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REVIEW OF THE ENVIRONMENTAL EFFECTS OF ASBESTOS

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NOT FOR QUOTATION

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NOTICE

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

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1.0 GENERAL SUMMARY

1.1 FINDINGS

Asbestos exposure is pathogenic to humans, causing asbestosis, lung abnormalities such as pleural plaques, lung cancer, pleural and peritoneal mesotheliomas, and gastrointestinal tract cancers. Its pathogenicity is well supported both by experimental animal data and human epidemiological studies of occupationally exposed populations.

An ideal summation of animal data would be a dose-response curve showing doses of various types of asbestos plotted against the incidence of asbestosis and cancer in different experimental animals; it is hoped that the results could then be extrapolated to humans. Unfortunately, these investigative data do not yet exist. We can conclude from available data, however, that all commercially important types of asbestos have the potential to produce asbestosis and cancer in all commonly used laboratory animals, including mice, rats, hamsters, guinea pigs, and monkeys (Section 4.0).

Species differ in the intensity and speed with which they respond to asbestos exposure (Section 4.4.1.3.1). The fibrotic response in the rat usually is multifocal and nonprogressive unless a chronic infection is present (Section 4.4.1.3.1). In guinea pigs, fibrosis is diffuse and progressive (Section 4.4.1.3.1). Considerable controversy exists concerning the fibrogenic potential of various asbestos types and fiber sizes (Section 4.4.1.3.2 and Section 4.4.1.3.3). Firm conclusions about pathogenic mechanisms are impossible because of the large number of physical and chemical variables that may influence the pathogenicity of asbestos (Section 4.2).

Drawing conclusions about the carcinogenic potential of asbestos is also problematic; neither mechanisms of action nor quantitative dose-response relationships have been defined (Section 5.3.3). Lung cancer and mesothelioma induction are positively associated with asbestos exposure, as shown in many epidemiological investigations of humans. Mesotheliomas in humans are associated with inhalation of crocidolite, amosite, and chrysotile asbestos fibers. The risk is greatest with crocidolite and less with amosite and chrysotile (Section 5.3.4.3). In animal experiments, chrysotile, amosite, as well as crocidolite, produce mesotheliomas when injected intrapleurally into rats

Table 1.1 RESPIRATORY CONDITIONS CAUSED BY ASBESTOS

Condition	Definition
Asbestosis	Lung fibrosis caused by inhalation of asbestos dust.
Pleural calcification	Hardening of pleural tissue.
Pleural plaques	A patch or small differentiated area on the surface of the pleura.
Pleural and peritoneal mesothelioma	A rare neoplasm derived from the lining cells of the pleura and peritoneum.
Lung cancer	Various types of malignant neoplasms, most of which invade surrounding tissues, and may metastasize to several sites.

Numerical
~~Well-defined~~ dose-response relationships between asbestos exposure and cancer induction cannot be derived readily from available data. The greatest risk occurs with long, heavy exposure, which is most likely to occur in industrial situations (Section 5.3.4.2). ~~An exception~~ may ~~be the development of carcinoma in one patient exposed to asbestos for only 12 months~~ (Section 5.3.4.2). Mesotheliomas have also been reported in persons who were indirectly exposed to asbestos through contact with clothing of occupationally exposed relatives, and in persons who live in the vicinity of asbestos industries (Section 5.3.4.2).

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Some epidemiological studies indicate that crocidolite is more carcinogenic than other types of asbestos; it is associated with a higher incidence of mesothelioma and lung cancer than are chrysotile, amosite, and anthophyllite (Section 5.3.4.3).

Cigarette smoking ~~may be~~ is a cofactor in lung cancer induction by asbestos ~~(Section 5.3.4.4)~~, Asbestos inhalation combined with cigarette smoking significantly increases lung cancer incidence over that occurring with exposure to either factor alone (Section 5.3.4.4).

Until 1969, diseases associated with asbestos exposure were considered only as occupational hazards (Section 5.3.6.2). More recently, investigators have realized that exposure of the general population to environmental asbestos pollution may also be hazardous, particularly in urbanized areas (Section 5.3.6.2). Asbestos bodies are commonly found in the lungs of urban residents, both in Europe and the United States (Section 5.3.6.2.1). ~~Data are insufficient to indicate the significance of the concentrations detected; nevertheless,~~ Reports of mesotheliomas and pleural lesions in persons who reside in the vicinity of asbestos industries indicate that ~~pollution of the environment~~ occupational exposure by asbestos may be a ~~serious~~ human health hazard ~~(Section 5.3.6.2.2)~~. (This is not mentioned in the Section Please note)

Asbestos is disseminated widely in the human environment (Section 6.2.1). Asbestos particulates are released into water, air, and soil, mainly from industrial sources, and are readily transported by wind or water (Section 6.2.2). Because of technical difficulties in monitoring the concentrations and distribution of asbestos in the environment, there is a significant lack of data concerning types, amounts, and size of asbestos fibers that contaminate the environment (Section 6.2.1). Ambient air concentrations in urban areas are considerably higher than for nonurban sites. Contamination of North American water

1.2 CONCLUSIONS

a. All types of asbestos are pathogenic, ~~in animals and~~ in humans, ~~causing~~ asbestosis, ~~lung cancer,~~ mesotheliomas, pleural lesions, and gastrointestinal cancer.

b. Because of the large number of variables that influence the effects of asbestos, the mechanisms of pathogenicity are poorly understood. The etiological significance of fiber size or type is controversial, ~~and the physicochemical properties of various asbestos types as related to biological effects are incompletely defined.~~ (~~To correct this situation, the Third International Conference on the Physics and Chemistry of Asbestos Minerals will be held in Laval University, Quebec City, August 17 to 25, 1975.~~)

c. Little is known about the clearance rates of asbestos from tissues, the transport of asbestos within the organism, or the metabolic alteration of asbestos in the body.

d. Animal models necessary to accurately predict the potential effects of asbestos in humans have not been developed.

e. Quantitative dose-response relationships between asbestos inhalation and related diseases have not been determined for animals or humans, and minimal exposure levels required to cause disease are not known. Generally, however, the incidence of asbestosis and cancer among occupationally exposed persons increases with increasing dose and/or duration of exposure. The inhalation of high concentrations for short durations can be as harmful as prolonged exposure to low concentrations.

f. Malignancies that arise after long-term occupational exposure have been most often studied. However, malignancies result from short-term, occupational exposure and nonoccupational exposure in the vicinity of asbestos industries.

g. A causal relationship between gastrointestinal cancer and asbestos ingestion has not been

Relevance is questioned. Suggest deletion

m. Asbestos literature to date is confusing. To present dependable, clinical lung function data of asbestos-related disease is difficult; reports rarely supply complete data.

Suggest this instead:

Due to many new publications and reports (Because?)

that are now being generated, the data base on asbestos is continually being updated.

Table 2.1 PROPERTIES OF COMMERCIALLY IMPORTANT TYPES OF ASBESTOS

Property	Chrysotile	Amosite	Anthophyllite	Crocidolite
Composition	Hydrous silicates of magnesia	Silicate of Fe and Mg	Mg silicate with iron	Silicate of Na and Fe with water
Chemical formula	$Mg_3Si_2O_5(OH)_4$	$(Fe^{++}Mg)_7Si_8O_{22}(OH)_2$	$(MgFe^{++})_7Si_8O_{22}(OH)_2$	$Na_2Fe_3^{++}Fe_2^{+++}Si_8O_{22}(OH)_2$
Color	White, grey, green, yellowish	Ash grey, greenish, or brown	Greyish-white, brown-grey, or green	Lavender, blue, greenish
Length	Short to long	Long	Short	Short to long
Texture	Soft to harsh; also silky	Coarse, but somewhat pliable	Harsh	Soft to harsh

asbestos and is mined in South Africa. Amosite fibers are generally straight, harsh, and brittle.

Crocidolite fibers from different parts of the world show marked differences in fiber structure, but they contain the lowest magnesium and highest iron concentrations of all the amphiboles (Timbrell et al., 1971).

