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

A Review of Epidemiology Literature and Study Recommendations on Asbestos

Performed Under Contract from the Minnesota Department of Health for the Minnesota Regional Copper-Nickel Study Environmental Impact Task Force

by

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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 serpentes (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"

```
asion

Serpentine       Amphiboles

| Chrysotile   | Crocidolite | "Amosite" | Tremolite | Actinolite | Anthophyllite |
```

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>
<thead>
<tr>
<th></th>
<th>SERPENTINE</th>
<th>AMPHIBOLES</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chrysotile</td>
<td>Crocidolite</td>
<td>&quot;Amosite&quot;</td>
<td>Tremolite</td>
<td>Actinolite</td>
<td>Anthophyllite</td>
<td></td>
</tr>
<tr>
<td>General Chemical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formula *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na(Fe(^{2+})Fe(^{3+}))Si(<em>{8})O(</em>{22})(OH)(_{2})</td>
<td>3Mg(<em>{2})Si(</em>{2})O(<em>{5})H(</em>{2})O</td>
<td>(Fe(<em>{6})Mg(</em>{6}))Si(<em>{8})O(</em>{22})(OH)(_{2})</td>
<td>Ca(<em>{2})(Mg(</em>{6})Fe(<em>{6}))Si(</em>{8})O(<em>{22})(OH)(</em>{2})</td>
<td>Ca(<em>{2})(Mg(</em>{6})Fe(<em>{6}))Si(</em>{8})O(<em>{22})(OH)(</em>{2})</td>
<td>(Fe(<em>{6})Mg(</em>{6}))Si(<em>{8})O(</em>{22})(OH)(_{2})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexibility **</td>
<td>Very flexible</td>
<td>Fair to good</td>
<td>Good</td>
<td>Brittle</td>
<td>Brittle</td>
<td>Brittle to flexible</td>
<td></td>
</tr>
<tr>
<td>Length **</td>
<td>Short to 3&quot;</td>
<td>Short to 3&quot;</td>
<td>(\frac{1}{2})&quot; to 6&quot;</td>
<td>Short to long</td>
<td>Short to long</td>
<td>Short</td>
<td></td>
</tr>
<tr>
<td>Texture **</td>
<td>Harsh to silky</td>
<td>Harsh or soft</td>
<td>Coarse but pliable</td>
<td>Harsh to soft</td>
<td>Harsh</td>
<td>Harsh to soft</td>
<td></td>
</tr>
<tr>
<td>Tensile Strength **</td>
<td>Very high</td>
<td>Very high</td>
<td>Fair</td>
<td>Weak</td>
<td>Very weak</td>
<td>Weak</td>
<td></td>
</tr>
<tr>
<td>Acid Resistance **</td>
<td>Fairly soluble</td>
<td>Very good</td>
<td>Good</td>
<td>Fairly resistant</td>
<td>Highly resistant</td>
<td>Fair to good</td>
<td></td>
</tr>
<tr>
<td>Spinnability **</td>
<td>Very good</td>
<td>Fair</td>
<td>Fair</td>
<td>Poor</td>
<td>Poor</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Resistance to heat **</td>
<td>Good</td>
<td>Poor</td>
<td>Good</td>
<td>Fair to good</td>
<td>-----</td>
<td>Very good</td>
<td></td>
</tr>
<tr>
<td>Estimated % of total production in 1963 ***</td>
<td>93</td>
<td>3.5</td>
<td>2.4</td>
<td>(&lt;1)</td>
<td>-----</td>
<td>(&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Related mineral system *</td>
<td>-----</td>
<td>Riebeckite-glaucophane</td>
<td>Grunerite-cummingtonite</td>
<td>actinolite-tremolite</td>
<td>actinolite-tremolite</td>
<td>anthophyllite-gedrite</td>
<td></td>
</tr>
</tbody>
</table>

*** 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."

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.¹

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

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>
<thead>
<tr>
<th>Process</th>
<th>Products Made or Used</th>
<th>Jobs Potentially at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mining</td>
<td></td>
<td>Rock mining, loading, trucking</td>
</tr>
<tr>
<td>Milling</td>
<td></td>
<td>Crushing, milling</td>
</tr>
<tr>
<td>Handling</td>
<td></td>
<td>Transport workers, dockers, loaders, those who unpack jute sacks (recently replaced with sacks that do not permit fibers to escape)</td>
</tr>
<tr>
<td>Primary uses in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spray insulation</td>
<td>Spray of fiber mixed with oil</td>
<td>Spray insulators (construction, shipbuilding)</td>
</tr>
<tr>
<td>Filler and grouting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacturing of Textiles</td>
<td>Cloth, curtains, lagging, protective clothing, mailbags, padding, conveyor belts</td>
<td>Blending, carding, spinning, twisting, winding, braiding, weaving, slurry mixing, laminating, moulding, drying</td>
</tr>
<tr>
<td>Cement products</td>
<td>Sheets, pipes, roofing shingles, gutters, ventilation shafts, flower pots</td>
<td>Blending, slurry preparation, rolling, pressing, pipe cutting</td>
</tr>
<tr>
<td>&quot;Paper&quot; products</td>
<td>Millboard, roofing felt, fine quality electrical papers, flooring felt, fillers</td>
<td></td>
</tr>
<tr>
<td>Friction materials</td>
<td>Automotive products: gaskets, clutch plates, brake linings</td>
<td></td>
</tr>
<tr>
<td>Insulation products</td>
<td>Pipe and boiler insulation, bulkhead linings for ships</td>
<td></td>
</tr>
<tr>
<td>Application</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Construction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New construction</td>
<td>Boards and tiles; putties, caulk, paints, joint fillers; cement products (tiles, pipes, siding, shingles)</td>
<td>Directly, carpenters, laggers, painters, tile layers, insulation workers, sheet metal and heating equipment workers, masons, indirectly all other workers on construction sites, such as plumbers, welders, electricians</td>
</tr>
<tr>
<td>Repair, demolition</td>
<td>Insulation materials</td>
<td>Demolition workers for all of these</td>
</tr>
</tbody>
</table>
### TABLE 2
(continued)

