6

Health Implications of Exposure to Asbestos

6.1 Asbestos-Related Diseases

Asbestos has probably been used by humans for millenia, but widespread production and manufacture date to the last quarter of the nineteenth century. An early report in 1907 described a case of severe lung fibrosis due to occupational exposure to asbestos. This was followed in the next two decades by more detailed clinical, pathologic, and radiologic descriptions of the disease (Murray 1907; Pancoast et al. 1917; Cooke 1927; Selikoff and Lee 1978). Measures to control occupational exposure date to the early 1930s.

The inhalation of airborne asbestos dust in an occupational setting can produce fibrosis of the lungs and pleura, as well as cancer in the lungs, pleura, peritoneum, and, possibly, at distant sites (Becklake 1976; American Thoracic Society 1986; Mossman and Gee 1989; Roggli 1989).

6.1.1 Asbestosis

Asbestosis refers to diffuse or multifocal interstitial fibrosis (scarring) in the lungs caused by the inhalation of asbestos fibers (Craighead et al. 1982; American Thoracic Society 1986; Mossman and Gee 1989). Inhaled asbestos fibers that penetrate the lung to the peripheral air spaces initiate an inflammatory response or alveolitis (Begin et al. 1986; Robinson et al. 1986). This inflammatory damage, if chronic, results in the development of scarring and fibrosis. The inflammation-fibrosis response in the lungs can be progressive, eventually destroying the lung's architecture and impairing its function, or it may arrest at various stages in its development (Becklake 1991a). The extent of lung inflammation and destruction is related to the amount of asbestos retained in the lungs, the fiber type and length, and individual susceptibility (Begin et al. 1986; Becklake 1991a). Some evidence suggests that more retained asbestos is required to produce asbestosis than to produce asbestos pleural plaques (Whitwell et al. 1977).

All forms of asbestos may cause lung fibrosis (Becklake 1991a) and there is some evidence to suggest that amphiboles are more potent than chrysotile in causing asbestosis (Mossman and Gee 1989; Becklake 1991a). It is also likely that an appreciable amount of asbestos must be retained to cause clinically detectable asbestosis. There is, therefore, likely to be a level below which fibrosis will not occur, or will be insignificant (Doll and Peto 1985).

The clinical presentation of asbestosis is nonspecific (American Thoracic Society 1986; Mossman and Gee 1989; Becklake 1991a); the most frequent symptom is shortness of breath, initially on exertion, but sometimes progressing to breathlessness at rest. A persistent cough, dry or productive of sputum, is common, even in nonsmokers. On physical examination, fine crackles may be heard posteriorly at the lung bases and in the axillae. They tend not to clear with coughing. Clubbing of the fingers is uncommon.

The radiologic appearance of asbestosis is of irregular linear opacities predominantly in the lower lobes. Pleural thickening or pleural plaques frequently coexist with the pulmonary fibrosis. Abnormality of lung function may precede radiographic abnormalities of asbestosis (Becklake 1976). Asbestos bodies (coated asbestos fibers) may be found in the patient's sputum or bronchoalveolar lavage fluid. They indicate exposure to asbestos but are not necessarily indicative of asbestosis. Pathologic asbestosis can be present with a normal chest radiograph and normal computed tomographic scan (Akira et al. 1991), but it is unlikely that the subject will have significant functional impairment or symptoms. Radiographic changes (Gamsu et al. 1989) and abnormalities of pulmonary function (Becklake 1991a) may precede symptoms and, less commonly, physical findings.

Although microscopic areas of lung fibrosis are almost always present in asbestos-exposed individuals with lung cancer, the extent to which lung fibrosis is associated with cancer remains controversial. However, since both asbestosis and asbestos-related lung cancer are more frequent with heavy exposure, they tend to occur in the same individuals (McDonald and McDonald 1987b; Wagner et al. 1988). The International Agency for Research on Cancer (IARC) recognizes asbestos as a human carcinogen (IARC 1982).

6.1.2 Pleural Diseases

The pleural diseases produced by inhaled asbestos fibers (Stephens et al. 1987; Jones et al. 1988a; Schwartz 1991) are as follows (see also Appendix 2, Nonmalignant Asbestos-Related Pleural Conditions):

1. *Fibrotic pleural plaques.* These are focal areas of hyaline fibrous thickening of the parietal and, less commonly, the visceral pleura. All types of asbestos can cause pleural plaques. Pleural plaques usually occur after a long latent period of more than 15 years. Their prevalence increases with latency (time from initial exposure) and dose (quantity of fibers inhaled × number of years of exposure). Pleural plaques can impair lung function, probably in proportion to the extent of pleural surface involved (Bourbeau et al 1990; Schwartz et al. 1990; Schwartz 1991), and also can cause respiratory symptoms (Bourbeau et al 1990; Ernst and Zejda 1991; Schwartz 1991). Pleural plaques also are associated with a higher incidence of lung fibrosis, and this can impair lung function (Staples et al. 1989; Schwartz 1991). Asbestos-related pleural plaques calcify in a small percentage of instances, making them more easily detected on radiographs and computed tomographic scans. Plaques are not thought to have malignant potential, but are related to asbestos exposure.

2. *Asbestos-related pleuritis.* Subacute exudative pleuritis, which is frequently symptomatic, has been described in about 5 percent of occupationally exposed asbestos workers (Gaensler and Kaplan 1971; Hillerdal and Özesmi 1987; Stephens et al. 1987). The condition is usually found in younger individuals within 7 to 15 years of the first exposure. These effusions invariably resolve but can result in an adhesive fibrothorax with severe impairment in lung function (Bourbeau et al. 1990).

3. *Diffuse pleural thickening.* Diffuse fibrosis of the pleura can result from the following (Hillerdal and Özesmi 1987; Schwartz 1991): (1) confluent pleural plaques; (2) extension of lung fibrosis to the subvisceral pleural interstitium (Stephens et al. 1987); (3) adhesive fibrothorax from pleuritis (McLoud et al. 1985).

   Pseudo pleural thickening from normal extrapleural fat can be difficult to distinguish on chest radiographs from true pleural thickening (Sargent et al. 1984).

6.1.3 Carcinoma of the Lung

An increased incidence of several neoplasms has been found in individuals occupationally exposed to asbestos. The most common is bronchogenic carcinoma or lung cancer (Saracci 1977; Selikoff and Lee 1978; Warnock and Isenberg 1986; McDonald and McDonald 1987b; Sébastien et al. 1989). These tumors are histologically indistinguishable from those caused by other agents such as cigarette smoke or radon decay products. Over the past 30 years, epidemiologic studies have confirmed an association between asbestos exposure and lung cancer, even in nonsmokers (Doll and Peto 1985; McDonald and McDonald 1987b). This association is considered causal, although the rates in various studies have differed (Doll and Peto 1985). The latency period for the development of lung cancer is measured in

years, and the risks tend to be greater for those with higher asbestos exposure (Doll and Peto 1985; McDonald and McDonald 1987b). A more-than-additive risk of lung cancer may result from exposure to asbestos in combination with cigarette smoke (McDonald and McDonald 1987b).

6.1.4 Pleural and Peritoneal Mesothelioma

Mesothelioma is a rare cancer of the mesothelial cells lining body cavities, including the pleural and peritoneal cavities, and is the classic tumor associated with asbestos exposure (Doll and Peto 1985; McDonald and McDonald 1987a) (see section 6.2.3, Time Trends in Mesothelioma Incidence). Pleural mesothelioma is approximately five times more common than peritoneal mesothelioma, except in a few occupationally exposed cohorts. The latency for the development of mesothelioma is usually 20 to 40 years or more from the time of initial exposure, even though instances of a shorter lapse time have been described. The annual incidence of mesothelioma in the United States is 1,500 to 2,500 new cases (see section 6.2.3, Time Trends in Mesothelioma Incidence). Most cases are associated with industrial asbestos exposure, either in an occupational setting or through household contact with an asbestos worker (McDonald and McDonald 1987a). In 10 to 30 percent of cases (McDonald and McDonald 1977), however, no asbestos exposure can be ascertained. Whether these cases are related to occult asbestos or other agents, or constitute the background incidence of the disease, remains uncertain. The risk of mesothelioma increases with increasing cumulative exposure. All asbestos fiber types have been implicated as a cause of mesothelioma, with the risk being greatest for crocidolite (McDonald and McDonald 1977; Doll and Peto 1985).

The pleural tumor usually originates in microscopic form as a small nodule that exfoliates at an early stage, causing seeding of the pleural cavity. The nodules then increase in size until both pleural surfaces are diffusely involved. The tumor can invade the chest wall and the lung, as well as spread by the lymphatic system and by a hematogenous route to other parts of the body in general (Craighead et al. 1982; Hillerdal 1983).

For a discussion of the history of mesothelioma, see Appendix 2.

6.1.5 Other Cancers

Tumors of the larynx, oropharynx, and upper and lower digestive tract have been reported to be increased in frequency in some cohorts of workers occupationally exposed to asbestos, although not in others (Doll and Peto 1987; Hillerdal 1983). The excess risks of these tumors have been small, and asbestos exposure for the general population is unlikely to contribute significantly to cancers at these sites.

6.1.6 Benign Lung Masses

Benign lung masses that can simulate neoplasm are found in up to 10 percent of workers occupationally exposed to asbestos (Lynch et al. 1988; Hillerdal 1989). Most consist of rounded atelectasis, a term that describes a mass of focal inflammation and infolding of the lung found with the adhesive fibrothorax of asbestos exposure. Other less extensive focal lung masses may also be found. These frequently occur in lobes containing lung scars, often with restriction of lung function. The masses may be mistaken for lung cancers and may require careful evaluation to exclude a neoplasm. Rounded atelectasis and other benign fibrous masses are unusual in workers who have not had prolonged exposure to asbestos.

6.1.7 Disease from Low Level Exposure

All the preceding diseases have been described in association with occupational exposure to asbestos. Past levels of airborne contamination were, on the whole, much greater than current workplace levels and standards (Nicholson et al. 1982). Exposures of this magnitude are not likely to occur in buildings under normal use, nor are they likely to occur in activities related to correct maintenance and removal of asbestos-containing materials (ACM). Some workers in maintenance and remediation, however, may be exposed to appreciably higher levels of airborne asbestos, equivalent to those that caused disease in previous circumstances.

However, mesothelioma (McDonald and McDonald 1977), pleural abnormalities including pleural plaques, and possibly a low profusion of small irregular opacities on the chest radiograph (Anderson et al. 1979), and asbestosis have all been described in household members of asbestos workers. Presumably, levels of exposure in households are lower than those in the workplace, though measurements are not available documenting such levels (a limited number of measurements have been reported for workplace changing rooms [see Langer and Nolan 1989a]).

The frequency and severity of disease that can be anticipated from much lower levels of exposure to asbestos are difficult to predict; such evidence as exists is reviewed in the following sections, and in Appendix 2, of this report. Recent reports of pleural plaques in school custodians are also reviewed in Appendix 2.

6.2 Exposure-Risk Relationships: Human Data

6.2.1 Tissue Burden Studies

The analysis of lung tissues for the presence of minerals suspected to cause disease has been carried out for more than a century. The earliest such studies focused on mineral dusts in the lung parenchyma and lesions associated with its presence. Crystalline silica and silicate minerals were among the first agents studied (Langer 1978). Mineral types, their amounts and character became important parameters in the evaluation of the nature of the agents responsible for production of the pneumoconioses. Protocols for tissue preparation were developed, as were analytical methodologies for dust analysis (Berkley et al. 1965, 1967; Langer et al. 1973). It was discovered that, depending on the dust type and its concentration in the lung, the techniques and instruments used for analysis necessarily ranged in sensitivity and specificity (Langer et al. 1973). Asbestos fiber analysis was difficult, especially for chrysotile (Beger 1933; Beattie and Knox 1961; Nagelschmidt 1965).

Regardless of the difficulties involved in tissue analysis, asbestos fiber type and character (for example, dimensions), the asbestos body, and asbestos concentration have been the focus of many studies for the past 70 years or more.

6.2.1.1 Asbestos Bodies: Optical Microscopy

The study of asbestos in the human host focused at first on the asbestos body, an iron-protein-coated asbestos fiber found with great frequency in the lungs of most asbestos-exposed workers. The instrumentation used for this assay was one of several forms of light microscopy, either bright field or phase contrast microscopy, and the bodies were enumerated in sputum, lung smears, lung scrapes, chemically digested bulk tissues, and

various physically and chemically modified tissue sections (see the review of Langer et al. 1973). Study designs, materials available, analytical protocols, and study populations were so variable that the resulting data sets were difficult, if not impossible, to compare. However, the general conclusions appeared to be similar: the more asbestos bodies found in these preparations, the more the worker's exposure to fiber-containing dusts. The asbestos body became an index of asbestos exposure. Its presence in scarred pulmonary tissues is required for the pathologic diagnosis of asbestosis today.

Various attempts were made to quantify the asbestos body burden. In 1967, Gold described a method by which asbestos bodies could be extracted from a known weight of lung tissue and quantified in a manner similar to the assessment of cell types in cerebrospinal fluid. Lung tissue was first dissolved in hot 40 percent potassium hydroxide, followed by several washings and centrifugation of the residue. This process, however, led to considerable loss of fiber on the glassware. The method was modified by Ashcroft and Heppleston (1973) and is still being used extensively in the estimation of lung fiber burden (Oldham 1973; Langer et al. 1971b; Whitwell et al. 1977; Case et al. 1988). Many laboratories have developed their own preparation techniques and analytical strategies.

Thomson and associates (1963) observed the presence of asbestos bodies in the lungs of 125 of 500 persons with no known exposure to asbestos, who came to autopsy in Cape Town, South Africa. Similar studies soon followed, each using the asbestos body as an exposure index and each seeking some information on the possible spread of asbestos exposure among persons in the general population, such as Oldham (1973), Selikoff and Hammond (1970), and Langer and coworkers (1971a).

The issue was then raised concerning the specificity of the asbestos body (see review in Langer et al. 1972a). Was this object a useful index of asbestos exposure, or was the body nucleated on many forms of mineral dust, not necessarily asbestos? Analysis of cores of asbestos bodies followed. It was found that workers exposed to the amphibole asbestos minerals had bodies which were nucleated on fibers specific for their exposures; that is, amosite workers had amosite bodies, etc. Analysis of bodies obtained from the lungs of persons in the general population tended to show what was then interpreted as altered chrysotile. In retrospect, these fibrous cores could have been called "other minerals," including nonasbestos fibers (Langer et al. 1970, 1972a, 1972b). The asbestos body was generally regarded as a useful exposure index, but had significant shortcomings due to its lack of specificity. Focus shifted back to the presence of uncoated fibers in lung tissue.

6.2.1.2 Uncoated Fibers: Optical Microscopy

Uncoated fibers in tissue have been studied by optical microscopy as well (for example, Beger 1933; Sundius and Bygden 1938; Beattie and Knox 1961; Berkley et al. 1965). However, the light microscope proved to be both limited in resolution and nondiagnostic in most cases; that is, the fiber's identity could not be ascertained (Berkley et al. 1965, 1967). Uncoated fibers were noted to occur with asbestos bodies, but again, their importance was decreased by the lack of definitive identification (Langer et al. 1971a).

6.2.1.3 Dust in Lungs: Bulk Techniques

By the late 1960s to early 1970s, the analysis of mineral burden in lungs involved bulk tissues (frequently whole lungs), a range of tissue digestion and residue recovery techniques, and the use of instruments designed specifically for the characterization of mineral powders. The bulk powder techniques and analytical protocols proved to have significant shortcomings, especially for asbestos. The fiber population recovered tended to

be of very small particle size, which confounded even the best of the bulk dust techniques, such as x-ray diffraction analysis. These same problems existed for other bulk techniques, such as infrared spectroscopy, differential thermal analysis, and mass spectroscopy. A major obstacle was that the various techniques used to destroy pulmonary tissues in order to recover particles were so harsh that the likelihood of the successful recovery of an entire population of particles was small. These techniques were reviewed in detail by Langer and colleagues (1973).

6.2.1.4 Electron Beam Techniques

The use of transmission electron microscopy as a means of visualizing and characterizing asbestos fibers recovered from human tissues was first reported by Kühn (1941).

In the late 1960s, several groups laid the foundation for the use of beam techniques for analysis of single, submicroscopic particles recovered from human tissues. Using morphology, structure (as provided by selected area electron diffraction analysis), and chemistry (by a probe technique, at first by crystal spectrometry, and later by energy dispersive spectroscopy), single fibers isolated from pulmonary tissues could be identified and characterized. The specific diagnostics required for the unequivocal identification of a single fiber were put forward by Langer and Pooley (1973). The electron beam technique permitted resolution of even the finest asbestos fibrils.

6.2.1.5 Distribution of Fiber in the Lung and Pleura

There is no agreement on the distribution of asbestos fibers in lung tissue. Asbestos bodies were described by Thomson and colleagues (1963) as being most frequently found at the base of the lower lobes. This has not been confirmed when asbestos fibers have been quantified from various sites in the lungs (Bossard et al. 1980). In fact, there has been considerable variation in adjoining blocks of tissue taken from the same lobe. Therefore, it is considered that tissue should be taken from a number of specific regions, and that these should be used for all investigations. Initial recommendations were made by the Pathology Working Group, International Union Against Cancer (UICC) (1965).

Only a few studies of asbestos dust in the pleura have been reported (Le Bouffant 1974; Sébastien et al. 1979; Dodson et al. 1990). These authors have found short chrysotile fibers and fibrils in pleural tissue. However, virtually all inorganic dust drifts to the pleura, and it is unlikely that chrysotile alone migrates preferentially to the site.

In conjunction with transmission electron microscopy (TEM), the size and number of individual fibers found in the lungs of animals suggest that both pulmonary fibrosis and carcinoma of the lung are associated with long fibers. Most workers consider that the development of mesotheliomas is associated with fibers of more than 8.0 μm in length and less than 0.25 μm in diameter (long and thin) (Pott 1978; Stanton et al. 1981). Unusual surface properties and fiber type may modify this specific size and dimension requirement (Langer and Nolan 1986).

In humans, one of the earlier findings, which was well-illustrated in the combined studies of Sébastien and Pooley, was that numerous fibers other than the commercial forms of asbestos were present in lungs (Gaudichet et al. 1980). The other finding was that all adult human lungs so far examined contained mineral fibers. These findings underscored two problems: (1) which fibers of a specific type had to be present to cause a specific disease, and (2) how many fibers of a specific type had to be present to cause that disease (Wagner 1986). These two questions have led to considerable debate.

Epidemiologic data suggest that all types of asbestos, provided that sufficient fibers are inhaled, can cause asbestosis, and the greater the amount of fiber inhaled, the more severe the disease. This also applies to the risk of carcinoma of the lung, especially in smokers (Selikoff et al. 1968). Difficulties arose concerning the amounts of chrysotile, and amphibole, required for the production of mesothelioma. If tissue burden data were calculated on fiber number, then there was far more chrysotile present in the lung than amphibole; however, on mass calculation, based on the same population, the amount of chrysotile was far less (Pooley and Mitha 1986). A difficulty in using chrysotile number data was that chrysotile fiber bundles tend to break up by longitudinal splitting into unit fibrils. It has been calculated that about 100 fibrils of chrysotile are the mass equivalent of one average amphibole fiber (approximately 0.3 μm diameter) (Pooley and Mitha 1986).

One final difficulty lies in the question of whether it is necessary for the fibers to be retained to cause fibrosis and carcinoma of the lung. One group of investigators states that long-term retention and fiber durability are required for these processes (Pooley and Mitha 1986; Wagner 1986; for review see Mossman et al. 1990). Another opinion is that the presence of the fiber in the lung for a short period is sufficient, so that although chrysotile is rapidly cleared from the lung, or solubilized in the lung, its presence is sufficient during this short period to initiate cell-mediated processes of either fibrosis or transformation (see discussion in Langer et al. 1978; Nicholson et al. 1982; Nicholson 1989). Although the chrysotile concentrations appear to level off, indicating an "equilibrium" between deposition and removal, the (more durable) amphibole asbestos fibers appear to accumulate in lung tissue with exposure. There is thus a greater retention of amphibole asbestos fiber than chrysotile in the human lung.

6.2.1.6 Importance of Tissue Burden Studies

It has been stated that parenchymal burden is a poor indicator of the mineral agent in the asbestos-induced diseases. However, much information continues to be derived from these studies:

1. Asbestos fibers found in lungs of most U.S. workers tend to be mixtures of mineral fibers rather than predominantly one type (Langer and Nolan 1989b). This is surprising because almost 95 percent of the total fiber consumed commercially in the United States during the past seven to eight decades has been chrysotile. Commercial consumption data are not indicative of exposure in the workplace, especially insofar as insulation workers and shipyard workers are concerned.

2. Amphibole asbestos fibers tend to occur with greater frequency and concentration in the lungs of persons who have died from mesothelioma as compared to their workmates who have died of other causes. This has been observed for populations studied at the friction product manufacturing facility in Ferodo, and for textile workers in Rochdale, U.K. In both sites, more crocidolite is found in the pulmonary tissues of workers dying with mesothelioma than in workers dying of other causes at the same plant (Wagner et al. 1982). The same is observed among U.S. insulation workers exposed to products that were primarily chrysotile. Amphibole asbestos is found with greater frequency in their pulmonary tissues (Langer and Nolan 1989b). Persons who died with malignant mesothelioma displayed high concentrations of amphibole asbestos as compared to control populations in the United Kingdom (Gibbs et al. 1989).

3. Tissue burden studies have enabled investigators to identify both the agents and their sources in the etiology of suspected asbestos-induced diseases. The occurrence of pleural plaques and mesothelioma in northwest Greece were shown to be related to exposure

to tremolite asbestos present in whitewash (stucco) (Constantopoulos et al. 1985; Langer et al. 1987). Mesothelioma among persons in eastern Turkey was attributed to exposure to tremolite asbestos, also present as a component of stucco (Yazicioglu et al. 1980). The occurrence of mesothelioma has been reported among persons on Cyprus exposed to tremolite and actinolite asbestos, an agent present in their environment (Pooley and Clark 1979; McConnochie et al. 1989).

4. Wagner and coworkers (1988) reported that the quantities of asbestos fiber present in workers dying with asbestosis were much greater than the levels of fiber found in their workmates dying with mesothelioma. Those with lung cancer had moderate to severe asbestosis, and both mesothelioma and lung cancer were associated with amphibole asbestos varieties rather than chrysotile. Tissue burden studies have expanded both the database and the understanding of the asbestos diseases.

6.2.1.7 Studies of Persons with No Reported Exposures to Asbestos Fibers

The question concerning asbestos exposure among persons in the general population was raised by Thomson and associates in 1963. As discussed above, they reported that 25 percent of 500 persons who died in Cape Town, South Africa, with no known occupational exposure to the mineral, had what appeared to be asbestos bodies present in their pulmonary tissues at the time of death.

The use of the asbestos body as an index of asbestos exposure was accepted, with limited reservations, and many similar studies soon followed in other parts of the world (for review, see Langer et al. 1973). The largest of these involved analysis, by light microscopy, of 3,000 consecutive autopsies among three affiliate institutions in New York City (Selikoff and Hammond 1970; Langer et al. 1971a). The random population proffered by these institutions, which represented diverse social and economic strata of society, contained the spectrum of potential exposures to asbestos: from insulation workers to "never-worked" housewives. The times of their death spanned 1966 to 1968.

Langer and colleagues (1971a) observed that about 45 percent of the 3,000 cases had asbestos bodies present in their lungs at death. However, these increased in both prevalence and number with gender (male greater than female) and age; occupation appeared to be a major factor as well. A secondary study, based on 300 selected cases among the population, demonstrated that occupation strongly affected outcome: Trades that handled asbestos directly were associated with the highest concentrations of asbestos bodies, followed by trades whose workers were employed in the same environment as "asbestos workers" (such as electricians in shipyards). Members of professional "white-collar" trades, such as lawyers and office workers, had levels of asbestos bodies indistinguishable from those found in housewives (Langer et al. 1979).

The shortcomings associated with this type of analysis have been recognized. Asbestos bodies are only a gross index of exposure. Most fibers, especially those found in the lungs of persons in the general population, are of sizes beyond the resolution of the instrument used.

A recent case report, which presented a tissue burden study of an individual who died with mesothelioma, concluded that the fibers found in the tissues were amosite. The individual's only known asbestos source was that from asbestos-containing products in the building where she worked (Stein et al. 1989). However, the published TEM and analytical data were found to be inconsistent for the asbestos materials in the building, bringing into question the conclusions of the study (Langer and Nolan 1990).

6.2.2 Exposure-Response Relationships for Lung Cancer and Mesothelioma

The health hazards caused by asbestos at the levels commonly encountered in buildings by the general public cannot be observed directly. The available data suggest that the cancer risk is roughly proportional to the level of exposure. Historically, asbestos workers were very heavily exposed, and average levels of asbestos often exceeded 10 f/mL. Cohort studies of such workers suggest that those who worked for 10 to 20 years at exposure levels on the order of 10 f/mL have suffered lifetime excess risks of about 1 in 10 for lung cancer and 1 in 20 or less for mesothelioma.

Mean airborne asbestos fiber levels in public and commercial buildings with ACM that have recently been sampled rarely exceed 0.001 f/mL with an overall average of about 0.0002 f/mL, which is on the order of 50,000 times lower than industrial exposure levels of the past. Attempts to estimate the risks that may be associated with such low exposure levels have been based on mathematical analyses of dose-response relationships derived from historically exposed cohorts of asbestos workers. Mathematical models relating cancer risk to age, level of asbestos exposure, and duration of exposure are needed to justify and refine such calculations, but unless the underlying assumptions are grossly wrong, the risks are unlikely to be large enough to be actually observed and measured. The scientific basis for such models is therefore essential to an assessment of the problem, and this section is devoted to this important issue.

The four major uncertainties underlying the calculations are:

1. The differential effects of different types of asbestos, particularly chrysotile as compared to amphibole varieties (amosite and crocidolite).

2. The untestable assumption that risk is proportional to exposure at levels 100,000 times lower than those that have been studied epidemiologically.

3. The inadequacy of the exposure data for all industrial cohorts so far studied.

4. The assumption that the concentration of fibers longer than 5 μm is an appropriate measure of risk.

The evidence relating to the first of these, and particularly whether or not chrysotile is much less dangerous than other types of asbestos, is contentious. This ambiguity may be of minor importance in framing public policy; however, since many buildings contain a mixture of asbestos types, with the result that the possibility that the overall risk assessment presented in this Report may overestimate the effects of pure chrysotile is likely to be of limited practical relevance.

The majority of published dose-specific estimates of the cancer risk caused by asbestos exposure have been based on the following statistical models:

1. The increase in relative risk of lung cancer is proportional to cumulative asbestos exposure, and the effects of asbestos and cigarette smoking multiply each other.

2. The increase in mesothelioma incidence caused by each brief period of exposure is proportional to the amount of that incremental exposure (exposure level × duration) and to a power of time since it occurred, independent of age or history of smoking. The power of time is approximately 2 or 3. This implies that incidence rises as the 3rd or 4th power of time since first exposure following prolonged exposure.

These or similar risk assessment models have been used in various Government-sponsored reports, including those of the U.S. Environmental Protection Agency (EPA) (Nicholson 1986), the National Research Council (NRC 1984), and the U.S. Consumer Product Safety Commission (CPSC 1983) in the United States; the U.K. Health and Safety Commission (HSC) (Doll and Peto 1985), in the United Kingdom, and the Ontario Royal Commission (1984) in Canada. Dose-specific risk estimates differ substantially between cohorts, but for each cohort the results of analyses by different groups and authors are similar (see Table 6-1).

Table 6-1. Comparison of Lung Cancer Risks Estimated by Various Groups or Individuals from Studies of Asbestos-Exposed Workers[a]

	Percent Increase in Lung Cancer Per f-y/mL of Exposure ($100 \times K_L$)				
Study	EPA[b]	CPSC[c]	NRC[d]	Ontario Royal Commission[e]	HSC[f]
Dement et al. (1983b)	2.8	2.3	5.3	4.2	
McDonald et al. (1983a)	2.5				1.25
Peto et al. (1985)[g]	1.1	1.0	0.8	1.0	0.54
McDonald et al. (1983b)	1.4				
Berry and Newhouse (1983)	0.058	0.06		0.058	
McDonald et al. (1984)	0.010				
McDonald et al. (1980)	0.06	0.06	0.06	0.020 – 0.046	
Nicholson et al. (1979)	0.17	0.12	0.15		
Rubino et al. (1979)	0.075	0.17			
Seidman (1984)	4.3	6.8[h]	9.1[h]		
Selikoff et al. (1979)	0.75	1.0	1.7	1.0	
Henderson and Enterline (1979)	0.49	0.50	0.3	0.069	
Weill et al. (1979)	0.53	0.31			
Finkelstein (1983)	6.7	4.8		4.2[i]	
Newhouse and Berry (1979)					
Males			1.3		
Females			8.4		
Values used for risk extrapolation	1.0	0.3 – 3.0	2.0	0.02 – 4.2	1.0

[a] Adapted from Nicholson (1986).

[b] U.S. Environmental Protection Agency (Nicholson 1986).

[c] U.S. Consumer Product Safety Commission (1983).

[d] National Research Council (1984).

[e] Ontario Royal Commission (1984).

[f] U.K. Health and Safety Commission (Doll and Peto 1985).

[g] Earlier reviews cited Peto (1978) or Peto (1980), and some noted that all men employed after 1951 suffered a higher dose-specific risk ($100 \times K_L = 1.5$).

[h] Data from Seidman and colleagues (1979).

[i] Unpublished data supplied to the Commission.

6.2.2.1 Lung Cancer

Dose-Response Model for Lung Cancer

The lung cancer model outlined above implies that the incidence (or standard mortality ratio [SMR]) for lung cancer following asbestos exposure is given by the formula:

$$I_L(a,y,d,f) = I_U(a,y) \times (1 + K_L \cdot f \cdot d) \quad (6.1)$$

or, equivalently, by

$$SMR = I_L/I_U = 1 + K_L \cdot f \cdot d \quad (6.2)$$

$I_L(a,y,d,f)$ denotes lung cancer incidence in a population of age a, in calendar period y, following asbestos exposure of duration d at an average exposure level f (measured in fibers or particles per unit volume of air).

$I_U(a,y)$ is the age-specific and calendar-year-specific lung cancer rate in an unexposed population with similar smoking habits. K_L is the proportional increase in lung cancer risk per unit cumulative dose. Thus, for example, a value of K_L of 0.01 per f/mL-year would imply that the lung cancer risk is doubled at a cumulative dose of 100 f/mL-years. It is assumed that K_L is independent of age and duration of exposure, and is the same for smokers and nonsmokers. K_L is thus a constant that reflects the carcinogenic potency of the asbestos. In practice the model is usually applied to lung cancer mortality rather than incidence.

