



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
SOLID WASTE AND EMERGENCY
RESPONSE

MEMORANDUM

DATE: 2/21/03

**SUBJECT: MISSING/OMITTED STUDIES FROM EPA DRAFT ASBESTOS
RISK REASSESSMENT RELEVANT TO:**

- 1. Mesothelial and lung tissue burden in mesothelioma cases**
- 2. Carcinogenicity of chrysotile asbestos**

FROM: Cate Jenkins, Ph.D.¹
jenkins.cate@epa.gov
Waste Identification Branch (Mail Code 5304 W)
Hazardous Waste Identification Division, OSW, OSWER

C Jenkins

TO: Richard Troast
Office of Solid Waste and Emergency Response
703/603-9019, Mail Code 5204 G

In response to the February 5, 3003 *Federal Register* notice, announcing a peer consultation workshop on EPA's draft asbestos cancer risk reassessment based on fiber size and fiber type,² I am sending you a compilation of studies that are relevant to the issue. See attachment.

The draft EPA asbestos re-assessment³ left out, missed, neglected, or omitted these important studies. Even if eventually found irrelevant or not compelling, they should be included and discussed fully during the risk reassessment process. Not including these studies serves only to bias the outcome of the risk reassessment.

¹ The conclusions and opinions in this memorandum are those of the author and do not necessarily reflect those of the U.S. Environmental Protection Agency. This memorandum is the result of the personal concerns of the author over the handling of the WTC cleanup.

² *Federal Register*, Volume 68 (24), pages 5873-5874, announcing the upcoming meeting in San Francisco from February 25 to 27, 2003 may be found at:
http://www.access.gpo.gov/su_docs/aces/aces140.html
Choose the year 2003. Insert the page number 5873 into the "search terms" box.

³ The draft EPA IRIS (Integrated Risk Information System) asbestos re-assessment may be found at the following web site (note that the *FR* notice gave the wrong web address):
<http://www.epa.gov/superfund/programs/risk/asbestos/method.htm>

ATTACHMENT

2/20/03

COMPILATION OF ABSTRACTS AND EXTENDED ABSTRACTS STUDIES RELEVANT TO:

- 1. Mesothelial Tissue and Lung Tissue Asbestos Burden Studies
in Human Mesothelioma Cases**
- 2. Carcinogenicity of Chrysotile Asbestos**

If anyone has the capacity to receive very large file size documents by email in PDF format, I would be happy to send the full studies to you.

My email address is jenkins.cate@epa.gov.

Ann N Y Acad Sci 2002 Dec;982:160-76

Asbestos fibers contributing to the induction of human malignant mesothelioma

Yasunosuke Suzuki and Steven R. Yuen

Department of Community and Preventative Medicine, Mt. Sinai School of Medicine, 1 Gustave L. Levy Place, New York City, New York, 10029, U.S.A.

To elucidate the features of the asbestos fibers contributing to the induction of human malignant mesothelioma, we determined the type, number and dimensions of the asbestos fibers seen in both the lung and mesothelial tissues in 168 cases of mesothelioma by high-resolution analytical electron microscopy. Results were as follows: 1. Asbestos fibers were present in almost all of the lung tissue as well as in the mesothelial tissues from the mesothelioma cases. 2. The most common types of asbestos seen in the lung were either an admixture of chrysotile with amphiboles or amphibole alone. Occasionally we encountered chrysotile alone. By contrast, in the mesothelial tissues, the vast majority of the asbestos fibers seen were chrysotile. 3. In the lung, amosite fibers were greatest in number per dry gram followed by chrysotile, crocidolite, tremolite/actinolite and anthophyllite. In the mesothelial tissues, chrysotile fibers were extremely large in number, much greater than the number of amphiboles (mainly amosite) fibers. 4. In some of the mesothelioma cases, the only asbestos fibers detected in either the lung or mesothelial tissue were chrysotile fibers. 5. The average number of asbestos fibers counted in both the lung (56.4×10^6 fibers/dry gram) and the mesothelial tissues (46.5×10^6 fibers/dry gram) was greater than the number of fibers in the general population's lung (0.44×10^6 fibers/dry gram) and the mesothelial tissue (0.41×10^6 fibers/dry gram). The number of chrysotile fibers in the mesothelial tissues was 30.3 times larger than that of amphiboles (mainly amosite) in the mesothelial tissues from mesothelioma patients. 6. The majority of asbestos fibers ($9,454/10,575$; 89.4%) detected in the lung and mesothelial tissues from the 168 mesothelioma cases were shorter than $5 \mu\text{m}$ in length. The observed disproportion in the type and number of the fibers between the lung and mesothelial tissues was considered to have been caused by chrysotile fibers' strong capacity to translocate from the lung to mesothelial tissues. Asbestos fibers that fit Stanton's hypothetical dimensions comprised only 2.3% ($247/10,575$) of the total fibers encountered since the majority of the actual fibers observed were shorter ($<8.0 \mu\text{m}$ in length) and thinner ($<0.25 \mu\text{m}$ in width) than would be predicted by Stanton's hypothetical model. We concluded that: a) to grasp a total picture of asbestos exposure and also to identify the types of asbestos fibers associated with the induction of human malignant mesothelioma,

asbestos fiber analysis should be done in both the lung and mesothelial tissues. Examination of lung tissue alone can be misleading since a disproportion in both the type and number of asbestos fibers was frequently present between the two tissues; b) short, thin asbestos fibers should be included in the list of fiber types contributing to the induction of human malignant mesothelioma, since such fibers were the majority detected in the lung and mesothelial tissue; c) The present study supports that chrysotile asbestos can induce human malignant mesothelioma, since in some mesothelioma cases the only asbestos fibers detected in the lung or mesothelial tissues were chrysotile fibers.

Introduction

It is well accepted that asbestos fibers are the cause of virtually all cases of human malignant mesothelioma. It is also known that all asbestos types including chrysotile and amphiboles have been shown in epidemiological and toxicological studies to be fully capable of inducing the tumor. In addition to a heavy asbestos exposure (an occupational exposure to asbestos), a milder asbestos exposure (such as a bystander's exposure to asbestos and a family contact to asbestos) can also induce the tumor.

...

It is known that some of the inhaled asbestos fibers translocate from the lung into various organs including regional lymph nodes, pleural and peritoneal mesothelial tissues 16-24 and other organs. Potential routes of passage of the fibers from the lung to these organs include a direct migration, migration via lymphatic capillary system and migration via blood capillary system.

Up to the present, for identification of asbestos fibers contributing to the induction of human malignant mesothelioma, most investigators have focused exclusively on the asbestos fibers in the lung from mesothelioma patients. However we have questioned the adequacy of such an approach since a) the primary site of malignant mesothelioma is not the lung but the mesothelial tissue. The fibers detected in the mesothelial tissue from the patients seems to be more important as a causal factor for their malignant mesothelioma compared with those detected in their lung, and b) the type and number of asbestos fibers seen in the lung may not be identical to those seen in the mesothelial tissue, since some of intrapulmonary asbestos fibers translocated to other organs including the mesothelial tissues.

...

It has been proposed on the basis of animal studies that long (greater than $8\mu\text{m}$ in length) and thin (less than $0.25\mu\text{m}$ in width) mineral fibers were strongly carcinogenic for the induction of malignant mesothelioma in rats (Stanton's hypothesis) and that shorter fibers pose less risk. Stanton's hypothetical dimensions were derived from his experimental studies using direct administration of heavy doses of various mineral fibers with different dimensions into rats' pleural cavities. Stanton stated that direct application of his results to the problem in man would be unwise. However his hypothetical model of asbestos fibers' relative carcinogenicity has been

directly applied to the counting of the asbestos fibers in the human situation.

...

Results . . .

1) Asbestos fibers were present in almost all of the lung tissue (117/119; 98.3%) as well as in the mesothelial tissues (114/123; 92.7%).

2) A disproportion in the types of asbestos fibers between the lung and the mesothelial tissues was common; it was seen in 49 of 74 cases (66.2%).

