

Copper-Nickel Mining, Smelting and Refining  
as an Environmental Hazard to Human Health

A Review of Epidemiology Literature  
and Study Recommendations on Asbestos

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## Summary and Recommendations

"Asbestos" is a general term applied to a group of fire-resistant mineral silicates that are similarly fibrous in structure but very different in respect to several other properties such as their metallic elemental content, flexibility, range of fiber length and diameter, tensile strength, surface properties, resistance to heat, acid resistance and spinnability. These characteristics not only determine the industrial uses of the various asbestos types but may also influence the biological responses associated with asbestos exposure in man and animals.

The two main mineral subdivisions are serpentines (chrysotile) and amphiboles (crocidolite, amosite, tremolite, actinolite, anthophyllite). Although there are many other types, these are the most common types mined for industrial use. In addition to the commercially important asbestos minerals, there are a number of non-commercial asbestiform minerals having fibrous cleavage. The distinction between fibers of natural commercial asbestos and cleavage fragments involves minor differences in their structural and chemical makeup. The actual fibers existing in Northern Minnesota are cummingtonite-grunerite cleavage fragments most closely resembling commercial amosite.

In many of the early studies of the health effects of exposure to asbestos, the type of asbestos fiber involved was either unknown or not reported. More recently, studies have identified the type(s) of asbestos fiber involved in examining differences in risk and possible chemical and physical factors involved in etiological mechanisms of asbestos-related disease. Few studies have examined the health effects of exposure to asbestos cleavage fragments.

Occupations at risk of exposure to asbestos can be broadly classified into mining, milling, and manufacturing of asbestos-containing products; manufacturing can be subdivided into textiles, construction products, paper products, friction materials, and insulation products. There is also evidence of non-occupational, environmental exposure to asbestos in ambient air, foods, beverages, and city water supplies. Family members of asbestos workers are exposed via soiled clothing.

Pathological effects associated with exposure to asbestos include "asbestos bodies" in the lung, pleural plaques, asbestosis, lung cancer, and malignant mesothelioma of the pleura (lining of the lung) and peritoneum (lining of the abdominal wall and organs). There is also

evidence to suggest an association between asbestos exposure and cancers of the gastrointestinal tract, and some evidence of an association with several other cancers.

Asbestos bodies, often referred to as ferruginous bodies, are located in the lung and consist of asbestos fibers coated by protein, iron and possibly other materials. Hyaline and calcified pleural plaques occur as discrete, raised lesions. Neither asbestos bodies nor pleural plaques alone cause clinical disease, but rather occur prior to or concomitantly with asbestosis or asbestos-related cancers.

Asbestosis is characterized by interstitial fibrosis of the lung, fibrosis and calcification of the pleura, fine rales, finger clubbing, dyspnea, and reduced vital capacity. Mesotheliomas are rare tumors in the general population and involve the pleura or the peritoneum. Once diagnosed, prognosis is very poor.

Experimental studies have demonstrated the carcinogenicity of asbestos fibers in laboratory animals. Studies differ in the types and species of animal used, types and sizes of asbestos fibers administered, dosage, route of administration, and various time factors of exposure and follow-up. No animal studies which have examined the effects of exposure to asbestos cleavage fragments are known.

Inhalation and ingestion experiments most closely imitate the human situation. In the inhalation experiments, carcinomas have been consistently found in laboratory animals exposed to all types of commercial asbestos fibers. On the other hand, most ingestion studies have reported negative results; there was little evidence of fiber penetration or tumor formation in the gastrointestinal tract after exposure to various types of asbestos fibers. Asbestos fibers administered intrapleurally have produced pleural mesotheliomas in animals; asbestos fibers administered intraperitoneally have produced peritoneal mesotheliomas in animals.

Epidemiological studies have attempted to ascertain the existence and strength of a relationship between asbestos exposure and disease in man. Human populations cannot be manipulated experimentally and exposed to various types, sizes and exposure levels of asbestos for specified lengths of time as can animals. Therefore, epidemiological studies have been mounted to test the association between disease occurrence and asbestos exposure.

Most of the evidence of an association between asbestos exposure and human disease has been acquired from epidemiological studies of occupationally exposed groups. Workers exposed to varying types, sizes, and concentrations of commercial asbestos fibers have experienced increased rates of asbestosis, respiratory cancers, gastrointestinal cancers, and pleural and peritoneal mesotheliomas. Estimates of increased risk of lung cancer range from 2-fold to 10-fold depending on the study; increased risk of gastrointestinal cancer is about 3-fold in most studies. Most of these studies computed relative risks or standardized mortality ratios by comparing observed rates of specific cancers to expected rates based on the United States population or population of the country involved. However, relative risks for asbestosis and mesotheliomas could not be calculated because these are rare causes of death in the general population and U.S. data were not available.

Some of the problems encountered when trying to evaluate, interpret and compare the results of these epidemiological studies are differences in exposure period, differences in follow-up period, overlapping exposure and follow-up periods, age differences, and reported or unreported differences in fiber type, fiber size, and exposure level. The earlier studies, in general, did not even take into consideration the possible variations in risk with different asbestos types, sizes and concentrations.

The potential carcinogenicity of non-commercial asbestos cleavage fragments has been examined in two epidemiological studies of occupational groups with inconsistent results. One study reported a 3-fold increase in respiratory cancer among gold miners exposed for at least 60 months to low levels of fibrous cleavage fragments of cummingtonite-grunerite. Expected deaths were based on the general white male population of South Dakota. The other study reported no increase in respiratory or abdominal cancer among gold miners exposed to cummingtonite-grunerite and with at least 21 years of employment with the mining company.

Epidemiological evidence also suggests human nonoccupational, environmental exposure to commercial asbestos fibers. Asbestos fibers and asbestos bodies have been found in the lungs of persons with no occupational exposure, radiological changes have been demonstrated in populations living in close proximity to an asbestos mine or factory, and mesothelial tumors have been found in persons with no occupational

exposures to asbestos fibers. Therefore, adverse health effects are not limited to occupational exposures.

Two non-occupational studies have reported no excess cancer rates due to ingestion of city water supplies containing high concentrations of non-commercial asbestos minerals in the cummingtonite-grunerite series. However, the elapsed interval from initial asbestos exposure to time of observation may not have been long enough for the development of cancers.

At present, the mechanism of carcinogenesis related to asbestos exposure remains unknown. Among those proposed are the fiber theory, the trace metal theory, the organic materials theory, and the multifactor theory. Some investigators attribute the pathological effects of asbestos to its physical, not its chemical, characteristics. The basis for this premise is that other fibers such as glass fibers are also highly carcinogenic in the pleura of rats. It has been proposed that trace metals associated with the fiber are the major factors of carcinogenesis, especially those metals already known to be human carcinogens. Carcinogenesis may be due to natural contaminating oils and minerals or those introduced as a result of contamination or treatment of the asbestos during processing. It is quite possible that the actual mechanism of carcinogenesis includes none, several, or all of the above theories concomitantly. Smoking appears to increase the risk of lung cancer among asbestos workers, but it is not known whether the effect of these two carcinogens in combination is additive or multiplicative. No association has been demonstrated between cigarette smoking and mesothelioma.

It is difficult to estimate the independent contributions of fiber type, fiber size, exposure level, duration of exposure, or occupation to the risk of disease because all these factors are interrelated to a certain degree. Moreover, the mechanisms of development of asbestosis, lung cancer, and mesothelioma due to asbestos exposure have not been adequately delineated so that we cannot assume that they are the same for all. Therefore, these several factors may vary in their contribution to risk according to disease.

Animal experiments and epidemiological studies have demonstrated that all commercial types of asbestos fibers produce asbestosis and lung cancer; all commercial types of asbestos, except perhaps anthophyllite are associated with mesothelial tumors. The risk of mesothelioma in

man and animals seems to be higher for crocidolite than amosite or chrysotile. There are not enough data to assess the carcinogenic risk associated with noncommercial forms of asbestos such as those in the cummingtonite-grunerite amphibole mineral category.

Fiber length and diameter appear to be related to pathogenicity of asbestos fibers. Long fibers seem to be more carcinogenic; thin fibers also seem to be more carcinogenic. In general, more disease is associated with higher exposure levels and longer lengths of exposure, except for mesotheliomas which have been reported following brief, low levels of exposure. However, this dose-response relationship is not fully understood at lower exposures; the threshold exposure, or the level below which disease will not occur, is not known. Moreover, significant increases in disease in humans associated with asbestos exposures generally do not develop until 15-20 years after initial exposures to the fibers and perhaps even 30-40 years for mesotheliomas. Observed variations in relative risk between occupations or industries utilizing asbestos are probably due to differences in other factors such as asbestos type, size of fiber and exposure levels within these industries.

At present, there is insufficient knowledge about the pathological effects of non-commercial asbestos fibers (cleavage fragments). However, since these non-commercial cleavage fragments are morphologically and chemically similar to commercial asbestos fibers known to cause certain cancers, they require further investigation. Therefore, the following recommendations have been made:

1. Animal studies to assess the health effects associated with the non-commercial forms of asbestos found in Northern Minnesota.
2. A continuation and periodic update of the literature review specific to exposure to non-commercial asbestos cleavage fragments.
3. Measurement of asbestos cleavage fragment levels in ambient air and water supplies in the copper-nickel mining area and surrounding areas.
4. Development of methodologies for baseline data and surveillance of morbidity and mortality in the proposed copper-nickel mining area.
5. Continued surveillance of cancer morbidity in the populations of Duluth, Two Harbors, Beaver Bay and Silver Bay.

## I. ASBESTOS MINERALS

### A. Physical Characteristics

"Asbestos" is a general term given to a group of fire-resistant mineral silicates. Asbestos minerals are similarly fibrous in structure and will subdivide into smaller fibers either naturally or when industrially processed. This structural property differentiates asbestos fibers from man-made inorganic fibers such as glass fiber or mineral wool.

Asbestos mineral types differ widely in other properties such as their metallic elemental content, flexibility, range of fiber length and diameter, tensile strength, surface properties, resistance to heat, acid resistance and spinnability. These characteristics not only determine the industrial uses of the various asbestos types but also the several biological responses associated with asbestos exposure in man and animals.

### B. Fiber Types

The two main mineral subdivisions are serpentines (chrysotile) and amphiboles (crocidolite, amosite, tremolite, actinolite, anthophyllite). Although there are many other types, these are the most common types mined for industrial use.

### "Asbestos"

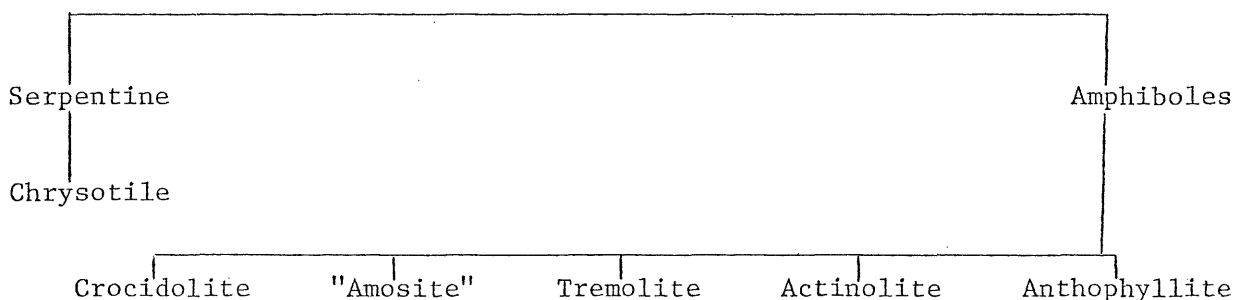


Table 1 summarizes the individual properties of chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite. Although these asbestos fibers are similar, they are far from identical.

In addition to the commercially important asbestos minerals discussed above, there are a number of non-commercial fibrous cleavage fragments.



TABLE 1  
TYPES OF ASBESTOS

	SERPENTINE	AMPHIBOLES				
	Chrysotile	Crocidolite	"Amosite"	Tremolite	Actinolite	Anthophyllite
General Chemical Formula *	$3MgO_2SiO_2 \cdot 2H_2O$	$Na(Fe_2^{3+}Fe_3^{2+})Si_8O_{22}(OH)_2$	$(Fe_6Mg)Si_8O_{22}(OH)_2$	$Ca_2(Mg_6Fe)Si_8O_{22}(OH)_2$	$Ca_2(MgFe_6)Si_8O_{22}(OH)_2$	$(FeMg_6)Si_8O_{22}(OH)_2$
Flexibility **	Very flexible	Fair to good	Good	Brittle	Brittle	Brittle to flexible
Length **	Short to 3"	Short to 3"	¼" to 6"	Short to long	Short to long	Short
Texture **	Harsh to silky	Harsh or soft	Coarse but pliable	Harsh to soft	Harsh	Harsh to soft
Tensile Strength **	Very high	Very high	Fair	Weak	Very weak	Weak
Acid Resistance **	Fairly soluble	Very good	Good	Fairly resistant	Highly resistant	Fair to good
Spinnability **	Very good	Fair	Fair	Poor	Poor	Poor
Resistance to heat **	Good	Poor	Good	Fair to good	-----	Very good
Estimated % of total production in 1963 ***	93	3.5	2.4	<1	-----	<1
Related mineral system *	-----	Riebeckite-glaucophane	Grunerite-cummingtonite	actinolite-tremolite	actinolite-tremolite	anthophyllite-gedrite

\* Source: IARC, 1977.

\*\* Source: Hendry, N.W., Ann N.Y. Acad Sciences, 1965.

\*\*\* Source: Becklake, 1976.

The distinction between fibers of commercial asbestos and cleavage fragments involves minor differences in their structural and chemical makeup. "The average crystal structure and chemical composition of these two types of fibers (cleavage fragments and asbestos) is essentially the same. Consequently, they cannot be distinguished by electron diffraction and x-ray microspectroscopy in air and water samples, although differences in their structural and chemical details may exist."<sup>1</sup>

However, the difference between commercial asbestos fibers and cleavage fragments must be acknowledged in this report because the actual fibers existing in Northern Minnesota are fibrous cleavage fragments of cummingtonite-grunerite most closely resembling commercial amosite. Few studies have examined the health effects of exposure to asbestos cleavage fragments.

In many of the early studies of the health effects of exposure to asbestos, the type of asbestos fiber involved was either unknown or not reported. More recently, studies have identified the type(s) of asbestos fiber involved to examine differences in risk and possible chemical and physical factors involved in etiological mechanisms of asbestos-related disease.

There is considerable confusion and misuse of mineralogical expressions dealing with asbestos. According to the Minnesota Pollution Control Agency, some of the most frequently misused mineralogical terms include: asbestiform, asbestos-like, asbestiform minerals, asbestos, asbestos minerals, asbestos fibers, asbestos-like fibers, amosite, amosite fibers, non-commercial asbestos, short-fiber asbestos, amphiboles in the grunerite-amosite-cummingtonite series, etc.<sup>1</sup>

This review of the health effects of "asbestos" exposure recognizes these problems of terminology but must concern itself with terms and expressions found in the medical literature.

#### C. Exposure to Asbestos

##### i) Occupational

Commercial exploitation of asbestos began in the latter part of

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<sup>1</sup>"Comments on Asbestiform and Fibrous Mineral Fragments, Relative to Reserve Mining Company Taconite Deposits," Minnesota Pollution Control Agency, March 24, 1976.

the nineteenth century as a result of the industrial revolution. Adverse health effects were not reported until the early 1900's.