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

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

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

- Recognition of association with asbestos exposure
  - Asbestosis: 1880-1900
  - Lung cancer: 1920-1940
  - Mesothelioma: 1940-1960
  - Other cancers: 1960-1980

- Start of commercial production of:
  - Chrysotile
  - Crocidolite
  - Amosite
  - Anthophyllite

- World Product of Asbestos (All Types) in 1000 Tons

- Key:
  - '?' = Suspected
  - '—' = Probable
  - '-----' = Established

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 mg/m³ 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 mg/m³ 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 mg/m³ 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 mg/m³ 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). Pontebracci 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 (Pontebracci, 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>
<thead>
<tr>
<th>Author and Year</th>
<th>Experimental Animal</th>
<th>Number of Animals</th>
<th>Type of Asbestos</th>
<th>Amount of Asbestos</th>
<th>Fiber Size</th>
<th>Period of Exposure and Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross 1967</td>
<td>Rats</td>
<td>72</td>
<td>chrysotile dust</td>
<td>86 mg/m³ for 30 hrs per week</td>
<td>unreported</td>
<td>at least 16 months (time of appearance of first tumor) or until death</td>
<td>Lung tumors: 17 adenocarcinomas 4 squamous-cell carcinomas 7 fibrosarcomas No tumors occurred in 39 controls</td>
</tr>
<tr>
<td>Reeves 1971</td>
<td>Rats</td>
<td>31</td>
<td>crocidolite</td>
<td>49 mg/m³ for 16 hrs per week</td>
<td>unreported</td>
<td>2 years</td>
<td>2 squamous-cell carcinomas of the lung</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td>chrysotile</td>
<td></td>
<td></td>
<td></td>
<td>5 with benign pulmonary adenomatosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>42</td>
<td>amosite</td>
<td></td>
<td></td>
<td></td>
<td>no adverse effects</td>
</tr>
</tbody>
</table>
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 oleomargarine 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>
<thead>
<tr>
<th>Author and Tear</th>
<th>Experimental Animal</th>
<th>Number of Animals</th>
<th>Type of Asbestos</th>
<th>Amount of Asbestos</th>
<th>Fiber Size</th>
<th>Period of Exposure and Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Westlake 1965</td>
<td>White Wistar female rats</td>
<td>60</td>
<td>chrysotile dust</td>
<td>6% of diet</td>
<td>most were .5(\mu)m - 1.0(\mu)m long</td>
<td>approx. 3 months</td>
<td>electron microscopy revealed asbestos crystals in many sites in the colonic epithelium and lamina propria.</td>
</tr>
<tr>
<td>Smith 1965</td>
<td>Golden Syrian male hamsters</td>
<td>45</td>
<td>soft chrysotile or amosite</td>
<td>1% of diet</td>
<td>not reported</td>
<td>until death</td>
<td>no gastric carcinomas, no tumors in gastrointestinal tract except a neoplasm in the mesentery of the colon.</td>
</tr>
<tr>
<td>Ponterfact 1973</td>
<td>Rats</td>
<td>100</td>
<td>chrysotile</td>
<td>1 dose of 9.4x10^9 fibers or 94x10^9 fibers injected into stomach</td>
<td>most were .2(\mu)m - 2(\mu)m long</td>
<td>2 days for 50 rats; 4 days for 50 rats</td>
<td>fibers in blood, spleen, omentum, heart, brain, lungs.</td>
</tr>
<tr>
<td>Davis 1974</td>
<td>Rats</td>
<td>not reported</td>
<td>chrysotile or crocidolite</td>
<td>100 mg in 20 g. butter each week</td>
<td>not reported</td>
<td>several rats 3 months; other rats followed to death</td>
<td>no penetration into the gut epithelial cells.</td>
</tr>
<tr>
<td>Webster 1974</td>
<td>Baboons</td>
<td>not reported</td>
<td>crocidolite</td>
<td>varied concentrations in food and water</td>
<td>not reported</td>
<td>up to 5 years</td>
<td>asbestos needles found in feces; no evidence of a peritoneal tumor or gastrointestinal tumor.</td>
</tr>
<tr>
<td>Author and Year</td>
<td>Experimental Animal</td>
<td>Number of Animals</td>
<td>Type</td>
<td>Amount</td>
<td>Fiber Size</td>
<td>Period of Exposure and Follow-up</td>
<td>Results</td>
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<td>---------</td>
</tr>
<tr>
<td>Reeves 1974</td>
<td>Mice</td>
<td>30</td>
<td>amosite</td>
<td>about 50 mg/m³ for 4 hrs/day for 4 days per week</td>
<td>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</td>
<td>2 years or until death</td>
<td>no tumors 2 bronchial tumors no tumors 1 bronchial tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>crocidolite</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>30</td>
<td>chrysotile</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gerbils</td>
<td></td>
<td>68</td>
<td>amosite</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>68</td>
<td>crocidolite</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>68</td>
<td>chrysotile</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>12</td>
<td>controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats</td>
<td></td>
<td>69</td>
<td>amosite</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>69</td>
<td>crocidolite</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>69</td>
<td>chrysotile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td>controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbits</td>
<td></td>
<td>20</td>
<td>amosite</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>crocidolite</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>20</td>
<td>chrysotile</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>12</td>
<td>controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guinea Pigs</td>
<td></td>
<td>32</td>
<td>amosite</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>32</td>
<td>crocidolite</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>32</td>
<td>chrysotile</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td>controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author and Year</td>
<td>Experimental Animal</td>
<td>Number of Animals</td>
<td>Type of Asbestos</td>
<td>Amount of Asbestos</td>
<td>Fiber Size</td>
<td>Period of Exposure and Follow-up</td>
<td>Results</td>
</tr>
<tr>
<td>-----------------</td>
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<td>---------</td>
</tr>
<tr>
<td>Wagner 1974</td>
<td>Caesarean rats of the Wistar Strain</td>
<td>49, 52, 24, 25, 21</td>
<td>amosite</td>
<td>approx. 10 mg/m³ for 7 hours/day and 5 days per week</td>
<td>unreported</td>
<td>Exposure: 1 day, 3 months, 6 months, 12 months, 24 months</td>
<td>Number with Lung Tumors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>49, 52, 24, 28, 19</td>
<td>anthophyllite</td>
<td></td>
<td></td>
<td>1 day, 3 months, 6 months, 12 months, 24 months</td>
<td>2, 6, 6, 10, 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>49, 52, 24, 26, 20</td>
<td>crocidolite</td>
<td></td>
<td></td>
<td>1 day, 3 months, 6 months, 12 months, 24 months</td>
<td>2, 14, 4, 18, 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>49, 52, 24, 23, 24</td>
<td>chrysotile (Canadian)</td>
<td></td>
<td></td>
<td>1 day, 3 months, 6 months, 12 months, 24 months</td>
<td>1, 18, 5, 11, 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>49, 52, 25, 27, 20</td>
<td>chrysotile (Rhodesian)</td>
<td></td>
<td></td>
<td>1 day, 3 months, 6 months, 12 months, 24 months</td>
<td>5, 16, 8, 19, 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48, 58, 48</td>
<td>controls</td>
<td></td>
<td></td>
<td>1 day, 3 months, 6-24 months</td>
<td>4, 3, 0</td>
</tr>
</tbody>
</table>