2.3 CHEMICAL PROPERTIES

The serpentine type of asbestos (chrysotile), which comprises 90 to 95 percent of the world's asbestos production, is essentially a pure magnesium silicate with the empirical formula, $3MgO \cdot 2SiO_2 \cdot 2H_2O$. Small amounts of other oxides are generally present, either in the crystal structure or as impurities. The most abundant are iron oxides, (which may be as high as 6 percent by weight), calcium oxide (up to 5 percent), and aluminum oxide (as much as 1.5 percent). Other minerals occur in trace quantities, and considerable interest is shown in these by investigators who believe that the deleterious effects of asbestos in the body may be due, at least partially, to these impurities. A recent review of this question is given by Cralley and Lainhart (1973). The metals of most interest seem to be chromium, cobalt, manganese, nickel, and scandium. Analyses of different types of asbestos from different locations show wide variations in the levels of these impurities (Morgan and Cralley, 1973). In addition to the interest shown in the inorganic material, considerable attention has been directed toward the analysis of various oils and other organic compounds that may be present.

Different types of asbestos vary considerably in resistance to attack by acids and alkalis. Chrysotile is readily attached by acids; 25 percent hydrochloric acid will dissolve up to 56 percent by weight of this asbestos type. Amosite is less readily dissolved (12 percent). Anthophyllite and crocidolite are more resistant, with less than 5 percent of their weight lost in hydrochloric acid (Badollet, 1951). Amosite is least resistant to a 25-percent sodium hyroxide solution which can leach 7 percent of its weight. The other types are more resistant, each losing less than 2.2 percent by weight.

The crystal structure of all asbestos varieties can be destroyed at elevated temperatures. This temperature varies with the different types from about 400 to 800 C. Anthophyllite is the most heat resistant, followed by chrysotile.

type and/or source of the material. A brief review of all the techniques that can be used to identify asbestos in biological tissues has been given by Langer (1973).

The problem of determining total amounts of asbestos in ambient air is a difficult one, and no totally satisfactory method has been achieved. Although satisfactory sampling can be done with a membrane filter and a pump, the chief difficulty is the identification of only a few asbestos fibers in the presence of a relatively large number and variety of other inorganic particles found in the same sample. The most direct method, counting of particles with an optical microscope, is both tedious and inaccurate. Some of the fibers are too small in diameter to be resolved by the optical microscope, and an electron microscope must be used. Rickards (1973) used electron microscopic methods in an effort to obtain lower detection limits than he had previously obtained by x-ray diffraction (Rickards, 1972). X-ray diffraction methods have been used by other workers (Crable, 1966; Goodhead and Martindale, 1969), and they have the advantages of speed and the possibility of a total mass determination. Their disadvantage is that they do not furnish a fiber count or fiber-size distribution. In a literature review by Sullivan and Athanassiadis (1969), references are cited describing the following methods and instruments for determining types and levels of asbestos:

a. Microscopic particle counting of samples on membrane filters

b. Thermal precipitators

c. Impingers

d. Royce particle counter

e. Mass concentration methods

f. Microsieving

g. Digestion

h. Column chromatography of organics adsorbed on the surface

i. X-ray diffraction

j. Low-temperature ashing

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are to undetermined mixtures of dusts, metals, oils, and other substances. The effectiveness of lung clearance mechanisms differs among animals, and the actual amount of asbestos deposited in the lungs in inhalation studies cannot be accurately determined. Other variables that must be controlled are the physical and chemical natures of the asbestos fibers. Any combination of the following may be involved in the pathogenicity of asbestos: fiber length, shape, diameter, weight, surface area, chemical composition of surface, trace metal content, and polycyclic hydrocarbon content. Because of the problems mentioned above, establishment of human dose-response curves from animal experiments is not feasible. However, since mammals do possess some similarities, perhaps the determination of mechanisms of action in animals will aid the identification of ways to modify asbestos to make it less hazardous to mankind.

4.3 ANIMAL METABOLISM

4.3.1 Uptake, Distribution, and Fate

The fate of asbestos in humans apparently depends on the size, shape, and route of entry of the asbestos fibers. Inhalation and ingestion are the primary routes of entry into man, but injection of various pharmaceutical preparations containing asbestos as a contaminant may also be of consequence. The animal studies presented here were conducted in an attempt to clarity and understand events that have occurred and been observed in man. Exposure of laboratory animals to asbestos has taken three general approaches: (1) inhalation experiments, (2) injection of asbestos into any one of several body cavities and, (3) ingestion. The effects and responses of the animals to asbestos will be discussed in Section 4.3.

4.3.1.1 Inhalation--Inhalation studies have great significance in that many of the apparent deleterious effects of asbestos in humans have followed the uptake of asbestos into the respiratory tract. Experimental studies using inhalation procedures have been performed primarily in rats and guinea pigs as well as other rodent species. The asbestos is usually presented to the test animal as a dust or aerosol. Exposure times have been as minimal as a single 1-hour exposure or as great as 400 hours over a 4-week period. In general, data interpretation is difficult because of a lack of uniformity of the experiments with respect to fiber types and sizes and with respect to the

The fiber length varied from 0.11 micrometers to 1.6 mm, with diameters from 0.01 micrometers to 3.48 micrometers; most fiber diameters, however, were less than 1.0 micrometers. All guinea pigs that had inhaled NWC crocidolite died within 273 days from the start of dusting. Some long fibers were found in giant cells and macrophages in interalveolar septa throughout the lungs. A few fibers reached the subpleural region and were seen in rats after about 500 days. Many long fibers were present in the peribronchiolar septa and in the muscular coats of bronchioles in older rats. Fibers were found projecting into the pleura in the older animals toward the end of the experiment (848 days). In these older animals, fibers had also penetrated the muscular coats of the bronchioles and arteries.

In contrast to guinea pig lung, rat lung showed fewer asbestos fibers in alveolar septa following inhalation of NWC crocidolite (Botham and Holt, 1972b).

Results of another study conducted by Botham and Holt (1972a) again suggest that rats are capable of clearing asbestos fibers from their lungs more efficiently than guinea pigs. In this study, the response of guinea pigs and rats to Finnish anthophyllite was compared. The animals were exposed to the dust for a maximum of 24 hours. Both species cleared most of the extracellular fibers from the terminal bronchioles within 2 weeks after the end of exposure; however, intracellular fibers were seen earlier in the rat--after 3 hours of exposure in the rat and 24 hours in the guinea pigs. Clearance from the respiratory bronchioles was similar in both species. Extracellular fibers were cleared rapidly during the first week after dusting. Intracellular fibers took longer to clear. Fibers spread into the alveoli near respiratory bronchioles within 3 hours after the start of dusting. Giant cells formed in guinea pig lungs but seldom in rat lungs. Since giant cells are more difficult to remove than individual macrophages, asbestos fibers are cleared more rapidly from rat lungs.

Radioactive tracer techniques have also been used to determine the distribution of asbestos in the respiratory tract of animals (Evans et al., 1973). Rats were exposed to an aerosol of radioactive UICC (International Union Against Cancer) standard crocidolite (made radioactive by neutron irradiation) at a concentration of 13.0 or 8.1 micrograms per liter. Median fiber length was 3 to 5 micrometers as measured by optical microscopy. The rats were exposed for 1 hour and received 36 to 74 micrograms of crocidolite. The mean value of asbestos located in the lower respiratory

gastrointestinal tract. Although some amphibole fibers were found in tissues from exposed rats and none in tissues from controls, it was felt that these fibers could have been present as a result of contamination. Some cancers were found in the long-term feeding study, but cancers also appeared in the controls.

4.3.1.3 Injection--Although injection is not a source of industrial asbestos exposure to humans, it is possible that a small amount of asbestos might be injected as a contaminant in various drugs that are filtered through asbestos pads during production (Duma, 1973). The value of injection as a route of exposure in animal studies, however, is not that it simulates human exposure but that it permits studies not possible in inhalation experiments. Injection experiments permit the examination of response once the asbestos is present in the pleural or peritoneal cavity in a large enough number of animals to give significant results. In animals, the main routes of injection used are intratracheal, intrapleural, intraperitoneal, and subcutaneous. Intrapleural, intraperitoneal, subcutaneous, intragastric and intravenous injection are discussed below.

4.3.1.3.1 Intrapleural injection--The translocation and fate of radioactive Rhodesian chrysotile injected into the pleura of two 3-month-old rats was studied by Holmes and Morgan (1967). Neutron irradiation of the asbestos forms gamma-emitting isotopes of the trace metals in the asbestos. In chrysotile, these are principally scandium-46, chromium-51, iron-59, and cobalt-60. The distribution and elimination of the trace metals and of fibers can thus be determined.

