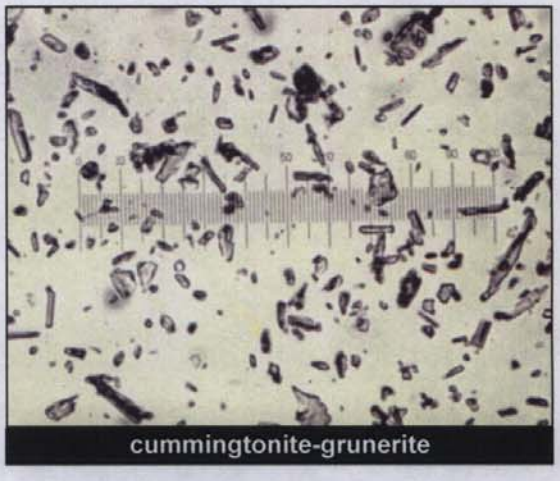
a. 
chrysotile

b. 
antigorite

c. 
crocidolite

d. 
riebeckite

e. 
amosite

f. 
cummingtonite-grunerite

(2.75 µm/divisions)

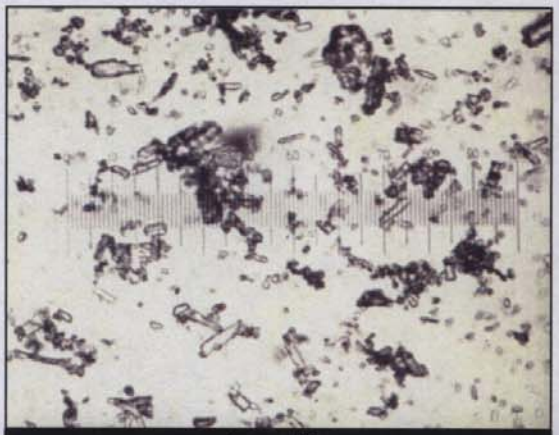
Asbestiform

g. anthophyllite asbestos

Nonasbestiform

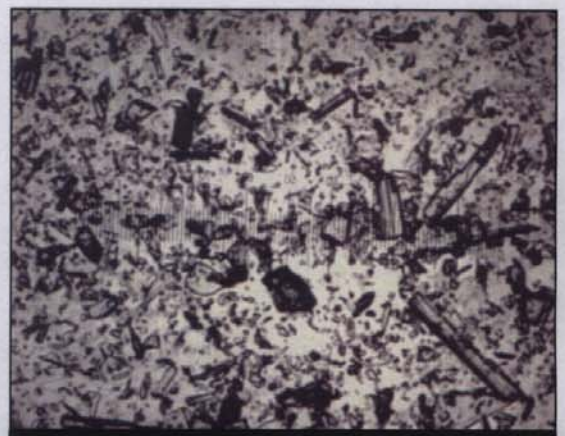
h. anthophyllite

i. tremolite asbestos



j. tremolite

k. actinolite asbestos



l. actinolite

REFERENCE EXHIBIT 4

The Aspect Ratio

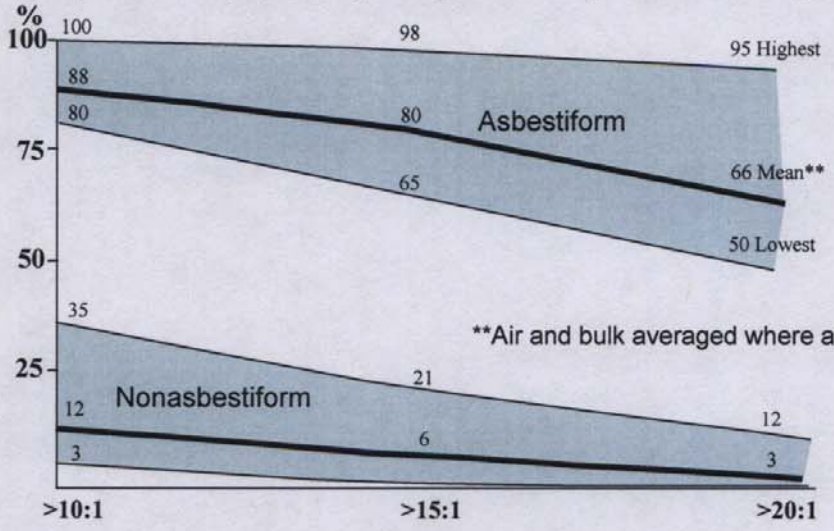
Existing regulatory standards for asbestos are based on a light microscopy analysis of airborne particles with a length-to-width ratio (aspect ratio) of 3:1 or greater and a length greater than 5 µm. This was arbitrarily set to obtain consistency among **asbestos** "fiber" counters. Unfortunately, this dimensionless parameter, adopted for asbestos quantification, has been misused by some as a means to "identify" asbestos. Since many other particles share these dimensions, it is improper to use the aspect ratio as a designator of asbestos.

However, the aspect ratio concept, when used with caution, can be useful in distinguishing the asbestiform or nonasbestiform nature of a given dust population. Due to the tendency of asbestiform fiber bundles to separate into thinner and thinner fibers when pressure is applied (i.e., ground), the aspect ratio tends to remain high. In contrast, because nonasbestiform minerals break or cleave in a more random fashion, few relatively long, thin particles are produced. Nonasbestiform dust populations will, therefore, generally retain low aspect ratio characteristics. This fundamental difference can be observed under the light microscope and used as one analytical parameter to distinguish an asbestiform dust population from a nonasbestiform dust population. It must be stressed, however, that this parameter is not a means to positively identify asbestos.

The following figure contrasts the typical aspect ratio difference between asbestiform dust populations and nonasbestiform dust populations. Starting with all particles that exceed a 3:1 aspect ratio (> 5 µm length), the asbestiform dust population maintains an elevated percentage of high aspect ratio particles while the nonasbestiform population does not.

COMPOSITE ASPECT RATIO DISTRIBUTION*
(from references 5 - 12)

*Aspect ratio for particles >5µm length and an aspect ratio of 3:1 or greater.



**Air and bulk averaged where applicable.

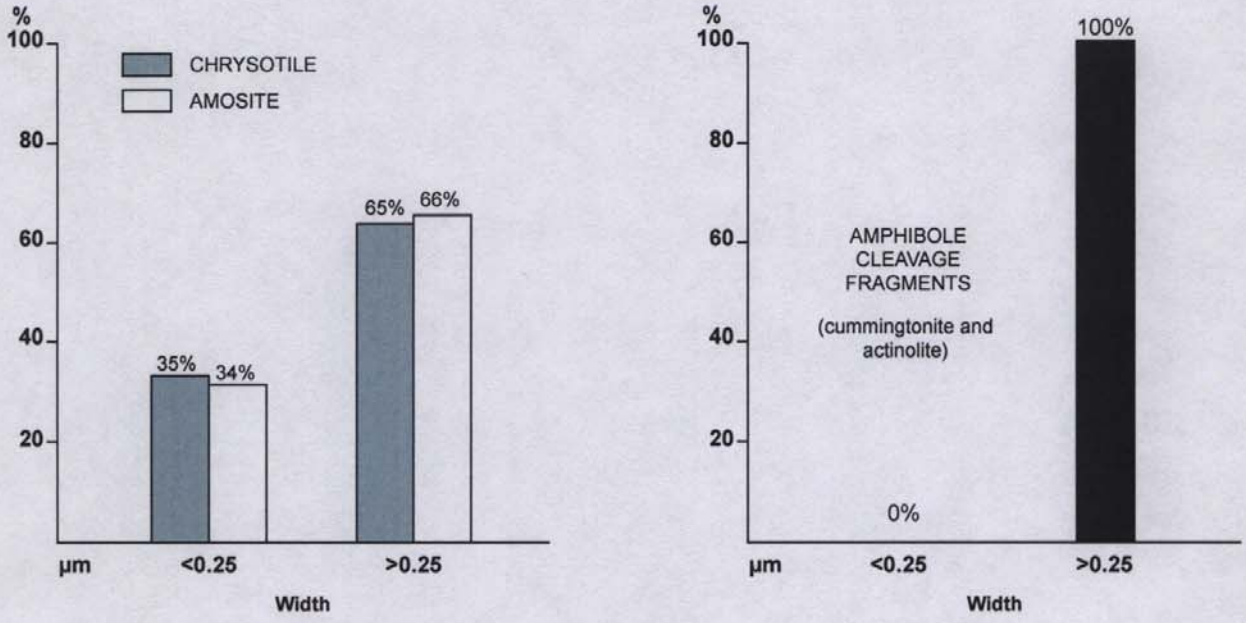
Example: Nonasbestiform particles with an aspect ratio of 3:1 or greater (> 5 µm length), 6% on average exceed an aspect ratio of 15:1 while asbestiform particles, 80% on average exceed this ratio.

Particle Width

Distinctions between populations of cleavage fragments and asbestos fibers can be drawn by comparing the frequency of widths for particles longer than 5 µm. In cleavage fragment populations, width increases with length; in asbestos populations, width is almost independent of length. Cleavage fragments are rarely less than 0.5 µm in width and almost never less than 0.25 µm. A significant fraction of asbestos fibers, however, are less than 0.25 µm in width, and most asbestos populations have at least 50% of the fibers with widths equal to or less than 0.5 µm. (75)

Since asbestos fibrils separate easily, wide fibers composed of multiple fibrils are uncommon in airborne populations or in laboratory preparations that involve dispersal in water by using ultrasound. Nonetheless, there is a slight tendency for very long fibers to be composed of more than one fibril and therefore to be slightly wider than the shorter fibers. In the examination of bulk asbestos under the light microscope, however, it is not uncommon to encounter very wide bundles since sample preparation does not involve fibrillar separation by sonication. However, the composite nature (fibrillar structure) of fibers wider than 1 µm can almost always be seen by light and electron microscopy.

Asbestos populations do vary in their fibril size, the range in fibril size, and their resistance to separation. For example, amosite fibrils are slightly wider than crocidolite fibrils and single fibrils of chrysotile have uniform widths. Nonetheless, taken as a group, the width distribution of a given dust population can be used to gauge the asbestiform or nonasbestiform nature of a mineral dust.

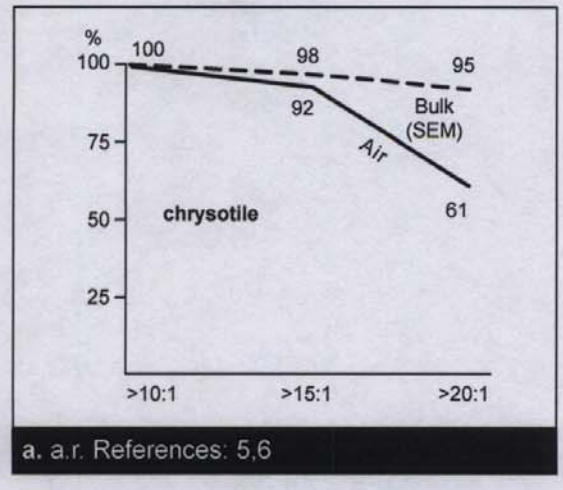


Average of 17 air samples. Width comparison by electron microscopy (STEM). All particles are 3:1 aspect ratio or greater, > 5 µm length (4).

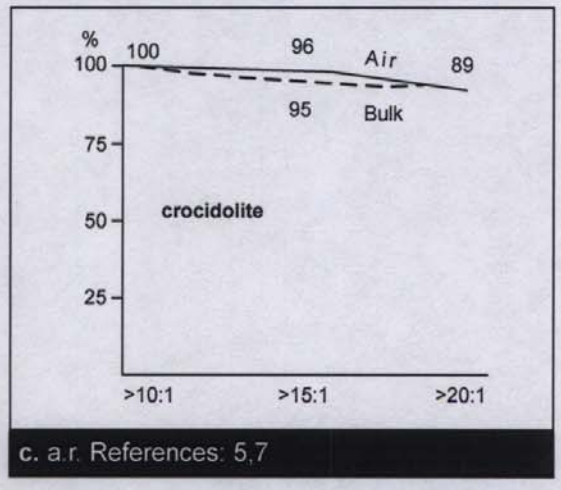
ASPECT RATIO COMPARISONS

Includes only particles with a 3:1 aspect ratio (a.r.) or greater and length > 5 µm.

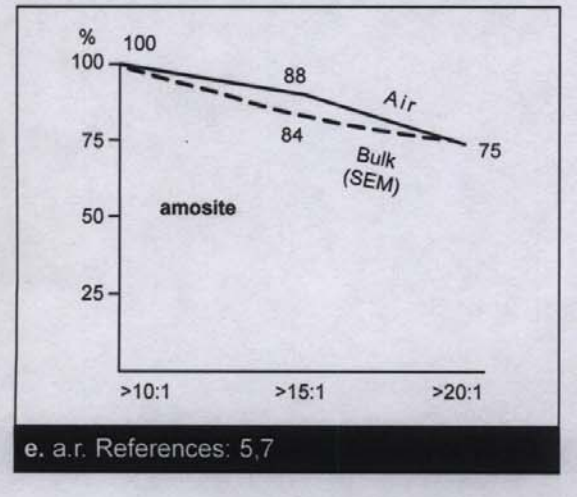
Asbestiform



a. a.r. References: 5,6

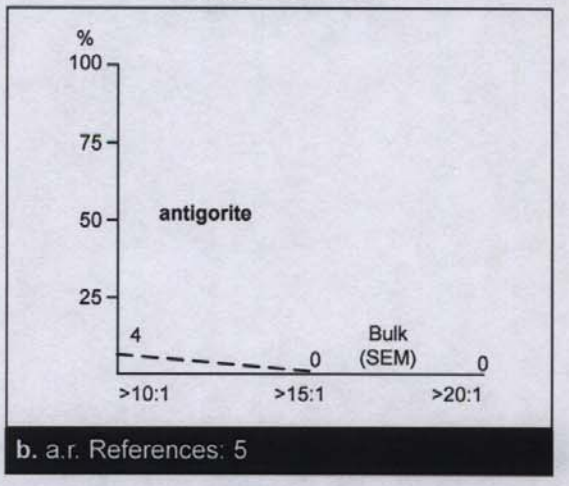


c. a.r. References: 5,7

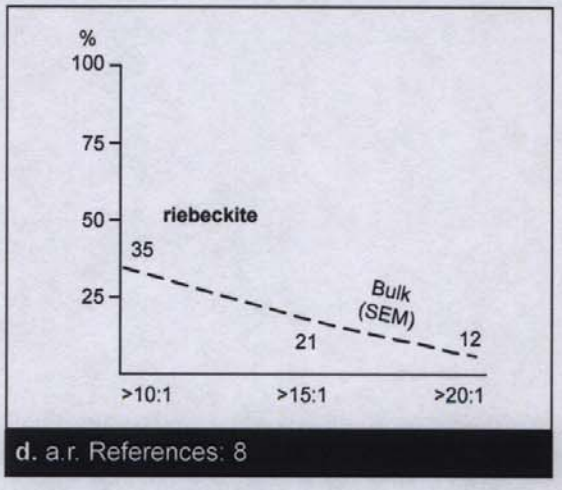


e. a.r. References: 5,7

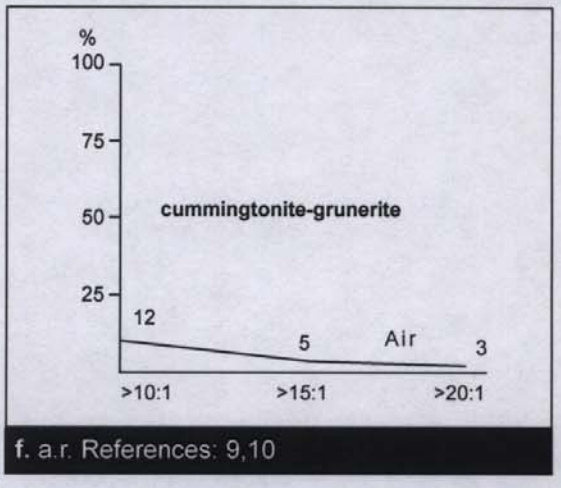
Nonasbestiform



b. a.r. References: 5

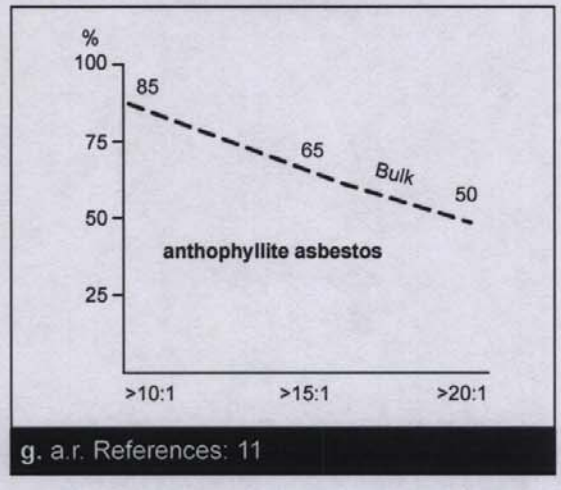


d. a.r. References: 8



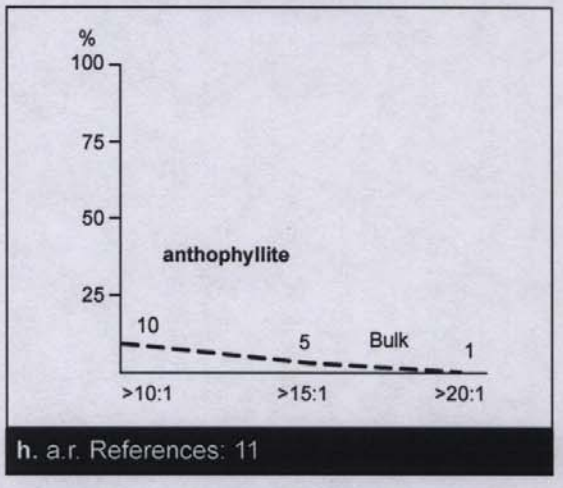
f. a.r. References: 9,10

Asbestiform

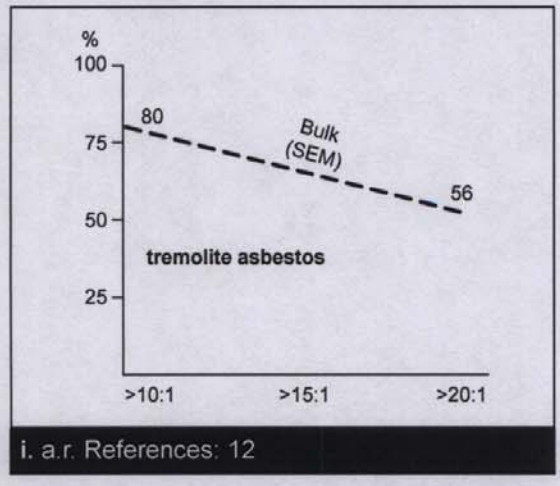


g. a.r. References: 11

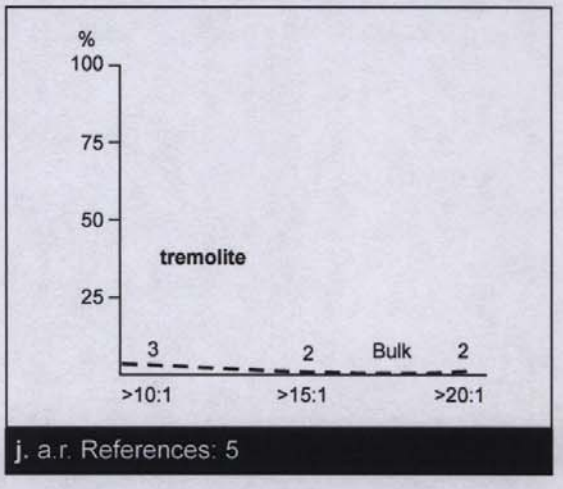
Nonasbestiform



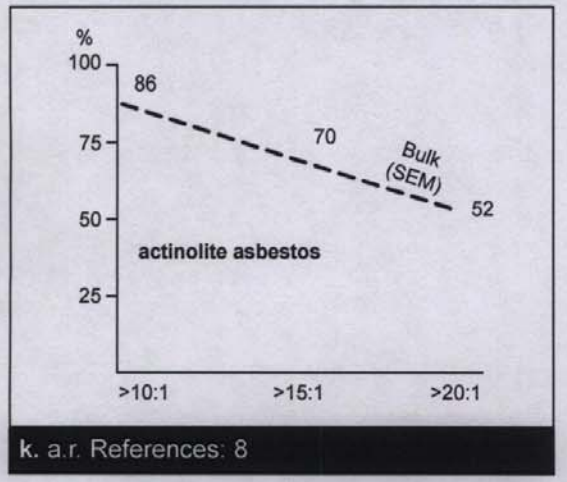
h. a.r. References: 11



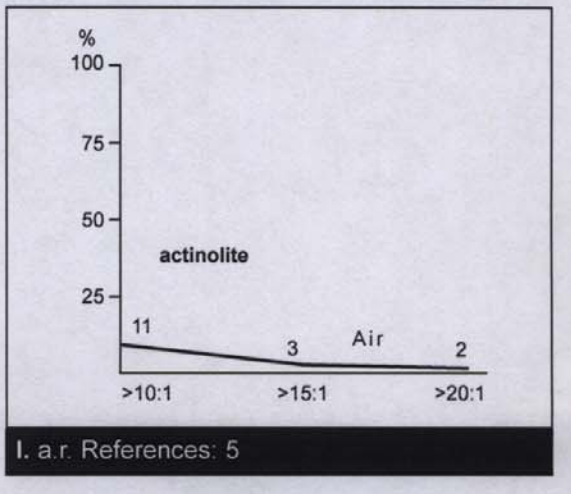
i. a.r. References: 12



j. a.r. References: 5



k. a.r. References: 8



l. a.r. References: 5

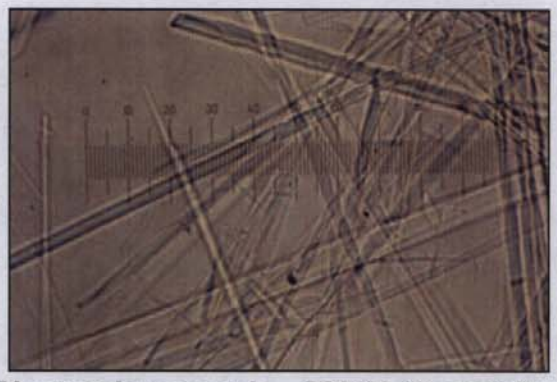
REFERENCE EXHIBIT 5

Byssolite
Unusual Needle-like Nonasbestiform Mineral Growth

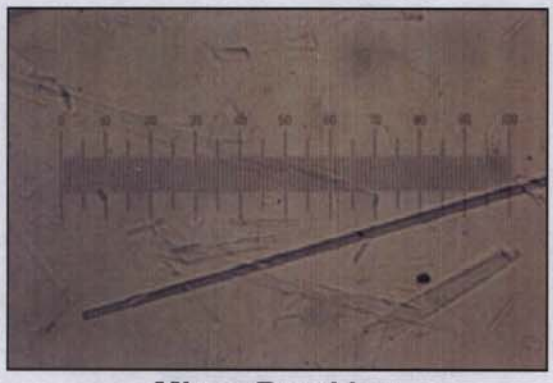
Although most nonasbestiform particulates appear as described and pictured in prior exhibits, nonasbestiform particles can appear in a very acicular or needle-like form. Although such particles do not exhibit characteristics unique to asbestos (fibrillar bundling, splayed terminations, extreme lengths, etc.), high length to width aspect ratios are possible. The Addison Italian and Dornie tremolite samples summarized in this pictorial exhibit (J and P respectively) reflect this rare particulate form. Byssolites, whose optical properties are often normal, sometimes exhibit their own distinctive optical property - a lack of optical extinction when oriented and viewed on the 010 crystallographic surface (79). This distinction, as well as a lack of other asbestiform morphological properties, allows one to distinguish the byssolite habit from the asbestiform habit.