TABLE 3. PATHOLOGICAL EFFECTS OF INHALED ASBESTOS ANIMAL EXPERIMENTAL STUDIES (continued)
<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Experimental Animal</th>
<th>Number of Animals</th>
<th>Type of Asbestos</th>
<th>Amount of Asbestos</th>
<th>Fiber Size</th>
<th>Period of Exposure and Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross 1974</td>
<td>male rats</td>
<td>10</td>
<td>ball-milled chrysotile</td>
<td>5% by weight in mix</td>
<td>not reported</td>
<td>21 months</td>
<td>no lesion in GI tract found by gross examination; no fibers found in sections of intestines examined by electron microscope</td>
</tr>
<tr>
<td>Gross 1974</td>
<td>male rats</td>
<td>10</td>
<td>amosite</td>
<td>10% content in oleomargarine</td>
<td>not reported</td>
<td>2 weeks</td>
<td>total of nine fibers found in the digests of the mesenteric tissue in all rats</td>
</tr>
<tr>
<td>Gross 1974</td>
<td>male rats</td>
<td>10</td>
<td>taconite tailings</td>
<td>20% content in oleomargarine</td>
<td>not reported</td>
<td>5 weeks</td>
<td></td>
</tr>
<tr>
<td>Gross 1974</td>
<td>SPF rats Wistar strain initially 12 weeks old</td>
<td>31</td>
<td>Rhodesian chrysotile</td>
<td>10 mg/week in butter</td>
<td>not reported</td>
<td>fed asbestos butter for 16 weeks, then followed to death</td>
<td></td>
</tr>
<tr>
<td>Gross 1974</td>
<td>SPF rats Wistar strain initially 12 weeks old</td>
<td>33</td>
<td>crocidolite</td>
<td>5 mg/week in butter</td>
<td>not reported</td>
<td>fed asbestos butter for 16 weeks, then followed to death</td>
<td></td>
</tr>
<tr>
<td>Gross 1974</td>
<td>SPF rats Wistar strain initially 12 weeks old</td>
<td>34</td>
<td>crocidolite</td>
<td>10 mg/week in butter</td>
<td>not reported</td>
<td>fed asbestos butter for 16 weeks, then followed to death</td>
<td></td>
</tr>
<tr>
<td>Author and Year</td>
<td>Experimental Animal</td>
<td>Number of Animals</td>
<td>Type of Asbestos</td>
<td>Amount of Asbestos</td>
<td>Fiber Size</td>
<td>Period of Exposure and Follow-up</td>
<td>Results</td>
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<td>---------</td>
</tr>
<tr>
<td>Gross 1974</td>
<td>SPF rats; Wistar strain; initially 12 weeks old</td>
<td>35</td>
<td>North West Cape crocidolite</td>
<td>10 mg/wk in butter</td>
<td>not reported</td>
<td>fed asbestos butter for 18 weeks, then followed to death</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SPF rats; Wistar strain; initially 12 weeks old</td>
<td>28</td>
<td>Transvaal crocidolite</td>
<td>10 mg/wk in butter</td>
<td>not reported</td>
<td>fed asbestos butter for 18 weeks, then followed to death</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SPF rats; Wistar strain; initially 12 weeks old</td>
<td>12</td>
<td>chrysotile</td>
<td>5 mg/gm butter fed ad libitum</td>
<td>not reported</td>
<td>1 or 3 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SPF rats; Wistar strain; initially 12 weeks old</td>
<td>12</td>
<td>crocidolite</td>
<td>5 mg/gm butter fed ad libitum</td>
<td>not reported</td>
<td>1 or 3 months</td>
<td></td>
</tr>
<tr>
<td>Bolton 1976</td>
<td>Male SPF Han rats; initially 10 weeks old</td>
<td>4</td>
<td>crocidolite</td>
<td>250-300 mg in 50-60 g margarine per week</td>
<td>not reported</td>
<td>1 killed at 2 weeks; 1 killed at 3 months; 1 killed at 6 months; 1 killed at 1 year</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male SPF Han rats; initially 10 weeks old</td>
<td>4</td>
<td>amosite</td>
<td>250-300 mg in 50-60 g margarine per week</td>
<td>not reported</td>
<td>1 killed at 2 weeks; 1 killed at 3 months; 1 killed at 6 months; 1 killed at 1 year</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>4</td>
<td>chrysotile</td>
<td>&quot;</td>
<td>not reported</td>
<td>&quot;</td>
<td></td>
</tr>
</tbody>
</table>
