PLAINTIFF'S EXHIBIT
UC-4932

RECENT ADVANCES IN DIAGNOSIS AND MANAGEMENT OF ASBESTOSIS

by

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"'When you come to a patient's home, you should ask him what sort of pains he has, what caused them, how many days he has been ill, whether or not the bowels are working and what sort of food he eats.' So says Hippocrates in his work Affections. I may venture to add one more question: What occupation does he follow?"

Bernardini Ramazzini (1700)
(trans. W. C. Wright, 1940)

Bernardini Ramazzini, because he suggested inquiring of a patient what his occupation was, is known as the Father of Occupational Medicine. In the practice of occupational medicine, this is the cornerstone of the relationship between the physician and his patient.

Asbestos has received, and is receiving, a great deal of attention from all quarters. Much is known about this fibrous mineral; much has yet to be discovered with regard to its biological effects. A small group of scientists have gained international reputations simply because they have maintained their interest in this subject over the course of many years, while the majority of their colleagues have been more concerned with illness and treatment than with prevention of disease. Some workers in this field, more recently arrived on the scene and with little practical experience of industry and occupational health, do not have the same attitude towards the subject or the same approach to its investigation as their older, and perhaps wiser colleagues have. Opinions are no longer solely based upon scientific reason, but are swayed by emotions. Reporters or television commentators who are able to portray the subject most dramatically, using medical and environmental evangelists to preach the gospel, while not necessarily stating all the facts, seem better able to influence politicians and regulatory agencies than the miners, manufacturers and producers of asbestos products.

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I am grateful to the Association of Clinical Scientists for this opportunity to put some of the problems relating to asbestos and health into their true perspective. I realize that the title of this lecture "Recent Advances in Diagnosis and Management of Asbestosis" may appear to be somewhat misleading to some of you, but I assure you that it is necessary to be specific about such mundane matters as fiber shape and size, minerological differences and geographic variations in disease prevalence and incidence, in order to understand and interpret the clinical situation. I haven't forgotten about Bernardini Ramazzini, and I am certain that were he alive today, and had he the instruments and knowledge we have, he would still place as much importance upon occupational history as he did in the year 1700. He would, however, be able to benefit from a much more detailed understanding of occupational hazards, how they create their effects and how such effects can sometimes be prevented.

A. WHAT IS ASBESTOS?

Asbestos is a generic term used to describe naturally ocurring durable mineral silicates of filamentary or fibrous nature. The varieties of asbestos in commercial use, their chemical description, their physical appearance and their main source of origin are shown in Table 1.

Asbestos is used in the construction industry,floor tiles, asbestos cements, roofing felts, shingles, insulation materials, cement powders, acoustical products, textiles, brake linings, clutch facings, paper, paints, roof coatings, plastics and miscellaneous other products. You have probably all heard about asbestos in hair dryers. Asbestos filter pads are used in wine-making, spirit distillation, beer production; in filters for blood transfusions, for filtering drugs and for purifying solutions for intravenous infusion.

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It should be appreciated that in the primary and immediate post-primary section of the asbestos industry, i.e., mines and manufacturing industry, relatively few people are involved, whereas millions of people are ultimately exposed to apparently ever decreasing amounts of fiber in the products of the entire industry. Furthermore, asbestos is ubiquitous in the earth's atmosphere and has been since the beginning of recorded time.

Fibers below 0.5 μm diameter and less than 5 μm in length are not visible with the optical microscope and need to be identified by transmission electron microscopy, scanning electron microscopy or combinations of these instruments and various forms of selected area diffraction or microprobe analysis. X-ray diffraction has been used for the quantitative determination of chrysotile and amphiboles in air and water samples. The latter technique has also been used to analyze asbestos in lung tissue.

B. WHAT ARE THE PATHOLOGICAL EFFECTS OF EXPOSURE IN MAN?

Knowledge of the type of asbestos to which a person has been exposed is of value because it may be an important factor in the appreciation of special risks involved.

Differences in the physical characteristics of the various types of asbestos fibers determine their particular commercial usefulness. Chrysotile consists of long, mainly pliable fibers that split progressively into finer fibrils and it may be used in textiles, whereas crocidolite and amosite can be used in marine insulation because of their acid resistant properties. (Figure 1.) Certain asbestos cement products may be made from blends of chrysotile and amosite and/or crocidolite.