The cumulative exposure, $f \cdot d$, is sometimes calculated allowing a lapse of 5 or 10 years, to allow for the delay between appearance of malignancy and diagnosis or death. The equation can be fitted in three different ways:

1. Using individual exposure estimates for each individual in a prospective study.

2. Using exposure estimates for lung cancer cases and matched controls. The relative risk (RR) rather than the SMR is then modeled.

3. Relating the average cumulative exposure of the whole cohort to the overall SMR.

Cigarette Smoking

The lung cancer model implies that the effects of cigarette smoking and asbestos on lung cancer risk are multiplicative. This would mean that the smoking-specific relative risk for asbestos exposure is the same in smokers and nonsmokers, so an exposure which doubles the rate among smokers (from a lifetime risk of about 1 in 10 to 1 in 5) will also double the rate among nonsmokers (from about 1 in 200 to 1 in 100). It is not known whether this is exactly true, as lung cancer is so rare among nonsmokers, even after quite heavy asbestos exposure, that their risk cannot be estimated precisely. The pooled data from published studies suggest that the smoking-specific relative risk due to asbestos exposure for nonsmokers is approximately twice that among smokers (Berry et al. 1985). These authors also noted, however, that this difference could be due entirely to misclassification of 1 percent to 2 percent of current or exsmokers as lifelong nonsmokers. The difference, if any, is of little practical importance, as the lung cancer risk is certainly low in nonsmokers, among whom mesothelioma is the major cause for concern, particularly when asbestos exposure begins at an early age.

In fitting equations 6.1 and 6.2, the most appropriate local or national rates should be used to estimate I_U, the rate in unexposed workers. To the extent that the workers' smoking habits differ from those of the community whose rates are used, the calculated SMRs will

be incorrect. This, however, is not likely to lead to errors in excess of 30 percent (Asp 1984; Axelson 1989). For example, correction for actual smoking rates among insulators decreased the calculated lung cancer SMR by only 10 to 20 percent (Nicholson 1986). In studies in which the relative risk of lung cancer exceeds 2.0, the absence of detailed smoking habits is of limited importance. Nevertheless, some authors have preferred to calculate relative risks, using controls from within a cohort, rather than SMRs, or to present both analyses.

Cohorts That Have Been Used to Calculate Dose-Specific Lung Cancer Risks

National reviews have varied in their selection of cohorts to use for deriving dose-specific lung cancer risk estimates. They range from the EPA review (Nicholson 1986), which presents risk estimates for all studies for which any exposure estimates were available, to the British HSC review (Doll and Peto 1985), which reviews only the three cohorts with individual employment records for which extensive measurements were available for the 1950s or earlier (the chrysotile textile factories in Rochdale, U.K., and in South Carolina, and the Quebec chrysotile miners and millers). The risk estimates derived by the various reviews from the studies then available are summarized in Table 6-1 (more recent reports on some of these cohorts are shown in Table 6-5). These include two cohorts with revised populations and exposure data and a longer follow-up.

1. An asbestos cement workers' study (Weill et al. 1979) has been updated in Hughes and associates (1987), which also includes a review of more recent evidence on asbestos cement workers.

2. The chrysotile textile cohort studied by Peto (1980), which has been enlarged and updated by Peto and associates (1985), includes methodological details of exposure estimation and dose-response modeling.

3. Three other dose-response studies, shown in Table 6-1, have also been updated: a friction product cohort study (Berry and Newhouse 1983), updated by Newhouse and Sullivan (1989); a mixed product manufacture study (Newhouse and Berry 1979), updated in Newhouse and coworkers (1985); and a chrysotile miners and millers study (Rubino et al. 1979), updated by Piolatto and colleagues (1990). In general, these updated and revised analyses have given similar results to those shown in Table 6-1.

4. The only qualitative addition to the evidence on dose-response that was available in 1984 is the update of the Australian crocidolite miners study (Armstrong et al. 1988; de Klerk et al. 1989), for which no exposure data were previously published. The surprising conclusion that their dose-specific lung cancer risk is similar to that of workers exposed to other types of asbestos is discussed under *Dose-Response Relationship for Amphiboles* in section 6.2.2.4, Risk Assessment.

The risk estimates, K_L, shown in Table 6-1, are subject to several substantial errors. The most important are statistical (Poisson) variations in numbers of lung cancer deaths and measurements of particles (subsequently converted to fibers) as an index of carcinogenicity. The risk estimates derived from different studies differ by two orders of magnitude, and it is not clear how much of this variation can be attributed to these sources of error. Further possible reasons for the observed heterogeneity include errors in the model, differences in fiber type and dimensions, random or systematic inaccuracies in exposure measurements, and the use of inappropriate lung cancer rates in calculating SMRs. Figure 6-1 summarizes the conclusions of the only review that has attempted a formal analysis of this variation between different studies. In the EPA report, Nicholson (1986) presented explicit confidence limits for each estimate of K_L, taking account of statistical variation (vertical bars in Figure

6-1) and assuming twofold (and in some cases greater) uncertainty in exposure estimates (vertical lines in Figure 6-1). For some cohorts, adjustments were also made for suspected biases, particularly the use of inappropriate lung cancer rates. Excluding the substantially lower risks per unit exposure observed for chrysotile mining and milling, this analysis gave an inverse variance-weighted geometric mean for K_L of 0.01. The only study that gave a risk estimate significantly higher than this central estimate was the Ontario asbestos cement products factory studied by Finkelstein (1983). In view of the dubious basis of the exposure estimates and the inconsistency of the exposure-response relationship to lung cancer, however, the dose-response data for this plant have been dismissed by other authors as too unreliable to justify consideration (Doll and Peto 1985; Liddell and Hanley 1985). The only other significant inconsistency was the low risk observed in chrysotile friction product manufacture.

The heterogeneity discussed above has been interpreted in various ways by different reviewers. The EPA report (Nicholson 1986) concluded that the dose-specific risk was lower among chrysotile miners and millers, but other cohorts did not differ significantly from the overall median, taking account of uncertainties in the exposure estimates. The U.K. Health and Safety Commission (HSC) report (Doll and Peto 1985) calculated the risk only for chrysotile textile workers, and stated that the exposure data for other cohorts were too unreliable to justify any firm conclusion. The CPSC (1983) presented risk estimates spanning a 10-fold range of uncertainty, centered on the overall median. The average adopted by the HSC and the median values calculated by the EPA, the CPSC, and the NRC (1984) were, however, all virtually identical.

Validity of the Lung Cancer Model

The model implies that the excess SMR or relative risk of lung cancer is (1) independent of age at exposure to asbestos, (2) independent of smoking habits, (3) independent of time since stopping exposure, (4) proportional to duration of exposure, and (5) proportional to average level of exposure for a given duration of exposure.

The first two predictions have been examined in a number of studies and are at least approximately true. There is evidence that the relative risk eventually falls after stopping exposure (Walker 1984; Peto et al. 1985), although this may be the result of selection of a survivor population at lower relative risk due to the preferential elimination of cigarette smokers or individuals who have had particularly high exposure. Evidence for the effect of exposure duration appears somewhat inconsistent, as short-term workers have suffered disproportionately large risks in some, but not all, cohorts. This may be due to various factors, including unusually heavy smoking habits among transient workers and the use of inappropriate reference rates to calculate the SMR. The last and crucial prediction, that risk is proportional to average level of exposure, cannot be adequately tested, as historical exposure levels can never be estimated accurately (see section 6.2.2.3, Measurement of Asbestos Exposure), and few cohorts have been simultaneously analyzed by both duration of exposure and average level of exposure. An approximately linear relationship between cumulative exposure and excess relative risk has, however, been observed in a number of studies.

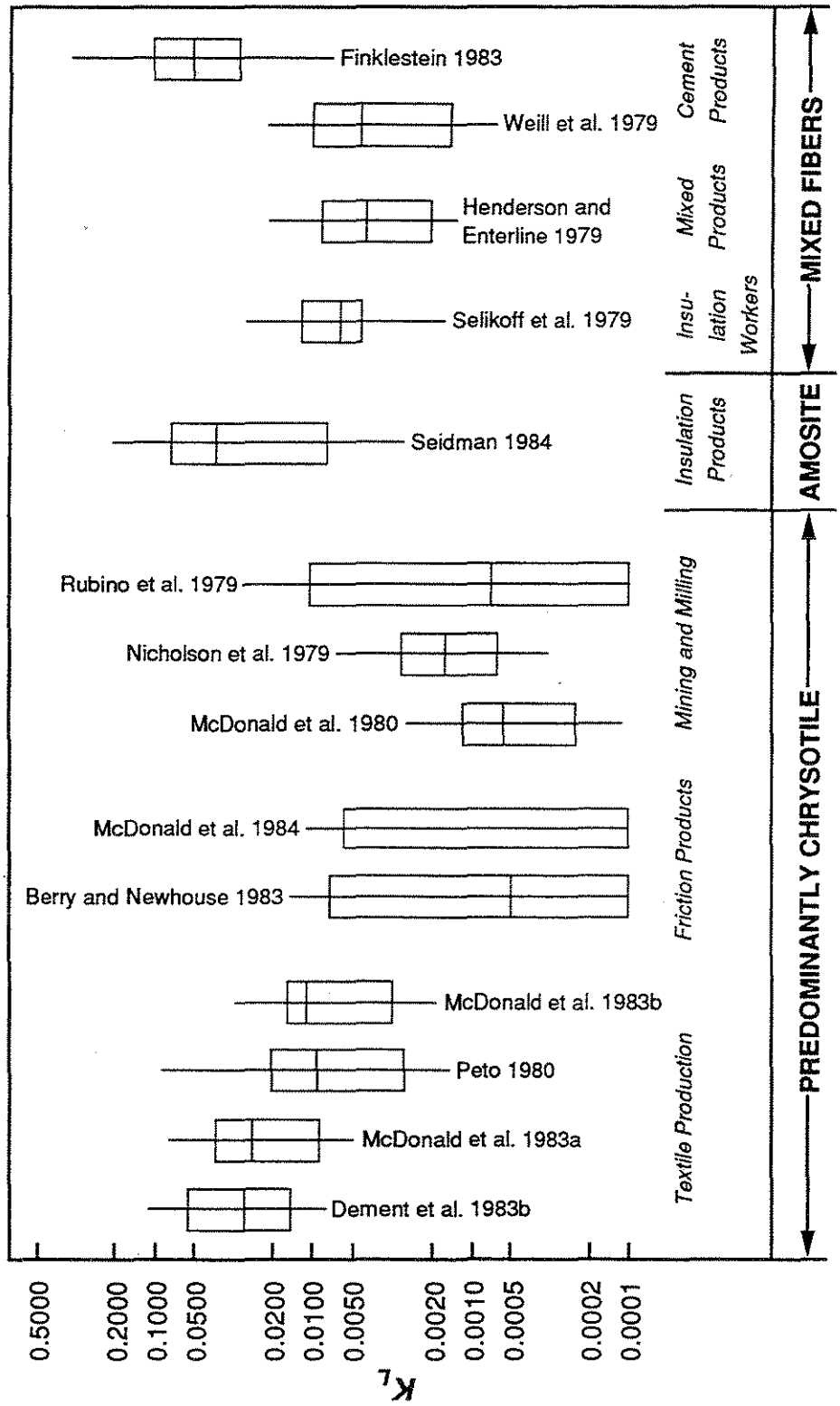

Figure 6-1. Reproduced with permission from Nicholson (1986). Values of K_L, the fractional increase in lung cancer per f-y/mL of exposure in 14 asbestos exposed cohorts. The open bar reflects the estimated 95 percent confidence limits associated with measures of response. The line represents the uncertainties associated with measures of exposure, generally plus or minus a factor of two. For discussion of uncertainties associated with exposure assessment and response measure, see text.

6.2.2.2 Mesothelioma

Dose-Response Model for Mesothelioma

According to the model for mesothelioma described above, the incidence or death rate caused by a period of exposure beginning at time t_1 and ending at time t_2 at a constant exposure level f (measured in fibers or particles per unit volume of air) is given by the following formula.

$$I_M(t) = K_M \cdot f \cdot [(t-t_1)^n - (t-t_2)^n] \quad (6.3)$$

$I_M(t)$ denotes the mesothelioma incidence (or death rate) at time t, and the exponent n is about 3 or 4. (In the basic model, the increase in incidence caused by a brief exposure is proportional to incremental cumulative dose multiplied by t^n, where t is time since the incremental exposure and n is 2 or 3. This formula is integrated to give equation 6.3.) K_M is a constant reflecting the mesothelioma risk per unit of exposure. Time since first exposure equals $(t-t_1)$, and time since stopping exposure equals $(t-t_2)$. The model implies that the risk will continue to increase after exposure ceases, and the risk at any given interval after exposure will be independent of both age and cigarette smoking. The effect of each increment of exposure is assumed to be additive, so for a series of exposures of different intensities f_i the overall incidence will be

$$I_M(t) = K_M \cdot \sum_i f_i[(t-t_{1i})^n - (t-t_{2i})^n] \quad (6.4)$$

where the ith period of exposure begins at time t_{1i} and ends at t_{2i}. It has been suggested that the model should be fitted with a lag of about 10 years (Peto et al. 1982; Nicholson 1986). This reduces the estimated value of n by about 1 and alters K_M, but has little effect on the overall pattern of predicted risk. For cohorts in which individual exposure data are not available, the model can be fitted approximately using equation 6.3, replacing f by average exposure level.

Cohorts That Have Been Used to Calculate Dose-Specific Mesothelioma Risks

One unsatisfactory aspect of the published literature on mesothelioma is the lack of adequately analyzed mortality data. The death rate rises sharply with time since exposure, yet only a few data sets have been analyzed by time since first exposure, and only four of these reports also provided estimates of average exposure level. These were analyzed by the CPSC (1983) and the EPA (Nicholson 1986), fitting equation 6.3 with a lag of 10 years and $n = 3$. Thus,

$$I_M(t) = K_M \cdot f \cdot [(t-t_1-10)^3 - (t-t_2-10)^3] \quad (6.5)$$

where $(t-t_1)$ is time since first exposure, and (t_2-t_1) equals duration of exposure. Three of the resulting estimates of K_M were similar (between 1 and 3×10^{-8}), but that from the study of Finkelstein was much higher (1×10^{-7}; Table 6-2). (A subsequent, more detailed analysis of the British textile workers' data, with an enlarged cohort and longer follow-up [Peto et al. 1985], gave a prediction for this cohort similar to that shown in Table 6-2, using individual exposure data to fit equation 6.4 with $n = 4$.) Pleural and peritoneal mesotheliomas were combined in these analyses. There are, however, serious weaknesses in all four studies shown in Table 6-2, particularly for assessing the effects of chrysotile. As noted above, the exposure data and results for the cement factory workers' study reported by Finkelstein (1983) are of doubtful reliability for quantitative risk assessment; also, the contemporary exposure data are very limited for the insulation workers (Selikoff et al. 1979) and for the amosite insulation products workers (Seidman et al. 1979). Moreover, none of these historical cohorts was exposed only to chrysotile. Some crocidolite was used in the textile factory studied by Peto and associates (1985), and the insulation workers were

heavily exposed to amosite and chrysotile, and in some cases, to small amounts of crocidolite.

Table 6-2. Four Estimates of K_M, the Index of Dose-Specific Mesothelioma Risk[a]

Study	Assumed Employment Duration	Assumed Exposure (f/mL)	Estimated Value of K_M
Insulation workers (Selikoff et al. 1979; Peto et al. 1982)	25	15	1.5×10^{-8}
Textile workers[b] (Peto 1980; Peto et al. 1982)	25	20	1.0×10^{-8}
Amosite factory workers (Seidman et al. 1979)	1.5	35	3.2×10^{-8}
Cement factory workers (Finkelstein 1983)	12	9	1.2×10^{-7}

[a] From Nicholson 1986 (reprinted with permission); see equation 6.5.

[b] Peto and associates (1985) derived similar results in an update of this study with an enlarged cohort.

In the absence of any satisfactory basis for direct estimation of the dose-specific mesothelioma risk caused by any specific type of asbestos, particularly chrysotile, this report evaluates previous reviewers' predictions for mesothelioma by comparing observed and predicted ratios of mesothelioma to excess lung cancer in different cohorts. The lifetime risks of mesothelioma shown in Table 6-3, which are similar to those in the EPA report, were calculated from equation 6.5 with $K_M = 10^{-8}$, although Nicholson's (1986) figures must be divided by about 4.5 to convert from continuous exposure to exposure for 40 hours per week. The lung cancer risks were calculated from equation 6.1 with $K_L = 0.01$, using U.S. lung cancer rates for 1986. The lifetime (to age 80) lung cancer risk in the U.S. general population is now 6 percent for men and 3 percent for women. Lung cancer risks to smokers are likely to be a least 50 percent higher than those shown in Table 6-3, while predicted risks to nonsmokers are more than 10 times lower. For mesothelioma, however, the risk is independent of smoking. The consistency of these predicted risks and their ratios to observed risks are discussed in *Dose-Specific Risk for Chrysotile and Mixed Exposures* and *Dose-Response Relationship for Amphiboles*, under section 6.2.2.4, Risk Assessment.

Validity of the Mesothelioma Model

The model for mesothelioma was proposed to explain the observation that mesothelioma incidence is independent of age and is approximately proportional to the third power of time since first exposure (or, almost equivalently, to the square of time since first exposure minus 10 years) (Peto 1979; Peto et al. 1982), but neither the predicted relationship to duration nor the assumption of a linear dose-response relationship has been adequately tested. In spite of its widespread adoption as a basis for risk assessment, the model has been formally fitted in only one cohort in which individual exposure data were available (Peto et al. 1985).

Table 6-3. Lifetime (Up to Age 80) Lung Cancer and Mesothelioma Risk Per 1,000,000 for Asbestos Exposure 40 Hours Per Week at an Average Level of 0.0001 f/mL[a]

Age at First Exposure	Type of Cancer	Duration of Exposure (years)			
		1	5	10	20
		Predicted Risks in Men			
0	Lung	0.1	0.3	0.6	1.3
	Meso	0.2	1.1	1.9	3.0
10	Lung	0.1	0.3	0.6	1.3
	Meso	0.1	0.6	1.1	1.7
20	Lung	0.1	0.3	0.6	1.3
	Meso	0.1	0.3	0.6	0.9
30	Lung	0.1	0.3	0.6	1.3
	Meso	0.04	0.2	0.3	0.4
50	Lung	0.1	0.3	0.7	1.3
	Meso	< 0.01	0.01	0.02	0.02
		Predicted Risks in Women			
0	Lung	0.03	0.1	0.3	0.6
	Meso	0.3	1.3	2.2	3.6
10	Lung	0.03	0.1	0.3	0.6
	Meso	0.2	0.8	1.3	2.1
20	Lung	0.03	0.1	0.3	0.6
	Meso	0.1	0.4	0.7	1.0
30	Lung	0.03	0.1	0.3	0.6
	Meso	0.05	0.2	0.3	0.4
50	Lung	0.03	0.1	0.3	0.6
	Meso	< 0.01	0.02	0.03	0.03

[a] Based on 1986 U.S. national lung cancer mortality rates. These lung cancer risks should be multiplied by about 1.5 for smokers, and about 0.1 for nonsmokers.

Differences in Predicted Patterns of Excess Lung Cancer and Mesothelioma Between Cohorts. The models outlined above (or similar alternatives, using different exponents and lag times in the equation for mesothelioma) have been used in a number of reports to calculate lifetime risks of lung cancer and mesothelioma for various ages at first exposure and durations of exposure at a given average fiber level (Peto 1979; CPSC 1983; Ontario Royal Commission 1984; NRC 1984; Doll and Peto 1985; Nicholson 1986). As is evident from Table 6-3, the eventual lung cancer risk is assumed to be independent of age at exposure, but the predicted mesothelioma risk is much greater when exposure begins at an early age. These models therefore predict that the mesothelioma risk exceeds the lung cancer risk, even among smokers, for childhood exposure, whereas exposure in middle age results in a substantially lower mesothelioma risk. Among nonsmokers, the lung cancer risk is much smaller than the mesothelioma risk irrespective of age at exposure.

Such calculations of lifetime lung cancer risk have to be based on national or local lung cancer rates, since the model for lung cancer gives an estimate of relative risk rather than absolute risk. There have, however, been substantial changes in lung cancer risk between about 1960 and 1980 (the period of observation in which most deaths occurred in the majority of cohort studies), as well as large differences between the sexes and between different countries. The effect such differences might have on the ratio of excess lung cancer to mesothelioma in different cohorts is shown in Table 6-4. Table 6-4a gives U.S. death rates for lung cancer for 1968, 1978, and 1986, and also rates for England and Wales for 1976 to 1980, together with lifetime lung cancer risks. Corresponding predicted ratios of excess lung cancer to mesothelioma, calculated as in Table 6-3, in cohorts observed over these periods are also shown. Prior to 1978, the ratio is always three or more times greater for men than for women, and higher in men in England and Wales than in the United States. Exposure from age 30 rather than 20 causes a similar lung cancer risk but a lower mesothelioma risk, and hence a higher ratio.

Table 6-4a. Annual U.S. and U.K. General Population Lung Cancer Death Rates ($\times 10^{-5}$)

	Lung Cancer Death Rate							
	U.S. 1986		U.S. 1978		U.S. 1968		England and Wales 1976 – 1980	
Age	M	F	M	F	M	F	M	F
35 – 39	4	3	6	3	8	3	5	3
40 – 44	16	9	20	11	22	8	14	6
45 – 49	41	23	50	23	45	13	40	16
50 – 54	94	47	104	40	87	22	100	36
55 – 59	170	76	167	56	145	28	178	48
60 – 64	270	108	262	75	225	33	332	85
65 – 69	362	138	347	84	288	39	494	102
70 – 74	468	161	448	85	349	42	663	111
75 – 79	542	149	450	81	308	46	795	113
Lifetime risk (%)	6%	3%	6%	2%	5%	1%	8%	2%

Table 6-4b. Corresponding Ratio of Lifetime (to Age 80) Lung Cancer to Mesothelioma Risks in Cohorts of Asbestos Workers Exposed for 20 Years

	Country and Period of Follow-up							
	U.S. 1986		U.S. 1978		U.S. 1968		England and Wales 1976 – 1980	
Exposed from:	M	F	M	F	M	F	M	F
Age 20	1.5	0.6	1.4	0.4	1.2	0.2	1.9	0.4
Age 30	3.6	1.3	3.4	0.9	2.8	0.4	4.7	1.0

This substantial variation in lung cancer rates over time and between sexes and countries and the even larger differences in mesothelioma risk related to age at first exposure have two important implications. First, lifetime predictions of lung cancer risk should be modified to allow for future trends and differences between countries. Over the last 10 years, U.S. rates below age 45 have declined substantially, particularly for men, due partly to reductions in smoking, but this decline is also thought to be related to reduction in tar level. Female rates are, however, still rising sharply at older ages, due to earlier increases in smoking. Lifetime risks to American children are thus likely to be lower than current figures would suggest, at least for males.

Second, crude comparisons of the ratio of excess lung cancer to mesothelioma between different cohorts must be interpreted cautiously. This ratio would be expected to be low among women, lower in the United States than in Britain, and higher in groups, such as the U.S. World War II shipyard workers, that included a disproportionate number of older recruits.

Differences Between Asbestos Types. *Peritoneal Mesothelioma.* Almost all reported mesotheliomas among chrysotile workers (usually with some exposure to crocidolite and/or tremolite) are pleural, whereas workers with some amosite exposure have suffered similar (and sometimes higher) risks of peritoneal and pleural mesothelioma. Evidence on the peritoneal-to-pleural ratio for mesotheliomas caused by crocidolite appears to be inconsistent. Several peritoneal mesotheliomas occurred among female gas mask workers exposed mainly to crocidolite (Table 6-5), but almost all mesotheliomas among Australian crocidolite miners were pleural (Armstrong et al. 1988). Differences between cohorts in the incidence of peritoneal mesothelioma may, however, be exaggerated by differences in the completeness of ascertainment. In five of the studies listed in Table 6-5 pathologic examination was undertaken of all available abdominal and disseminated tumors to verify the diagnosis (Newhouse et al. 1985; Selikoff et al. 1979; Seidman et al. 1979). In each case a substantial number of peritoneal mesothelioma deaths were misrepresented on death certificates. The five cohorts described in these three reports account for three-quarters of the peritoneal mesotheliomas that have occurred in published cohort studies of asbestos workers (Table 6-5), and all five cohorts had extensive exposure to amosite. Comparable reviews were not conducted for most of the cohorts exposed predominantly to other asbestos types.

Pleural Mesothelioma. Direct comparison of workers exposed for similar durations to different forms of asbestos (such as in mining or gas mask manufacture) indicates a much higher mesothelioma risk for crocidolite than for chrysotile. Chrysotile friction products workers in Britain suffered no detectable increase in lung cancer, and most of the mesotheliomas in this cohort occurred in the subgroup of workers who were known to have been exposed to crocidolite (Berry and Newhouse 1983; Newhouse and Sullivan 1989). Chrysotile textile workers in Britain suffered a high risk of mesothelioma (Peto et al. 1985), in contrast to those in South Carolina (Dement et al. 1982), although in both cohorts there was a substantial lung cancer risk. One difference between these two textile plants was the use of some crocidolite in the British plant. This was less than five percent of the fiber processed, although there are no data on the resulting contribution to the airborne level.

Table 6-5. Lung Cancer and Mesothelioma Mortality in Various Studies[a]

Study and Fiber Type	Lung Cancer[b]			Mesothelioma[c]		
	Observed[d]	Expected	Observed-Expected	Pleural	Peritoneal	Total[e]
Chrysotile						
Acheson et al. 1982 (F)[f]	6	4.5	1.5	1	0	1
Dement et al. 1983a,b	35	11.1	23.9	0	1	1
McDonald et al. 1983a	59	29.6	29.4	0	1	1
McDonald et al. 1980	230	184.0	46.0	10	0	10
Nicholson et al. 1979	25	11.1	13.9	1	0	1
McDonald et al. 1984	73	49.1	23.9	0	0	0
Piolatto et al. 1990	22	19.9	2.1	2	0	2
Weiss 1977	4	4.3	–0.3	0	0	0
Predominantly chrysotile						
McDonald et al. 1983b	53	50.5	2.5	10	4	14
Robinson et al. 1979	49	36.1	12.9	4	5	13
Robinson et al. 1979 (F)	14	1.7	12.3	1	1	4
Mancuso and El-Attar 1967	33	14.8	18.2	1	8	9
Peto et al. 1985	152	106.0	46.0	18	0	18
Thomas et al. 1982	22	25.8	–3.8	2	0	2
Ohlson and Hogstedt 1985	9	5.7	3.3	0	0	0
Gardner et al. 1986	41	42.4	–1.4	1	0	1
Amosite						
Acheson et al. 1984	57	29.1	27.9	4	1	5
Seidman et al. 1979	83	21.9	61.1	7	7	14
Predominantly crocidolite						
Acheson et al. 1982 (F)	13	6.6	6.4	3	2	5
Armstrong et al. 1988	91	34.5	56.5	32	1	33
Jones et al. 1980 (F)	12	6.3	5.7	13	4	17
Wignall and Fox 1982 (F)	10	3.7	6.3	9	3	12
McDonald and McDonald 1978	7	2.4	4.6	3	6	9
Anthophyllite						
Meurman et al. 1974	21	12.6	8.4	0	0	0

Table 6-5 (continued). Lung Cancer and Mesothelioma Mortality in Various Studies[a]

Study and Fiber Type	Lung Cancer[b]			Mesothelioma[c]		
	Observed[d]	Expected	Observed-Expected	Pleural	Peritoneal	Total[e]
Talc (tremolite)						
Kleinfeld et al. 1974	13	4.5	8.5	0	1	1
Brown et al. 1979	9	3.3	5.7	0	0	1
Lamm et al. 1988	12	5	7	0	0	1
Mixed exposures						
Alies-Patien and Vallerou 1985	12	5.5	6.5	3	1	4
Albin et al. 1984	12	6.6	5.4	4	0	4
Newhouse and Sullivan 1989	229	221.4	7.6	11	0	11
Newhouse and Sullivan 1989 (F)	12	21.1	–9.1	2	0	2
Clemmesen and Hjalgrim-Jensen 1981	47	27.3	19.7	3	0	3
Elmes and Simpson 1977	27	5.0	22.0	8	5	24
Finkelstein 1983	20	3.3	16.7	6	5	11
Henderson and Enterline 1979	63	23.3	39.7	?	?	5
Selikoff et al. 1979 (U.S.)	390	93.7	296.3	61	109	170
Selikoff et al. 1979 (NY-NJ)	93	13.1	79.9	11	27	38
Kleinfeld et al. 1967	10	1.4	8.6	1	2	3
Kolonel et al. 1980	35	32.5	2.5	0	0	0
Lacquet et al. 1980	21	22.3	–1.3	1	0	1
Newhouse et al. 1985	196	73.9	122.1	38	29	67
Newhouse et al. 1985 (F)	37	5.0	32.0	14	11	25
Raffu et al. 1989	161	89.8	71.2	12	1	13
Nicholson 1976	27	8.4	18.6	8	7	15
Puntoni et al. 1979	123	54.9	68.1	0	0	0
Rossiter and Coles 1980	84	100.3	–16.3	29	2	31
Hughes et al. 1987	154	115.5	38.5	4	0	4

[a] Adapted from Nicholson (1986), plus additional studies published from 1985 to 1990.

[b] Lung cancer includes all respiratory cancers in some reports.

[c] Cases of mesothelioma occurring outside the cohort or period for which lung cancer results were presented are excluded.

[d] In a few reports it is not clear whether or not pleural mesotheliomas have been excluded from the observed lung cancers.

[e] Total mesothelioma column includes cases of unknown site, and sometimes exceeds the pleural plus peritoneal total.

[f] (F) indicates a female cohort. Other cohorts are all (or in a few cases, almost all) male, except for McDonald and McDonald (1978), in which 45 percent were female.