World production of asbestos has grown to over 5 thousand million kilograms (approximately 5,000,000 tons) in 1976 (IARC, 1977). Although there are over 3,000 identified uses of asbestos, over two-thirds is used in the construction industry. Occupations at risk can be broadly classified into mining, milling, and manufacturing of asbestos-containing products. Manufacturing can be subdivided into textiles, construction products, paper products, friction materials, and insulation products. These industries manufacture a wide variety of asbestos-containing products ranging from cloth, protective clothing, mailbags, and flower pots to gutters, automotive products such as clutch plates and brake lining, and insulation materials. A more detailed list of occupations at risk appears in Table 2.

ii) Non-Occupational

Both direct and indirect evidence suggests non-occupational, environmental exposure to asbestos. High concentrations of asbestos have been discovered in ambient air, especially near asbestos factories and mines, and also in foods, beverages, and city water supplies. Although less research has been done on the health effects of ingested asbestos, there has been a recent upsurge in interest, in part due to the realization of extensive pollution of Duluth waters with asbestos from mine residues. Also, the occurrence of mesothelioma in family members of asbestos workers has been attributed to household and neighborhood exposures.

TABLE 2

OCCUPATIONS AT RISK FOR ASBESTOS EXPOSURE IN MINING  
MILLING, MANUFACTURING, AND SECONDARY USES

Process	Products Made or Used	Jobs Potentially at Risk
Production		
Mining		Rock mining, loading, trucking
Milling		Crushing, milling
Handling		Transport workers, dockers, loaders, those who unpack jute sacks (recently replaced with sacks that do not permit fibers to escape)
Primary uses in		
Spray insulation	Spray of fiber mixed with oil	Spray insulators (construction, shipbuilding)
Filler and grouting		
Manufacturing of Textiles	Cloth, curtains, lagging, protective clothing, mailbags, padding, conveyor belts	Blending, carding, spinning, twisting, winding, braiding, weaving, slurry mixing, laminating, moulding, drying
5 Cement products	Sheets, pipes, roofing shingles, gutters, ventilation shafts, flower pots	Blending, slurry preparation, rolling, pressing, pipe cutting
"Paper" products	Millboard, roofing felt, fine quality electrical papers, flooring felt, fillers	
Friction materials	Automotive products: gaskets, clutch plates, brake linings	
Insulation products	Pipe and boiler insulation, bulkhead linings for ships	
Application		
Construction		
New construction	Boards and tiles; putties, caulk, paints, joint fillers; cement products (tiles, pipes, siding, shingles)	Directly, carpenters, ladders, painters, tile layers, insulation workers, sheet metal and heating equipment workers, masons, indirectly all other workers on construction sites, such as plumbers, welders, electricians
Repair, demolition	Insulation materials	Demolition workers for all of these

TABLE 2  
(continued)

OCCUPATIONS AT RISK FOR ASBESTOS EXPOSURE IN MINING  
MILLING, MANUFACTURING, AND SECONDARY USES

Process	Products Made or Used	Jobs Potentially at Risk
Shipbuilding		
Construction	Insulation materials (boards, mattresses, cloth) for engines, hull, decks, lagging of ventilation and water pipes, cables	Laggers, refitters, strippers, steam fitters, sail-makers, joiners, shipwrights, engine fitters, masons, painters, welders, caulkers
Repair, refits	Insulation materials, as described for "construction"	Directly, all above jobs on refits, dry dock, and other repairs operations Indirectly, maintenance fitters and repair men, electricians, plumbers, welders, carpenters
Automotive industry		
Manufacture	Gaskets, brake linings, undercoating	Installation of brake linings, gaskets, and so on
Repair	Gaskets, brake linings, undercoating	Service men, brake repairmen, body repairmen, auto mechanics

Source: Becklake, M.R., "Asbestos-Related Diseases of the Lung and Other Organs: Their Epidemiology and Implications for Clinical Practice", AM REV RESPIR DIS, Vol. 114, July 1976, p. 192.

## II. ASBESTOS RELATED DISEASES

### A. Introduction

Pathological effects attributed to asbestos exposure in man are "asbestos"bodies in the lung, pleural plaques, asbestosis, carcinoma of the lung, and malignant mesothelioma of the pleura (lining of the lung cavity) and peritoneum (lining of the abdominal wall and organs). Several other cancers including cancer of the gastrointestinal tract have a suspected association with asbestos exposure. Figure 1 traces the history of medical recognition of adverse health effects in relation to the growth of the asbestos industry (Becklake, 1976).

### B. Respiratory Disease

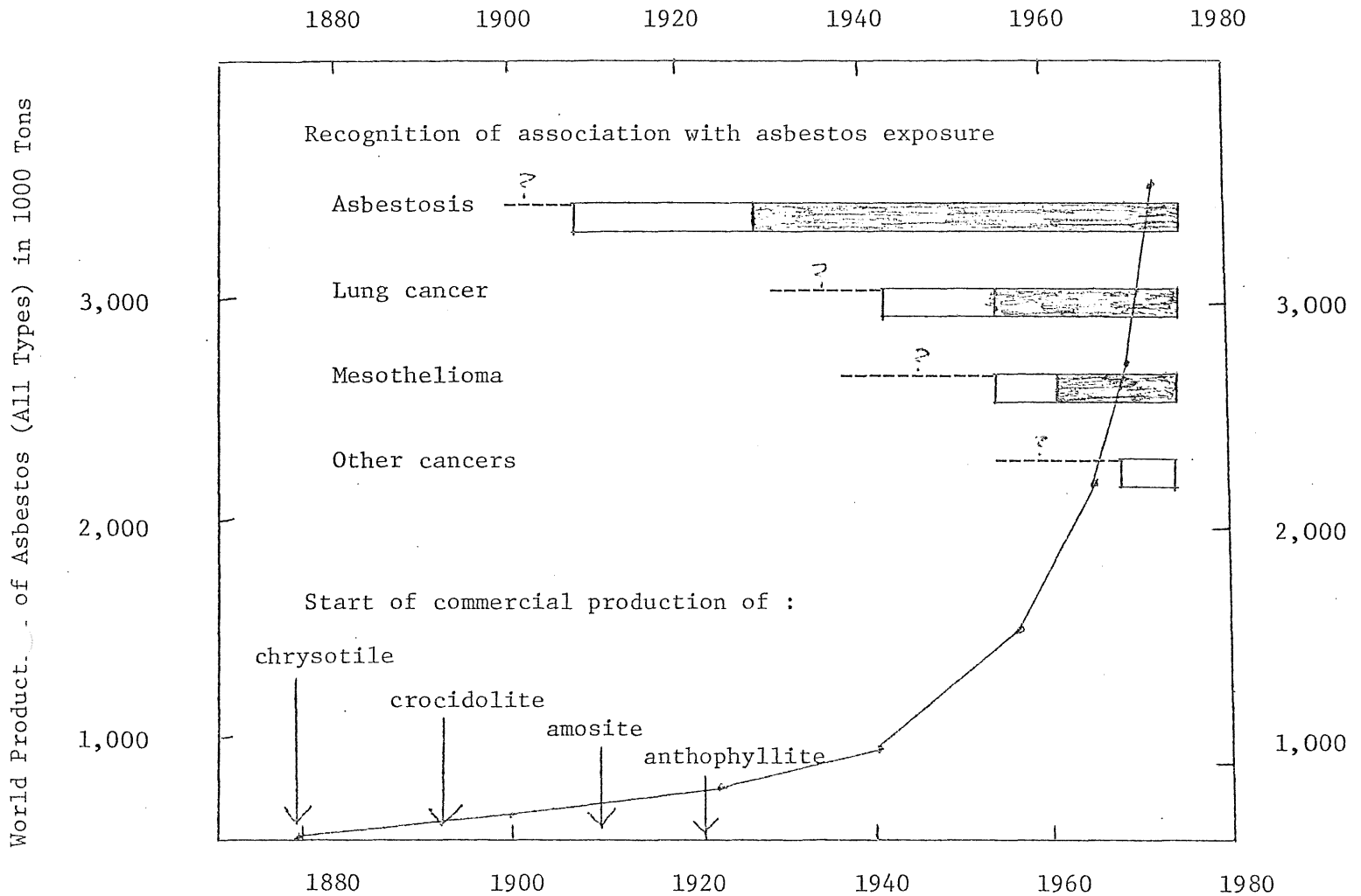
Asbestos bodies, first recognized in the lungs in the early 1900's, consist of asbestos fibers coated by protein, iron, and possibly other materials. They have a characteristic rod-shaped structure with clubbed ends, are often beaded lengthwise, and are yellow to brown in color. The coating is now thought to be the result of interaction between the asbestos fibers and the alveolar macrophages. Asbestos fibers are engulfed by macrophages in the lung or several macrophages may fuse to engulf large fibers, after which coating begins. Not all coated fibers seen in the lung have an asbestos core and it is for this reason that the term "ferruginous body" is preferred by some authors in the absence of positive identification of the fiber core (Suzuki, 1969; Becklake, 1976).

Both hyaline and calcified pleural plaques are associated with asbestos exposure. Pleural plaques occur as discrete, raised lesions and diagnosis is made radiographically. Neither asbestos bodies or pleural plaques alone cause clinical disease, but rather occur prior to or concomitantly with asbestosis or asbestos-related cancers.

### C. Asbestosis

Asbestosis was recognized in the early years of the twentieth century as being associated with asbestos exposure. It is characterized by a pattern of roentgenographic changes in the lung consistent with diffuse interstitial fibrosis of variable degree and, at times, fibrosis and calcification of the pleura, clinical changes that include fine rales and finger clubbing, and physiologic changes consistent with a restrictive lung disorder such as dyspnea (labored or difficult breathing) and reduced vital capacity (NTIS, 1972). The first case of this

Figure 1. Diagrammatic Representation of the Growth of the Asbestos Industry and the Recognition of the Associated Biologic Effects



? = Suspected,  = Probable,  = Established

Source: Becklake, M.R., "Asbestos-Related Diseases of the Lung and Other Organs: Their Epidemiology and Implications for Clinical Practice," AM REV RESPIR DIS, 114: 192, July, 1976.

pneumoconiosis was described in 1907 by H. Montague Murray. However, it was not until 1927 that the term "asbestosis" was first used by Cooke to describe a case in a female asbestos textile worker.

#### D. Lung Cancer

In 1935 asbestos exposure and carcinoma of the lung were first suggested to be causally related (National Research Council, 1971). Primary sites are more often in the lower lobes, in contrast with the usually higher frequency of upper lobe tumors. Lung cancer shows a very high relative risk which appears to vary with intensity and duration of cigarette smoking. In addition to lung cancer, there is substantial evidence to suggest an association between asbestos exposure and cancers of the gastrointestinal tract. These cancers may result from ingestion of asbestos fibers. (Merliss, 1971; Gross, 1974; Lee, 1974; Bolton, 1976).

#### E. Mesothelioma

Mesotheliomas are relatively rare tumors with an estimated incidence of about 1 per 1,000,000 per year in the general population (Becklake, 1976). Most mesotheliomas related to asbestos exposure involve the pleura, but they may also involve the peritoneum. These tumors spread quickly and a patient seldom lives more than a year after mesothelioma has been diagnosed. The first clinical signs of this disease are chest pain and breathlessness. It has been suggested that asbestos fibers migrating through the lung or gut wall are associated with the development of these tumors.

#### F. Other Cancers

Several other cancers such as laryngeal, ovarian, breast, gastrointestinal, and leukemia, multiple myeloma, and Waldenstrom's macroglobulinemia have a suspected but unsubstantiated association with asbestos exposure (Becklake, 1976; IARC, 1977; Gilson, 1976).



### III. PATHOPHYSIOLOGY - ANIMAL STUDIES

#### A. Introduction

Experimental studies have demonstrated the carcinogenicity of asbestos fibers in laboratory animals. Studies differ in the type and species of animal used, types and sizes of asbestos fibers administered, dosage, route of administration, and various time factors of exposure and follow-up. No known animal studies have examined the effects of exposure to asbestos cleavage fragments.

Animal studies have been grouped by route of administration of the asbestos fibers in this review: inhalation, ingestion, intratracheal, intrapleural, and intraperitoneal.

The inhalation and ingestion experiments most closely imitate the human situation. However, experiments using intratracheal, intrapleural, and intraperitoneal routes of administration are also useful for investigating certain questions such as the relative carcinogenicity of different samples because the asbestos fibers are administered directly to the site of interest and there is less variation in deposition or retention of fibers.

#### B. Inhalation

Gross et. al. observed 28 lung tumors in 72 rats exposed to chrysotile dust ( $86 \text{ mg/m}^3$  for 30 hours/week), for at least 16 months. No tumors occurred in the 39 controls. The authors suggested that trace metals from the mill hammer used to prepare the fibre might be a causal factor for these tumors (Gross, 1967).

Reeves observed 31 rats exposed to crocidolite at a concentration of  $49 \text{ mg/m}^3$  for 16 hours/week for 2 years. Of these 31 rats, 2 developed squamous cell carcinomas of the lung. No tumors were observed in the rats exposed to chrysotile or amosite (Reeves, 1971).

A subsequent study by Reeves examined 90 mice, 204 gerbils, 207 rats, 60 rabbits, and 96 guinea pigs exposed to amosite, crocidolite or chrysotile fibers at a concentration of  $50 \text{ mg/m}^3$  for 4 hours/day for 4 days per week. Animals were evenly divided into fiber groups and exposed for 2 years or until death. Each animal type had a control group with no exposure to asbestos. There were not tumors detected in any of the

gerbils, rabbits, or guinea pigs. No tumors were detected in mice exposed to amosite or chrysotile, however two tumors developed in mice exposed to crocidolite, and one in the controls. Rats demonstrated the highest number of tumors with three for amosite (2 mesotheliomas), five for crocidolite, three for chrysotile (1 mesothelioma) and none in the controls. Results of this study show a difference in response according to the experimental animal used (Reeves, 1974).

Wagner in 1974 exposed Caesarian rats of the Wistar strain to either amosite, anthophyllite, crocidolite, Canadian chrysotile or Rhodesian chrysotile. The rats were exposed for one day, three months, six months, 12 months or 24 months at an approximate concentration of  $10 \text{ mg/m}^3$  for seven hours a day and five days/week. All types of asbestos produced asbestosis which continued to progress after removal from exposure. Lung tumors were observed in each group of rats regardless of asbestos type or length of exposure, even in groups of rats with only one day of exposure. The incidence of mesothelial tumors was lower. None were observed among the control groups or the groups exposed to Rhodesian chrysotile (Wagner, 1974).

A summary of these studies is presented in Table 3.

### C. Ingestion

There is some evidence that ingested asbestos may penetrate the intestinal wall, at least of rats. Westlake fed chrysotile dust to 60 White Wistar female rats as 6% of their diet for approximately three months and observed chrysotile and crystals in many sites in the colonic epithelium and lamina propria (Westlake, 1965). Ponterfact injected a dose of  $9.4 \times 10^9$  chrysotile fibers into the stomachs of 100 rats and 2-4 days later found fibers in the blood, spleen, omentum, heart, brain, and lungs (Ponterfact, 1973).

Several other studies of similar design using various types of asbestos have reported negative results; there was little evidence of fiber penetration or tumor formation in the GI (gastrointestinal) tract. Smith fed chrysotile or amosite to 45 golden Syrian male hamsters as 1% of their diet until death and found no gastric carcinomas or tumors of the GI tract (Smith, 1965).