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Exposure to asbestos at work or elsewhere may result in five conditions:

1. The presence of asbestos in tissues without disease - e.g. asbestos bodies in the general population.
2. The presence of asbestos in the tissues causing benign changes - e.g. skin warts, pleural plaques.
3. The presence of asbestos in the tissues and the development of malignant mesothelioma of the pleura or peritoneum.
4. Asbestos in the lungs with tissue damage and the development of lung cancer.
5. Asbestos present with potentially fatal damage to the lungs (pulmonary fibrosis or asbestosis), but no cancer.

The ranking order of the five situations outlined above is intentional and tends to indicate the diseases associated with the least exposure through the worst exposure. It is, however, easier to discuss the pathological effects in the reverse order.

There are two other conditions which have been detected in greater numbers among asbestos workers than would be expected from a similar sample of the general population:

a. Cancer of the gastro-intestinal system involving oesophagus, stomach and colon and rectum.
b. Cancer of the larynx.

These two conditions are listed separately, because at the present time, there is insufficient published information regarding the presence or absence of asbestos in human tissue in these cases and the association has been established on purely epidemiological grounds.

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C. HOW DO PHYSICAL FACTORS RELATE TO CAUSATION OF DISEASE?

Whether or not inhaled asbestos fibers will reach the depths of the lung depends on the aerodynamic behavior of the particles, the size of the airways they enter, and the individual's breathing pattern. The larger dust particles are trapped in the nose and throat. Smaller fibers get down into the trachea, bronchi and smaller airways, but because of the turbulent air-flow as it passes down in the large airways, fibers are thrown outward and deposit on the sticky lining of the airways. These fibers are carried back out of the lungs on the muco-ciliary escalator by the beating of the cilia. When they reach the larynx, they are swallowed. Thus three factors are involved:

1. deposition (or inertial forces in large airways),
2. gravitational (settling of fibers in smaller airways),
3. diffusional forces in alviolar spaces.

Other physical factors would be:

1. Respirability is dependent upon the size and shape of fibers inhaled.
2. Larger particles are trapped in the upper airways and removed from the lungs by the muco-ciliary escalator.
3. Fibers with an aerodynamic diameter less than 3 μm are respirable, although their length may be as much as 100 μm - 200 μm.
4. Fibers with an aerodynamic diameter less than 3 μm and greater than 10 to 20 μm in length are thought to be those most likely to cause disease.

The nature of inhaled particles, aside from size per se, determines in part their deposition characteristics. Long, irregular particles such as asbestos fibers settle much less than would be expected from their total fiber mass.

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Other irregularly shaped particles (e.g. quartz, coal) are aerodynamically equivalent to spherical particles one-half to three-quarters of their measured diameters. Most models consider particles in terms of unit density spherical shapes (i.e., as aerosols), to reach a reasonable agreement between theoretical predictions and experimental observations. In addition to shape, the density of a particle determines its deposition characteristics.

Differences in disease-producing potentials of fibers may arise from the fact that curly, flexible, soft chrysotile fibers are more likely to be caught and filtered out by this system than the straight fibers of the other forms of asbestos in commercial use. To escape this filter mechanism, the fibers must be light enough to remain in suspension and short enough not to be intercepted by the branching of the smaller airways. Examination of human lungs has revealed straight fibers in the lung up to 200 µm in length and also coils of chrysotile which may be even longer if stretched out. Once a fiber is carried beyond the ciliated part of the airway, it may still be deposited and stay there or it may be carried out again with the next expiration of air. The proportion of fibers trapped at this stage still depends on size - long fibers are caught, small ones breathed out. Because in a typical dust cloud there are millions of very small fibers, more are retained in the lung than larger ones. Many of these very small fibers are too small to be counted with a light microscope and can only be counted by examining the lung or digests of the lung under the electron microscope. Their biological effects, if any, are not yet known.