The Ratio of Excess Lung Cancer to Mesothelioma. Several reports have drawn attention to the marked differences between cohorts in the ratio of excess lung cancer to mesothelioma. These are summarized in Table 6-5. Peritoneal mesotheliomas can usually be attributed to amphibole exposure, but even when only pleural tumors are considered, the ratio varies remarkably. In one study, English shipyard workers with mixed exposure, including a substantial amount of crocidolite, suffered a high mesothelioma risk but no excess of lung cancer (Rossiter and Coles 1980), while among workers at a South Carolina chrysotile textile plant there was a marked excess of lung cancer and no pleural mesothelioma (Dement et al. 1982; McDonald et al. 1983a). These data have been widely accepted as indicating that amphiboles, particularly crocidolite, cause a disproportionate mesothelioma risk. There is, however, disagreement over the magnitude of the difference, since the ratio is subject to several potentially serious errors and biases, such as:

First, inappropriate choice of reference rates for lung cancer could either inflate or reduce the observed excess. For example, the very high relative risk among amosite workers observed by Seidman and colleagues (1979) could be due to the use of inappropriately low rates, as the relative risk in this study was disproportionately high for men with very short exposure. Alternatively, short-term employees may have suffered particularly heavy exposure. Peto and coworkers (1985) observed an excess among men employed for less than a year, although not in those employed for 1 to 5 years. These authors suggested that short-term workers are a self-selected group with unusually high lung cancer rates (the opposite of the "healthy worker" effect seen in long-term employees). Conversely, incidence of lung cancer was low (84 observed, 100.3 expected) in shipyard workers studied by Rossiter and Coles (1980), although 31 mesotheliomas were observed. Lung cancer rates vary substantially in relation to period, country, region, and social class, probably due almost entirely to differences in past smoking habits, and there is no reliable means of establishing appropriate adjustments for a particular group of workers.

Second, mesothelioma was certainly underdiagnosed in the past, although this is now less likely to occur. Conversely, among migrant workers for whom follow-up is incomplete, such as many of the crocidolite miners in Western Australia (Hobbs et al. 1980; Armstrong et al. 1988), mesothelioma deaths may be noted and included more frequently than deaths from lung cancer or other causes.

Third, the observed ratio of excess lung cancer to mesothelioma is subject to substantial random variation. Thus, for example, the apparently extraordinary difference in the ratio between the South Carolina textile workers (59 observed, 29.6 expected for lung cancer, and no pleural mesotheliomas) and the Quebec chrysotile miners (230 observed, 184 expected, and 10 mesotheliomas) (McDonald et al. 1980) is only just statistically significant ($p = 0.01$, or 0.05 if the peritoneal case at South Carolina is included).

Fourth, as noted in the section above, the ratio would be expected to vary substantially with age at exposure, period of observation, and region. Table 6-3 also indicates that the proportional excess of mesothelioma would be expected to be greatest in workers exposed for relatively short duration.

Finally, lung cancer rates in old age are much lower for women than for men, due largely to differences in smoking, as noted above. The ratio of excess lung cancer to mesothelioma would therefore be expected to be much lower among women.

After pooling the various cohorts, Doll and Peto (1985) and Nicholson (1986) concluded that among men the ratio of excess lung cancer to pleural mesothelioma is about 3 times greater for chrysotile than crocidolite, varying from at least 4 for chrysotile to between 1 and 2 for

crocidolite, with substantially lower ratios for women. These reviewers also noted that peritoneal mesothelioma is common following amosite exposure, but has almost never been reported in chrysotile workers not exposed to amphiboles. Nicholson (1986) suggested, however, that this apparently marked difference might have been exaggerated by differences in diagnostic standards (see above, *Differences Between Asbestos Types*, in this section).

In view of the difficulties noted above, such pooling of potentially inconsistent data is certainly of limited value. The EPA report (Nicholson 1986) attempted to avoid the effects of differences in underlying lung cancer rates by examining the ratio of the increase in lung cancer relative risk to the absolute mesothelioma incidence. The latter cannot be estimated directly for most cohorts from published data, but Nicholson (1986) pointed out that a reasonable estimate of lifelong mesothelioma risk can be obtained by dividing mesothelioma deaths by total deaths. (The EPA analysis in fact used an equivalent procedure, in which the lifelong mesothelioma risk was divided by cumulative dose to give a dose-specific measure of mesothelioma risk. This was then compared against K_L, the dose-specific increase in relative risk of lung cancer.) This analysis eliminates differences in the ratio of mesothelioma to excess lung cancer due to differences in underlying lung cancer rates between men and women, and between different periods and countries. Some inconsistencies remain, however, most notably the marked excess of mesothelioma in the absence of any detectable excess of lung cancer observed among shipyard workers by Rossiter and Coles (1980), and in the subgroup of friction product workers with crocidolite exposure studied by Berry and Newhouse (1983).

The opposite view is that virtually all mesotheliomas are due to amphibole exposure, and that chrysotile causes a negligible mesothelioma risk. The only strong evidence against the inference that mesothelioma is almost never caused by chrysotile alone is the observation of substantial numbers of cases among Quebec chrysotile miners and millers. It has, however, been suggested that these are due to the presence of fibrous tremolite in this material (reviewed by Churg and Wright 1989; McDonald et al. 1989a; Mossman et al. 1990; Weill et al. 1990). Tremolite constituted much less than 1 percent of the fibers extracted but constituted a large proportion of the long (greater than 5 μm) fibers found in the lung tissue of the workers, apparently because chrysotile is cleared much more rapidly than tremolite (Sébastien et al. 1989). Similarly, high levels of crocidolite were found in lung tissue from British textile workers who were exposed mainly to chrysotile but suffered a high incidence of mesothelioma (Wagner et al. 1982).

The evidence that chrysotile rarely causes pleural mesothelioma is not conclusive. There are only two cohorts of heavily exposed asbestos workers who worked only with chrysotile (in both cases exposed to Quebec fiber, and hence possibly contaminated with tremolite). The absence of pleural mesothelioma in the South Carolina plant, in spite of the substantial risk of lung cancer (59 observed, 29.6 expected; Dement et al. 1982; McDonald et al. 1983a), seems likely to be due at least in part to chance. The Quebec chrysotile miners and millers had suffered 230 lung cancers, compared with 184 expected, and 10 mesotheliomas by 1975, and about 20 further cases of mesothelioma are known to have occurred subsequently in this cohort (McDonald and McDonald 1990). Lung burden studies show no marked differences between these cohorts in the type, size, or amount of either chrysotile or tremolite fibers (Sébastien et al. 1989). No other study addresses the mesothelioma-inducing potency of chrysotile directly. The substantial incidence of pleural mesothelioma in various cohorts exposed to both chrysotile and amphiboles is consistent with the belief that these tumors were caused by amphibole exposure, but constitutes weak evidence that chrysotile does not cause mesothelioma. The only reasonable conclusion is that a substantial but

unknown proportion of the mesotheliomas in such cohorts may be due to amphibole exposure.

6.2.2.3 Measurement of Asbestos Exposure

The calculation of dose-specific risk depends as much on measurement of dose as on estimation of excess risk, yet remarkably little attention has been paid to the quality of these vital data. Only three cohorts in which substantial excess risks have been observed also have reasonably extensive historical dust measurements from which individual exposures can be estimated. In each case, however, there was little or no measurement of exposure in some of the dustiest areas, and conversion of particle to fiber counts was based on inconsistent measurements at relatively low levels. In another study, of a friction products factory in the United Kingdom, extensive and probably reliable individual exposure estimates were calculated. The study does not provide a very useful dose-specific lung cancer risk estimate, however, as exposures were so low that the risk estimate (which was virtually zero) has very wide confidence limits.

Quebec Chrysotile Miners and Millers (McDonald et al. 1980)

This cohort of almost 11,000 men was extensively monitored between 1949 and 1966 using a midget impinger to measure particle counts in millions of particles per cubic foot (mppcf). Earlier levels were "estimated after interviews with long-service employees" (McDonald et al. 1980). The exposure data and lung cancer mortality are summarized in Table 6-6. The observed excess was confined to the 1,688 men exposed for over 5 years to average levels of about 50 mppcf or more (very high), or exposed for over 20 years to about 20 mppcf (high). The relative risks in these three cells of Table 6-6 are all about 2.5 and do not differ significantly, while in the remainder of the cohort (9,251 men) there was no significant evidence of excess risk, either overall (158 observed, 154 expected) or in relation to duration or estimated level of exposure. The only direct evidence that estimated exposure is related to risk is thus (1) the absence of any excess in men exposed at lower average levels; and (2) the difference in relative risk for men with 5 to 20 years of exposure between the "high" (17 mppcf: 7 observed, 8.4 expected) and "very high" (62 mppcf: 16 observed, 7.4 expected) cells in Table 6-6. Against this must be weighed the similarity of relative risks seen among men with over 20 years of exposure in the "high" (19.2 mppcf: 24 observed, 10.9 expected) and "very high" (46.8 mppcf: 32 observed, 12.1 expected) cells, a significant departure from linear dose-response with cumulative dose. These data thus demonstrate that the highest risk occurred in men with long heavy exposure, but they constitute extremely weak evidence of a linear quantitative relationship between risk and measured intensity of exposure. Any study in which prolonged heavy exposure causes significantly increased risk will yield an apparent dose-response relationship if large numbers of men with very much lower or shorter exposure are included.

The data described above are not in any way inferior to those for other cohorts; they are more extensive and more completely described than those of any other study. It is a paradox of industrial risk assessment that internal evidence of inconsistency or weakness can be identified only in the best-described and extensively analyzed studies. The appropriate conclusion is that dose-response estimates derived in the majority of other cohorts, in which past exposure—level estimates were based on little or no historical data, are even less reliable.

Table 6-6. Lung Cancer Mortality, Average Exposure Level (mppcf), and Cumulative Dose (mppcf-years) of Quebec Miners and Millers[a]

Duration	No. of Deaths	Exposure Category			
		Low	Medium	High	Very High
< 1 Year	Observed	19	12	9	7
	Expected	16.2	13.2	10.2	8.8
	Average level	2.6	4.3	14.4	78.0
	Cumulative dose	0.5	1.7	5.8	39
	No. of men	1,022	838	571	576
1 to 5 Years	Observed	5	13	6	5
	Expected	7.6	13.7	7.3	6.4
	Average level	2.5	6.2	23.6	82.6
	Cumulative dose	3.3	13.6	59.0	231.3
	No. of men	593	867	484	380
5 to 20 Years	Observed	13	14	7	16
	Expected	9.2	11.5	8.4	7.4
	Average level	2.5	5.6	17.0	62.3
	Cumulative dose	3.3	58.2	178.5	704.0
	No. of men	714	758	544	487
20+ Years	Observed	28	20	24	32
	Expected	23.1	18.5	10.9	12.1
	Average level	4.2	9.4	19.2	46.8
	Cumulative dose	104.6	261.3	549.1	1,441.4
	No. of men	1,037	867	565	636

[a] Source: Adapted from McDonald and associates (1980).

The only basis for converting these particle counts to fiber counts was a series of parallel samples taken after dust levels had been reduced to an average of about 1 mppcf (Figure 6-2; Dagbert 1976). The parallel measurements showed low correlation, and the highest particle count was less than 5 mppcf. The weakness of these data as a basis for converting particle counts, which often exceeded 50 mppcf, to fiber counts is self-evident. Indeed, on the basis of the inconsistency of parallel measurements, Dagbert (1976) suggested a 95 percent confidence interval of 0.6 to 58 f/mL for conversion of 1 mppcf, and 3 to 270 f/mL for 10 mppcf. The conclusion that exposure in chrysotile mining is 20 to 100 times less dangerous than in chrysotile textile production at the same measured fiber level (see Table 6-1) is thus extremely insecure. It should be pointed out that the authors of this study

are well aware of the dubious validity of any conversion of their exposure data to fiber counts, and have consistently presented their dose-response relationships in terms of the original particle counts.

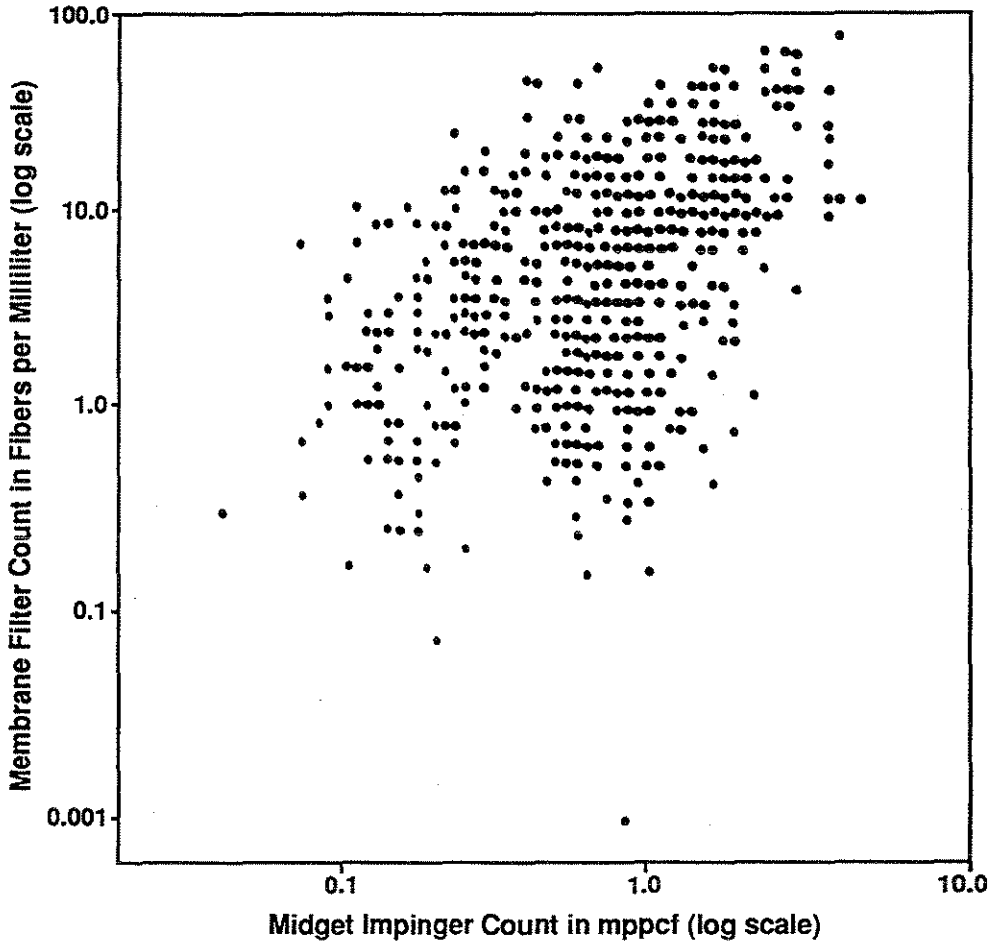

Figure 6-2. Average particle counts in 1960 and fiber counts in 1961 in different areas of the Rochdale, U.K. textile factory. Peto and associates (1985); reproduced by permission.

Rochdale (U.K.) Chrysotile Textiles (Peto et al. 1985)

Particle counts were taken routinely in most areas of this factory between 1951 and 1960 using a thermal precipitator. Fibers were subsequently counted, initially collected with a thermal precipitator, and also after 1965 with a membrane filter. Substantial reductions in particle counts occurred in many of the dustiest areas between 1950 and 1955. Conversion of particles to fibers was based on average levels in various areas for 1960 and 1961, although these showed extremely poor correlation (Figure 6-3). As in the Quebec mines and mills, no measurements were taken in certain dusty areas, and inconsistencies between nominally comparable personal and fixed sample measurements were noted. Although their estimated exposures were lower, the observed excess lung cancer risk was higher

(although not quite significantly) in men first exposed after 1951, perhaps indicating biologically significant changes in fiber dimension. The correlation between excess lung cancer risk and estimated exposure was qualitatively similar to that observed in Quebec miners and millers, although the estimated risk per unit dose was much higher. An apparently linear relationship with cumulative dose was observed, but when men exposed to low levels or employed for less than 5 years were excluded the relationship with estimated dose and duration was unimpressive (Table 6-7). As noted above, a major difficulty in interpreting these results is the fact that some crocidolite was used and a high incidence of mesothelioma was observed. Crocidolite constituted a small proportion (less than 5 percent) of the fiber processed, and the authors halved their resulting mesothelioma risk estimate for chrysotile to allow for this, observing that "this rather arbitrary assumption constitutes an uneasy compromise between the South Carolina results, the observation of several cases [of mesothelioma] among Quebec chrysotile miners and millers, and the data reported here" (Peto et al. 1985).

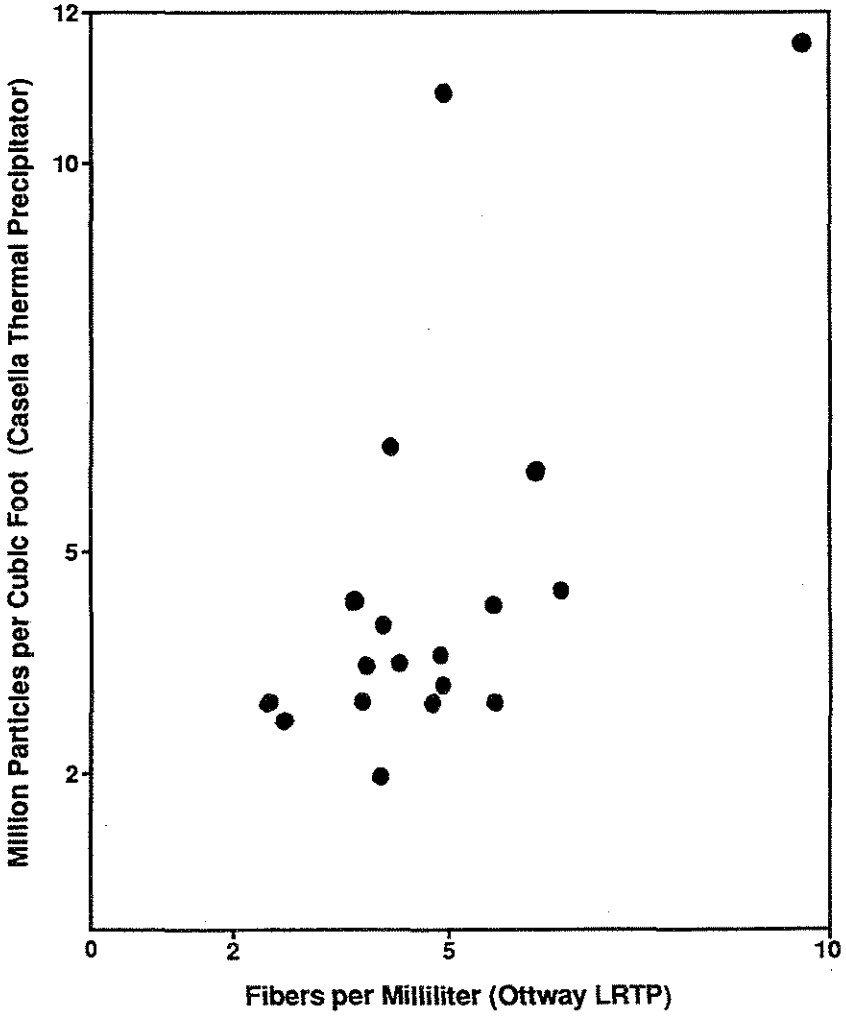

Figure 6-3. Average particle counts in 1960 and fiber counts in 1961 in different areas of the Rochdale, U.K. textile factory. Peto and associates (1985); reproduced by permission.

Table 6-7. Lung Cancer Mortality by Average Exposure Level and Duration of Rochdale (U.K.) Chrysotile Textile Workers[a]

Duration	No. of Deaths	Average Exposure Level (particles/mL)			
		Nil	1 to 199	200 to 399	400+
< 1 Year	Observed	3	5	2	12
	Expected	2.8	3.6	1.7	7.5
1 to 5 Years	Observed	2	3	1	2
	Expected	2.3	2.2	1.2	1.9
5 to 10 Years	Observed	1	3	1	10
	Expected	0.8	5.6	1.8	6.2
10 to 20 Years	Observed	2	8	12	7
	Expected	0.6	7.9	3.7	3.2
20+ Years	Observed	0	8	6	5
	Expected	0.7	5.2	3.2	2.9

[a] Source: Adapted from Peto and associates (1985).

South Carolina (U.S.): Chrysotile Textiles (Dement et al. 1982, 1983a,b; McDonald et al. 1983a)

This factory was independently studied by Dement and associates (1982, 1983a,b) and McDonald and associates (1983a), who observed a large lung cancer excess but no pleural mesotheliomas. (There was one peritoneal mesothelioma, possibly due to earlier amphibole exposure.) More than 5,000 samples were taken before 1975, but only 376 midget impinger samples were taken before 1960, and many of the dustiest activities were unmonitored. According to Dement and coworkers (1983a), later parallel measurements suggested a conversion factor of about 3 f/mL per mppcf, although a factor of about 8 f/mL per mppcf seemed more appropriate in some areas. Nicholson (1986) calculated that the results published by Dement and colleagues (1983b), assuming a conversion factor of 3 f/mL per mppcf, implied that $K_L = 0.03$. The increase in SMR per mppcf-year was, however, estimated to be 0.075 by McDonald and coworkers (1983a), who suggested a conversion factor of 6 f/mL per mppcf, giving $K_L = 0.013$.

Friction Products (U.K.): Mainly Chrysotile (Berry and Newhouse 1983; Newhouse and Sullivan 1989)

This study showed no excess of lung cancer among men (229 observed, 221.4 expected), and a deficit in women (12 observed, 21.1 expected). Thirteen mesotheliomas occurred, but most were exposed to crocidolite, which was used only during two periods (1929 to 1933 and 1939 to 1944). Historical fiber-level estimates were based on an extensive study involving reconstruction of earlier working conditions (Skidmore and Dufficy 1983), and

are likely to be reasonably reliable, as conditions did not alter greatly in most areas between 1932 and 1967, when regular fiber counting began. The resulting dose-specific estimate of lung cancer risk was close to zero (K_L = 0.0006), but most cumulative exposures were low, and the upper 95 percent confidence limit for K_L exceeded 0.01. The primary reference for this study is Berry and Newhouse (1983), which includes a detailed analysis of dose-response. The mortality pattern was unaltered during the further seven years of follow-up (1980 to 1986) reported by Newhouse and Sullivan (1989).

Other Studies

Members of the Literature Review Panel differed in their interpretation of the reliability of exposure estimates for other cohorts (see *Cohorts That Have Been Used to Calculate Dose-Specific Lung Cancer Risks*, under section 6.2.2.1, Lung Cancer). Detailed descriptions of the derivation of such estimates comparable to those outlined above have not been published, but it appears that none was derived from extensive historical dust measurements combined with contemporary fiber and particle counts.

Some Panel members regarded this lack of evaluable published information as crucial, but others considered that several of the quoted average levels, if not the individual exposure estimates, were probably accurate within a factor of about 2, which would certainly be adequate for risk assessment purposes.

6.2.2.4 Risk Assessment

Relevance of Tremolite

A fundamental difficulty in relation to chrysotile risk assessment is the fact that most cohorts of chrysotile workers have been exposed to some amosite or crocidolite, while the two major cohorts exposed only to chrysotile handled material from the Quebec mines, which contain a small but variable amount of tremolite. The ratio of all amphiboles, including tremolite, to chrysotile is often higher in the lung tissue of workers exposed solely or principally to chrysotile than in the material itself, apparently because chrysotile disappears from the lung more rapidly than the amphiboles. Some authors have therefore concluded that mesotheliomas among chrysotile workers are largely or even perhaps entirely due to tremolite (Churg 1988; Mossman et al. 1990) or other amphiboles. While the similarity of tremolite and chrysotile lung burdens at the time of death in chrysotile workers is suggestive of a role for tremolite, it is not conclusive. First, the action of asbestos in causing mesothelioma may involve early stage events, in which case tissue concentrations early in exposure would be more relevant. Second, concentrations in the pleura are of greater importance than those in the lung with respect to mesothelioma risk. Sébastien and coworkers (1979) and Dodson and colleagues (1990) have shown that the ratio of chrysotile to amphibole concentrations is greater in the pleura than in the lung. Thus, lung concentrations at death are unlikely to be representative of pleural tissue concentrations at times of relevant exposure. For the purpose of risk assessment it is therefore prudent to assume that most of the mesotheliomas observed among Quebec chrysotile miners were caused by chrysotile. This is a pragmatic hypothesis rather than a proven scientific statement, and future evidence may prove that it is wrong. In addition to scientific uncertainty and the principle that risk assessment should err on the side of caution, a further reason for this decision is the possibility that tremolite may be often encountered where chrysotile is found. Substantial amounts of tremolite were found in lung tissue both in chrysotile textile workers and in miners (Sébastien et al. 1989), and tremolite may therefore be present in certain other occupational and environmental situations in which chrysotile fibers are released.

Assumption of Linear Dose-Response Relationship for Mesothelioma

The specific model for mesothelioma induction described under *Dose-Response Model for Mesothelioma* (in section 6.2.2.2, Mesothelioma) predicts that lifelong risk increases almost linearly with increasing duration of exposure up to about 5 or 10 years, and more slowly thereafter. The available data are broadly consistent with this assumption. The studies of Jones and coworkers (1980) and Hobbs and associates (1980) provide information on mesothelioma risk according to duration of employment in, respectively, crocidolite gas mask manufacturing and crocidolite mining. Both studies are compatible with a linear relationship. The study of Seidman and colleagues (1979) suggests a relationship that rises less steeply than linear. As noted above, however, this study also exhibits a similar pattern for lung cancer, possibly because short-term workers were more heavily exposed. Peto and associates (1985) observed a disproportionately low risk in men exposed for less than 10 years compared with longer-service employees in a chrysotile textile factory, but this departure from the predicted pattern was not statistically significant.

These results demonstrate that brief exposure does not cause a high mesothelioma risk. Unfortunately, however, there are no useful data on the effect of level of exposure, as distinct from duration. Some, although not all, carcinogens exhibit upward (possibly quadratic) curvature in dose-response in cell transformation assays or in experimental tumor induction, and it has been suggested that the risk at low dose levels may be negligible[1]. There is, however, no good experimental evidence of such an effect for chrysotile or other asbestos minerals. The prediction that risk is proportional to level of exposure at very low concentrations cannot be tested epidemiologically. Exposure levels have never been recorded accurately, and the predicted risks at low levels shown in Table 6-3 are far too low to be observable. Nor is the opposite belief, that the mesothelioma risk is anomalously high following very low levels of exposure, supported by observation.

Assumption of Linear Dose-Response Relationship for Lung Cancer

The observation that excess lung cancer risk is roughly proportional to cumulative dose at high concentrations does not constitute strong evidence of a linear relationship with fiber level, particularly at very low levels. This prediction is even more difficult to test directly for lung cancer than for mesothelioma, since lung cancer is so common in the general population, affecting more than one smoker in 10 and about one nonsmoker in 200, that even quite large increases in risk are difficult to estimate reliably. (The risk is smaller in women, but it is not clear whether this is due largely, or even entirely, to differences in smoking.) Prolonged low exposure to chrysotile in friction products, asbestos cement, and chrysotile mining (Table 6-6) has produced no statistically significant excess of lung cancer. Even in chrysotile textile production, the sector in which the highest dose-specific risks for chrysotile have been observed, over 10 years' exposure at low average levels (under 200 particles/mL, or about 5 f/mL; see Table 6-7) produced little increase in risk in the U.K. study reported by Peto and coworkers (1985), although workers employed for less than 10 years in the South Carolina plant studied by Dement and colleagues (1983b), who were more heavily exposed, suffered an increased risk (SMR = 1.9). None of these observations, however, invalidates the assumption of a linear dose-response relationship, and Panel members are not aware of any clear evidence that our model for lung cancer either overestimates or underestimates the long-term risk for brief or low exposure.

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[1] See also Ilgren and Brown (1991), published too recently to be included in the Panel's review.

Although it is in principle impossible to demonstrate the linearity or otherwise of dose-response at very low levels from epidemiologic observations, there is some evidence that the ratio of lung cancer to mesothelioma may alter as exposure levels fall. One interesting inconsistency relates to groups such as the British dockyard workers (Rossiter and Coles 1980) and a subgroup of the chrysotile friction product workers (Berry and Newhouse 1983). Both were exposed to some crocidolite and suffered a substantial risk of mesothelioma but no detectable excess of lung cancer. In contrast, the more heavily exposed Australian crocidolite miners appear to have suffered a larger excess of lung cancer than of mesothelioma (Armstrong et al. 1988). One interpretation of these (and many other) differences is that different sizes of fiber have different parenchyma effects, either in their ability to reach the airways or to reach the lung and penetrate the pleura, or in their biological activity in different tissues. Unfortunately, the understanding of fiber carcinogenesis is too limited to justify any very specific conclusions in relation to fiber dimensions, apart from the consistent experimental evidence that fibers much shorter than 5 μm cause much less fibrosis and cell transformation than longer fibers. The implicit assumption that all fibers longer than 5 μm of a given type are equally potent is almost certainly incorrect, but in the present state of knowledge, it cannot be inferred from epidemiologic data whether a thin fiber is more or less potent than a thicker fiber of the same length (Peto 1989). An alternative explanation, however, is that as exposure levels fall, risk falls more rapidly for lung cancer than for mesothelioma. Lung tissue studies indicate higher fiber counts and more extensive asbestosis in lung cancer cases than in cases with mesotheliomas (for example, Wagner et al. 1986, 1988). Such observations have been cited as evidence that lung cancer risk is associated with the fibrosis in asbestosis, in which case very low exposure may be associated with much less lung cancer risk than the linear model suggests. Conversely, however, there are plausible models of carcinogenesis which predict the opposite effect, particularly for childhood exposure. The assumption of dose-linearity for low-dose risk assessment purposes is thus a widely accepted and scientifically reasonable compromise rather than an established scientific principle of carcinogenesis.

Dose-Specific Risk for Chrysotile and Mixed Exposures

The Panel has ignored the very low dose-specific risk estimates for lung cancer derived from chrysotile friction products and chrysotile mining, and has accepted the value of $K_L = 0.01$ recommended by the EPA (Nicholson 1986), the CPSC (1983), and the HSC (Doll and Peto 1985) in calculating the risks at low levels shown in Table 6-3. (This is the geometric mean of the range $K_L = 0.003$ to 0.03 suggested by the CPSC [1983]). The NRC (1984) calculated a median of $K_L = 0.011$, but rounded this up to 0.02 for the risk assessment. The estimates of K_L for chrysotile textiles for both the U.K. study (Peto et al. 1985) and the South Carolina study, as analyzed by McDonald and coworkers (1983a), were approximately 0.01, although in an earlier and smaller study of the same U.S. factory Dement and coworkers (1983a,b) derived a higher value ($K_L = 0.03$, according to Nicholson 1986). Other industrial exposures of chrysotile have given lower risk estimates.

The mesothelioma risks in Table 6-3 were calculated from equation 6.5 assuming a value of 10^{-8} for K_M. This specific model was the basis of the risk assessments presented by the EPA and the CPSC (again with threefold confidence limits). The analysis of mesothelioma incidence in a U.K. textiles factory by Peto and associates (1985), who fitted equation 6.3 with $n = 4$ and $K_M = 1.2 \times 10^{-10}$, gives dose-specific predictions that are similar to those of this model. In the HSC report (Doll and Peto 1985), however, these mesothelioma estimates were halved in the risk assessment for chrysotile, on the grounds that a substantial proportion of mesotheliomas in this cohort (arbitrarily taken to be 50 percent: see *Rochdale (U.K.) Chrysotile Textiles*, under section 6.2.2.3 Measurement of Asbestos Exposure) were likely to have been caused by the crocidolite used in the factory. The HSC risk estimates

for mesothelioma are thus approximately half those of the EPA and CPSC. It should, however, be noted that the HSC estimates were explicitly restricted to chrysotile exposure, whereas the EPA and CPSC estimates were median values based on all available data, including mixed and (in one case) pure amosite exposure.