Urine samples contained chromium-51 and cobalt-60. After 50 days, 19 percent of the chromium-51 and 57 percent of the cobalt-60 had been excreted in the urine, indicating that they are leached from chrysotile in vivo. The small amounts of all four nuclides found in feces could be a result of some asbestos fibers entering the lungs from the pleura, with subsequent clearance to the gastrointestinal tract (Holmes and Morgan, 1967). Small amounts of all four nuclides were also found in tissue samples. For example, iron-59 was found in blood and liver.

About 90 percent of the remaining nuclides at time of death were located in the lungs and pleural cavity. In general, Holmes and Morgan (1967) concluded that though some translocation of fibers does occur, the process is comparatively slow.

bloodstream. Most asbestos fibers probably travel inside macrophages, although some larger fibers may be free in the lymph or blood (Kanazawa et al., 1970). Selective transport of fibers to the subserosal tissue, as suggested in the earlier study, was not supported by the present evidence.

4.3.1.3.4 Intragastric injection--Two to four days after chrysotile fibers were injected into the stomachs of rats (9.4 billion fibers in the two-day group and 94 billion fibers in the 4-day group), fibers were isolated from the blood, spleen, liver, kidney, omentum, muscle, lung, and brain (Cunningham and Pontefract, 1973). The omentum surrounding the small intestine had the most asbestos at 4 days after injection (18.25 million fibers per g). Tissues of control rats contained surprising amounts of asbestos: the levels were similar to those found in tissues of humans who died of natural causes (0.114 to 0.378 million fibers per g in brain, 0 to 0.253 in spleen, and 0.773 to 0.915 in peritoneum). How fibers were absorbed is undetermined.

A recent report by Gross et al. (1974) questions the validity of this experiment because of artifacts inherent in Cunningham and Pontefract's technique.

4.3.1.3.5 Intravenous injection--Asbestos administered intravenously was shown to accumulate mostly in the liver and lungs (Cunningham and Pontefract, 1973). Later, transplacental transport of asbestos in rats was demonstrated by these same workers (Cunningham and Pontefract, 1974). Chrysotile asbestos at a dose of 1 to 3 mg (1 mg per ml in water) was injected intravenously at 2-day intervals into pregnant Wistar rats from the 10th through 14th day of gestation. Total dose varied from 4 to 12 mg of asbestos. Fetuses were removed by Caesarean section the day before parturition in a manner preventing cross contamination from the mother. The livers and lungs were analyzed by electron microscopy. Values of asbestos found were quite variable, with livers from some fetuses containing large numbers of asbestos fibers. Whether transport is by individual fiber penetration, a mass breakthrough, or by both methods is unknown.

4.4 Animal Effects

Effects occurring in vivo in various experimental animals exposed to asbestos can be generally classified as fibrogenic or carcinogenic and are treated separately in subsections. Subjects to be discussed under the fibrogenesis heading include phagocytosis of asbestos fibers, giant cell formation, collagen production, fibrosis,

asbestos fiber is termed an asbestos body. Only fibers partly surrounded by a macrophage or giant cell can be coated; free fibers are not coated.

A similar process was reported following brief exposure (3 or 50 hours) of guinea pigs to anthophyllite dust (Botham and Holt, 1968). The asbestos caused a release of red blood cells from alveolar capillaries. Granules of iron-containing degradation products of hemoglobin (hemosiderin) from these red blood cells were found in macrophages along with a solubilized iron-containing substance (possibly ferritin). This substance was then adsorbed onto an asbestos fiber in the macrophage, with only one fiber per cell (usually the longest) being coated. Additional information on asbestos body formation can be found in papers by Suzuki and Churg (1969a, 1969b).

Guinea pigs, Vervet monkeys, and rabbits were exposed to chrysotile, amosite, or crocidolite dusts (Wagner, 1963). Asbestos bodies were produced in all three species by each dust but were more plentiful after amosite exposure.

Asbestos bodies are not produced in rats (Botham and Holt, 1972a, 1972b; Davis, 1970b; Gross and De Treville 1967).

Gross et al., (1967) proposed the term ferruginous body instead of asbestos body, since identical-appearing structures were formed after exposure to materials other than asbestos (e.g., following intratracheal injection of aluminum silicate into hamsters). Similar results were reported by Davis et al. (1970). The term asbestos body should be used only when the central fiber is identified as asbestos.

4.4.1.3 Fibrotic Response--Dissimilarities in the fibrogenic potential of different asbestos types (Wagner, 1963), as well as species differences in extent and severity of the fibrotic responses (Davis 1964) have been shown in experimental animals. Several methods of asbestos administration have been used to induce and study asbestosis. Fibrosis of the lung following the inhalation or intratracheal injection of various asbestos types has been observed in rats (Holt, et al., 1964; Davis, 1964, 1970a, 1970b; Gross et al., 1967b; Burger and Engelbrecht, 1970, and Wagner et al., 1974), guinea pigs (Davis, 1964; Wagner, 1963; Szymczykiewicz, 1970; and Holt et al., 1966), hamsters (Gross and De Treville, 1967), dogs (Motlagh and Falor, 1968), rabbits (Ford, 1972), monkeys (Zaidi et al., 1973), baboons (Webster, 1963), and donkeys (Webster, 1963). Local

Another example of a species difference in the fibrotic response following inhalation of asbestos was demonstrated by Gross and De Treville (1967). Chrysotile dust was administered to rats and hamsters either intratracheally or by inhalation. Lung clearance was less effective in hamsters than in rats. Hamster lung tissue was more reactive, and a progressive fibrosis was noted.

Species differences were also noted by Wagner (1963). In that study, guinea pigs, Vervet monkeys, and rabbits were exposed to chrysotile, amosite, or impure crocidolite (only 10% asbestos) dust. Impure crocidolite produced severe lesions in guinea pigs and monkeys, and these animals succumbed more readily to respiratory infections. Chrysotile produced no effect in rabbits.

The injection of asbestos into the pleural or peritoneal cavity has demonstrated that species differences in the fibrotic response is not restricted to lung tissue.

The injection of chrysotile or crocidolite into the pleural cavity of mice, rats, and guinea pigs lead to granular formations by 7 days (Davis, 1970a). Generally, the fibrotic response to asbestos following pleural or peritoneal injection appears to be qualitatively similar but quantitatively greater than the fibrotic response in the lungs. In the guinea pig, the granulomas were composed mainly of giant cells and were surrounded by capsules of fibrous tissue. In rats and mice, the granulomas contained mostly mononuclear cells and no distinct capsule was present. In guinea pigs, the granulomas remained cellular for 6 to 12 months, in mice, 11 to 15 months, and in rats, only 3 to 4 months.

4.4.1.3.2 Asbestos type--The potential of UICC reference amosite, anthophyllite, crocidolite, Canadian chrysotile, or Rhodesian chrysotile for causing fibrosis was investigated by Wagner et al. (1974). Rats were exposed via inhalations of 6 hours per day, 5 days per week, with total exposure times ranging from 1 day to 24 months. Almost all rats exposed for less than 12 months survived during the total length of their planned exposure. Only 53 percent of the rats survived for the full length of their planned exposure in the 24-month group.

All samples produced asbestosis; and after 6 months of exposure, asbestosis was progressive, even when exposure stopped. The progressive response was in contradiction to other work in the rat (Holt et al., 1964; Davis, 1964; 1970a; Gross et al., 1967b; Burger and Engelbrecht, 1970).

remember that most fiber types studied have produced a fibrotic response.

4.4.1.3.3 Fiber size--In addition to the controversy that surrounds the fibrogenic potential of asbestos types, the input of fiber length is also controversial. In this regard, the results of Burger and Engelbrecht (1970) have already been discussed (Section 4.4.1.3.1). The effect of fiber length on tissue response was also studied by Szymczykiewicz (1970). Sixty mg of chrysotile dust containing fibers either 5 or 10 micrometers long were administered intratracheally to guinea pigs. The dynamics and extent of the fibrotic reaction were most marked in the bronchi and peribronchial tissue, probably because of selective filtration by air passages. Location and site of fibrotic reaction were concluded to be dependent on structure of the fiber. The injurious effect on lung tissue was also attributed to the crystalline structure of the fibers.