In the tissues of the lung, and elsewhere where the fibers may lodge because of transportation in the body by blood, lymphatics and tissue fluid, the fibers may be coated with a brown iron-pigmented material called ferritin, to form 'asbestos bodies'. Asbestos bodies are thought to be innocuous. Not all

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ACL Doc 19439 · Page 7 of 19 asbestosclaims.law/library/19439/7

asbestos fibers are coated in this way and in humans it has been estimated that for every asbestos body in the lung there are 1,000 uncoated asbestos fibers. It is not known whether this is the case in all types of asbestos or in other tissue. It is known that asbestos bodies form rapidly, reside in tissue many years and gradually degenerate over the years releasing their fiber core. It is not known whether these released fibers, after many years, are still capable of causing disease. It is also known that uncoated fibers are capable of causing tissue damage when first inhaled, but it is not known whether they retain this potential indefinitely or are dealt with by some unknown defense mechanism other than the ferritin coating process. Chrysotile fibers have been shown to dissolve in tissue fluids so that it may be impossible to confirm that a person has been exposed by looking for these fibers in the tissues thirty or forty years later, unless exposure was continuous throughout the individual's lifetime up to the time of retirement. Crocidolite and amosite can be identified in tissue even after as long an interval as this, and it has been claimed by one investigator that it is actually possible to identify the geological origin of such fibers by the use of electron microscopic techniques.

The physical factors outlined above may be invoked to explain why asbestos miners seem to be less at risk than primary process workers who in turn seem less at hazard than those who use processed asbestos under dusty conditions. It is possible that freshly mined asbestos is still aggregated in bundles and less likely to be respirable or retained in the lung and thus less likely to be damaging. The more processing the asbestos receives, the finer the division of the fiber bundles and the more dangerous it becomes. Dust studies to support this physical characteristic have been reported. Chrysotile fibers collected in the carding area of an asbestos textile plant tended to have smaller diameters

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than fibers collected in the dryer and bagging areas of an asbestos mill.

It should not be forgotten that primary and secondary use of asbestos usually takes place in highly polluted urban environments by people exposed to many additional non-respiratory toxic agents. Cigarette smoking may be a co-factor in the production of occupational disease - it is not usually permitted underground in mines. There may be a synergy between cigarette smoke and asbestos dust only when they are inhaled simultaneously, but this is unlikely and difficult to deduce from epidemiologic studies.

D. WHAT IS THE EVIDENCE FOR STATING THAT ASBESTOS MAY BE PRESENT IN TISSUE WITHOUT DISEASE?

Examination of material from random autopsy series in several large cities has revealed the presence of asbestos in lung tissue. The frequency of this finding depends upon the diligence of the search. When digested lung tissue is examined, prevalence approaches 100%. These findings can occur in the absence of any asbestos associated diseases.

E. DOES A DOSE-RESPONSE RELATIONSHIP EXIST IN ASBESTOS-RELATED DISEASES?

The concept of a dose relationship of response to stimulus is a familiar one in pharmacology. This same concept has been invoked in an effort to explain the biologic response to inhaled dust.

An important question immediately arises - Why is one person affected and not the person working alongside? A third factor that has to be introduced into the concept is that a given dose-response curve can be developed for a given population (or person), but that it will be applicable only to another population (or person) of the same "susceptibility". Susceptibility may depend upon several biological factors such as the efficiency of pulmonary clearance mechanisms, the

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anatomic characteristics of the lung/airway system, or the physical fitness of the person. Susceptibility can also be related to immuno-genetic factors. Another important variable, not biological, is the differences in work practices and habits of individuals doing essentially the same job.

Although asbestos dose-response relationships are evident to a greater or lesser extent for all responses, the degree of correlation is difficult to ascertain precisely because of inadequate records of past exposure in all situations studied. The observed response is usually the result of past, rather than current exposure. This poor correlation has led to the current interest in "susceptibility", i.e., factors accounting for between-subject differences in response.

F. WHAT ARE THE BENIGN CHANGES IN TISSUES FOUND IN THE PRESENCE OF ASBESTOS AND WHAT ARE THEIR SIGNIFICANCE IN TERMS OF PROGNOSIS?

Warts on the fingers and hands, and a discrete reaction involving the parietal pleura, usually in more than one place and referred to as pleural plaques, are often found in people who have been occupationally exposed to asbestos. Pleural plaques are usually a radiographic diagnosis in an otherwise healthy person. Pleural plaques may calcify. Pleural plaques have also been described in people exposed by living in the vicinity of certain mines or tilling soil with a high asbestos fiber content.