3) The most common asbestos types seen in the lung were an admixture of chrysotile with amphiboles (43/119; 36.1%) or amphiboles alone (43/119; 36.1%). Chrysotile alone was seen occasionally (31/119; 26.1%). Rarely, no asbestos fibers were seen (2/119; 1.7%).

4) In the mesothelial tissues, the major asbestos type seen was chrysotile alone (90/123; 73.2%), followed by chrysotile plus amphibole (22/123; 17.9%), no asbestos fibers detected (9/123; 7.3%) and amphibole alone (2/123; 1.6%). The amphiboles included anthophyllite (mixed with chrysotile in 15 cases and exclusively in 1 case), followed by tremolite (mixed with chrysotile in 4 cases) and amosite (mixed with chrysotile in 3 and amosite alone in 1 case),

...

The average number of each type of asbestos fibers in the lung (49 cases) was greatest in amosite (36.9×10^6 fibers/dry gram), followed by chrysotile (19.4×10^6 fibers/dry gram), crocidolite (3.13×10^6 fibers/dry gram), tremolite/actinolite (1.69×10^6 fibers/dry gram) and anthophyllite (0.27×10^6 fibers/dry gram). By contrast, in the mesothelial tissues (22 cases), the average number of asbestos fibers was greatest in chrysotile (45.2×10^6 fibers/dry gram) followed by amosite (1.3×10^6 fibers/dry gram), anthophyllite (1.03×10^6 fibers/dry gram), crocidolite (0.01×10^6 fibers/dry gram) and tremolite/actinolite (0×10^6 fibers/dry gram). It was obvious that a disproportion of the average number of asbestos types was present between the lung and mesothelial tissues among the 22 cases of malignant mesothelioma.

...

From the 168 cases of human malignant mesothelioma, dimensions (length and diameter) of a total of 10,575 asbestos fibers which were detected in the lung and the mesothelial tissues (mesotheliomatous tissue and fibrotic serosa including hyaline plaque) were measured. . . . it was concluded that asbestos fibers detected in the lung and mesothelial tissues from mesothelioma patients were predominantly short and thin in dimensions; 89.4% of asbestos fibers seen in these tissues were shorter than 5 μm and the percentage of asbestos fibers that confirms Stanton's hypothetical dimensions (longer than 8 μm in length and smaller than 0.25 μm in diameter) was only 2.3%.

...

Discussion . . .

Our present study revealed that the majority of asbestos fibers detected in the lung and mesothelial tissues were shorter than 5 μm ; only 10.5% (1,115/10,575) of the fibers were longer than 5 μm in length.

Thinness of asbestos fibers has been emphasized as an important factor for their penetration from the proximal area to the peripheral part in the lung and also for their translocation from the lung to the pleura. It was also suggested that the thinness was related to the carcinogenicity of asbestos fibers.

The present study supports such ideas since the vast majority of asbestos fibers translocated into the mesothelial tissues (the original site in which malignant mesothelioma develops) were very thin in their diameter (0.04 μm in G.M.).

Our present study also revealed that asbestos fibers fitting Stanton's hypothetical dimensions (=8 μm in length and =0.25 μm in width) comprised only 2.3% (247/10,575) among the fibers detected in both the lung and mesothelial tissues.

From these findings, it is obvious that if we exclusively count asbestos fibers longer than 5 μm or if we select only asbestos fibers fitting to Stanton's hypothetical dimensions, a large proportion of asbestos fibers in these tissues will be omitted, since the majority are shorter than 5 μm in length, although the diameter of these short fibers does generally fit well Stanton's width parameter.

On the basis of the data presented here, we conclude that short, thin asbestos fibers should be carcinogenic. The present study showed that they were the principal type of asbestos fiber encountered in the lung and mesothelial tissues taken from mesothelioma cases.

...

J Toxicol Environ Health A 2002 Aug 23;65(16):1109-20

Asbestos burden in two cases of mesothelioma where the work history included manufacturing of cigarette filters.

Dodson RF, Williams MG, Satterley JD.

University of Texas Health Center at Tyler, 11937 U.S. Highway 21, Tyler, TX 75708, USA.
ronald.dodson@uthct.edu

Asbestos has been used in many applications, but possibly one of the more unique was in the manufacturing of filters for cigarettes. The type of asbestos used in this application was crocidolite. Data from several resources indicate that crocidolite was one of the least utilized types of commercial asbestos in the United States. The present study provides quantitative tissue burden analysis data for two mesothelioma cases where the work histories included manufacturing of cigarette filters that contained crocidolite. The data include the number of asbestos bodies and uncoated fibers per gram of tissue, as well as the dimensions of these structures. The conclusion of the findings indicates that the individuals had an appreciable homogeneous exposure to crocidolite asbestos.

...

Case Reports — Case 1

The first man (case 1) in the study had a history of working in various vocations. ... While some of this individual's jobs may have had the potential for exposures such as Becklake (1976) described, one assignment clearly involved direct exposure to asbestos.

It was discovered that the individual worked for a period of time extending from 1953 into 1954 for a company making asbestos-containing filters for cigarettes. . .

The individual was a 67-yr-old male who first sought medical attention in early August 1998 with his chief complaints being shortness of breath and right-side chest pain. . .

...

Case Reports — Case 2

The second man (case 2) had worked in the filter manufacturing facility from 1951 until his retirement in 1983. . . The individual presented in 1998 as a 67-year-old male complaining of exertional dyspnea and shortness of breath. . .

...

DISCUSSION . . .

A patient's risk for the occurrence of disease from any asbestos including exposure to crocidolite includes factors such as its clearance rate. This has been reported as lowest for the commercial amphibole fibers, including crocidolite (Du Toit, 1991). The high aspect ratio of crocidolite, among other features, has also resulted in it being labeled in one publication as the most fibrogenic asbestos in the lung (Murai et al., 1994). . . . Shorter fibers are considered more readily cleared than longer fibers. Yet even with clearance over time from last exposure, fibers making up 39% (case 2, right lung) to 54% (case 1, left lung) of the total fiber burden were less than 5 μm [5 *micrometers*] in length. Thus, the remaining fibers at the time of death must reflect a fraction of the fibers that had earlier been in the tissue. . .

Occup Environ Med 2002 Sep;59(9):643-6

Chrysotile and tremolite asbestos fibres in the lungs and parietal pleura of Corsican goats.

Dumortier P, Rey F, Viallat JR, Broucke I, Boutin C, De Vuyst P.

Chest Department, CUB Hopital Erasme, 808 Route de Lennik, B1070 Brussels, Belgium.
pdumorti@ulb.ac.be

BACKGROUND AND AIMS: Environmental exposures to chrysotile and tremolite from the soil cause pleural plaques and mesothelioma in northeast Corsica. Goats grazing in the contaminated areas inhale asbestos fibres. We used this natural animal model to study whether these exposures actually result in increased fibre burdens in the lungs and parietal pleura.

METHODS: Ten goats from areas with asbestos outcrops and two from other areas were slaughtered. Fibre content of lung and parietal pleural samples was determined by analytical transmission electron microscopy. **RESULTS:** Both chrysotile and tremolite fibres were detected. In the exposed goats, the geometric mean concentrations of asbestos fibres longer than 1 µm were 0.27 x 10(6) fibres/g dry lung tissue and 1.8 x 10(6) fibres/g dry pleural tissue. Asbestos fibres were not detected in the lungs of the two control goats. Chrysotile fibres shorter than 5 µm were predominant in the parietal pleura. Tremolite fibres accounted for 78% and 86% of the fibres longer than 5 µm in lung and parietal pleural samples, respectively.

CONCLUSIONS: Environmental exposure in northeast Corsica results in detectable chrysotile and tremolite fibre loads in the lung and parietal pleura of adult goats. Tremolite fibres of dimensions with a high carcinogenic potency are detected in the parietal pleura.

...

DISCUSSION ...