Davis (1972) studied the relative fibrogenicity of a series of mineral dusts that were injected intrapleurally into mice. The chrysotile sample had fiber bundles ranging in size from 200 micrometers long by 10 micrometers in diameter to 1 micrometer long by 25 to 30 micrometers in diameter; most fibers, however, were less that 5 micrometers long by 0.1 to 1.0 micrometers in diameter. All dust samples produced granulomata in the pleural cavity with collagen production. The final degree of fibrosis was paralleled by the initial accumulation of cells around the injected material. Long fiber samples produced much larger and more cellular lesions and led to adhesion formation. When long fiber dusts were finely ground and sieved, only small, distinct lesions without adhesions were formed. Longer fibers may clump and attract more cells, producing larger lesions. Susceptibility of dust to clearance may be the most important factor affecting fibrosis.

Recent studies using electron microscopic procedures would seem to indicate that small uncoated fibers are the most fibrogenic (Miller et al., 1965). However, definitive conclusions regarding fiber length and fibrosis are still to be made.

4.4.1.3.4 Miscellaneous effects--An interesting technique for the production of fibrosis was used by Stanton et al. (1969). These workers used an asbestos-saturated, fibrous-glass pad applied to the pleura and pericardium of rats to induce fibrosis and cancer. Although this method of exposure was unlike any exposure man might encounter, it was

TABLE 4.1 INCIDENCE OF MESOTHELIOMA INDUCTION

IN RATES INJECTED INTRAPERITONEALLY WITH ASBESTOS (in %)[a]

Asbestos type	SPF Rats	Standard Rats
Amosite	40	31
Crocidolite	64	69
Chrysotile	59	68
Oil-extracted chrysotile	59	64
Saline control	0	0

[a] Source: modified from Wagner and Berry, 1969.

4.4.2.2 Lung Cancer--Lung cancers are also induced by asbestos. A direct association between lung cancer and chrysotile was reported by Gross et al. (1966). Rats, hamsters, and guinea pigs were exposed to 42 to 146 mg chrysotile dust per cubic meter for 62 weeks. Thirty-five percent of the rats surviving 16 months or more from the end of exposure developed lung cancer. No hamsters or guinea pigs exposed at the same time developed lung cancer.

The cancer rate in rats pretreated with 5-percent NaOH to reduce clearance of asbestos from the lungs was 48 percent, compared to 24 percent in those not pretreated with NaOH (Gross et al., 1967b).

Sixty-four other rats received intratracheal injection of chrysotile dust; of the 19 that survived 16 months or longer, 16 percent developed lung cancer (Gross et al., 1967b). Of all the cancers in the rats, 71 percent were adenocarcinomas, 14 percent were squamous cell carcinomas, and 25 percent were fibrosarcomas. The authors attributed the high cancer rate to trace metal contaminants from the hammer milling (Gross et al., 1967b), but later studies did not support this conclusion (Wagner et al., 1973).

Lung cancers and mesotheliomas were induced in rats inhalaing UICC amosite, anthophyllite, crocidolite, Canadian chrysotile, or Rhodesian chrysotile (Wagner et al., 1974; Reeves et al., 1974). Mean dose varied from 1,880 mg per cubic meter-hour for a 5-week exposure to 33,400 mg per cubic meter-hour for a 24-month exposure. No tumors occurred within the first 300 days from start of exposure, but all dusts eventually induced tumors. Sixteen of 20 metastasized tumors resulted from chrysotile exposure.

The hypothesis that asbestos may serve a passive role in tumor induction by adsorbing a chemical carcinogen such as benzo(a)pyrene was tested by Miller et al. (1965). The effect of chrysotile (which efficiently adsorbs BP) and amosite (which does not adsorb BP as well) on the carcinogenicity of BP in the hamster respiratory tract was examined. Chrysotile promoted BP carcinogenesis, whereas amosite had no effect.

Tumors have also been induced in white leghorn chickens by injection of crocidolite into the air sac (Peacock and Peacock, 1963). Tumors appeared in two of 30 birds that survived 1 year or more. One developed 1 year, and the other 3 years after injection.

yield in pig kidney cells. The reduced yields were due to a toxic factor rather than to removal of a necessary nutrient: prewashing of a filter pad would reduce or eliminate toxicity, and the first batch of medium filtered through a pad would be more toxic than later batches filtered through the same pad. The toxic factor was not identified.

Both nonfibrous serpentine and asbestos were found to inhibit growth, migration, and the early phases of cell mitosis in a culture of human embryo pulmonary tissue (Kogan and Dorinovskaya, 1966). Asbestos dust was more inhibitory. Particle size of both dusts was mostly under 4 micrometers with 80 percent below 2 micrometers.

The cytotoxicity of various asbestos dusts on guinea pig peritoneal macrophages in vitro was determined by measuring the production of lactic acid and the release of lactate dehydrogenase and acid phosphatase from the cells, and by loss of fluorochromasia (Parazzi et al., 1968). Both Balangero chrysotile and South African crocidolite were cytotoxic. The toxic effect of crocidolite was evident in 100 percent of the cells within 30 minutes, while chrysotile was somewhat less toxic, affecting only 60 percent of the cells. The toxic activity was related primarily to the fiber content of the dusts rather than to the particulate matter, which was only slightly toxic. Pretreatment of the asbestos dusts with polyvinylpyrrolidone-N-oxide (PVPNO) or ethylenediaminetetraacetic acid (EDTA) did not reduce the cytotoxicity, leading the authors to conclude that the physical characteristics rather than the chemical composition were involved in cytotoxicity.

Release of cellular components may be the result of cell leakage during phagocytosis of asbestos fibers and not a reflection of cell damage (Hain et al., 1973).

Another study on the cytotoxic effects of asbestos on guinea pig peritoneal macrophages gave somewhat different results (Beck et al., 1971b). Toxicity was measured by O_2 respiration and nigrosine staining. Chrysotile B was most toxic, damaging 85 percent of the cells; chrysotile A damaged 65 percent; anthophyllite 49 percent, crocidolite 38 percent, and amosite 38 percent. Addition of 5% serum did not reduce the cytotoxicity. Heating chrysotile to 600 C gradually increased cytotoxicity with respect to O_2 respiration, suggesting that the crystalline and electronic structure were related to the biological effects.

Asbestos dusts were also found to be cytotoxic to peritoneal macrophages from rats (Koshi et al., 1968).

Another aspect of asbestos toxicity that has been examined in some detail is hemolysis. Chrysotile was shown to be as hemolytic as silica powder towards sheep erythrocytes (MacNab and Harington, 1967). Under identical conditions crocidolite and amosite were inactive; however, after prolonged incubation with sheep erythrocytes, the latter two asbestos types did cause some lysis. The hemolytic action of chrysotile was prevented by disodium versenate and simple phosphates, but PVPNO and aluminum, two agents that prevent lysis by silica, are only partially active against lysis by chrysotile. This observation suggested that the nature of the hemolytic activity differed between silica and chrysotile. Mechanical action was ruled out as a cause of lysis. The authors concluded that magnesium ions on the surface of the fibers were responsible for the lytic action of chrysotile.

Similar results were reported in later studies (Schnitzer and Pundsack, 1970; Schnitzer and Bunescu, 1970), but it was concluded that the lytic action related to the surface area and openness of the fibers.

The hypothesis that magnesium is the principal agent in hemolysis by asbestos was supported by experiments reported by Harington et al. (1971). Sialic acid prevented hemolysis to a greater degree than EDTA, but poly-2-vinylpyridine-1-oxide had little effect. The authors also reported that chrysotile was much more active hemolytically than amosite or crocidolite. The surface area of asbestos fibers was not related to hemolytic activity, except possibly in asbestos forms with low magnesium content.

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There is no known nutritional requirement for asbestos in animals.

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fibers of a given length increases with decrease in airway diameter (Timbrell, 1965). Consequently, in human and animal lungs, the long fibers generally concentrate in respiratory bronchioles and alveolar ducts, and shorter fibers are transported more deeply into air sacs (Timbrell et al., 1970). Fibers deposited higher in the respiratory tract are removed more readily by mucociliary lung clearance mechanisms (Timbrell, 1965; Thomson and Short, 1969).