The models fitted by the EPA and the CPSC (Table 6-3) can be tested by examining their predictions for a mixed population of smoking and nonsmoking male asbestos workers in the United States who enter the industry at various ages between 20 and 40. The estimates shown in Table 6-3 for men aged 30 years at entry suggest that the ratio of mesothelioma to excess lung cancer will be about 1:3 and that about 4 percent of deaths will be due to mesothelioma following 20 years' exposure at 10 f/mL. Among younger recruits, the ratio may be about 1:2. Even higher mesothelioma rates have occurred in men heavily exposed to mixed fiber types, but there appears to be consistent evidence that even heavy exposure to chrysotile alone does not cause a mesothelioma risk as high as this, either in absolute terms or relative to the lung cancer excess. The risks shown in Table 6-3 are thus representative of the estimates obtained for both lung cancer and mesothelioma from cohorts who suffered mixed exposures under a variety of conditions, and for lung cancer among chrysotile textile workers. However, in view of the dose-specific risks for both lung cancer and mesothelioma among Quebec miners and millers, which are very much lower than those shown in Table 6-3, and the absence of pleural mesothelioma in the South Carolina chrysotile textile workers (McDonald et al. 1983a), the mesothelioma risk caused by chrysotile alone may well be less than the rates shown in Table 6-3, perhaps by a large factor in some conditions.

The mesothelioma risk estimate for chrysotile was an issue of disagreement; some members of the Literature Review Panel held the view that a lower estimate should be recommended, as it would be more consistent with the available data. The crucial issues, neither of which can be resolved unequivocally, are (1) what proportion of the mesotheliomas observed in groups such as the U.K. textile workers and the U.S. insulation workers were caused by their exposure to crocidolite or amosite; and (2) whether the best general estimate of the ratio of mesothelioma to excess lung cancer caused by chrysotile is provided by the Quebec miners and millers (about 1:4 or 1:5), or by the South Carolina textile workers handling Quebec fiber (zero). In view of the Panel's decision not to calculate a separate mesothelioma risk estimate for pure chrysotile, the present estimates probably err on the side of conservatism. In addition to the difficulty of agreeing on an appropriate adjustment, the Panel decided that a single estimate for mixed exposure would be of more practical value for the purposes of this report. Most exposure in buildings in the United States involves chrysotile or amosite, and often to both. The frequency with which crocidolite is encountered is thought to be lower.

Dose-Response Relationship for Amphiboles

No extensive measurements of historical exposure levels are available for the cohorts exposed predominantly to crocidolite or amosite. Estimated levels published for the crocidolite miners of Western Australia (Armstrong et al. 1988) varied from 20 to 100 f/mL. Most of this cohort were employed for less than a year, however, and more than half had estimated cumulative exposures of under 10 f/mL-years, while only 5 percent exceeded 100 f/mL-years. There was a marked excess of lung cancer (an overall SMR of about 200, allowing for incompleteness of follow-up) and a high incidence of mesothelioma. In a subsequent publication (de Klerk et al. 1989), a case-control analysis of the same data suggested a value of K_L of 0.01 (equation 6.1), and indicated a significantly elevated lung cancer risk only in the minority of workers (about 3 percent) exposed for more than five years, among whom the relative risk was 2.2, based on 11 deaths. It is difficult to reconcile

these results with the cohort analysis reported by Armstrong and colleagues (1988), which suggests that about half of the 91 lung cancer deaths were due to crocidolite. There were 33 deaths due to mesothelioma (32 pleural and 1 peritoneal), so the ratio of excess lung cancer to mesothelioma may have been between 1:1 and 2:1. If the estimate $K_L = 0.01$ is accepted, the pattern of dose-specific risk for both lung cancer and mesothelioma for exposure of up to five years' duration shown in Table 6-3 would thus appear to fit this cohort quite closely. This would imply that the lung cancer risk per fiber for crocidolite mining is similar to that for chrysotile textiles (although much greater than for chrysotile mining), and the mesothelioma risk per fiber is of the same order as that observed for various mixed exposures, including, for example, the U.K. textile factory studied by Peto and associates (1985), in which less than 5 percent of the fiber processed was crocidolite. No other study provides any useful exposure data for pure crocidolite, however, and this study alone was not considered an adequate basis for these surprising conclusions in view of the questionable basis for the exposure estimates, the incompleteness of follow-up, and the inconsistency noted above. Conversely, however, the suggestive evidence that a relatively small proportion of crocidolite caused many, and possibly most, of the mesotheliomas in several studies cannot be interpreted quantitatively, as crocidolite may generate much higher fiber levels when used in the same way as chrysotile.

The situation for amosite is almost as unsatisfactory as for crocidolite. The only study of amosite workers for which dose estimates have been provided (Seidman et al. 1979; see Nicholson 1986 for updated lung cancer data) is on a cohort of men manufacturing amosite insulation in Paterson, New Jersey, before and during World War II. The dose estimates were largely based on limited measurements taken more than 25 years later in two different factories using similar materials and equipment. There was a marked increase in lung cancer SMR even in men employed for less than two months (SMR = 264, based on 15 deaths), and possible estimates of K_L vary from 0.01 (using the lung cancer rate in short-term workers as the baseline) to 0.04 (by regression on the SMR, based on local rates) (Nicholson 1986). The SMR for men exposed for more than two years was 650, and there were 14 mesotheliomas (7 pleural, 7 peritoneal). There are three major difficulties in interpreting this study: the lack of any reliable exposure data, the anomalous pattern of SMR in relation to duration of exposure, and the uncertainties related to extrapolation from brief very high exposure to prolonged low exposure. If the exposure data are accepted, however, both the lung cancer rate (based on the SMR) and the mesothelioma rate (see Table 6-2) in this study suggest dose-specific risks for amosite substantially higher than those shown in Table 6-3. However, both mesothelioma and lung cancer risk estimates similar to those in Table 6-3 have been derived for the U.S. insulation workers' data, including the large number of peritoneal mesotheliomas identified among insulators by tissue review. The exposure of these workers was to amosite and chrysotile in roughly equal amounts, and estimates of their average exposures are as unreliable as those of the amosite factory workers.

Both amosite and crocidolite have caused high risks of mesothelioma after brief exposure, which has never been observed for chrysotile. Short intense amosite exposure can also cause a high lung cancer rate. Moreover, there is consistent evidence that the ratio of mesothelioma to excess lung cancer is substantially higher for crocidolite compared to chrysotile and amosite.

Consistency of the Predicted Risks

The risk estimates shown in Table 6-3 are clearly inconsistent with some of the observations and risk estimates derived from individual studies. In view of the absence of any adequate quantitative basis for estimating dose-specific risks for crocidolite, and the weakness of all the quantitative exposure data, differences in dose-specific risk between fiber types cannot be conclusively demonstrated. In any case, one of the largest observed differences is between the South Carolina chrysotile textile workers and the Quebec chrysotile miners and millers, whose lung burdens indicate that they were exposed to fibers of similar type and dimension. Most exposure in buildings involves chrysotile or amosite, and a primary concern has been to achieve a reasonable degree of caution in the risk assessment for this situation, in the sense that none of the predictions is likely to seriously underestimate the risk, rather than to choose estimates and models which may be scientifically more reliable or internally consistent. For example, in concluding that crocidolite is more dangerous than chrysotile or amosite, the possibility has been taken into account that the high mesothelioma rate among British chrysotile textile workers was due largely to the relatively small amount of crocidolite to which they were exposed; a corresponding proportion of their lung cancer excess has not been attributed to crocidolite in calculating their dose-specific lung cancer risk for chrysotile. It would therefore not be appropriate to use these estimates as a basis of industrial hygiene limits, particularly in chrysotile mining or friction product manufacture, where observed risks are substantially lower than those predicted. They are intended solely as guidelines for conservative risk management in relation to low-level nonoccupational exposure in buildings in the United States, which usually involves chrysotile or amosite, and rarely crocidolite.

6.2.2.5 Summary of Human Dose-Response Data

1. In cohorts of persons exposed occupationally to elevated concentrations of airborne asbestos fibers, the risks of lung cancer and mesothelioma have been observed to increase with the extent (level and duration) of exposure.

2. The data do not suffice to define the exposure-risk relations precisely but are consistent with conventional risk-assessment models under which the relative risk of lung cancer increases in proportion to the extent of exposure to asbestos, and the increase in absolute risk of mesothelioma caused by each brief increment of exposure is proportional to the extent of the additional exposure and to the 2nd or 3rd power of time thereafter.

3. The effects of asbestos and of cigarette smoking on the risk of lung cancer appear to be more nearly multiplicative than additive.

4. The risk of mesothelioma is not detectably influenced by cigarette smoking.

5. Comparisons among the different cohorts provide evidence that the risk of pleural mesothelioma is appreciably higher with exposure to crocidolite than with exposure to chrysotile or amosite. Peritoneal mesotheliomas have almost always been attributed to amosite or crocidolite exposure.

6. The absence of adequate exposure measurements for the cohorts studied to date severely limits the reliability of any quantitative risk assessments that can be made at this time, especially insofar as the risks of low-level exposure to fibers of different sizes and types may be concerned.

7. Many of the groups of asbestos workers that have been studied epidemiologically were exposed to more than one type of asbestos, and the data on risks caused by each separate variety are inadequate and inconsistent. The Panel therefore calculated average risks for mixed exposures. These are appropriate for the purpose of this report, as some buildings contain more than one type of asbestos.

6.2.3 Time Trends in Mesothelioma Incidence

6.2.3.1 General Comments

Historical Perspective

Primary malignant mesotheliomas have distinctive diagnostic features and are strongly associated with asbestos exposure; for these reasons, the epidemiology (distribution and determinants) of these tumors has been studied as a means of assessing the impact of exposure to asbestos on populations (Peto et al. 1981; McDonald 1985; Gardner and Saracci 1989; McDonald et al. 1989b). The relationship of malignant mesotheliomas to asbestos, alluded to in several earlier reports, was brought to general medical attention in the 1960s as a result of the landmark report by Wagner and associates (1960) describing a cluster of 33 cases from the crocidolite mining area of North-West Cape, South Africa; 18 of these individuals had worked in the mines while 14 were residents of the area, that is, their exposure had been non-occupational. Within a few years of this report, case-control studies carried out in the industrialized countries of Europe and North America confirmed the association of this tumor with exposure, and again both occupational and nonoccupational exposures, domestic and residential, were implicated (McDonald and McDonald 1977). Several high-risk occupations were also identified as well as a concentration of cases in the shipyard cities of Europe and North America.

Subsequently, evidence from a variety of sources (reviewed elsewhere in this report) has accumulated to suggest that crocidolite exposure is more potent in eliciting this tumor than chrysotile exposure (Wagner 1985; McDonald and McDonald 1987a). For instance, proportional mortality due to mesothelioma has been found to be higher, and the number of mesothelioma cases to exceed the excess lung cancer rates, in crocidolite- as opposed to chrysotile-exposed cohorts (McDonald and McDonald 1977; Hughes and Weill 1986). More recently, analysis of lung tissues at autopsy has shown that lung dust concentrations, particularly of long amphibole fibers (crocidolite and amosite), but not of chrysotile, sharply distinguish mesothelioma cases from matched referents (McDonald et al. 1989a). In addition, analyses of case series material have shown that the lung dust burden of chrysotile-associated mesotheliomas is considerably higher than that of amphibole-associated mesotheliomas (Churg and Wright 1989).

Mesotheliomas Without an Asbestos Exposure History

A comprehensive review of over 3,700 cases of mesothelioma reported up to 1977 revealed that, while occupational exposure to asbestos had been identified in approximately 43 percent of cases and domestic or household exposure in 9 percent, no known exposure to asbestos could be ascertained in approximately 38 percent of cases (McDonald and McDonald 1977). Similar findings were reported in a more recent review of published material including planned studies and case series, all of which included cases in which asbestos exposure was neither reported nor considered likely (Gardner and Saracci 1989). However, the proportion of such cases has varied considerably from study to study (ranging from 33 to 63 percent in case-control studies, and from 3 to 50 percent in case

series), at least in part because of differences in study methods, including selection and diagnostic criteria for the cases, and the care with which the exposure history was sought.

Explanations for mesotheliomas without an asbestos exposure history include: (1) occupational and/or nonoccupational exposure to asbestos unknown to the respondent or his or her family, for instance in occupations not known or yet recognized as being at risk; (2) occupational and/or nonoccupational exposure to other agents with mesotheliomagenic potential that is recognized (as for radiation), suspected (as with certain metals), and/or as yet unrecognized (Peterson et al. 1984); and (3) nonoccupational exposure to asbestos from contamination of indoor air, including exposure in buildings. This possibility, not surprisingly, is a major cause for individual as well as for public health concern, and stimulated this study of time trends in mesothelioma incidence.

Incidence Trends in Mesothelioma as a Measure of the Impact of Asbestos Exposure in Populations

Several authors have suggested that mesothelioma incidence can be used as a measure of the impact of asbestos exposure on populations (Peto et al. 1981; Archer and Rom 1983; McDonald 1985), and as a basis for predictive models of future incidence trends over time. Such a model, which took into account the dramatic increase in world production and use of asbestos from the 1920s to the 1950s, is illustrated in Figure 6-4 (McDonald 1985). Mesothelial tumors were considered under four main etiologic categories, three related to asbestos exposure (occupational, household, and environmental) and a background group due to other causes known and unknown. In the model, occupational exposures were considered as being dominant in men and the other three categories of exposure were dominant in women. In addition, the model incorporated the suggestion, attributed by McDonald to Archer and Rom (1983), that a comparison of time trends in tumor incidence in men and women might be used as an indirect indicator of the impact on a population of nonoccupational exposure to asbestos which would include among other things exposure in buildings containing ACM.

Based on this model, the following predictions were made:

1. Prior to the commercial exploitation of asbestos, which began in Canada, Russia, and South Africa in the 1890s, background rates for mesothelioma would be low and comparable in men and in women.

2. In parallel to the rise in production and use of asbestos in the period after World War I, a rise in tumor incidence would occur in men, but would lag by a period of 30 years, which is consistent with what is known about the latent period of the tumor.

3. As the impact of occupational exposures gained force, rates in men would diverge increasingly from those in women, starting probably in the 1950s and continuing well into the 1980s.

4. With the introduction of workplace controls and the fall in the production and industrial use of asbestos from the late 1960s and onward, overall annual rates in men would rise more slowly, stagnate, and eventually again fall to approach those in women.

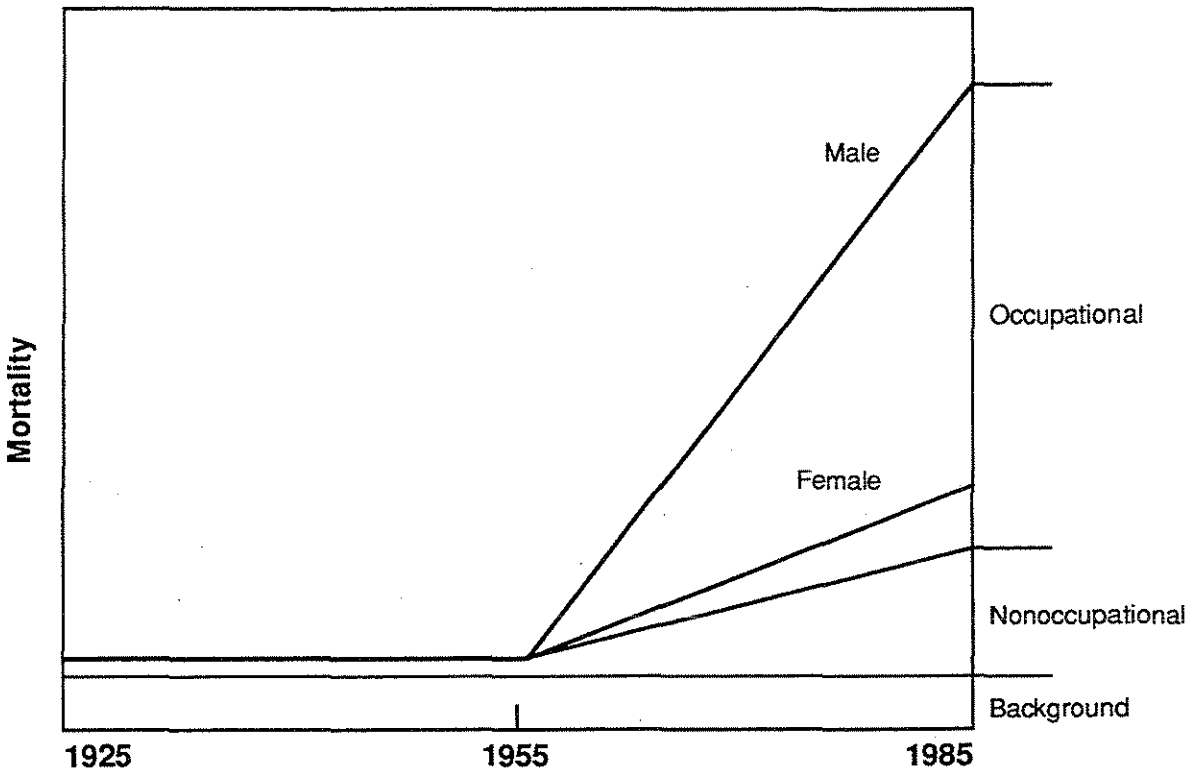


Figure 6-4. Conceptual model for mesothelioma mortality, assuming complete ascertainment. Reproduced with permission from McDonald (1985).

5. Age-specific incidence rates would also reflect these trends, with rates in men in the younger cohorts whose first exposure dated from the 1960s showing less evidence of an exposure effect than rates in older men, which would continue to reflect the heavier exposures in the 1920s and 1930s.

6. An increase in the impact of nonoccupational exposures would be reflected in a trend toward an increase in incidence rates in women.

Published data have supported predictions 1, 2, and 3 of the model (McDonald 1985). Indeed, the increase in incidence rates probably occurred earlier than the 1960s when cases were first noted in the Northern Cape mining region, and a little later in asbestos plants in London that used fiber from the Cape, and in the shipyards of Europe; the delay was due to infrequent recognition of the tumor by physicians and pathologists prior to 1960 (McDonald 1985). There was, however, no comment by the author on evidence in support of predictions 4, 5, and 6; nor was any other published systematic evaluation of published data for such evidence found. Based on more formal models, projected rates for mesothelioma mortality related to occupational exposure to asbestos have been published by Peto and colleagues (1981) and Nicholson and associates (1982). Peto and coworkers

(1981) also reported age specific rates for non occupational (background) mesothelioma in Los Angeles. These were similar in men and women, and corresponded to an annual total of about 400 non occupational cases in the U.S. or a lifetime risk of about 1 in 5,000.

Objectives, Approach, and Material Reviewed

The Asbestos Literature Review Panel, therefore, called for a review of published material on time trends in mesothelioma incidence to examine overall national trends as well as the age-specific trends in mesothelioma rates for evidence of: (1) any abatement in rates in men consistent with a decrease in the impact of occupational exposure, which should eventually follow the reduction in the use of asbestos and control of occupational exposures that started in the late 1960s; and (2) an increase in the rates in women consistent with an increase in the impact of environmental asbestos exposure, including in the latter exposure in buildings containing ACM.

The review was conducted as follows: Relevant publications were sought by employing the Medline computer search. Articles, published in the years 1985 through June 1990, were scanned for reference to "mesothelioma" and "asbestos" as key words. Using both key words in a search, 366 articles were identified; 310 were in the English language. The same computer database was further queried under the following more specific subject headings: (1) Mesothelioma and Asbestos (limited to human studies); (2) Mesothelioma and Trends; (3) Mesothelioma and Environmental Exposure; and (4) Mesothelioma and Rates. Author-title-source listings of publications for each of the above subject headings were reviewed; the abstracts corresponding to articles of interest were scrutinized, and those pertinent to this mandate were reviewed in greater detail. Only English and French language publications were reviewed. No formal search was conducted after June 1990, though several papers that appeared subsequently have been incorporated into this section.

In the tables that follow, the material is presented by region, first for North America, where exposure has occurred primarily as a result of industrial applications of asbestos (United States and Canada) and in mining (Canada); next for the industrialized countries of Europe; and finally for other countries such as South Africa and Australia, where both industrial and mining operations have been responsible for exposure. Data from these various sources are displayed to show first national trends over time (Tables 6-8 to 6-12), then age-specific trends to see which age cohorts were responsible for the trends in the national data (Table 6-13). Information about the source of material and sites of tumor studied is also presented in the tables. Note that the age of subjects included varies between reports, a factor which will obviously contribute to between-study differences in estimated rates.

6.2.3.2 National Trends: Selected Data from Different Regions

North America (Table 6-8)

In the United States, Archer and Rom (1983) were the first to comment on trends in mesothelioma incidence; their analysis was based on deaths recorded in the National Cancer Institute (NCI) register of cancer deaths and coded to pleural malignancy (International Classification of Disease Code No. 162.2) prior to 1968, and to malignant neoplasms of the pleura subsequent to that date. Rates in men and women were comparable prior to 1969, and no significant time trends in rates for either men or women were noted for the period 1958 to 1969. However, after 1969, rates in men and women appeared to diverge over age 45, consistent with the increase in occupational exposures of men in the 1930s and 1940s. Rates in both men and women, however, appeared to remain relatively stable at these higher rates over the period 1970 to 1977.

Table 6-8. Mesothelioma Rates in North America: Results of Selected Studies Illustrating Time Trends

Country; First Author (year)	Years of Study	Age	Incidence per Million Men	Incidence per Million Women	Comments[a] • Source • Sites • Diagnostic criteria • Reference population • Other, including authors' comments
U.S.; McDonald (1985)	1970	All	5.0	< 2.0	• Third National Cancer Survey 1970 – 1972; SEER program 1973 – 1980 • All sites • Pathologic (over 95%) • Rates increased in men from 1970 to 1980, not in women
	1972		5.5	< 2.0	
	1974		9.0	< 2.5	
	1976		9.0	2.5	
	1978		10.5	2.0	
	1980		15.0	2.5	
U.S.; Connelly et al. (1987)	1973	All	5.1	< 2.0	• SEER program; white subjects • Pleural tumors • Pathologic (over 95%) • Rates[b] for 1973 – 1984 standardized to 1970 U.S. population • Geographic patterns related to presence of shipyards or local asbestos industry
	1976		9.0	< 2.0	
	1978		15.0	< 2.0	
	1980		15.0	< 2.0	
	1982		11.0	< 2.0	
	1973 – 1984	All	10.6	1.9 (white)	
	1973 – 1981	All	5.0	1.7 (black)	
U.S.; Spirtas et al. (1986)	1973 – 1980	15+	Average annual increase in men 12% ($p < 0.01$); no significant increase in women		• Cancer registries in Los Angeles County (1972 –1980), New York State (except New York City) (1973 – 1980), SEER program (1973 – 1980) • Pleural tumors • Pathologic
	1973 – 1980	15+	11.3	1.7 (white)	• Standardized to 1970 U.S. population
	Los Angeles		5.9	1.6 (black)	
	1973 – 1980	15+	7.1	1.7 (white)	• Standardized to 1970 U.S. population
	New York		0.0	1.1 (black)	
Canada; McDonald (1980)	1966 – 1975	15+	3.0	1.3	• Canadian Association Pathologists, Quebec Association Laboratory Physicians, Quebec Tumor Registry • Pleural and peritoneal • Death certificates and review by panel of pathologists
	1966 – 1975	45+	7.0	2.5	

[a] Entries in this column correspond to these listed categories.

[b] Rates are approximate only, being derived from figures or other information in the text.

McDonald (1985) and subsequently Connelly and coworkers (1987) both published analyses of data from the Surveillance Epidemiology and End Result (SEER) program extending beyond 1977. Since 1973, this program has monitored cancer incidence in approximately 10 percent of the U.S. population. Results in these studies were consistent, showing an increase in rates in men over the 1970s, but with stagnation in the early 1980s. By contrast, rates in women appear to have been stable over the same period. Connelly and colleagues (1987) comment on the fact that the effects of age and time period on rates were always significant, but that cohort effects appear to have risen to a peak for the 1905 to 1909 cohort (for example, those aged 30 to 35 during World War II) and then declined. A peak in the 1905 to 1909 cohort had been predicted, corresponding to the large number of men in this cohort with shipyard exposures during World War II (Peto et al. 1981; Nicholson et al. 1982). Geographic areas with high rates were usually those with asbestos manufacturing plants or shipyards. Spirtas and associates (1986), in an analysis of tumor registries from Los Angeles County, New York state (excluding New York City), and SEER data, showed significant increases in rates from 1973 to 1980 in men but not in women, changes that did not appear to be attributable to changing diagnostic patterns. Rates in New York state were lower than those in Los Angeles County, an area with shipyard activities. Also of interest is the observation that, in the SEER data, which are nationwide in scope (Connelly et al. 1987), as well as in the Los Angeles County and in the New York state data (Spirtas et al. 1986), rates in black men and women were lower than in white men and women, contrary to what might be predicted on the basis of the distribution of blue collar occupations, a number of which involve asbestos exposure. Unequal access in the past of blacks to certain blue collar occupations may have been a factor. Neither of these studies extended into the mid-1980s, probably the earliest decade in which an effect of decreasing use or improved workplace controls might have been anticipated.

The overall trends in mesothelioma rates in men and women reported for Canada are similar to those found in the United States (McDonald and McDonald 1980). Thus, prior to 1966, rates in men and women appear to have been comparable, while during the period 1966 to 1975 rates in men increased but in women appeared stable. When reexamined in 1983, rates in men had increased considerably while rates in women continued at a stable level comparable to the rates recorded in 1974 (McDonald et al. 1989b). No data on annual rates were available between the mid-1970s and 1984 to determine whether the rate of increase in men is abating. A study in British Columbia, Canada (Churg 1985), led to estimates of incidence for that province in 1982 that were considered consistent with what would be predicted from the national survey of all other provinces excluding British Columbia (McDonald et al. 1989b).

United Kingdom (Table 6-9)

In the United Kingdom, since the late 1960s when rates for mesothelioma were first documented, those in men have exceeded those in women, by a factor of 5 in the period from 1967 to 1968 (Greenberg and Lloyd-Davies 1974) and by a factor of 2.5 in the period from 1968 to 1975 (Gardner et al. 1982). In other words, in contrast to the U.S. data (Archer and Rom 1983), documentation does not appear to exist for a time period when rates were comparable in men and women. There is also some clinical evidence (cited by McDonald 1985) that gender differences in U.K. rates began to appear in the 1950s. Rates continued to rise in both men and women between the two periods, 1968 to 1971 and 1980 to 1983, not only for pleural tumors (Gardner et al. 1982), but also for peritoneal tumors (Gardner et al. 1985), even though the latter constitute only a small proportion of the overall population burden of this tumor in the United Kingdom.

Table 6-9. Mesothelioma Rates in the United Kingdom: Results of Selected Studies Illustrating Time Trends

Country; First Author (year)	Years of Study	Age	Incidence per Million Men	Incidence per Million Women	Comments[a] • Source • Sites • Diagnostic criteria • Reference population • Other, including authors' comments
England, Scotland and Wales; Greenberg and Lloyd-Davies (1974)	1967 – 1968	All	Male:Female 5:1		• Department of Employment Medical Services Division • Pleural and peritoneal • Pathologic criteria • Not pertinent • 68% with asbestos exposure: overall rate 2.29 per million; rates over 8 per million in Clyde and Mersey side
England and Wales; Gardner et al. (1982)	1968 – 1975	All	5.0	2.0	• Offices of Population Census and Surveys • Pleural tumors only • Death certificates • 1971 census • Rates increased over time in men, not in women; geographical pattern followed asbestos industries
Great Britain; Jones et al. (1988b)	1968 – 1971 1972 – 1975 1976 – 1979 1980 – 1983	All	4.9 7.1 11.4 15.3	1.5 1.7 2.4 3.2	• British Mesothelioma Register • Pleural and peritoneal • Death certificates • Registrar General's annual population data • Rates increased approximately 10% annually in men, 6% in women
England and Wales; Gardner et al. (1985)	1967 – 1982	All	0.8	0.4	• HSE Mesothelioma Register • Peritoneal tumors • Death certificates • Standardized to 1971 census data • Rates increased in men and women over time

[a] Entries in this column correspond to these listed categories.

Other Countries in Europe (Table 6-10)

Data have also been reported for several Scandinavian countries. In Denmark (Anderson and Olsen 1985) and in Norway (Mowe 1982), as in the United Kingdom (see above), rates for mesothelioma in men have exceeded those in women since they were first documented. In Denmark, documentation dates from 1943 and in Norway from 1969. In Finland, by

contrast, cancer registry statistics suggest that the tumor was equally frequent in men and women until the mid-1960s, when their rates began to diverge (Nurminen 1975). In line with the predictive model, this suggests that in Norway and Denmark, men had experienced significant occupational exposures in the period between World Wars I and II, and in Finland this had occurred a little later, possibly during World War II. All three countries are maritime and support shipping and marine activity. The only asbestos mining in the region was in Finland, and the fiber mined was anthophyllite, a fiber which has not been associated with mesothelioma occurrence (McDonald and McDonald 1977).

Table 6-10. Mesothelioma Rates in Other Countries in Europe: Results of Selected Studies Illustrating Time Trends

Country; First Author (year)	Years of Study	Age	Incidence per Million Men	Incidence per Million Women	Comments[a] • Source • Sites • Diagnostic criteria • Reference population • Other, including authors' comments
Denmark; Anderson (1985)	1943 – 1947	All	1.5	< 1.0	• National Cancer Registry • Pleural and peritoneal • Pathologic reports and death certificates • European standard population • Rates[b] increased in men and women until the early 1970s but then appear to stagnate
	1948 – 1952		2.0	< 1.0	
	1953 – 1957		3.0	1.5	
	1958 – 1962		7.0	1.5	
	1963 – 1967		10.0	3.2	
	1968 – 1972		13.0	5.0	
	1973 – 1977		14.5	6.0	
	1978 – 1980		14.7	7.0	
Norway; Mowe (1982)	1970 – 1974	15+	4.5	1.1	• Cancer Registry of Norway • Pleural and peritoneal • Pathologic reports • Central Bureau of Statistics 1972 and 1976 population midpoint • 82% men, 17% women reported occupational exposure; from 1970 to 1979, rates increased in men but remained relatively constant in women
	1975 – 1979		7.4	1.3	
Netherlands; Meijers (1990)	1970 – 1978	All	10.8	2.5	• Central Bureau of Statistics • Pleural • Death certificates • Not given • Rates in men exhibited a stronger upward trend than rates in women; clusters related to shipping, building, and heavy industry
	1979 – 1987	All	20.9	3.6	

[a] Entries in this column correspond to these listed categories.