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, anthophyllite, 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 mpcf 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 (Klenfield, 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 associa-
tion 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 asbes-
tiform 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
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$^3$ 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>
<thead>
<tr>
<th>Study Author Date</th>
<th>Population</th>
<th>Source of Data</th>
<th>Basis for Expected Deaths</th>
<th>Type of Asbestos</th>
<th>Exposure Level</th>
<th>Period of Exposure &amp; Follow-up</th>
<th>Total No. of Deaths</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doll 1955</td>
<td>Asbestos workers in an English asbestos works</td>
<td>Company Records</td>
<td>England &amp; Wales</td>
<td>Not reported</td>
<td>Not reported</td>
<td>At least 20 years of exposure prior to 1953</td>
<td>39</td>
<td>Cancer of the Lung O/E = 11/ .8 = 13.8 (p&lt;.000001)</td>
</tr>
<tr>
<td>Braun 1958</td>
<td>Asbestos miners in Thetford Mines, Quebec 5,958 Total 4,673 Smokers 1,265 Non-Smok. 20 Unknown</td>
<td>Company Records</td>
<td>Province of Quebec</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Miners on employment rolls in 1950; 5+ years exposure prior to 1950; followed through 1955</td>
<td>187</td>
<td>Cancer of the Lung O/E = 9/6 = 1.5</td>
</tr>
<tr>
<td>Selikoff 1964</td>
<td>New York &amp; New Jersey Insulation workers 632 workers (35 yrs. old in 1943)</td>
<td>Union Records</td>
<td>U.S. White Males</td>
<td>Not reported</td>
<td>Not reported</td>
<td>On Union rolls as of Jan. 1, 1943; at least 20 years exposure before they died; followed through December 31, 1963</td>
<td>255</td>
<td>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</td>
</tr>
<tr>
<td>Kleinfeld 1967</td>
<td>Asbestos insulation workers 152 asbestos workers</td>
<td>Union Records; Death Certif.</td>
<td>U.S. White Males in 1948</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Employed in 1945; Either 15 yrs. exposure prior to 1945 or 15 years exposure between 1945 - 1965; followed through 1965</td>
<td>46</td>
<td>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)</td>
</tr>
<tr>
<td>Study Author Date</td>
<td>Study Source</td>
<td>Population</td>
<td>Basis for Expected Deaths</td>
<td>Type of Asbestos</td>
<td>Exposure Level</td>
<td>Period of Exposure &amp; Follow-up</td>
<td>Total No. of Deaths</td>
<td>Results</td>
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<tr>
<td>Enterline 1967</td>
<td>Social Security Records</td>
<td>U.S. Asbestos building products workers 12,402 white males age 15 - 64</td>
<td>U.S. White Males</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Employed and exposed to asbestos sometime during period 1948 - 1951; followed thru June 30, 1963</td>
<td>840</td>
<td>Cancer of Respiratory System (ICD 160-164) O = 46 SMR=130.4</td>
</tr>
<tr>
<td></td>
<td>Social Security Records</td>
<td>U.S. Asbestos textile products workers 1,843 white males age 15 - 64</td>
<td>U.S. White Males</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Employed and exposed to asbestos sometime during period 1948 - 1951; followed thru June 30, 1963</td>
<td>186</td>
<td>Cancer of Respiratory System (ICD 160-164) O = 14 SMR=228.6</td>
</tr>
<tr>
<td></td>
<td>Social Security Records</td>
<td>U.S. Asbestos friction materials workers 7,510 white males age 15 - 64</td>
<td>U.S. White Males</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Employed and exposed to asbestos sometime during period 1948 - 1951; followed thru June 30, 1963</td>
<td>567</td>
<td>Cancer of Digestive System (ICD 150-159) O = 36 SMR=88.8</td>
</tr>
</tbody>
</table>
TABLE 5. SUMMARY OF THE EPIDEMIOLOGIC STUDIES OF CANCER MORTALITY AMONG EMPLOYEES EXPOSED TO ASBESTOS (continued)