To a great extent, the deposition of fibers in the lung is proportional to the particle free-falling speed as a function of fiber diameter; therefore, differences in fiber diameter among various asbestos types influence the efficiency of passage to the lung (Timbrell, 1965; Timbrell et al., 1969). In both animals and humans, asbestos fibers with diameters greater than 3 micrometers are deposited readily in the upper respiratory tract by sedimentation and inertial impact; fibers with smaller diameters have lower free-falling speeds and succeed in penetrating terminal air sacs (Timbrell, 1970b; Timbrell, 1965; Timbrell et al., 1970). By these mechanisms, some long fibers (up to 200 micrometers) are able to penetrate the lung efficiently. For example, chrysotile may penetrate deeply because the fibers consist of bundles that divide into numerous fibrils with small diameters (approximately 0.016 micrometer) and low free-falling speeds (Timbrell, 1970a).

5.5.2 Fate of Asbestos in the Lungs

5.2.2.1 Cellular Response--Study of the cellular reaction of human lung tissue to inhaled asbestos dust revealed that small particles (up to 0.5 micrometer long and 0.1 micrometer in diameter) are phagocytosed directly by alveolar macrophages and deposited in cytoplasmic phagosomes (Morgenroth, 1973). Larger particles (up to 5.0 micrometers long and 0.7 micrometer in diameter), either coated or uncoated, locate in the alveoli and connective tissue septa.

5.2.2.2 Asbestos Body Formation--Asbestos fibers inhaled into the lungs may become coated with a segmented deposit of protein-iron granules, forming club-shaped asbestos bodies (Milne, 1971; Davis, 1964). Embedding sites are located intracellularly in macrophages and fibroblasts or seated among collagen tissues (Davis, 1964). Asbestos bodies may vary in length from 10 micrometers to more than 200 micrometers (Pooley, 1972). In early stages, the body coating is a thin, beaded yellow shape that thickens with progressing maturity and changes from yellow to brown (Milne, 1971).

alone merely indicates exposure to asbestos (Milne, 1971; Longley, 1969).

5.2.2.3 Uncoated Fibers--Chemical analyses of uncoated amosite, anthophyllite, and chrysotile fibers from human lungs show that significant alteration in fiber chemistry occurs in the lung tissue, probably because of biochemical interactions (Langer et al., 1970; 1972). It has been suggested that the smallest uncoated fibers are the most fibrogenic (Gaensler, 1969, Miller et al., 1975). Predominant changes include the depletion of magnesium and an increase in iron content (Langer, et al., 1970; 1972). In biologic environments, chrysotile fibers are considered to be chemically unstable (Miller et al., 1975). Magnesium is lost from the surface exposing the silica layer to chemical degradation. The biological and etiological implications of in vivo magnesium loss from asbestos fibers are unknown; iron gain possibly reflects the incipient early stages of asbestos body formation (Langer, et al., 1972).

5.2.3 Transport

The presence of asbestos bodies, fragments, and dust particles in the hilar and mediastinal nodes, in pleural lymphatics, and in the spleen, abdomen, and intestinal mucosa of mesothelioma patients indicates that asbestos is transported via lymphatic channels and is widely distributed throughout the body (Godwin and Jagatic, 1970). The lymphatic transport of foreign particles from lungs is a physiological mechanism of pulmonary clearance whereby small fibers and dust particles penetrate the alveolar membrane into the lung interstitium; from there they are transported to satellite lymph nodes by tissue fluids (Gross et al., 1973). Electron microscope studies have estimated lymph node fiber concentrations as high as 125 million per g of dry tissue in fiber glass workers and 60 million per g of dry tissue in nonoccupationally exposed females; approximately 6 percent of the fibers were chrysotile (Gross et al., 1973). The transport of asbestos from the lungs to pleural tissue via lymphatic vessels may explain the formation of pleural abnormalities by small asbestos fibers less than 5 micrometers in length (Taskinen, et al., 1973).

Gravity and constant motion of the lungs can induce downward lateral movement of inhaled asbestos fibers that are too long to be phagocytosed by lung macrophages; eventually, these fibers may reach the pleura and peritoneum by direct penetration through soft lung tissue (Thomson, 1970).

5.3.1.1 Pulmonary Changes--Interstitial lung fibrosis may develop as early as 3 to 6 years after initial asbestos exposure (Solomon, 1970a). At first it involves thickening of the interlobular septa in subpleural, posterior portions of the lower lobes; gradual progression causes distortion of terminal bronchioles and distal air spaces (MacKenzie, 1971). Early radiological signs frequently are manifested as a ground glass appearance with clouding of lower lung fields (Hurwitz, 1961). More definite stages show fine, striated, fibrillar changes in lung structure, resulting in progressive reduction of radiolucency and blurring of vascular lung markings (Hurwitz, 1961). The types of radiological changes that are manifested in asbestosis are highly variable and difficult to classify into development stages (Gelfand and Morton, 1970). Solomon (1970b) and Blum (1962) defined numerous radiological patterns of asbestos lung fibrosis as follows:

a. Bead-like disruption of normal basal vascular patterns in early stages;

b. Simple, diffuse fibrosis consisting of fine, linear, fibrillary changes;

c. Nodular changes that give a mottled appearance to the parenchyma;

d. Pneumonitic fibrosis producing localized, irregularly shaped areas of solid fibrosis;

e. Coarse fibrosis, made up of broad, linear, fibrotic bands with gross, vascular distortion; and

f. Massive fibrosis resulting from the confluence of nodulations.

Nodular, pneumonitic, and massive fibrotic changes often occur in combination (Solomon, 1970b). In South African miners exposed to high asbestos dust concentrations for more than 10 years, the basic pathological pattern of fibrotic lesions was diffuse hyaline fibrosis with areas of concentric fibrosis
(Solomon et al., 1971).

5.3.1.2 Benign Pleural Changes--Pleural abnormalities commonly accompany asbestotic lung fibrosis and often are the only radiological manifestations of the disease (Hurwitz, 1961; Solomon, 1969). In many roentgenological studies of asbestos workers, pleural lesions such as

The significance of pleural plaques in the development of mesotheliomas is not known (Hourihane et al., 1966; Dalquen et al., 1970). However, it has been suggested that both are caused by similar dust conditions, since they frequently coexist with or without asbestosis (Dalquen et al., 1970): they also develop within the same latency period and are macroscopically similar (Hourihane et al., 1966). Though it is possible that benign plaques are forerunners of mesotheliomas, transitional stages between the two have never been observed.

5.3.1.3 Physiological effects--The primary physiological alteration resulting from asbestos inhalation and asbestosis involves the impairment of pulmonary function as a result of structural changes in the lung tissue. Lung function abnormalities related to asbestos exposure represent a restrictive rather than obstructive ventilatory defect, as reflected by reduction in carbon monoxide diffusing capacity, lung compliance, residual volume, vital capacity, and total lung capacity, along with impaired ventilation-perfusion relationships (Thomson et al., 1965; Gandevia, 1967; Kleinfield et al., 1966; Regan et al., 1971; Jodoin et al., 1971).

Lung function defects may be manifested independently of clinical and radiological signs of asbestosis (Smither, 1971) and may not reflect the progression of fibrosis, particularly in the early stages (Busser et al., 1971; Hunt, 1965). The following studies demonstrate this fact. Results of function tests conducted on 17 asbestos workers by Bader et al. (1961) showed that although all patients with radiological abnormalities had functional impairment, six patients with only minimal radiological involvement exhibited severe functional impairment. Among 21 workers exposed to chrysotile and amosite for 14 to 55 years, vital capacity, total lung capacity, and diffusion capacity were significantly lower in those with radiological abnormalities; however, lung function did not reflect the degree of pulmonary infiltration (Kleinfield et al., 1966). In a 10-year study of 13 asbestos workers who were exposed for 4 to 24 years, reduced vital capacity correlated well with radiological changes in half of the cases; but the rest showed reduced values in the absence of radiological signs (Bader et al., 1965). Busser et al. (1971) studied 100 asbestos workers for several years by chest x-ray and lung function diagnostic procedures; early phases of asbestosis were represented by decreased vital capacity and lung compliance, accompanied by less rapid development of radiological changes.