Further comminution of these elongated nonasbestiform particles, as illustrated to the right, demonstrates the essential difference in mineral habit. Nonasbestiform minerals cleave to shorter prismatic particles, while asbestos continues to separate along crystal surfaces into smaller and smaller bundles of fibrils.

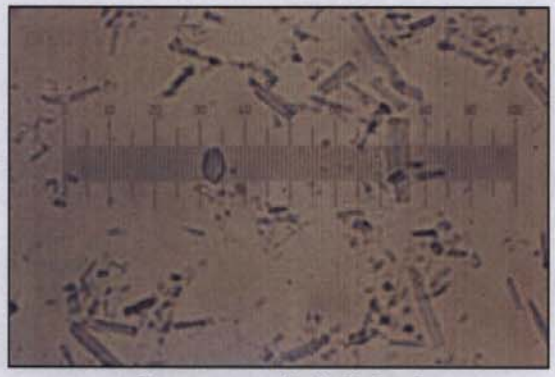
Comminution of Byssolite



Photomicrograph - 265 X (2 µm/Div.)



Minor Breaking
Photomicrograph - 265 X (2 µm/Div.)



Commercial Grind
Photomicrograph - 265 X (2 µm/Div.)

QUESTION

DOES THIS MINERALOGICAL (MORPHOLOGICAL) DIFFERENCE = BIOLOGICAL DIFFERENCE?

A Review of Asbestiform and Nonasbestiform Cancer Studies

The following "EXPOSURE EXHIBITS" summarize human and animal studies relative to nonasbestiform amphiboles. The majority of studies available in this area involve tremolite.

A large body of literature amply addresses the most commonly encountered, commercially exploited asbestos minerals (*chrysotile*, *crocidolite*, and *amosite*). For the purpose of this presentation, further health review of these asbestos minerals is not considered necessary.

These asbestiform exhibits sufficiently demonstrate previously described mineralogical distinctions and provide the most appropriate contrast to nonasbestiform amphibole health studies.

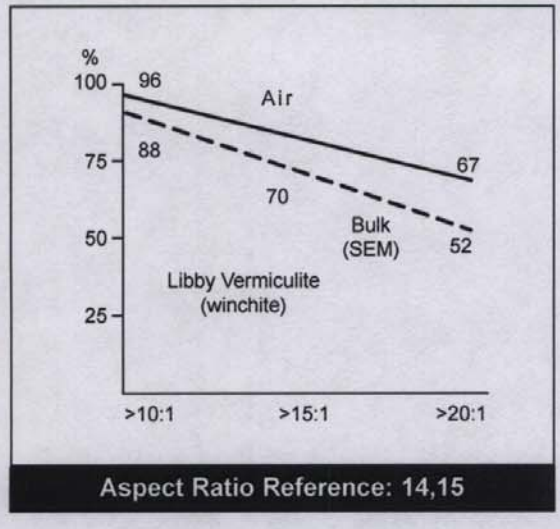
EXPOSURE EXHIBIT A *LIBBY MONTANA VERMICULITE*

Asbestiform Winchite — Human Mortality Study

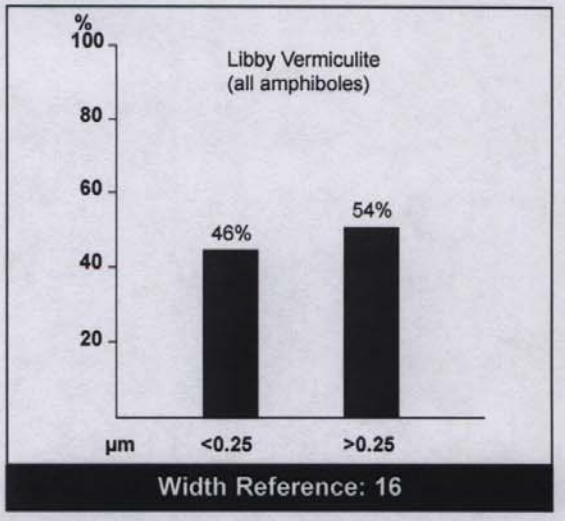
Light Microscopy: 320 X

SEM: 1180 X

ORE: "The vermiculite ore as fed to the mill contained 4-6% amphibole in the tremolite series" (13). More recent analysis of the Libby ore reports the asbestiform amphibole to be winchite asbestos (formally called soda tremolite) (74).



Aspect Ratio Reference: 14,15



Width Reference: 16

ADDITIONAL MINERAL PARTICLE DATA:

Range of: Diameters = 0.1 - 0.2 µm
Length = 1 - 70 µm (62% > 5 µm)
Aspect Ratio = 3:1 - 100:1 (13)

For fibers > 0.45 µm in width and > 5 µm in length, collected on air filters, 96% had aspect ratios > 10:1, 67% had 20:1 or greater aspect ratios and 10% were 50:1 or greater. (15)

HEALTH STUDIES:

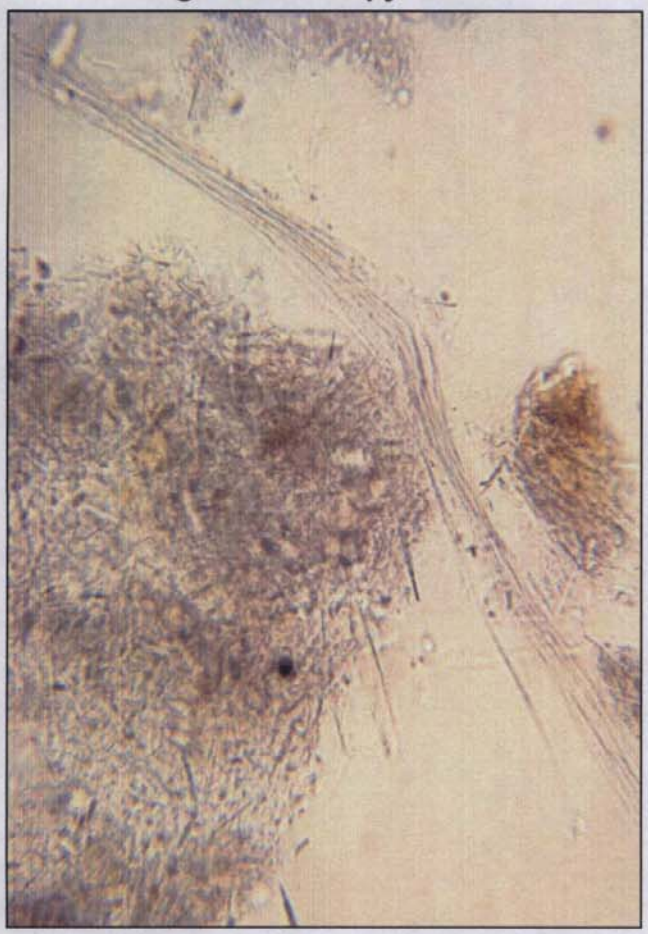
Authors: McDonald, J.C., et al (13) Pub. 1986
Cohort: 406 men, >1 yr. exposure, hired prior to 1963
Vital Status Cut Off: July 1, 1983 **SMR** (resp. cancer) - 245
Conclusion: "The cohort studied was not large but sufficient to show that workers in this mine experienced a serious hazard from lung cancer, pneumoconiosis, and mesothelioma."

Authors: Amandus, H.E., et al (15) Pub. 1987
Cohort: 575 men, >1 yr. exposure, hired prior to 1970
Vital Status Cut Off: December 31, 1981 **SMR** (resp. cancer) - 223
Conclusion: "Results indicated that mortality from nonmalignant respiratory disease and lung cancer was significantly increased."

OVERALL CONCLUSION: **Asbestiform winchite in this mining operation is reasonably linked to excess lung cancer and mesothelioma.**

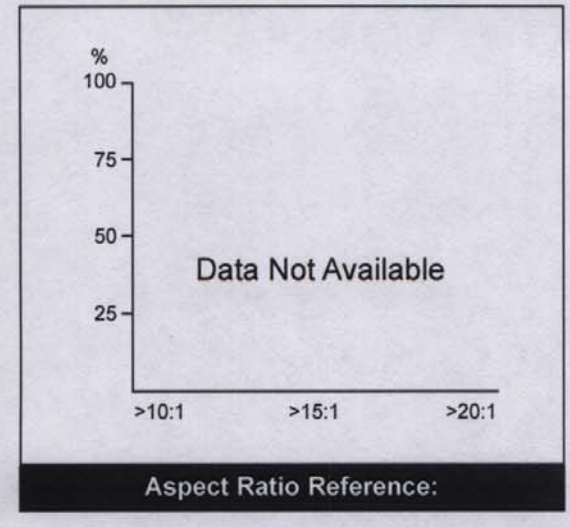
Asbestiform Tremolite — Human Mortality Study

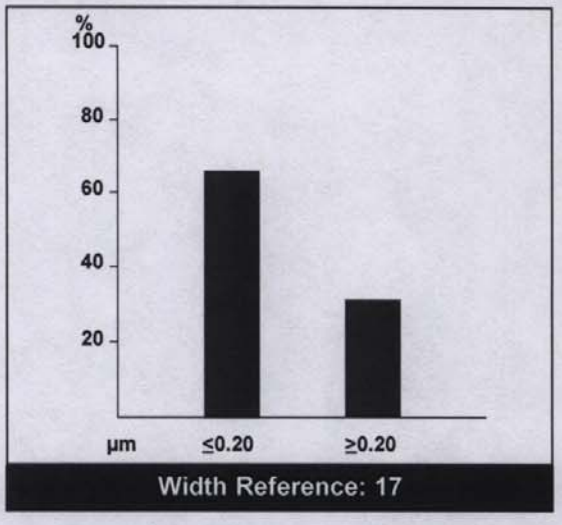
Light Microscopy: 320 X



SEM: 1900X

ORE: "This tremolite is linked to whitewash used in Greek villages. The villages involved Milea, Metsovo, Anilio and Votonosi (Metsovo area in North Western Greece)" (18).





ADDITIONAL MINERAL PARTICLE DATA:

"These fine fibers were unlike the usual tremolite laths, they had aspect ratios in excess of 100:1; they were curvilinear; they had parallel extinction, and they formed polyfilamentous bundles of fibers" (18). Only 6.7% of fibers exceeded a 0.61 µm width. Fifty-three percent of all fibers were < 1.0 µm in length while 6% exceeded 5 µm in length (17).

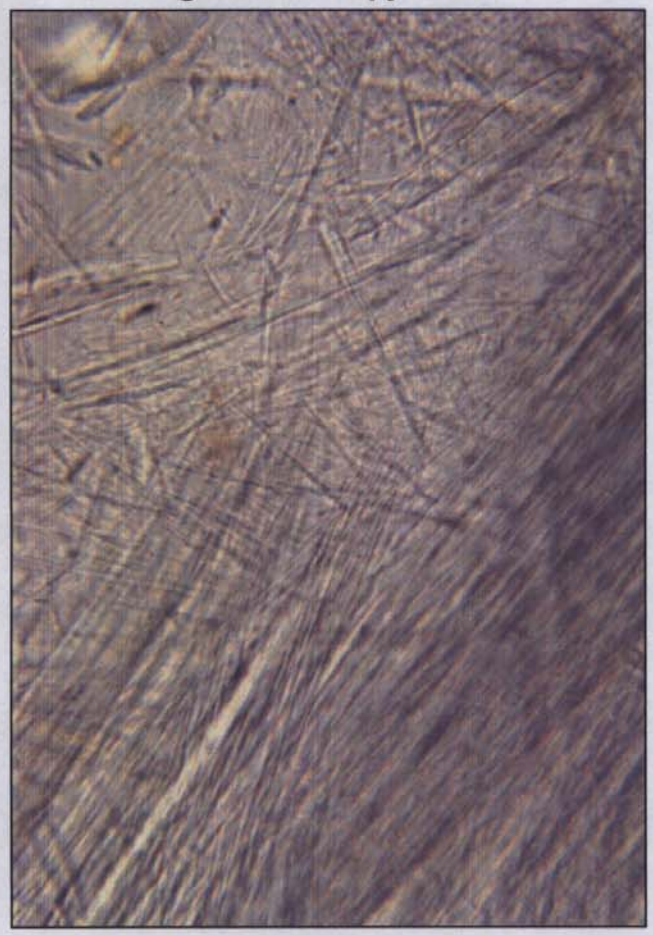
HEALTH STUDIES:

Authors: Langer, A.M., et al (18) Pub. 1987
Cohort: Population of Metsovo in Northwestern Greece
Conclusion: Substantial incidence of mesothelioma in certain towns is linked to tremolite asbestos found in whitewash and stucco.

OVERALL CONCLUSION: **Asbestiform tremolite in whitewash has been linked to substantial incidences of mesothelioma.**

Asbestiform Tremolite — Animal Study

Light Microscopy: 320 X

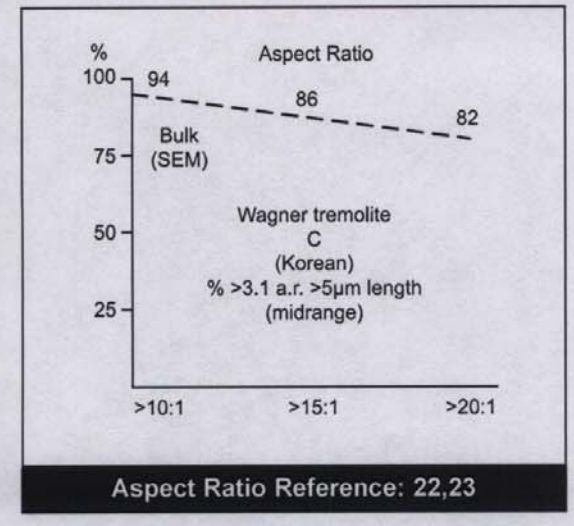


SEM: 1900 X

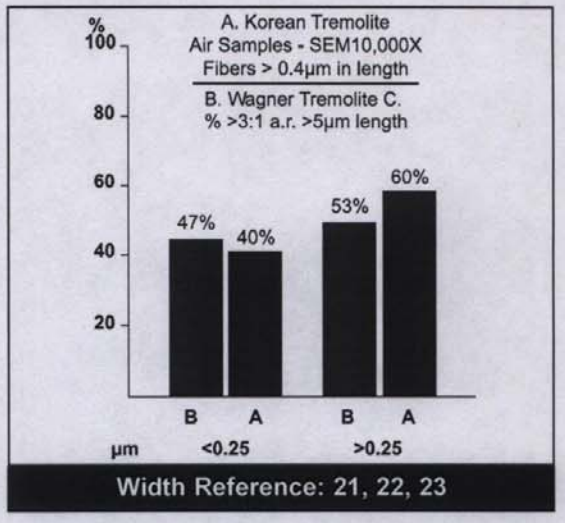
SAMPLE: Reported as commercial asbestos originating from S. Korea. Contains by mass approx. 95% asbestiform tremolite. It is reported this same material was used in three separate animal studies (19).

ADDITIONAL MINERAL PARTICLE INFORMATION

"In the optical microscopy and SEM examinations, the asbestos tremolites were found to be typical of that form in displaying polyfilamentous fiber bundles, curved fibers, fibers with splayed ends, and long, thin, parallel-sided fibers. Most of the fibers showed straight extinction when observed with polarized light under crossed polarizers, indicating the presence of multiple twinning of the crystals." "Samples did contain some elongated fragments of tremolite with oblique extinction, stepped ends, and nonparallel sides indicating that they were cleavage fragments." (20)



Aspect Ratio Reference: 22,23



Width Reference: 21, 22, 23

ANIMAL STUDIES:

Authors: Wagner, J.C., et al (22) Pub. 1982
Test Animals: Sprague-Dawley rats, 6-10 weeks old when injected.
Test Type: Pleural injection
Protocol: A single 20 milligram injection into the right pleural cavity of 48 rats. "The sample was prepared by milling in a small agate mill and ultrasonic dispersion, large particles being removed by sedimentation in water."
Findings: "Sample C produced 14 mesotheliomas in 47 rats."

Authors: Davis, J.M., et al (21) Pub. 1985
Test Animals: SPF male Wistar rats
Test Type: Inhalation and interperitoneal injection
Protocol: For inhalation, 48 rats were exposed for 7 hours each day, 5 days per week, over a 12 month period, to approx. 10 mg of respirable dust per cubic meter of air. For interperitoneal injection, a 25 mg dose of tremolite was collected from the inhalation chamber and injected (in saline) into the peritoneal cavities of rats.
Findings: For the inhalation study, a total of 16 carcinomas and 2 mesotheliomas occurred in 39 animals. None were observed in controls. For the interperitoneal study, a total of 27 animals out of 29 examined were found to have mesothelioma tumors. Mean survival time was 352 days.

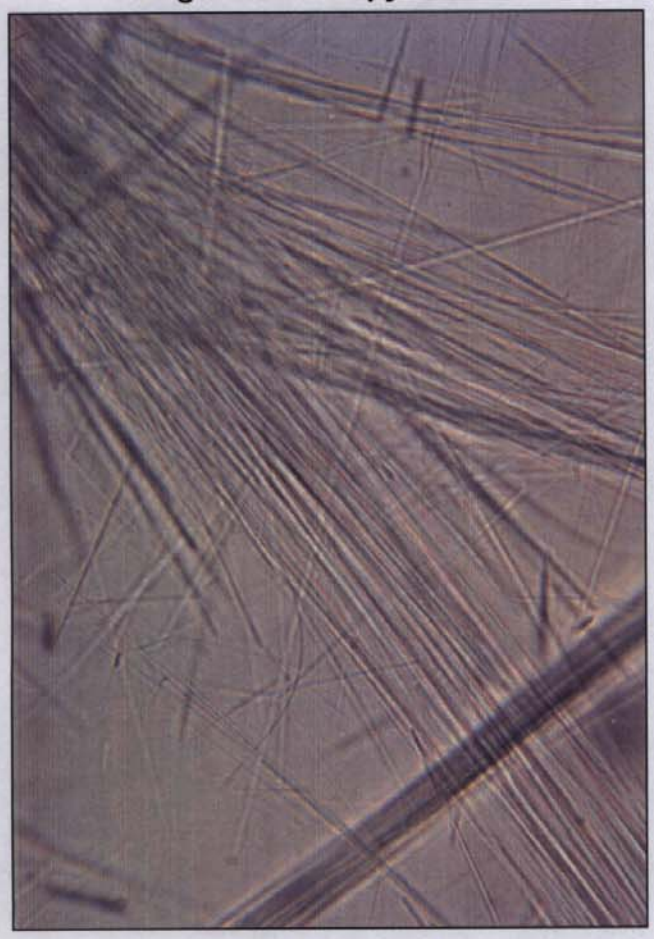
Authors: Davis, J.M.G., Addison, J. (20) Pub. 1991
Test Animals: AF/Han strain rats
Test Type: Peritoneal injection
Protocol: Fractions of this sample were obtained by generating an airborne dust cloud in an experimental chamber (Timbrell dust dispensers) with fine fractions collected using a vertical elutriator. A single 10 mg dose was injected into the peritoneal cavities of the animals. All animals lived out of their full life span or were killed when moribund.
Findings: 32 mesothelioma deaths out of 33 animals were observed with a median survival time of 428 days.