[b] Rates are approximate, being derived from figure(s) or other information in the text.

Subsequent trends in incidence rates in Norway and Denmark were different. In Norway, rates increased in men between the periods 1970 to 1974 and 1975 to 1979, but probably not in women. If the predictive model is correct, then in Norway the stable rates in women imply that nonoccupational exposures did not contribute to tumor burden of that population up to 1979. By contrast, in Denmark mesothelioma rates in both men and women increased from the 1940s onward through 1980, though rates in men at least, and perhaps in women, may have stagnated toward the late 1970s. This would be consistent with an effect of workplace controls, affecting men directly and women indirectly through domestic and, to a lesser extent, occupational exposures.

In the Netherlands, incidence rates in men exceeded those in women for the period 1970 to 1978; in addition, there was an upward trend, more marked in men than in women for the period 1979 to 1987 (Meijers et al. 1990). Also, the geographical distribution showed clustering in men in relation to conurbations and around the harbors, shipyards, and heavy industry bordering on the North Sea coast. In women, a somewhat different distribution was noted, with apparent clustering in the northeast and eastern parts of the country, a distribution for which the authors were able to offer no explanation. Rates were predicted to increase until the end of the century.

Australia (Table 6-11)

In Australia, where the national data are among the most complete for any country, rates in the immediate post World War II period and up to the late 1960s were low and comparable in men and women (Musk et al. 1989). This was followed by a dramatic rise in the rates for men in the late 1960s, a rise which has continued into the 1980s. Currently, estimated incidence rates for Australian men are some of the highest if not the highest reported national rates, and the situation has been characterized as an epidemic (Ferguson et al. 1987; Ferguson 1989). The epidemic may be stagnating according to figures given in the latest report of the Australian Mesothelioma Register for 1982 to 1988 (National Institute of Occupational Safety and Health [NIOSH], Australia 1990). This epidemic does not appear to have been due to overreporting. If anything, in the view of those responsible for the Australian Mesothelioma Surveillance Program, the rates reported are an underestimate of the true incidence (Ferguson et al. 1987). Rates for men and women in Western Australia, the location of the Wittenoom crocidolite mine, are higher than for any other state.

Amphiboles including crocidolite were widely used across the country in local asbestos cement products, for home construction in particular, as well as in thermal insulation. First exposure occurred in 1930 to 1939 in 24 percent of cases reported to the program up to 1985, and was less than one year in duration in 7 percent (Ferguson et al. 1987). According to the predictive model, the rising rates in men in the 1970s are likely to reflect the impact of occupational exposures in the 1930s, and the possible stagnation of rates in the 1980s is likely to reflect the impact of the closure of the Wittenoom mines in 1966, but is probably too early to reflect the impact of industrial regulations brought in during the late 1960s. The increase in rates in women is consistent with the impact of occupational and/or domestic exposure, though environmental exposure cannot be excluded as contributing to these rising rates. The distribution of exposure categories for the 107 women registered up to 1985 is not given, but the facts that the rates in both men and women appear to be following a parallel course and that both appear to be stagnating in the 1980s suggest common exposure sources.

Table 6-11. Mesothelioma Rates in Australia: Results of Selected Studies Illustrating Time Trends

Country; First Author (year)	Years of Study	Age	Incidence per Million Men	Women	Both	Comments[a] • Source • Sites • Diagnostic criteria • Reference population • Other, including authors' comments
All states; Musk (1989)	1947 – 1959	35+	< 1.0	< 1.0	< 1.0	• Cancer Registries; Mesothelioma Surveillance Program[b]; pathologists • All sites • Pathologic criteria • Standard world population • 59% with confirmed exposure; rates[c] in men and women increasing
	1959 – 1963		< 1.0	< 1.0	< 1.0	
	1969 – 1973		5.0	1.0		
	1974 – 1978		17.0	2.5		
	1979 – 1980		28.0	4.0	15.5	
All states; Ferguson (1989)	1982	20+	23.1	2.8	12.8	• Mesothelioma Surveillance Program • All sites • Pathologic criteria • Reference population not given
All states; Ferguson (1987)	1982 – 1985	20+	27.0	3.5	15.1	• See above; 68% reported exposure, 27% did not
All states; Ferguson (1989)	1986	20+	28.9	4.7	18.0	• See above: epidemic thought to be rising
Western Australia; Armstrong (1984)	1960 – 1964	35+	6.0	0.0		• Records of public hospitals, State Health Lab Service, Perth Chest Clinic, and Pneumoconiosis Board • All sites • Pathologic criteria • Standardized to world population 20 years+ • 70% reported asbestos exposure
	1965 – 1969		8.0	1.0		
	1970 – 1974		16.0	1.0		
	1975 – 1979		39.0	4.0		
	1980 – 1982		66.0	7.0		
All states; Mesothelioma Register (1990)[d]	1982	20+	22.2	2.6	11.8	• Mesothelioma Registry • All sites • Pathologic criteria • World standard population 20 years+ • Rates[c] published without comment
	1983		22.0	2.7	11.9	
	1984		27.5	2.8	14.5	
	1985		23.0	2.6	12.0	
	1986		35.0	3.5	18.0	
	1987		25.0	3.4	13.0	
	1988		32.5	3.3	17.0	

[a] Entries in this column correspond to these listed categories.

[b] The program started in New South Wales in 1970, and attempted to cover all Australia from 1981.

[c] Rates are approximate, being derived from figure(s) or other information in text.

[d] See National Institute of Occupational Safety and Health, Australia (NIOSH 1990).

In Australia (Ferguson et al. 1987), as elsewhere (McDonald and McDonald 1977), a substantial proportion of cases (27.6 percent) do not report exposure to asbestos; in other words, these are cases which are potentially attributable to environmental exposure, including exposure to ACM in buildings. However, if the rates in women are indeed stagnating, this is contrary to what could be expected from the predictive model if environmental exposures in post World War II buildings containing ACM were having an impact on the public's health. Of course, the climate of Australia may mean that Australians spend much less time indoors compared to North Americans, who on average spend over 90 percent of their time indoors (Samet et al. 1988), though the number of working hours spent inside office buildings may nevertheless be comparable in the United States and Australia.

Table 6-12. Mesothelioma Rates in South Africa: Results of Selected Studies Illustrating Time Trends

Country; First Author (year)	Years of Study	Age	Incidence per Million Men	Incidence per Million Women	Comments[a] • Source • Sites • Diagnostic criteria • Other, including authors' comments
All provinces[b]; Botha (1986)	1968 – 1980	35 – 74	21.0	6.0 (white)	• Department of Statistics
			13.0	9.0 (colored)	• All sites
					• Death certificates
Crocidolite mining areas; Botha (1986)	1978 – 1980	0 – 44	< 1.0	< 1.0 (white)[c]	• Department of Statistics
		45 – 54	9.0	6.0	• All sites and/or asbestosis
		55 – 64	16.0	7.0	• Death certificates[c]
		65 – 74	69.0	30.0	• High age-specific rates in mining areas, especially for women who were not employed in mines till 1950, implicate environmental rather than occupational exposure
		75+	43.0		
		0 – 44	1.0	2.0 (colored)	
		45 – 54	8.0	8.0	
		55 – 64	28.0	6.0	
		65 – 74	36.0	0.0	
All provinces[b]; Zwi (1989)	1976	15+	27.6	3.9 (white)	• Cases registered by doctors and hospitals in/near mining areas and factories, by the Medical Bureau for Occupational Disease, and by Mesothelioma Register and SA Asbestos Tumor Reference Panel
	1978		31.4	10.5	
	1980		41.6	8.5	
	1982		32.7	8.9	
			40.5	12.7	
All provinces Zwi (1989)	1976 – 1984	15+	32.9	8.9 (white)	• Pleural and peritoneal
			24.8	13.9 (colored)	• Pathologic criteria
			7.6	3.0 (black)	• Rates[c] high but apparently stable in men and women in the 1980s: 58% men, 50% women reported occupational or environmental exposure; in 10% of both no exposure was reported

[a] Entries in this column correspond to these listed categories.

[b] Data from the homelands not available: reference population from Department of Statistics for the midpoint of the years cited.

[c] Factors contributing to different rates by population group include differential access to health services, and for blacks absence of data from the homelands.

South Africa (Table 6-12)

Two studies are pertinent to the present issue. In the first (Botha et al. 1986), the authors cite the national rates for mesothelioma for 1968 to 1980 as being among the highest ever reported. For men, incidence rates were higher in white people than in colored people (a designation indicating a person of mixed race) (21 vs. 13 per million); for women the reverse occurred (6 vs. 9 per million). They then go on to report on their analysis of data from the crocidolite mining areas of the country, in which they showed SMRs for mesothelioma and/or asbestosis for men and women from the crocidolite mining areas of the North-West Cape (where 2 to 4 percent of adults were employed in mining) to be considerably higher than those for contiguous areas (where under 1 percent of adults were employed in mining); for white men and women these were 7.9 and 10.3 per million, for colored men and women 8.4 and 8.7 per million. Elevated SMRs were also found for lung and stomach cancer. Both occupational and environmental exposure were implicated, the latter especially in colored women.

In the second study, ascertainment of mesothelioma cases from 1976 to 1984 was carried out on a nationwide basis using various sources of information (Zwi et al. 1989), and annual rates were calculated for the period. Annual rates were unstable, so trends should be interpreted with caution. Nevertheless, age-standardized incidence rates in all population groups appeared to increase during the 1970s, whereas thereafter in the 1980s there was no clear evidence of an increase in any of them. Levels of exposure in South African workplaces were reduced progressively from the 1940s to the 1980s; production of asbestos also fell in the 1980s, as did the use of crocidolite (Becklake 1987), factors which may have contributed to the stabilization of rates. In addition, in all population groups, rates were higher in men than in women. Estimated incidence was also higher in white men than in colored men, and higher in colored men than in black men. Among the women, the highest rates were in colored women. The low rates in black people were attributed largely to underascertainment and unequal access to health care facilities. Note the rates in white South African men are among the highest national rates reported, and comparable to those of Australia, the only other country with a crocidolite mining industry.

6.2.3.3 Age-Specific Trends: Data from Selected Regions

United States

As already discussed, overall annual rates for mesothelioma incidence in men in the United States increased steadily though the 1960s and 1970s with a possible stagnation of the rate of increase in the 1980s (see Table 6-8). Age-specific data for men are also available from several sources, including the National Cancer Institute record of cancer deaths (Archer and Rom 1983), the SEER data and certain regional cancer registries (Spirtas et al. 1986), and the University of Pittsburg mortality and population data system (Enterline and Henderson 1987). All age-specific rates in men and women in the United States are lower than those in the other countries represented in Table 6-13; only in Norway do the rates for women approach those in the United States. In addition, all U.S. studies are consistent in showing that during the 1970s mesothelioma rates appear to be stable for cohorts under age 54, and all U.S. studies except Archer and Rom (1983) showed that rates in those 65 years of age and over have continued to increase. However, certain modifications in these trends through 1986 are suggested in the analysis of SEER data up to that date (Hoel 1990) (see Figures 6-5 and 6-6). Thus, in men 45 to 54 years old, incidence rates in the 1980s were on the whole lower compared to those in the 1970s, and rates in the older cohorts (55 to 64,

65 to 74, and 75 to 84 years of age), though higher than those in the 1970s, may be stabilizing. The data in women are less easy to interpret because the number of cases is smaller and consequently there is less stability in rates. Nevertheless, the trends are similar to those in men. Thus in women 45 to 54 years old, incidence rates in the 1980s appear to be lower than those in the 1970s, while rates in the older cohorts (55 to 64, 65 to 74, and 75 to 84 years of age), though higher than those in the 1970s, may be stabilizing.

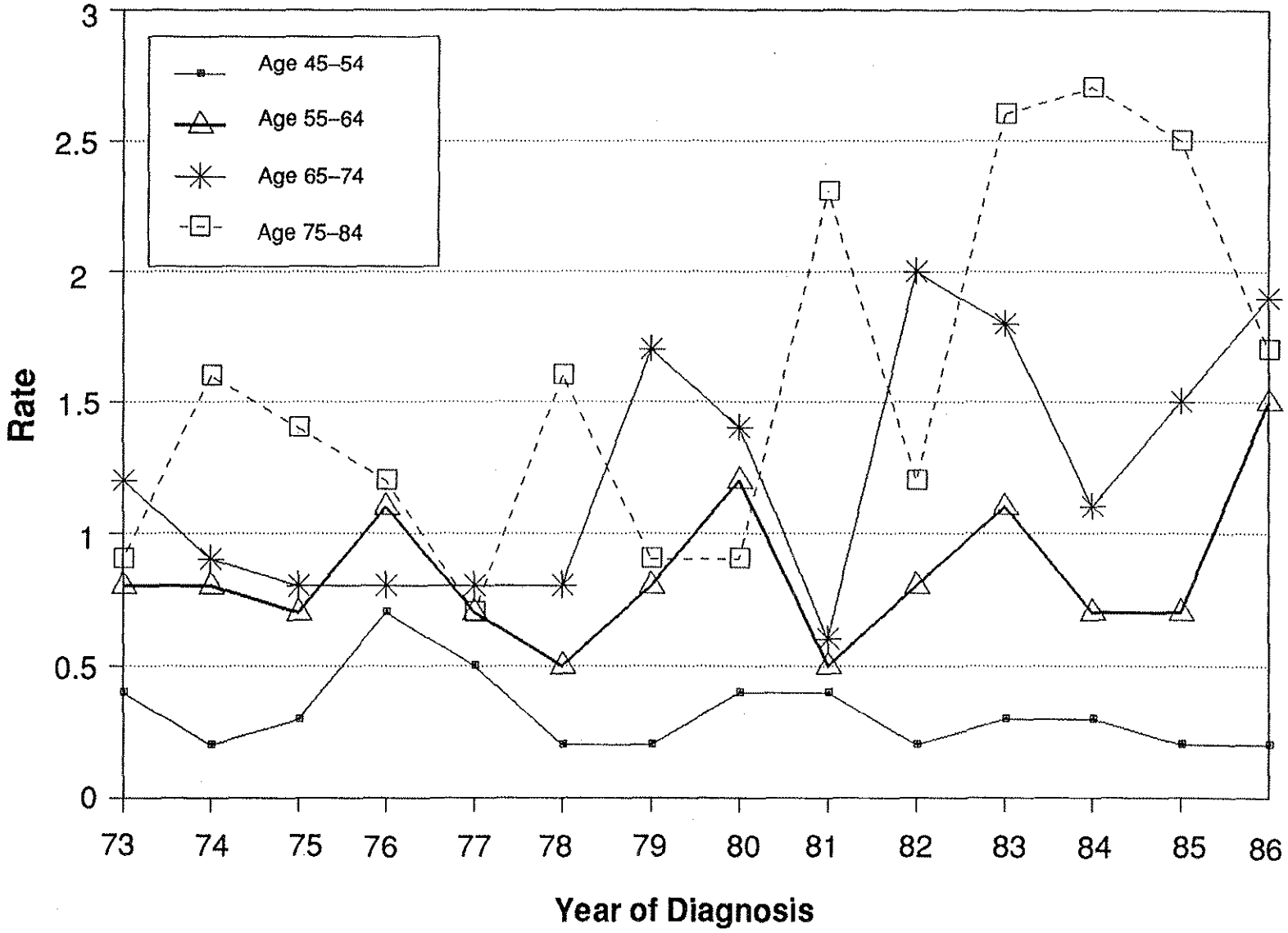
The parallel trends in age-specific rates in men and women are somewhat surprising since they suggest similar, not different, exposure sources, contrary to what is proposed in the predictive model. Nor are reasons obvious for the apparently lower rates in the United States in the 1980s compared to the 1970s in both men and women in 45- to 54-year-old cohorts. Occupational asbestos exposure is unlikely to have affected either men or women in this cohort prior to 1951, though both may have been subject to environmental or domestic exposures associated with World War II and post World War II increases in asbestos use. It is surprising that rates in men at least do not reflect occupational exposure associated with the postwar increase in asbestos use; the reason may be inadequate latency. Nor do the data in these age cohorts of men and women provide evidence in support of an increase in the contribution of exposure in buildings containing ACM to the mesothelioma burden of the U.S. population. Again, this may be due to inadequate latency. It may also be due to insensitivity of these rates and this type of analysis to the effects of low exposures.

The rise in incidence rates in the 1980s compared to the 1970s in the older cohorts of men and women (55 to 64, 65 to 74, and 75 to 84 years of age) probably still reflects their asbestos exposures during World War II, occupational, domestic, and environmental. The fact that the rates appear to be stabilizing in the 1980s could also be interpreted as evidence against a contribution from exposures in buildings containing ACM. However, even given the higher rates in older individuals, latency may be inadequate and incidence trends too insensitive to detect the consequences of low-level exposure.

European Countries

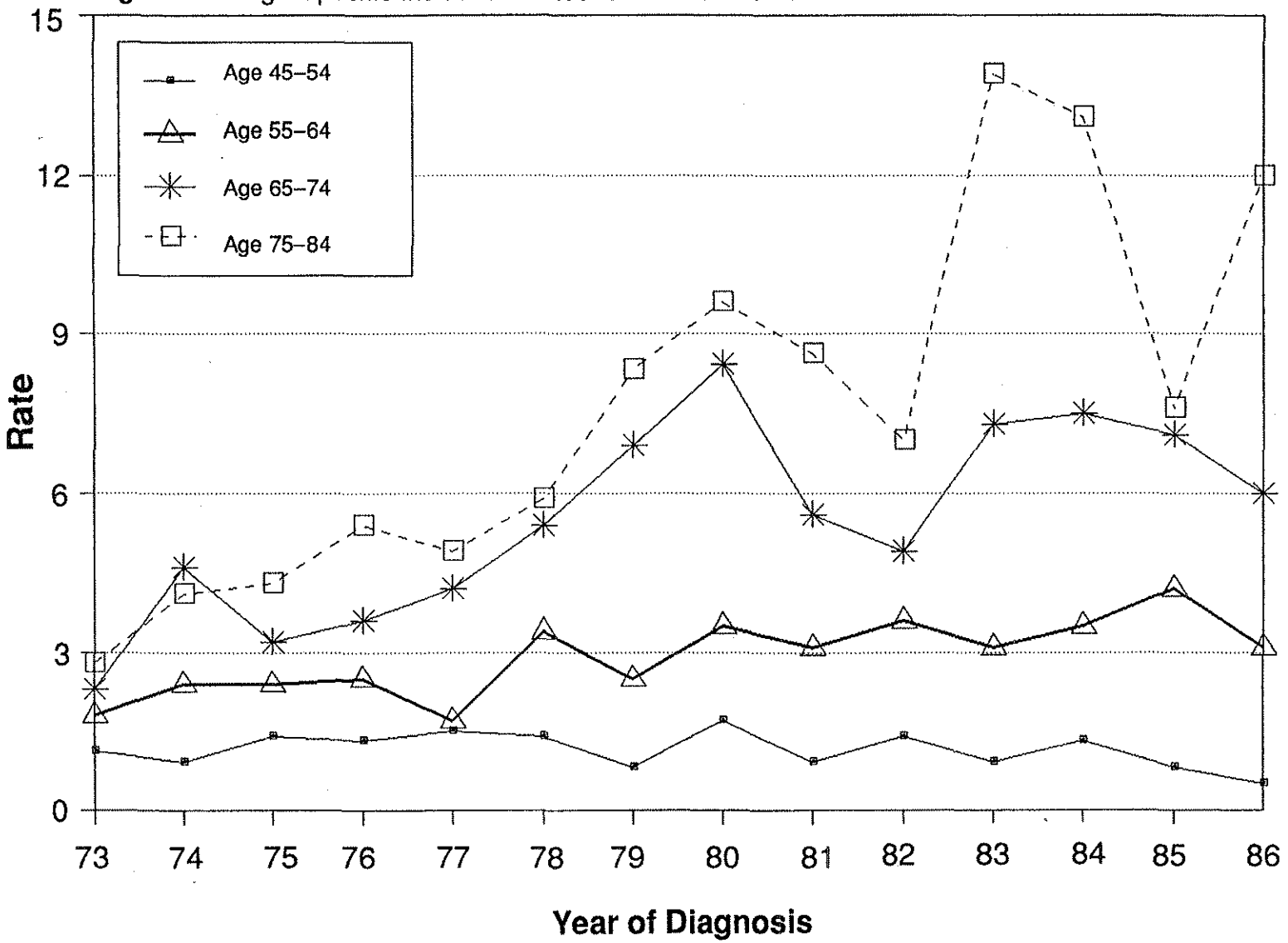
Of the four industrialized countries of Europe for which overall rates in men continued to increase up to the 1980s and for which age-specific rates have been reported, namely the United Kingdom (Jones et al. 1988b), Denmark (Anderson and Olsen 1985), the Netherlands (Meijers et al. 1990), and Norway (Mowe 1982), the increase in all was confined to age cohorts 45 years and up. Only in Denmark is there perhaps evidence for a stagnation in the rate of increase, and this is seen only in the youngest of these age cohorts, that is, age 45 to 54, by the period 1978 to 1980; this may reflect the effects of precautions in the use of asbestos implemented in that country in the 1950s, prior to a subsequent prohibitive ban (Anderson and Olsen 1985). Also of interest is the fact that in Norway, as in the United States, age-specific rates in men under 45 for the period 1975 to 1979 appear to have declined to a level close to that of Norwegian women of the same age, suggesting perhaps the beginning of the control of the epidemic of the 1970s in that country. By contrast, in the United Kingdom and the Netherlands, age-specific rates for older men continued to increase into the 1980s, with men in the Netherlands aged 65 to 74 years experiencing some of the highest rates recorded anywhere for their age cohort, exceeded only in South Africa. This age group reflects those entering the workforce in the immediate postwar period, a group which would have accumulated 20 years of exposure prior to the introduction of controls in the United Kingdom (Jones et al. 1988b) and 30 years of exposure prior to the introduction of controls in the Netherlands (Meijers et al. 1990).

Figure 6-5. Age-Specific Incidence Rates for Mesothelioma for Women



Rate per 100,000 population for U.S. women, based on Surveillance Epidemiology and End Result (SEER) data from 1973 to 1986. From D. Hoel, National Institute of Environmental Health Sciences, personal communication (1990).

Figure 6-6. Age-Specific Incidence Rates for Mesothelioma for Men



Rate per 100,000 population for U.S. men, based on Surveillance Epidemiology and End Result (SEER) data from 1973 to 1986. From D. Hoel, National Institute of Environmental Health Sciences, personal communication (1990).

In regard to the mesothelioma rates in women in the four industrialized countries of Europe referred to above, only in Norway (Mowe 1982) have these not shown an increase in the 1960s and 1970s. In that country also age-specific rates in women appear to have been stable for all but the oldest reported cohort, aged 65 to 74 years; that is, an age cohort which reflects exposures during the 1940s. In the other three countries, though age-specific rates for women up to age 45 have been stable with the possible exception of Denmark (Anderson and Olsen 1985), age-specific rates for women in cohorts aged 45 years and over have consistently shown a tendency to increase, a tendency which is strongest in the data from Denmark (Anderson and Olsen 1985), less strong in the U.K. data (Jones et al. 1988b), and least in the data from the Netherlands (Meijers et al. 1990). Indeed, in the Netherlands the evidence is consistent with the epidemic of mesothelioma affecting women in the 1970s coming under control.

Australia and South Africa

In the last two countries listed in Table 6-13, exposure has, as already mentioned, resulted from mining operations as well as industrial uses; and both countries have supported a not insubstantial crocidolite mining industry, in Australia lasting from 1943 to 1966 (Armstrong et al. 1984) and in South Africa from the late 1890s to date.

Age-specific rates for Australia are available only for the three years 1986, 1987, and 1988 (National Institute for Occupational Safety and Health, Australia 1990). Annual rates over such a short time are probably too unstable to display time trends reliably; nevertheless, they provide some insight into the distribution of cases by age in the 1980s. Thus, while there is a strong effect of age on rates in men (those for older age groups being considerably higher than those for younger age groups), the data also suggest that age-specific rates were stable or declining in all except the older age group (75 years and older), in which rates increased. The same pattern is observed in Australian women; thus, though their overall rates increased in the 1970s and early 1980s, these appear to be stable over the period 1986 to 1988 (age-specific rates for less than 45 years and 45 to 54 years) or decreasing (age-specific rates for 55 to 64 years, 65 to 74 years, and 75 plus years). These findings suggest that the epidemic among men and women which developed in the 1960s and 1970s may be coming under control, and that common exposures were influencing rates in both men and women. Thus the data do not permit speculation about the relative contributions of occupational or environmental exposure to tumor rates in this country.

The data from South Africa, though in some ways more complete, are also less consistent (Zwi et al. 1989). Age-specific rates for white men and women in all the cohorts shown in Table 6-13 are the highest reported, higher than for the Netherlands (the highest in Europe), higher even than for Australia. Unlike Australia, in which for the 1980s the trend toward an increase in age-specific rates is seen only in men 75 and over, in South Africa this trend is also seen in men and possibly in women aged 65 to 74 years. In addition, in South Africa, all age-specific rates in all cohorts of women studied increased over the 1980s, an increase which may reflect not only occupational and domestic exposure, but also environmental exposure to asbestos, both indoor and outdoor. The increase over the 1980s was more evident in white women than in colored and black women (Zwi et al. 1989).

Table 6-13. Age-Specific Mesothelioma Rates per Million: Time Trends in Selected Studies from Various Countries

Country; First Author (years)	• Source[a] • Site • Other Comments	Years of Study	Men by Age Group					Women by Age Group				
			< 45	45 – 54	55 – 64	65 – 74	75+	< 45	45 – 54	55 – 64	65 – 74	75+
U.S.; Enterline (1987)	• Mortality and population data • Pleural	1968 – 1970	> 1	> 2	6	11[b]	NA[c]	< 1	2	3	5[b]	NA
		1971 – 1974	1	2	7	13	NA	< 1	2	2	4[b]	NA
		1975 – 1978	0.8	2	7	13	NA	< 1	2	2	4	NA
		1979 – 1981	0.3	< 2	7	15	NA	< 1	< 2	2	4	NA
Norway; Mowe (1982)	• National Cancer Registry[d] • Pleural and peritoneal	1970 – 1974	0.6	2	15	20	NA	0.2	0.8	3	4	NA
		1975 – 1979	0.3	9	19	30	NA	0.2	—	3	5	NA
Denmark; Anderson (1985)	• National Cancer Registry • Pleural and peritoneal	1948 – 1952	< 1	2	5	6		< 1	2[e]	2[f]	< 1	
		1958 – 1962	< 1	5	30	47		< 1	1	7	12	
		1968 – 1972	2	20	42	55		2	9	8	35	
		1978 – 1980	2	18	57	80		2	10	10	48	
U.K.; Jones et al. (1988b)	• Mesothelioma Register of Deaths[d] • All sites	1968 – 1971	< 2	< 10	15	18	18	< 2	3	4	5	3
		1972 – 1975	< 2	12	20	28	22	< 2	3	5	7	6
		1976 – 1979	< 2	15	30	45	45	< 2	3	7	8	8
		1980 – 1983	< 2	18	45	60	65	< 2	4	9	11	8
Netherlands; Meijers (1990)	• Central Bureau of Statistics[d] • Pleural	1970	< 2	8	33	51	8	< 1	8	11	9	7
		1975	< 2	13	30	65	30	< 1	4	10	12	8
		1980	< 2	18	55	145	48	< 1	4	12	20	17
		1985	< 2	25	58	127	58	< 1	3	8	8	6
		1987	< 2	28	96	147	68	< 1	4	6	13	12
Australia; NIOSH (1990)	• National Mesothelioma Register • All sites • Rates are for first five years of decade indicated	1986	< 2[e]	19	81	147	106	< 2[g]	5	8	26	21
		1987	< 2	11	58	133	123	< 2	5	8	19	15
		1988	5	13	83	113	222	< 2	5	3	6	9
South Africa; Zwi (1989)	• National survey • Pleural and peritoneal • White	1976	11[h]	43	74	149	82	4[h]	5	11	8	30
		1978	0	47	102	176	105	4	23	22	54	28
		1980	16	69	118	180	102	7	14	16	21	40
		1982	16	27	103	184	99	7	9	32	21	39
		1984	15	43	101	204	240	10	18	26	67	25

[a] Entries in this column correspond to these listed categories.
[b] Rates for 65+.
[c] NA = Not available.
[d] Note that for these studies, rates are approximate, derived from figure(s) and other information in the text.
[e] Rates for age 45 to 59.
[f] Rates for age 60 to 74.
[g] Rates for age 35 to 40.
[h] Rates for age 35 to 44.

6.2.3.4 Synthesis

Interpretation of Time Trends in Mesothelioma Incidence

National data on mesothelioma incidence have been reviewed in light of the predictive model which holds that rates in men reflect primarily occupational exposures and that rates in women reflect primarily nonoccupational exposures, whether domestic or environmental (the latter including exposure in buildings containing ACM). Published data were assessed for evidence of (1) abatement of the impact of occupational exposures, and (2) increase in the impact of nonoccupational exposures on national incidence rates. The first change would be reflected in a stagnation of the trend of increasing incidence of mesothelioma in men. Because their exposure is primarily occupational, rates for men would reflect the impact of the improvement in workplace controls which started in the 1960s and might be anticipated by the late 1980s. The second change might be reflected in rising incidence rates in women, starting probably in the 1980s or the 1990s, that is, some 30 years or more after the widespread use of ACM in industrial, office, and home and school building construction.

Evidence from Time Trends in Men

As regards evidence for an abatement of the impact of occupational exposures, the increase in overall incidence rates for men does appear to be stagnating in certain countries such the United States, Denmark, and Norway, and possibly though not certainly in Australia and South Africa. By contrast, in the United Kingdom there is little evidence to suggest abatement, with rates in men continuing to increase well into the 1980s. The same probably holds for the Netherlands. However, even in countries in which overall rates in men appear to be stagnating, age-specific rates in older age cohorts continue to increase (age 55 years and over in the United States, and in Denmark). By contrast, rates for U.S. men under 55 years of age were on the average lower in the 1980s than in the 1970s. Currently available data from several countries, including the United States, are therefore consistent with predictions 4 and 5 above, namely, that the impact of workplace exposures on the population burden of this tumor is decreasing. In addition, all age-specific rates for men and women in the United States are lower than these rates in any of the other countries for which data were available for comparison (see Table 6-13).