TABLE 3. PATHOLOGICAL EFFECTS OF INHALED ASBESTOS  
ANIMAL EXPERIMENTAL STUDIES

Author and Year	Experimental Animal	Number of Animals	Type of Asbestos	Amount of Asbestos	Fiber Size	Period of Exposure and Follow-up	Results
Gross 1967	Rats	72	chrysotile dust	86 mg/m <sup>3</sup> for 30 hrs per week	unreported	at least 16 months (time of appearance of first tumor) or until death	Lung tumors: 17 adenocarcinomas 4 squamous-cell carcinomas 7 fibrosarcomas No tumors occurred in 39 controls
Reeves 1971	Rats	31	crocidolite	49 mg/m <sup>3</sup> for 16 hrs per week	unreported	2 years	2 squamous-cell carcinomas of the lung
		40	chrysotile				5 with benign pulmonary adenomatosis
		42	amosite				no adverse effects

Davis fed rats 100 g of either chrysotile or crocidolite in 20 grams of butter each week for at least three months. No penetration into the gut epithelial cells was observed (Davis, 1974). Webster reported no pathological effects in baboons fed varied concentrations of crocidolite in food and water for up to five years (Webster, 1974).

Gross in 1974 administered several types of asbestos (chrysotile, amosite, crocidolite, and taconite tailings) in butter or oleo-margarine to rats in varying dosages and varying lengths of time. No evidence of penetration of asbestos fibers into the tissues was observed (Gross, 1974). Findings of a similar experiment by Bolton were consistent with those of Gross (Bolton, 1976).

A summary of these studies is presented in Table 4.

#### D. Intratracheal

No tumors were found in the respiratory tract of hamsters given repeated intratracheal injections of 25 mg. amosite per week for 11 months or 6.25 mg. chrysotile per week for six months (Smith, 1965).

Reeves et. al. also observed no neoplasms in rats, rabbits, guinea pigs and hamsters 24 months after an intratracheal injection of amosite, crocidolite or chrysotile. Rats were given a 6 mg. dose, rabbits a 10 mg. dose, guinea pigs a 6 mg. dose, and hamsters a 4 mg. dose. However, it may be possible that the number of treated animals was too small (12 - 16 for each species) (Reeves, 1971).

#### E. Intrapleural Administration

Reeves et. al. administered intrapleural injections of amosite, crocidolite, or chrysotile into rats (10 mg. dose), rabbits (16 mg. dose) guinea pigs (10 mg. dose), and hamsters (10 mg. dose). None of the animals given amosite developed mesotheliomas, one rat and two rabbits given crocidolite developed a pleural mesothelioma, and two rats given chrysotile developed a pleural mesothelioma (Reeves, 1971).

Wagner et. al., using SPF Wistar rats inoculated intrapleurally with asbestos, reported that the risk of developing mesothelioma

TABLE 4. PATHOLOGICAL EFFECTS OF INGESTED ASBESTOS  
ANIMAL EXPERIMENTAL STUDIES

Author and Year	Experimental Animal	Number of Animals	Type of Asbestos	Amount of Asbestos	Fiber Size	Period of Exposure and Follow-up	Results
Westlake 1965	White Wistar female rats	60	chrysotile dust	6% of diet	most were .5 $\mu$ m - 1.0 $\mu$ m long	approx. 3 months	electron microscopy revealed asbestos crystals in many sites in the colonic epithelium and lamina propria
Smith 1965	Golden Syrian male hamsters	45	soft chrysotile or amosite	1% of diet	not reported	until death	no gastric carcinomas, no tumors in gastrointestinal tract except a neoplasm in the mesentery of the colon
Ponterfact 1973	Rats	100	chrysotile	1 dose of 9.4x10 <sup>9</sup> fibers or 94x10 <sup>9</sup> fibers injected into stomach	most were .2 $\mu$ m - 2 $\mu$ m long	2 days for 50 rats; 4 days for 50 rats	fibers in blood, spleen, omentum, heart, brain, lungs
Davis 1974	Rats	not reported	chrysotile or crocidolite	100 mg in 20 g. butter each week	not reported	several rats 3 months; other rats followed to death	no penetration into the gut epithelial cells
Webster 1974	Baboons	not reported	crocidolite	varied concentrations in food and water	not reported	up to 5 years	asbestos needles found in feces; no evidence of a peritoneal tumor or gastrointestinal tumor

TABLE 3. PATHOLOGICAL EFFECTS OF INHALED ASBESTOS  
ANIMAL EXPERIMENTAL STUDIES (continued)

Author and Year	Experimental Animal	Number of Animals	Type	Amount	Fiber Size	Period of Exposure and Follow-up	Results
Reeves 1974	Mice	30	amosite	about 50 mg/m <sup>3</sup> for 4 hrs/day for 4 days per week	amosite: 3-5 μm in length; 0.2 - 0.5 μm in diameter crocidolite: 3-6 μm in length; 0.4 - 0.5 μm in diameter; chrysotile: 6-15 μm in length; 0.2 μm in diameter	2 years or until death	no tumors
		30	crocidolite				2 bronchial tumors
		30	chrysotile				no tumors
		10	controls				1 bronchial tumor
	Gerbils	68	amosite				no tumors
		68	crocidolite				no tumors
		68	chrysotile				no tumors
		12	controls				no tumors
	Rats	69	amosite				1 lung tumor
		69	crocidolite				2 mesotheliomas
		69	chrysotile				5 lung tumors
		12	controls				2 lung tumors 1 mesothelioma
	Rabbits						no tumors
		20	amosite				no tumors
		20	crocidolite				no tumors
		20	chrysotile				no tumors
	Guinea Pigs	12	controls				no tumors
		32	amosite				no tumors
		32	crocidolite				no tumors
		32	chrysotile				no tumors
			no tumors				

TABLE 3. PATHOLOGICAL EFFECTS OF INHALED ASBESTOS  
ANIMAL EXPERIMENTAL STUDIES (continued)

Author and Year	Experimental Animal	Number of Animals	Type of Asbestos	Amount of Asbestos	Fiber Size	Period of Exposure and Follow-up	Number with Lung Tumors	Number with Mesothelioma			
Wagner 1974	Caesarean rats of the Wistar Strain	49 52 24 25 21	amosite	approx. 10 mg/m <sup>3</sup> for 7 hours/day and 5 days per week	unreported	Exposure:	3 10 2 10 13	1 0 0 0 1			
						1 day					
						3 months					
						6 months					
						12 months					
		24 months									
		49 52 24 28 19	anthophyllite			49 52 24 28 19	anthophyllite	1 day	2 6 6 20 16	0 0 0 1 1	
											3 months
											6 months
											12 months
											24 months
		49 52 24 26 20	crocidolite			49 52 24 26 20	crocidolite	1 day	6 14 4 18 13	1 1 0 2 0	
											3 months
											6 months
											12 months
											24 months
		49 52 24 23 24	chrysotile (Canadian)			49 52 24 23 24	chrysotile (Canadian)	1 day	1 18 5 11 10	0 0 0 3 1	
											3 months
											6 months
											12 months
											24 months
		49 52 25 27 20	chrysotile (Rhodesian)			49 52 25 27 20	chrysotile (Rhodesian)	1 day	5 16 8 19 11	0 0 0 0 0	
											3 months
											6 months
12 months											
24 months											
48 58 48	controls	48 58 48	controls	1 day	4 3 0	0 0 0					
							3 months				
							6-24 months				

TABLE 4. PATHOLOGICAL EFFECTS OF INGESTED ASBESTOS  
ANIMAL EXPERIMENTAL STUDIES (continued)

Author and Year	Experimental Animal	Number of Animals	Type of Asbestos	Amount of Asbestos	Fiber Size	Period of Exposure and Follow-up	Results
Gross 1974	male rats	10	ball-milled chrysotile	5% by weight in mix	not reported	21 months	no lesion in GI tract found by gross examination; no fibers found in sections of intestines examined by electron microscope
Gross 1974	male rats	10	amosite	10% content in oleomargarine	not reported	2 rats-1 week 2 rats-2 weeks 2 rats-3 weeks 2 rats-4 weeks 2 rats-5 weeks	total of nine fibers found in the digests of the mesenteric tissue in all rats
	male rats	10	taconite tailings	20% content in oleomargarine	not reported	2 rats-1 week 2 rats-2 weeks 2 rats-3 weeks 2 rats-4 weeks 2 rats-5 weeks	
Gross 1974	SPF rats Wistar strain initially 12 weeks old	31	Rhodesian chrysotile	10 mg/week in butter	not reported	fed asbestos butter for 16 weeks, then followed to death	no penetration of GI mucosa or transmigration of optically visible fibers by light microscope
	SPF rats Wistar strain initially 12 weeks old	33	crocidolite	5 mg/week in butter	not reported	fed asbestos butter for 16 weeks, then followed to death	
	SPF rats Wistar strain initially 12 weeks old	34	crocidolite	10 mg/week in butter	not reported	fed asbestos butter for 16 weeks, then followed to death	



TABLE 4. PATHOLOGICAL EFFECTS OF INGESTED ASBESTOS  
ANIMAL EXPERIMENTAL STUDIES (continued)

Author and Year	Experimental Animal	Number of Animals	Type of Asbestos	Amount of Asbestos	Fiber Size	Period of Exposure and Follow-up	Results
Gross 1974	SPF rats Wistar strain; initially 12 weeks old	35	North West Cape crocidolite	10 mg/wk in butter	not reported	fed asbestos butter for 18 weeks, then followed to death	no penetration by asbestos fibers into tissues observed by electron microscope examination
	SPF rats Wistar strain; initially 12 weeks old	28	Transvaal crocidolite	10 mg/wk in butter	not reported	fed asbestos butter for 18 weeks, then followed to death	
	SPF rats Wistar strain; initially 12 weeks old	12	chrysotile	5 mg/gm butter fed ad libitum	not reported	1 or 3 months	
	SPF rats Wistar strain; initially 12 weeks old	12	crocidolite	5 mg/gm butter fed ad libitum	not reported	1 or 3 months	
Bolton 1976	Male SPF Han rats initially 10 weeks old	4	crocidolite	250-300 mg. in 50-60 g margarine per week	not reported	1 killed at 2 weeks; 1 killed at 3 months; 1 killed at 6 months; 1 killed at 1 year	no evidence of penetration of asbestos fibers into the tissues by examination with stereoscopic microscope; no pathological lesions
	Male SPF han rats initially 10 weeks old	4	amosite	250-300 mg. in 50-60 g margarine per week	not reported	1 killed at 2 weeks; 1 killed at 3 months; 1 killed at 6 months; 1 killed at 1 year	
	"	4	chrysotile	"	not reported	"	

was approximately proportional to the dose at any given time after injection. Crocidolite was the most carcinogenic of all the samples tested. However, all types of asbestos tested produced mesotheliomas (amosite, anthophyllitè, chrysotile, crocidolite) (Wagner, 1973).

Stanton and Wrench applied several types of asbestos fibers on a fibrous glass vehicle to the pleura of rats. After two years, amosite, chrysotile, and four different crocidolite types produced mesotheliomas in 58 - 75% of rats (Stanton and Wrench, 1972).

#### F. Intraperitoneal

Reeves et. al. using rats and hamsters, examined the effects of intraperitoneal injections of amosite, crocidolite, or chrysotile asbestos fibers. Hamsters showed no effects, and rats exposed to amosite showed no effects. However, three rats exposed to crocidolite and three rats exposed to chrysotile developed peritoneal mesotheliomas as early as seven months following the injection (Reeves, 1971).

#### IV. EPIDEMIOLOGIC STUDIES

##### A. Introduction

Epidemiologic studies have attempted to ascertain the existence and strength of the relationship between asbestos exposure and disease in man. Human populations cannot be manipulated experimentally and exposed to various types, sizes and exposure levels of asbestos for specified lengths of time as can animals. Therefore, epidemiologic studies have been mounted to test the association between disease occurrence and asbestos exposure.

When comparing the results of two or more studies, several differences in study design should be kept in mind: differences in characteristics of the populations studied (such as age, race, social class, etc.), exposure period, length of follow-up, outcomes measured (mortality, morbidity), fiber type, fiber size and dose.

Most of the evidence of an association between asbestos exposure and human disease has been acquired from epidemiologic studies of occupationally exposed groups. The ideal control group for these occupational studies would be an internal control consisting of a group under study except for exposure to the agent of interest (Enterline, 1976). However, since this is not usually possible, comparison rates for certain cancers have generally been drawn from the U.S. white population or population of the country involved. This choice of control group has been criticized because of the variation in specific cancer death rates throughout the United States. Control groups should be chosen from nearby counties, or at least from the same state as the group under study.

Studies should also ascertain smoking status because it appears that among asbestos workers, smokers have a much higher risk of lung cancer than non-smokers.

##### B. Occupationally Exposed Groups

###### i) Asbestosis

Asbestosis, or asbestotic pneumoconiosis, has been clearly related to asbestos exposure. Clinical symptoms characteristic of asbestosis have been discussed earlier in this report. Clinical cases were first reported in asbestos workers in the very early 1900's and epidemiologic data were available as early as the 1930's. It was shown at that time that a large proportion

of individuals exposed for long periods to high concentrations of asbestos dust developed asbestosis (in studies by Merewether (1930), Fulton (1935), and Dreesen (1938) (NTIS, 1971). Although there is general agreement that all forms of commercial asbestos can produce fibrotic effects in the lung, epidemiologic data on relative fibrogenicity of different asbestos fibers are still inconclusive.

Selikoff examined 1,117 asbestos insulation workers in the New York-New Jersey metropolitan area for radiological evidence of asbestosis. Of the 392 workers with 20 or more years of exposure, radiological evidence of asbestosis was found in 339 (about 85%); among the remaining 725 workers with less than 20 years of exposure, only about 30% had radiological evidence of asbestosis. The cases of asbestosis were less severe among workers with less than 20 years of exposure than those cases of asbestosis among workers with 20 or more years of exposure (Selikoff, 1965).

Enterline studied 21,755 white men, age 15 to 64, who worked in certain U.S. asbestos product plants at some time during the period 1948 through 1951 and compared them with a control group of 6,281 cotton textile plant workers. The 21,755 asbestos workers were separated into 3 groups (12,402 building products workers, 7,510 friction materials workers, and 1,843 textile product workers) for comparison of rates among the various asbestos dust exposure levels. Although exposure levels were not actually measured, physical inspection of the plants showed the textile factories to be the most dusty. A higher death rate with asbestosis mentioned as the underlying or contributory cause of death was found in the asbestos textile industry (about 13 per 1,000 workers studied) than in the asbestos friction materials industry (about 4 per 1,000) or the asbestos building products industry (less than 1 per 1,000 studied). There were no deaths with asbestosis mentioned among cotton textile workers (Enterline, 1967).

Murphy studied the effects of low concentrations of amosite and chrysotile by comparing the prevalence of asbestosis in 101 pipe coverers in a ship construction yard with low-level exposure to 94 unexposed controls in the yard matched for age, duration of employment, and smoking habits. Dust levels in the yard had been

near the recommended 5 mppcf for 20 years prior to the survey. Asbestosis was 11 times more common in pipe coverers than in the controls (Murphy, 1971).

Epidemiological data regarding morbidity due to occupational exposure to anthophyllite asbestos among 1,249 Finnish miners and millers exposed for at least 3 months between 1936 and 1972 revealed 105 new cases of asbestosis (8.4%). Of 46 workers who were exposed over 25 years, 47% suffered from asbestosis. There were no controls (Ahlman, 1973).