OVERALL CONCLUSION: **This asbestiform tremolite produced a strong carcinogenic response in the test animals.**

EXPOSURE EXHIBIT D *ADDISON/DAVIS-TREMOLITE (Jamestown)*

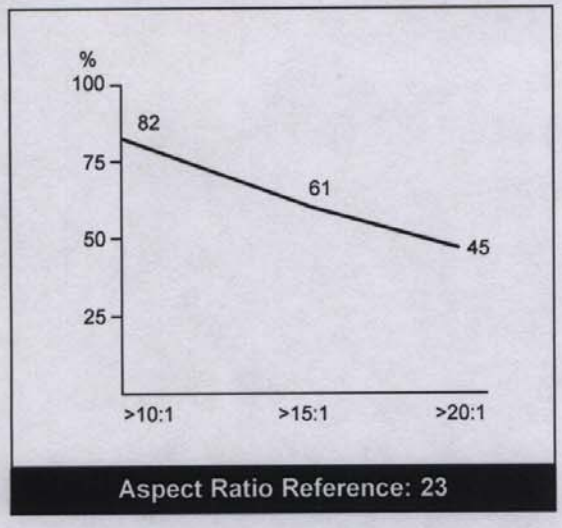
Asbestiform Tremolite — Animal Study

Light Microscopy: 320 X

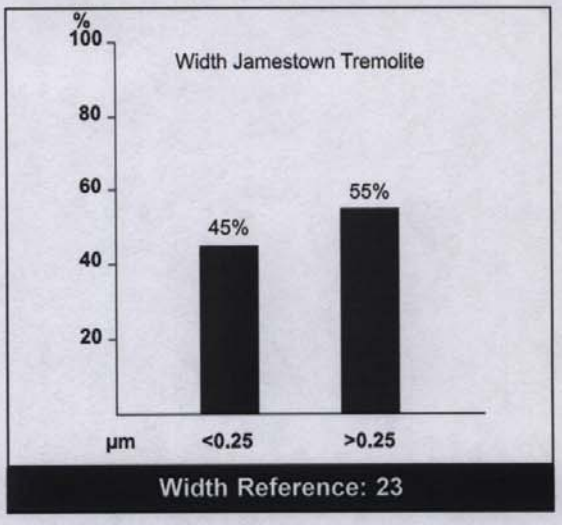


SEM: 1900 X

SAMPLE: "Fine white tremolite asbestos, Jamestown, California" (20). (Above photomicrographs were taken from bulk material.)



Aspect Ratio Reference: 23



Width Reference: 23

ADDITIONAL MINERAL PARTICLE DATA:

"In the optical microscopy and SEM examinations, the asbestos tremolites were found to be typical of that form in displaying polyfilamentous fiber bundles, curved fibers, fibers with splayed ends, and long, thin, parallel-sided fibers. Most of the fibers showed straight extinction when observed with polarized light under crossed polarizers, indicating the presence of multiple twinning of the crystals." "Samples did contain some elongated fragments of tremolite with oblique extinction, stepped ends, and nonparallel sides indicating that they were cleavage fragments." (20)

ANIMAL STUDIES

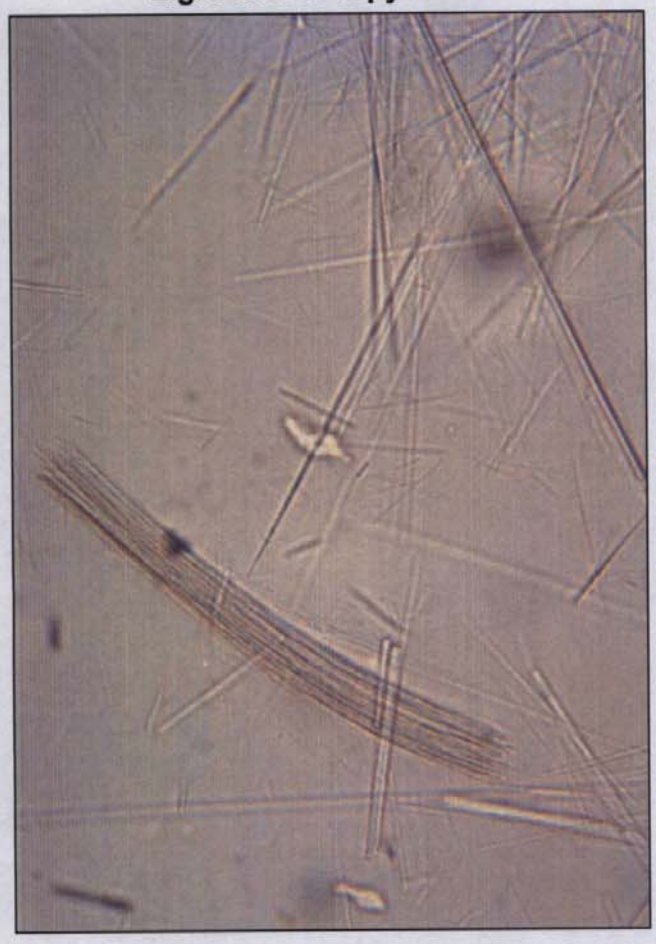
Authors: Davis, J.M.G., Addison, J. (20) Pub. 1991
Test Animals: AF/Han strain rats
Test Type: Peritoneal injection
Protocol: Fractions of this sample were obtained by generating an airborne dust cloud in an experimental chamber (Timbrell dust dispensers) with fine fractions collected using a vertical elutriator. A single 10 mg dose was injected into the peritoneal cavities of the animals. All animals lived out of their full life span or were killed when moribund.
Findings: 36 mesothelioma deaths out of 36 animals were observed with a median survival time of 301 days.

OVERALL CONCLUSION: **This asbestiform tremolite produced a strong carcinogenic response in the test animals.**

EXPOSURE EXHIBIT E *ADDISON/DAVIS-TREMOLITE (Swansea)*

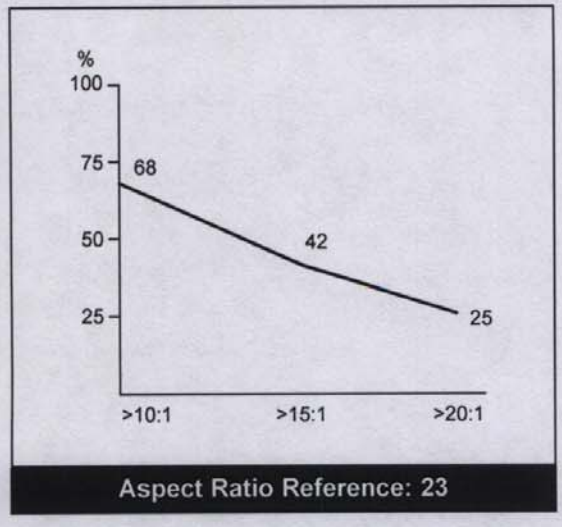
Asbestiform Tremolite — Animal Study

Light Microscopy: 320 X

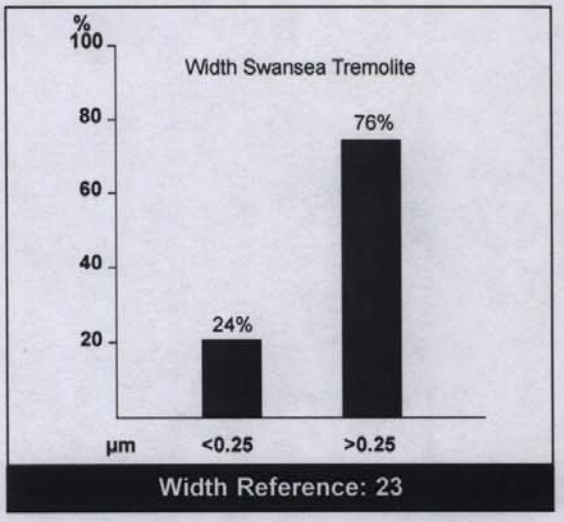


SEM: 1900 X

SAMPLE: "Fine white tremolite asbestos, Swansea Laboratory" (20). (Above photomicrographs were taken from bulk material.)



Aspect Ratio Reference: 23



Width Reference: 23

ADDITIONAL MINERAL PARTICLE DATA:

"In the optical microscopy and SEM examinations, the asbestos tremolites were found to be typical of that form in displaying polyfilamentous fiber bundles, curved fibers, fibers with splayed ends, and long, thin, parallel-sided fibers. Most of the fibers showed straight extinction when observed with polarized light under crossed polarizers, indicating the presence of multiple twinning of the crystals." "Samples did contain some elongated fragments of tremolite with oblique extinction, stepped ends, and nonparallel sides indicating that they were cleavage fragments." (20)

ANIMAL STUDIES

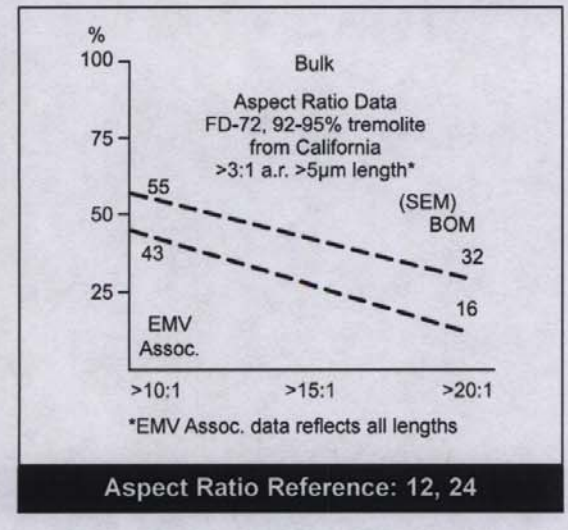
Authors: Davis, J.M.G., Addison, J. (20) Pub. 1991
Test Animals: AF/Han strain rats
Test Type: Peritoneal injection
Protocol: Fractions of this sample were obtained by generating an airborne dust cloud in an experimental chamber (Timbrell dust dispensers) with fine fractions collected using a vertical elutriator. A single 10 mg dose was injected into the peritoneal cavities of the animals. All animals lived out of their full life span or were killed when moribund.
Findings: 35 mesothelioma deaths out of 36 animals were observed with a median survival time of 365 days.

OVERALL CONCLUSION: **This asbestiform tremolite produced a strong carcinogenic response in the test animals.**

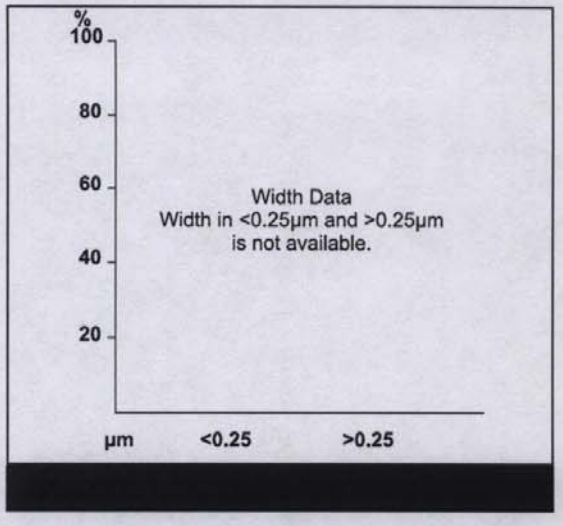
Asbestiform Tremolite — Animal Study

SEM: 1250 X

SAMPLE: FD-72 was supplied to Dr. Smith from Dr. Merle Stanton and indirectly from Johns-Manville. This material, reportedly from California, is described as asbestiform and may have been used by Dr. Stanton in his work (tremolite 1 and 2).



Aspect Ratio Reference: 12, 24



ADDITIONAL MINERAL PARTICLE DATA:

The sample preparation of FD-72 is unclear, although a portion of this sample was provided to the Bureau of Mines (BOM) for characterization. The sample was dispersed in water, ultrasonically agitated and filtered through a nucleopore filter for SEM preparation. Petrographic preparation required no such processing. There is some question as to how exact the BOM samples are to Dr. Smith's analysis (EMV Assoc), but major differences are not indicated. For FD-72, 9 particles with a length of >10 µm were observed in 200 total particles by SEM.

ANIMAL STUDIES

Authors: Smith, W.E., et al (25) Pub. 1979
Test Animals: Male LUG: LAK hamsters, injected at 2 months of age.
Test Type: Intrapleural injection
Protocol: Single intrapleural injection of two dosages (10 and 25 mg). The sample was suspended in saline and sterilized by autoclave. The occurrence of tumors (unspecified) was noted at necropsies for a starting group of 50 animals per dose. After short-term sacrifice of some animals and the loss of others through acute enteritis, the occurrence of tumors was noted in nonsurvivors up to 600 days.
Findings: Four tumors out of 13 animals were found at the 10 mg dose, and 13 out of 20 animals were found at the 25 mg dose.

OVERALL CONCLUSION: **Asbestiform tremolite produced pleural tumors.**

Asbestiform Tremolite — Animal Study

Light Microscopy: 320 X

SEM: 1800 X

SAMPLE: The exact origin of this tremolite asbestos from California, provided to Dr. Stanton by Johns-Manville, is unknown (26). "Both of these samples were from the same lot of asbestos and were in the optimal range of size for carcinogenesis" (27).

Aspect Ratio and Width Data

Aspect ratio and width data has not been developed due to concerns over the reliability of transcribing data presented in the literature (28). These difficulties result from questions over the accuracy (reproducibility) of size distribution data (especially for asbestiform samples — see discussion below). Size-data, however, does reflect a broad size distribution with many very long and very narrow fibers (i.e., < 0.25 width, > 20:1 aspect ratios).

ADDITIONAL MINERAL PARTICLE DATA:

Obtaining accurate dimensional data for these tremolite samples was difficult as reported by the investigators on page 965 of their report: "Of special interest are the data on the amphibole asbestoses: amosite, tremolite and crocidolite, though estimates of the dimensions of the asbestoses are especially liable to error." And on page 973: "In preparations of amphibole asbestos (which included the crocidolites and tremolites), we observed that both clumping and fragmentation of the particles were greater than those in other minerals, and estimates of particle size distribution in that the asbestiform characteristic of fiber bundles (reported as clumping), and the splitting of these bundles (reported as fragmentation), was the reason for the difficulty in obtaining accurate fiber size distributions.

ANIMAL STUDIES

Authors: Stanton, M.F., et al. (27) Pub. 1981
Test Animals: 20-week-old, outbred female Osborne-Mendal rats
Test Type: Pleural implantation
Protocol: A standard 40 mg dose of each tremolite asbestos sample was uniformly dispersed in hardened gelatin and applied by open thoracotomy directed to the left pleural surface. The animals were followed for 2 years, at which time the survivors were sacrificed and the tissue examined for pleural sarcomas.
Findings: Exposure to these tremolite asbestos samples resulted in tumor incidences in 22 out of 28 animals for Sample 1 and 21 out of 28 animals in Sample 2.

OVERALL CONCLUSION: **These asbestiform tremolites resulted in a significant carcinogenic response in the study population.**

EXPOSURE EXHIBIT H — *COOK/COFFIN — FERROACTINOLITE*

Asbestiform Ferroactinolite — Animal Study

Light Microscopy: 400 X

SEM: 200 X

SAMPLE: "Test fibers were prepared from loose surface iron-formation rocks" (29).

NOTE: Although the reference photo-micrograph reflects actinolite asbestos, ferroactinolite is not a designated asbestos mineral. It appears, however, to be asbestiform.

Ferroactinolite Prior to Placement in the Animals			
	Mean	Median	Range
Length	3.18	1.50	0.3 - 52.3
Width	0.41	0.24	0.03 - 5.23
Aspect Ratio	9.0	6.0	3.0 - 130.0

Ferroactinolite After Placement in the Animals			
	Mean After		
	1 Month	4 Months	12 Months
Length	2.10	2.00	1.77
Width	0.19	0.17	0.11
Aspect Ratio	17.1	22.3	30.1

ADDITIONAL MINERAL PARTICLE DATA:

"The estimated mineral particle content by volume was as follows: ferroactinolite fibers (50%), sheet silicate plates (20%), magnetite (5%), ferroactinolite and hornblende fragments (20%), and other minerals (5%)" (29). "Examination by transmission electron microscopy of low temperature ashed whole lung specimens of animals killed sequentially, indicated that the mineralogical characteristics of both ferroactinolite and amosite fibers changed in time. Longitudinal splitting of the fibers resulted in a greater number of thinner fibers with increased aspect ratio." "The ferroactinolite splitting reaction is more rapid and results in the formation of thinner and more numerous fibers than the amosite splitting reaction" (30).

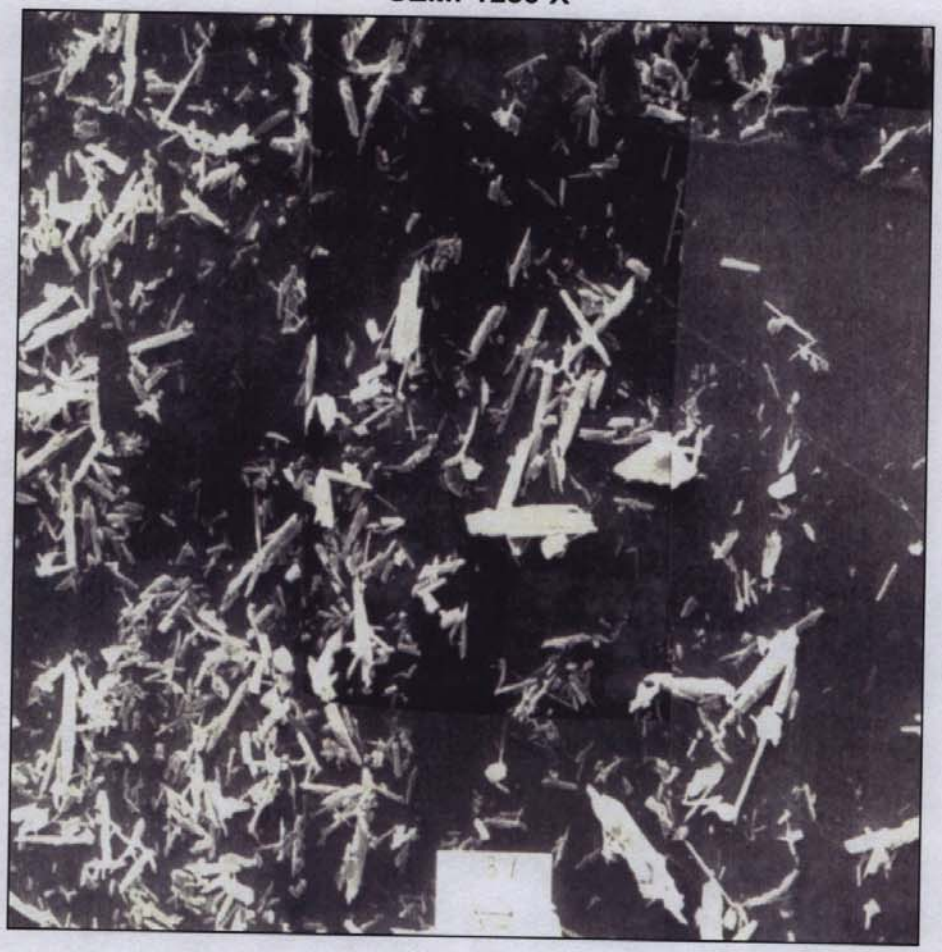
ANIMAL STUDIES

Authors: Cook, P.M., Coffin, D.L., et al (29-30) 1982
Test Animals: Male Fischer - 344 rats
Test Type: Intratracheal instillation and intrapleural injection
Protocol: The intratracheal instillation experiment involved twelve week injections of 0.5 and 0.25 mg each in groups of 561 and 139 rats (ferroactinolite and amosite, respectively). For study of early pathological sequences and for the evaluation of clearance and fate of mineral fibers by electron microscopy, the animals were killed at various intervals up to 1 year, while others were allowed to live out their lives. The intrapleural injection experiment involved a single injection of 20 mg in groups of 135 and 137 rats. Animals were allowed to live out their lives.
Findings: "The data demonstrates that ferroactinolite produced neoplastic lesions through both routes of inoculation. On the basis of mass dose by intratracheal instillation on cogenic potency, it was greater for the ferroactinolite, whereas, by intrapleural inoculation, potency was greater for amosite, however, the difference was not statistically significant."