<table>
<thead>
<tr>
<th>Study Author</th>
<th>Population</th>
<th>Source of Data</th>
<th>Basis for Expected Deaths</th>
<th>Type of Asbestos Exposure Level</th>
<th>Period of Exposure &amp; Follow-up</th>
<th>Total No. of Deaths</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mancuso 1967</td>
<td>Asbestos workers</td>
<td>Social Security records</td>
<td>Employees with Level I cumulative employment experience used as internal controls</td>
<td>Not reported</td>
<td>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</td>
<td>361</td>
<td>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 )</td>
</tr>
<tr>
<td>Study Author Date</td>
<td>Study Population</td>
<td>Source of Data</td>
<td>Basis for Expected Deaths</td>
<td>Type of Asbestos</td>
<td>Exposure Level</td>
<td>Period of Exposure &amp; Follow-up</td>
<td>Total No. of Deaths</td>
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</tr>
<tr>
<td>Enterline 1973</td>
<td>533</td>
<td>Industry Records and Death Certificates</td>
<td>U.S. White Males</td>
<td>Not reported</td>
<td>&lt; 125 mppcf - yr</td>
<td>Lifetime employee in asbestos industry; retired in 1941 - 1967 followed thru 1969</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>305</td>
<td>Industry Records and Death Certificates</td>
<td>U.S. White Males</td>
<td>Not reported</td>
<td>125 - 249 mppcf - yr</td>
<td>Lifetime employee in asbestos industry; retired in 1941 - 1967 followed thru 1969</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>328</td>
<td>Industry Records and Death Certificates</td>
<td>U.S. White Males</td>
<td>Not reported</td>
<td>250 - 499 mppcf - yr</td>
<td>Lifetime employee in asbestos industry; retired in 1941 - 1967 followed thru 1969</td>
<td>Not reported</td>
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<tr>
<td>Study Author Date</td>
<td>Population</td>
<td>Source of Data</td>
<td>Basis for Expected Deaths</td>
<td>Type of Asbestos</td>
<td>Exposure Level</td>
<td>Period of Exposure &amp; Follow-up</td>
<td>Total No. of Deaths</td>
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<tr>
<td>Enterline 1973 Cont.</td>
<td>126</td>
<td>Industry Records and Death Records</td>
<td>U.S. White Males</td>
<td>Not reported</td>
<td>500 - 749 mppcf - yr</td>
<td>Lifetime employee in asbestos industry; retired in 1941 - 1967 followed thru 1969</td>
<td>Not reported</td>
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<tr>
<td></td>
<td>56</td>
<td>Industry Records and Death Records</td>
<td>U.S. White Males</td>
<td>Not reported</td>
<td>750 + mppcf - yr</td>
<td>Lifetime employee in asbestos industry; retired in 1941 - 1967 followed thru 1969</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>All = 1,348</td>
<td>Industry Records and Death Records</td>
<td>U.S. White Males</td>
<td>Not reported</td>
<td>ALL</td>
<td>Lifetime employee in asbestos industry; retired in 1941 - 1967 followed thru 1969</td>
<td>754</td>
</tr>
<tr>
<td>Study Author</td>
<td>Date</td>
<td>Population</td>
<td>Source of Data</td>
<td>Basis for Expected Deaths</td>
<td>Type of Asbestos</td>
<td>Exposure &amp; Level</td>
<td>Period of Exposure &amp; Follow-up</td>
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</tbody>
</table>
| Selikoff     | 1973 | New York - New Jersey asbestos insulation workers | 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 thru 1971 | 421 | Cancer of the Lung $O/E = 84/10.1 = 8.3$
|              |      | 623        |                |                          |                 |                 |                               |                     |         |
|              |      |            |                |                          |                 |                 | Cancer of the Stomach, colon, rectum, esophagus $O/E = 41/13.0 = 3.2$ |         |         |