Cooper, in studies of asbestos insulation workers, reported that persons exposed to insulation materials containing amosite, chrysotile or crocidolite have consistently been shown to have high prevalence rates of asbestosis (Cooper, 1973). McDonald reported results of epidemiological surveys of chrysotile production workers in Quebec, Italy, and Cyprus and concluded that the risk of clinically significant disease can be kept under 1% for 50 years of exposure if dust levels are maintained under 2 mmcpf (McDonald, 1973).

ii) Cancer

Workers exposed to varying types, sizes and concentrations of asbestos have experienced increased rates of respiratory cancer, gastrointestinal cancers, and pleural and peritoneal mesotheliomas. Epidemiological studies of occupational exposure to asbestos have become more precise over the years. The earlier studies, in general, did not take into consideration the possible variations in risk with different asbestos types, sizes and concentrations.

Table 5 provides a summary of the occupational studies reviewed below. Most of these studies compared observed rates of specific cancers to expected rates calculated from the United States population or the population of the country involved. Expected rates for mesotheliomas could not be calculated because these tumors are rare causes of death in the general population and U.S. data were not available.

Doll carried out one of the first epidemiological studies on mortality from lung cancer in asbestos workers. Inconclusive results from animal experiments and clinical reports of lung cancer

in persons with asbestosis prompted this study of 113 men in a large asbestos works in England who had at least 20 years of exposure to asbestos dust prior to 1953. Eleven deaths due to lung cancer occurred in the group whereas only 0.8 were expected. All cases were associated with the presence of asbestosis. Doll concluded that certain asbestos workers were at about 10 times the risk of developing lung cancer than the general population (Doll, 1955).

Braun in 1958 showed an increased risk of lung cancer among 5,958 asbestos miners in the Thetford Mines of Quebec. These miners were on the employment rolls in 1950 with 5 or more years of exposure prior to 1950 and were followed through 1955. There were 9 deaths due to lung cancer by 1955 among these miners, compared to 6 expected based on rates from counties in Quebec with no asbestos mining. Among the exposed miners, lung cancer deaths did not appear to be related to length of employment or degree of exposure. Degree of exposure was based on a weighted average of the years spent at three levels of estimated dustiness. (Category II was twice as dusty as Category I, and Category III was three times as dusty as Category I) (Braun, 1958).

Selikoff in 1964 reported cancer rates for a group of 632 New York and New Jersey building trades insulation workers with relatively light, intermittent, exposure to asbestos. These workers were on the union rolls as of January 1943 and had at least 20 years of exposure to asbestos before they died. Of 255 total deaths as of 1963, 45 had died of cancer of the lung or pleura compared to 6.6 such deaths expected based on the U.S. white male population. There were 29 deaths due to cancer of the stomach, colon or rectum compared with 9.4 expected, a three-fold increase. Pleural mesothelioma accounted for 3 deaths and peritoneal mesothelioma accounted for 1 death. Although smoking habits were not ascertained in the original cohort, 320 of the 377 surviving members were interviewed after 1963 and compared with a sample of men drawn from the general population. From these data, the authors concluded that even if all 632 members had smoked at least a pack of cigarettes a day, their smoking habits could not

account for a lung cancer death rate 6-7 times as high as that of white males in the general population (Selikoff, 1964). A subsequent follow-up of this group of asbestos workers through 1971 revealed similar results with an eight-fold increase in cancer of the lung or pleura and a three-fold increase in cancer of the stomach, colon, or rectum (Selikoff, 1973).

Kleinfield presented mortality data on a group of 152 asbestos insulator workers who had 15 or more years of asbestos exposure by 1945 or had achieved 15 years of exposure to asbestos between 1945 and 1965. By 1965, there were 46 deaths, 12 of which were due to cancer of the lung or pleura. The proportional mortality of deaths due to cancer of the lung or pleura was 26.1 per cent compared to the 3.1 per cent expected based on U.S. white males in the year 1948. The observed proportional mortality of gastrointestinal and peritoneal cancer was 15.2 compared to 3.9 expected (Kleinfield, 1967).

In the study by Enterline referred to above (Enterline, 1967), the mortality data were scrutinized for respiratory tract cancers. Standardized mortality ratios based on the U.S. white male population for these cancers were 130.4 for asbestos building products workers, 123.7 for asbestos friction materials workers, 228.6 for asbestos textile products workers and 31.1 for cotton textile plant workers. These data showed higher respiratory cancer mortality rates in all three groups of asbestos workers compared to the experience of cotton textile workers without asbestos dust exposures and to the U.S. white male population. Asbestos textile workers had the highest rate, probably due to the heavy asbestos exposures (Enterline, 1967).

A subsequent study by Enterline reported on the mortality of men who had completed their working lifetime in the asbestos industry and retired between the years 1941 and 1967. Average exposure to asbestos for these 1,348 men was 25 years. Their overall mortality was 14.5% higher than the population of U.S. white males of the same ages. Respiratory cancer mortality (ICD 162-163) was about 2.5 times higher than expected, with 58 observed deaths as opposed to 21.7 expected deaths. Maintenance

service workers had a higher respiratory cancer death rate than production workers. Respiratory cancer death rates increased for higher cumulative asbestos dust exposure levels (mppcf-years). However, no association was found between asbestos dust exposure and respiratory cancer below 125 mppcf-years. This cumulative exposure was calculated for each man by summing the products of dust levels for each job and time period (expressed in mppcf) and years at each level. Smoking histories were not taken (Enterline, 1973).

Mancuso defined a cohort of 1,492 asbestos workers for the years 1938-1939 utilizing Social Security records. These 1,265 male and 228 female workers were followed to mid-1964 and were classified according to duration of employment. Cumulative employment experience was divided into the following levels: (I) 0.1-2.0 years (321 males; 39 females); (II) 2.1-7.0 years (349 males; 77 females); (III) 7.1-12.0 years (139 males; 39 females); (IV) 12.1-17.0 years (75 males; 16 females); (V) 17.1-27.5 years (381 males; 57 females). Employees falling into Level I were selected as an internal control. Males in this study showed higher respiratory cancer mortality rates (lung, bronchus, trachea) as the cumulative employment experience increased; among females there were only 6 respiratory cancer deaths (Mancuso, 1967).

Another study by Selikoff et. al. consisted of the entire membership of the insulation workers union in the United States and Canada on January 1, 1967. These 17,000 members were followed utilizing union records and observed until December 31, 1971. Of the 1,092 deaths thru 1971, 213 were from lung cancer (44.42 were expected), and 55 were due to cancer of the stomach, colon, rectum or esophagus (27.34 were expected). Pleural mesothelioma accounted for 26 deaths and peritoneal mesothelioma for 51 deaths (Selikoff, 1973).

iii) Cancer: Effect of fiber type, fiber size and duration of exposure

Recognition of the importance of fiber type began in the late 1960's when researchers started to identify and report the types of asbestos fibers to which workers were exposed. Exposure to a single asbestos type is, however, unusual in industry



because most industrial enterprises utilize a combination of types of fibers.

Knox, et. al. in 1968 examined lung cancer mortality rates among textile workers in England exposed to chrysotile predominantly, but also small amounts of crocidolite. Increased lung cancer rates were noted among workers with exposure prior to 1933 when the provisions of the Asbestos Industry Regulations of 1931 had been applied. However, in men exposed for 20 or more years after 1933, the rates were no greater than expected in the general population (Knox, 1968).

Another study of textile workers in London exposed to a mixture of crocidolite, amosite, and chrysotile revealed a dose-response relationship between lung cancer and mesothelioma rates to both intensity and length of dust exposure. Among males, there was a significant excess of gastrointestinal cancer deaths, but not among women (Newhouse, 1973).

A study of 170 asbestos insulation workers in Belfast exposed to amosite, chrysotile and crocidolite revealed mortality rates for cancers of the lower respiratory tract and pleura, about 17 times higher than the rates for all men in Northern Ireland over the same period. The study group consisted of all men employed as insulation workers in Belfast in 1940. The mortality experience observed through 1966 was far in excess of that expected and could not be accounted for by other known factors such as smoking, domicile or social class. Four pleural mesotheliomas and three peritoneal mesotheliomas were reported, an exceptionally high incidence among these 170 workers (Elmes, 1971).

Enterline in 1973 examined the mortality experience of 1,348 retirees from the U.S. asbestos industry, grouped by type of fiber exposure, to assess differences in carcinogenic potential. After adjustment for cumulative dust exposure, workers exposed to a combination of chrysotile and crocidolite had the highest respiratory cancer mortality rate which was 5.3 times that expected. Workers exposed to amosite alone had a respiratory cancer mortality rate of 4.4 times that expected and workers exposed to chrysotile alone had a respiratory cancer mortality

rate of 2.4 times that expected (Enterline, 1973).

Exposure to amosite alone has been examined in 230 amosite asbestos insulation materials workers. These men initiated their employment between 1941 and 1945, had at least one year of exposure before 1960 and were alive on January 1, 1960. The subsequent mortality of these men through 1971 revealed a serious risk of respiratory cancer due to amosite exposure; the mortality rate was 10 times greater than expected. The mortality rate for cancer of the stomach, colon and rectum was three times greater than expected. There were also five deaths from mesothelioma (Selikoff, 1972). Selikoff reported similar results from mortality data among 933 men from the same factory but with a minimum of one day of exposure. Lung cancer mortality was approximately 7 times higher than expected in the general population; there was a two-fold increase in cancer of the stomach, colon, rectum and esophagus (Selikoff, 1973).

McDonald examined mortality rates in the chrysotile asbestos mines and mills of Quebec. Although overall mortality rates of 9,692 workers born between 1891 and 1920 and exposed at least one month were lower than for the population of Quebec, mortality rates for respiratory cancer were higher than expected. On the basis of Quebec death rates, mortality from respiratory cancer was 50% above expectation and on the basis of estimated rates in mining regions, mortality from respiratory cancer was 25% higher. Respiratory cancer rates increased with length and severity of exposure. Cancer of the gastrointestinal tract showed about a two-fold rise in the two highest categories of dust exposure (McDonald, 1974).

Enterline, as stated before, found that retired U.S. asbestos workers exposed only to chrysotile had a respiratory cancer mortality rate 2.4 times greater than expected (Enterline, 1973).

Anthophyllite asbestos miners in Finland first employed between 1936 and 1967 were followed through May, 1969. These 1,092 miners had a minimum exposure of three months. Age and sex matched controls were selected from a township 60 km from the mines. There were 21 lung cancer deaths among these miners compared with 13 lung cancer deaths in the controls and 12.6

expected lung cancer deaths based on the 1958 Finnish population. Observed gastrointestinal rates were lower than in the controls or the Finnish population. Smoking status was not known for the entire group of miners and controls. However, smoking habits, based on a postal questionnaire, among the 787 miners and controls alive in 1969 revealed that the asbestos miners were smokers more often than were their controls. There were no mesotheliomas noted (Meurman, 1974).

Short term amosite asbestos exposure was examined in 909 men who worked for various periods of time in an amosite insulation plant from 1941-1945 during World War II. Persons with prior asbestos exposure or later asbestos exposure were excluded. After 30 years of follow-up, even workers with as little as one month exposure to amosite asbestos showed a clear excess risk of lung cancer. The ratio of observed to expected deaths of lung cancer from 1946-1974 was 2.24 for workers with less than one month exposure, 3.47 for those with one month exposure, and 6.15, 3.57, 5.52, and 7.84 for those with 2 months, 3-5 months, 6-11 months, and one year of exposure, respectively (Seidman, 1976).

### C. Non-Occupationally Exposed Groups

Epidemiologic evidence of human non-occupational or environmental exposure to asbestos either through inhalation or ingestion has been reported in several types of studies. First, asbestos fibers, asbestos bodies, and pleural calcification have been found in populations with no history of occupational exposure. Second, radiological evidence of pleural changes that are commonly associated with asbestos exposure has been demonstrated in neighborhoods or communities living in close proximity to an asbestos mine or factory. Third, mesothelial tumors have been found in persons without occupational exposure to asbestos fibers, but who have resided in communities located near an asbestos mine or factory.

Although there is evidence that asbestos dust can cause biological effects in a non-occupationally exposed population, estimation of the magnitude of the risk of developing specific asbestos related diseases

is more difficult than in the occupational situation. It is more difficult to define a population at risk (family, neighborhood, community) and it is also difficult to single out the effects of a single agent, asbestos, from general environmental exposure to a number of factors responsible for disease.

Routine autopsies have revealed asbestos bodies in the lungs of persons in the general population. Thomson in 1963 found 26.4% of lung smears showed asbestos bodies in 500 consecutive routine autopsies of subjects age 15 and over in Cape Town, South Africa, suggesting that asbestos was being inhaled by urban dwellers (Thomson, 1963).

The National Academy of Sciences summarized nine other studies from the United States and other countries which also found a high prevalence of asbestos bodies in routine autopsies presumably from urban environmental exposure (National Academy of Sciences, 1971). Selikoff and Hammond analyzed 1,975 consecutive routine autopsies from three hospitals in New York City and found asbestos bodies in 47% of the lungs, again suggesting general urban environmental exposure (Selikoff and Hammond, 1969). These studies did not determine the core fiber of these bodies and it was assumed, perhaps incorrectly, that these ferruginous bodies were asbestos bodies since they resembled those found in the lungs of asbestos workers.

Meurman reviewed several studies strongly suggesting an association between pleural calcification and non-occupational exposures to asbestos. A 5-10% prevalence of pleural calcification was found in populations near an asbestos mine or factory, or in agricultural populations with soil containing asbestos (Meurman, 1968). Endemic pleural plaques were found in Finnish populations living in tobacco-growing regions with anthophyllite, tremolite, and sepiolite asbestiform particles in the soil; no pleural plaques were found in the farming populations without asbestos in the soil (Burlikov, 1970). These studies suggest that asbestos fibers are inhaled and deposited in the lungs of persons not occupationally exposed.

Mesotheliomas are relatively rare tumors, and it was not until after 1960 that asbestos was seriously considered as an etiologic factor. The association between mesothelioma and asbestos exposure has been consistent in all parts of the world. The most alarming

aspect of the association is that it has been documented even with brief, low levels of exposure to asbestos (IARC, 1977; Becklake, 1976).

Mesothelioma has been diagnosed in patients with no occupational exposure to asbestos. Eleven of the 33 patients with mesothelial tumors reported by Wagner in 1960 had no occupational exposure to crocidolite asbestos but lived in the area near the mines (Wagner, 1960). Bohlig studied 119 cases of mesothelioma in Hamburg and found 38 to have non-occupational exposure to asbestos. The distribution of these cases in the neighborhood of the factory depended on the prevailing direction of the wind (Bohlig, 1970). Additional reports have documented cases of mesothelioma from household contact exposure to asbestos (Anderson, 1976).

Epidemiologic surveillance of mesothelioma in Canada for the period 1960-1970 found a relatively small proportion of tumors associated with asbestos exposure. An association between mesothelioma and definite and probable exposure to asbestos was shown, but not with possible or unlikely exposure (McDonald, 1973).

Two non-occupational epidemiologic studies have reported no excess cancer rates due to ingestion of city water supplies containing high concentrations of asbestos fibers (non-commercial minerals in the cummingtonite-grunerite series) (Masson, 1974; Levy, 1976, Sigurdson, 1977). In June 1973, the U.S. Environmental Protection Agency reported a high concentration of asbestos-like fibers in Lake Superior which is the main source of tap water for the residents of Duluth, Minnesota. One source of these fibers is from taconite ore mining wastes which have been dumped into Lake Superior since 1955. Both epidemiological studies have compared cancer rates from other areas without high concentrations of asbestos in the tap water to determine if there is a relationship between ingested asbestos and cancer, especially gastrointestinal cancer.