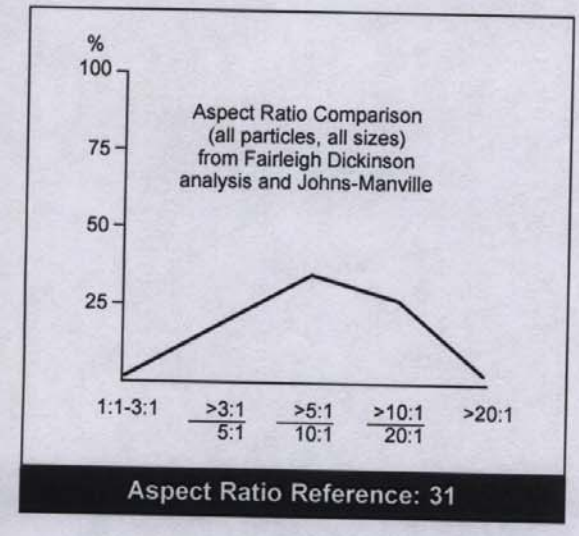
OVERALL CONCLUSION: **This study demonstrates a carcinogenic effect to asbestiform ferroactinolite.**

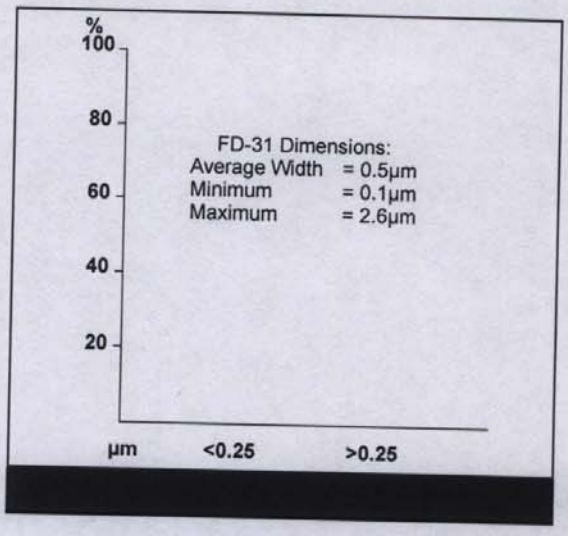
Asbestiform or Highly Fibrous Tremolite — Animal Study

SEM: 1250 X



SAMPLE: FD-31 was provided through Johns-Manville Corp. from a tremolitic talc in the Western United States (JM Sample 4368-31-3). The exact origin of this sample is unknown. This sample is generally considered a mineralogical curiosity.





ADDITIONAL MINERAL PARTICLE DATA:

The exact origin and preparation of this sample is unclear. Subsequent analysis of this sample suggests that: "The particle distribution in the sample is not typical of cleavage fragments of tremolite. The particles in Sample 31 appear to be composed of true fibers whose shape was attained by growth rather than cleavage." "Particles with a 20:1 aspect ratio are quite common." "There is at least one particle which appears to be a bundle of fibers although the photograph is too fuzzy to be absolutely sure,. . ." "This sample is probably not true asbestos, and would be more appropriately characterized as a stiff fibrous variety of amphibole, which is probably byssollite" (32).

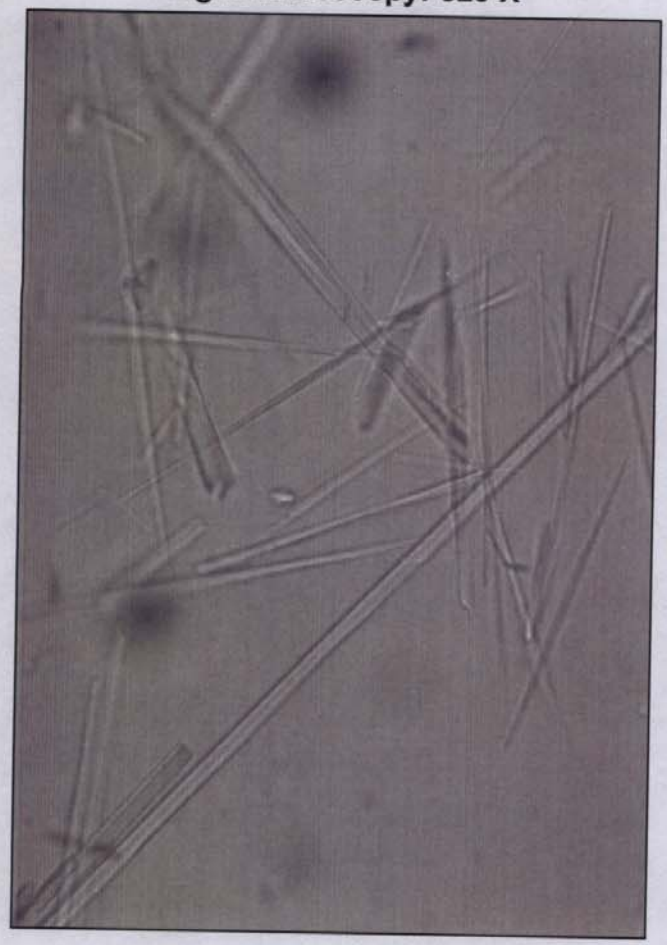
ANIMAL STUDIES

Authors: Smith, W.E., et al (25) Pub. 1979
Test Animals: Male LUG:LAK hamsters, injected at 2 months of age.
Test Type: Intrapleural injection
Protocol: Single intrapleural injection of two dosages (10 and 25 mg). The sample was suspended in saline and sterilized by autoclave. The occurrence of tumors (unspecified) was noted at necropsies for a starting group of 50 animals per dose. After short-term sacrifice of some animals and the loss of others through acute enteritis, the occurrence of tumors was noted in nonsurvivors up to 600 days.
Findings: Three tumors out of 41 animals were found at the 10 mg dose, and 12 out of 28 animals were found at the 25 mg dose.

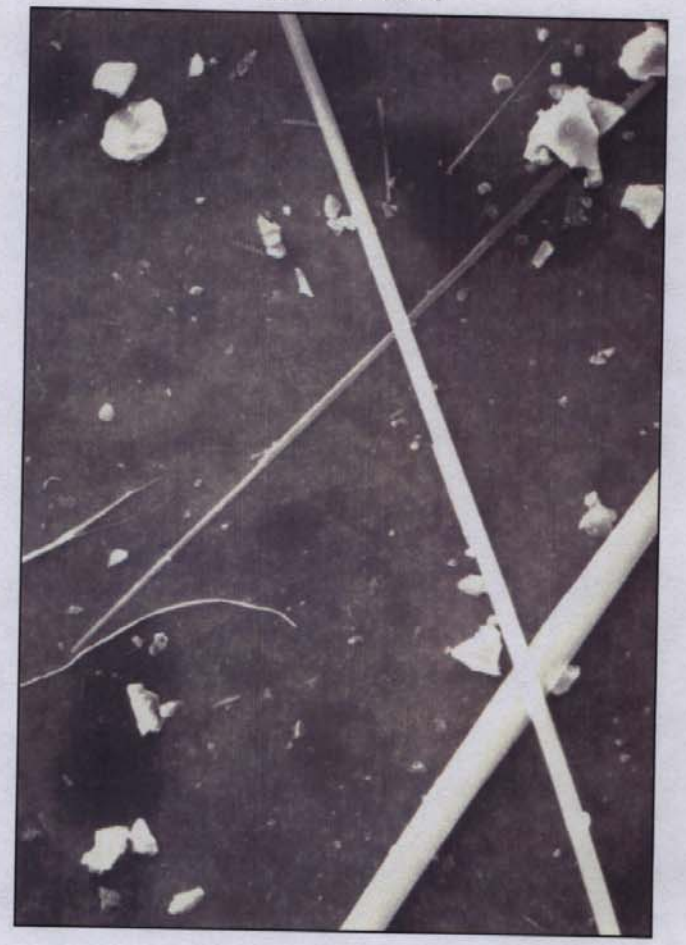
OVERALL CONCLUSION: **A highly fibrous, possibly asbestiform tremolite (or byssollite) produced pleural tumors.**

Nonasbestiform Tremolite with Asbestiform Subpopulation — Animal Study

Light Microscopy: 320 X



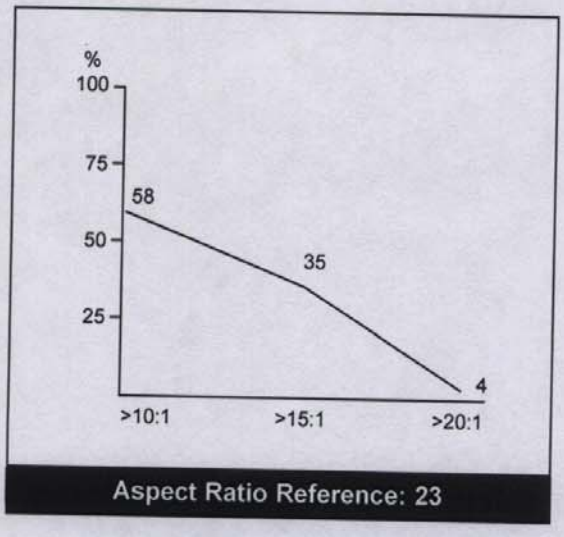
SEM: 1800 X



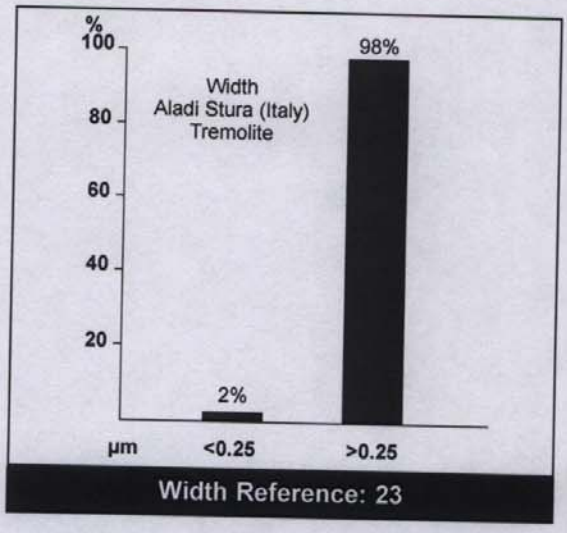
BULK MATERIAL

SAMPLE: The sample "consisted of large bundles of very long (often >5cm) needle-like fibers which were flexible and very elastic but quite brittle." "The tremolite from Italy contained mostly cleavage fragments, but some very long, thin fibers were observed." "The overall impression gained from dense SEM preparations, as shown in this paper, is that the Italian tremolite specimen did contain a certain amount of what observers would consider asbestiform fibers" (20).

Minerals have been characterized and verified as tremolite by x-ray diffractometry, optical microscopy, scanning electron microscopy and energy dispersive x-ray spectroscopy.



Aspect Ratio Reference: 23



Width Reference: 23

ANIMAL STUDIES

Authors: Davis, J.M.G., Addison, J. (20) Pub. 1991
Test Animals: AF/Han strain rats
Test Type: Peritoneal injection
Protocol: Fractions of this sample were obtained by generating an airborne dust cloud in an experimental chamber (Timbrell dust dispensers) with fine fractions collected using a vertical elutriator. A single 10 mg dose was injected into the peritoneal cavities of the animals. All animals lived out of their full life span or were killed when moribund.
Findings: 24 mesothelioma deaths out of 36 animals were observed with a median survival time of 755 days (contrasted to much shorter survival time for samples containing many tremolite asbestos fibers).

OVERALL CONCLUSION: **Sample suggests the asbestiform subpopulation influenced late tumor development.**

EXPOSURE EXHIBIT K — *HOMESTAKE GOLD MINE*

Nonasbestiform Grunerite — Human Mortality Study

Light Microscopy: 320 X

SEM: 1200 X

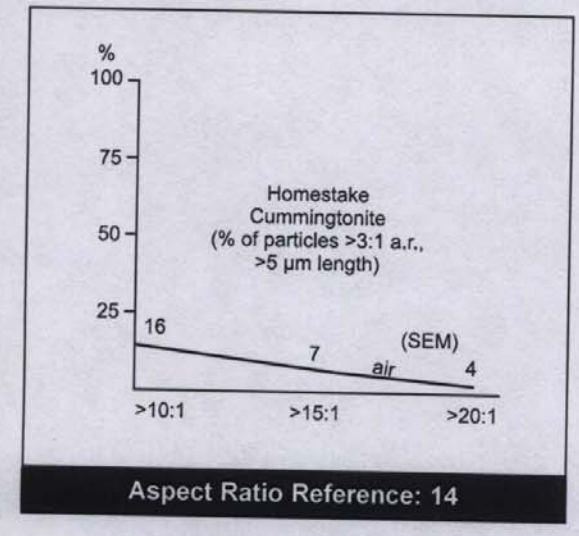
ORE: The ore is a cummingtonite-grunerite (CG), quartz deposit mined for its gold in Lead, S. Dakota (33).

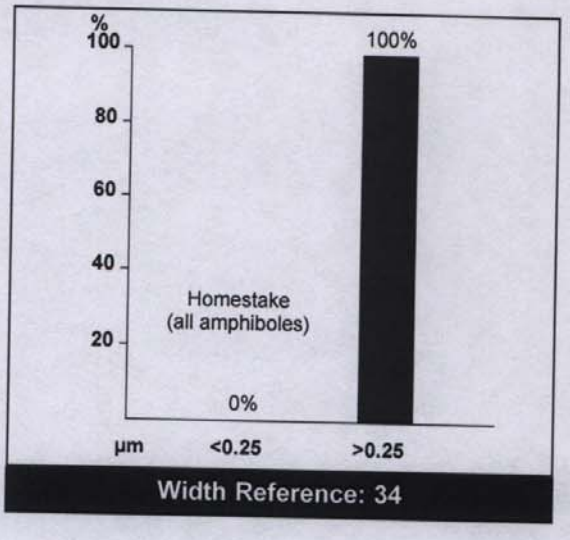
ADDITIONAL MINERAL PARTICLE DATA:

266 Fibers examined with aspect ratio of > 2:1 (air)

Minimum Width	=	0.3 µm	Minimum Length	=	0.9 µm
Mean Width	=	1.1µm	Mean Length	=	4.6 µm
Maximum Width	=	4.8 µm	Maximum Length	=	17.5 µm

"Eighty-four percent of the airborne fibers were identified as amphiboles." "Sixty-nine percent of the amphiboles were characterized as CG, 15% as tremolite-actinolite, with the remaining 16% identified as fibrous hornblende minerals" (33). Note: tremolite-actinolite is reported as an atypical heterogeneous occurrence.





HEALTH STUDIES

Authors: McDonald, J.C., et al (35) Pub. 1978
Cohort: 1,321 men, worked > 21 years (in Co. Veteran's Assoc.)
Vital Status Cut Off: 1973
SMR (respiratory cancer): 103
Conclusion: "There was no convincing evidence of an increase in respiratory cancer." Relative to a high mortality from silicosis - "It is difficult to believe that deaths with so wide a distribution could systematically have blocked the appearance of respiratory cancer."

Authors: Brown, D.P., et al (33) Pub. 1986
Cohort: 3,328 men, > 1 year experience underground work between 1940 and 1965
Vital Status Cut Off: June 1, 1977
SMR (respiratory cancer): 100
Conclusion: "No association as measured by length of employment underground, by dose (total dust x time), or by latency was apparent with lung cancer mortality.

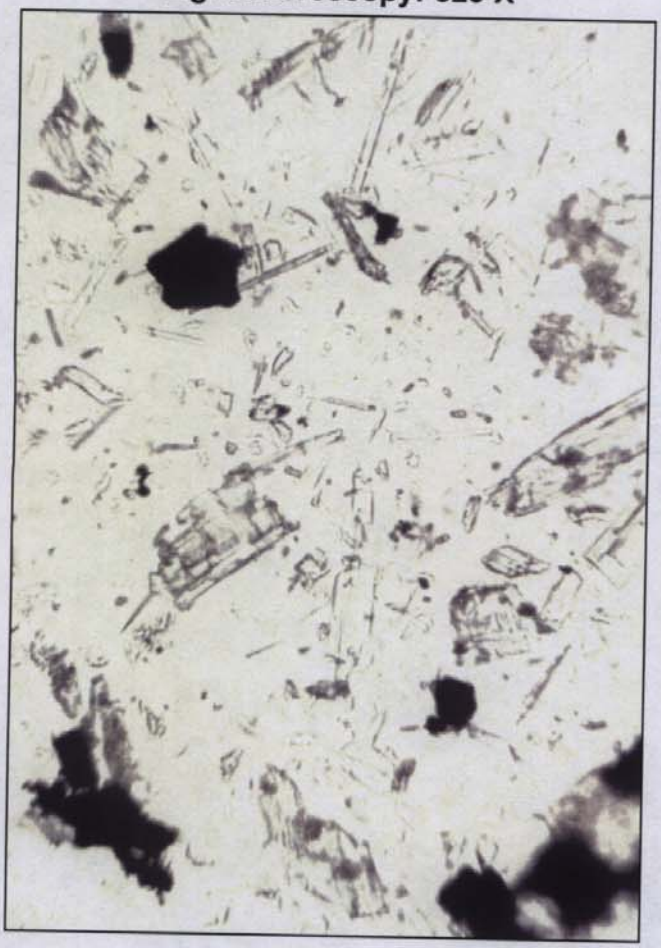
Authors: Steenland, K. et al (67) Pub. 1995
Cohort: 3,328 men, >1 year experience underground between 1940 and 1965
Vital Status Cut Off: Dec. 12, 1990
SMR (respiratory cancer): 115 (CI 94-136)
Conclusion: "Neither exposure to nonasbestiform amphiboles nor silica was likely to be responsible for the observed excess of lung cancer, at least not in a way related to quantitative exposure to dust." "There was only one death from asbestosis in this cohort -- it would therefore appear that the nonasbestiform fibers in this mine did not cause any marked excess of either asbestosis or lung cancer."

OVERALL CONCLUSION: **Nonasbestiform amphibole exposure in this mining operation is not linked to excess lung cancer or mesotheliomas.**

EXPOSURE EXHIBIT L — *EAST MESABI RANGE TACONITE*

Nonasbestiform Grunerite — Human Mortality Study

Light Microscopy: 320 X



SEM: 1200 X

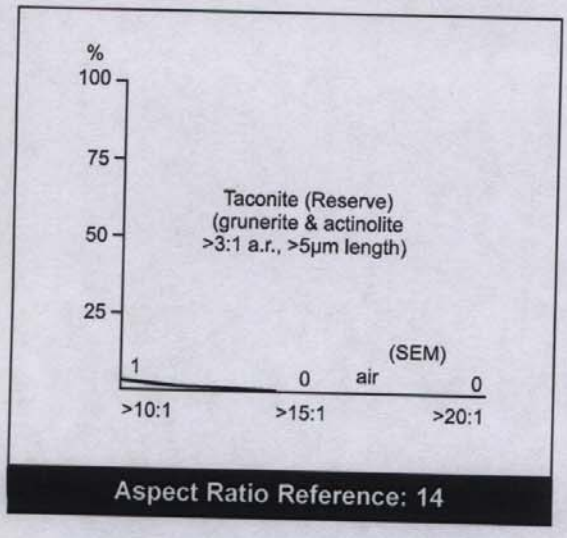
ORE: Minnesota taconite contains cummingtonite-grunerite, actinolite and hornblende amphiboles. Trace amounts of riebeckite also occur (36).

ADDITIONAL MINERAL PARTICLE DATA:

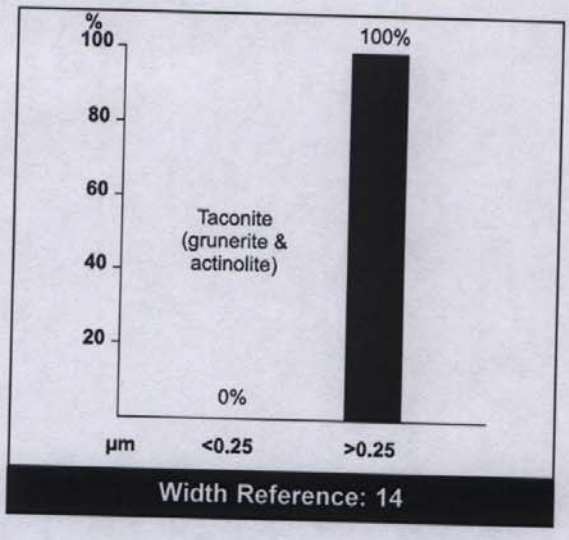
464 Fibers characterized with aspect ratio of > 2:1 (air)

Minimum Width =	0.25 µm	Minimum Length =	1.0 µm
Mean Width =	1.2 µm	Mean Length =	5.5 µm
Maximum Width =	5.0 µm	Maximum Length =	32.4 µm

"Zoltai and Stout (1976) in a report prepared for the Minnesota Pollution Control Agency, concluded that the cleavage fragments of cummingtonite-grunerite found in the Peter Mitchell Pit (Reserve Mining) should not be referred to as asbestiform" (37). "The fibers of taconite are short in length, the vast majority being less than 10 µm" (14).