The above conditions are not in themselves disabling, although the pleural plaques may indicate a level of exposure sufficient to progress to more serious disease. The effect of pleural plaques on pulmonary function, although detectable in population studies, is modest and is mainly seen as small reductions

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in lung volumes. By contrast, X-ray changes may be very striking, particularly in the presence of calcification.

Although the presence of pleural plaques alone does not appear to cause symptoms of disability, there is some evidence that they affect prognosis. They have been associated by some authorities with increased incidence of lung cancer and malignant mesothelioma has been reported as developing in the cells at the edge of the plaque.

G. WHAT IS ASBESTOSIS AND HOW DOES IT AFFECT THE EXPOSED INDIVIDUAL:

1. Asbestosis is a fibrosis or scarring of the lungs and includes the associated thickening of the visceral pleura, but not that of the parietal pleura.
2. The lower (dependent) parts of the lungs are affected first progressing as the years go by even after exposure ceases.
3. Asbestosis may be diagnosed using the following criteria:
   a. Obtaining a history of "adequate" exposure,
   b. Eliciting fine end-inspiratory crackles at the lung bases on auscultation,
   c. Finger clubbing (may or may not be present),
   d. X-ray changes - small irregular and/or rounded opacities (ILO U/C Classification)
   e. Pulmonary function changes indicative of restriction of ventilation or impairment of gas exchange. (Airways obstruction is not usually a feature of asbestosis, but has been reported in some studies.)

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4. The ILO U/C Classifcation, developed for epidemiologic purposes, is descriptive, not diagnostic. Serial radiographs over a period of time have to be studied to determine the significance of abnormalities noted.

5. A diagnosis of asbestosis can only be made by examining the worker, all the available X-ray films, the pulmonary function tests made over a period of time and the complete occupational history.

6. Other respiratory diseases such as chronic bronchitis, emphysema, asthma and certain chronic lung diseases can be mistaken for asbestosis.

7. The severity and progression of asbestosis depends on the amount of asbestos retained in the lung. This can be related to dust concentrations in the work place and length of exposure.

8. From the time symptoms are first noted, most workers can continue with light work for 10 to 15 years and may live another 5 to 10 years after finishing such work.

9. Asbestosis is unusual under the age of 50. Other conditions leading to the necessity for light work and retirement may precede it in this age group.

10. Improving industrial conditions over the past 20 years have resulted in a type of asbestosis less severe than in the 1930's, 1940's and 1950's. At the present time life expectancy may not be appreciably shortened by this disease.

11. The effect of improvements in industry on the incidence of excess deaths appears to have reduced this complication of exposure in parallel with the reduction in asbestosis, but further evidence is still needed to prove this observation conclusively.

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H. WHAT ARE THE FEATURES OF ASBESTOS-ASSOCIATED MALIGNANT DISEASE OF THE LUNGS?

1. The risk of premature death from malignant chest disease seems to be confined to those with high dust exposure, though sometimes of brief duration.

2. Asbestosis is no longer an inevitably fatal condition because improved dust conditions have resulted in a "milder" form of disease, or in fact a sub-clinical entity which is not always recognized. Less mortality from asbestosis occurring after longer periods of exposure to lower concentrations of dust than in past years has resulted in survival of workers through the long latent period of lung cancer.

3. The interaction of cigarettes and asbestos exposure as risk factors is of great importance. Non-smoking asbestos workers rarely get lung cancer.

4. The primary lung cancers in smoking asbestos workers do not differ in their effects from primary lung cancers in other people, and the results of treatment do not differ either.

5. Although lung cancer is usually associated with asbestosis, some authorities believe that this is not necessarily so.

I. WHAT ARE THE CURRENT VIEWS REGARDING MALIGNANT MESOTHELIOMA?

1. Epidemiologic evidence indicates a gradation of effect related to fiber type. Crocidolite, particularly fiber from the North West Cape Province of South Africa and from Western Australia, is considered to be the type of fiber most frequently associated with mesothelioma. Chrysotile is considered to be least likely to cause it andamosite has been allocated an intermediate status. Although anthophyllite has been associated with asbestosis, pleural plaques and lung cancer, no cases of

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mesothelioma have been attributed to it.