Masson calculated age-adjusted mortality rates for 21 cancer sites for Duluth, Hennepin County, and the state of Minnesota. He then calculated risk ratios (Duluth/H.C.; Duluth/State of Minnesota) for individual cancer sites in both men and women during four time periods (1950 - 54, 1955 - 59, 1960 - 64, 1965 - 69). Only cancer of the rectum increased over time for both males and females. Risk ratios for the total digestive tract were in the

range 0.76 to 1.44 and did not increase over time. Masson concluded that a longer follow-up period might have shown an increase in cancer rates over time due to the long latent period associated with asbestos induced carcinogenesis (Masson, 1974).

A study begun by Levy et. al. and continued by Sigurdson reported incidence data for gastrointestinal cancer, lung cancer, and mesothelioma in male and female residents of Duluth, Two Harbors, Beaver Bay, and Silver Bay (Levy, 1976; Sigurdson, 1977). Both age and sex-adjusted rates and age and sex-specific rates were compared to data from the Minneapolis - St. Paul Component of the Third National Cancer Survey (TNCS) 1969 - 1971. Rates for gastrointestinal cancer and lung cancer in Duluth residents in 1969 - 1971 and in 1972 - 1974 were not significantly higher than corresponding rates in Minneapolis - St. Paul. There also appeared to be no excess in Two Harbors, Beaver Bay and Silver Bay although the numbers were small. Both Levy and Sigurdson pointed out that the induction period from initial asbestos exposure to onset of asbestos-associated cancer may not have been long enough in this study for definitive results and recommended continued surveillance of these cancers (Sigurdson, 1977).

In 1973, the Advisory Committee on Asbestos Cancers concluded that there was no evidence of fibrosis in the general public with low levels of asbestos exposures. They also found no evidence of increased risk of cancer resulting from asbestos in city water supplies or food (IARC, 1973). However, it has been suggested that mesothelioma may follow very low asbestos exposure levels 20-30 years prior (NTIS, 1972).

The potential carcinogenicity of non-commercial asbestos cleavage fragments has been examined in two occupational epidemiological studies.

Gillam reported excess respiratory cancer mortality in a group of hard rock gold miners exposed to fibrous amphibole cleavage fragments of cummingtonite-grunerite contained in the mining ore dust. The exposure level was less than 2.0 fibers/cm<sup>3</sup> greater than 5  $\mu$ m in length and also fibers shorter than 5  $\mu$ m in length. Four hundred and thirty-nine miners had at least 60 months of exposure prior to 1960 and were followed through 1973. Of 70 total deaths, 10 were due to respiratory cancer compared with the 2.7 expected

based on the general white male population of South Dakota. Exposures to other known carcinogens in the mine were negligible or did not exceed normal ambient residential levels (Gillam, 1976).

McDonald also studied gold miners exposed to cummingtonite-grunerite in Lead, South Dakota. The cohort consisted of all 1,321 men who had completed 21 years service with the mining company. All but 10 men were traced until the end of 1973. There were 17 deaths from respiratory cancer compared to 16.5 expected and 39 deaths from abdominal cancer compared to 35.1 expected. McDonald concluded that long exposure to cummingtonite-grunerite among hard rock miners was not a serious cancer hazard (McDonald, 1977).

TABLE 5. SUMMARY OF THE EPIDEMIOLOGIC STUDIES OF CANCER MORTALITY  
AMONG EMPLOYEES EXPOSED TO ASBESTOS

Study Author Date	Population	Source of Data	Basis for Expected Deaths	Type of Asbestos	Exposure Level	Period of Exposure & Follow-up	Total No. of Deaths	Results
Doll 1955	Asbestos work- ers in an English asbestos works 113 men	Company Records	England & Wales	Not reported	Not reported	At least 20 years of exposure prior to 1953	39	Cancer of the Lung O/E = 11/.8 = 13.8 (p < .000001)
Braun 1958	Asbestos miners in Thetford Mines, Quebec 5,958 Total 4,673 Smokers 1,265 Non-Smok. 20 Unknown	Company Records	Province of Quebec	Not reported	Not reported	Miners on employ- ment rolls in 1950; 5+ years exposure prior to 1950; followed through 1955	187	Cancer of the Lung O/E = 9/6 = 1.5
Selikoff 1964	New York & New Jersey Insulation workers 632 workers (35 yrs. old in 1943)	Union Records	U.S. White Males	Not reported	Not reported	On Union rolls as of Jan. 1, 1943; at least 20 years exposure before they died; followed through December 31, 1963	255	Cancer of the Lung or Pleura O/E = 45/6.6 = 6.8 Cancer of the Stomach, Colon, or Rectum O/E = 29/9.4 = 3.1 Pleural Meso- thelioma O = 3 Peritoneal Meso- thelioma O = 1
Kleinfield 1967	Asbestos insulation workers 152 asbestos workers	Union Records; Death Certif.	U.S. White Males in 1948	Not reported	Not reported	Employed in 1945; Either 15 yrs. exposure prior to 1945 or 15 years exposure between 1945 - 1965; followed through 1965	46	Cancer of the Lung or Pleura O/E = 12/1.4 = 8.6 (p ≤ .01) Cancer of the GI Tract or Peritoneum O/E = 7/1.8 = 3.9 (p ≤ .01)



TABLE 5. SUMMARY OF THE EPIDEMIOLOGIC STUDIES OF CANCER MORTALITY  
AMONG EMPLOYEES EXPOSED TO ASBESTOS (continued)

Study Author Date	Population	Source of Data	Basis for Expected Deaths	Type of Asbestos	Exposure Level	Period of Exposure & Follow-up	Total No. of Deaths	Results
Enterline 1967	U.S. Asbestos building products workers 12,402 white males age 15 - 64	Social Security Records	U.S. White Males	Not reported	Not reported	Employed and exposed to asbestos some- time during period 1948 - 1951; followed thru June 30, 1963	840	Cancer of Respiratory System (ICD 160-164) O = 46 SMR=130.4  Cancer of Digest. System (ICD 150-159) O = 36 SMR=88.8
34	U.S. Asbestos friction materials workers 7,510 white males age 15 - 64	Social Security Records	U.S. White Males	Not reported	Not reported	Employed and exposed to asbestos some- time during period 1948 - 1951; followed thru June 30, 1963	567	Cancer of Respiratory System (ICD 160-164) O = 37 SMR=123.7  Cancer of Digest. System (ICD 150-159) O = 36 SMR=119.2
	U.S. Asbestos textile products workers 1,843 white males age 15 - 64	Social Security Records	U.S. White Males	Not reported	Not reported	Employed and exposed to asbestos some- time during period 1948 - 1951; followed thru June 30, 1963	186	Cancer of Respiratory System (ICD 160-164) O = 14 SMR=228.6  Cancer of Digestive System (ICD 150-159) O = 11 SMR=146.3

TABLE 5. SUMMARY OF THE EPIDEMIOLOGIC STUDIES OF CANCER MORTALITY  
AMONG EMPLOYEES EXPOSED TO ASBESTOS (continued)

Study Author Date	Population	Source of Data	Basis for Expected Deaths	Type of Asbestos	Exposure Level	Period of Exposure & Follow-up	Total No. of Deaths	Results
Mancuso 1967	Asbestos workers  1,493 white employees (1,265 males) (228 females)	Social Security records	Employees with Level I cumulative employment experience used as internal controls	Not reported	Not reported	Employed between 1938 and 1939; followed to mid-1964; classified by years of employment experience: Level I 0.1-2.0 yrs II 2.1-7.0 yrs III 7.1-12.0 yrs IV 12.1-17.0 yrs V 17.1-27.5 yrs	361	Cancer of the Lung, Bronchus, and Trachea (ICD 162-163) O = 41  Consistent increase in lung cancer rates as the cumulative employment experience increased  Cancer of Digestive Organs and Peritoneum: O = 29  Pleural or Peritoneal Mesothelioma: O = 9

TABLE 5. SUMMARY OF THE EPIDEMIOLOGIC STUDIES OF CANCER MORTALITY  
AMONG EMPLOYEES EXPOSED TO ASBESTOS (continued)

Study Author Date	Population	Source of Data	Basis for Expected Deaths	Type of Asbestos	Exposure Level	Period of Exposure & Follow-up	Total No. of Deaths	Results
Enterline 1973	533 Asbestos worker retirees, production or maintenance workers	Industry Records and Death Certificates	U.S. White Males	Not reported	< 125 mppcf - yr	Lifetime employee in asbestos industry; retired in 1941 - 1967 followed thru 1969	Not reported	Respiratory Cancer (ICD 162-163) O = 15 E = 9.0 SMR = 166.7
	305 Asbestos worker retirees, production or maintenance workers	Industry Records and Death Certificates	U.S. White Males	Not reported	125 - 249 mppcf - yr	Lifetime employee in asbestos industry; retired in 1941 - 1967 followed thru 1969	Not reported	Respiratory Cancer (ICD 162-163) O = 12 E = 4.8 SMR = 250.0
	328 Asbestos worker retirees, production or maintenance workers	Industry Records and Death Certificates	U.S. White Males	Not reported	250 - 499 mppcf - yr	Lifetime employee in asbestos industry; retired in 1941 - 1967 followed thru 1969	Not reported	Respiratory Cancer (ICD 162-163) O = 17 E = 5.2 SMR = 326.9

TABLE 5. SUMMARY OF THE EPIDEMIOLOGIC STUDIES OF CANCER MORTALITY  
AMONG EMPLOYEES EXPOSED TO ASBESTOS (continued)

Study Author Date	Population	Source of Data	Basis for Expected Deaths	Type of Asbestos	Exposure Level	Period of Exposure & Follow-up	Total No. of Deaths	Results
Enterline 1973 Cont.	126 Asbestos worker retirees, production or maintenance workers	Industry Records and Death Certificates	U.S. White Males	Not reported	500 - 749 mppcf - yr	Lifetime employee in asbestos industry; retired in 1941 - 1967 followed thru 1969	Not reported	Respiratory Cancer (ICD 162-163) O = 9 E = 1.8 SMR = 500.0
	56 Asbestos worker retirees, production or maintenance workers	Industry Records and Death Certificates	U.S. White Males	Not reported	750 + mppcf - yr	Lifetime employee in asbestos industry; retired in 1941 - 1967 followed thru 1969	Not reported	Respiratory Cancer (ICD 162-163) O = 5 E = 0.9 SMR = 555.6
	All = 1,348	Industry Records and Death Certificates	U.S. White Males	Not reported	ALL	Lifetime employee in asbestos industry; retired in 1941 - 1967 followed thru 1969	754	Respiratory Cancer (ICD 162-163) O = 58 E = 21.7 SMR = 267.3  Cancer of Digestive System (ICD 150-159) O = 53 E = 41.8 SMR = 126.8

TABLE 5. SUMMARY OF THE EPIDEMIOLOGIC STUDIES OF CANCER MORTALITY  
AMONG EMPLOYEES EXPOSED TO ASBESTOS (continued)

Study Author Date	Population	Source of Data	Basis for Expected Deaths	Type of Asbestos	Exposure Level	Period of Exposure & Follow-up	Total No. of Deaths	Results
Selikoff 1973	New York - New Jersey asbestos insulation workers  623	Union records	U.S. White Males	Not reported	Not reported	On union rolls as of Jan. 1, 1943; at least 20 years expo- sure before they died; followed thru 1971	421	Cancer of the Lung O/E = 84/10.1 = 8.3  Cancer of the Stomach, colon, rectum, esophagus O/E = 41/13.0 = 3.2  Pleural Mesothelioma O=8 Peritoneal Mesothelioma O=24
38 Selikoff 1973	Entire member- ship of insulation workers union in U.S. and Canada  17,800	Union records	U.S. White Males	Not reported	Not reported	All members in union on Jan. 1, 1967; no minimum exposure; followed thru Dec. 31, 1971	1,092	Cancer of the Lung O/E = 213/44.42 = 4.8  Cancer of the stomach: O/E = 16/6.62 = 2.4  Cancer of the Colon and Rectum: O/E = 26/17.51 = 1.5  Cancer of the Esophagus: O/E = 13/3.21 = 4.0  Cancer of Stomach, Colon, Rectum, Esophagus: O/E = 55/27.34 = 2.0  Pleural Mesothelio O=7, Peritoneal

TABLE 5. SUMMARY OF THE EPIDEMIOLOGIC STUDIES OF CANCER MORTALITY  
AMONG EMPLOYEES EXPOSED TO ASBESTOS (continued)

Study Author Date	Population	Source of Data	Basis for Expected Deaths	Type of Asbestos	Exposure Level	Period of Exposure & Follow-up	Total No. of Deaths	Results
Knox 1968	Asbestos textile workers in England 57 men	Factory Records	Population of England	Predominantly chrysotile, small amounts of crocidolite	Dust level since 1960 approx. 1-8 particles per c.c. (5-100 $\mu$ m) long	10 or more yrs. of exposure prior to 1933; 20+ years exposure by June 1966	48	Cancer of the Lung or Pleura (ICD 162-163) O/E = 12/1.18 10.2 ( $p < .001$ )
	63 men	Factory Records	Population of England	Predominantly chrysotile, small amounts of crocidolite	Dust level since 1960 approx. 1-8 particles per c.c. (5-100 $\mu$ m) long	Less than 10 years exposure prior to 1933; 20+ years exposure by June 1966	23	Cancer of the Lung or Pleura (ICD 162-163) O/E = 5/1.57 = 3.2 ( $p < .05$ )
39	136 men	Factory Records	Population of England	Predominantly chrysotile, small amounts of crocidolite	Dust level since 1960 approx. 1-8 particles per c.c. (5-100 $\mu$ m) long	No exposure before 1933; 20+ years by June 1966	15	Cancer of the Lung or Pleura (ICD 162-163) O/E = 2/1.35 = 1.5 ( $p < .05$ )
	538 men	Factory Records	Population of England	Predominantly chrysotile, small amounts of crocidolite	Dust level since 1960 approx. 1-8 particles per c.c. (5-100 $\mu$ m) long	No exposure before 1933; 10 - 19 years by June 1966	54	Cancer of the Lung or Pleura (ICD 162-163) O/E = 6/6.41 = 0.9 ( $p > .05$ )
	220 women	Factory Records	Population of England	Predominantly chrysotile, small amounts of crocidolite	Dust level since 1960 approx. 1-8 particles per c.c. (5-100 $\mu$ m) long	No exposure before 1933; 10+ years by June 1966	10	Cancer of the Lung or Pleura (ICD 162-163) O/E = 2/0.24 = 8.3 ( $p < .05$ )

TABLE 5. SUMMARY OF THE EPIDEMIOLOGIC STUDIES OF CANCER MORTALITY  
 AMONG EMPLOYEES EXPOSED TO ASBESTOS (continued)

Study Author Date	Population	Source of Data	Basis for Expected Deaths	Type of Asbestos	Exposure Level	Period of Exposure & Follow-up	Total No. of Deaths	Results
Elmes 1971	Total population of insulation workers in Belfast in 1940  170 men	Union records	Population of Northern Ireland	amosite, chrysotile & crocidolite	Not reported	Identified as on union rolls in 1940; followed thru 1966; no minimum length of exposure	98	Cancer of the Lung, Larynx, and Pleura: O/E = 28/1,639 = 17.1 SMR = 1760  Gastrointestinal Cancer: 0 = 1  Pleural Mesothelioma: 0 = 4 Peritoneal Mesothelioma 0 = 3

TABLE 5. SUMMARY OF THE EPIDEMIOLOGIC STUDIES OF CANCER MORTALITY  
AMONG EMPLOYEES EXPOSED TO ASBESTOS (continued)