113 thousand particles per cubic meter years or 4 mppcf yrs (Telleson, 1961). Signs of rheumatoid pneumoconiosis in a 49-year-old man included multiple nodular rheumatoid lesions, massive fibrosis (asbestosis), and asbestos bodies in the lung parenchyma, but no symptoms of rheumatoid arthritis were present. The patient was exposed to asbestos for 20 years as a pipe welder in the interior of ships (Morgan, 1964).

Immunological analyses (Turner-Warwick and Parkes, 1970) have demonstrated rheumatoid (antiglobulin) and antinuclear factors in 46.5 percent of 80 patients who had a history of asbestos exposure; this represents a fourfold increase over the incidence in random populations. Similar results often are manifested in connective tissue disorders such as rheumatoid arthritis. In asbestosis cases, both diffuse interstitial fibrosis and large necrobiotic nodules were observed, and circulating rheumatoid factor was demonstrated in one-fourth of these patients. Polyarthritis was present in four of the 17 cases with rheumatoid factor. Though the pathogenic role of these antibodies is unknown, they appear to correlate with severe, progressive, radiologic lung changes rather than with duration of asbestos exposure.

collected by nonstandardized techniques and expressed in terms that cannot be compared from study to study; furthermore, they fail to determine the spectrum of fiber length and types of asbestos encountered. Consequently, only a low correlation between human epidemiological data and environmental asbestos exposure exists, and even this reflects the noticeable lack of definitive information concerning the etiologic role of asbestos (Gilson, 1965). In the following review of dose-response studies, quantified exposure levels usually were not available but were included whenever possible.

In general, the development of asbestosis appears to be closely related to the dose and duration of asbestos exposure and to the length of asbestos residence in the lung, as shown in the results of the following investigations.

In a 1970 study of South African amosite miners, the incidence of asbestosis increased with employment time (Sluis-Cremer, 1970). 1970).

Among 252 insulation workers in Belfast, the proportion of men with abnormal chest x-rays increased with age and duration of exposure; the frequency of lung or pleural abnormalities increased from 13 percent in workers employed for less than 10 years to 85 percent for those employed for at least 30 years (Langlands et al., 1971). Radiographs showed 62 workers with lung field abnormalities; fibrosis or calcification was detected in 67 percent of these. Ten men who had been exposed for a minimum of 25 years exhibited both pleural fibrosis and calcification in the presence of lung fibrosis. Reduction in vital capacity and carbon monoxide diffusing capacity indicated impairment of lung function in 40% of the men with radiological lung abnormalities and in only 3 percent of the men with normal chest x-rays. A summary of results is shown in Tables 5.1 and 5.2.

Chest roentgenograms of 39 workers exposed to tremolite and anthophyllite in commercial talc dust revealed only one individual with pneumoconiosis; mean exposure time was 16.2 years, with a range of 11 to 22 years (Kleinfield et al., 1973). Mixed dust concentrations ranged from 171 to 1370 thousand particles per cubic meter (6 to 48 mppcf) with asbestos fiber counts of 8 to 260 per ml for fibers longer than 5 micrometers. In another talc plant, 35 workers exposed to higher concentrations 57 to 2,000 thousand particles per cubic meter or 62 to 371 fibers per ml for

Table 5.2 RELATION OF EMPLOYMENT TIME TO TYPE OF CHEST X-RAY ABNORMALITY IN INSULATION WORKERS[a]

No. of men	Years as an insulator		No. of men	Lung field abnormality	Pleural abnormality	
	Mean	Range			Calcification	Fibrosis
23	18	9-44	23	No	No	Yes
5	13	6-23	5	No	Yes	Yes/No
21	21	7-39	21	Yes	No	No
31	25	10-45	31	Yes	No	Yes
10	35	25-48	10	Yes	Yes	Yes

[a]Source: modified from Langlands et al., 1971.

Occupational Safety and Health) level of 2 fibers per cubic centimeter (greater than 5 micrometers in length), determined as a time-weighted, average exposure for an 8-hour work day, reflects a deepening concern for this hazard (National Institute for Occupational Safety and Health. 1972).

Weill, et al. (1973) studied the health effects of asbestos and silica dust exposure in 908 asbestos cement workers. The frequency of irregular and linear opacities increased as the cumulative dust exposure was increased. The incidence of diffuse radiological changes correlated better with total dust exposure than with duration of employment in the industry. Although it was not possible to distinguish between constituent exposures to asbestos or silica in the study, results suggest that irregular opacities were due primarily to asbestos exposure.

A similar study was conducted on 347 workers exposed to asbestos silica in an Egyptian pipe factory (El-Sewefy et al., 1970). The percentage of persons with positive chest symptoms and signs increased proportionally with the duration of exposure; 73.4 percent of the cases with dyspnea, 91 percent of those having finger clubbing, and 74.4 percent of the cases with positive x-ray findings had been employed for 10 to 20 years. Cigarette smoking and age did not account for the high incidence of chest symptoms and signs. Dust counts in factory locations where asbestos was mixed ranged from 19.7 to 626.3 mg per cubic meter; it is significant to note that, like the previous study, this one also did not distinguish between the silica and asbestos as components of the counts.

Not all studies correlate the development of asbestosis with long durations of exposure. In 247 cases of asbestosis that developed between 1955 and 1963 in Great Britain, age at initial employment was not a factor in the development of asbestosis, and the disease manifested itself following exposures of less than ten years (McVittie, 1965). Lung biopsy revealed asbestosis in a 47-year-old man 16 years after he was exposed to crocidolite (Goff and Gaensler, 1972). He handled raw asbestos for only 9 months in a cigarette filter manufacturing process. Pulmonary insufficiency resulting from advanced pleural and pulmonary fibrosis, progressed to total disability within 2 years. This case suggests that the inhalation of large doses for limited durations may be as harmful as the cumulative effect of low concentrations over many years of exposure.

of exposure showed elevated concentrations of the immunoglobulin fractions IgM, IgG, and IgA in more than 50 percent of the samples. The increase in IgM and IgG is a characteristic response to chronic inflammatory disease; the IgA increase may reflect an autoimmune response (El-Sewefy and Hassan, 1971). These changes were not related to the duration of exposure or to the degree of asbestosis.

Cigarette smoking and asbestos inhalation may have an additive or synergistic effect on the incidence and severity of pulmonary fibrosis in occupationally exposed workers (Langlands et al., 1971; Weiss, 1971; McDonaldd et al., 1972). Langlands et al. (1971) observed that impairment of lung function in 252 insulation workers was more closely related to the amount of cigarette smoking than to radiological abnormalities. Statistical analysis of the age, sex, smoking habits, duration of asbestos exposure, and radiological evidence for 98 asbestos textile workers clearly implicates both asbestos exposure and cigarette smoking as causes of pulmonary fibrosis. The incidence was 40 percent in smokers, compared with 24 percent in nonsmokers, and it rose with increasing amounts and duration of smoking and asbestos exposure (Weiss, 1971). The results are summarized in Table 5.3.

5.3.4 Carcinogenicity

Asbestos has been implicated as the causative agent of several types of human cancers. The most predominant are lung cancer and pleural and peritoneal mesotheliomas. Cancer of the gastrointestinal tract (Stumphius and Meyer, 1968; Gerber, 1970; Selikoff et al., 1965b, 1968, 1972a; Newhouse et al., 1969) and ovarian cancer (Graham and Graham, 1967) have also been associated with asbestos exposure.

5.3.4.1 Cancer Types

5.3.4.1.1 Lung cancer--The first report of a relationship between asbestosis and lung cancer was as early as 1935, by Lynch and Smith (Stumphius and Meyer, 1968). A report in 1965 estimated that asbestosis progressed to malignant neoplasms in 10 to 15 percent of the cases (Telischi and Rubenstone, 1965); later figures postulate that more than 50 percent of the persons who develop asbestosis will also develop lung cancer (Roe, 1968). The first statistical review was that of Merewether (1947) who reported finding lung cancer in 13.2 percent of 235 necropsies on patients with asbestosis (Merewether, 1947). The majority of

recorded lung carcinomas associated with asbestosis have been the squamous cell type (Cordova et al., 1962).