2. Cigarette smoking does not seem to be a causative factor.
3. Exposure may be of brief duration and there is a long lapsed period (latent interval) between first exposure and diagnosis or death. This lapsed period may be from 20 to 40 years or more - disease diagnosed today had its causation in working conditions between 20 to 40 years ago or longer.
4. The tumor affects the pleura, grows slowly, doesn't spread readily and kills by slowly compressing first the lung on one side and then the vital structures in the center of the chest or the lung on the other side. Peritoneal tumor is less common and is similar in its effects.
5. The tumor can occur from about the age of 35 onwards, but more than 50% do not develop until over the age of 60.
6. Domestic or neighborhood exposure has resulted in the development of this disease.
7. Mesothelioma is not uniquely associated with asbestos exposure and in most reported series a small proportion (15%-30%) cannot be related to asbestos.

In 1978, the suspicion that other materials could be partly responsible for mesothelioma cases without known exposure to asbestos, was apparently verified by the finding in Turkey that asbestos related diseases, mainly calcified pleural plaques, chronic fibrosing pleuritis and malignant pleural mesothelioma are endemic in some villages without asbestos deposits. In one village, where 11 mesothelioma deaths occurred in 1974, there are no deposits of asbestos in the area, nor has there been any processing of such material brought in from elsewhere. Research has shown many fibers in the respirable size range in rock samples, samples from streets and fields of the village, but not from control villages 4 and 7 km

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further up the valley. These fibers were shown to be erionite type zeolite. Thus, it would seem that fiber-shape and size is important in the eitology of malignant mesothelioma and fibrous minerals from sources other than asbestos mining or processing may be implicated in the epidemiology of this disease.

J. DOES ASBESTOS HAVE OTHER CARCINOGENIC PROPERTIES?

1. Cancer of the gastro-intestinal tract involving oesophagus, stomach, colon and rectum, has been reported in excess in asbestos insulation workers and other asbestos workers.
2. An association has been found in some reported studies between an an excess incidence of cancer of the larynx and asbestos exposure.
3. At present there is insufficient published information regarding the presence or absence of asbestos in human tissue in these conditions and the association has been established purely on epidemiologic grounds.

K. IS THERE A SAFE STANDARD TO PROTECT AGAINST THESE DISEASES?

There is a scarcity of adequate data from which to derive a safety standard which would give a 100% assurance of preventing the diseases associated with asbestos.

The present standard is based upon evidence presented in a 1968 report published by the British Occupational Hygiene Society. The data upon which this report was founded was obtained from an asbestos textile factory which had personnel and medical records available for study, as well as dust measurements, from 1951 onwards. The standard assumed that a combination of two variables, namely length of exposure and concentration of fibers during the exposure period, could be statistically analyzed and correlated with the earliest signs of the effects of asbestos exposure recognizable by the plant physician. As a result, it was postulated on this evidence that a cumulative exposure of 100 fibers per cubic

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centimeter would result in only 1% of persons exposed developing these early signs of asbestosis. The committee speculated that a worker could work for 50 years in dust concentrations of 2 fibers/cc. and only run a 1% risk of developing asbestosis. The committee did not propose the standard for protection against lung cancer or mesothelioma.

The crucial issue at stake is whether exposure to dust levels of 2 fibers/cc. will also prevent lung cancer and mesothelioma. Furthermore, should the same standard apply to all types of asbestos fiber or should there be an even tighter control on the use of crocidolite.

There is circumstantial evidence from the same factory that the high excess incidence of lung cancer deaths in the heavily exposed groups of workers who were employed before the regulations were introduced in 1931 and became effective in 1933 has been much reduced in the more recently exposed groups, i.e., the post 1933 cohort, although a slight excess may still be detected even in the cohort first exposed after 1950. This slight excess is not highly statistically significant and might be drastically influenced in the future by increasing the follow-up population. Furthermore, it can be explained by the fact that conditions in the factory were by no means all in compliance with the standard requirements of today and not until this is achieved will this small excess number of deaths abate. There is no numerical data with regard to mesothelioma upon which to build a dose-response curve, although some authorities do believe that a dose-response has been demonstrated based upon historical descriptions of conditions allowing jobs to be classified as severe, moderate, light and negligible exposures.

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The present situation is that in the United States no data is available for study, which enables asbestos fiber counts to be correlated with morbidity or mortality. The best data still comes from the factory in the U.K. mentioned previously and it is currently under review by the BOHS.

Cancer is an emotional word. NIOSH and OSHA, both under criticism and charged with being inefficient, respond to pressure groups readily and over-react regularly. Nobody seems to know what to do.