|              |      |            |                |                          |                 |                 | Pleural Mesothelioma $O=8$ |         |         |
|              |      |            |                |                          |                 |                 | Peritoneal Mesothelioma $O=24$ |         |         |
| Selikoff     | 1973 | Entire membership of insulation workers union in U.S. and Canada | 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 $O/E = 213/44.42 = 4.8$
<p>|              |      | 17,800     |                |                          |                 |                 | 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 Mesothelioma $O=4$, Peritoneal Mesothelioma $O=2$ |         |         |</p>
<table>
<thead>
<tr>
<th>Study Author Date</th>
<th>Population</th>
<th>Source of Data</th>
<th>Basis for Expected Deaths</th>
<th>Type of Asbestos</th>
<th>Exposure Level</th>
<th>Period of Exposure &amp; Follow-up</th>
<th>Total No. of Deaths</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knox 1968</td>
<td>Asbestos textile workers in England 57 men</td>
<td>Factory Records</td>
<td>Population of England</td>
<td>Predominantly chrysotile, small amounts of crocidolite</td>
<td>Dust level since 1960 approx. 1-8 particles per c.c. (5-100 μm)</td>
<td>10 or more yrs. of exposure prior to 1933; 20+ years exposure by June 1966</td>
<td>48</td>
<td>Cancer of the Lung or Pleura (ICD 162-163) O/E = 12/1.18 = 10.2 (p &lt; .001)</td>
</tr>
<tr>
<td>63 men</td>
<td>Factory Records</td>
<td>Population of England</td>
<td>Predominantly chrysotile, small amounts of crocidolite</td>
<td>Dust level since 1960 approx. 1-8 particles per c.c. (5-100 μm)</td>
<td>Less than 10 years exposure prior to 1933; 20+ years exposure by June 1966</td>
<td>23</td>
<td>Cancer of the Lung or Pleura (ICD 162-163) O/E = 5/1.57 = 3.2 (p &lt; .05)</td>
<td></td>
</tr>
<tr>
<td>136 men</td>
<td>Factory Records</td>
<td>Population of England</td>
<td>Predominantly chrysotile, small amounts of crocidolite</td>
<td>Dust level since 1960 approx. 1-8 particles per c.c. (5-100 μm)</td>
<td>No exposure before 1933; 20+ years by June 1966</td>
<td>15</td>
<td>Cancer of the Lung or Pleura (ICD 162-163) O/E = 2/1.35 = 1.5 (p &lt; .05)</td>
<td></td>
</tr>
<tr>
<td>538 men</td>
<td>Factory Records</td>
<td>Population of England</td>
<td>Predominantly chrysotile, small amounts of crocidolite</td>
<td>Dust level since 1960 approx. 1-8 particles per c.c. (5-100 μm)</td>
<td>No exposure before 1933; 10 - 19 years by June 1966</td>
<td>54</td>
<td>Cancer of the Lung or Pleura (ICD 162-163) O/E = 6/6.41 = 0.9 (p &gt; .05)</td>
<td></td>
</tr>
<tr>
<td>220 women</td>
<td>Factory Records</td>
<td>Population of England</td>
<td>Predominantly chrysotile, small amounts of crocidolite</td>
<td>Dust level since 1960 approx. 1-8 particles per c.c. (5-100 μm)</td>
<td>No exposure before 1933; 10+ years by June 1966</td>
<td>10</td>
<td>Cancer of the Lung or Pleura (ICD 162-163) O/E = 2/0.24 = 8.3 (p &lt; .05)</td>
<td></td>
</tr>
<tr>
<td>Study Author</td>
<td>Study Date</td>
<td>Population</td>
<td>Source of Data</td>
<td>Basis for Expected Deaths</td>
<td>Type of Asbestos</td>
<td>Exposure Level</td>
<td>Period of Exposure &amp; Follow-up</td>
<td>Total No. of Deaths</td>
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<tr>
<td>Elmes</td>
<td>1971</td>
<td>Total population of insulation workers in Belfast in 1940</td>
<td>Union records</td>
<td>Population of Northern Ireland</td>
<td>amosite, chrysotile &amp; crocidolite</td>
<td>Not reported</td>
<td>Identified as on union rolls in 1940; followed thru 1966; no minimum length of exposure</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>170 men</td>
<td></td>
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TABLE 5. SUMMARY OF THE EPIDEMIOLOGIC STUDIES OF CANCER MORTALITY
AMONG EMPLOYEES EXPOSED TO ASBESTOS (continued)