5.3.4.1.2 Mesothelioma--Mesotheliomas are rare primary tumors of the serosa. These ordinarily are associated with asbestos exposure via the presence of asbestos bodies in the lungs. Asbestos bodies have been found in lung sections in more than 25 percent of mesothelioma cases (Selikoff et al., 1965a) and epidemiological studies show that 80 percent of mesotheliomas occur in persons exposed to asbestos (Anonymous, 1973a). Detection of asbestos bodies and naked fibers in the mesothelioma itself is very difficult. Incineration of the sample along with HCl treatment, evaporation, filtration, microscopic examination, and selected area electron diffraction (SAED) analysis are required in this type of analysis (Le Bouffant et al., 1969; Langer et al., 1972; Pooley, 1972).

5.3.4.1.2.1 Pleural mesothelioma--Pleural mesothelioma occurs primarily in the male population after the age of 40 (Heller et al., 1970) and has been diagnosed with increasing frequency in recent years (Hitchock, 1970). Possibly the only primary malignant tumor of the pleura is the pleural mesothelioma (Solomon, 1970c).

The most common symptom is dyspnea, followed in frequency by nonspecific chest pain (Heller et al., 1970). The lung parenchyma can be invaded by pleural mesothelioma, and with tumor progression, the entire thoracic cavity may become encased.

5.3.4.1.2.2 Peritoneal mesothelioma--Ascites commonly occur in peritoneal mesothelioma. Tumor growth is unevenly distributed, consisting of a main large mass with scattered, smaller deposits (Smith et al., 1968). Common signs and symptoms of peritoneal mesothelioma are:

a. Bilateral pleural thickening and calcifications;

b. basal pulmonary parenchymal changes; and

c. abdominal pain, vomiting, and distention with x-ray evidence of intraabdominal tumefaction and/or obstruction of varying degrees (Smith 35 al., 1968; Enticknap and Smither, 1964; Adelman et al., 1972; Roberts and Irvine, 1970).

The abdominal cavity may eventually become obliterated by confluent growth. Obviously, the prognosis for either type of mesothelioma is poor.

Information on the effects of asbestos ingestion in humans is severely limited.

5.3.4.2 Exposure Level and Duration--The greatest risk from asbestos occurs with heavy exposure for long periods, which is most likely to occur in industrial situations. The younger the individual when first exposed, the earlier the development of the pulmonary carcinoma (Cordova et al., 1962).

Most lung cancer requires an average induction time of 25 years (Roe, 1968). One report indicated that individuals who had been exposed to asbestos and had developed carcinoma of the lung had an average exposure time of 15 years, ranging from 3 to 27 years (Cordova, et al., 1962). The latent period, or induction time, varied from 15 to 22 years. One exception--an individual who developed pulmonary carcinoma approximately 20 years after exposure--had been exposed to asbestos dust for only 12 months.

The induction time for mesotheliomas averages 35.5 years, with a range of 16 to 55 years (Smith et al., 1968). Individuals with peritoneal mesothelioma may have a considerable amount of asbestos in their lungs without the presence of a pleural or intrapulmonary tumor (Gold, 1971). Lungs in persons with pleural mesothelioma can contain relatively little asbestos, whereas lungs with bronchial carcinoma tend to have a high asbestos content. Mesotheliomas may occur at exposure levels below those required for prevention of radiologically evident asbestosis (National Institute for Occupational Safety and Health, 1972). Cases of mesothelioma have been reported in persons indirectly exposed to asbestos--particularly through contact with clothing of a person occupationally exposed to asbestos--or in persons environmentally exposed by living in the vicinity of asbestos industries (National Institute for Occupational Safety and Health, 1972; Smith et al., 1968).

5.3.4.3 Mechanism of Action--The mechanism of carcinogenic activity remains undetermined; however, several associated possibilities have been suggested (Harington and Roe, 1965):

a. the organic materials associated with the fibers, either naturally or as a result of contamination of the asbestos during processing,

b. the presence of certain carcinogenic metals or metal complexes in asbestos, and

encountered during transport and industrial treatment (Harington and Roe, 1965). Analysis of 12 materials containing chrysotile revealed that a third of the samples contained benzo(a)pyrene, benzo(a)anthracene, and dibenzo(a,h)anthracene (Boiteau et al., 1972). These compounds apparently are not present in concentrations large enough to be strongly carcinogenic; however, the possibility exists that the asbestos oils possess incomplete carcinogenic activity of either the tumor-initiating or tumor-promoting type (Harington and Roe, 1965).

5.3.4.4 Cocarcinogenesis--Asbestos exposure combined with cigarette smoking has been shown to markedly increase the incidence of lung cancer over that observed with either factor alone (Churg and Kannerstein, 1970). Cigarettes have also been suggested as a cofactor in the development of mesothelioma (Whitwell and Rawcliffe, 1971), although other data indicate no apparent relationship (Selikoff et al., 1970).

For asbestos workers who smoke, the risk of dying from bronchogenic carcinoma is reportedly 92 times greater than for men who neither work with asbestos nor smoke cigarettes (Selikoff et al., 1968). However, surveys of three naval dockyards--Portsmouth, Chatham, and Rosyth--showed no evidence that smoking habits were involved in the incidence of parenchymal or pleural disease associated with asbestos exposure (Harries et al., 1972). Another study indicated that a significant excess in mortality from lung cancer occurred in smokers who were heavily exposed to asbestos but not in smokers or nonsmokers with only low to moderate exposure (Berry, 1972).

5.3.5 Mutagenesis and Teratogenesis

There is no available literature on the mutagenic or teratogenic effects of asbestos exposure in humans.

5.3.6 Epidemiological Studies

Several types of asbestos exposure occur as the result of air pollution (Selikoff et al., 1971): direct and indirect occupational exposure, exposure of families, neighborhoods, entire communities, and random (close) exposures.

5.3.6.1 Cancer Mortality and Occupational Exposure--A survey (1936-67) of over 1,000 anthophyllite asbestos miners in Finland who were exposed from 3 months to more than 20 years revealed the following causes of death in 33 cases

TABLE 5.4 RELATION OF TOTAL DUST EXPOSURE TO DEATHS AND STANDARD MORTALITY RATIOS (SMR) FOR RESPIRATORY CANCER IN ASBESTOS WORKERS[a]

Total Dust Exposure				No. of Men	Respiratory Cancer		
Range		Mean					
Metric Equivalent[b]	(English Equivalent)[c]	Metric Equivalent	(English Equivalent)		Observed Deaths	Expected Deaths	SMR
Under 708	(25)	314	(11.1)	75	2	1.3	153.8
708-1766	(25-62.4)	1248	(44.1)	181	8	3.1	258.1
1769-3535	(62.5-124.9)	2522	(89.1)	277	5	4.6	108.7
3538-7047	(125-249)	5122	(181.0)	305	12	4.8	250.0
7075-14122	(250-499)	9933	(353)	328	17	5.2	326.9
14150-21197	(500-749)	17153	(606.1)	126	9	1.8	500.0
21225 and over	(750)	27175	(960.2)	56	5	0.9	555.6

a. Study of 1348 men retired from the asbestos industry 1941 to 1967 and observed through 1969. Source: Modified from Enterline et al., 1973.
b. In thousand particles per cubic meter of air per year (TPPCM/yr).
c. In million particles per cubic foot of air per year (MPPCF/yr).

TABLE 5.6 DUST EXPOSURES, DEATHS, AND STANDARD MORTALITY RATIOS (SMR) FOR RESPIRATORY CANCER IN ASBESTOS WORKERS, BY TYPE OF ASBESTOS[a]

Type of asbestos	No. of men	Average cumulative dust exposure: Metric equivalent[b]	English equivalent[c]	Total deaths	Respiratory Cancer: Observed deaths	Expected deaths	SMR	Adjusted SMR
Amosite only	59	9430	(330.2)	47	4	0.9	444.4	390.7
Chrysotile only	1,013	6980	(244.4)	572	39	16.5	236.4	237.7
Amosite and chrysotile	102	7600	(266.3)	50	3	1.7	176.5	171.2
Chrysotile and crocidolite	120	5960	(208.6)	54	10	1.9	526.3	563.0
Amosite, chrysotile and crocidolite	54	7810	(273.4)	31	2	0.8	250.0	239.8
Any amosite	215	8160	(285.6)	128	9	3.4	264.7	249.0
Any chrysotile	1,289	6970	(244.0)	707	54	20.9	258.4	260.0
Any crocidolite	174	6540	(228.9)	85	12	2.8	428.6	442.5

a. Study of 1,348 men retired from the asbestos industry 1941 to 1967 and observed through 1969. Source: Modified from Enterline and Henderson, 1973.

b. In thousand particles per cubic meter of air per year (tppcm/yr).

c. In million particles per cubic foot of air per year (mppcf/yr).

associated with pulmonary changes, and were regarded as the result of contamination of urban atmosphere.