Evidence from Time Trends in Women

As regards evidence for an impact of environmental exposures on national population statistics, overall rates for women in some countries, namely, the United States, Norway, and possibly South Africa, appear to have been stable since the 1970s and therefore provide no evidence that environmental exposures, including exposure in buildings containing ACM, have had a public health impact. In other countries, such as the United Kingdom, Denmark, and Australia, rates in women continue to rise, a rise to which such environmental exposures may be contributing. However, in these countries too, the rise is invariably confined to the older age groups, and age-specific incidence trends for cohorts under age 55 appear to be stable in the Netherlands and Australia, and possibly in the United Kingdom, Denmark, and South Africa.

In the case of the United States, though overall rates in women are low and have been stable since the 1970s, age-specific rates for the age cohorts 55 years and over appear to be higher in the 1980s than the 1970s while the opposite holds for the age cohort 45 to 54 years (see Figure 6-6). Since the trends in overall and age-specific rates in women parallel

those in men, common exposure pressures seem likely despite the predictive model. Thus, all sources of exposure may be implicated in the older cohorts of women, including occupational (as more women entered the workforce during World War II in blue-collar occupations), domestic (reflecting the work exposures of their menfolk especially during World War II), and environmental. Within the latter category of environmental exposure, it is therefore not possible to exclude a contribution from exposure to asbestos in outdoor air or in buildings containing ACM affecting rates in both men and women. On the other hand, the observation that rates in both men and women aged 45 to 54 years appear to be lower in the 1980s compared to the 1970s provides some contrary evidence. It must, however, be emphasized that cancer rates in any cohorts under age 55 tend to be low, given that cancer is a disease with a long latency period, and that the latency period in these cohorts is possibly too short to reflect the impact of the low levels of exposure which would be experienced by C1 building occupants (that is, general occupants whose working week is spent in the building but who are unlikely to disturb asbestos in place).

Distribution Among Men and Women of Mesotheliomas Without an Asbestos Exposure History

It has previously been noted that for mesothelioma, cases without an asbestos exposure history were more or less equally distributed among men and women (Peto et al. 1981). For instance, in a study of Los Angeles County (Peto et al. 1981), of 41 such cases, 22 were in men and 19 in women. In a study based on the Cancer Registry of Norway, of 41 such cases, 21 were in men and 20 in women (Mowe and Gylseth 1986). In a U.K. clinical case series of 23 such cases, 13 were in men and 10 in women (Law et al. 1983). In a study of 10 such cases from France, 6 were in men, 4 in women (Hirsch et al. 1982). This suggests one of two possibilities: either background rates for mesothelial tumors which are unrelated to environmental exposure of any sort are similar in men and women (McDonald 1985), that is, spontaneous rates for this tumor are similar in men and women; or whatever environmental factors are operative in these background cases are similar in men and women. Only in the South African study were there more men than women (40 vs. 20) among cases for which no asbestos exposure was reported (Zwi et al. 1989).

6.2.3.5 Estimated Impact on Mesothelioma Incidence of Exposure in Buildings

The average exposure level for recently-surveyed asbestos-containing buildings is about 0.0005 f/mL for schools and 0.0002 for public and commercial buildings (see Chapter 4). The calculations in section 6.2.2 and Chapter 8 lead to the prediction that the number of background mesotheliomas in the United States each year might be increased from the present level of about 400 per year (200 in men and 200 in women) to about 410 if the whole population were exposed for 20 years at work to an average level of 0.0002 f/mL, and a similar risk is predicted for 13 years of school exposure at 0.0005 f/mL. The whole population does not work in asbestos-containing buildings, however, and the risk assessment model discussed in section 6.2.2 predicts that only a few mesotheliomas are likely to occur each year due to such exposure (see also Chapter 8). Even an increase of 10 mesotheliomas per year would not be detectable in national age-specific rates; that is, they would be beyond the detection capability of the analysis conducted in this section. Nevertheless, national mesothelioma trends, and particularly trends in nonoccupational cases and in women, are of interest. First, a major outstanding concern is that these average levels for ACM-containing buildings may not be representative. These data provide a low upper limit, albeit much higher than that predicted, for the possible impact of environmental exposure. Second, much heavier nonoccupational exposure probably occurred in the past and may still occur in some situations, and such data provide a means of identifying any such unsuspected serious hazard.

The observation of little or no increase in incidence rates of mesothelioma in women below age 50, almost all of which is likely to be nonoccupational, thus cannot confirm the risk assessment model discussed in sections 6.2.2 and 8. It does, however, indicate that any overall risk to the whole population is likely to be very much less than the lifetime background mesothelioma rate, which is about 1 in 5,000.

6.2.3.6 Summary and Conclusions

The analysis of time trends in mesothelioma incidence by country permits the following conclusions:

1. Mesothelioma incidence rates in men increased in most industrialized countries during the second half of the twentieth century, with documentation being available from the 1940s for Denmark and Australia, from the 1960s for the United Kingdom, and from the 1970s for the United States, Canada, Norway, the Netherlands, and South Africa. Though in the United States, rates for women have remained low and stable over the same period, in all other countries overall rates in women have also increased, though at a much slower rate than have the rates in men in the same country. In South Africa, the reported annual rates in women, though somewhat variable and much higher than in the United States, may have stabilized in the late 1970s and early 1980s.

2. In countries for which data are available for the 1980s, overall incidence rates for mesothelioma in men appear to be stagnating in the United States and Denmark, and possibly in Australia and South Africa. Thus, the decrease in use of asbestos and improved workplace controls already appear to have had a favorable impact on the public health in these countries. In other countries, such as the United Kingdom and Denmark, rates continued to rise in the 1980s.

3. Overall rates for mesothelioma incidence in women have been stable since the 1970s in some countries, including the United States, Norway, and possibly South Africa, and therefore provide no evidence of an impact on the public health from environmental exposure to asbestos, including exposure in buildings containing ACM. In other countries such as the United Kingdom and the Netherlands, rates in women, like those in men in the same country, continued to increase in the 1980s, while in Denmark rates in women continued to increase, though those in men already appeared to show signs of stagnation.

4. In countries where overall incidence rates have continued to rise and age-specific rates are available for analysis, the rise has been attributable, not surprisingly, to higher rates in the older cohorts; for example, in the United Kingdom and Denmark in cohorts aged 55 years and over. Even in countries such as the United States where overall rates in men appear to be stagnating, rates in older cohorts aged 65 years and over, and possibly aged 55 to 64 years are still increasing. On the other hand, rates in the United States in men and women 45 to 54 years of age may even be decreasing (Figures 6-5 and 6-6).

5. The risk assessment model discussed in section 6.2.2 and Chapter 8 predicts that the number of background (that is, not asbestos-related) mesotheliomas in the United States might be increased by 10, from approximately 400 per year (200 each in men and women) to about 410 per year, if the whole population were exposed for 20 years in buildings to the average level of 0.0002 f/mL, observed in the data reviewed in Chapter 4, or for 13 years to the average level of 0.0005 found for schools. This small increase

would not be detectable by an analysis of national age-specific trends in mesothelioma incidence nor could such an analysis confirm the risk assessment model discussed in section 6.2.2 and Chapter 8. The data do, however, indicate that the overall risk to the population for mesothelioma in buildings is likely to be smaller in comparison to the lifetime background mesothelioma rate, which is about 1 in 5,000.

6.3 Data from Experiments with Laboratory Animals and Cultured Cells

6.3.1 Data from Experiments with Laboratory Animals

6.3.1.1 Influence of Fiber Type, Fiber Size, and Fiber Number

The use of animal experimentation to examine the possibility of adverse effects resulting from exposure to very low doses of asbestos has been hampered by the theoretical impossibility of proving a negative, given the background levels of the effects in question, and also by sheer cost. The most biologically accurate way to examine the dose-response relationship for effects caused by dusts is to undertake a series of long-term inhalation studies with large groups of experimental animals over a wide range of doses. The costs of this type of work in general prove prohibitive, and only one such study has been reported (Table 6-14), paradoxically not with asbestos but with aramid fibers (Lee et al. 1988). In this work rats were exposed to dose levels ranging from 2.5 f/mL to 800 f/mL. While the highest doses killed animals in the early stages of the experiment due to excessive pulmonary reaction, and the highest dose that allowed full life-span survival produced pulmonary fibrosis and pulmonary tumors, the dose level of 2.5 f/mL produced no signs of pulmonary disease. The only study in which animals were exposed to different asbestos doses in long-term inhalation studies was that reported by Davis and associates (1978). In this study, rats were exposed to chrysotile at doses of 2 mg/m^3 (390 f/mL, length greater than 5 μm by phase-contrast optical microscopy [PCOM]) and 10 mg/m^3 (950 f/mL, length greater than 5 μm by PCOM), with crocidolite being used at doses of 5 mg/m^3 (430 f/mL, length greater than 5 μm by PCOM) and 10 mg/m^3 (860 f/mL, length greater than 5 μm by PCOM). The crocidolite sample was the Union International Contre Le Cancer (UICC) reference sample, which is now considered as being composed largely of fibers too short for maximum pathogenic effect, and little disease was produced by either dose. While the 10 mg dose of chrysotile produced far more fibrosis and pulmonary tumors than the 2 mg dose, the difference in both cases was less than the fivefold difference in dust exposure.

Wagner and coworkers (1974) adopted an alternative approach, by which rats were exposed to a range of asbestos fiber types at a constant dose (10 mg/mL) but over times varying from one day to two years. Production of both pulmonary fibrosis (Table 6-15) and pulmonary tumors (Table 6-16) increased with time for all dusts, but the response was not regular enough to determine if the dose-response pattern was linear or indeed the same in all cases.

Table 6-14. Degree of Fibrosis (Asbestosis) and Pulmonary Tumors Produced in Rats by the Inhalation of Mineral Fibers at Varying Dose Levels

Study	Dust	Dose	Fibrosis[a] (%)	Tumors[b] (%)
Davis et al. 1978	UICC chrysotile A	10 mg/m^3	9.2	37.5
Rats, Wistar (Han) male[a]		2 mg/m^3	3.8	21.4
	UICC crocidolite	10 mg/m^3	1.4	2.5
		5 mg/m^3	0.8	6.9
Lee et al. 1988	Kevlar	400 f/mL	NC[c]	M 8.3
Rats 50% male,				F 14.2
50% female;		100 f/mL	NC	M 1.5
Charles River strain				F 10.1
		25 f/mL	NC	M 0
				F 1.5
		0.5 f/mL	NC	M 1.5
				F 0

[a] Pecentage fibrosis was calculated by recording the percentage of lung tissue occupied by fibrosis in microscope slides from each individual animal and taking the mean for all animals in each exposure group.

[b] Percentage tumors refers to the proportion of each experimental group developing pulmonary tumors.

[c] NC = Not calculated.

Table 6-15. Severity of Pulmonary Fibrosis (Asbestosis) Produced in Rats by the Administration of Five Different Asbestos Samples for Varying Periods of Time[a]

	Mean Asbestosis Scores of Survivors[b] (mean survival in months)				
Length of Exposure	Amosite	Anthophyllite	Crocidolite	Chrysotile (Canadian)	Chrysotile (Rhodesian)
1 day	1.3 (26)	1.3 (26)	1.2 (26)	1.2 (25)	1.4 (23)
3 mo	2.9 (25)	3.2 (26)	3.1 (27)	3.3 (26)	2.8 (28)
6 mo	3.3 (24)	4.2 (20)	3.2 (24)	3.7 (20)	4.2 (23)
12 mo	4.8 (23)	6.0 (25)	5.6 (25)	5.1 (25)	6.1 (27)
Up to 24 mo	6.0 (23)	6.4 (22)	4.2 (14)	5.1 (16)	6.1 (22)
24 mo	6.3 (28)	7.0 (28)	6.6 (29)	—	6.8 (28)

[a] This table was originally published by Wagner and associates (1974) and reprinted with permission.

[b] 1 = nil, 2 = minimal, 4 = slight, 6 = moderate, 8 = severe.

Table 6-16. Lung Tumors and Mesotheliomas in Rats Following Inhalation of Five Different Asbestos Samples For Varying Periods of Time[a]

Exposure	No. of Rats at Risk[b]	No. with Lung Tumor	Types of Lung Tumor				
			Adenoma	Adenomatosis	Adeno-carcinoma[c]	Squamous Carcinoma[c]	No. with Mesothelioma
Amosite							
1 day	45	3	3	0	0	0	1
3 mo	37	10	7	3	0	0	0
6 mo	18	2	1	0	1	0	0
12 mo	25	10	5	4	1	0	0
24 mo	21	13	3	1	3	6	0
Total	146	38	19	8	5	6	1
Anthophyllite							
1 day	44	2	2	0	0	0	0
3 mo	37	6	6	0	0	0	0
6 mo	18	6	3	1	1	1	0
12 mo	28	20	9	6	4(1)	1	1
24 mo	18	16	2	5	3	6	1
Total	145	50	22	12	8(1)	8	2
Crocidolite							
1 day	43	6	5	0	1	0	1
3 mo	36	14	10	2	1	1(1)	1
6 mo	18	4	2	2	0	0	0
12 mo	26	18	5	4	3	6	2
24 mo	18	13	4	5	2(1)	2(1)	0
Total	141	55	26	13	7(1)	9(2)	4
Chrysotile (Canadian)							
1 day	42	1	0	0	1(1)	0	0
3 mo	34	18	15	0	3	0	0
6 mo	17	5	2	2	0	1	0
12 mo	23	11	1	3	6(1)	1(1)	3
24 mo	21	10	2	3	1(1)	4(2)	1
Total	137	45	20	8	11(3)	6(3)	4
Chrysotile (Rhodesian)							
1 day	45	5	4	0	1	0	0
3 mo	36	16	11	2	3(1)	0	0
6 mo	19	8	2	3	3(1)	0	0
12 mo	27	19	2	4	7(2)	6(4)	0
24 mo	17	11	0	1	5(2)	5	0
Total	144	59	19	10	19(6)	11(4)	0
Control							
1 day	44	4	4	0	0	0	0
3 mo	40	3	3	0	0	0	0
6 – 24 mo	42	0	0	0	0	0	0
Total	126	7	7	0	0	0	0

[a] This table was originally published by Wagner and associates (1974) and reprinted by permission.

[b] Rats which survive at least 30 days after start of exposure.

[c] Numbers in parentheses are those with metastases.

Table 6-17. Mesothelioma Production in Relation to Dose from Published Intrapleural and Intraperitoneal Injection Studies

Study	Dust	Dose (mg)	Tumors (%)
Smith et al. 1968	"Harsh" chrysotile	25	21
Intrapleural injection		10	9
Hamsters		1	0
	Amosite	10	9
		1	0
Stanton and Wrench 1972	UICC crocidolite	20	48
Intrapleural implantation		10	41
Osbourne-Mendel rats, female		2	22
		1	8
Wagner et al. 1973	SFA chrysotile	8	66.7
Intrapleural injection		4	33.3
Wistar rats		2	41.7
50% male, 50% female		1	27.2
(Results not separated by sex)		0.5	8.3
	Crocidolite	8	45.5
	(own preparation)	4	15.4
		2	25.0
		1	0
		0.5	9
Pott et al. 1987	UICC chrysotile B	1	81.6
Wistar rats, female		0.25	61.8
		0.05	19.4
	Actinolite	0.25	55.6
		0.05	30.6
		0.01	8.6
Davis and Cowie 1990	UICC amosite	15	79.2
Wistar rats (Han), male		10	75.0
		7.5	62.5
		5.0	70.8
		2.5	59.4
		0.5	46.9
		0.05	25.0
		0.01	8.3
	UICC crocidolite	15	70.8
		10	41.7
		7.5	62.5
		5.0	41.7
		2.5	56.3
		0.5	31.3
		0.05	25.0
		0.01	0.0
	UICC chrysotile A	15	79.2
		10	83.3
		7.5	83.3
		5.0	79.2
		2.5	68.8
		0.5	80.6
		0.05	37.5
		0.01	4.3

Table 6-17 (continued). Mesothelioma Production in Relation to Dose from Published Intrapleural and Intraperitoneal Injection Studies

Study	Dust	Dose (mg)	Tumors (%)
Davis and Cowie 1990	Erionite	25	94.4
Wistar rats (Han), male		10	83.3
		5	87.5
		2.5	93.8
		0.5	81.3
		0.05	46.9
		0.01	8.3
		0.005	0.0

Injection studies allow a less expensive alternative to inhalation experiments, by which a wide range of doses can be administered to many groups of animals. The mesothelioma dose-response data obtained from injection studies are summarized in Table 6-17. Studies by Smith and coworkers (1968), Wagner and colleagues (1973), and Stanton and Wrench (1972), all demonstrated a clear dose-response relationship for mesothelioma production over a few doses of asbestos injected into the pleural cavity. Pott and coworkers (1987) included several dose levels for both actinolite and chrysotile, with the lowest dose injected being 0.01 mg for the former and 0.05 mg per animal for the latter. Both these doses produced some mesotheliomas. The pattern of mesothelioma dose response following intraperitoneal injection in rats has been examined in detail by Davis and associates (1991). In this work the UICC reference samples chrysotile (A), crocidolite, and amosite, as well as erionite, were administered to rats by intraperitoneal injection over a dose range of 0.01 to 25 mg (for erionite the lowest dose was 0.005 mg). For all four dusts, the mesothelioma production rate was linear in the log scale over a wide range of doses, although for chrysotile and erionite a plateau effect was seen at the highest few doses once a maximum response had been produced. Crocidolite, which had shown the lowest response curve, produced no mesotheliomas at 0.01 mg, although the other three dusts still produced an occasional tumor at this level of exposure. Erionite did not produce any mesotheliomas at 0.005 mg. For all dust types, while the number of tumors produced fell progressively with each reduction in dose, both the mean tumor induction period and the time to the first tumor rose in similar fashion. The fiber doses of crocidolite and erionite (greater than 8 μm in length) that failed to produce tumors were 148,000 and 80,000 per animal, respectively, which might be considered to be relatively high doses for fibers concentrated together in contact with the most sensitive tissue (for fibers of all lengths the corresponding figures were 21.4×10^6 and 3.9×10^6 per animal). The lowest dose of chrysotile which produced an occasional tumor was 870,000 fibers greater than 8 μm in length (55.8×10^6 fibers of all lengths). It is possible that in experimental groups larger than the groups of 50 rats each used in these studies, occasional tumors would have been observed at lower dose levels.

The use of the artificial technique of direct intrapleural or intraperitoneal injection to examine the dose-response relationship for mesothelioma production may seem inappropriate when, with humans, all fibers reaching the lungs and eventually the pleura are inhaled. In one respect, however, the results of injection studies demonstrate an important point. While there is good evidence for a roughly linear dose response for lung cancer in human workers exposed to high doses of asbestos, mesothelioma production seems less clearly related to inhaled dose. It has to be remembered that following deposition in the lung parenchyma after inhalation, fibers have to be transported to the mesothelial surfaces for mesothelioma production to occur. Rates of fiber transport may

vary among individuals, and the numbers of fibers reaching the mesothelial tissues may not be closely related to the fiber content of the pulmonary parenchyma. What animal injection studies have demonstrated is that mesothelioma production is closely related to the dose of fibers actually reaching the sites where the tumors occur.

Respirable dust clouds composed of asbestos or other fibrous minerals are made up of fibers ranging from a fraction of a micron in length to several hundred microns in length, but the longest fibers seldom penetrate as far as the alveolar spaces. Considerable evidence has been obtained from experimental studies that the pathogenicity of fibers varies with their length, the long fibers being the most pathogenic. The first work on fiber dimensions was included in the original program of Gardner, with unexpected results. Because it was known that quartz-related pathology increased with a reduction in particle size, Gardner's group included finely ground (short fiber) chrysotile asbestos in their experiments. Not only did the short fibers fail to increase pulmonary fibrosis, compared to long fiber material, but reducing fiber length significantly reduced the level of fibrosis in the treated animals (Vorwald et al. 1951). Further substantiation of these findings is found in the work of King and colleagues (1946), in which asbestos cut to different lengths on a special microtome was administered to rabbits by intratracheal injection. Far more pulmonary fibrosis was produced by long fibers (15 μm) than short fibers (2.5 μm). Similar findings were subsequently reported by other groups of workers (Scymczykiewicz and Wiecek 1960; Klosterkötter 1968). That pulmonary fibrosis, resulting from glass fiber administration, depended on fiber length was demonstrated by Wright and Kuschner (1977), who injected specially sized glass fibers intratracheally into rats. It has been suggested that some techniques used to produce short fiber dust samples, especially for chrysotile, may have modified the surface chemistry of fibers and perhaps modified their biological activity (Langer et al. 1978; Langer and Nolan 1985). It is, however, not possible to verify these suggestions for any of the published studies which have covered a range of different fiber types.

The importance of fiber length in relation to neoplasia was demonstrated in two laboratories by Stanton and Wrench (1972), Stanton and associates (1977), Stanton and Layard (1978), and Pott and coworkers (Pott and Friedrichs 1972; Pott 1978). The data suggest that following the intrapleural or intraperitoneal implantation of asbestos and other mineral fibers, the induction of mesotheliomas by any dust preparation was most closely related to the number of fibers that were longer than 8 μm and less than 0.25 μm in diameter. The type of mineral appeared unimportant in these studies, with fine glass fiber being almost as carcinogenic as asbestos and no minerals containing long thin fibers producing negative results. Some studies have, however, suggested that short-fiber asbestos may be carcinogenic when injected intrapleurally or intraperitoneally (Kolev 1982; Le Bouffant et al. 1985), but these results are difficult to interpret since the short fibers are usually only reported as a proportion of the total. With the ability of asbestos to split longitudinally as well as transversely, it is quite possible to reduce the mean fiber length of a sample greatly while actually increasing the number of long fibers per unit mass. Wagner and coworkers (1984) demonstrated that following the injection of finely ground short crocidolite, the small proportion of long fibers present were selectively retained in the pleural granulomas produced by this dust.

Since injection techniques exaggerate tissue responses to fibers by overcoming or bypassing clearance mechanisms, it is important to determine whether or not fibrosis and neoplasia are related to fiber length in dust that is inhaled. The difficulties in preparing suitable dusts in large quantities have inhibited the study of this question, since, as indicated, simple grinding of long-fiber samples does not necessarily reduce the number of long fibers present. So far, very few studies with satisfactory dusts have been feasible. In 1986, Davis

and colleagues (1986) reported long-term inhalation and injection studies in rats in which an amosite dust preparation with almost all fibers less than 5 μm in length was compared to a normal amosite dust preparation containing many long fibers. The short-fiber material produced neither fibrosis nor neoplasia, apart from a single mesothelioma at the highest dose injected, while the long fibers were highly pathogenic. An attempt was made to duplicate this study using chrysotile (Davis and Jones 1988), but the intended short-fiber preparation contained a small proportion of long fibers. Although it produced some fibrosis and pulmonary tumors in rats, the response was much less than with long-fiber chrysotile. When injected, the short-fiber chrysotile produced fewer tumors at any dose than did the long.

Perhaps the most dramatic demonstration of the importance of fiber length was reported by Wagner and colleagues (Wagner et al. 1985; Wagner 1990). The mesothelioma incidence of almost 100 percent following the inhalation of erionite in rats was reduced to zero when short-fiber preparations of this material were used. Data from two experimental inhalation studies published by Davis and associates (1978, 1986) may indicate that the fiber lengths needed to produce disease in the pulmonary parenchyma may be different from those that cause mesothelioma. Of the amosite samples tested, both a very short sample and the medium-length UICC reference sample produced minimal pulmonary fibrosis and almost no pulmonary tumors. In contrast, a long-fiber sample produced large amounts of fibrosis and significant numbers of pulmonary tumors. When the three dusts were injected at the same dose, both the long-fiber sample and the UICC material produced mesotheliomas in almost all animals, while the short-fiber material produced none. The implications of these results are that very short fibers produce little or no disease at any site, medium-length fibers (8 to 10 μm) can cause mesotheliomas, and longer fibers (perhaps 15 to 25 μm) are needed to produce disease in the pulmonary parenchyma.

While experimental studies have clearly demonstrated the importance of fiber length in the production of pulmonary fibrosis, pulmonary tumors, and mesotheliomas, the exact hazard for fibers of any dimension compared to any other could be definitively determined only with fiber preparations in which all fibers are of uniform lengths, and these have not so far been available. The routine counting procedures used for asbestos monitoring in the workplace count only fibers greater than 5 μm in length as seen by PCOM. The choice of a 5 μm cutoff was based on little evidence at the time when it was introduced but seems to have been a fortunate one (Walton 1982). Fibers below this length certainly seem less harmful than fibers 10 to 20 μm in length, but whether or not there is a fiber length below which there is no biological potency remains to be determined. The relative carcinogenicity of short fibers is of particular importance when environmental or building occupation exposures are considered, since most of the asbestos fibers found in these circumstances are well below 5 μm in length.

In addition to evidence that asbestos fiber dimensions are of great importance in disease production, there appears to be variation depending on the mineral type of asbestos involved. There is good evidence from human epidemiologic studies that the risk of mesothelioma is higher with crocidolite, and perhaps amosite, than with chrysotile. Initially, animal experimentation appeared to contradict these findings, with chrysotile preparations being reported as equally hazardous as the amphiboles when administered by inhalation and injection (Wagner et al. 1973, 1974, 1980; Davis et al. 1978, 1986; Bolton et al. 1982; Davis and Jones 1988). The earlier of the above studies involving inhalation demonstrated that much less chrysotile was present in lung tissue at the end of the inhalation period, but it was suggested that this was due to the curly fibers of chrysotile penetrating less well to the lung parenchyma than the straight amphibole fibers. In later studies (Davis 1989), however, it was demonstrated that much of the difference was due

to the very rapid removal of chrysotile from lung tissue, probably by dissolution. In these rat studies it was reported that while clearance rates for long and short amosite preparations over a six-month period were 14 and 20 percent, respectively, the comparable figures for long and short chrysotile were 55 percent and 90 percent. In experimental conditions where massive doses are administered over a large proportion of the rat life span, enough chrysotile can obviously remain in the lung tissue to cause high levels of disease comparable with the amphiboles, in spite of rapid removal. In human situations where even past industrial exposures were at least an order of magnitude lower than in the animal experiments, it has been suggested that the dissolution of chrysotile is likely to be much more important (Davis 1989). Being a chemical process, chrysotile dissolution may be assumed to occur at much the same rates in the lungs of rats and humans. Tumor production, however, is known to require a significant proportion of the life span of any species, and in long-lived humans, rapid chrysotile dissolution may result in keeping fiber concentrations in the lung below the level where significant numbers of tumors would be detected. Rapid removal of chrysotile from human lung tissue has been confirmed by many investigators (Pooley 1976; Rowlands et al. 1982; Gylseth et al. 1983).

Risk assessments relating to tumor production by asbestos in humans are based on extrapolation from populations of heavily exposed asbestos workers, for whom such exposure data as are available are generally consistent with a linear response, at least for pulmonary carcinomas. These extrapolations are based on the idea of a continuous linear response down to the extremely low levels of asbestos met in the nonworking environment. One theory assumes that asbestos fibers initiate carcinogenesis by direct damage to DNA or chromosomes, so that theoretically at least one fiber would be capable of initiating the formation of a tumor. This method of carcinogenesis by fibers is not established, however, and the assumption that the dose-incidence curve should remain linear over the entire dose range conflicts with the well-established principles of DNA repair and tumor promotion. Other mechanisms of fiber carcinogenesis have also been postulated. For example, it has been suggested that pulmonary carcinomas develop only after there has been sufficient pulmonary damage to produce fibrosis a process generally accepted as requiring relatively high fiber levels (Browne 1986). It is postulated that in these circumstances widespread pulmonary damage, with concomitant hyperplasia and metaplasia of alveolar epithelial cells, creates an environment where the chances of spontaneous carcinogenic mutations are increased. Some support for this suggestion is found in animal experiments, in which groups of animals developing large numbers of pulmonary tumors have been reported as having high levels of fibrosis as well. Early pulmonary tumors are frequently seen to arise from the centers of highly fibrosed areas of lung tissue, and Davis and Cowie (1990) (Table 6-18) reported that in a group of 85 old rats from a number of asbestos inhalation experiments, all with pulmonary tumors, an average of 12.5 percent of lung tissue was occupied by advanced fibrosis. In contrast, the lungs of 59 rats of similar age from the same studies but without tumors averaged only 7.3 percent of advanced fibrosis. While there is less evidence that mesothelioma production requires significant pleural damage, and therefore relatively high fiber doses to cause it, a requirement for preliminary pleural fibrosis has been suggested by Suzuki and Kohyama (1984) and Kuschner (1987). If this theory of asbestos carcinogenesis were to prove correct, then very low fiber doses might have little or no carcinogenic potential, and the models for human risk assessment would have to be revised accordingly. Hence, the actual mechanisms of fiber carcinogenesis, discussed further in the next section of the Report, remain a most important topic for future research.

Table 6-18. The Relationship Between Tumor Production and Advanced Pulmonary Fibrosis in Rats Treated by Inhalation with a Variety of Mineral Fibers[a]

Type of Dust	Malignant Pulmonary Tumors	Benign Pulmonary Tumors	Mean Areas of Interstitial Fibrosis in Old Animals
UICC chrysotile A + titanium dioxide	22	4	12.9
Tremolite	18	2	14.5
Long amosite + titanium dioxide	18	1	9.5
Long chrysotile	15	8	12.6
Wet dispersed chrysotile (WDC)	14	7	9.6
Milled chrysotile	14	2	8.8
Milled WDC	13	5	12.8
Factory WDC	10	11	12.1
Long amosite	10	4	10.0
UICC chrysotile A	8	7	9.1
Short fiber chrysotile	7	1	2.4
Factory chrysotile	3	8	7.7
Ceramic aluminum silicate	3	1	5.0
Brucite	2	3	2.9
Factory amosite	0	0	8.5
UICC amosite	0	2	2.6
UICC crocidolite	0	1	1.4
Short fiber amosite	0	0	0.1

[a] This table was published by Davis and Cowie (1990) and illustrates that significant levels of carcinogenicity found in animal experiments using mineral fibers are almost invariably associated with advanced pulmonary fibrosis in the same group of animals. Reprinted with permission.

Ilgren (1989) surveyed the data from all experimental studies on mesothelioma production and inferred that the combined evidence supports the concept of a threshold, based on the fact that the numbers of mesotheliomas reported in untreated controls were similar to those in animals given very low fiber doses[1]. However, adequate evaluation of Ilgren's conclusions regarding the existence of a mesothelioma threshold is not possible on the basis of his preliminary report, which provides no rigorous statistical analysis of the data or of the dose-response relationship represented. Nevertheless, his summary draws attention to the fact that all types of tumors may sometimes occur spontaneously, and that examination of a response to low doses of any carcinogen is complicated by background tumor levels.

[1] The same interpretation appeared in publications by Ilgren and Brown (1991) and Ilgren and Wagner (1991); however, these papers were published too recently to be included in the Panel's review.