Study Author Date	Population	Source of Data	Basis for Expected Deaths	Type of Asbestos	Exposure Level	Period of Exposure & Follow-up	Total No. of Deaths	Results
Newhouse 1973	Asbestos textile and insulation workers in England and Wales 6,760 men 922 women	Factory Records	Population of England and Wales	Crocidolite, Amosite, Chrysotile	Males and Females placed into either low- moderate or severe exposure category	Males and females grouped by: 1) < 2 years on job 2) 2+ years on job and by years of follow-up 10-14 years 15-19 years 20-24 years 25+ years of exposure	No. of deaths by March 1970 in men = 350  No. of deaths by December 1968 in women = 111	Among those with short but severe exposure, there is a significant excess of lung cancer mortality (ICD 162-163) which is seen after 15 years of follow-up;  Among those with short and low-moderate exposure, significant excess lung cancer mortal- ity seen after 25+ years of exposure;  Much more mark- ed excess for those who had worked 2+ years with severe exposure  GI Cancer:  Males O/E = 31/20.35 = 1.5 (p<.05)  Females O/E = 11/7.3 = 1.5 (p=0.12)  Pleural and peritoneal Meso-



TABLE 5. SUMMARY OF THE EPIDEMIOLOGIC STUDIES OF CANCER MORTALITY  
AMONG EMPLOYEES EXPOSED TO ASBESTOS (continued)

Study Author Date	Population	Source of Data	Basis for Expected Deaths	Type of Asbestos	Exposure Level	Period of Exposure & Follow-up	Total No. of Deaths	Results						
Enterline 1973	1,348	Industry Records and Death Certificates	U.S. White Males			Lifetime employee in asbestos industry; retired in 1941 - 1967; followed through 1969								
	Retired asbestos workers													
	59								Industry Records and Death Certificates	U.S. White Males	Amosite only	Average mppcf - yr 330.2	47	Respiratory Cancer (ICD 162-163) O/E = 4/0.9 4.4 SMR = 444.4
	1,013								Industry Records and Death Certificates	U.S. White Males	Chrysotile only	244.4	572	Respiratory Cancer (ICD 162-163) O/E = 39/16.5 = 2.4 SMR = 236.4
	102								Industry Records and Death Certificates	U.S. White Males	Amosite and Chrysotile	266.3	50	Respiratory Cancer (ICD 162-163) O/E = 3/1.7 = 1.8 SMR 176.5
	120								Industry Records and Death Certificates	U.S. White Males	Chrysotile and Crocidolite	208.3	54	Respiratory Cancer (ICD 162-163) O/E = 10/1.9 = 5.3 SMR = 526.3
54	Industry Records and Death Certificates	U.S. White Males	Amosite, Chrysotile, Crocidolite	273.4	31	Respiratory Cancer (ICD 162-163) O/E = 2/0.8 = 2.5 SMR = 250.0								

TABLE 5. SUMMARY OF THE EPIDEMIOLOGIC STUDIES OF CANCER MORTALITY  
AMONG EMPLOYEES EXPOSED TO ASBESTOS (continued)

Study Author Date	Population	Source of Data	Basis for Expected Deaths	Type of Asbestos	Exposure Level	Period of Exposure & Follow-up	Total No. of Deaths	Results
Selikoff 1972	Eastern U.S. Insulation workers 230 men	Factory Records	U.S. White Males	Amosite	Not Reported	Employment began between June 1941 and December 1945; at least one year of ex- posure; alive on January 1, 1960; followed through June 30, 1971	105	Cancer of the Lung O/E = 25/2.4 10.4 Cancer of the lung, pleura, bronchus, trachea O/E = 27/2.4 11.3 Cancer of the Stomach, Colc or Rectum O/E = 5/1.6 = 3.1 Pleural Meso- thelioma O = Peritoneal Me thelioma O =
Selikoff 1973	Eastern U.S. asbestos insulation workers 933 workers	Factory Records	U.S. White Males	Amosite	Not Reported	Employment began between June 1941 and December 1945; at least <u>one</u> day of exposure; followed until June 30, 1971	484	Cancer of the Lung O/E = 73/11.4 6.4 Cancer of the Stomach O/E = 11/4.58 2.4 Cancer of the Colon, Rectum O/E = 15/7.05 2.1 Cancer of the Esophagus O/E = 0/1.23 0 Pleural Meso- thelioma O = Peritoneal Me

TABLE 5. SUMMARY OF THE EPIDEMIOLOGIC STUDIES OF CANCER MORTALITY  
AMONG EMPLOYEES EXPOSED TO ASBESTOS (continued)

Study Author Date	Population	Source of Data	Basis for Expected Deaths	Type of Asbestos	Exposure Level	Period of Exposure & Follow-up	Total No. Of Deaths	Results
McDonald 1974	Employees of the Quebec asbestos mining industry born between 1891 - 1920 9,692 males and females	Company Records	Quebec population	Chrysotile	Dust Index (mppcf-years) 1) < 10 2) 10 - 100 3) 100 - 200 4) 200 - 400 5) 400 - 800 6) 800 +	Variable length of exposure; short follow- up; retrospective study of all workers currently or previously employed as of November 1, 1966 and born between the years 1891 and 1920; deaths to December 1969	3,270	Lung Cancer show a rising rate wi increasing dust exposure; cancer of the G.I. trac showed a rise in the two highest categories; Pleural Mesothe- lioma: O = 5 Peritoneal Mesothelioma: O = none
44								
Meurman 1974	Finnish asbestos miners 1,092 males and females	Company Records	Age-sex- matched controls from a township 60 km from the mines and also population of Finland in 1958	Anthophyl- lite	Not reported	First employed in one of two mines between 1936 and 1967; worked and were exposed for at least 3 months; followed through May 1969	248	Cancer of the Lung (ICD 162): O/E = 21/12.6 = 1 Cancer of the Digestive Organs O/E = 7/14.9 = 0 No Mesotheliomas

TABLE 5. SUMMARY OF EPIDEMIOLOGIC STUDIES OF CANCER  
MORTALITY AMONG EMPLOYEES EXPOSED TO ASBESTOS (continued)

Study Author Date	Population	Source of Data	Basis for Expected Deaths	Type of Asbestos	Exposure Level	Period of Exposure and Follow-up	Total No. of Deaths	Results
Seidman 1977	909 U.S. Navy asbestos factoryworkers in New Jersey during World War II with no previous occupational work exposure	U.S. Navy Records and death certificates	New Jersey white males	Amosite	Not reported	Exposure between 1941-1945; followed through Dec. 31, 1974		Lung cancer mortality from 1946-1947:
	65 men					Length of Exposure: < 1 month	Not reported	O/E = 2.24
	101 men					1 month	" "	O/E = 3.47
	101 men					2 months	" "	O/E = 6.15
	165 men					3-5 months	" "	O/E = 3.57
	148 men					6-11 months	" "	O/E = 5.52
	130 men					1 year	" "	O/E = 7.84
	199 men					2+ years	" "	Not reported

TABLE 5. SUMMARY OF THE EPIDEMIOLOGIC STUDIES OF CANCER MORTALITY  
 AMONG EMPLOYEES EXPOSED TO ASBESTOS (continued)

Study Author Date	Population	Source of Data	Basis for Expected Deaths	Type of Asbesots	Exposure Level	Period of Exposure & Follow-up	Total No. of Deaths	Results
Gillam 1976	Hard rock gold miners in Lead, South Dakota 439	Social Security Records and the govern- ment agen- cies	General white male popula- tion of South Dakota	Ore dust containing non-commer- cial forms of amosite asbestos in the cummingtonite- grunerite amphibole mineral category	$< 2.0$ fibers/ $\text{cm}^3$ greater than $5\mu\text{m}$ in length and also fibers shorter than $5\mu\text{m}$ in length	Employed in 1960; 60 months of underground mining at that facility prior to 1960; had never mined elsewhere; followed to December 31, 1973	70	Respiratory Cancer $O/E = 10/2.7 =$ $3.7 (p < .01)$
McDonald 1977 abstract	Gold miners in Lead, South Dakota 1,321 men	Not report- ed	Not report- ed	Cummingtonite- grunerite	Not reported	21 years service with mining company; follow to end of 1973	660	Respiratory Cancer $O/E = 17/16.5 =$ 1.0  Abdominal Cancer $O/E = 39/35.1 =$ 1.1

SMR = Standardized Mortality Ratio  $\{(\text{Observed deaths}/\text{Expected Deaths}) * 100\}$   
 mppcf = million particles per cubic foot of air  
 \*U.S. death rates not available (rare causes of death in U.S.)

## V. MECHANISMS OF ASBESTOS CARCINOGENESIS

### A. Introduction

At present, the mechanism of carcinogenesis related to asbestos exposure remains unknown. Several theories have been proposed with emphasis on:

- 1) The fibers themselves,
- 2) Trace metals associated with the fibers, and
- 3) Organic materials associated with the fibers.

It is generally accepted that the pathological mechanisms of carcinogenesis cannot be completely explained by any one of these theories alone. Some researchers have speculated that different etiologic factors may be involved in the causation of lung cancer and mesothelioma (Gibbs, 1975; Reeves, 1974, 1976) and that not only may all three mechanisms be operative but that other factors, additive or synergistic, may play important roles, thus giving rise to:

- 4) A multifactorial theory.

### B. Fiber Theory

This theory attributes the pathological effects of asbestos to its physical, not its chemical, characteristics. The basis for this premise is that other fibers such as glass fibers are highly carcinogenic in the pleura of rats.

Smith produced pleural mesotheliomas in rats after intrapleural injections of chrysotile 5.3 - 6.9 microns in length, but not after injections of chrysotile 0.37 - 0.86 microns in length (Smith, 1972). Gross reported that short-fibered asbestos (less than 5 microns in length) was incapable of causing fibrosis or cancer (Gross, 1974). Stanton estimated that long, fine fibers (less than 3 microns in diameter and greater than 20 microns in length) are more carcinogenic than shorter or thicker fibers (diameters less than 3 microns and lengths less than 2 microns, or diameters greater than 3 microns) (Stanton, 1974). The 1977 IARC Report (International Agency for Research on Cancer) concluded that fibers less than 0.5 microns in diameter produce a higher incidence of tumors (IARC, 1977).

### C. Trace Metal Theory

Trace metals associated with asbestos fibers are a possible cause of asbestos cancers. Metals are contained in asbestos as an integral

feature of the molecular structure. In addition, extramolecular trace metals are present on fibers as isomorphous substitutes for structural elements, as fragments of host rock, or fine particles of alloy produced by abrasive action with equipment during industrial or laboratory milling (Cralley, 1967).

Harington and Roe suggested in 1965 that asbestos carcinogenesis may be caused by the presence of trace metals (chromium or nickel) known to be carcinogenic under certain circumstances (Harington and Roe, 1965).

Cralley analyzed uniform samples of amosite, chrysotile and crocidolite for the presence of nickel, chromium and manganese. Chrysotile was higher in nickel and chromium; amosite was higher in manganese. Crocidolite had the lowest metal content (Cralley, 1968).

Dixon in 1970 presented an alternative trace metal theory. He suggested that trace metals associated with asbestos, rather than causing cancers themselves, inhibit the metabolism of benzpyrene, thus increasing the residence time of this carcinogen in the lung. Asbestos plays a passive role as a metal carrier, trace metals play an active role, and benzpyrene, a polycyclic aromatic hydrocarbon commonly found in small amounts in ambient air, a critical mediating role (Dixon, 1970).

Cralley has more recently suggested that trace metals associated with asbestos fibers may produce biologically active cations at local tissue sites which may be responsible for asbestos carcinogenesis. However, he pointed out that there has been a lack of reasonable correlation between metal content and observed cancer in animal experiments which he attributed to the extreme variability in the nature of the associated metals (Cralley, 1971).

Stanton doubts the role of trace metals in asbestos carcinogenesis because of the minute amounts involved (Stanton, 1974). The 1973 Report of the Advisory Committee on Asbestos Cancers concluded that trace metals are not likely to be a major factor in the production of asbestos cancers on the basis of animal experiments (IARC, 1973).

#### D. Organic Material Theory

Carcinogenesis may result from the presence of natural contaminating oils and minerals plus those introduced as a result of contamination or treatment of the asbestos during processing. A description of

these primary and secondary oils is given by Harington (Harington, 1965.)

Oils from amosite, chrysotile and crocidolite have been found to be weak carcinogens. Both crocidolite and chrysotile appear more potent than amosite (Harington, 1967). However, unpublished data from animal experiments by Wagner and Berry in 1969 and Wagner in 1972 demonstrates that asbestos oils contribute little to asbestos carcinogenesis. Using amosite, anthophyllite, and Canadian and Rhodesian chrysotile and crocidolite, similar samples with and without the oil were injected intrapleurally into rats. No differences in numbers of mesotheliomas developed were seen (Harington, 1973).

Stanton maintains that contaminating hydrocarbons are not present in sufficient amounts to account for the carcinogenic effects of asbestos (Stanton and Wrench, 1972). The 1973 Report of the Advisory Committee on Asbestos Cancers concluded that waxes and oils are unlikely to be contributory factors in carcinogenesis (IARC, 1973).

#### E. Multifactor Theory

It is quite possible that all or several of the above theories may be responsible for carcinogenesis concomitantly.

Another proposed theory is an additive or synergistic effect of cigarette smoking and asbestos exposure. Smoking may possibly reduce clearance of asbestos in the lungs, asbestos may act as a transport vehicle for cigarette smoke carcinogens, or one factor may promote the cancer initiated by the other (National Research Council, 1971).

It appears that smoking increases the risk of lung cancer among asbestos workers. No association has been demonstrated between cigarette smoking and mesotheliomas or other cancers such as those of the gastrointestinal tract among asbestos workers.

Several studies have examined the interrelationship between cigarette smoking and asbestos exposure in the etiology of lung cancer. It is not known whether the effect of these two factors is additive or multiplicative (synergistic).

Selikoff in 1968 demonstrated a higher risk of lung cancer among smoking asbestos insulation workers than non-smoking asbestos insulation workers with at least 20 years of exposure. Asbestos workers who smoked had 8 times the lung cancer risk of all smokers and 92 times the risk of non-smokers who were not exposed to



asbestos. Although these results suggested a multiplicative effect, the numbers were small. A follow-up of this study by Hammond Selikoff in 1973 found similar results (Selikoff & Hammond, 1973). Hammond and Selikoff also presented smoking data on 17,800 asbestos insulation workers registered with the insulation workers union in the U.S. and Canada on January 1, 1967. Of these 17,000 workers, 2,066 had no history of cigarette smoking, 9,590 had a history of cigarette smoking, and in 6,144 the smoking history was not known. Follow-up was continued through 1971. Results of this study showed lung cancer to be uncommon among non-smoking workers, (O/E = 2/5.98). Among smoking workers, the observed number of lung cancer deaths was about 5 times higher than that expected based on rates in the U.S. white male population, disregarding smoking. They concluded that the lung cancer risk of asbestos insulation workers was much higher among smokers than non-smokers (Selikoff & Hammond, 1973).

Weiss found a higher prevalence of fibrosis among smokers than non-smokers in a group of 100 asbestos workers, but again the numbers were small (Weiss, 1971).

A study by Berry supported the multiplicative hypothesis for female asbestos workers, but came to no conclusion for men because the number of non-smokers was too small among the men. These results were based on 1,300 male and 480 female asbestos factory workers (Berry, 1972).

The International Agency for Research on Cancer reviewed two recent studies, one by NIOSH (1977) and the other by Martischig (1977). Both are consistent with an increased risk of lung cancer of low order among non-smoking asbestos workers (IARC, 1977). The literature has not reported differences in risk of mesotheliomas or gastrointestinal cancers among smoking and non-smoking asbestos workers.