Aspect Ratio Reference: 14



Width Reference: 14

HEALTH STUDIES

Authors: Higgins, I.T.T., et al (38) Pub. 1983 (Reserve Mining Co.)
Cohort: 5,751 men, worked > 1 year, 1952 to 1976
Vital Status Cut Off: July 1, 1976
SMR (respiratory cancer): 84 (full cohort), 102 (> 15 years latency)
Conclusion: "This study does not suggest any increase in cancer mortality from taconite exposure."

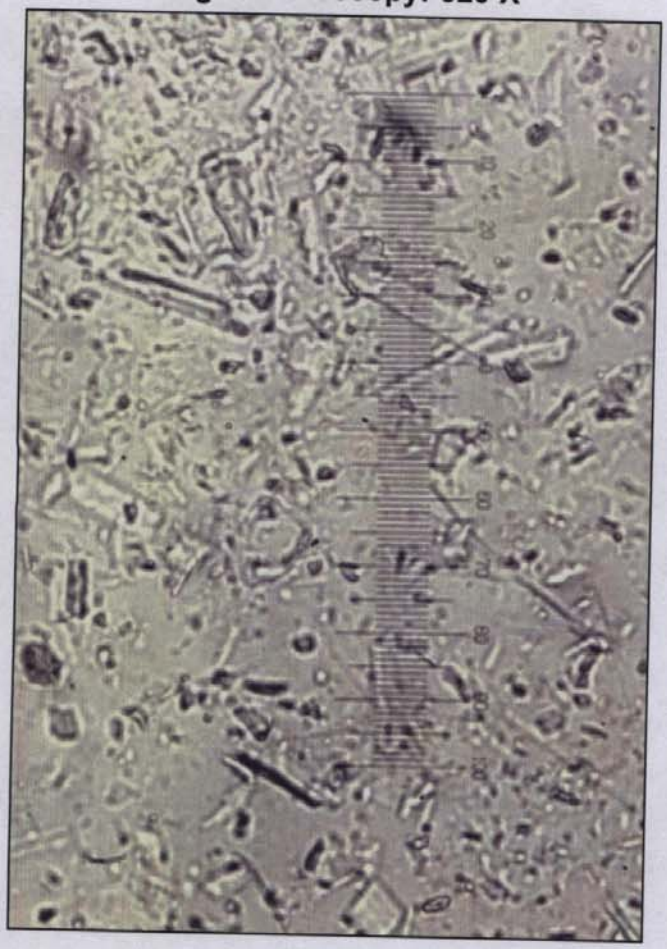
Authors: Cooper, W.C., et al (39) Pub. 1988 (Erie & Minntac Miners)
Cohort: 3,444, worked > 3 months 1947 to January 1, 1959
Vital Status Cut Off: 1983
SMR (respiratory cancer): 61 (full cohort), 57 (> 20 years latency)
Conclusion: "Respiratory tract cancer deaths were 39% fewer than expected (U.S. comparison) and 15% fewer than expected for Minnesota white men. Even when analysis was limited to deaths 20 or more years after first exposure, which provided ample opportunity for the leading edge of any excess in latent tumors to appear, there was no excess.

Authors: Cooper, W. C. et al (68) Pub. 1992 (Erie & Minntac Miners)
Cohort: 3,341 men, worked >3 months 1947 to Jan. 1, 1959
Vital Status Cut Off: Dec. 1988 (update - minimum 30 yr. observation period)
SMR (respiratory cancer): 67 (full cohort)
Conclusion: "no evidence to support any association between exposure to quartz or elongated cleavage fragments of amphibole with lung cancer, nonmalignant respiratory disease or any other specific disease."

OVERALL CONCLUSION: **Nonasbestiform amphibole exposure in this mining operation is not linked to excess lung cancer.**

Nonasbestiform Tremolite — Human Mortality Studies and Animal Studies

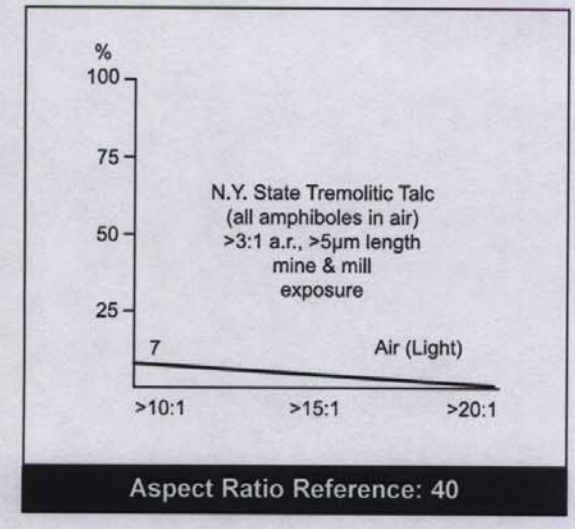
Light Microscopy: 320 X



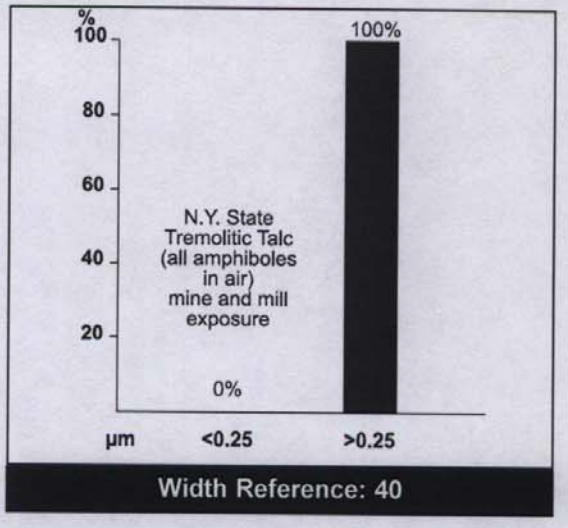
SEM: 1250 X

ORE: As mined and milled at the R. T. Vanderbilt Co., Gouverneur N.Y. mine: mainly talc (20-40%), and tremolite (40-60%) with minor antigorite and anthophyllite. Quartz trace, if detected at all (40).

Also contains minor but observable rod-like mixed talc/amphibole and ribbon-like talc fiber. (69).



Aspect Ratio Reference: 40



Width Reference: 40

ADDITIONAL MINERAL PARTICLE DATA:

R. T. Vanderbilt Mine: NIOSH reported upwards of 70% amphibole asbestos based upon % of all 3:1 aspect ratio or greater particles in air (41). However, the mining company states that **all** of the tremolite and anthophyllite in its talc products appear only in the nonasbestiform habit (42,43). Varying in concentration from one grade to another, fibers of the mineral talc and to a much smaller extent "transitional" particles (talc evolving from anthophyllite) may also be found in this ore deposit. Some of these fibers do exhibit gross morphological characteristics consistent with an asbestiform habit. Such fibers, however, are rare and possess certain physical-chemical properties very different from amphibole asbestos (i.e. harshness, surface properties, etc.). Once fibrous talc is recognized in the analysis, the absence of asbestos in this material is consistently confirmed (40,44-49).

Stanton-Tremolitic Talc Samples 6 and 7: These talcs were positively identified as N.Y. State tremolitic talcs (50), and described as "refined raw materials for commercial products" (27). Sample 6 contained some very elongated particles which are likely to be talc fibers (see discussion above). These fibers did satisfy Stanton's critical dimension range (< 0.25 μm width, > 8 μm length). Sample 7 was reported as containing no particles in this dimensional range but is likely to be another fraction of the same sample.

Smith-Tremolitic Talc FD-14: This sample was supplied by the R. T. Vanderbilt Company and represents a high fiber product grade known as IT-3X (as sold). Analysis reported 50% tremolite, 10% antigorite, 35% talc (of which 25% was fibrous), 2-5% chlorite. Median particle length was 8.5 μm. Diameters (2,000X): < 1 μm = 20%, 1-2 μm = 36%, 2-4 μm = 32%, 4-6 μm = 8%, 6-8 μm = 2%, 10 μm = 2% (51). Tremolite varied considerably in their size lengths, ranging from 1 μm to 40-50 μm. "Talc fiber is abundant in the specimens, occurring as finely fibrous material with high aspect ratio. The talc fibers are also mineral mixtures, structurally talc and a magnesium amphibole. These minerals are also mixtures compositionally. The tremolite contained within the talc occurs as cleavage fragments and is not asbestiform on any level of examination" (45). (Reference includes specific analysis of International Talc-3X product.) In this animal study, this sample was used without comminution or separation.

HEALTH STUDIES (R. T. Vanderbilt Company, Inc.)

Authors: Brown, D.P., Wagoner, J.K., (NIOSH) (41) Pub. 1980
Cohort: 398 men, any work period between 1947-1959
Vital Status Cut Off: 1979
SMR (resp. cancer): 270
Conclusion: "Exposures to asbestiform tremolite and anthophyllite stand out as the prime suspect etiologic factors associated with the observed increase in bronchogenic cancer. . ." No confirmed mesotheliomas.
Critique: Amphibole asbestos is not involved. Excess lung cancer was not reasonably shown to be casually associated with the dust exposure (52-58).

Authors: Stille, W.T., Tabershaw, I.R. (59) Pub. 1982
Cohort: 708 men, any work period between 1947-1977
Vital Status Cut Off: 1978
SMR (resp. cancer): 157
Conclusion: "Elevated mortalities but no significant increases in number of deaths from lung cancer. . ." ". . .workers with exposures in other jobs prior to work at the TMX were found to have excessive mortality from lung cancer. . ."
Critique: Inadequate latency analysis, small cohort and missing data (i.e., smoking) (60).

Authors: Lamm, S.H., et al (61) Pub. 1988
Cohort: 705, worked any time between 1947-1977
Vital Status Cut Off: 1978
SMR (resp. cancer): 220
Conclusion: "This increase in lung cancer mortality. . .has been shown to be concentrated in short term employees (in contrast with nonmalignant respiratory disease). This increase. . . is most likely due to risk acquired elsewhere, such as prior employments, or to differences in smoking experience or other behavioral characteristics." "The risk did not appear to be associated with either the magnitude or the duration of exposure of GTC and was not different from that of workers at talc plants where ores did not contain tremolite or anthophyllite."
Critique: "The findings of these analyses. . . are based on assumptions, small numbers and short latency" (62).

Authors: Brown, D. P. et al (NIOSH) (70) Pub. 1990. Health Hazard Evaluation Report: Update of original NIOSH 1980 study
Cohort: 710, worked any time between 1947-1978
Vital Status Cut Off: 1983
SMR (resp. cancer): 207
Conclusion: "Workplace exposures at GTC are, in part, associated with these excesses in mortality. Possible confounding factors, such as cigarette smoking and other occupational exposures from employment elsewhere, may have contributed to these risks as well."
Critique: "When stratified by smoking, the odds ratios decreased with tenure and the trend analysis were significant. In short, the analysis showed a strong association between lung cancer and cigarette smoking, and there appeared to be an inverse relationship between exposure and the development of lung cancer." (71).

Authors: Gamble, J., et al (71) Pub. 1993
Cohort: Case control applied to above NIOSH Cohort
SMR (resp. cancer): 207
Conclusion: "When stratified by smoking status, risk of lung cancer decreased with talc tenure and remained negative when excluding cases with <20 years latency and short-term workers. These data suggest that non-talc exposures are not confounding risk factors (for lung cancer) while smoking is, and that temporal and exposure-response relationships are consistent with a smoking etiology but not an occupational etiology for lung cancer."
Critique: No dust data and disagreement over whether the elevated smoking rates would or would not account for all the excess.

Authors: Honda, Y. et al (73) Pub. 2002
Cohort: 818 men, worked any time between 1947-1998 (Retrospective Mortality study update with exposure estimation study)
Vital Status Cut Off: January 1, 1990
SMR (resp. cancer): 254

Conclusion: "The results of this study are similar to those of earlier investigations. The cohort giving rise to the lung cancer was seen among subjects unexposed to GTC talc. These features suggest that some of the apparent increase is due to exposure to tobacco smoke. Mill workers and mine workers had similar estimated cumulative dust exposures, yet the excess of lung cancer was considerably stronger among miners than among millers. This indicates that GTC talc dust, per se, did not produce the excess. Most important, the presence of an inverse relationship between estimated cumulative exposure and lung cancer is inconsistent with the hypothesis that GTC talc dust is a carcinogen. The results of experimental animal studies also do not provide any support for this hypothesis."

ANIMAL STUDIES

Authors: Stanton, M.F., et al (27) Pub. 1981
Test Animals: 20-week-old outbred female Osborne-Mendal rats
Test Type: Pleural implantation
Protocol: A standard 40 mg dose of each sample was uniformly dispersed in hardened gelatin and applied by open thoracotomy directly to the left pleural surface. The animals (30-90 for each experiment) were followed for 2 years, at which time all surviving animals were sacrificed and the tissues examined for pleural sarcomas.
Findings: Exposure to these tremolitic talc samples resulted in no incidence of tumors. Similarly tested tremolite asbestos reflected a high tumor rate (see Exposure Exhibit G).

Authors: Smith, W. E., et al (25) Pub. 1979
Test Animals: Male LUG:LAK hamsters, injected at 2 months of age
Test Type: Intrapleural injection
Protocol: Single intrapleural injection of two dosages (10 and 25 mg). The sample was suspended in saline and sterilized by autoclave. The occurrence of tumors (unspecified) was noted at necropsies for a starting group of 50 animals per dose. After short term sacrifice of some animals and the loss of others through acute enteritis, the occurrence of tumors was noted in nonsurvivors up to 600 days.
Findings: No tumor development was noted. In contrast, tremolite asbestos similarly tested did produce tumors (see Exposure Exhibit F).

CELL STUDIES

Authors: Wylie, A. G., et al (72) Pub. 1997
Study: In vivo cytotoxicity and proliferative potential in HTE & RPM cells contrasting asbestos fibers to similar dose talc and transitional fibers (concentrate) from RTV talc.
Conclusion: "Our experiments also show that fibrous talc does not cause proliferation of HTE cells or cytotoxicity equivalent to asbestos in either cell type despite the fact that talc samples contain durable mineral fibers with dimensions similar to asbestos. These results are consistent with the findings of Stanton, et al (1981) who found no significant increases in pleural sarcomas in rats after implantation of materials containing fibrous talc."

OVERALL CONCLUSION: **Human Studies - A definite link between nonasbestiform tremolite and respiratory cancer in the R. T. Vanderbilt Company talc mining population has not been demonstrated.**

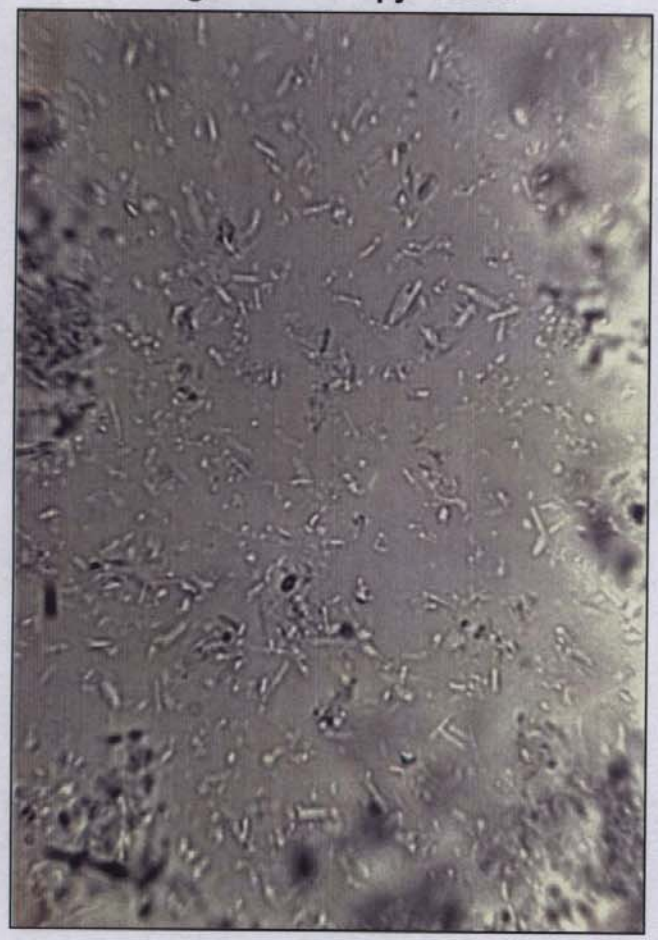
Animal Studies - N. Y. State tremolitic talc containing a high nonasbestiform tremolite content produced no carcinogenic response in rats or hamsters.

EXPOSURE EXHIBIT N

SMITH-TREMOLITE FD-275-1 AND MCCONNELL TREMOLITE 275

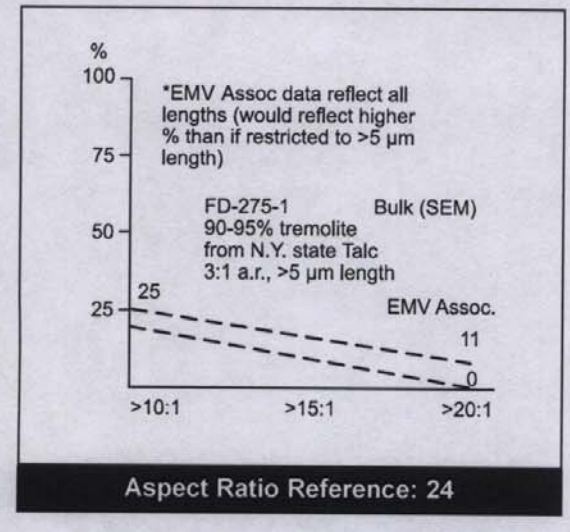
Nonasbestiform Tremolite — Animal Studies

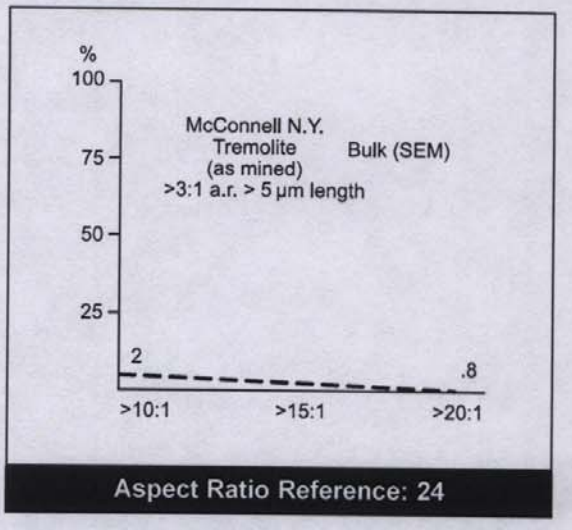
Light Microscopy: 320 X



SEM: 1250 X

SAMPLE: Both FD-275-1 and 275 originated from N.Y. State tremolitic talc ore. Both samples represent tremolite concentrates from this ore.





ADDITIONAL MINERAL PARTICLE DATA:
Tremolite 275 was selected from N.Y. tremolitic talc ore from an area rich in tremolite. This ore was provided to the Bureau of Mines (BOM) for mineral and elemental particle size characterization as well as use in an animal feeding study by Dr. E. McConnell (sample contained approximately 70% tremolite with the remainder talc and antigorite). Also, an aliquot of this sample was further processed to obtain a higher tremolite concentrate for use in another animal study by Dr. William Smith (approximately 95% tremolite).

The processing of FD-275-1 involved crushing, milling, separation via sedimentation and filtering to obtain only the respirable fraction. Particle size characterization of FD-275-1 was undertaken by Dr. Smith (via EMV Assoc. Inc.), and by the BOM.