Only four studies including no more than 63 cases have investigated parietal pleura asbestos fibre burden in cases with pleural diseases, either pleural plaques or mesothelioma. Our findings among goats are in agreement with these observations: in general fibres in the pleura are on the average shorter than fibres in the lungs. Most chrysotile fibres in the parietal pleura are shorter than 5 µm and approximately 80% of the “Stanton fibres” are amphibole fibres.” ... As with humans, the distribution of fibres in the pleura is heterogeneous. Fibres retained in the parietal pleura are shorter than those retained in the lungs. Short chrysotile fibres predominate in the pleura, but tremolite fibres of dimensions with a high carcinogenic potency are also detected. ...

Ind Health 2001 Apr;39(2):150-60

Asbestos tissue burden study on human malignant mesothelioma.

Suzuki Y, Yuen SR.

Department of Community and Preventive Medicine, Mount Sinai School of Medicine, New York, New York, USA.

Asbestos fibers in the lung and mesothelial tissues (mesotheliomatous tissue and hyaline plaque) taken from 151 human malignant mesothelioma cases were identified and characterized by high resolution analytical electron microscopy. Asbestos fibers were present in almost all of the lung tissue as well as in the mesothelial tissue. The most common asbestos types seen in the lung were an admixture of chrysotile with amphiboles followed by amphiboles alone and chrysotile alone. The majority of asbestos types seen in the mesothelial tissues were chrysotile alone, followed by chrysotile plus amphibole and amphibole alone. A disproportion of asbestos types between the lung and mesothelial tissues was frequently observed. The most common pattern of the disproportion was chrysotile plus amphibole(s) in the lung and chrysotile only in the mesothelial tissues, followed by amphibole(s) in the lung and chrysotile only in the mesothelial tissues. Such a disproportion was considered to have been caused by chrysotile fiber's strong capacity to translocate from the lung to mesothelial tissues. The number of asbestos fibers in the lung was 456.4×10^6 fibers/dry gram in maximum, 0.08×10^6 fibers/dry gram in minimum and 105×10^6 fibers/dry gram on average; in the mesothelial tissues it was 240.0×10^6 fibers/dry gram in maximum, 0.03×10^6 fibers/dry gram in minimum and 49.84×10^6 fibers/dry gram on average. These numbers were greater than those seen in the general population. The majority of asbestos fibers detected in the lung and mesothelial tissues were shorter than $5 \mu\text{m}$ in length. Asbestos fibers fit to Stanton's hypothetical dimensions ($\geq 8.0 \mu\text{m}$ in length and $\geq 0.25 \mu\text{m}$ in diameter) were only 4.0%, since the majority of these fibers were shorter ($< 8 \mu\text{m}$) and thinner ($< 0.25 \mu\text{m}$) fibers. We concluded that such short, thin asbestos fibers should not be excluded from those contributing to the induction of human malignant mesothelioma. The present study supports that chrysotile asbestos can induce human malignant mesothelioma, since, in some of the mesothelioma cases, asbestos fibers detected in both the lung and mesothelial tissues, or lung tissue alone or mesothelial tissues alone were exclusively chrysotile fibers.

Introduction

It is well known that human malignant mesothelioma is caused almost exclusively by

exposure to asbestos. It is also known that inhaled asbestos fibers are durable in the lung and persist in the lung and that a part of the fibers are transformed into asbestos bodies after hemosiderin deposits on the surface of the fibers. Interestingly, however, some of intrapulmonary asbestos fibers, particularly chrysotile fibers are cleared from the lung. It is also known that asbestos fibers are capable of translocating from the lung into other tissues including lymph nodes and mesothelial tissue. There were reports that asbestos bodies were found in various organs other than the lung, supporting that asbestos fibers were disseminated from the lung to other organs.

Asbestos fibers in human tissues can be identified and characterized by a high resolution analytical electron microscope, even if they are short and thin in dimension ($\geq 0.1 \mu\text{m}$ in length and $\geq 0.03 \mu\text{m}$ in width).

Up to the present, to clarify asbestos fibers associated with the induction of human malignant mesothelioma, researchers have been focusing almost exclusively on asbestos fibers in the lung tissue taken from mesothelioma patients.

We have questioned the adequacy of such an approach since; a) the primary site of malignant mesothelioma is not the lung but the mesothelial tissue (pleural or peritoneal). Accordingly, asbestos fibers translocated into the mesothelial tissue should be considered as a more important contributory factor for the induction of malignant mesothelioma, and b) there is evidence that type and number of asbestos fibers are frequently different between the lung and the mesothelial tissue in mesothelioma cases. Therefore, it may not be logical to say that intrapulmonary asbestos fibers can be blindly used as a definite marker for the induction of the tumor.

... However, our previous studies revealed that the majority of asbestos fibers in human lung and mesothelial tissues taken from mesothelioma patients did not fit Stanton's hypothetical dimensions; less than 2% of chrysotile fibers and less than 10% of amosite fibers in these tissues fit with Stanton's criteria. Short, thin asbestos fibers [$< 5 \mu\text{m}$] were the majority among asbestos fibers detected in these tissues. It was strongly suggested that short, thin asbestos fibers are contributive to the induction of malignant mesothelioma and that they should not be categorically excluded from carcinogenic fibers.

Asbestos tissue burden study is an effective approach to clarify whether chrysotile fibers are capable of inducing human malignant mesothelioma. If the asbestos type seen in the lung and mesothelial tissues of mesothelioma cases is solely chrysotile, such mesothelioma cases can be considered to have been caused by chrysotile exposure.

Indeed, such cases have been reported elsewhere.

...

Summary ...

3) A disproportion of asbestos types between the lung and mesothelial tissues was frequently

observed. The most common pattern of the disproportion was chrysotile plus amphibole(s) in the lung and chrysotile only in mesothelial tissues (18/64), followed by amphiboles(s) in the lung and chrysotile only in mesothelial tissues (13/64). It was considered that such a disproportion was caused by chrysotile fibers' strong capacity to translocate from the lung to the mesothelial tissues.

...

5) The majority (81.4%; 2347/2884) of asbestos fibers detected in the lung and mesothelial tissues were shorter than 5 μm in length. . . . Such short, thin asbestos fibers should not be excluded from those contributing to the induction of human malignant mesothelioma, since they are the major asbestos fibers detected in the lung and the mesothelial tissues in the mesothelioma cases. . . .

6) The present study supports that chrysotile asbestos can induce human malignant mesothelioma. In some of the mesothelioma cases, asbestos fibers detected in both the lung and mesothelial tissues (15/64; 23.3%); or in lung tissue alone (10/43; 23.3%) or in mesothelial tissues (30/44; 68.2%) were exclusively chrysotile fibers.

Asbestos in extrapulmonary sites: omentum and mesentery.

Dodson RF, O'Sullivan MF, Huang J, Holiday DB, Hammar SP.

Department of Cell Biology and Environmental Sciences, The University of Texas Health Center at Tyler, Tyler, TX 75708, USA.

STUDY OBJECTIVES: Asbestos fibers have not been reported in tissues from the peritoneal cavity. Therefore, omentum, mesentery, and lung tissues from 20 individuals in whom mesothelioma was diagnosed were analyzed for asbestos bodies and asbestos fibers. **DESIGN:** Tissue was digested and prepared filters were analyzed by light microscopy and analytical transmission electron microscopy. **RESULTS:** Asbestos bodies were found in the lungs of 18 individuals, mesentery samples from 5, and omentum samples from 2. Uncoated asbestos fibers were found in lungs of 19 patients, 17 of whom had fibers in at least one extrapulmonary site. The most common asbestos in the omentum and mesentery was amosite. Several features of asbestos found in lung influenced the likelihood of amphibole fibers being found in the omentum or mesentery. Lung features included total amphibole fiber burden, length, aspect ratio, and ferruginous body burden. An increased total ferruginous body burden was strongly associated with increased likelihood of detecting amphiboles in the omentum ($p < 0.05$). **CONCLUSION:** Asbestos fibers reach areas in the peritoneal cavity where some mesotheliomas develop. This study suggests their presence can be predicted based on concentrations and characteristics of fiber burdens in lung tissue.