6.3.1.2 Influence of Temporal Distribution of Dose

Most experimental inhalation studies have been undertaken at a constant dose throughout the inhalation period, whereas human exposure may vary dramatically from time to time, with high peaks for short periods interspersed with longer periods of much lower exposure. The effects of peak exposures have been difficult to examine experimentally, since human peak exposures can often be two orders of magnitude higher than background exposures, and replications of such a differential, although feasible, would necessitate working at overall exposure levels too low to produce disease in the short life span of the rodent. Little damage is likely to be found in mice or rats at less than a one-year exposure at a 1 mg/m^3 mass dose level, and even if a respirable dust cloud as dense as 100 mg/m^3 could be generated this would be administered on only about two separate days during the experiment.

Davis and colleagues (1980) used a much lower differential between peak and background exposures in rat inhalation studies. With both amosite and chrysotile, peak exposures for one day each week produced similar levels of disease for the same dust mass given over five days. It is now inferred that for a given cumulative dose, peak exposures have no greater effect than the same total mass of dust administered over a longer period unless the peaks are high enough to cause pulmonary overload. Pulmonary overload is extremely unlikely to result from human exposure through the occupation of buildings, although peaks could be important to workers who, during building maintenance, disturb asbestos materials without proper protection. Conversely, almost all animal experimentation has been undertaken at exposure levels that produce pulmonary overload.

6.3.1.3 Influence of Host Factors: Species, Gender, and Age at Exposure

Results from animal experimentation vary with the species and even with the strain of animal used. For asbestos-related disease, a satisfactory animal model must be able to develop pulmonary fibrosis as well as pulmonary carcinomas and mesotheliomas in response to inhalation of asbestos. Theoretically, the best models for human disease would be based on experiments on primates, but the cost of undertaking work with these species is prohibitive. Nonetheless, baboons have been used in some long-term asbestos inhalation studies, and these animals have developed the main asbestos lesions observed in human lungs. Most work, as with other research in experimental toxicology, has been undertaken with small rodents. Of these species, the rat shows the three main types of asbestos-related disease observed in humans, and it has been the animal of choice for most studies. Hamsters seem to develop pulmonary fibrosis and pulmonary tumors less readily than rats following asbestos inhalation but seem to develop rather more pleural mesotheliomas. Guinea pigs develop pulmonary fibrosis when treated with asbestos but are resistant to tumor production. Mice have been shown to develop pulmonary fibrosis but are unsuitable for the study of asbestos-related pulmonary neoplasia since some strains have a high spontaneous incidence of such tumors.

Much information has now been accumulated on asbestos-related disease using the rat model, but caution needs to be used in extrapolating results to the human situation. Qualitatively, extrapolation is probably reliable. Thus, a type or size of fiber shown to be hazardous in rats is likely to prove hazardous in humans, and a mechanism of disease production elucidated in rats will probably be found to be similar in humans. Quantitative extrapolation is much more uncertain. Thus, while a dose response to asbestos has been clearly demonstrated in experimental animals and has been used to examine the possibility

of a threshold, animal data cannot be used to determine a safe exposure level for humans. In general, asbestos-related disease occurs when sufficient levels of fiber have built up in tissues, and an inhaled dose that has failed to produce disease within the two-year life span of a rat might prove dangerous to humans, in whom dust may accumulate for 50 years or longer.

Two factors that could influence the development of asbestos-related disease in rats and also in humans are age and gender. Unfortunately, little information is available on gender differences in response, since laboratories have generally standardized on the use of one sex only, generally the male, in their experiments. In studies where equal numbers of both sexes were used, tumor numbers were not significantly different between males and females (Wagner et al. 1973). Similarly, most studies have commenced with young animals, so that the maximum proportion of the life span is available for disease development. Only one study has demonstrated an age effect; Berry and Wagner (1976) demonstrated that rats injected with asbestos in middle age developed mesotheliomas more rapidly than did those injected while young. This finding is important since Doll and Peto (1985) have pointed out that in asbestos-exposed workers, there does not appear to be an age effect for mesothelioma in contrast to other types of human tumors. Berry and Wagner's results were obtained by implanting dust directly into the pleural cavity, suggesting that the lack of a clear age effect in humans may well be due to the very variable transport of dust from lung parenchyma to pleura. Once fibers have accumulated in the pleural tissues, it appears that mesothelioma development does show an age effect, at least in the rat.

6.3.1.4 Influence of Other Modifying Factors

Almost all experimental studies have been undertaken with the purest asbestos samples possible, whereas humans inhale asbestos in combination with other atmospheric pollutants, so the effects of the other materials need to be considered. By far the most important particulate pollutant inhaled with asbestos is tobacco smoke, which is carcinogenic in its own right and which has been shown to act synergistically with asbestos to produce very high frequencies of pulmonary tumors in populations of asbestos workers. Experimental examination of this synergism has been hampered by the fact that no suitable animal model has been developed for tobacco smoke carcinogenesis on its own. This problem was fully discussed at a conference held in 1988, the report of which was published by Wehner (1989). Experimental studies have, however, recently indicated that dusts other than tobacco smoke may enhance asbestos carcinogenesis. Davis and associates (1991) demonstrated that the administration of either titanium dioxide (normally considered an innocuous dust) or quartz increased the numbers of pulmonary tumors in rats treated with chrysotile and amosite. Of particular interest was the finding that quartz appeared to enhance the penetration of asbestos fibers through the pleural surface and that this was accompanied by the production of more mesotheliomas than previously found with the same types of asbestos when used alone. It is possible that variations in quartz exposure, perhaps nonoccupational, might have played a part in the variations in numbers of mesotheliomas reported in different populations of asbestos workers.

6.3.2 In Vitro Studies of Mechanisms of Asbestos-Related Disease

The mechanisms through which asbestos produces disease have been examined in many studies using cells in vitro (reviewed in Mossman and Begin 1989; Mossman et al. 1990; Voytek et al. 1990; Rom et al. 1991). These experiments have employed both human and rodent cells from a variety of tissues. Most recently, research has focused on the effects of

asbestos on "target" cells of disease, including the lung fibroblast (asbestosis), epithelial cells of the respiratory tract (lung cancer), and mesothelial cells (mesothelioma). The available information suggests that asbestos causes cytotoxic changes in these cell types at high concentrations, whereas at lower concentrations asbestos fibers (depending on the cell type used) may or may not induce other biological effects including chromosomal changes and growth alterations. Unfortunately, many studies have not included examination of inert particles or "nuisance" dusts as comparative controls. Moreover, dose-response studies over a range of concentrations of asbestos and nonasbestos fibers have been reported by only a few laboratories. In vitro studies are best grouped according to the biological changes and endpoints examined as discussed below.

6.3.2.1 Cell Death and Cytotoxicity

A number of studies have examined the comparative short-term, cytotoxic effects of fibers and particles on cells (reviewed in Brown et al. 1980; Beck and Bignon 1985; Mossman and Begin 1989). The relevance of these findings to the development of asbestos-induced lung disease is speculative. However, results of these in vitro bioassays have been remarkably consistent: long fibers are more toxic to cells than equal mass equivalents of short fibers regardless of fiber type (Brown et al. 1986a,b; Wright et al. 1986).

In a comprehensive examination of 13 fibrous (asbestos and nonasbestos) samples of known fiber numbers and dimensions, the cytotoxicity of fibrous dusts was related to the number of fibers longer than 8 μm (Wright et al. 1986). In this regard, the increased cytotoxicity of long fibers correlated with their ability to cause inflammation and activation of macrophages after injection into the peritoneal cavity of mice (Donaldson et al. 1989). A single injection of long, crocidolite fibers into the peritoneal cavity caused an intense inflammatory reaction, elaboration of active oxygen species (AOS), and cell death (Goodglick and Kane 1990). These events occur after five daily injections, but were minimal after a single injection of short fibers. Both long and short fibers were cytotoxic to peritoneal macrophages in vitro.

In a number of in vitro studies, chrysotile asbestos tends to be more cytotoxic than amphibole asbestos on an equal weight (milligram) basis. As discussed below, this trend is reversed if toxicity is expressed on a fiber number per cell basis. This phenomenon may be related to surface area in that both fiber number and surface area increase in concert.

6.3.2.2 Cell Proliferation and Abnormal Differentiation

Altered cell proliferation, a phenomenon occurring during hyperplasia and tumor promotion, can be indicated in vitro by increased colony-forming efficiency (CFE), for example, increased numbers of colonies of cells occurring after a seven-day exposure of low-density cultures to asbestos (Sesko and Mossman 1989); by increased incorporation of ^{3}H-thymidine, an indication of increased DNA synthesis (Lemaire et al. 1986; Sesko and Mossman 1989); and by increased activity of ornithine decarboxylase (ODC), a rate-limiting enzyme in the biosynthesis of polyamines (Landesman and Mossman 1982; Marsh and Mossman 1988). Polyamines are growth regulatory molecules which are increased in cells before cell division occurs. Increased accumulation of diacylglycerol in cells reflects an alteration in lipid metabolism activating protein kinase C, a protein kinase playing a key role in the transduction of extracellular signals leading to increased cell proliferation (Nishizuka 1986).

Table 6-19. Biologic Changes in Cells of the Respiratory Tract In Vitro Indicative of Altered Cell Proliferation

Study	Biologic Endpoint	Cell Type	Particulate	Minimum Concentration Causing Change	Cell No.	Maximum Concentration Showing No Effect
Sesko and Mossman 1989[a]	CFE[b]	Hamster, HTE[b]	Crocidolite (UICC) Riebeckite Antigorite	0.05[c] 0.05 0.05	18/cm^2 dish 18/cm^2 dish 18/cm^2 dish	0.01[c] 0.01 0.01 Chrysotile 0.05, 0.01
Marsh and Mossman 1988	ODC[b] activity	Hamster, HTE	Crocidolite (UICC) Chrysotile (UICC) Code 100 glass Chrysotile (> 10 μm) Chrysotile (> 2 μm) (both Manville preparations)	2.60[c] 0.32 1.30 0.18 0.36	6.8×10^4 6.8×10^4 6.8×10^4 6.8×10^4 6.8×10^4	Riebeckite (2.6) Antigorite (5.8) Glass particle (2.6)
Landesman and Mossman 1982	ODC activity	Hamster, HTE	Crocidolite (UICC) Chrysotile (UICC)	0.64[c] 0.064	6.8×10^4 6.8×10^4	Hematite (2.6)
Sesko et al. 1990	> Diacylglycerol	Hamster, HTE	Crocidolite (UICC)	0.10[c]	6.8×10^4	Glass beads (0.1 – 5.0) Riebeckite (0.1 – 5.0)
Sesko and Mossman 1989	> ^{3}H-thymidine incorporation	Hamster, HTE	Crocidolite (UICC)	0.10[c]	6.8×10^4/cm^2 dish	0.01, 0.05
Lemaire et al. 1986	> ^{3}H-thymidine incorporation (sustained)	Human, embryonic lung fibroblasts (WI-38)	Chrysotile (UICC)	10[d]	5×10^4	Chrysotile 5.0[d] Latex (5.0 – 100) TiO_2 (5.0 – 100)

[a] Dose-response studies using three or more concentrations of fibers and demonstrating the absence of a statistically significant biologic endpoint at lower concentrations of asbestos.

[b] CFE = colony forming efficiency; HTE = hamster tracheal epithelial cells; ODC = ornithine decarboxylase.

[c] Micrograms per dish (cm^2).

[d] Micrograms per milliliter of medium.

One can draw several general conclusions from examination of the data in Table 6-19. First, both crocidolite and chrysotile asbestos cause manifestations of increased cell proliferation in tracheal epithelial cells. Second, long chrysotile fibers (on an equal weight basis) are more potent than shorter fibers in inducing increased ODC activity (Marsh and Mossman 1988). This observation supports the results of previous studies in which increased numbers of cells incorporating ^{3}H-thymidine, as well as enhanced squamous metaplasia, were noted in hamster tracheal organ cultures exposed to lower concentrations of long (greater than 10 μm) versus short (less than or equal to 2 μm) chrysotile fibers (Woodworth et al. 1983). Third, nonfibrous particles including the chemically similar analogues of crocidolite (such as riebeckite) and chrysotile (for example, antigorite) are inactive or less active than asbestos in bioassays of altered cell proliferation (Table 6-19) with the exception of the long-term CFE assay, which measures an increase in percentage of cell survival relative to untreated cells (Sesko and Mossman 1989). It should be noted that the effects of particulates in this bioassay are serum dependent. In contrast to crocidolite, riebeckite, or antigorite, chrysotile was inactive at a range of concentrations (0.01 to 0.5 μg/cm^2 dish, the latter a lethal dose) in a 2 percent serum-containing medium; none of these fibers caused an increase in relative cell survival in a 10 percent serum-containing medium. Last, low concentrations of chrysotile (5 μg/mL medium) or crocidolite (0.01, 0.05 μg/cm^2) fibers caused no significant increases in cell proliferations (Lemaire et al. 1986; Sesko and Mossman 1989).

6.3.2.3 Mutagenesis and Cell Transformation

Neither amphibole asbestos nor chrysotile has been observed to cause base substitution and frameshift mutations in bacterial mutation assays or positive results in rodent bone marrow assays for detection of chromosomal aberrations or micronucleated erythrocytes (Chamberlain and Tarmy 1977; Shelby 1988). Although crocidolite, amosite, and chrysotile were observed to be weakly mutagenic in Chinese hamster lung cells in vitro, when all data points were considered as a whole (Huang 1979), crocidolite and chrysotile were not mutagenic in liver epithelial cells or in Syrian hamster embryo (SHE) fibroblasts at the ouabain or HGPRT locus (Reiss et al. 1983; Oshimura et al. 1984). In hamster-human hybrid (A_L) cells, crocidolite caused an increase in the frequency of mutations at the a_1 locus of human chromosome 11 (Hei et al. 1991). However, there was no consistent pattern or dose-response relationship for mutant yield at the HGPRT locus.

Morphologic transformation assays have been performed with asbestos and nonasbestos fibers in a number of fibroblast cell lines. These systems differ, since some investigators use normal cells (SHE) while others use already immortal, aneuploid cell lines (C3H10T1/2). Significant increases in the transformation frequency of SHE cells have been observed using asbestos alone in some studies (Hesterberg and Barrett 1984; Oshimura et al. 1984; Mikalsen et al. 1988), but transformation has been rare in other reports (di Paolo et al. 1983). The differences in transformation frequencies between laboratories using this bioassay are attributable in part to differing protocols, serum concentrations, or possibly, modification of fibers by heat sterilization (Mikalsen et al. 1988). After exposure to asbestos in vitro, C3H10T1/2 cells do not exhibit chromosomal aberrations and/or morphologic transformation (Brown et al. 1988; Hei et al. 1985). Asbestos also does not transform Balb/c 3T3 cells unless used in combination with the tumor promoter, 12–0–tetradecanoylphorbol-13-acetate (TPA) (Lu et al. 1988).

The mechanism of in vitro transformation by asbestos may involve the induction of aneuploidy in some cell types, including mesothelial cells (Jaurand et al. 1986). However,

chromosomal aberrations in rat mesotheliomas (Craighead et al. 1987) and human mesotheliomas (Gibas et al. 1986; Popescu et al. 1988; Tiainen et al. 1988) appear to be complex. The most common abnormalities are inversions, translocations, and deletions of chromosomes 1, 3, 7, 9, 17, and 22.

Table 6-20 presents data from studies in which asbestos fibers have been tested for their ability to cause aneuploidy or chromosomal changes in cells of the respiratory tract, including lung fibroblasts, mesothelial cells, and bronchial epithelial cells. Data from the SHE bioassay (Oshimura et al. 1984) are included in Table 6-20, since this paper and others from this laboratory (Hesterberg and Barrett 1984, 1985; Hesterberg et al. 1986) provide information on the size characteristics and geometry of particulates relevant to these responses. In these studies, both morphologic transformation (defined as piling up of contact-inhibited cells and formation of foci) and cytogenetic effects were dependent on fiber dimension, long fibers being most potent. For example, both crocidolite and chrysotile, as well as thin Code 100 glass fibers of similar dimension, caused an increased incidence of aneuploidy and morphologic transformation in comparison to untreated cells. Thick Code 110 glass, milled glass, or alpha-quartz were inactive at the same concentrations as were asbestos and fine glass fibers (2.0 $\mu g/cm^2$ dish). Milling reduced the average length of the fibers from 10 to 16 μm to less than 1.7 μm and completely eliminated morphologic transformation at the dosages tested. When the average length of glass was reduced to 0.95 μm, transforming ability was totally absent (Hesterberg and Barrett 1984). Alpha-quartz and Min-U-Sil were inactive in increasing the transformation frequency of SHE cells at doses of up to 5.0 $\mu g/cm^2$ dish.

Experiments by Price-Jones and coworkers (1980) showed that Min-U-Sil (1 to 15 μg/mL medium) did not induce aneuploidy or sister chromatid exchanges (SCE) in V79-4 cells, whereas crocidolite caused aneuploidy, but no increases in SCE, at higher concentrations tested (15 and 30 μg/mL medium). In contrast, crocidolite (10 μg/mL medium) caused increased SCE in rat pleural mesothelial cells, whereas attapulgite (10 and 20 μg/mL) was inactive (Achard et al. 1987). In all studies using two or more concentrations of crocidolite or chrysotile fibers, there were concentrations (1 to 30 μg/mL medium) at which no effects were observed. It should be noted that amosite and crocidolite asbestos did not cause single-strand breakage of DNA in human mesothelial or bronchial epithelial cells (Fornace et al. 1982; Gabrielson et al. 1986). However, duplicate exposures of human mesothelial cells to cytotoxic concentrations of amosite caused increased aneuploidy and population doublings (Lechner et al. 1985). The demonstration that chromosomal changes occur in asbestos-exposed mesothelial cells is consistent with the hypothesis that asbestos is an initiator of carcinogenesis in mesothelioma.

It has been reported that chrysotile causes malignant transformation of mesothelial cells. After injection of rat mesothelial cells (passage 75) exposed to chrysotile fibers in vitro into nude mice, mesotheliomas developed in four out of five mice injected with cells exposed to chrysotile (single exposure) and in five out of five mice injected with cells exposed continuously to chrysotile in vitro (Fleury-Feith et al. 1989). However, three out of five mice injected with untreated mesothelial cells developed mesotheliomas, an indication that mesothelial cells exhibit spontaneous transformation in vitro. In vitro data and tracheal implantation studies suggest that asbestos may also act as a cocarcinogen or a promoter in the development of lung tumors (reviewed in Mossman et al. 1990).

Table 6-20. Biologic Changes in Cells of the Respiratory Tract In Vitro Indicative of Aneuploidy or Chromosomal Damage by Fibers

Study	Biologic Endpoint	Species and Cell Type	Particulate	Minimum Concentration Causing Change	Cell No.	Maximum Concentration Showing No Effect
Palekar et al. 1987[a]	Aneuploid cells	Chinese hamster, lung fibroblasts (V79)	Crocidolite (UICC)	134[b]	6×10^5	33.6[b]
			Chrysotile (UICC)	840	6×10^5	210
			Erionite (Oregon)	43.2	6×10^5	10.8
	Cells with chromatid and chromosomal aberration	Chinese hamster, lung fibroblasts (V79)	Crocidolite (UICC)	134[b]	6×10^5	33.6
			Chrysotile (UICC)	210	6×10^5	NR[c]
			Erionite (Oregon)	108	6×10^5	10.8 – 65
Price-Jones et al. 1980[a]	Aneuploidy (No. greater in sister chromatid exchange with any dust at 1 – 30)[d]	Chinese hamster, lung fibroblasts (V79-4)	Crocidolite (UICC)	15[d]	10^5, 10^6 (at plating)	Crocidolite (1.5) Min-U-Sil (1,5,15)
Oshimura et al. 1984[a]	Incidence of aneuploidy and morphologic transformation	Hamster, embryo fibroblasts (SHE)[e]	Crocidolite (UICC)	2.0[f]	2.5×10^5 (at plating)	NR
			Chrysotile (UICC)	1.0		0.5
			Code 100 glass (thin)	2.0		Milled glass (2.0), quartz (2.0, Code 110 thick)
Jaurand et al. 1986[a]	Aneuploidy	Rat, PMC[c]	Chrysotile (UICC)	1.4[f]	8×10^5 (at seeding)	0.4, 1.0[f]
Lechner et al. 1985	Aneuploidy, greater than population doublings	Human, mesothelial cells	Amosite (UICC)	0.3[f] (2×)	2×10^4 (per cm^2 dish)	NR
Mikalsen et al. 1988	Morphologic transformation (1% level)	SHE	Crocidolite (UICC)	2.60[g]	200 (at plating)	≤ 1.0
			Chrysotile (UICC)	0.15		≤ 0.1
			Amosite (UICC)	3.0		≤ 2.0
			Anthophyllite (UICC)	3.5		≤ 2.0
			Code 100 glass (thin)	1.15		≤ 1.0
						Code 100 (>10)
						TiO_2 (>10)

Table 6-20 (continued). Biologic Changes in Cells of the Respiratory Tract In Vitro Indicative of Aneuploidy or Chromosomal Damage by Fibers

Study	Biologic Endpoint	Species and Cell Type	Particulate	Minimum Concentration Causing Change	Cell No.	Maximum Concentration Showing No Effect
di Paolo et al. 1983	Morphologic transformation	SHE	Crocidolite (UICC) Chrysotile (UICC) Amosite (UICC) Anthophyllite (UICC)		300 (at plating)	≤ 40.0[h]
Achard et al. 1987	Sister chromatid exchange	Rat, PMC	Crocidolite (UICC)	10[d]	NR	Attapulgite (10 – 20)
Paterour et al. 1985	Morphologic tranformation	Rat, PMC	Chrysotile (UICC)	0.4[f]	NR	NR
Gabrielson et al. 1986	DNA single-strand breaks	Human, mesothelial cells	Amosite (UICC)	NR	NR	100[d]
Fornace et al. 1982	DNA single-strand breaks	Human, bronchial epithelial cells	Amosite (UICC) Crocidolite (UICC)	NR	NR	25[d]

[a] Dose-response studies using three or more concentrations of fibers and demonstrating the absence of a statistically significant biologic endpoint at lower concentrations of asbestos.

[b] Number of fibers × 10^6/mL; 6 × 10^5 cells were exposed to fibers in 2 mL suspensions.

[c] PMC = Pleural mesothelial cells; NR = not reported.

[d] Micrograms per milliliter of medium.

[e] These cells are not of lung origin, but have been compared by the authors to cell types resulting in pleural sarcoma.

[f] Micrograms per dish (cm^2).

[g] Particulates were added at two stages in the incubation protocol ($\mu g/cm^2$ dish).

[h] Micrograms per 20 cm^2 surface area.

In vitro studies to date have assessed the biological effects of asbestos and nonasbestos fibers comparatively on a mass basis (milligrams of fibers per dish or milliliter of medium) rather than a numerical basis (numbers of fibers of a given type per dish or target cell). Cytogenetic and cytotoxic effects of chrysotile, crocidolite, and erionite fibers were recently compared in hamster lung fibroblasts (V79 cells) on the basis of both fiber mass and fiber number (Palekar et al. 1987, 1988). Although no differences in fiber potency could be demonstrated when fiber dose was calculated on a mass basis, numbers of chrysotile fibers required to produce cytogenetic changes were approximately 6-fold higher than that required for crocidolite and 20-fold higher than that required for erionite, the most potent fiber (Table 6-20).

A critical question is whether a "threshold" of biological response can be demonstrated in vitro; that is, are there concentrations of asbestos fibers which do not induce biological endpoints? While many dose-response studies have shown no response at one or more low asbestos doses, it is not possible to conclude, on the basis of this evidence alone, that thresholds exist. The studies may simply be insensitive or have had insufficient statistical power to detect small responses at low doses. Evaluation of the existence of a threshold would require a statistical analysis of the shape of the observed dose-response curves, which is yet to be satisfactorily accomplished.

6.3.2.4 Liberation of Growth Factors and Other Pharmacologically-Active Materials

A number of studies have documented the release of growth factors, proteases, prostaglandins, active oxygen species (AOS), and so on, from both rodent and human alveolar macrophages, neutrophils, and other cell types after exposure to asbestos, and/or other particulates in vitro (for recent review, see Mossman and Begin 1989). Whether these responses are causally related to the induction or pathogenesis of asbestos-related lung diseases in vivo is unclear. In most studies, asbestos and nonasbestos fibers or particles have not been evaluated comparatively. However, a few reports have examined different types of asbestos and nonasbestos materials to determine if different degrees of reactivity occur.

For example, chrysotile asbestos causes dosage-dependent secretion of both cyclooxygenase and lipoxygenase metabolites from alveolar macrophages. Phagocytosis of iron beads also induces secretion of the same metabolites, but in larger quantities, probably reflecting the lack of cytotoxicity of the particle (Kouzan et al. 1985). In human umbilical vein epithelium, stimulation of arachidonate metabolism was observed with amosite, attapulgite, and chrysotile fibers, but not with fiberglass or glass beads (Garcia et al. 1989). These results suggest that increases in arachidonic acid metabolism may be linked to cytotoxicity. In cultures of pleural mesothelial cells, both crocidolite and chrysotile asbestos cause synthesis of a protein fraction with chemotactic activity for neutrophils (Antony et al. 1989). However, crocidolite produced greater chemotactic activity than did chrysotile at higher concentrations of fibers (5 to 30 μg/mL medium).

Generation of AOS from phagocytic cells after exposure to asbestos has been demonstrated by a number of laboratories (Doll et al. 1982; Donaldson and Cullen 1984; Case et al. 1986; Hansen and Mossman 1987; Hedenborg and Klockars 1987). These metabolites of oxygen are also generated from fibers in cell-free solutions due to redox reactions occurring on the fiber surface (Zalma et al. 1987). Iron, an integral component of the amphiboles, crocidolite and amosite, drives a modified Haber-Weiss reaction resulting in production of the potent hydroxyl ($OH\cdot$) radical. Since asbestos-induced cell injury and lipid peroxidation are

prevented in a variety of cell types by addition of scavengers of OH· and other AOS, as well as by chelation of iron on the surface of fibers (Goodglick and Kane 1986; Mossman et al. 1986; Brown et al. 1987; Gulumian and Kilroe-Smith 1987; Shatos et al. 1987; Turver and Brown et al. 1987; Garcia et al. 1989), cell damage by asbestos may be mediated by AOS produced by fibers alone or upon phagocytosis of fibers. At higher concentrations, generation of AOS from human neutrophils correlates with the relative toxicity of dusts; for example, quartz is greater than chrysotile A, which is greater than crocidolite, which is greater than chrysotile B, which is greater than amosite, which is greater than anthophyllite (Hedenborg and Klockars 1987). However, at nontoxic concentrations, nonfibrous particles (riebeckite, mordenite, and glass beads) are less active than the respective fibers (crocidolite, erionite, or glass) of similar chemical composition in rodent alveolar macrophages (Hansen and Mossman 1987). The enhanced ability of long fibers to trigger release of AOS is attributed to their inability to be phagocytized completely, whereas small fibers and particles can be engulfed in membrane-bound phagolysosomes.

6.3.2.5 Modulating Factors

Factors such as species differences in response, which may play a role in cellular response to asbestos, have not been explored systematically to date, presumably because of the difficulty in obtaining, culturing, and maintaining human cells of the respiratory tract in vitro. However, several investigators have explored the interactions of fibers in vitro with chemical carcinogens such as components of cigarette smoke. In some experiments, asbestos enhances the mutagenic and transforming effects of chemical carcinogens and radiation. For example, both crocidolite and chrysotile are inactive alone, but increase the frequency of mutation and transformation in rodent epithelial cells exposed to benzo[*a*]pyrene (B*a*P) (Reiss et al. 1983) or irradiated fibroblasts (C3H10T1/2 cells) (Hei et al. 1985; Brown et al. 1988). In contrast, asbestos and B*a*P do not have synergistic effects on transformation in rat mesothelial cells (Paterour et al. 1985). In one study, B*a*P and asbestos had synergistic effects on transformation of SHE cells (di Paolo et al. 1983), but synergism was not observed using the SHE transformation system according to another laboratory (Mikalsen et al. 1988).

The capacity of asbestos and nonasbestos particulates to adsorb B*a*P and other chemical carcinogens has been examined by several laboratories (Eastman et al. 1983; Harvey et al. 1984; Gerde and Scholander 1988). In studies examining the binding of B*a*P, nitrosonornicotine (NNN), and *N*-acetyl-2-aminofluorene (NAAF) to chrysotile, the most adsorptive fiber, and a number of other fibers and particles, a good correlation existed between the charge of the mineral fibers, carcinogen binding, and toxicity in a macrophage-like cell line ($P388D_1$) (Harvey et al. 1984). However, others have shown that both asbestos fibers (chrysotile, anthophyllite, and amosite) and nonasbestos fibers (rock wool, glass wool, and slag wool) weakly adsorb B*a*P at about the same order of magnitude (Gerde and Scholander 1988). These investigators demonstrate that B*a*P is readily solubilized in phosphatidylcholine (PC), a component of pulmonary surfactant, and hypothesize that phospholipid adsorption by fibers is the crucial parameter to be considered in assessing uptake of B*a*P by coated fibers. Coating of both crocidolite and chrysotile asbestos with radiolabeled B*a*P enhances the uptake of the carcinogen by HTE cells and its alkylation to DNA over a four-day post-treatment period, in comparison to the situation observed when B*a*P is added directly to medium (Eastman et al. 1983). In this regard, hamster tracheal organ cultures exposed in vitro to crocidolite, asbestos, Fe_2O_3, kaolin, or carbon coated with the chemical carcinogen 3-methylcholanthrene (3MC), develop tumors after implantation of tissues into syngeneic hosts in a fashion directly related to the concentration of 3MC on

the particulates (Mossman and Craighead 1982). In contrast, tumors do not develop from tissues exposed in vitro to uncoated fibers or particles.

Others have demonstrated that prior exposure to cigarette smoke can increase the uptake of amosite asbestos fibers by rat tracheal explants, inducing greater amounts of cell proliferation and squamous metaplasia (Hobson et al. 1988). In isolated bacteriophage DNA, both cigarette smoke and asbestos synergistically increase DNA damage by stimulating $OH^{\cdot}$ production, whereas $OH^{\cdot}$ is not detected in preparations containing cigarette smoke or asbestos alone (Jackson et al. 1987). Some workers have examined asbestos fibers as a vehicle for transfection of viral RNA and DNA into cells (Appel et al. 1988; Dubes and Mack 1988). However, on a mass basis, both chrysotile and amphibole asbestos are intermediate in potency to other particles evaluated (such as talc and kaolin). Thus, the significance of these findings to mechanisms of carcinogenesis is unclear.