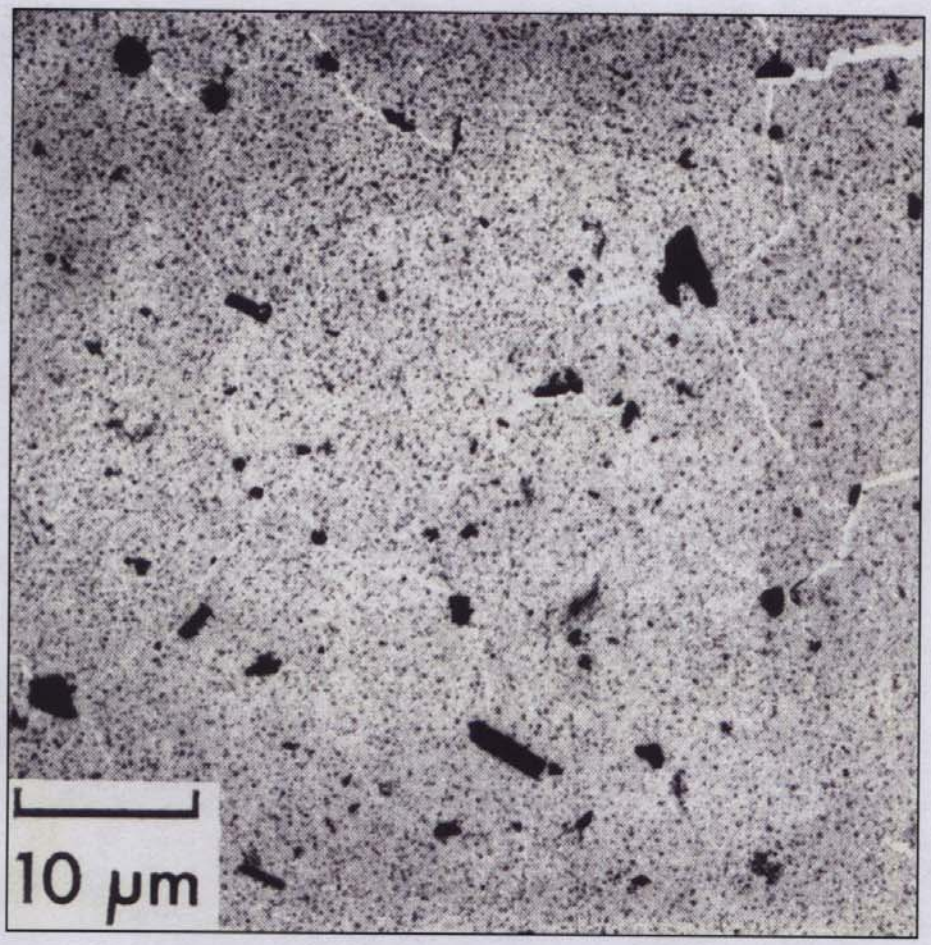
For FD-275-1, no particles with a width < 1 µm and length of > 10 µm were observed (200 particles via SEM). For FD-275 (McConnell tremolite), a mean width of 3.4 µm for particles > 6 µm in length was recorded (for amosite similarly sized mean width = 0.4 µm).

ANIMAL STUDIES
Authors: Smith, W.E., et al (25) Pub. 1979
Test Animals: Male LUG:LAK Hamsters **Test Type:** Intrapleural injection
Protocol: Single intrapleural injection of two dosages (10 and 25 mg). The occurrence of tumors (unspecified) was noted at necropsies for a starting group of 50 animals per dose. After short term sacrifice of some animals and the loss of others through acute enteritis, the occurrence of tumors was noted in nonsurvivors up to 600 days.
Findings: No tumor development was noted. In contrast, tremolite asbestos similarly tested did produce tumors (see Exposure Exhibit F).

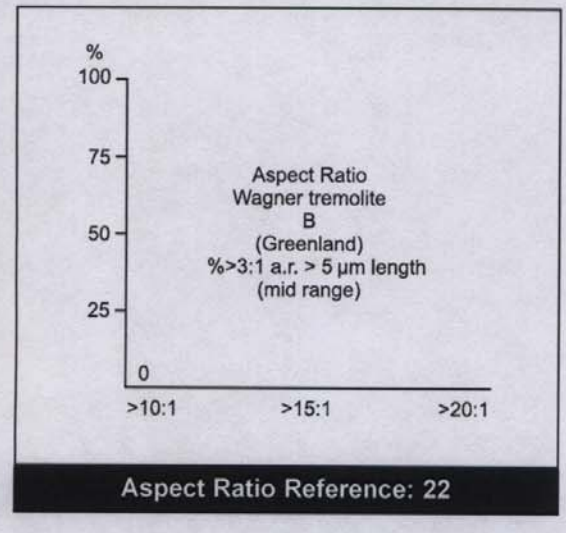
Authors: McConnell, E.E., et al (64) Pub. 1983
Test Animals: Male and female Fischer 344 rats **Test Type:** Ingestion
Protocol: Nonasbestiform tremolite and amosite were administered alone and in combination at a concentration of 1% in the daily diet of rats. Rats were sacrificed when exhibiting specified symptoms, or when less than 10% of the test group survived. Group size varied from 100 to 250 animals.
Findings: No toxic or neoplastic lesions were observed in the target organs - gastrointestinal tract, or mesothelioma for either the tremolite or the amosite.

OVERALL CONCLUSION: **A concentrate of N.Y. State tremolite nonasbestiform produced no pleural tumors in hamsters and no gastrointestinal tract neoplastic lesions in rats.**

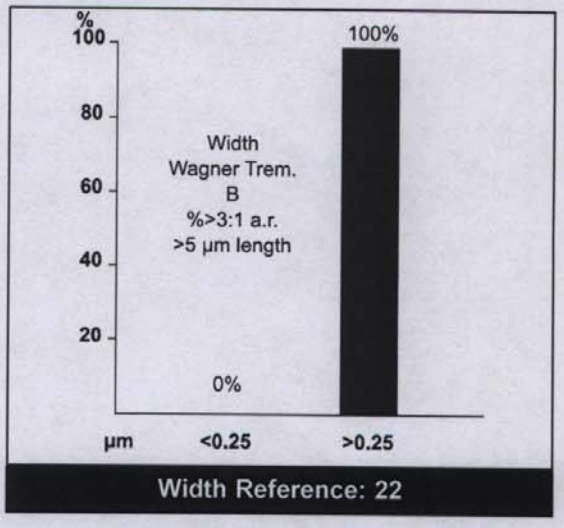
Nonasbestiform Tremolite — Animal Study



SAMPLE: Prepared from a rock specimen from Greenland. Referenced as tremolite "B" (22).



Aspect Ratio Reference: 22



Width Reference: 22

ADDITIONAL MINERAL PARTICLE DATA:

100% of particles > 5 µm have diameters > 1.0 µm
100% of particles are less than 10 µm long
100% of particles > 5 µm length have aspect ratios < 10:1 (22)

ANIMAL STUDIES

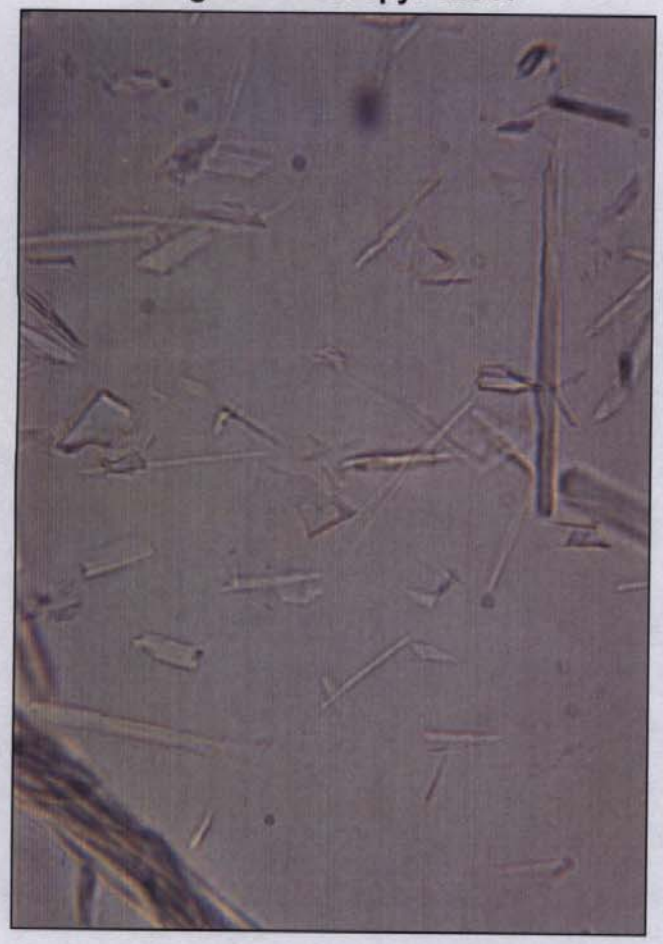
Authors: Wagner, J.C., et al (22) Pub. 1982
Test Animals: Sprague-Dawley rats 6-10 weeks old when injected
Test Type: Pleural injection
Protocol: A single 20 mg injection into the right pleural cavity of 48 rats was applied. "The sample was prepared by milling in a small agate mill and ultrasonic dispersion, large particles being removed by sedimentation in water." The sample was sterilized by autoclave and introduced in saline solution. All animals were allowed to live out their lives or necropsied when moribund for tumors (unspecified-reported as "mesotheliomas").
Findings: No tumors were noted in 48 rats. One sample of tremolite asbestos was tested under the same protocol (see Exposure Exhibit C).

OVERALL CONCLUSION: **Nonasbestiform tremolite produced no tumors in the test animals.**

EXPOSURE EXHIBIT P *ADDISON/DAVIS-TREMOLITE (Dornie)*

Nonasbestiform Tremolite — Animal Study

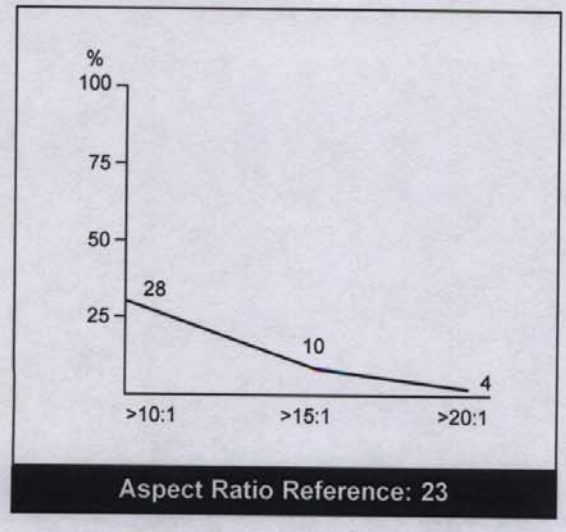
Light Microscopy: 320 X



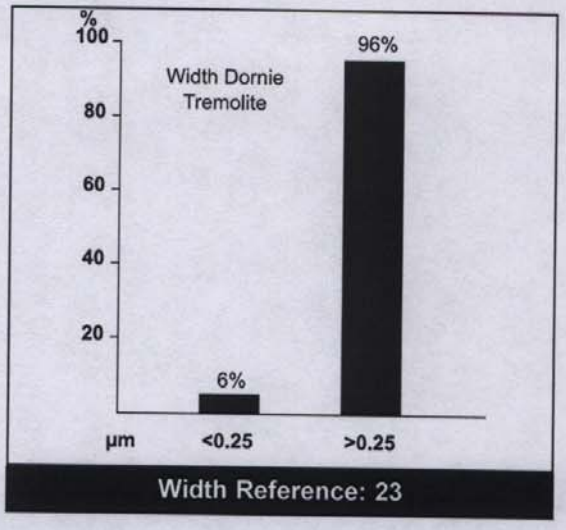
SEM: 190 X

SAMPLE: Like the tremolite from Italy (see exhibit J), this sample "contains mostly cleavage fragments, but some very long, thin fibers were also observed." There are more fibers longer than 8 µm in this sample than in the Italian sample, but most were >1 µm in diameter. A small amphibole asbestiform subpopulation may also exist in this sample as it does in the Italian sample (though this is less clear). "The material contains several populations of varying habits of a member of the tremolite-actinolite solid solution series. (65). Both this sample and the Italian sample are not typical of tremolite nonasbestiform cleavage fragment populations. Both exhibit the presence of byssolite in the samples.

Minerals were characterized and verified as a tremolite by x-ray diffractometry, optical microscopy, scanning electron microscopy and energy dispersive x-ray spectroscopy.



Aspect Ratio Reference: 23



Width Reference: 23

ANIMAL STUDIES

Authors: Davis, J.M.G., Addison, J. (20) Pub. 1991
Test Animals: AF/Han strain rats
Test Type: Peritoneal injection
Protocol: Fractions of this sample were obtained by generating an airborne dust cloud in an experimental chamber (Timbrell dust dispensers) with fine fractions collected using a vertical elutriator. A single 10 mg dose was injected into the peritoneal cavities of the animals. All animals lived out of their full life span or were killed when moribund.
Findings: 4 mesothelioma deaths out of 33 animals were observed with no median survival time published (too few tumors for median survival times to be calculated). It is important to note - as stated in the study - "The intraperitoneal injection test is extremely sensitive, and it is usually considered that, with a 10 mg dose, any dust that produced tumors in fewer than 10% of the experimental group is unlikely to show evidence of carcinogenicity following administration by the more natural route of inhalation - the material from Dornie is probably to be considered harmless to human beings."

OVERALL CONCLUSION: **This predominantly nonasbestiform tremolite produced no significant carcinogenic response in the test animals and is likely harmless to humans.**

EXPOSURE EXHIBIT Q *ADDISON/DAVIS-TREMOLITE (Shinness)*

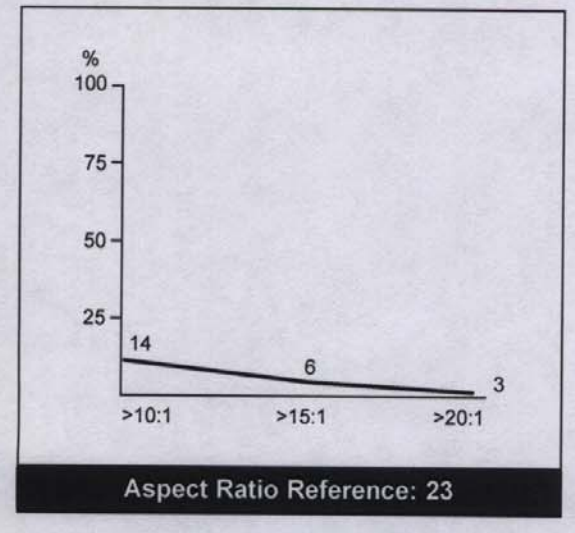
Nonasbestiform Tremolite — Animal Study

Light Microscopy: 45 X

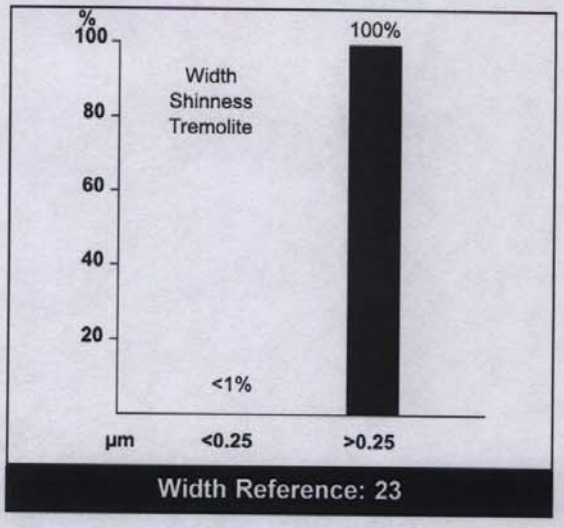
SEM: 1800 X

SAMPLE: "The Shinness tremolite dust was almost exclusively composed of cleavage fragments, only a small portion of which had an aspect ratio greater than 3:1."

Minerals were characterized and verified as tremolite by x-ray diffractometry, optical microscopy, scanning electron microscopy and energy dispersive x-ray spectroscopy.



Aspect Ratio Reference: 23



Width Reference: 23

ADDITIONAL MINERAL PARTICLE DATA:

"In the optical microscopy and SEM examinations, the asbestos tremolites were found to be typical of that form in displaying polyfilamentous fiber bundles, curved fibers, fibers with splayed ends, and long, thin, parallel-sided fibers. Most of the fibers showed straight extinction when observed with polarized light under crossed polarizers, indicating the presence of multiple twinning of the crystals." "Samples did contain some elongated fragments of tremolite with oblique extinction, stepped ends, and nonparallel sides indicating that they were cleavage fragments." (20)

ANIMAL STUDIES

Authors: Davis, J.M.G., Addison, J. (20) Pub. 1991
Test Animals: AF/Han strain rats
Test Type: Peritoneal injection
Protocol: Fractions of this sample were obtained by generating an airborne dust cloud in an experimental chamber (Timbrell dust dispensers) with fine fractions collected using a vertical elutriator. A single 10 mg dose was injected into the peritoneal cavities of the animals. All animals lived out of their full life span or were killed when moribund.
Findings: 2 mesothelioma deaths out of 36 animals were observed (well below background for test method). There were too few tumors for median survival times to be calculated. Authors state: "Human exposure to a material such as that obtained from Shinness Scotland, whether as a pure mineral dust or as a contaminant of other products, will almost certainly produce no hazard."

OVERALL CONCLUSION: **This nonasbestiform tremolite produced no carcinogenic response in the test animals.**

Nonasbestiform Actinolite - Animal Study

No photograph available.

SAMPLE: Origin of sample unknown.

DIMENSIONAL DATA: Not provided by author.

ANIMAL STUDIES:
Authors: Pott, F. et al (66) Pub. 1974
Test Animals: Wistar rats
Test Type: Peritoneum injection.
Protocol: Assorted fibrous dust (chrysotile, anthophyllite asbestos, actinolite asbestos, wollastonite, glass fibers, gypsum, etc.) and granular dust (nonasbestiform actinolite, biotite, talc, etc.) were intraperitoneally injected (up to 12.5 mg/ml) into varying test groups of 40 rats at various dosages.
Findings: The "fibrous" dusts (with some exceptions such as gypsum, slag wool, and wollastonite), induced varying tumor development while the granular dusts reflected little to no tumors (nonasbestiform actinolite - no tumors). "Very low doses between 0.05 and 0.5 mg asbestos led to tumor incidences of about 20% to 80%."

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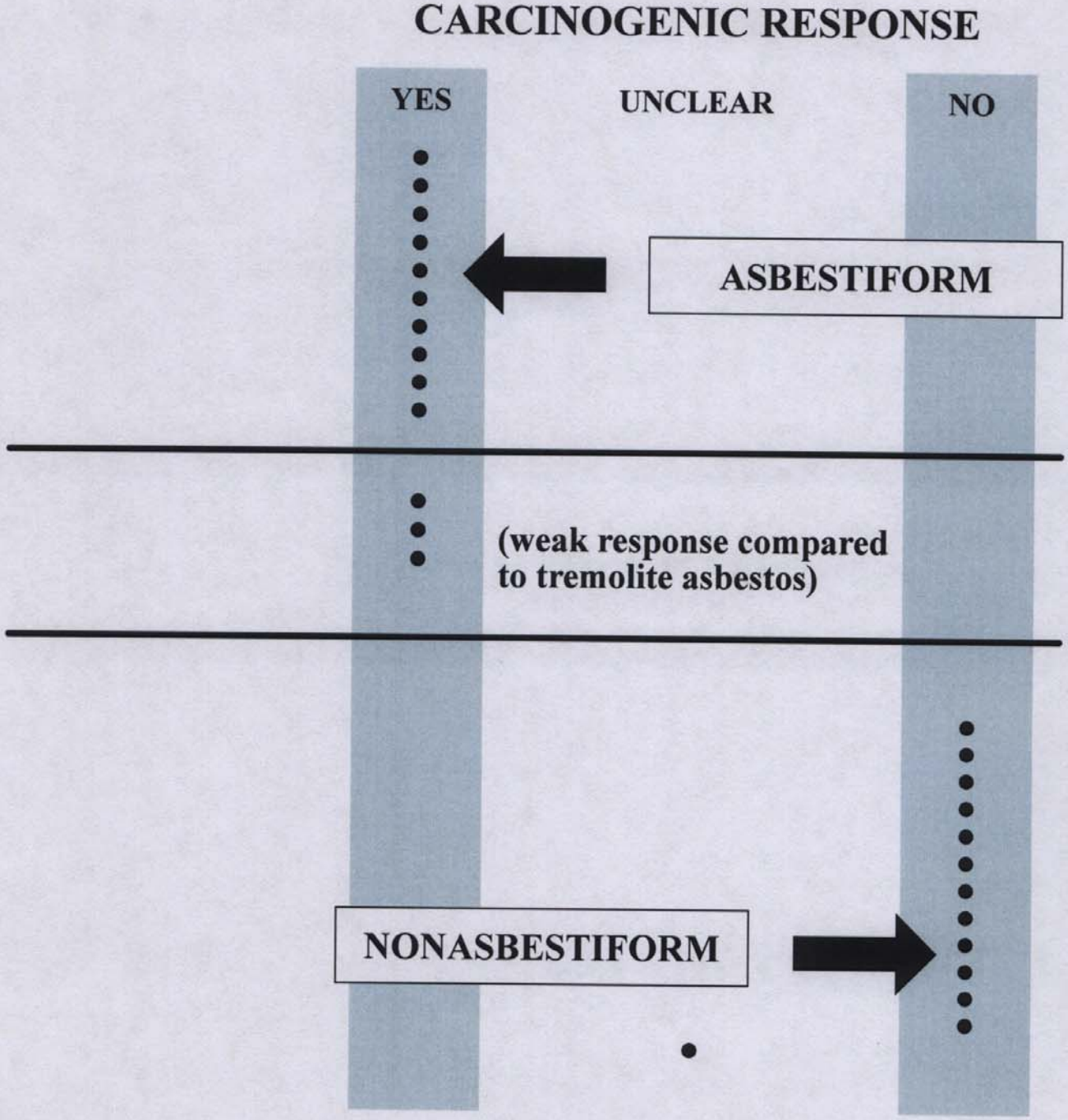
SUMMARY
MINERAL HABIT AND CARCINOGENICITY

CLEAR AMPHIBOLE ASBESTOS EXPOSURES (amphibole asbestos)	**Libby Vermiculite (H)** **Greek Tremolite (H)** **Smith FD-72 (A)** **Stanton Tremolite #1 (A)** **Stanton Tremolite #2 (A)** **Wagner Korean Tremolite (A)** **Davis Korean Tremolite (A)** **Addison/Davis Jamestown Tremolite (A)** **Addison/Davis Korean Tremolite (A)** **Addison/Davis Swansea Tremolite (A)**
PREDOMINANTLY ASBESTIFORM AND/OR HIGHLY FIBROUS	**Cook/Coffin-Ferroactinolite (asbestiform) (A)** **Smith FD-31 (unique Tremolite/Byssolite) (A)** **Addison/Davis Italian Tremolite (highly fibrous with asbestos subpopulation) (A)**
COMMON NONASBESTIFORM AMPHIBOLE EXPOSURES	**Homestake (C-G) (H)** **Mesabi Range-Taconite (C-G, trace Actinolite) (H)** **Smith FD-14 (Tremolitic Talc) (A)** **Smith FD-275 (conc. Tremolite) (A)** **McConnell Tremolite (conc. Tremolite) (A)** **Stanton Talc #6 (Tremolitic Talc) (A)** **Stanton Talc #7 (Tremolitic Talc) (A)** **Pott-Granular Actinolite (A)** **Wagner California Tremolite (A)** **Wagner Greenland Tremolite (A)** **Addison/Davis Dornie Tremolite (A)** **Addison/Davis Shinness Tremolite (A)** **N.Y. State Tremolitic Talc (neg. for animals) (H)**

(H) = Human Studies

(A) = Animal Studies

C-G = Cummingtonite-grunerite


CARCINOGENIC RESPONSE
YES
UNCLEAR
NO
ASBESTIFORM
(weak response compared
to tremolite asbestos)
NONASBESTIFORM

CONCLUSION

Difference Exists Mineralogically

AND

Biologically

In 1992, after many years of scientific review, the Occupational Safety and Health Administration (OSHA) specifically excluded elongated nonasbestiform cleavage fragments from the scope of their asbestos standard. OSHA's decision to recognize the key mineralogic and biologic distinctions reviewed in this pictorial presentation was instrumental in that decision.