Abbreviations: AB – asbestos body; ATEM – analytical transmission electron microscopy; FB – ferruginous body

...

Inhaled particles are removed by several mechanisms, including the mucociliary escalator of larger airways and additional mechanisms at the alveolar level.

The lymphatics relocate particles from the lung to pleura and to hilar and more distant lymph nodes. Becklake and Hillerdal suggested the lymphatic route for asbestos relocation from the lung (the original site of deposition) to other parts of the body. A limited number of studies have reported asbestos bodies in the hilar and mediastinal lymph nodes.

Our laboratory has compared the burden of uncoated fibers and asbestos bodies from thoracic nodes to the concentration of asbestos fibers in pleural plaques and lung tissue.

Although we have shown asbestos fibers in thoracic loci where mesotheliomas develop, few or no data exist concerning the presence or absence of asbestos fibers in the linings of the peritoneal cavity, where 10 to 15% of mesotheliomas occur. It is reasonable to assume that asbestos fibers relocate to these sites and, through their physical and chemical properties, stimulate tissue reactions that favor the development of mesothelioma. Based on our previous findings, it is assumed that fibers reaching the peritoneal cavity will require transmission electron microscopy to be detected.

In this study, tissue from 20 individuals with mesotheliomas, most with a history of asbestos exposure, were evaluated. The questions to be answered included whether asbestos fibers would be found in the omentum and mesentery, and, if so, would their presence be predicted by various qualitative and quantitative features of asbestos bodies (ABs) and asbestos fibers in the lung from the same individuals.

...

Results

Uncoated Asbestos Fibers

Uncoated asbestos fibers were found in the lungs of 19 of 20 individuals (95%). Only in case 19 were asbestos fibers not found, as based on the detectable limits within the study. The range of uncoated asbestos fibers in lung tissue was from 13,601,236/g dry weight in an individual with a peritoneal mesothelioma (case 7) to nondetectable (Table 2, Fig 1). The second highest lung burden of uncoated fibers (12,908,314 fibers/g dry weight) occurred in an individual with pleural mesothelioma (case 1). Ten cases (50%) had an uncoated asbestos burden of > 1.4 million asbestos fibers/g dry weight, with all peritoneal mesothelioma cases (cases 6, 7, and 9) having > 1 million asbestos fibers/g dry weight. Two cases of peritoneal mesothelioma (cases 7 and 9) were in the top five for total uncoated asbestos burden.

Seventeen cases (85%) were found to have uncoated asbestos fibers in at least one extrapulmonary site. Fourteen individuals (70%) had uncoated asbestos fibers in the mesentery and omentum (Table 2, Fig 2).

The most prevalent type of asbestos in the mesentery and omentum was amosite (Fig 2). Thirteen mesentery samples (65%) and 14 omentum samples (70%) contained amosite.

The range of amosite fibers among 13 positive mesentery samples was 175 to 5,445 fibers/g dry weight, while in the 14 positive omentum samples, amosite concentrations ranged from 174 to 6,208 fibers/g dry weight. Amosite was found in all three sites (lung, mesentery, and omentum) in 11 cases (55%; Table 2). The longest uncoated amosite fiber found in the lung was 100 μm (case 2) and the shortest amosite fiber was 0.5 μm (case 7). The average length of uncoated amosite fibers in lung from all 20 cases was 11.23 μm . The width of uncoated amosite fibers found in lung ranged from 0.03 μm (case 7) to 1.6 μm (case 7).

The longest amosite fiber in the omentum was 70.0 μm (case 2); the longest in the

mesentery was 40.0 μm (case 11). The width of amosite in the mesentery ranged from 0.06 to 1.1 μm ; and in the omentum, 0.06 to 0.8 μm .

Other results showed that 74.1% of amosite in the lung sampled was $\geq 5.0 \mu\text{m}$ long. The percentage of those in the omentum that were $\geq 5.0 \mu\text{m}$ long was 73.3%, and in the mesentery, 72.4%. The evidence that both long chrysotile and amosite fibers reach these extrapulmonary sites is presented in Table 3.

The second most common type of asbestos found in the extrapulmonary samples, chrysotile, was found in 10 lungs (50% of cases). There were five positive mesentery samples (25% of the sites) and three positive omentum samples (15% of the sites; Fig 2). The amount of chrysotile ranged from 172 to 743 fibers/g dry weight in mesentery samples and from 799 to 1,029 fibers/g dry weight in the omentum. Chrysotile was found in the lung tissue from each of the individuals with positive omentum samples and in three of five individuals with positive mesentery samples (Table 2).

The length of the uncoated chrysotile fibers in lung tissue ranged from 0.50 μm (case 1) to 23.0 μm (case 4). In samples of mesentery, chrysotile fibers ranged from 1.2 to 17.0 μm long. In the omentum, chrysotile length ranged from 1.0 to 14.5 μm . The width of chrysotile fibers ranged from 0.04 to 0.4 μm in lung, from 0.04 to 0.34 μm in the mesentery, and from 0.04 to 0.2 μm in the omentum. The percentage of chrysotile $\geq 5.0 \mu\text{m}$ long in each site was 57.1% in the lung, 42.9% in mesentery samples, and 10.0% in the omentum (Table 3).

Crocidolite was found in five lung samples (25%; range, 20,482 to 224,058/g dry weight), in three mesentery samples (15%; range, 209 to 2,228/g dry weight), and in one omentum sample (5%; 289/g dry weight), as shown in Table 2 and Figure 2.

The individual with a positive omental sample for crocidolite was positive for crocidolite in the lung sample (Table 2). One of three positive mesentery samples was from a patient (case 3) found to have crocidolite in his lung sample (Table 2). The length of crocidolite fibers in the lung ranged from 2.0 μm (case 2) to 35.0 μm (case 2), and the length of uncoated crocidolite in the mesentery ranged from 1.0 μm (case 4) to 26.0 μm (case 3). In the omentum, the crocidolite fiber was 9.0 μm long; 74.1% of the crocidolite fibers in the lung were $\geq 5.0 \mu\text{m}$. In the mesentery, 40% of crocidolite fibers were $\geq 5.0 \mu\text{m}$, and in the omentum, 100% were that length. One omentum sample contained an anthophyllite fiber, and another sample was positive for tremolite (Table 2). Two samples of the mesentery were positive for anthophyllite (Table 2).

Two of three mesentery samples positive for tremolite (cases 10 and 16) were from individuals who had tremolite in their lung tissue, while only one sample of omentum was positive for tremolite (case 1). Although this subject had the second highest level of total uncoated asbestos fibers, no tremolite was detected in his lung tissue.

Tremolite fibers ranged from 1.6 μm (case 14) to 23.5 μm long (case 14) in lung tissue, from 3.0 μm (case 16) to 10.5 μm long (case 10) in the mesentery, and 18.0 μm to 30.0 μm long (case 1) in the omentum. The percentage of tremolite fibers $\geq 5.0 \mu\text{m}$ was 34.1% in lung, 100%

in the omentum, and 66.6% in the mesentery.

In the one subject (case 10) whose lung tissue was negative for ABs and uncoated asbestos fibers, the omentum and mesentery also were negative.

...

Discussion

We demonstrated that asbestos fibers were found in the omentum and mesentery, and that the likelihood of this occurrence could be predicted by features of the asbestos in the lung tissue. Heavier inhaled exposures, especially as evidenced by increased FB counts, and, to a lesser extent, total amphibole burden tended to favor the migration of amphibole fibers to these extrapulmonary sites. The longer and thinner amphibole fibers seemed to migrate more readily to the omentum than to the mesentery. This raises an interesting question regarding the nature of the lymphatic or other mechanisms involved for relocation to extrapulmonary sites.

In this cohort, there was a considerable amphibole burden in all asbestos-positive sites sampled. These primarily consisted of amosite and crocidolite, both commercial amphiboles. The presence of these types of fibers in the omentum and mesentery was less surprising than their size was.