Time will tell. Even if the uses of asbestos decline, the deposits in the earth's crust will be there to exploit again when the dust of past misuse settles and the dose-response can be more clearly determined based upon adequate dust measurement records now being compiled and better record-keeping of morbidity and mortality statistics.

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ACL Doc 19439 · Page 18 of 19

TABLE 1.

Characteristics of main types of asbestos fibre

Characteristic	Chrysotile	Crocidolite	Amosite	Anthophyllite	Tremolite	Actinolite
Theoretical Formula	$Mg_3[Si_2O_5](OH)_4$	$Na_2Fe^{II}_3Fe^{III}_2[Si_8O_{22}](OH)_2$	$(Fe,Mg)_7[Si_8O_{22}](OH)_2$	$(Mg,Fe)_7[Si_8O_{22}](OH)_2$	$Ca_2Mg_5[Si_8O_{22}](OH)_2$	$Ca_2(Mg,Fe)_5[Si_8O_{22}](OH)_2$
Colour	Usually white to pale green, yellow[1], pink[1]	Blue	Light grey to pale brown	White to grey, pale brown	White to grey	Pale to dark green
Decomposition temperature[a] (°C)	450–700	400–600	600–800	600–850	950–1040	820–960
Fusion temperature of residual material (°C)	1500	1200	1400	1450	1315	1400
Density g/cm³	2·55	3·3–3·4	3·4–3·5	2·85–3·1	2·9–3·1	3·0–3·2
Resistance to acids	Undergoes fairly rapid attack	Good	Attacked slowly	Very good	Very good	Attacked slowly
Resistance to alkalis	Very good	Good	Good	Very good	Good	Good
Mechanical properties of fibre as taken from rock samples :						
Tensile strength 10^3 kg/cm²	31	35	17	(<7)	6	6
(Average) (10^3 psi)	(440)	(495)	(250)	(<100)	(<70)	(<70)
Young's Modulus 10^3 kg/cm²	1,820	1,860	1,620	—	—	—
(Average) (10^6 psi)	(23)	(27)	(23)			
Texture	Usually flexible, silky and tough	Flexible to brittle and tough	Usually brittle	Usually brittle	Usually brittle	
Producing countries	USSR Canada China Rhodesia USA Italy South Africa Swaziland	South Africa	South Africa	Finland USA Mozambique	USA Italy	

Notes [a] Dehydroxylation or dehydrogenation accompanied by disruption of crystal lattice and major loss of strength. [1] From serpentinised dolomite deposits

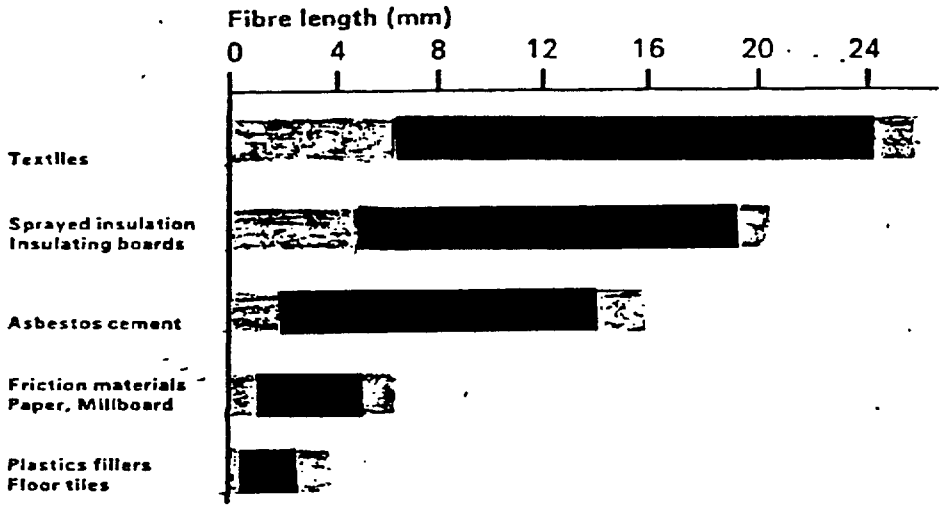
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FIGURE 1.

PRINCIPAL LENGTH RANGES OF ASBESTOS FIBERS

FOR DIFFERENT USES.



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