<table>
<thead>
<tr>
<th>Study Author Date</th>
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<th>Total No. of Deaths</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newhouse 1973</td>
<td>Asbestos textile and insulation workers in England and Wales 6,760 men 922 women</td>
<td>Factory Records Population of England and Wales</td>
<td>Crocidolite, Amosite, Chrysotile Males and females grouped by: 1) &lt; 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</td>
<td>Males and females placed into either low-moderate or severe exposure category</td>
<td>No. of deaths by March 1970 in men = 350 No. of deaths by December 1968 in women = 111</td>
<td></td>
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</tr>
</tbody>
</table>

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 mortality seen after 25+ years of exposure;

Much more marked excess for those who had worked 2+ years with severe exposure

GI Cancer:

Males
\[ \frac{O}{E} = 31/20.35 = 1.5 \] (p<.05)

Females
\[ \frac{O}{E} = 11/7.3 = 1.5 \] (p=.12)
<table>
<thead>
<tr>
<th>Study</th>
<th>Date of Enterline Retired asbestos workers</th>
<th>Population Basis for Exposure Type of Asbestos</th>
<th>Period of Follow-up</th>
<th>No. of Deaths</th>
<th>Total Deaths</th>
<th>Respiratory Cancer (ICD 162) O/E = 39/7.6 = 5.2 SMR = 235.4</th>
<th>Respiratory Cancer (ICD 162) O/E = 163/107 = 1.5 SMR = 176.5</th>
<th>Cancer (ICD 160) 163 O/E = 4/0.9 SMR = 444.4</th>
<th>Cancer (ICD 160) 163 O/E = 5/1.0 SMR = 500.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td>U.S. White Amosite and Crocidolite</td>
<td>Lifetime</td>
<td>Industry Records and Death Certificates Males only</td>
<td>273.4</td>
<td>54</td>
<td>31/1.9 = 5.3 SMR = 250.0</td>
<td>163/10.3 = 16.0 SMR = 210.0</td>
<td>4/0.9 = 4.4 SMR = 444.4</td>
<td>5/1.0 = 5.0 SMR = 500.0</td>
</tr>
<tr>
<td>120</td>
<td>U.S. White Chrysotile and Crocidolite</td>
<td>1973</td>
<td>Industry Records and Death Certificates Males only</td>
<td>206.3</td>
<td>50</td>
<td>10/1.9 = 5.2 SMR = 235.4</td>
<td>163/10.3 = 16.0 SMR = 210.0</td>
<td>4/0.9 = 4.4 SMR = 444.4</td>
<td>5/1.0 = 5.0 SMR = 500.0</td>
</tr>
<tr>
<td>102</td>
<td>U.S. White Amosite</td>
<td>1973</td>
<td>Industry Records and Death Certificates Males only</td>
<td>266.3</td>
<td>59</td>
<td>10/1.9 = 5.2 SMR = 235.4</td>
<td>163/10.3 = 16.0 SMR = 210.0</td>
<td>4/0.9 = 4.4 SMR = 444.4</td>
<td>5/1.0 = 5.0 SMR = 500.0</td>
</tr>
<tr>
<td>1,013</td>
<td>Industry White Chrysotile</td>
<td>1941 - 1967</td>
<td>Industry Records and Death Certificates Males only</td>
<td>330.2</td>
<td>47</td>
<td>3/1.7 = 1.8 SMR = 176.5</td>
<td>163/10.3 = 16.0 SMR = 210.0</td>
<td>4/0.9 = 4.4 SMR = 444.4</td>
<td>5/1.0 = 5.0 SMR = 500.0</td>
</tr>
<tr>
<td>31</td>
<td>Industry White Crocidolite</td>
<td>1941 - 1967</td>
<td>Industry Records and Death Certificates Males only</td>
<td>330.2</td>
<td>47</td>
<td>3/1.7 = 1.8 SMR = 176.5</td>
<td>163/10.3 = 16.0 SMR = 210.0</td>
<td>4/0.9 = 4.4 SMR = 444.4</td>
<td>5/1.0 = 5.0 SMR = 500.0</td>
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<td>47</td>
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<td>4/0.9 = 4.4 SMR = 444.4</td>
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<td>50</td>
<td>Industry White Chrysotile</td>
<td>1941 - 1967</td>
<td>Industry Records and Death Certificates Males only</td>
<td>330.2</td>
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</tr>
<tr>
<td>Selikoff 1972</td>
<td>Eastern U.S. Insulation workers 230 men</td>
<td>Factory Records</td>
<td>U.S. White Males</td>
<td>Amosite</td>
<td>Not Reported</td>
<td>Employment began between June 1941 and December 1945; at least one year of exposure; alive on January 1, 1960; followed through June 30, 1971</td>
<td>105</td>
<td>Cancer of the Lung 0/E = 25/2.4 10.4 Cancer of the lung, pleura, bronchus, trachea 0/E = 27/2.4 11.3 Cancer of the Stomach, Colon or Rectum 0/E = 5/1.6 = 3.1 Pleural Meso-thelioma 0 = Peritoneal Meso-thelioma 0 =</td>
<td></td>
</tr>
<tr>
<td>Selikoff 1973</td>
<td>Eastern U.S. asbestos insulation workers 933 workers</td>
<td>Factory Records</td>
<td>U.S. White Males</td>
<td>Amosite</td>
<td>Not Reported</td>
<td>Employment began between June 1941 and December 1945; at least one day of exposure; followed until June 30, 1971</td>
<td>484</td>