By comparison, no ABs were found in our earlier studies of pleural plaques, and only a small percentage of uncoated fibers in the plaques were $> 5.0 \mu\text{m}$ long. Unlike those extrapulmonary sites, 67.2% of the asbestos fibers in the omentum and 70.5% in the mesentery were $\geq 5.0 \mu\text{m}$. Asbestos fibers in these sites were predominantly longer amphiboles, particularly amosite. While the shorter chrysotile fibers arguably may clear more readily from the lung, longer chrysotile fibers did reach these extrapulmonary sites: 42.9% of chrysotile fibers in the mesentery and 10% in the omentum were $\geq 5.0 \mu\text{m}$. These percentages exclude ABs, which are formed only on fibers that are $\geq 8.0 \mu\text{m}$ long.

There was a match between at least one type of asbestos found in the extrapulmonary sites in this study with the type(s) of asbestos found in the lung. Animal studies have concluded that chrysotile fibers clear more rapidly from the lung than do amphiboles. Chrysotile has also been suggested as having a relatively rapid turnover in human lungs, whereas amphiboles have a slower rate of turnover. Lippmann has even suggested that those chrysotile fibers that do escape clearance by the mucociliary escalator may be insufficiently biopersistent because of dissolution during translocation to extrapulmonary sites, which influences the transformation or progression to mesothelioma.

While we do not choose to comment on chrysotile clearance from the lung, we note that chrysotile fibers reached the omentum and/or mesentery in 25% of the cases. Furthermore, there was no apparent degradation of these fibers, and a portion of them were long fibers ($\geq 5.0 \mu\text{m}$).

Long fibers of chrysotile reached the omentum in several cases, which indicates that chrysotile is also translocated and could be potentially important in the pathogenesis of

peritoneal mesothelioma. We conclude that individuals whose exposure and lung burdens conform to the defined population parameters would reasonably be expected to have fiber relocation to the omentum and mesentery. Vulnerable individuals in such groups with sufficient exposures would have fiber burdens available for the stimulation of cells in the omentum and mesentery, which could pose additional risks for the development of peritoneal mesothelioma.

Am J Ind Med 1998 Oct;34(4):314-7

Carcinogenic implications of the lack of tremolite in UICC reference chrysotile.

Frank AL, Dodson RF, Williams MG.

Department of Cell Biology and Environmental Sciences, University of Texas Health Center, Tyler 75710, USA.

Using light and electron microscopy analysis, as well as electron diffraction, and energy-dispersive x-ray analysis, an aliquot of UICC chrysotile B was analyzed with special attention given to any tremolite contamination. Polarized light microscopy, with its limit of detection of approximately 1 micron when using dispersion staining, revealed chrysotile as the only fibrous asbestos component. Analytical electron microscopy at 333,000x of more than 20,000 consecutive fibers showed only the tubular morphology characteristic of chrysotile. These findings highlight that when this sample was used for exposure disease induced in animal models correlates with chrysotile-induced pathology, and does not support an explanation based on the "amphibole hypothesis." Thus, chrysotile should be considered as having the biologic ability to produce cancers, including mesotheliomas, based on the extensive use of this material as a standard reference material.

INTRODUCTION . . .

Another area of controversy has been over the ability of chrysotile to produce lung cancer and mesothelioma. In spite of much evidence to the contrary, some still hold to the view that chrysotile does not cause these diseases. Central to this belief has been what has been called the "amphibole hypothesis." . . . Other proponents of the "amphibole hypothesis" include Case (1991), Dunningan (1998), Mossman and Gee (1989), and Mossman et al. (1990). Certain policy questions may be influenced by the claimed lack of chrysotile's ability to cause disease. . . . One should recall that some have advocated that only certain fiber types, such as tremolite in chrysotile, play the singular role, or disproportionate share, in producing disease especially cancer . . . but other data have shown this to be untenable . . . Few populations have ever been identified in which only chrysotile exposure had taken place, but Mancuso (1988) documented mesotheliomas among such workers in the United States.

. . .

The most widely used standardized preparations of asbestos are those of the International Union Against Cancer, better known by their French language initials, UICC . . . These reference

samples have long been used for in vivo and in vitro experiments. Among the relevant in vivo experiments central to this paper is an inhalation experiment conducted by Wagner et al. (1974) that produced lung cancers and mesotheliomas and one reporting mesotheliomas after intrapleural inoculations (Wagner et al., 1973). . . . We have been unable to locate any specific report of tremolite contamination of this material [*used by Wagner et al.*], and we are not aware of a systematic search for tremolite, using both light and analytical electron microscopy. The present report documents the findings of such a detailed evaluation . . .

DISCUSSION . . .

The lack of tremolite in one of the best characterized and most widely used chrysotile standards does not support the amphibole hypothesis. The hazards of chrysotile must be fully recognized .

..

Ultrastruct Pathol 1997 Jul-Aug;21(4):321-36

Analysis of asbestos fiber burden in lung tissue from mesothelioma patients.

Dodson RF, O'Sullivan M, Corn CJ, McLarty JW, Hammar SP.

Department of Cell Biology and Environmental Sciences, University of Texas Health Center at Tyler 75710, USA.

Mesothelioma is a rare neoplasm that occurs most frequently in individuals with previous asbestos exposure. Differences for risk of development of asbestos-related mesothelioma and lung cancer have been attributed to the various types of asbestos, as well as to the dimension of the inhaled fibers. In the present study, 55 individuals with the pathological diagnosis of mesothelioma were evaluated as to ferruginous body and fiber content in lung tissue. The procedures used in the analysis included tissue digestion and analysis of the collected material for ferruginous bodies by light microscopy and for uncoated fibers by analytical transmission electron microscopy. Forty-six of the samples had ferruginous body concentrations of over 1000/per gram dry weight of lung tissue. The majority of the cores of these ferruginous bodies were amosite. Likewise, the most common uncoated asbestos fiber in the tissue was amosite. Only a small percentage of each type of asbestos would have been visible by light microscopy or even potentially by electron microscopy if the magnification was not sufficient to detect those with thin (< 0.2 micron [μm or *micrometer*]) diameters. The consistent finding in most of the cases was a considerable presence of asbestos, often of mixed types.

Introduction . . .

The data from tissue analysis are further limited because few studies have been carried out by transmission electron microscopy (TEM) at a sufficiently high magnification to permit a counting scheme that includes short . . . as well as long, thin fibers. The inclusion of such fibers is necessary for an accurate assessment of uncoated fiber burden. Numbers of chrysotile fibrils, as well as thinner amphibole fibers, could also be ignored by TEM if the counting protocol includes only longer fibers ($\geq 5 \mu\text{m}$) and does not use a sufficiently high magnification to compensate for these thin "fibrils." This may be particularly important in mesothelioma, since these are the geometrically defined fibers shown to reach extrapulmonary sites, including the lymph nodes and pleural plaques.

The primary purpose of the present study is to characterize the body burden in tissue in a series of mesothelioma cases. Unlike most previous studies, this group had diverse exposures ranging from shipyards, where some amphibole exposures would be expected, to vocations

where the more likely exposure would be to chrysotile such as cement production and brake shoe factories.

...

Results ...

Chrysotile was either found in equal concentration with amphiboles or as the majority asbestiform mineral in only three of the patients [*out of 55 total mesothelioma cases*]. . . These individuals had an overall low asbestos burden. . . . As has been reported in previous studies, chrysotile fibers were generally short, with the length (based on geometric means) being 6.36 μm and a very thin width of 0.076 μm .

...

Table 5B Fibers meeting and countable by the NIOSH criteria

Fiber type	Percentage >5 μm	Percentage detectable by light microscopy*
Amosite	70	33.0
Crocidolite	67	16.0
Anthophyllite	67	53.7
Actinolite	60	37.9
Chrysotile	55	1.4
Tremolite	36	27.6

* >5 μm length and $\geq 0.25 \mu\text{m}$ diameter.

...

Analytical ...