Because this matter involves scientific issues ranging from geology, mineralogy and health, the authors believe it is important that these complex relationships be explained as simply as possible. This matter remains a source of confusion to many and the consequences of misunderstanding can be immense.

Sustaining confusion is an unfortunate array of overly broad asbestos analytical protocols and definitions now being applied in mixed dust environments. To address analytical ambiguities, appendix II is provided.

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APPENDIX I

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APPENDIX II

Analytical Issues

INTRODUCTION:

As shown in this pictorial presentation, the properties of asbestos are unique. These properties include very long, thin, fibrillar fiber bundles that are flexible and strong. The ability of excessive exposure to asbestos to cause serious pulmonary disease has been extensively studied and documented.

Analytical procedures designed to identify and quantify asbestos must incorporate the unique characteristics of asbestos as fully as possible if the method is to be as specific to asbestos as possible. Minimizing mischaracterization (false positives and negatives) defines the value of any analytical protocol and is a key element to meaningful measurement of risk.

The most common analytical approach used for airborne asbestos fiber quantification is phase contrast microscopy (PCM). PCM methods typically measure airborne elongated particulate with a length to width ratio of at least 3 to 1 and a length 5 µm or greater (e.g. NIOSH 7400). Since there is little reason to measure airborne elongated particulates other than for asbestos, this relatively cheap, simple to apply method, is most often used to collect and count asbestos fibers. Although PCM will count all asbestos fibers observable under light microscopy (400X), it unfortunately also counts elongated nonasbestiform cleavage fragments, insect legs and any other elongated particulate collected on the air monitoring filter that meet the simple dimensional counting criteria. Consequently, the simple PCM method works well in an environment where commercial asbestos is known to be the predominate elongated particle in the air being sampled. In mixed dust environments, however, the PCM method must be enhanced to measure asbestos from the other particulate in the sample more selectively.

Fiber counting criteria employed in microscopy methods are often mistakenly viewed as the *definition* of an asbestos fiber. The fiber counting criteria employed in most PCM methods are, in fact, merely arbitrary parameters used to promote consistency in fiber counting. The 5 µm minimum length, and the 3:1 minimum aspect ratio criteria, originated in England's asbestos textile mills as a means to improve reproducibility of commercial asbestos fiber measurements. These counting parameters were **not** deemed to be the dimensions that corresponded to a specific health risk (Holmes, 1965).

The PCM method is unable to detect fibers below approximately 0.2 µm in width and has always been viewed as an ***index of exposure*** versus an absolute measure of all fibers present in a sample. It is also unable to characterize the mineral composition or crystal structure of the particles examined. Again, in an environment where it is known that the primary elongated particle present is commercial asbestos, these limitations become less important. In environments where there are mixed dusts and where asbestos may or may not be present, the PCM method, with its simple counting criteria, becomes wholly inadequate.

This inadequacy is clearly demonstrated in the 1986 OSHA asbestos standard preamble discussion of its quantitative risk analysis and its decision to exclude studies of Canadian asbestos miners. The asbestos miners were excluded because the fiber count dose-response relationship observed differed significantly from the fiber count dose-response observed for other asbestos exposed populations under review by OSHA.

OSHA found that the miners had been exposed to similar or higher "fiber" concentrations than textile or other commercial asbestos exposed populations but showed significantly less adverse health effects. The asbestos "fiber" exposure was based solely on 3 to 1 aspect ratio or greater, 5 μm or longer, light microscopy fiber counts.

In Canadian asbestos mines, asbestos often represents no more than 5% of the ore being mined with the remaining host rock predominantly being the nonasbestiform serpentine mineral, antigorite. The apparent "asbestos" fiber count in this mixed mineral dust environment therefore included antigorite cleavage fragments as well as chrysotile fibers. Inclusion in the fiber count of elongated nonasbestiform fragments which have never been shown to produce asbestos-like disease, significantly inflated the asbestos dose reported without a corresponding increase in response.

Had nonasbestiform cleavage fragments been properly identified and excluded from the asbestos fiber count, the asbestos risk observed for the Canadian asbestos miners may well have been comparable to that observed among the commercial asbestos exposed groups that were used in the OSHA risk analysis. In this example, analytical methods that failed to address what is and is not asbestos clearly impacted risk assessment (Wylie and Bailey, 1992).

Sub-light microscopic methods such as transmission electron microscopy (TEM) and scanning electron microscopy (SEM) present another analytical confounder when improperly applied. In contrast to the limitations of PCM, electron microscopic analytical methods such as TEM are capable of detecting asbestos fibers well below the resolution limit of the light microscope, identifying mineral type and can address crystal growth distinctions important to proper asbestos identification.

Despite the elevated costs associated with electron microscopic analyses, the desire to identify and quantify lower and lower asbestos levels in building materials and in asbestos abatement projects has contributed significantly to the proliferation of TEM laboratories across the country. These types of samples are typically limited to chrysotile, undergo highly prescriptive analytical protocols and require little to no mineralogical expertise in the analysis. For all its sophistication and sensitivity, electron microscopy presents a different set of analytical variables that will affect risk assessments when its results are improperly interpreted or improperly compared to health exposure standards.

The health literature on asbestos exposed populations overwhelmingly involves exposure to commercial asbestos. Asbestos exposure levels reported in epidemiological studies used to establish exposure limits have been obtained through light microscopy methods. Permissible exposure standards for airborne asbestos are based upon this light microscopy ***index of exposure***. Efforts to use electron microscopic analytical data for risk assessment purposes must include a means to correlate results to what would be observable under light microscopy.

Unfortunately, the difference between asbestos fibers observed under the light microscope and asbestos fibers observed by electron microscopy is highly variable. This variability is influenced by asbestos type, how the fibers become airborne and the nature of fiber bundle separation in each exposure setting. "One size fits all" correlations are difficult (if not impossible) to reliably establish. Electron microscopy views only a very tiny fraction of the sample being studied and is therefore a poor quantification tool. Unless coupled with other investigation techniques, electron microscopy does not adequately address populations of particles in a sample. In an unknown or mixed dust environment, this is an important indicator of the asbestiform or nonasbestiform nature of a given exposure.

Electron microscopy methods are unquestionably the best analytical tool for asbestos identification, but not for quantification unless coupled with other methodologies. The health significance of asbestos fibers observed only through electron microscopy and not correlated to PCM-observable exposure levels, is unknown at this time. The authors are not aware of any studies of asbestos-related disease where the asbestos exposure was not readily observable under light microscopy.

SOLUTIONS:

While the strengths and weaknesses of every asbestos analytical approach has not been addressed, most analysts would agree that there is no perfect, single asbestos analytical methodology. Certainly each approach is made more reliable in the hands of experienced, knowledgeable analysts. Effectively combining different analytical tools in a tiered approach can overcome individual method weaknesses, control costs and yield highly reliable results.

The following analytical guides reflect asbestos analytical approaches considered most reliable for asbestos identification and quantification. In each case, the unique characteristics of asbestos fibers and asbestos fiber populations are used to the fullest extent possible.

In the case of PCM, for example, dimensional fiber counting criteria that are more specific to asbestos are recommended as a more sensitive screening technique if standard PCM counts exceed established asbestos fiber permissible exposure limits. This additional PCM step significantly improves PCM as an inexpensive, easy to apply asbestos screening tool and assists the investigator in deciding if more specific, more costly analysis is warranted.

A polarized light microscopy method for bulk analysis is also provided. This method is designed with more guidance into what is and is not asbestos and, in the hands of a skilled analyst with mineral expertise, can be more informative than electron microscopic analysis.

The effective utilization of any asbestos analytical methodology, used singularly or in combination with others, does require a clear understanding of what asbestos is and what it is not. Methodologies that do not or can not recognize these distinctions should not be used.

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Differential PCM Fiber Counting Methodology for Air Samples

BACKGROUND:

In environments where the presence of asbestos is unknown or may be present as a mixed dust, the NIOSH 7400 PCM membrane analytical method must be supplemented with differential counting criteria to assist in determining what proportion of the dust is asbestiform and what part is not. This need for differential counting was recognized by the Occupational Safety and Health Administration (OSHA) in its final asbestos standard published in 1994 (Fed Reg. Vol. 59, No. 153, pp. 41073 - 41079 - Aug. 1994).

There is also concern among some researchers that abandonment of the traditional fiber counting criteria (fibers with a minimum length of 5 µm and a length to width aspect ratio of at least three to one) would forsake the historical database that has been created over many decades. The simplistic counting criteria alone, derived from an effort to improve analytical consistency in commercial asbestos textile exposure samples in the 1960s, is totally inappropriate for noncommercial asbestos exposure environments. Recognizing the fundamental morphological differences between asbestiform and nonasbestiform particle populations, the method must address those differences.

METHOD SUMMARY:

To satisfy historical preservation of exposure trends, the NIOSH 7400 method must be performed. Where the fiber count reaches or exceeds 0.1 fiber/cc (or the current exposure limit), supplemental measurements that allow a better characterization of the asbestiform nature of the sample must be done. These measurements will necessitate the use of a modified Walton Beckett graticule that assists in the measurement of those 3:1 or greater aspect ratio and 5 µm and longer particles that are equal to and longer than 10 µm and less than or equal to 0.5 µm in width. All fiber bundles need to be counted. This modified graticule is shown in Figure 1.

If the population of fibers has 50 % equal to or longer than 10 µm or if 50% of the fibers are equal to or less than 0.5 µm in width (unless a bundle), then the exposure can be considered to be asbestiform.

Samples that reflect an asbestiform nature must have PCM observable fibers (widths between 0.15 and 0.5 µm or bundles) analyzed by electron microscopy. Analysis by electron microscopy will evaluate morphology, chemistry and crystal structure if using TEM. The percentage PCM fibers that are regulated asbestiform fibers is then calculated and compared to the permissible exposure limit. The procedure is shown diagrammatically in Figure 2.

Mineralogical expertise is needed for those samples requiring electron microscopy and the standards for classifying amphibole minerals must conform to the International Mineralogical Association recommendations (Leake, B.E., Nomenclature of Amphiboles. American Mineralogist. Vol. 82, 1019 - 1037, 1997).

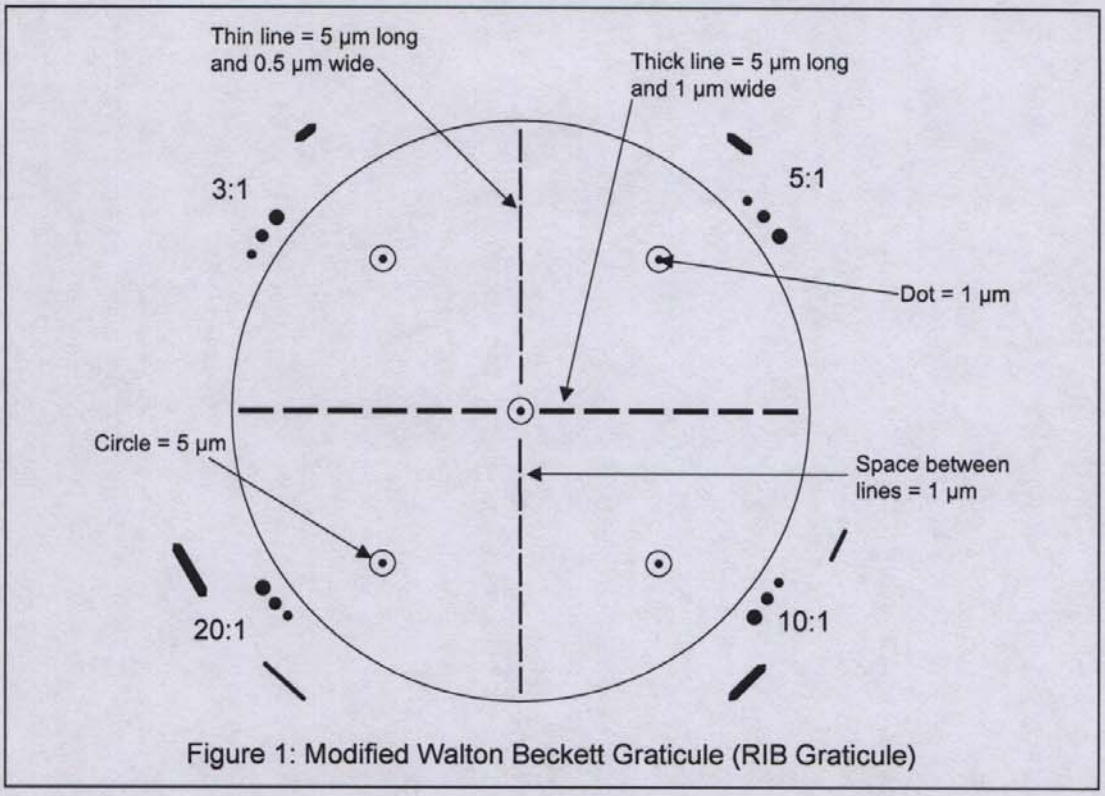

Figure 1: Modified Walton Beckett Graticule (RIB Graticule)

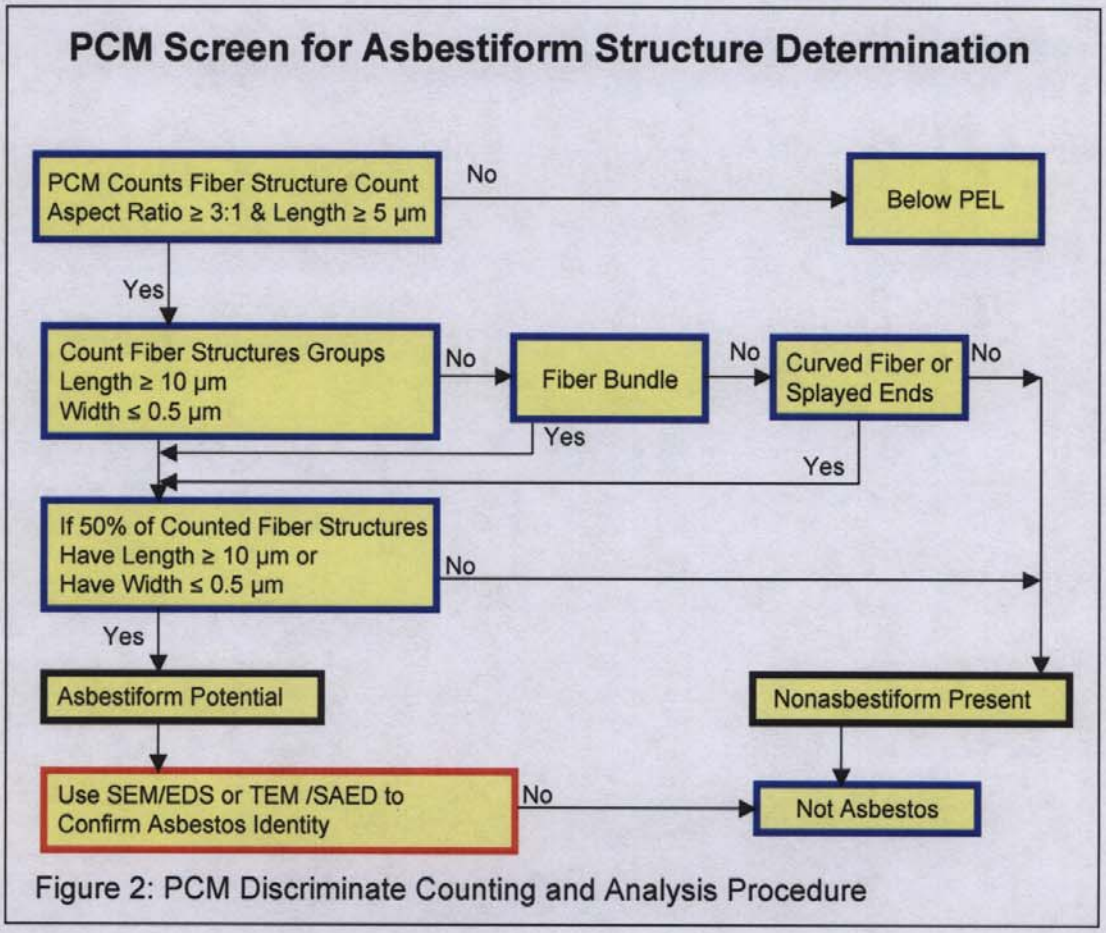

Figure 2: PCM Discriminate Counting and Analysis Procedure

Standard Method of Testing for Asbestos Containing Materials by Polarized Light Microscopy

1. SCOPE

1.1 The method describes the procedures for the determination of the presence or absence of six types of asbestos: chrysotile-asbestos, grunerite-asbestos (amosite), crocidolite (riebeckite-asbestos), anthophyllite-asbestos, tremolite-asbestos and actinolite-asbestos and for the determination of a quantitative estimate of the percent of asbestos. This method may be applied to bulk materials other than building materials, but the accuracy of the method under these circumstances is not characterized. For non-building materials, there may be more interference with a greater possibility for false positives or fibers may be dispersed below the resolution of the light microscope, yielding a higher possibility of false negatives. When the content of asbestos in a sample is close to the 1% level, other more precise methods of quantification may be necessary if it is important to determine whether or not asbestos content is more or less than 1% by weight. This distinction may be important because the EPA defines asbestos-containing materials as those materials containing greater than 1% asbestos (Ref. 2 and 3).

2. APPLICABLE DOCUMENTS

2.1 U.S. Environmental Protection Agency, "Interim Method for the Determination of Asbestos in Bulk Insulation Samples," EPA 600/M4-82-020, Dec. 1982.

2.2 U.S. Environmental Protection Agency, "Guidance for Controlling Asbestos-Containing Materials in Buildings," EPA 560/5-85-024, 1985.

2.3 U.S. Environmental Protection Agency, "Asbestos-Containing Materials in School Buildings: Guidance for Asbestos-Analytical Programs," EPA 560/13-80-017A, 1980 (under revision).

2.4 ASTM STD 834, Definitions for Asbestos and Other Health-related Silicates, B. Levadie, ed., ASTM, 1916 Race Street, Philadelphia, PA 19103, 1984.

3. TERMINOLOGY

3.1 Asbestos: A commercial term applied to a group of highly fibrous silicate minerals that readily separate into long, thin, strong fibers of sufficient flexibility to be woven, are heat resistant and chemically inert, and possess a electric insulation properties, and therefore, are suitable for uses (as in yarn, cloth, paper, paint, brake linings, tiles, insulation, cement, fillers, and filters) where incombustible, nonconducting, or chemically resistant material is required. Federal regulation of asbestos is restricted to chrysotile-asbestos, grunerite-asbestos (amosite), crocidolite (riebeckite-asbestos), anthophyllite-asbestos, tremolite-asbestos and actinolite-asbestos.