<td>Cancer of the Lung 0/E = 73/11.4 6.4 Cancer of the Stomach 0/E = 11/4.5 = 2.4 Cancer of the Colon, Rectum 0/E = 15/7.0 = 2.1 Cancer of the Esophagus 0/E = 0/1.23 0 Pleural Meso-thelioma 0 = Peritoneal Meso-thelioma 0 =</td>
<td></td>
</tr>
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<th>Total No. Of Deaths</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDonald 1974</td>
<td>Employees of the Quebec asbestos mining industry born between 1891 - 1920, 9,692 males and females</td>
<td>Company Records</td>
<td>Quebec population</td>
<td>Chrysotile</td>
<td>Dust Index (mppcf-years) of exposure; 1) &lt; 10; 2) 10 - 100; 3) 100 - 200; 4) 200 - 400; 5) 400 - 800; 6) 800 +</td>
<td>Variable length period of exposure; 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</td>
<td>3,270</td>
<td>Lung Cancer showed a rising rate with increasing dust exposure; cancer of the G.I. tract showed a rise in the two highest categories; Pleural Mesothe-mioma: 0 = 5 Peritoneal Mesothe-lioma: 0 = none</td>
</tr>
<tr>
<td>Meurman 1974</td>
<td>Finnish asbestos miners, 1,092 males and females</td>
<td>Company Records</td>
<td>Age-sex-matched controls from a township 60 km from the mines and also population of Finland in 1958</td>
<td>Anthophyl-lite</td>
<td>Not reported</td>
<td>First employed in one of two mines between 1936 and 1967; worked and were exposed for at least 3 months; followed through May 1969</td>
<td>248</td>
<td>Cancer of the Lung (ICD 162): 0/E = 21/12.6 = 1 Cancer of the Digestive Organs 0/E = 7/14.9 = 0 No Mesothe-liomas</td>
</tr>
<tr>
<td>Study Author</td>
<td>Date</td>
<td>Population</td>
<td>Source of Data</td>
<td>Basis for Expected Deaths</td>
<td>Type of Asbestos Exposure</td>
<td>Period of Exposure and Follow-up</td>
<td>Total No. of Deaths</td>
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<tr>
<td></td>
<td></td>
<td>101 men</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 1 month reported</td>
<td></td>
<td>O/E = 3.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>101 men</td>
<td></td>
<td></td>
<td></td>
<td>1 month</td>
<td></td>
<td>O/E = 6.15</td>
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<tr>
<td></td>
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<td>165 men</td>
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<td></td>
<td></td>
<td>2 months</td>
<td></td>
<td>O/E = 3.57</td>
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<tr>
<td></td>
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<td>148 men</td>
<td></td>
<td></td>
<td></td>
<td>3-5 months</td>
<td></td>
<td>O/E = 5.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>130 men</td>
<td></td>
<td></td>
<td></td>
<td>6-11 months</td>
<td></td>
<td>O/E = 7.84</td>
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<td></td>
<td>199 men</td>
<td></td>
<td></td>
<td></td>
<td>2+ years</td>
<td></td>
<td>Not reported</td>
</tr>
<tr>
<td>Study Author</td>
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</tr>
<tr>
<td>Gillam 1976</td>
<td>Hard rock gold miners in Lead, South Dakota 439</td>
<td>Social Security Records and the government agencies</td>
<td>General white male population of South Dakota</td>
<td>Ore dust containing non-commercial forms of amosite asbestos in the cummingtonite-grunerite amphibole mineral category</td>
<td>&lt;2.0 fibers/cm³ greater than 5μm in length and also fibers shorter than 5μm in length</td>
<td>Employed in 1960; 60 months of underground mining at that facility prior to 1960; had never mined elsewhere; followed to December 31, 1973</td>
<td>70</td>
<td>Respiratory Cancer O/E = 10/2.7 = 3.7 (p&lt;.01)</td>
</tr>
<tr>
<td>McDonald 1977 abstract</td>
<td>Gold miners in Lead, South Dakota 1,321 men</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Cummingtonite-Not reported grunerite</td>
<td>21 years service with mining company; follow to end of 1973</td>
<td>660</td>
<td>Respiratory Cancer O/E = 17/16.5 = 1.0 Abdominal Cancer O/E = 39/35.1 = 1.1</td>
<td></td>
</tr>
</tbody>
</table>

SMR = Standardized Mortality Ratio \[ \frac{(Observed \, deaths/Expected \, deaths) \times 100} \]
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, \( \frac{O}{E} = 2/5.98 \). 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 mesotheliomatal 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 relation 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

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