The risk for mesothelioma appears to be clearly tied in most cases to the exposure to asbestos. The relationship of longer amphibole fibers to the risk of developing mesothelioma may, as suggested by Churg and Vedal, simply constitute the major component at the time of autopsy due in part to its reduced rate of clearance. While chrysotile burden among the patients in the present study was overshadowed by the amphibole burdens, 55% of the chrysotile burden is made up of fibers longer than 5 μm . Once again, either indicating a selective inhalation of longer chrysotile fibers to the exclusion of shorter fibers or more likely the resultant impact of clearance on the short fiber burden. This observation should not be used to exclude the composite importance of shorter fibers as contributors to the disease, nor, from the present data, can arguments be offered in support of varying levels of risk for mesothelioma from exposure to the various types of asbestos. In fact, the present data offer the opposite argument. The common link in these mesothelioma patients appears to be the presence of asbestos of various types and variable lengths.

Black spots concentrate oncogenic asbestos fibers in the parietal pleura. Thoracoscopic and mineralogic study.

Boutin C, Dumortier P, Rey F, Viallat JR, De Vuyst P.

Pneumology Department, Conception Hospital, Marseilles, France.

Epidemiologic and pathologic data demonstrate that malignant mesothelioma occurs preferentially after exposure to long amphibole asbestos fibers. However, mineralogic studies have rarely detected such fibers in the parietal pleura. We hypothesized that the distribution of asbestos fibers in the pleura was heterogeneous and that they might concentrate in certain areas, as does coal dust in patients showing anthracotic "black spots" of the parietal pleura during thoracoscopy. We collected thoracoscopic biopsy samples from these black spots and from normal areas of the parietal pleura and lung from 14 subjects (eight with and six without asbestos exposure). Asbestos content was determined by transmission electron microscopy. In exposed subjects, mean fiber concentrations were $12.4 \pm 9.8 \times 10^6$ fibers/g of dry tissue in lung, 4.1 ± 1.9 in black spots, and 0.5 ± 0.2 in normal pleura. In unexposed patients, concentrations were 0, 0.3 ± 0.1 , and 0, respectively. Amphiboles outnumbered chrysotile in all samples. A total of 22.5% of fibers were ≥ 5 microns in length in black spots. A histologic similarity of these black spots with milky spots is suggested by conventional and electron microscopy. We conclude that the distribution of asbestos fibers is heterogeneous in the parietal pleura. Indeed, the fibers concentrate in black spots, where they can reach high concentrations. These findings could explain why the parietal pleura is the target organ for mesothelioma and plaques.

Current Issues in Public Health 1996 2:118-123

Asbestos: a status report.

William J. Nicholson and Philip J. Landrigan

Mt. Sinai Medical Center, City University of New York, New York, NY, USA

...

This review considers epidemiologic studies of the health effects of asbestos in populations exposed to commercial chrysotile and to mixtures of chrysotile and other forms of asbestos. We show that evidence for the human carcinogenicity of chrysotile asbestos is incontrovertible. We suggest that effort to describe chrysotile asbestos as “safe” are false, self-serving and commercially motivated.

...

THE SPECTRUM OF ASBESTOS DISEASES

...

A seminal study that established much of our current knowledge of the spectrum of asbestos diseases was conducted by Selikoff and Siedman . . . It followed 17,800 heavily exposed asbestos insulation workers for 20 years . . . Of these malignant diseases, bronchogenic carcinoma and mesothelioma were the two most important . . . Nearly 24% of the deaths in this group of workers were due to bronchogenic carcinoma and 9% to mesothelioma. Lesser degrees of excess cancer mortality were seen at other sites, including the esophagus, stomach, colon and rectum, larynx, pharynx and buccal cavity, gall bladder and bile ducts, and kidney . . . additionally another 8.6% of deaths in this population were due to asbestos. . . . [Table 1 of this study also indicates that 10% of the deaths were due to noninfectious pulmonary disease, 3.5 times higher than expected.]

...

LUNG CANCER . . .

The risk of lung cancer *per cumulative fiber exposure* is very similar for all exposure circumstances except chrysotile mining and milling. Risks in the three chrysotile textile manufacturing studies ranged from 1% to 2.6%/1-year exposure [*increased of 1% to 2.6% increased risk for every year of exposure*] to 1 fiber/mL. These risks are not statistically different from one another and cannot be attributed to the small use of commercial amphibole asbestos in two of the textile plants. Indeed, the highest lung cancer risk was found in the textile plant that used no commercial amphiboles.

Among the remaining non-mining studies, the percentage increase in lung cancer for each year of

exposure to 1 fiber/mL ranged from 0.5% to more than 4%, irrespective of the type of fibers used in the production process. The only exceptions were two studies of friction product manufacturing and one of asbestos cement production. In each of these three studies, severe uncertainties limit the validity of nonliving lower risks reported. All remaining risks, involving substantial amphibole exposure, are similar to those of predominantly chrysotile exposures, within the statistical uncertainties of the data. . . .

...

In summary, the available data on workers employed in the production of asbestos products strongly indicate a chrysotile lung cancer risk similar to those seen in workers exposed to amosite and crocidolite asbestos. [*Amosite and crocidolite are both amphiboles.*] The best estimate of lifetime lung cancer risk for worker exposure to chrysotile in the using industries (as opposed to the mining and milling industries), is an increase of 1% in risk for each year of exposure to 1 fiber/mL ($K_L = 0.01$). Higher fiber exposure would give directly proportional higher risks. In certain textile operations, the unit exposure risk appears to be as much as three times higher than this lower limit. No data are available to indicate the presence of a threshold below which there is no risk from exposure to any asbestos mineral.

MALIGNANT MESOTHELIOMA . . .

Were mesotheliomas produced only by amphiboles, one would have expected large differences in the mesothelioma risk between populations with pure chrysotile exposure and those with extensive amphibole exposure. . . . The ratio of mesothelioma to excess lung cancer is seen to be the same for exposures to 100% chrysotile, 97%+ chrysotile, 100% amosite, and mixtures of chrysotile, amosite, and crocidolite, within statistical uncertainty. . . . The data strongly suggest that much of the mesothelioma risk in predominantly chrysotile exposures is due to the chrysotile.

...

In this model there is a very low risk of mesothelioma for approximately 20 years from first exposure to asbestos. Thereafter, however, the risk rises very rapidly such that in long-term asbestos-exposed populations mesothelioma may actually become the dominant cancer risk. . . . Barring unknown exposures to amphiboles prior to 1935, the data present strong evidence that chrysotile is the substantial, indeed the dominant contributor to the mesothelioma risk experienced by this group of insulation workers.

...

One can estimate risk of mesothelioma due to chrysotile through direct calculations in mixed exposure circumstances . . . These analyses show that risk of mesothelioma/fiber exposure, as measured by K_M , is virtually the same for exposures to 97 % chrysotile + 3 % crocidolite, 60 % chrysotile + 40 % amosite, and 100 % amosite.

...

CONCLUSIONS . . .

The case is strong that chrysotile is a potent causative factor for both lung cancer and malignant

mesothelioma among exposed workers. Data to support this case derive from more than 40 studies of different fiber exposure circumstances. Chrysotile is shown to be a powerful carcinogen when the time course of risk is considered in mixed fiber exposures. Chrysotile is shown also to be a potent human carcinogen in direct calculations of risk.

...

Chrysotile is a proven human carcinogen. Assertions that it is safe and claims that it can be used safely in developing nations are contrary to fact and extremely dangerous.