3.2 Asbestiform: said of a mineral that is like asbestos, i.e., crystallizes with the habit of asbestos. Some asbestiform minerals may lack the properties which make asbestos commercially valuable such as long fiber length and high tensile strength. All asbestos exhibits a fibrillar structure, i.e., parallel growth of fibrils in bundles. Under the light microscope, the asbestiform habit is generally recognized by the following characteristics:

3.2.1. mean aspect ratios ranging from 20:1 to 100:1 or higher for fibers longer than 5 μm.
3.2.2. very thin fibrils, usually less than 0.5 μm in width, and
3.2.3. two or more of the following:
a. parallel fibers occurring in bundles
b. fiber bundles displaying splayed ends
c. matted masses of individual fibers, and
d. fibers showing curvature

3.3 Fiber: an elongated single crystal or similarly elongated polycrystalline aggregate.

3.4 Fibril: the smallest unit fiber in a bundle of fibers characteristic of the asbestiform habit.

4. SUMMARY OF THE METHOD

4.1 Bulk samples of building materials taken for asbestos identification are first examined with a low-power binocular microscope for homogeneity, the presence or absence of fibrous constituents, preliminary fiber identification, and an estimate of fiber content. Possible identification of fibers or the confirmation of the absence of fibers is made by analysis of subsamples with the polarized light microscope.

5. SIGNIFICANCE AND USE

5.1 This method of testing is applicable to building materials including insulation, ceiling tiles, surface coatings, asbestos board, pipe coverings, etc. It is not recommended for floor tiles. However, if fibers can be liberated from a non-friable matrix, they can be identified by this method.

5.2 If the estimate of the percentage of asbestos in a sample is close to the 1% by weight level, other methods of quantification may be necessary if it is important to determine whether or not asbestos content is more or less than 1% by weight. This distinction may be important because the EPA defines asbestos-containing materials as those materials containing greater than 1% by weight asbestos (Ref. 2 and 3).

5.3 The details of the methods used to determine the optical properties of minerals are not included in this method. The method assumes that the analyst is proficient in making these measurements.

6. INTERFERENCES

6.1 Cellulose may have approximately the same index of refraction as chrysotile-asbestos. For this reason, it is frequently confused with chrysotile. However, cellulose fibers frequently pinch and swell along their length, exhibit internal cellular structure, and lack splayed ends: they are not composed of bundles of smaller fibers.

6.2 Cleavage fragments of many natural minerals including amphiboles, talc, gypsum, wollastonite and vermiculite may appear as elongated anisotropic particles. The aspect ratio of these particles may be as great as 20:1. Therefore, aspect ratio alone is not sufficient for the identification of asbestos. Other properties of the asbestiform habit, such as curved fibers, fiber bundles exhibiting splayed ends, and fibers with aspect ratios in excess of 20:1 must be observed in order to be sure asbestiform material is present in the sample. However, these properties need not be characteristic of every fiber or fiber bundle in the sample. Therefore, once asbestos is known to be present, other properties such as index of refraction and aspect ratio can be used to identify asbestos and determine which particles will be counted in making a quantitative estimate of the amount of asbestos in the sample.

6.3 Sprayed-on binder materials may coat fibers and affect color or obscure optical characteristics. Fine particles of other materials may also adhere to fibers. Occasionally, procedures other than those described in this test method may be helpful if the analyst is unable to observe fibers clearly. Some of these are described in Reference 1.

6.4 Vermiculite may be confused with chrysotile because it has a similar index of refraction and, while it is not fibrous, its extinction characteristics under crossed polars may give the impression that the particles are composed of masses of matted fibers. The problem is compounded by the fact that chrysotile and vermiculite are a common mixture in sprayed-on coatings.

6.5 Certain materials may be found in construction materials, which are fibrous or asbestiform but which are not asbestos. Those include but are not limited to fibrous talc, fibrous brucite (nemalite), zeolites and dawsonite.

6.6 Man-made fibers such as carbon, aluminum oxide, polyamides (nylon), polyester (Dacron) and polyolefins (polyethylene), and rayon are occasionally encountered in building materials.

6.7 Fibrous glass including both mineral wool and fiberglass is very common in building materials. Its isotropic character makes it readily distinguishable from asbestos.

6.8 Animal hair is occasionally encountered.

6.9 Heat and acid treatment may alter the index of refraction of asbestos and change its color. Heat can cause chrysotile and amosite to turn brown and may raise the indices of refraction significantly.

6.10 Moisture can interfere with the determination of optical properties. Wet samples should be dried at a temperature less than 150°C before examination.

7. EQUIPMENT

7.1 A magnifying glass or a low power binocular microscope, approximately 10-45x, with built-in or separate light source

7.2 Forceps, dissecting needles and probes

7.3 Glassine paper or clean glass plate

7.4 Polarized light microscope complete with a port for wave retardation plate, 360 degree graduated rotating stage, substage condenser, lamp and lamp iris

7.5 Objective lenses: low power (10x); high power (40-50x). Medium power (20-25x) and very low power (2-4x) lenses are optional.

7.6 Dispersion staining objective lens (optional)

7.7 Ocular lens: 8x minimum

7.8 Eyepiece reticle: cross hair

7.9 Compensator (wave retardation plate): 550 nanometer (first-order red or gypsum)

7.10 Microscope slides

7.11 Coverslips

7.12 Mortar and pestle: agate or porcelain

8. REAGENTS

8.1 Index of refraction liquids: N_D = 1.490-1.720 in increments of 0.002 or 0.004.

8.2 Index of refraction liquids for dispersion staining: high dispersion series, N_D = 1.550, 1.605, and 1.680. (Optional. Required only if dispersion staining will be used to measure the index of refraction.)

8.3 Reference materials:

8.3.1 Asbestos Materials

a. Commercial asbestos, including amosite, chrysotile, crocidolite, and anthophyllite asbestos. (UICC Asbestos Reference Sample Set available from UICC MRC Pneumoconiosis Unit, Llandough Hospital, Penarth, Glamorgan, CF6 1XW UX and commercial distributors.)

b. Tremolite-asbestos: available from commercial distributors, such as Ward's Natural Science Establishment, Inc., P.O. Box 92912, Rochester, New York, 14692-9012.

c. Actinolite-asbestos: source to be determined (very rare; not used commercially).

8.3.2 Suggested Matrix and Non-asbestos materials.

a. Cellulose

b. Vermiculite: source to be determined.

c. Non-asbestiform amphiboles: available from commercial distributors, such as Ward's Natural Science Establishment, Inc., P.O. Box 92912, Rochester, New York 14692-9012.

d. Other silicates, such as fibrous talc, wollastonite, gypsum, nemalite (brucite): available from commercial distributors, such as Ward's Natural Science Establishment, Inc., P.O. Box 92912, Rochester, New York 14692-9012.

e. Synthetic fibers, such as fiberglass and mineral wool.

9. PRECAUTIONS

9.1 This method involves the analysis of material (asbestos), which may be hazardous if inhaled. It does not address the safety problems associated with its use. In addition, it should be noted that some immersion oils manufactured prior to 1978 might contain Polychlorinated Biphenols (PCB). PCB's have been identified as hazardous materials. It is the responsibility of whoever uses this method to establish appropriate safety and health practices to ensure that asbestos is not inhaled and exposure to PCB does not occur.

10. SAMPLING

10.1 Samples should be taken in the manner prescribed in Reference 2. Information on design of sampling and analysis programs may be found in Reference 3. If there are any questions about the representative nature of the sample, another sample should be requested before proceeding with the analysis.

11. GENERAL METHOD DESCRIPTION

11.1 Bulk samples of building materials are first examined with a low power binocular microscope or magnifying glass for homogeneity, the presence or absence of fibrous constituents, preliminary fiber identification and an estimate of fiber content.

11.2 Positive identification of fibers or the confirmation of the absence of fibers is made by analysis of subsamples with the polarized light microscope according to the outline presented in Table I. The optical properties of six types of asbestos are given in Table II. The use of plane polarized light allows the determination of index of refraction parallel to elongation. Morphology and color are observed. Orientation of the two polarizers such that their vibration directions are perpendicular (crossed polars) allows the distinction between anisotropic and isotropic materials to be made. It also allows observation of the birefringence and extinction characteristics of anisotropic particles. When a compensator is inserted into the optical path, the sign of elongation of the particle can be determined. Also, the fibrillar structure of asbestos is most evident under crossed polars.

11.3 Identification of the fibrous constituents is facilitated by comparison of the unknowns to materials in the reference collection.

11.4 A quantitative estimate of the amount of asbestos present is derived from the combination of the estimate made from slide preparations and the estimate of total fiber made from examination of the bulk sample.

12. SAMPLE PREPARATION

12.1 For initial observation, the sample should be placed on a clean glass plate or glassine paper and placed under the binocular microscope or examined with a magnifying glass. Color, the presence or absence of fibers, and homogeneity should be observed and recorded. If only an occasional fiber is observed, one or two should be isolated with forceps and prepared for examination by polarized light microscopy. A preliminary estimate of total fiber content can be made at this time.

12.2 Subsamples for polarized light microscopy are usually best prepared by using forceps to sample at several places from the bulk material. These subsamples are immersed in a refractive index liquid on a microscope slide, teased apart and covered with a cover glass. At a minimum, two slide preparations should be made.

12.3 If the material is obviously layered or comprised of two or more materials that differ in color or texture, slide preparations of each component should be made.

12.4 If the sample is not readily friable or if the sample consists of a coarse-grained matrix, a mortar and pestle can sometimes be used to crush the sample.

12.5 Other methods of sample preparation for homogenization and to remove interferences, such as milling, acid and sodium metaphosphate treatment and ashing, are not normally necessary. They are described in Reference 1.

13. IDENTIFICATION OF ASBESTOS

13.1 Positive identification of asbestos requires the determination of the following optical properties: morphology, color and pleochroism, index of refraction parallel to elongation, birefringence, extinction characteristics and sign of elongation. Techniques

for determining these properties are described in References 4 through 8. Characteristics of the asbestiform habit (morphology) are described in References 9 and 10. The sign of elongation is determined by use of a compensator and crossed polars. Index of refraction may be determined by the Becke line method (Reference 4) or by dispersion staining (Reference 8). The optical properties are given in Table II. General optical properties of silicates other than asbestos are found in References 4-7.

14. QUANTIFICATION OF ASBESTOS CONTENT

14.1 A quantitative estimate of the amount of asbestos present is most readily obtained by visual comparison of the bulk sample and slide preparations to other slide preparations and bulk samples with known amounts of asbestos present in them. Reference samples containing known amounts of asbestos will be available in the future from the National Institute of Standards and Technology, Office of Standard Reference Materials. Until these standards are available, laboratories should make their own standards for training and intra-laboratory comparison.

14.2 Point counting of slide preparations is not generally recommended. Point counting only produces accurate quantitative data when the material has uniform thickness. In practice, the thickness of asbestos-containing materials placed on a glass slide for petrographic analysis is often highly variable, rendering quantitative volume estimates inaccurate. However, the method recommended by the EPA for determining the amount of asbestos uses point counting techniques. It is described in Reference 1.

14.3 Estimates of the quantity of asbestos obtained by the method described in 14.1 above are neither volume nor weight-percent estimates. They are based on estimating the projected area from observation of the distribution of particles over the two-dimensional surface of the glass slide and on an observation of the bulk material. A basis for correcting to a weight or volume percent basis has not been established. However, the error introduced by assuming that the estimates are equivalent to weight percent is probably within the precision of the visual estimate techniques.

15. DATA PRESENTATION

15.1 The following information should be reported for each sample: color, presence or absence of asbestos, type or types of asbestos present, estimate of the area percentage of each type of asbestos present, area percentage of other fibrous materials present, and identity of other fibrous materials if known.

15.2 If the sample submitted for analysis is inhomogeneous and subsamples of the components were analyzed separately, the data for each subsample should be recorded separately. However, the separate components should be combined in proportion to their abundances and a single analysis should be provided for the sample as a whole.

15.3 Example Sample Analysis Sheet

Analysis of Asbestos in Bulk Materials

Sample Identification

Analyst:

Date:

Macroscopic Examination:

1. Size and Condition of Sample:
2. Texture: (occurrence of fibrous and other components)
3. Color:
4. Homogeneity:
5. Comments

Microscopic Examination:

1. Number and Size of Subsamples:
2. Preparation: (incl. Grinding, ashing, acid washing, ...)
3. Method of estimation if other than visual estimation:
4. Standards used for quantitation (if any):
5. Index of refraction of the immersion medium

Sample Identification:

Analysis of fibrous component:

	Component 1	Component 2
a. Morphology		
b. Color		
c. Birefringence		
d. Extinction characteristics		
e. Indices of refraction (dispersion characteristics)		
f. Sign of elongation		
g. Estimated range (percent area) of fibrous component		

Comments: (Describe any unusual characteristics or problems with analysis and if possible, briefly describe non-fibrous matrix components.)

Sample Summary

Sample Identification:

Conclusions

1. Asbestos present: yes no
2. Fibrous-nonasbestos component present: yes no
3. Number of distinct fibrous components:
4. Types of fibers:
5. Estimated range (percent area) of each fiber type:
6. (Optional information on nonfibrous components).

16. QUALITY ASSURANCE

16.1 Laboratories performing this test method should have demonstrated proficiency in the method. This would include adequate training of the analyst, an internal quality assurance program and participation in the EPA's Bulk Sample Analysis Quality Assurance Program or the National Institute of Standards and Technology Laboratory Accreditation Program for the Analysis of Asbestos. The laboratory should have a complete set of reference materials.

16.2 In order to obtain the accuracy indicated in 17.3, it is suggested that the analyst have completed a college-level course in mineralogy, had formal training in polarized light microscopy and its application to crystalline materials including instruction in the measurement of the index of refraction by the immersion method through Becke line technique and/or dispersion staining, and have experience analyzing asbestos samples. If this training is lacking, two years of participation in the EPA's Bulk Sample Analysis Quality Assurance Program with a 100% success rate is a good indication of proficiency in the application of this method.

16.3 An internal quality assurance program should involve blind samples and replicate analyses. It is also necessary to analyze blank samples to check for contamination of immersion oils, probes, slides and general sample preparation.

16.4 A record of the sample analyses should be kept that includes all the sample and analysis data. An example analysis recording form can be found in section 15.3. While the format of the record is not required, all the information detailed in the sample should be recorded for each sample.

17. PRECISION AND BIAS

17.1 The upper detection limit is 100%. The lower detection limit is less than 1%.

17.2 A preliminary evaluation of a method similar to that outlined in this document is found in Reference 11.

17.3 If used by a properly trained and experienced analyst, the accuracy in the determination of the presence or absence of greater than 1% asbestos is greater than 99%. If the analyst does not have the training specified in 16.2, the accuracy may be considerably reduced.

17.4 The error associated with the quantitative estimate of weight or area percent asbestos may be quite large. When the percentage of asbestos in the bulk sample is small, the error in the estimate may exceed 100% relative. Relative errors are particularly large in estimates near 1%. When the percentage of asbestos is large, however, the error is significantly reduced and may be as low as 10% relative or less. The precision and accuracy of the quantitative estimate are highly dependent on the training and experience of the analyst.

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11. U.S. Environmental Protection Agency, "Bulk Sample Analysis for Asbestos Content: Evaluation of the Tentative Method," EPA 600/4-82-021, May 1982.

TABLE I: Flow Chart for Qualitative Analysis of Bulk Samples by Polarized Light Microscopy

Polarized light microscopy qualitative analysis: For each type of material identified by examination of sample at low magnification, mount spatially dispersed sample in 1.550 RI liquid. (If using dispersion staining, mount in 1.550 ND.) View at approximately 100x with both plane polarized light and crossed polars. More than one fiber type may be present.

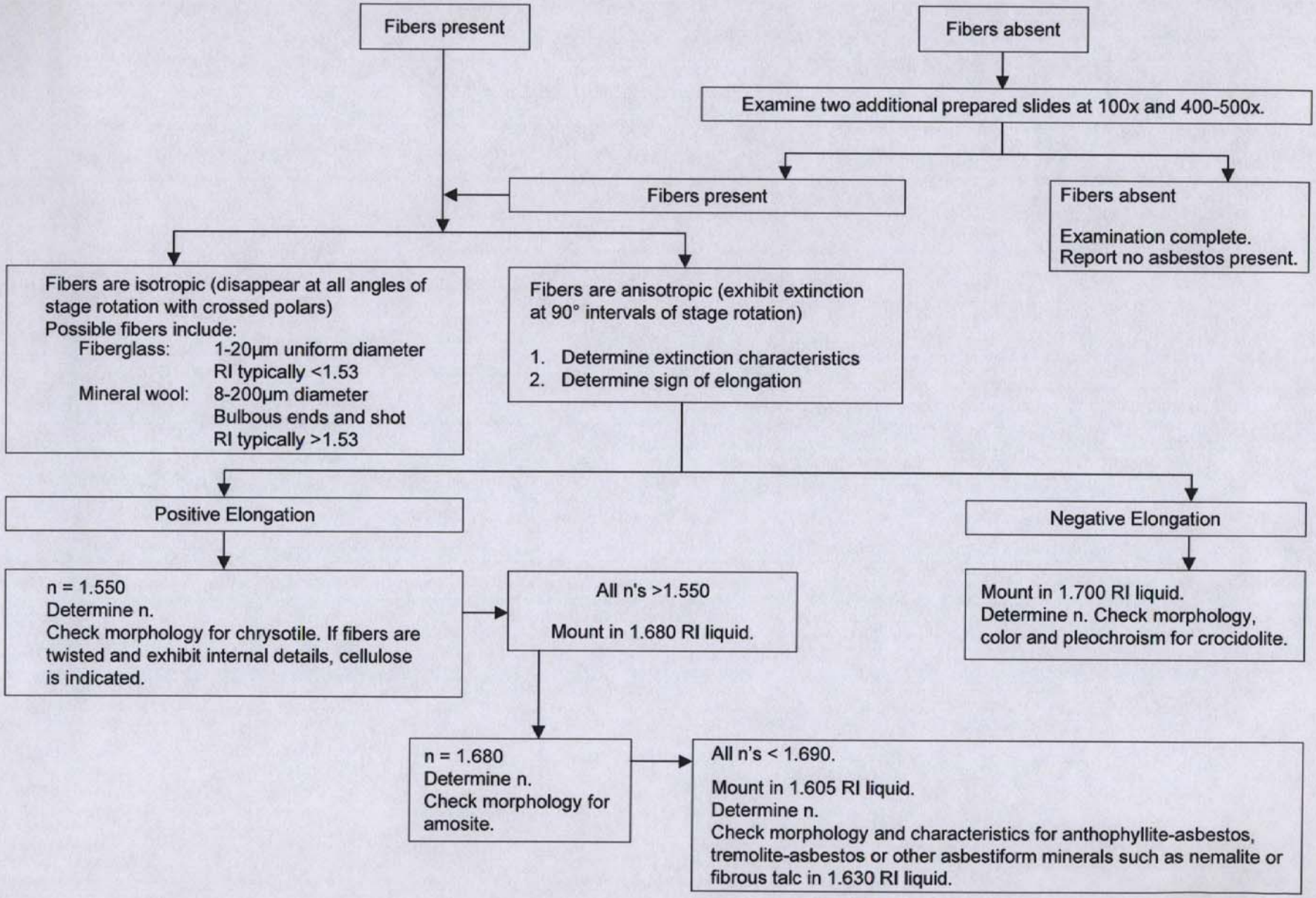

TABLE II

Mineral	Morphology and Color	Refractive Indices (Approximate Values)		Birefringence	Extinction	Sign of Elongation
		Parallel to Elongation	Perpendicular to Elongation			
Chrysotile-asbestos	Wavy fibers with "kinks" common. Large fiber bundles may show splayed ends. Colorless and nonpleochroic. Very common in building materials.	1.55	1.54	0.002-0.014	Parallel	Positive (length slow)
Cummingtonite-grunerite-asbestos (Amosite)	Straight fibers and fiber bundles. Only long fibers show curvature. Fiber bundles usually show splayed ends. Colorless to brown; may be weakly pleochroic. Common in building materials.	1.70	1.67	0.02-0.03	Parallel	Positive (length slow)
Crocidolite	Straight and curved fibers showing splayed ends are common. Blue color characteristic. Pleochroism marked. Uncommon in building materials.	1.70	1.71	0.014-0.016 Interference colors may be masked by blue color	Parallel	Negative (length fast)
Anthophyllite-Asbestos	Straight fibers and fiber bundles showing splayed ends. Colorless to light brown. Pleochroism absent. Rare in building materials.	1.63	1.61	0.013-0.028	Parallel	Positive (length slow)
Tremolite-asbestos and actinolite asbestos	Straight and curved fibers and fiber bundles. Large bundles show splayed ends. Tremolite is colorless. Actinolite is green and weakly to moderately pleochroic. Both actinolite and tremolite are extremely rare in building materials.	1.62-1.64 (tremolite) 1.64-1.68 (actinolite)	1.60-1.62 (tremolite) 1.62-1.67 (actinolite)	0.02-0.03	Parallel in most fibers. Narrow fibers may show oblique extinction (c$\wedge$Z up to 20°) in some samples	Positive (length slow)