5.3.6.2.2 Significance of nonoccupational exposure--Data are presently insufficient to determine the significance of the amounts of asbestos generally detected in lung tissues of urban residents (Selikoff et al., 1971). Currently, no direct evidence suggests that the presence of asbestos dust particles or similar materials--either coated or uncoated--in the lungs of persons not occupationally exposed to these particles is making any contribution to pulmonary disease, either inflammatory or neoplastic (Utidjian et al., 1968).

The Advisory Committee on Asbestos Cancers (1973) supports the above statements concerning low levels of asbestos exposure to the general public and also states that no evidence exists showing increased risk of cancer from asbestos contamination of water, beverages, or food. However, in neighborhoods with a source of asbestos dust, mesothelial tumors, as well as asbestos bodies or calcified asbestos pleural plaques, do occur in the general population (Newhouse, 1973).

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6.0 ENVIRONMENTAL DISTRIBUTION AND PROCESSES

6.1 SUMMARY

Asbestos has manifold applications in today's industrialized society and is often referred to as the "mineral of a thousand uses." One result of its industrial popularity has been a widespread dissemination into the environment.

Emission into the environment results from losses during manufacture, transportation, or use of the product, and from industrial waste disposal. Contamination probably also occurs as a result of natural processes, including erosion of asbestos outcrops, farming of asbestos-laden soils, and passage of water through asbestiform rocks.

Asbestos fibers are easily disseminated by wind and water and are generally regarded as being persistent in the environment. Degradation occurs under extremes of heat, mechanical stress, or acidity. When these minerals are broken into fine fibers, a large surface area is exposed to chemical degradation. However, conditions severe enough to cause alteration of the mineral usually are not encountered in the normal human environment.

A drawback to establishing a hazardous level of asbestos in the environment is the apparent lack of standardized sampling and detection techniques for collecting, identifying, and quantifying the fibers in air, water, and soil. Although many tests of varying sensitivity are now used, standard methods that are reliable, rapid, and economically feasible have not been established. Measurements made with the same analytical procedure, preferably by the same laboratory, can be used to compare asbestos concentrations in different samples.

6.2 FATE OF ASBESTOS IN THE ENVIRONMENT

6.2.1 Distribution

It generally is acknowledged that asbestos is commonly present in water and ambient air, particularly in urban areas. However, there is a noticeable lack of published

approximately 2.0 million fibers per liter, river water concentrations range from 8.1 to 9.5 million fibers per liter, and melted snow from Ottawa contains 33.5 million fibers per liter.

Attention concerning the problem has been focused primarily on Duluth, where asbestos contamination is the result of industrial effluent discharge into Lake Superior, the city's water supply. Duluth water samples taken on August 28, 1973 were analyzed by seven different laboratories. An average fiber concentration of 12 million amphibole fibers per liter was measured. When adjusted for seasonal fluctuations, it is estimated that the average concentration in Duluth's drinking water is 43 million amphibole fibers per liter. Daily and seasonal fluctuations in amphibole concentrations have been determined by x-ray diffraction (Cook et al., 1974). Concentrations as high as 8 billion fibers per liter have been estimated for turbid Duluth tap water (United States of America et al. vs. Reserve Mining Company et al., No 5-72, Cov. 19).

There is an indication that the San Francisco water supply contains as much or more asbestos than Duluth, although the source of contamination is natural rather than industrial (Anonymous, 1974a,d). Other municipal water systems may be contaminated as a result of leaching of asbestos fibers into the water supply from asbestos-cement pipe contained within the system (Anonymous, 1974b).

Asbestos fiber concentrations are higher in water near points of emission than in areas remote from such points (Anonymous, 1974c). For example, water sample concentrations of fibers in Silver Bay, Minnesota (the site of the industrial source) were determined as 1.10 million fibers per liter but samples taken near Superior, Wisconsin (approximately 80 miles south, but served by the same water supply) contained only 0.37 million fibers per liter (Anonymous, 1974c).

6.2.1.3 Soil--Asbestos is a component of many fibrous silicate minerals. These minerals are divided into two groups: (a) serpentine, which contains chrysotile, and (b) amphibole, which contains anthophyllite, amosite, crocidolite, tremolite, and actinolite (May and Lewis, 1970). Asbestiform, amphibole, and serpentine occur in metamorphic rocks, which are distributed over much of the United States (Anonymous, 1974c).

Major commercial deposits of asbestos are found in Vermont, California, Arizona, and North Carolina (May and

capable of widely dispersing industrial emissions and entraining weathered fibers from natural outcrops. Precipitation removes particles from the atmosphere (Sullivan and Athanassiadia, 1969).

6.2.2.2 Water--No studies specifically concerned with the water mobility of asbestos were found in the literature. However, testimony in a Duluth-related court case revealed that a 1.4-micrometer taconite tailing (a source of asbestos) deposited in Lake Superior in the vicinity of Silver Bay at a depth of 98 feet would travel 120 miles before settling to the bottom (that is, assuming a current speed of 1 centimeter per second and no vertical turbulence). If vertical turbulence is considered, the same particle would travel 294 miles before settling. In still water, a 2-micrometer particle will settle to a depth of 600 feet in approximately 1 year (Anonymous, 1974a). Particles which have settled, however, can easily reenter the water currents if the settling point is disturbed by water movement such as that caused by wind or thermal gradients.

6.2.2.3 Soil--No specific studies concerning the mobility of asbestos within soil have been located in the literature. It is probable that asbestos is transported on and within the soil by natural processes such as weathering, erosion, movement of wind or water, and by human activity such as farming or construction (Burilkov and Michailova, 1970).

6.2.3 Persistence in Air, Water, and Soil--No study was found that would indicate that biological transformation or degradation of asbestos occurs in the environment. Asbestiform minerals are subject to chemical degradation in extreme conditions that would rarely occur at the earth's surface: the magnesium hydroxide layers are soluble at low pH and in boiling water, the fibers decompose at around 1,000 c, and they are converted to other minerals under severe mechanical degradation (Speil and Leniweber, 1969). Since the conditions for degradation are so severe, it may be assumed that asbestos would persist in the normal human environment.

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sources. The potential for emissions from wet-process milling is much less than that of typical dry milling operations (U.S. Environmental Protection Agency, 1973). No land-use conflicts seem likely to inhibit the production of asbestos (May and Lewis, 1970). Virtually all of the deposits are in rugged country far removed from populated areas. The mining operations are on privately owned or leased lands. Waste rock is hauled to nearby dumps,and, as the pile builds up, a bulldozer spreads it out. Water sprays allay the dust as the tailings are discharged. The milling of asbestos is generally a dry operation, and all the screens are hooded and operate under a slight negative pressure for dust control (May and Lewis, 1970).

Atmospheric asbestos dust settles or is washed out by precipitation, returning to the soil and to waterways and thereby contributing to the contamination of ground and surface waters. Some industrial wastes containing asbestiform fibers are dumped directly into surface waters (e.g., Reserve Mining Company, Duluth, Minnesota) (Cook et al., 1974). Some fibers have been found in various public drinking water systems (see Section 6.2.1.2).

Available data are inadequate to determine the contribution that asbestos-cement pipes make to the amount, size, and persistence of the asbestos fibers found in potable water distribution systems (American Water Works Association, 1974).

Environmental asbestos concentrations are highest in urbanized areas and near asbestos mines; however, asbestos fibers are easily resuspended by wind and water and can be redistributed widely. Asbestos differs from many other pollutants in that it is stable with respect to decomposition (U.S. Environmental Protection Agency, 1973). Because of this stability, asbestos fibers are regarded as persistent in the environment.

7.2.2 Food Chains

No data were found to suggest the transfer of asbestos in food chains. Some foods and beverages, however, are contaminated with asbestos fibers through certain food processing procedures (see Section 6.2.1.4).

7.3 EFFECTS OF ASBESTOS POLLUTION