Environmental Health Perspectives Volume 102, Supplement 5, October 1994

Chrysotile Biopersistence in the Lungs of Persons in the General Population and Exposed Workers

Arthur M. Langer and Robert P. Nolan

Environmental Sciences Laboratory, Applied Sciences Institute of Brooklyn College, Brooklyn, New York

Lung burden analysis was performed on 126 autopsy cases of persons who died in New York City from 1966 through 1968. Of the 126 cases, 107 were probably non-occupationally exposed, judging by occupational history and asbestos body content of lung. Fifty-three of the 107 cases contained short chrysotile fibers/fibrils, $<5 \mu\text{m}$ [*less than 5 micrometers*] in length, present in 3-fold greater amounts than were found in laboratory background controls. The fiber concentrations ranged from 1.8 to 15.7×10^6 f/gm/dry lung tissue, and the proportion of fibers $\geq 5 \mu\text{m}$ in length was only 0.34% of the total chrysotile population found. Other inorganic particles present included fragments of amphiboles. In contrast to these data, the lung parenchyma of persons occupationally exposed to asbestos commonly showed the presence of other fiber types, especially amosite and crocidolite, at very much higher concentrations and greater fiber length. Any chrysotile present would usually be in fiber bundle form, with both fibers and fibrils $>5 \mu\text{m}$ in length. Comparison of the lung fiber content of occupationally exposed persons with that of the general population showed marked qualitative and quantitative differences. Fibers are durable, and are retained in a range of concentrations. Their length and dose, among other factors, which control their biological potential are different in the two populations; the risk factors for chrysotile-induced disease are not the same.

Durability, Retention, and Biopersistence

Biopersistence of inorganic dust in the lung is held to be a requirement for the production of chronic disease. Durability, particle size, and depositional pattern affect the ability of scavenging cells to intercept, phagocytize, and sweep breakdown products out of the lung parenchyma.

If a fiber is not broken down within a phagolysosome, translocation may only decrease lung retention at the expense of accumulation at another tissue site. Persistence in the host is preserved. For mineral fiber, especially the amphibole asbestos varieties, the mucociliary escalator may save the lung but at the expense of increased risk of malignancy in other organs. Pleural drift and mesothelioma indicate that this is biologically important.

Biopersistent, durable, inorganic particles may have very low biological activities,

causing for example, benign pneumoconioses. Chest radiographs obtained on workers occupationally exposed to barite, tin oxide in the absence of free silica, zircon dust (zirconium silicate) in the refractory industry, and dust in iron foundries show a profusion of opacities with little or no clinical disease.

Chrysotile asbestos is considered to possess low carcinogenic potential because of its inherent instability in a biological host, since it lacks both durability and biopersistence. Studies using electron microscopy showed some magnesium loss from the chrysotile structure, detectable only for relatively thin fibers. By using radiolabeling, chrysotile has been shown to degrade *in vivo*. Electron microscopy studies have also shown what appears to be fibril disaggregation from the fiber bundle, as well as some thinning of the fibril wall, within the phagolysosome. Animal studies have shown that chrysotile is effectively eliminated from the lung after exposure by inhalation. These data, and more, have led some investigators to conclude that "chrysotile disappears from the lung," i.e., it lacks biopersistence. The implications of such a statement regarding carcinogenicity are obvious. If chrysotile is neither durable nor retained, the likelihood of its exerting a lasting or chronic biological effect is significantly diminished.

However, the study of human tissues shows that sometimes, even many years after cessation of exposure, chrysotile fiber is encountered in lung tissues, and occasionally at exceedingly high concentrations. Trace amounts of chrysotile have been reported in lungs of persons in the general population, and high concentrations in lungs of some occupationally exposed workers. This study explores the phenomenon of chrysotile persistence in human lungs.

...

Discussion and Conclusions

The presence of chrysotile in lung tissues indicates durability, retention, and host, biopersistence; and the trace amounts found in the general population are predominantly short fibrils. Rare outliers were found. Only in lungs of some heavily exposed workers were high chrysotile concentrations found; in these instances they appeared to be long unaltered fiber. The present study supports the tissue assay guidelines used in our laboratory, which exclude fibrils less than 1 μm in length from analysis, since they appear to represent nonoccupational exposure. Chrysotile fiber elimination most certainly occurred in all cases, but in proportions that could only be estimated.

...

Am J Ind Med 1993 Aug;24(2):235-40

Technique dependent variations in asbestos burden as illustrated in a case of nonoccupational exposed mesothelioma.

Dodson RF, O'Sullivan M, Corn C.

Department of Cell Biology and Environmental Sciences, University of Texas Health Center, Tyler 75710.

INTRODUCTION

Malignant mesothelioma is a tumor which, in many occupationally exposed populations, has clearly been linked to the inhalation of asbestos fibers . . .

The physical characteristics of length and width have been established by Pott (1987) and Stanton et al. (1981) as parameters which contribute to the potential carcinogenicity of a fiber. The long, thin fibers of chrysotile tend to have a more curved structure than equal length amphibole fibers and are, therefore, less likely to reach the lower respiratory system (Craighead and Mossman, 1982; Wagner, 1972). This, in part, forms the basis for the “amphibole theory” which attributes greater carcinogenic risk to these forms of asbestos.

Tissue analysis which characterizes fiber burden by light and electron microscopy can offer a supportive technology in clinical assessments. These techniques have been particularly useful in confirming past exposure in mesothelioma cases with occupational exposures (Roggli, 1990) and may be the only method of confirming elevated levels of asbestos as causal factors in cases of mesothelioma in nonoccupationally exposed individuals.

...

Different levels of information attainable from tissue digestion studies are typified in a mesothelioma patient whose background indicated no past occupational or “blue collar” exposures.

The patient was a 45-year-old white male who succumbed to malignant mesothelioma of the peritoneum. . . Careful review of his history indicated that he worked in the legal profession and had no prior exposure to asbestos in an occupational setting nor could any contact with asbestos be linked to past hobbies or other factors in his life-style. However, the patient did recall being in areas within the public schools where asbestos had been present.

No ferruginous bodies were found by light microscopy analysis of the digested lung material. For fiber evaluation by analytical transmission electron microscopy, filters were prepared (Dodson et al., 1990) and analyzed at 5,000 x, 15,000 x, and 20,000 x. A fiber was defined as a structure with a length/width ratio of greater than 3:1 and with substantially parallel sides for a majority of its length.

Only 1 chrysotile fiber was found (17,900/gm dry wt) in the scan at the lower magnification (5,000 x). This lower magnification has a $\geq 5 \mu\text{m}$ fiber limit and excluded short ($< 5 \mu\text{m}$) fibers from the counting scheme. The average total asbestos burden for the two scans at the higher magnifications (15,000 x and 20,000 x) were 1.7×10^6 fibers per gram dry and consisted of 79% chrysotile and 21% amphiboles.

DISCUSSION . . .

A major question remains as to the carcinogenicity associated with exposure to chrysotile asbestos. . . Several factors should be considered when attempting to assess environmental or tissue samples for this form of asbestos. These include the tendency, upon disturbance, or the chrysotile fibers to break into both shorter and/or thinner forms. The thinnest form (fibril) is sufficiently thin that only the resolution in transmission electron microscope permits reliable detection. This limitation applies to any attempt to quantify even the “longer” fibers of this form (Dodson et al., 1990). It is, therefore, difficult to extrapolate data from one study to another with regard to chrysotile unless the same counting scheme and TEM magnification are applied. Furthermore, a counting scheme which includes only longer fibers ($\geq 5 \mu\text{m}$) would selectively exclude the majority of the fiber burden. . . Furthermore, these $< 5 \mu\text{m}$ are the components of the burden that are more readily relocated to extrapulmonary sites . . . including those where mesothelioma originates.

. . .

Med Lav 1993 Sep-Oct;84(5):373-8

Characterization of asbestos fibers in pleural tissue from 21 cases of mesothelioma

Paoletti L, Falchi M, Batisti D, Zappa M, Chellini E, Biancalani M.

Department of Ultrastructures, Istituto Superiore di Sanita, Rome, Italy.

Pleural biopsies from 21 patients with pleural mesothelioma and different asbestos exposure were analyzed by means of analytical electron microscopy with the aim of investigating the presence, quantity, types and sizes of asbestos fibers in pleural tissue. The majority of fibers found consisted of ultrathin (< 0.3 micron [*micrometers*, μm]) and short (< 5 microns) fibers regardless of asbestos types and subject exposure. Concentrations appeared to be poorly related to the estimated exposure level. Fiber dimensions appeared to be the most important characteristic which determined their translocation in the pleural region.