Thus, the interrelationship of smoking and asbestos exposure needs further study and clarification. Although it appears that among asbestos workers, smokers have a much higher risk of lung cancer than non-smokers, it is not known whether the effect of these two carcinogens is additive or multiplicative.

## VI. Conclusions

It is difficult to estimate the independent contributions of fiber type, fiber size, exposure level, duration of exposure, or occupation to the risk of disease because all these factors are interrelated to a certain degree. Moreover, the mechanisms of production of asbestosis, lung cancer, and mesothelioma due to asbestos exposure have not been adequately delineated so that we cannot assume that they are the same for all three. Therefore, these several factors may vary in their contribution to risk according to disease. "It is possible that different carcinogenic entities are responsible for the causation of lung tumors and mesothelial tumors. Lung tumors seem to depend on the adsorptive capacity of asbestos fibers, allowing other carcinogens (heavy metals, polycyclic hydrocarbons, cigarette smoke) to attain a critical focal concentration. Mesothelial tumors, on the other hand, might arise in response to mechanical irritation by fibers which may become lodged during lymphatic spread. Tissues subject to constant respiratory movement (e.g. pleura or peritoneum) are specifically vulnerable to the latter action." (Reeves, 1976).

Animal experiments and epidemiological studies show that all commercial types of asbestos produce asbestosis and lung cancer; all commercial types of asbestos, except perhaps anthophyllite, are associated with mesotheliomal tumors (IRAC, 1973). There are insufficient data to assess the carcinogenic risk associated with noncommercial forms of asbestos such as those in the cummingtonite-grunerite amphibole mineral category.

Information on relative pathogenicity gathered from animal experimental work has shown that chrysotile produces less severe fibrosis than does amosite or crocidolite in equal doses (Wagner, 1971; Kleinfeld, 1973). Moreover, the risk of mesothelioma in animals seems to be higher for crocidolite than amosite or chrysotile (Wagner, 1971; Reeves, 1976). However, Kleinfeld has expressed caution about applying these results to man because of the unusually large doses of asbestos required to produce pathological effects in animals (Kleinfeld, 1973).

Assessment of relative pathogenicity of fiber types in man from epidemiological studies is less straightforward because of the lack of quantitative data on other modifying variables such as fiber characteristics, dose and duration of exposure, and other possible factors or cofactors such as trace metals, oils, and smoking. Another problem is that it is rare to have an occupational exposure to only one type of asbestos fiber alone; most occupational exposures involve a mixture of several types. Exposure to chrysotile, amosite, crocidolite, anthophyllite or a mixture of these has been associated with an increased risk of lung cancer, but one type has not been shown to produce a greater relative risk of lung cancer in man compared to the others. Selikoff did not find evidence of a greater risk of lung cancer associated with chrysotile than amosite among insulation workers or vice versa (Selikoff, 1973). There is much clearer evidence of a difference in risk of mesothelioma varying with the type of asbestos than there is in the case of lung cancer. On the basis of prospective and retrospective mortality studies from many countries, the 1973 Report of the Advisory Committee on Asbestos Cancers has suggested that the risk of mesotheliomas is greatest with crocidolite, less with amosite, and apparently less with chrysotile (Becklake, 1976; IARC, 1973).

Fiber length has been studied in relationship to pathogenicity. Both Smith and Gross maintain that short asbestos fibers ( $< 5$  microns in length) are far less fibrogenic and carcinogenic than long fibers (Gross, 1974; Smith, 1972). Stanton, who supports the fiber theory of carcinogenesis, has found long, thin fibers ( $< .3$  microns in diameter and  $> 20$  microns in length) to be far more carcinogenic in the pleura of rats than short or thick fibers regardless of the type of asbestos or other material used (Stanton, 1974).

Fiber diameter may also be related to pathogenicity. The 1977 IARC Report concluded that fibers less than 0.5 microns in diameter produce a higher incidence of tumors (IARC, 1977). Timbrell has suggested that fibers appear to be more carcinogenic as their diameters approach the thickness of cell membranes (Timbrell, 1973). This explanation for differences in biologic activity relates to the degree

of penetration and deposition in the lung; the smaller fiber diameter of crocidolite may be the reason for its greater mesothelioma potential compared to amosite, anthophyllite, and chrysotile.

Intensity and length of exposure are related to the risk of asbestosis and lung cancer. There is less evidence of a relationship of risk of mesothelioma to these two factors. Cases of mesothelioma have been reported following brief, low levels of exposure (Becklake, 1976; IARC, 1977).

Estimates of dose in epidemiologic studies are relatively crude and have usually been measured in one of several ways: number of years employed in an industry using asbestos, number of years since first exposure, or total years of exposure together with an assessment of light, moderate or heavy dustiness. Despite all of these shortcomings, there has been a consistent relationship between estimated dose and response in man found in mining, milling, and manufacturing with more disease at higher exposure levels and longer lengths of exposure (Enterline, 1967; Enterline, 1973; Newhouse, 1973; McDonald, 1974; Becklake, 1976). However, for example, it is still unknown whether 10 years of exposure at a certain intensity produces the same amount of damage as one year's exposure at ten times the concentration.

Observed variations in relative risk between occupations or industries utilizing asbestos are probably due to differences in factors such as asbestos type, size of fiber and exposure levels within these industries. For example, variations in fiber concentrations prior to 1971 for various asbestos-using industries are presented in Table 6 below (IARC, 1977, p. 37):

Table 6: Concentrations of Fibers in Various Asbestos-Using Industries in the U.S. before 1971

<u>Industry</u>	<u>Range of Means (Fibers &gt; 5<math>\mu</math>m/ml)</u>	<u>Range of Individual Samples (fibers &gt; 5<math>\mu</math>m/ml)</u>
Textile	0.1 - 29.9	0.0 - 143.9
Insulation	0.1 - 74.4	0.0 - 208.4
Paper Packing and Asphalt Production	0.2 - 13.6	0.0 - 18.9
Cement Shingles, Mill-board and Gasket	0.1 - 4.4	0.0 - 16.6
Friction Cement Pipe	0.1 - 14.4 0.2 - 6.3	0.1 - 32.4 0.0 - 13.4

Workers in different occupations are exposed to asbestos fibers of differing physical parameters depending on the stage of processing involved or the type of fiber best suited for a particular product.

## BIBLIOGRAPHY

- Ahlman, K., Partanen, T.J., Rintala, E. and Wiikeri, M. Anthophyllite mining and milling as a cause of asbestosis, *Biological Effects of Asbestos*, 165-168, 1973
- Anderson, H.A., Lilis, R., Daum, S.M., Fischbein, A.S. and Selikoff, I.J. Household-contact asbestos neoplastic risk, *Ann. N.Y. Acad. Sci.* 271: 311-323, May 28, 1976
- Beck, E.G. Interaction between fibrous dust and cells in vitro, *Ann. Anat. Path. (Paris)* 21(2):227-36, March - April 1976
- Becklake, M.R., Fournier-Massey, G., Rossiter, C.E. and McDonald, J.C. Lung function in chrysotile asbestos mine and mill workers of Quebec, *Arch. Environ. Health* 24: 401-409, June 1972
- Becklake, M.R. Asbestos-related disease of the lung and other organs: their epidemiology and implications for clinical practice, *Am. Rev. Respir. Dis.* 114(1): 187-227, July 1976
- Berry, G., Newhouse, M.L. and Turok, M. Combined effects of asbestos exposure and smoking on mortality from lung cancer in factory workers, *Lancet* 2: 476-479, 1972
- Bohlig, H., Dabbert, A.F., Dalquen, P., Hain, E. and Hinz, I. Epidemiology of malignant mesothelioma in Hamburg, *Environ. Res.* 3: 365-372, 1970
- Bolton, R.E., Davis, J.M.G. The short-term effects of chronic asbestos ingestion in rats, *Ann. Occup. Hyg.* 19(2): 121-128, Nov. 1976
- Braun, D.C. and Truan, T.D. An epidemiological study of lung cancer in asbestos miners, *A.M.A. Arch. Ind. Hlth.* 17: 634-653, June 1958
- Brown, A. Commentary: Lymphohematogenous spread of asbestos, *Environ. Health Perspect.* 9: 203-204, 1974
- Bruckman, L. and Rubino, R.A. Asbestos: rationale behind a proposed air quality standard, *Journal of the Air Pollution Control Association* 25(12): 1207-1215, Dec. 1975
- Burlikov, T. and Michailova, L. Asbestos content of the soil and endemic pleural asbestosis, *Environ. Res.* 3: 443-451, 1970
- Cook, P.M. Glass, G.E. and Tucker, J.H. Asbestiform amphibole minerals: detection and measurement of high concentrations in municipal water supplies, *Science* 185: 853-855, Sept. 6, 1974
- Cooper, W.C. Asbestos as a hazard to health, *Arch. Environ. Health* 15: 285-290, Sept. 1967

Cooper, W.C. and Miedema, W.C. Asbestosis in the manufacture of insulating materials, Biological Effects of Asbestos, 175-178, 1973

Cralley, L.J. and Lainhart, W.S. Are trace metals associated with asbestos fibers responsible for the biological effects attributed to asbestos?, J. Occ. Med. 15(3): 262-266, March 1973

Cralley, L.J., et al Characterization and solubility of metals associated with asbestos fibers, Am. Ind. Hyg. Assoc. J. 29: 569-573, Nov. - Dec. 1968

Cralley, L.J., Keenan, R.G. and Lynch, J.R. Exposure to metals in the manufacture of asbestos textile products, Am. Ind. Hyg. Assoc. J. 28: 452-461, Sept. - Oct. 1967

Cunningham, H.M. and Pontefract, R.D. Asbestos fibres in beverages and drinking water, Nature 232: 332-333, July 30, 1971

Davis, J.M.G., Bolton, R.E. and Garrett, J. Penetration of cells by asbestos fibers, Environ. Health Perspect. 9: 255-260, 1974

Dement, John M., Zumwalde, R.D. and Wallingford, K.M. Discussion Paper: Asbestos fiber exposures in a hard rock gold mine, Ann. N.Y. Acad. Sci. 271: 345-352, 1976

Dixon, J.R., et al The role of trace metals in chemical carcinogenesis: asbestos cancers, Cancer Res. 30: 1068-1074, April 1970

Doll, R. Mortality from lung cancer in asbestos workers, Br. J. Ind. Med. 12: 81-86, 1955

Doniach, I., Wettenham, K.V. and Hathorn, M.K.S. Prevalence of asbestos bodies in a necropsy series in East London: association with disease, occupation, and domiciliary address, Br. J. Ind. Med. 32: 16-30, 1975

Dunn, J.E. and Weir, J.M. Cancer experience of several occupational groups followed prospectively, A.J.P.H. 55(9): 1367-1375, Sept. 1965

Dunn, J.E., Linden, G. and Breslow, L. Lung cancer mortality of men in certain occupations in California, A.J.P.H. 50(10): 1475-1487, Oct. 1960

Elmes, P.C. Current information on the health risk of asbestos, Royal Society of Health Journal 96(6): 248-252, December 1976

Elmes, P.C. and Simpson, M.J.C. Insulation workers in Belfast, Brit. J. Indust. Med. 28: 226-236, 1971

- Enterline, P.E. Mortality among asbestos products workers in the United States, *Ann. N.Y. Acad. Sci.* 132: 156-165, 1965
- Enterline, P.E. Estimating health risks in studies of the health effects of asbestos, *Amer. Rev. Resp. Dis.* 113: 175-180, 1976
- Enterline, P.E. Pitfalls in epidemiological research. An examination of the asbestos literature, *J. Occup. Med.* 18(3): 150-156, March 1976
- Enterline, P.E., DeCoufle, P. and Henderson, V. Respiratory cancer in relation to occupational exposures among retired asbestos workers, *Br. J. Ind. Med.* 30: 162-166, April 1973
- Enterline, P., DeCoufle, P. and Henderson, V. Mortality in relation to occupational exposure in the asbestos industry, *J. Occup. Med.* 14: 897-903, Dec. 1972
- Enterline, P.E. and Henderson, V. Type of asbestos and respiratory cancer in the asbestos industry, *Arch. Environ. Health* 27: 312-317, Nov. 1973
- Enterline, P.E. and Kendrick, M.A. Asbestos-dust exposures at various levels and mortality, *Arch. Environ. Health* 15: 181-186, Aug. 1967
- Fears, T.R. Cancer mortality and asbestos deposits, *Amer. J. Epidemiol.* 104(5): 523-526, Nov. 1976
- Ferris, B.G., Ranadive, M.V., Peters, J.M., Murphy, R.L.H., Burgess, W.A. and Pendergrass, H.P. Prevalence of chronic respiratory disease asbestosis in ship repair workers, *Arch. Environ. Health*, 23: 220-225, September 1971
- Gee, B., and Bouhuys, A. Editorial: Action on asbestos, *New. Engl. J. Med.* 285(23): 1317-1318, Dec. 2, 1971
- Gibbs, G.W. and LaChance, M. Dust exposure in the chrysotile asbestos mines and mills of Quebec, *Arch. Environ. Health* 24: 189-197, March 1972
- Gibbs, G.W. and Hwang, C.Y. Physical parameters of airborne asbestos fibres in various work environments - preliminary findings, *Amer. Ind. Hyg. Assoc. J.* 36: 459-466, June 1975
- Gibbs, G.W. and LaChance, M. Dust-fiber relationships in the Quebec chrysotile industry, *Arch. Environ. Hlth.* 28: 69-71, Feb. 1974
- Gillam, J.D., Dement, J.M., Lemen, R.A., Wagoner, J.K, Archer, V.E. and Blejer, H.P. Mortality patterns among hard rock gold miners exposed to an asbestiform mineral. *Ann. N.Y. Acad. Sci.*, 271: 336-344, 1976
- Gilson, J.C. Asbestos cancers as an example of the problem of comparative risks, *Inserm.* 52: 107-116, 1976



- Graham, S., Blanchett, M. and Rohrer, T. Cancer in asbestos mining and other areas of Quebec, unpublished
- Gross, P. Is short-fibered asbestos dust a biological hazard?, Arch. Env. Hlth. 29: 115-117, Aug 1974
- Gross, P., DeTreville, R.T., Tolker, E.B., et.al. Experimental asbestosis, Arch. Environ. Health 15: 343-355, Sept. 1967
- Gross, P., Harley, R.A., Swinburne, L.M., Davis, J.M.G., and Greene, W.B. Ingested mineral fibers: do they penetrate tissue or cause cancer, Arch. Environ. Health 29: 341-347, Dec. 1974
- Hammond, E.C., Selikoff, I.J. and Churg, J. Neoplasia among insulation workers in the United States with special reference to intra-abdominal neoplasia, Ann. N.Y. Acad. Sci. 132: 519-525, 1965
- Harrington, J.S. and Roe, F.J.C. Studies of carcinogenesis of asbestos fibers and their natural oils, Ann. N.Y. Acad. Sci. 132: 439-450, 1965
- Harrington, J.S. Chemical factors (including trace elements) as etiological mechanisms, Biological Effects of Asbestos, pp. 304-309, 1973
- Harrington, J.S., Roe, F.J.C. and Walters, M. Studies of the mode of action of asbestos as a carcinogen, S.Afr. Med. J. 41: 800-804, August 26, 1967
- Harrington, J.S. Fibrogenesis, Environ. Health Perspect. 9:271-279, Dec. 1974
- Harrington, J.S. The biological effects of mineral fibres, especially asbestos, as seen in vitro and in vivo studies, Ann. Anat. Path. (Paris) 21(2): 155-198, March - April 1976
- Harrington, J.S. Chemical studies of asbestos, Ann. N.Y. Acad. Sci. 132: 31-47, 1965
- Harries, P.G. Asbestos dust concentrations in ship repairing: a practical approach to improving asbestos hygiene in naval dockyards, Ann. Occup. Hyg. 14: 241-254, 1971
- Holt, P.F. Small animals in the study of pathological effects of asbestos, Environ. Health Perspect. 9: 205-211, 1974
- IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Lyons, France, International Agency for Research on Cancer, Vol. 2, pp. 17-47, 1973

- IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Asbestos. Lyons, France, International Agency for Research on Cancer, 1973, Vol. 14, pp. 1-106, 1977
- Jodoin, G., Gibbs, G.W., Macklem, P.T., McDonald, J.C. and Becklake, M.R. Early effects of asbestos exposure on lung function, American Review of Respiratory Disease, 104: 525-535, 1971
- Kanazawa, K., Birbeck, M.S.C., Carter, R.L. and Roe, F.J.C. Migration of asbestos fibers from subcutaneous injections sites in mice, Brit. J. Ca. 24: 96-106, 1970
- Kay, G.H. Asbestos in drinking water, Jour. Am. Water Works Assn. 66(9): 513-514, 1974
- Kelly, R.T. Asbestos - health hazards in perspective, Royal Society of Health Journal 96(6): 246-248, December 1976
- Kleinfeld, M. Biologic response to kind and amount of asbestos, J. Occup. Med. 15: 296-300, March 1973
- Kleinfeld, M., Messite, J., Kooyman, O. and Zaki, M.H. Mortality among talc miners and millers in New York state, Arch. Environ. Health 14: 663-667, 1967
- Kleinfeld, M., Messite, J. and Kooyman, O. Mortality experience in a group of asbestos workers, Arch. Environ. Health 15: 177-180, August 1967
- Knox, J.F., Holmes, S., Doll, R. and Hill, I.D. Mortality from lung cancer and other causes among workers in an asbestos textile factory, Brit. J. Ind. Med. 25: 293-303, 1968
- Kovarik, J.L. Primary pleural mesothelioma, Cancer 38(4): 1816-1825, October 1976
- Langer, A.M. Inorganic particles in human tissue and their association with neoplastic disease, Environ. Health Perspect. 9: 229-233, 1974
- Langer, A.M., Selikoff, I.J. and Sastre, A. Chrysotile asbestos in the lungs of persons in New York City, Arch. Environ. Health 22: 348-361, 1971
- Lee, D.H. Biological effects of ingested asbestos: report and commentary, Environ. Health Perspect. 9: 113-122, Dec. 1974
- Levy, B.S., Sigurdson, E., Mandel, J., Laudon, E. and Pearson, J. Investigating possible effects of asbestos in city water surveillance of gastrointestinal cancer incidence in Duluth, Minnesota, Amer. J. Epid. 103(4): 362-368, 1976

- Lieben, J. Malignancies in asbestos workers, Arch. Environ. Health 13: 619-621, November 1966
- Mancuso, T.F. and El-Attar, A.A. Mortality pattern in a cohort of asbestos workers, J. Occup. Med. 9: 147-162, 1967
- Mancuso, T.F. and Coulter, E.J. Methodology in industrial health studies: A cohort approach with special reference to an asbestos company, Arch. Environ. Health 6: 210-226, February 1963
- Masson, T.J., McKay, F.W. and Miller, R.W. Asbestos-like fibers in Duluth water supply. Relation to cancer mortality, J.A.M.A. 228(8) 1019-1020, May 20, 1974
- McCullagh, S.F. The biological effects of asbestos, Med. J. Aust. 2: 45-49, 1974
- McDonald, A.D. and McDonald, J.C. Epidemiologic surveillance of mesothelioma in Canada, Can. Med. Assoc. J. 109: 359-362, 1973
- McDonald, J.C., Gibbs, G.W., Liddell, F.D.K., McDonald, A.D. Abstract: Mortality after long exposure to cummingtonite-grunerite, Amer. Rev. Respir. Dis. 115(4): 230, April 1977
- McDonald, J.C., Becklake, M.R., Fournier-Massy, G. and Rossiter, C.E. Respiratory symptoms in chrysotile asbestos mine and mill workers of Quebec, Arch. Environ. Health 24: 358-363, 1972
- McDonald, J.C., McDonald, A.D., Gibb, G.W., Siemiatycki, J. and Rossiter, C.E. Mortality in the chrysotile asbestos mines and mills of Quebec, Arch. Environ. Health 22: 677-686, 1971
- McDonald, J.C., Becklake, M.R. and Gibbs, G.W. The health of chrysotile asbestos mine and mill workers of Quebec, Arch. Environ. Health 28: 61-68, February 1974
- Merliss, R.R. Talc-treated rice and Japanese stomach cancer, Science 173(4002): 1141-1142 September 1971
- Meurman, L.O., Kiviluoto, R. and Hakama, M. Mortality and morbidity among the working population of anthophyllite asbestos miners in Finland, Br. J. Ind. Med. 31: 105-112, April 1974
- Meurman, L.O. Pleural fibrocalcific plaques and asbestos exposures, Environ. Res. 2: 30-46, 1968
- Murphy, R.L.H., Gaensler, E.A., Redding, R.A., Belleau, R., Keelan, P.J., Smith, A.A., Goff, A.M. and Ferris, B.G. Low exposure to asbestos, gas exchange in shippipe coverers and controls, Arch. Environ. Health 25: 253-264, October 1972
- Murphy, R.L.H., Ferris, B.G., Burgess, W.A., Worchester, J. and Gaensler, E.A. Effects of low concentration of asbestos, New. Eng. J. Med. 285: 1271-1278, December 2, 1971
- NTIS, National Institute for Occupational Safety & Health: Occupational Exposures to Asbestos, Washington U.S. Department of H.E.W. (PHS, HSMHA, 1972 - HSM72 - 10267)

National Research Council, Committee on Biological Effects of Atmospheric Pollutants and Asbestos. The need for and feasibility of pollution controls. Nat. Ac. Sci., Washington, D.C., 1971

Newhouse, M.L. and Berry, G. Asbestos and laryngeal carcinoma, Lancet 2(1): 615, 1973

Newhouse, M.L. and Berry, G. Predictions of mortality from mesothelial tumours in asbestos factory workers, Brit. J. Ind. Med. 33: 147-151, 1976

Newhouse, M.L. and Wagner, J.C. Validation of death certificates in asbestos workers, Br. J. Industr. Med. 26: 302-307, 1969

Newhouse, M.L. Asbestos in the workplace and the community, Ann. Occup. Hyg. 16: 97-102, 1973

Newhouse, M.L. Cancer among workers in the asbestos textile industry, In: Bogovski, P., Timbrell, V., Gilson, J.C. and Wagner, J.C. Biological Effects of Asbestos, IARC Scientific Publication No. 8, Lyon, France, 1973, pp. 203-208

Newhouse, M.L. A study of the mortality of workers in an asbestos factory, Brit. J. Industr. Med. 26: 294-301, 1969

Nicholson, W.J. Case study 1: Asbestos - the TLV approach, Ann. N.Y. Acad. Sci. 271: 152-169, 1976

Nurminen, Markku The epidemiologic relationship between pleural mesothelioma and asbestos exposure, Scand. J. Work Environ. Health 1: 128-137, 1975

Olson, H.L. Asbestos in potabe water supplies, J. Amer. Water Works Assn. 66(9): 516-518, 1974

Ponterfract, R.D. Commentary: Penetration of asbestos through the digestive wall in rats, Environ. Health Perspect. 9: 213-214, 1974

Ponterfract, R.D. and Cunningham, H.M. Penetration of asbestos through the digestive tract of rats, Nature 243(5406) 352-353, 1973

Reeves, A.L. Experimental asbestos carcinogenesis, Environ. Res. 4: 496-511, 1971

Reeves, A.L. The carcinogenic effect of inhaled asbestos fibers, Ann. Clin. Lab. Sci. 6: 459-466, 1976

Reeves, A.L., Puro, H.E. and Smith, R.G. Inhalation carcinogenesis from various forms of asbestos, Environ. Res. 8: 178-202, 1974

Roe, F.J.C., Carter, R.L., Walters, M.D. and Harrington, J.S. The pathological effects of subcutaneous injections of asbestos fibers in mice. Migrations of fibers to submesothelial tissues, Int. J. Ca. 2: 628-638, 1967

Rohl, A.N., Langer, A.M. and Selikoff, I.J. Environmental asbestos pollution related to use of quarried serpentine rock, Science 196(4296): 1319-1322, June 1977

Rossiter, C.E., Bristol, L.J., Cartier, P.H., Gilson, J.C., Grainger, T.R. and McDonald, J.C. Radiographic changes in chrysotile asbestos mine and mill workers of Quebec, Arch. Environ. Health 24: 388-400, 1972

Roy-Chowdhury, A.K., Mooney, T.F. and Reeves, A.L. Trace metals in asbestos carcinogenesis, Arch. Environ. Health 26: 253-255, May 1973

Schneiderman, M.A. Digestive system cancer among persons subjected to occupational inhalation of asbestos particles: a literature review with emphasis on dose response, Environ. Health Perspect. 9: 307-311, 1974

Seidman, H., Lilis, R. and Selikoff, I.J. Short-term asbestos exposure and delayed cancer risk, Presented at 3rd Int. Symp. on Det. and Prev. of Cancer, New York, April 26 to May 1, 1976

Selikoff, I.J., Churg, J. and Hammond, E.C. Asbestos exposure and neoplasia, J.A.M.A. 188: 22-26, April 6, 1964

Selikoff, I.J., Churg, J. and Hammond E.C. The occurrence of asbestosis among insulation workers in the United States, Ann. N.Y. Acad. Sci. 132: 139-153, 1965

Selikoff, I.J. and Hammond, E.C. Environmental epidemiology III, community effects of non-occupational environmental asbestos exposure, Amer. J. Pub. Health 58(2): 1658-1666, 1968

Selikoff, I.J., Hammond, E.C. and Churg, J. Carcinogenicity of amosite asbestos, Arch. Environ. Health 25: 183-186, 1972

Selikoff, I.J., Hammond, E.C. and Seidman, Cancer risk of insulation workers in the United States, In: Bogovski, P., Timbrell, V., Gilson, J.C. and Wagner, J.C. Biological Effects of Asbestos, IARC Scientific Publication No. 8, Lyon, France, 1973, pp. 203-208

Selikoff, I.J. Epidemiology of gastrointestinal cancer, Environ. Health Perspect. 9: 299-305, 1974

Selikoff, I.J. and Hammond, C.E. Asbestos bodies in the New York City population in two periods of time, Internat. Conf. of Pneumoconiosis, Johannesburg, pp. 47-53, (April-May), 1969

- Sigurdson, E.E., Mandel, J., McHugh, R., Levy, B.S., Jagger, H., Knorr, R., Laudon, E. and Pearson, J. Incidence of gastrointestinal and lung cancer in residents of Duluth, Two Harbors, Beaver Bay, and Silver Bay 1969-1974, unpublished
- Smith, W.E., Miller, L., Elsasser, R.E. and Hubert, D.D. Tests for carcinogenicity of asbestos, *Annals of the N.Y. Acad. of Sci.* 132: 456-488, December 31, 1965
- Smith, W.E. Asbestos, talc and nitrates in relation to gastric cancer, *Am. Ind. Hyg. Assoc. J.* 34: 227-228, 1973
- Smith, W.E., Hubert, D.D. and Badollet, M.S. Biological differences in response to long and short asbestos fibers, *Amer. Ind. Hyg. Assoc. J.* 33: 67, 1972
- Stanton, M.F. and Wrench, C. Mechanism of mesothelioma induction with asbestos and fibrous glass, *U.S. J. Natl. Cancer Inst.* 48(3): 797-821, March 1972
- Stanton, M.F. Fiber carcinogenesis: Is asbestos the only hazard?, *U.S. J. Natl. Cancer Inst.* 52(3): 633-634, March 1974
- Suzuki, Y. and Churg, J. Structure and development of the asbestos body, *Amer. J. Pathol.* 55: 79-91, 1969
- Taryle, D.A., et. al. Pleural mesotheliomas - an analysis of 18 cases and review of the literature, *Medicine (Baltimore)* 55(2): 153-162, March 1976
- Thomson, J.G., Kaschula, R.O.C. and MacDonald, R.R. Asbestos as a modern urban hazard, *S. Afr. Med. J.* 37: 77-81, 1963
- Thomson, J.C. and Path, F.C. Asbestos as an urban air contaminant, *Arch. Path.* 81: 458-464, May 1966
- Timbrell, V. The inhalation of fibrous dusts, *N.Y. Acad. Sci.* 132: 255, 1965
- Timbrell, V. Physical factors as etiological mechanisms. In: Bogovski, P., Timbrell, V., Gilson, J.C. and Wagner, J.C. Biological Effects of Asbestos, IARC Scientific Publication No. 8, Lyon, France, 1973, pp. 295-303
- Wagg, R.M. Safety measures when handling asbestos, *Royal Society of Health Journal* 96(6): 252-255, December 1976
- Wagner, J.C., Berry, G. and Timbrell, V. Mesothelioma in Rats In: *Pneumoconiosis, Proceedings of the International Conference Johannesburg, 1969.* (H.A. Shapiro, Ed.) P. 216, Oxford Univ. Press, Capetown, 1970.
- Wagner, J.C., Berry, G. and Timbrell, V. Mesothelioma in rats after inoculation with asbestos and other materials, *Brit. J. Cancer* 28: 173-185, 1973
- Wagner, J.C., Sleggs, C.A. and Marchand, P. Diffuse pleural mesothelioma and asbestos exposure in Northwestern Cape Province, *Br. J. Ind. Med.* 17: 260-271, 1960

- Wagner, J.C. Tumours in experimental animals following exposure to asbestos dust, *Ann. Anat. Path* 21(2): 211-214, 1976
- Wagner, J.C., Gilson, J.C., Berry, G. and Timbrell, V. Epidemiology of asbestos cancers, *Br. Med. Bull.* 27: 71-76, 1971
- Wagner, J.C., Berry, G. Skidmore, J.W. and Timbrell, V. The effects of the inhalation of asbestos in rats, *Br. J. Cancer* 29: 252-269, 1974
- Warnock, M.L. and Churg, A.M. Association of asbestos and bronchogenic carcinoma in a population with low asbestos exposure, *Cancer* 35: 1236-1242, 1975
- Webster, I. The ingestion of asbestos fibers, *Environ. Health Perspect.* 9: 199-202, 1974
- Weill, H. Epidemiologic methods in the investigation of occupational lung disease, *Amer. Rev. Respir. Dis.* 112: 1-6, 1975
- Weiss, W. Cigarette smoking, asbestosis, and pulmonary fibrosis, *Amer. Rev. of Respiratory Disease* 104: 223-227, 1971
- Wells, A.H. Asbestos in Duluth water, *Minnesota Medicine* 458-459, June 1975
- Westlake, G.E, Spjut, H.J. and Smith, A.A. Penetration of colonic mucosa by asbestos particles. An electron microscopic study in rats fed asbestos dust, *Lab. Invest.* 14: 2029-2033, 1965
- Westlake, G.E. Commentary: Asbestos fibers in the colonic wall, *Environ. Health Perspect* 9: 227, 1974
- Zaidi, S.H. Commentary: Ingestion of asbestos, *Environ. Health Perspect.* 9: 239-240, 1974