...

Introduction . . .

In order to investigate the total amount, type and granulometry of asbestos fibers in the pleural region, using analytical transmission electron microscopy (TEM), we studied the mineral burden of 21 pleural tissue samples for mesothelioma cases coming from a series of occupationally and non-occupationally exposed subjects . . .

...

Results . . .

Asbestos fibers were detected only in 12 samples. Crocidolite and chrysotile fibers were found. Only in two cases were both asbestos types present (table 2). Fiber concentrations ranged from 0.1 to about 1.0×10^6 fibers per gram of dry tissue (fibers/g); but in one case the concentration accounted for more than two million fibers/g. In this sample, only chrysotile (2.6×10^6 fibers/g) fibers were found. In the 9 samples where fibers were not detected, the DL [*detection limit*] was generally high because of the small quantity of pleural tissue collected . . . Fiber concentrations were not related to the estimated exposure levels. Non-positive cases for asbestos detection were randomly distributed in relation to the estimated exposure levels (table 1). In four of the five cases with heavier fiber burden, chrysotile was the only, or the more frequently detected asbestos type. . . . About 80% (48/60) of detected fibers were shorter than 5 μm , 68% were thinner than 0.3 μm

DISCUSSION . . .

The more frequent detection of small asbestos fibers in the pleural region, according to

the hypothesis on the role of lymphatic vessels in the translocation of asbestos fibers from pulmonary parenchyma to pleura, could be related to: 1) increased probability of deposition in the alveolar region; 2) increased probability of being engulfed in macrophages or in epithelial cells without causing lethal cellular damage; 3) increased probability of reaching lymphatic vessels both by a macrophage mediated translocation or by mechanisms of transcellular transport by epithelial alveolar cells. Further investigations are needed to assess the role of these small fibers in determining a pathological response by the mesothelium.

...

Environ Res 1992 Aug;58(2):163-75

Asbestos in organs and placenta of five stillborn infants suggests transplacental transfer.

Haque AK, Mancuso MG, Williams MG, Dodson RF.

Department of Pathology, University of Texas Medical Branch, Galveston 77550.

Digests of lungs, liver, and placenta from five stillborn infants of 22 to 38 weeks gestational age were examined for asbestos and other fibers using light and electron microscopy, energy dispersive X-ray analysis, and selected area diffraction analysis. Uncoated chrysotile asbestos fibers were found in the digests of at least one of the three tissues examined from each stillborn infant. The asbestos fiber burdens ranged from 71,000 to 357,000 fibers/g wet tissue. Most of the fibers were small, with the mean length ranging from 0.83 to 2.53 microns. While appreciable numbers of uncoated chrysotile fibers were present, no coated asbestos fibers were found in any of the stillborns. Both coated and uncoated nonasbestos fibers were found in at least one of the tissue digests of all five stillborns. The uncoated nonasbestos fibers were characterized as aluminum silicates, diatomaceous earth fragments, or other fibers. The coated nonasbestos fibers or ferruginous bodies were consistent with being formed on diatomaceous earth fragments, black carbon cores, or sheet silicate cores. Since the placenta is the only route of communication between the fetus and the outside environment, our findings strongly suggest a transplacental transfer of asbestos and other fibers in humans.

...

OMITTED FROM 2/5/03 EPA DRAFT IRIS ASBESTOS RISK RE-ASSESSMENT

Ann N Y Acad Sci 1991 Dec 31;643:5360

A comparison of asbestos burden in lung parenchyma, lymph nodes, and plaques.

Dodson RF, Williams MG Jr, Corn CJ, Brollo A, Bianchi C.

Department of Cell Biology and Environmental Sciences, University of Texas Health Center,
Tyler 75710.

Am Rev Respir Dis 1990 Oct;142(4):843-7

Asbestos content of lung tissue, lymph nodes, and pleural plaques from former shipyard workers.

Dodson RF, Williams MG Jr, Corn CJ, Brollo A, Bianchi C.

Department of Cell Biology and Environmental Sciences, University of Texas Health Center, Tyler 75710.

Autopsy samples from eight former shipyard workers were collected from lung parenchyma, tracheal lymph nodes, and pleural plaques. The tissue from each respective area was prepared by a modified bleach digestion technique, and the residue was collected on a 0.2-micron [2 micrometers, or μm] pore polycarbonate or 0.22-micron mixed cellulose ester filter. Quantitation of ferruginous bodies and uncoated fibers was done by light and transmission electron microscopy, respectively. Differences in the asbestos burden were noted for each site. Ferruginous bodies were observed in both parenchyma and nodes but not in plaques. Three subjects were found to have more ferruginous bodies per gram dry weight in their lymph nodes than in their lung parenchyma. Likewise, all subjects were found to have more uncoated fibers per gram in the nodes than in the parenchyma. Amphibole and chrysotile fibers were noted in the lung and extrapulmonary sites, with chrysotile being the predominant asbestiform in plaques. The majority of the uncoated fibers in both the nodes and the plaques were less than or equal to 5 microns [5 μm , or 5 micrometers] in length. However, some fibers with dimensions conforming to the "Stanton hypothesis" reached both areas. These residual patterns most likely reflect the impact of clearance on lung burden as opposed to the eventual accumulation and stasis in the extrapulmonary areas.

INTRODUCTION . . .

Much of the inhaled asbestos is in the form of thin fibers, and tissue data obtained by transmission electron microscopy indicate that many of these fibers retained in lung tissue are short, uncoated fibers ($\leq 5 \mu\text{m}$ in length).

These small uncoated asbestos fibers are more easily moved and are thus likely candidates for relocation from lung parenchyma either via airway clearance or through interstitial routes to other tissues. However, most information about asbestos in extrapulmonary sites has been derived by light microscopy, which is selectively restricted by resolution limits (0.2 μm) and which identifies only ferruginous bodies (FB) or longer uncoated fibers.

...

RESULTS . . .

The physical features of the two types of uncoated asbestiforms in the lungs did vary . . . As shown in table 4, 86% of the chrysotile was $\leq 5 \mu\text{m}$ in length, whereas 59% of the amphibole was $\leq 5 \mu\text{m}$ in length. The mean length of chrysotile was $2.87 \pm 1.07 \mu\text{m}$, whereas that for amphibole was twice that figure ($5.82 \pm 6.71 \mu\text{m}$).

. . .

DISCUSSION . . .

. . . It must further be recognized that the data from this study require a resolution best attained by the transmission electron microscope and counting criteria that include short, thin fibers. . .

Although this study was not intended to address issues of long versus short fibers and their potential toxicity, it nevertheless has shown that some longer fibers ($>5 \mu\text{m}$) and large numbers of short ($\leq 5 \mu\text{m}$) fibers reach lymph nodes and plaques.

IARC Sci Publ 1980;(30):237-46

Asbestos retention in human respiratory tissues: comparative measurements in lung parenchyma and in parietal pleura.

Sebastien P, Janson X, Gaudichet A, Hirsch A, Bignon J.

Asbestos fibres in respiratory tissues from 29 cases diversely exposed to asbestos dusts have been characterized, sized and counted using a transmission electron microscope. Comparison of data obtained by measurement of fibres in lung parenchyma and in parietal pleura samples showed the following: -- In each case, the proportion of chrysotile fibres (as opposed to amphiboles) was higher in parietal pleura than in lung parenchyma. (The proportion of chrysotile in pleura was greater than 90% in 30 of the 40 samples.) -- Fibres encountered in parietal pleura were shorter than those in the parenchyma. -- There was no evident correlation between numerical concentrations of fibres in lung parenchyma and those in parietal pleura. This study has shown that characteristics of asbestos retention in parietal pleura cannot be derived from measurements in lung parenchyma. On the basis of the cases analysed here, who were exposed to mixed types of asbestos dust, chrysotile seems to be the asbestos type retained almost exclusively in parietal pleural tissues. These findings might be taken into account when assessing the risk of pleural diseases (especially mesothelioma) attributable to each type of asbestos fibre.