6.3.2.6 Leaching of Chrysotile Versus Amphiboles

The dissolution, retention, and translocation of asbestos and man-made mineral fibers (MMMF) have been recently reviewed (Lippmann 1990). The structural magnesium (Mg) of chrysotile asbestos fibers can be removed by acid leaching, but an important question is whether or not chrysotile, in comparison to amphiboles, undergoes dissolution in cells of the lung or in simulated lung fluids in vitro. Using electron probe microanalysis, Jaurand and colleagues (1984) examined intracellular chemical modification (Mg:Si ratio) of Rhodesian chrysotile fibers after uptake by rabbit alveolar macrophages and pleural mesothelial cells (PMCs). These studies indicate that biodegradation of chrysotile occurs in the phagolysosomes of both cell types. A comparison between the results of these cellular ingestion studies versus incubation of fibers in cell-free citrate buffers (pH 7 or 4) showed that the kinetics of leaching by alveolar macrophages corresponded to trends in citrate buffer at pH 4. In contrast, leaching of chrysotile at pH 7 corresponded to patterns observed in PMCs. The leaching of chrysotile in vitro supports the results of experimental studies in rats and studies on the composition of native chrysotile fibers versus chrysotile extracted from human lungs (reviewed in Morgan and Holmes 1986). Leaching was variable from fiber to fiber, but more occurred in thin fibers with a high ratio of surface area to volume in comparison to fibers of a diameter greater than 1.5 μm.

Limited work has been done on the solubility of amphibole asbestos fibers in vitro, in animals, or in humans. Using electron probe microanalysis, Langer and associates (1972b) found measurable loss of magnesium from anthophyllite and amosite after residence in the lungs of asbestos workers, but no degradation of crocidolite was observed. Small amounts of iron were leached following recovery of crocidolite from human lungs or after subcutaneous injection into rats (reviewed in Morgan and Holmes 1986). In a cell-free flow system using simulated extracellular fluids, the chemical dissolution of UICC crocidolite and chrysotile was compared to that of erionite and a number of MMMF (Scholze and Conradt 1987). The kinetics of dissolution were greatest for MMMF, followed by chrysotile, crocidolite, and erionite, the most durable fiber.

6.3.3 Conclusions

1. In laboratory animals, as in humans, asbestos fibers can cause asbestosis, lung cancer, and mesothelioma under appropriate conditions of exposure.

2. In cultured cells, exposure to asbestos fibers under certain experimental conditions can cause cell death, chromosome aberrations, aneuploidy, cell transformation, release of growth factors, cell proliferation, and various other alterations.

3. The mechanisms through which asbestos causes the above effects are not known in detail but depend heavily on the sizes and shapes of the asbestos fibers, as well as on their durability in tissue.

4. Both in vivo and in vitro experimental studies, using a variety of techniques, have demonstrated a dose-response relationship for asbestos-induced effects. While many publications report lack of response at the lowest doses tested, the data are insufficient to indicate whether there is a significant departure from linearity.

5. There is a general agreement from both in vivo and in vitro studies that long fibers (> 5 μm) are more potent than short fibers. There is some evidence that very long fibers (for example, > 20 μm) are particularly damaging to the pulmonary parenchyma. Good evidence exists that thick fibers (> 2 to 3 μm in diameter) are less harmful than thin fibers.

6. Support for the importance of fiber length in the production of biological effects has been obtained from the use of nonfibrous analogues of asbestos and other fibers. In general, these materials produce no detectable biological effects, or do so only at high dose levels.

7. In both in vivo and in vitro studies, where dose has been measured by mass, chrysotile has often proved more potent than the amphiboles. When dose has been measured by fiber number, however, it has been demonstrated that more chrysotile fibers are required to produce a given level of response than the number of amphibole fibers required.

6.4 Key Factors Affecting Fiber Uptake and Toxicity

In considering the risks to all categories of building occupants, the factors that affect the uptake and toxicity of asbestos fibers also must be considered. The evidence bearing on these questions, which has been reviewed in various preceding sections of this report, is summarized in this section. In vitro studies indicate that fiber length, diameter, and composition are critical determinants of cytotoxicity and cell transformation. Likewise, studies of laboratory animals exposed by inhalation or injection show that fiber dimensions and composition affect fibrosis and cancer yields. Reviews of the human exposure studies show that the proportions of the different diseases caused by asbestos (for example, asbestosis, lung cancer, and mesothelioma) vary among occupational cohorts, and that the ratio of mesothelioma to lung cancer tends to increase with decreasing fiber diameter for the durable amphibole forms of asbestos (Lippmann 1988).

6.4.1 Influence of Fiber Diameter

Fiber diameter affects airborne fiber penetration into and along the lung airways, and thereby the initial deposition patterns. The aerodynamic diameters of mineral fibers are about three times their physical diameters (Stöber 1972; Timbrell 1972). Thus, fibers with

diameters larger than approximately 3 μm will not penetrate in the lungs (Lippmann 1990). Fibers with diameters less than or equal to 0.1 μm are less well retained in the lungs than larger fibers (Lippmann and Timbrell 1991). Those sufficiently durable not to dissolve can readily penetrate the epithelial surface and be translocated to the lung interstitium and pleural surfaces. The fibers that remain in the lungs can cause fibrosis and lung cancer, while those durable fibers that are translocated to pleural surfaces can cause mesothelioma. Thus, for asbestosis and lung cancer, the upper fiber diameter limit is on the order of 3 μm. For mesothelioma, the upper fiber diameter limit is likely to be much less, for two reasons. First, the thinner fibers penetrate to the gas-exchange region to a greater extent. Second, fibers thinner than 0.5 μm are translocated from the deposition sites to lymphatic channels to a greater degree than are the thicker fibers, and thus they can reach any organ of the body (Oberdörster et al. 1988).

6.4.2 Influence of Fiber Length

Fiber length can also affect fiber penetration into and along the airways. As the length increases beyond about 10 μm, the interception mechanism begins to enhance deposition significantly (Sussman et al. 1991). Thus, longer fibers have proportionately more airway deposition and less deposition in the gas-exchange region. Lung retention also increases markedly with increasing fiber length above 10 μm, both on theoretical grounds (Yu et al. 1990), and on the basis of analysis of residual lung dust in humans (Timbrell 1982; Churg and Wiggs 1987; Pooley and Wagner 1988) and animals (Morgan 1979). Furthermore, fibers shorter than about 6 μm in length can be readily transported through tracheobronchial lymph nodes and translocated to more distant organs (Oberdörster et al. 1988).

Exact specification of the critical lengths for the different diseases remains difficult, since the experimental studies generally have had, of practical necessity, to use imperfectly classified fiber suspensions. Also, the experimental studies have used large concentrations, and the extent to which the observed variations in cytotoxicity and pathology are attributable to differences in fiber size, as opposed to dust overload phenomena, is difficult to assess. The experimental results described in this review indicate that short fiber preparations have a lower toxicity than long fiber preparations but do not exclude their contributions to the lesions caused by the smaller numbers of long fibers in the tail of the fiber length distribution. In general, however, individual fibers shorter than approximately 5 μm appear to possess much less toxicity than those longer than 5 μm, as demonstrated in the in vivo inhalation and injection studies of Davis and colleagues (1986) with long UICC and short amosite fiber preparations, and those of Wagner and associates (1985) with long and short erionite fibers (Wagner 1990).

6.4.3 Influence of Fiber Composition

Studies of the comparative retention and toxicity of various kinds of asbestos fibers, and other kinds of fibrous minerals, ceramics, and glasses indicate that properties other than fiber dimensions affect fiber retention and toxicity. Among these are solubility, specific surface area, and surface electrical charges that may contribute to redox reactions generating active oxygen species. Thus dimensional characteristics alone, while important, are insufficient indicators of fiber toxicity. It is now time to revise the Stanton hypothesis which acknowledges the critical importance of fiber length and diameter in biological responses, and to recognize the importance of the other physical-chemical properties that impart biological potential to fibers. A major research need is a systematic exploration of

the surface properties and factors affecting solubility of fibers in lung fluids and cells, so that due consideration can be given to fiber composition in hazard assessment.

6.4.4 Influence of Temporal and Spatial Variations in Exposure Levels on Biological Response to Fiber Inhalation

The HEI-AR mandate includes an explicit request to examine the influence of peak episodes of exposure. One could interpret this to be a charge to evaluate whether the asbestos inhaled during intermittent peaks of fiber concentration may contribute disproportionately to the hazard beyond its contribution to the long-term average exposure. If it does, then information on short-term peak fiber concentrations, as well as long-term average concentrations, would be needed in evaluating inhalation hazard potentials. This would complicate matters considerably, since all recent risk assessments have been based on health experience in workers having measured or estimated long-term average exposures. Additional human data have been obtained from studies of accumulated lung dust in workers' lungs obtained at autopsy. In such studies, it has been shown that the retention of asbestos fibers is directly related to the extent of lung fibrosis, with the fractional retention increasing with lung loading (Lippmann and Timbrell 1991).

Similar findings have been made in many animal inhalation studies with cytotoxic dusts such as asbestos and quartz, as well as in high-dust-loading studies with "nuisance" dusts. Morrow (1988) has summarized these studies and has developed a mechanistic hypothesis to explain dust overloading of the lungs, concluding that:

> "... particle overloading occurs when a certain cumulative or composite particulate volume is reached in the alveolar macrophage, and that this, in turn, results, directly or indirectly, in the loss of alveolar macrophage mobility and alveolar macrophage-mediated particle transport. The capability of the lung to clear particles, even of low inherent toxicity, is an important defense mechanism. The longer insoluble particles reside in the lung, the more opportunities exist for adverse developments. Accumulation of sufficient number of persistently retained particles may lead to a variety of adverse effects including, pneumoconiosis, hypersensitivity pneumonitis, and tumorigenesis. While it is clear that retardation of particle clearance represents a departure from normal behavior, it is unclear whether lung overloading or in the extreme, cessation of particle clearance by itself represents a toxic endpoint or whether it merely leaves the lung more susceptible to infection and other sources of injury. While this general picture is derived from limited experimental data, it appears to provide coherence to an assortment of highly germane, but seemingly isolated experimental results."

Morrow has found that the inability of the dust-laden alveolar macrophages to translocate to the mucociliary escalator is correlated with an average composite particle volume per alveolar macrophage in the lung. When this particulate volume exceeds approximately 60 μm^3/alveolar macrophage, or about 10 percent of the cell volume, the overload effect appears to be initiated.

For humans exposed to asbestos at the current Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) of 0.2 f/mL, one can roughly calculate the daily dust burden. Some assumptions are necessary, such as 10 m^3 inhaled over an 8-hour shift, 20 percent pulmonary deposition, particle density of 2.5 g/cm^3, and

some fiber to mass equivalence. Using the Ontario Royal Commission (1984) value of 1 f/mL being equivalent to 33 $\mu g/m^3$ and the Weibel (1984) value of 7 mL of alveoli per human lung, one can calculate that the daily deposited volume of asbestos is less than one millionth of the volume of alveoli. Even if asbestos is only 1 percent of the total dust, and accumulation takes place over the two- to three-week lifetime of a macrophage, there will still be less than 1 percent loading in lung macrophages. Thus, an overloading situation is unlikely to occur at permissible occupational exposures, and the possibility of such overloading at the much lower exposures currently taking place in buildings (for example, at 0.0001 f/mL and below) is remote. On the other hand, for exposures at 10 mg/m^3, as are used in most animal inhalation studies, lung burdens would be about 1,500 times higher than those at the PEL, and overloading almost certainly occurs.

Oberdörster and coworkers (1990) performed additional lung instillation and inhalation studies to explore further the Morrow hypothesis and the respective roles of both alveolar macrophages and polymorphonuclear leukocytes (PMNs), the influx of which is indicative of a cellular inflammatory response. On the basis of their studies, they concluded that:

- The delivered dose rate of particles to the lung is a determinant for the acute inflammatory PMN response: The same dose delivered over days by inhalation as opposed to sudden instillation leads to a very low response.

- The process of phagocytosis of "nuisance" particles by alveolar macrophages, rather than the interstitial access of the particles, appears to initiate the influx of PMNs into the alveolar space.

- The surface area of the retained particles correlates best with inflammatory parameters rather than the phagocytized particle numbers, mass, or volume.

- Interstitialization of particles appears to be important for inducing interstitial inflammatory responses including the induction of fibrotic reactions.

The human data are quite limited, and the interpretation of the more numerous data from the laboratory studies on rats must be interpreted cautiously in view of the uncertainties of interspecies extrapolation. Still, the literature base lends support to the following inferences:

1. In rats, there are thresholds of dust concentration for short-term exposure, above which the capacity for normal baseline rates of alveolar macrophage-mediated particle clearance are exceeded. While comparable data are not available for humans, there is reason to expect that similar increases in retention rates would occur following exposures at sufficiently high concentrations.

2. In chronic high-level occupational exposures of asbestos workers in the past, and in high-level exposures of laboratory animals, lung dust retention rates have increased with increasing lung dust burden and pulmonary fibrosis.

3. Based on the lung burden measurements and on information on current concentrations of asbestos in buildings (as summarized in section 4.6, Airborne Asbestos Levels in Nonoccupational Settings) it is inferred that exposures of general building (C1)

occupants are far below the levels that are likely to result in overloaded alveolar macrophages. Hence, expected variations in concentration are unlikely to produce peaks of exposure of a large enough magnitude to affect macrophage function.

4. If C2 (custodial) and C3 (maintenance) workers have exposures that substantially exceed the occupational permissible exposure limit (PEL) in the United States, they could approach the levels that have caused overload-related lung disease in historic occupationally exposed cohorts. On the other hand, if their exposures are kept below the PEL, then their peak exposures are of concern primarily insofar as they contribute to their cumulative exposure, rather than to any enhancement of risk associated with lung overloading.

6.5 Recommendations for Future Research into the Health Effects of Low Levels of Exposure to Asbestos Fibers

1. Epidemiologic studies of carefully selected populations should be carried out to explore further the long-term effects of low to intermediate levels of exposure, such as may be encountered by building custodial and maintenance workers.

2. The mechanisms of asbestos carcinogenesis in pulmonary epithelial cells and mesothelial cells call for further study, using the latest techniques in molecular biology. At present there are conflicting theories of asbestos carcinogenesis; on the one hand, direct interaction between asbestos fibers and DNA is suggested, which some have interpreted as implying that, theoretically at least, one fiber could initiate a tumor. On the other hand, some studies suggest that asbestos must cause damage to a relatively large volume of tissue to create the environment necessary for tumor formation. The elucidation of this problem is vital, since current risk assessment models are based on acceptance of the first hypothesis, and the hazards of low doses would be lower than predicted by these models if the latter hypothesis were correct.

3. A major requirement for further studies on the dose-response relationships and mechanisms of asbestos carcinogenesis is the availability of asbestos and man-made mineral fiber samples of defined and uniform sizes. Although the necessary fiber separation techniques have not yet been developed, they probably could be developed if the necessary expertise and funding were made available.

4. With dust samples of uniform size, in vivo and in vitro studies should more effectively examine such factors as the hazards (if any) of short fibers, the shape of the dose-response curve at low exposure levels, and whether or not different fiber types produce different levels of biological response when compared at equal dose levels (equal fiber number and equal fiber length).

5. The importance of the fibers reaching the parietal pleura, as compared to those found in the lung parenchyma, must be clarified. To do so will require a multicenter investigation, by TEM/energy dispersive x-ray analysis (EDXA) of cases of mesothelioma, lung cancer, and asbestosis, in comparison with controls. The cases should come from the areas mining the three main types of asbestos and from industrial plants in the United States and Europe.

6. A major research need is a systematic exploration of the surface properties and factors affecting solubility of fibers in lung fluids and cells, so that due consideration can be given to fiber composition in hazard assessment.

7. Future research should, however, focus on studies of cases of mesothelioma without known exposure to asbestos or other known mesotheliomagenic agents. For instance, an analysis of time trends in the distribution of such cases among men and women would be of interest, as well as further work on determining what percentage indeed had, or may have had, exposures to mesotheliomagenic agents, known or suspected. Complementary lung analyses could then establish what percentage without any known exposure do in fact have lung dust burdens implicating asbestos exposure. In addition, surveillance of national and age-specific trends in tumor incidence should be continued to provide the framework for interpreting research into the causes of mesotheliomas as well as for international comparisons.

6.6 References

Achard S, Perderiset M, Jaurand MC. 1987. Sister chromatid exchanges in rat pleural mesothelial cells treated with crocidolite, attapulgite, or benzo-3,4-pyrene. Br J Ind Med 44:281–283.

Acheson ED, Gardner MJ, Pippard EC, Grime LP. 1982. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: A 40-year follow-up. Br J Ind Med 39:344–348.

Acheson ED, Gardner MJ, Winter PD, Bennett C. 1984. Cancer in a factory using amosite asbestos. Int J Epidemiol 13:3–10.

Akira M, Yokoyama K, Yamamoto S, Higashihara T, Morinaga K, Nobuhiko K, Morimoto S, Ikezoe J, Kozuka T. 1991. Early asbestosis: Evaluation with high-resolution CT scans. Radiology 178:409–416.

Albin M, Jakobsson K, Englander V, Ranstan J, Welinder H, Westrup C, Moller T. 1984. Mortality and cancer morbidity in a cohort of asbestos cement workers. In: Sixth International Pneumoconiosis Conference, Vol. 2, pp. 825–829. September 1983, Bochum, West Germany. Verlang für neue Wissenschaft GmbH, Bremerhaven, West Germany.

Alies-Patin AM, Vallerou AJ. 1985. Mortality of workers in a French asbestos cement factory 1940–82. Br J Ind Med 42:219–225.

American Thoracic Society. 1986. The diagnosis of non-malignant diseases related to asbestos. Am Rev Respir Dis 134:363–368.

Anderson HA, Lilis R, Daum SM, Selikoff IJ. 1979. Asbestosis among household contacts of asbestos factory workers. Ann NY Acad Sci 330:387–399.

Anderson M, Olsen J. 1985. Trend and distribution of mesothelioma in Denmark. Br J Cancer 51:699–705.

Antony VB, Owen CL, Hadley KJ. 1989. Pleural mesothelial cells stimulated by asbestos release chemotactic activity for neutrophils in vitro. Am Rev Respir Dis 139:199–206.

Appel JD, Fasy TM, Kohtz DS, Kohtz JD, Johnson EM. 1988. Asbestos fibers mediate transformation of monkey cells by exogenous plasmid DNA. Proc Natl Acad Sci USA 85(20):7670–7674. (Published erratum appears in Proc Natl Acad Sci USA 1989 86(3):997.)

Archer J, Rom W. 1983. Trends in mortality of diffuse malignant mesothelioma of the pleura. Lancet 2:112–113.

Armstrong BK, de Klerk NH, Musk AW, Hobbs MST. 1988. Mortality in miners and millers of crocidolite in Western Australia. Br J Ind Med 45:5–13.

Armstrong BK, Musk AW, Baker J. 1984. Epidemiology of malignant mesothelioma in Western Australia. Med J Aust 141:86–88.

Ashcroft T, Heppleston AG. 1973. The optical and electron-microscopic determination of pulmonary asbestos fibre concentration and its relation to the human pathological reaction. J Clin Pathol 26:224–234.

Asp S. 1984. Confounding by variable smoking habits in different occupational groups. Scand J Work Environ Health 10(5):325–326.

Axelson O. 1989. Confounding from smoking in occupational epidemiology. Br J Ind Med 46(8):505–507.

Beattie J, Knox FJ. 1961. Studies of mineral content and particle size distribution in the lungs of asbestos textile workers. In: Inhaled Particles and Vapours (Davies CN, ed.) pp. 419. Pergamon Press, New York, NY.

Beck EG, Bignon J, eds. 1985. In Vitro Effects of Mineral Dusts. Series G: Ecological Sciences, Vol. 3. Springer-Verlag, New York, NY.

Becklake MR. 1976. Asbestos-related diseases of the lungs and pleura. Am Rev Respir Dis 114:187–194.

Becklake MR. 1987. Control of asbestos-related disease in the RSA. S Afr Med J 71:118–119.

Becklake MR. 1991a. The epidemology of asbestosis. In: Mineral Fibers and Health (Liddell D, Miller K, eds.) pp. 103–119. CRC Press, Boca Raton, FL.

Becklake MR. 1991b. Asbestos and other fiber-related diseases of the lungs and pleura: Distributions and determinants in exposed populations. Chest 100:248–254.

Beger PJ. 1933. Uber die Asbestosiskorperchen. Virchows Arch [A] Pathol Anat 290:280.

Begin R, Masse S, Sébastian P, Bassi J, Rola-Pleszczynski M, Boctar M, Côte Y, Fabi D, Dalle D. 1986. Asbestos exposure and retention as determinants of airway disease and asbestos alveolitis. Am Rev Respir Dis 134:1176.

Berkley C, Churg J, Selikoff IJ. 1965. Detection and localization of mineral fibers in tissue. Ann NY Acad Sci 132:48.

Berkley C, Langer AM, Baden V. 1967. Instrumental analysis of inspired fibrous pulmonary particulates. NY Acad Sci Trans 30:331.

Berry G, Newhouse ML. 1983. Mortality of workers manufacturing friction materials using asbestos. Br J Ind Med 40:1–7.

Berry G, Newhouse ML, Antonis P. 1985. Combined effects of asbestos and smoking on mortality from lung cancer and mesothelioma in factory workers. Br J Ind Med 42:12–18.

Berry G, Wagner JC. 1976. Effects of age at innoculation of asbestos on occurrence of mesothelioma in rats. Int J Cancer 17:477–483.

Bolton RE, Davis JMG, Donaldson K, Wright A. 1982. Variations in the carcinogenicity of mineral fibers. Ann Occup Hyg 26:569.

Bossard E, Stolkin I, Spycher MA, Ruttner JR. 1980. Quantification
and particle size distribution of inhaled fibres in the lungs. In: Biological Effects of Mineral Fibres, Vol. 1 (Wagner JC, Davis W, eds.) pp. 35–41. IARC Scientific Publications No. 30. International Agency for Research on Cancer, Lyon, France.

Botha J, Irwig L, Strebel P. 1986. Excess mortality from stomach cancer, lung cancer, and asbestosis and/or mesothelioma in crocidolite mining districts in South Africa. Am J Epidemiol 123:30–40.

Bourbeau J, Ernst P, Chrome J, Armstrong B, Becklake MR. 1990. The relationship between respiratory impairment and asbestos-related pleural abnormalities. Am Rev Respir Dis 142:837–842.

Brown GM, Cowie H, Davis JMG, Donaldson K. 1986a. In vitro assays for detecting carcinogenic mineral fibres: A comparison of two assays and the role of fibre size. Carcinogenesis 7(12):1971–1974.

Brown DP, Dement JM, Wagner JK. 1979. Mortality patterns among miners and millers occupationally exposed to asbestiform talc. In: Dusts and Disease: Proceedings of the Conference on Occupational Exposures to Fibrous and Particulate Dust and Their Extension into the Environment (Lemen R, Dement JM, eds.) pp. 317–324. Pathotox Publishers, Forest Park, IL.

Brown RC, Gormley IP, Chamberlain M, Davies B, eds. 1980. The In Vitro Effects of Mineral Dusts. Academic Press, London, England.

Brown RC, Poole A, Fleming GTA. 1988. The influence of asbestos dust on the oncogenic transformation of C3H10T½ cells. Cancer Lett 18:221–227.

Brown RC, Poole A, Turver CJ. 1986b. In vitro correlates of mineral dust toxicity. Food Chem Toxicol 24:535–538.

Brown RC, Poole A, Turver CJ, Vann C. 1987. Role of iron-mediated free-radical generation in asbestos-induced cytotoxicity. Toxicol in Vitro 1:67–70.

Browne K. 1986. Is asbestos or asbestosis the cause of increased risk of lung cancer in asbestos workers? Br J Ind Med 43:145–149.

Case BW, Ip MPC, Padilla M, Kleinerman J. 1986. Asbestos effects on superoxide production: An in vitro study of hamster alveolar macrophages. Environ Res 39:299–306.

Case BW, Sébastien P, MacDonald JC. 1988. Lung fibre analysis in accident victims: A biological assessment of general environmental exposures. Arch Environ Health 2:178–179.

Chamberlain M, Tarmy EM. 1977. Asbestos and glass fibres in bacterial mutation tests. Mutat Res 43:159–164.

Churg A. 1985. Malignant mesothelioma in British Columbia in 1982. Cancer 55:672–674.

Churg A. 1988. Chrysotile, tremolite and malignant mesothelioma in man. Chest 93:621–628.

Churg A, Wiggs B. 1987. Accumulation of long asbestos fibers in the peripheral upper lobe in cases of malignant mesothelioma. Am J Ind Med 11:563–569.

Churg A, Wright JL. 1989. Fibre content of lung in amphibole-and chrysotile-induced mesothelioma: Implications for environmental exposure. In: Non-occupational Exposure to Mineral Fibres. IARC No. 90 (Bignon J, Peto J, Saracci R, eds.) pp. 314–318. International Agency for Research on Cancer, Lyon, France.

Clemmesen J, Hjalgrim-Jensen S. 1981. Cancer incidence among 5,686 asbestos-cement workers followed from 1943 through 1976. Ecotoxicol Environ Saf 5:15–23.

Connelly R, Spirtas R, Myers M, Percy C, Fraumeni J. 1987. Demographic patterns for mesothelioma in the United States. JNCI 78:1053–1060.

Constantopoulos SH, Goudevenos JA, Saratzis N, Langer AM, Selikoff IJ, Moutsopoulos HM. 1985. Metsovo lung: Pleural calcification and restrictive lung function in northwestern Greece: Environmental exposure to mineral fiber as etiology. Environ Res 38:41–53.

Consumer Product Safety Commission, U.S. 1983. Report to the U.S. Consumer Product Safety Commission by the chronic hazard advisory panel on asbestos. Directorate for Health Sciences, U.S. Consumer Product Safety Commission, Washington, DC.

Cooke WE. 1927. Pulmonary asbestosis. Br Med J 2:1024.

Craighead JE, Abraham JL, Churg A, Green FH, Kleinerman J, Pratt PC, Scemayer TA, Vallyathan V, Weill H. 1982. The pathology of asbestos-associated diseases of the lungs and pleural cavities: Diagnostic criteria and proposed grading schema. Arch Pathol Lab Med 106(11):544–596.

Craighead JE, Akley NJ, Gould LB, Libbus BL. 1987. Characteristics of tumors and tumor cells cultured from experimental asbestos-induced mesotheliomas in rats. Am J Pathol 129(3):448-462.

Dagbert M. 1976. Etudes de correlation de mesures d'empoussierage dans l'industrie de l'amiante. Document 5 Beaudry Report. Quebec Comite d'Etude sur la Salubrite dans l'Industrie de l'Amiante, Montreal, Ontario, Canada.

Davis JMG. 1989. Mineral fiber carcinogenesis: Experimental data relating to the importance of fiber type, size, deposition, dissolution and migration. In: Non-occupational Exposure to Mineral Fibers (Bignon J, Peto J, Saracci R, eds.) pp. 33–34. IARC Scientific Publications No. 90. International Agency for Research on Cancer, Lyon, France.

Davis JMG, Addison J, Bolton RE, Donaldson K, Jones AD, Smith T. 1986. The pathogenicity of long versus short fiber samples of amosite asbestos administered to rats by inhalation and intraperitoneal injection. Br J Exp Pathol 67:415.

Davis JMG, Beckett ST, Bolton RE, Collings P, Middleton AP. 1978. Mass and number of fibers in the pathogenesis of asbestos-related lung disease in rats. Br J Cancer 37:673.

Davis JMG, Beckett ST, Bolton RE, Donaldson K. 1980. The effects of intermittent high asbestos exposure (peak dose levels) on the lungs of rats. Br J Exp Pathol 61:272–280.

Davis JMG, Bolton RE, Miller BG, Niven K. 1991. Mesothelioma dose response following intraperitoneal injection of mineral fibers. Br J Exp Pathol, in press.

Davis JMG, Cowie H. 1990. The relationship between fibrosis and cancer in experimental animals exposed to asbestos and other fibers. Environ Health Perspect 88:305–309.

Davis JMG, Jones AD. 1988. Comparisons of the pathogenicity of long and short fibers of chrysotile asbestos in rats. Br J Exp Pathol 69:717.

de Klerk NH, Armstrong BK, Musk AW, Hobbs MST. 1989. Cancer mortality in relation to measures of occupational exposure to crocidolite at Wittenoom Gorge in Western Australia. Br J Ind Med 46:529–536.

Dement JM, Harris RL Jr, Symons MJ, Shy C. 1982. Estimates of dose-response for respiratory cancer among chrysotile asbestos workers. Ann Occup Hyg 26:869–887.

Dement JM, Harris RL Jr, Symons MJ, Shy C. 1983a. Exposures and mortality among chrysotile asbestos workers. Part I: Exposure estimates. Am J Ind Med 4:399–419.

Dement JM, Harris RL Jr, Symons MJ, Shy C. 1983b. Exposures and mortality among chrysotile asbestos workers. Part II: Mortality. Am J Ind Med 4:421–433.

di Paolo JA, DeMarinis AJ, Doniger J. 1983. Asbestos and benzo[*a*]pyrene synergism in the transformation of syrian hamster embryo cells. Pharmacology 27:65–73.

Dodson RF, Williams MG Jr, Corn CJ, Brollo A, Bianchi C. 1990. Asbestos content of lung tissue, lymph nodes, and pleural plaques from former shipyard workers. Am Rev Respir Dis 142(4):843–847.

Doll NJ, Stankus RP, Goldbach S, Salvaggio JE. 1982. In vitro effect of asbestos fibers on polymorphonuclear leukocyte function. Int Arch Allergy Appl Immunol 68:17–21.

Doll R, Peto J. 1985. Asbestos: Effects on Health of Exposure to Asbestos, pp. 1–58. Health and Safety Commission, Her Majesty's Stationery Office, London, England.

Doll R, Peto J. 1987. Other asbestos-related neoplasms. In: Asbestos-Related Malignancy (Antman K, Aisner J, eds.) pp. 81–98. Grune & Stratton, Orlando, FL.

Donaldson K, Brown GM, Brown DM, Bolton RE, Davis JMG. 1989. Inflammation generating potential of long and short fibre amosite asbestos samples. Br J Ind Med 46:271–276.

Donaldson K, Cullen RT. 1984. Chemiluminescence of asbestos-activated macrophages. Br J Exp Pathol 65:81–90.

Dubes GR, Mack LR. 1988. Asbestos-mediated transfection of mammalian cell cultures. In Vitro Cell Dev Biol 24(3):175–182.

Eastman A, Mossman BT, Bresnick E. 1983. Influence of asbestos on the uptake of benzo[*a*]pyrene and DNA alkylation on hamster tracheal epithelial cells. Cancer Res 43:1251–1255.

Elmes PC, Simpson MJC. 1977. Insulation workers in Belfast: A further study of mortality due to asbestos exposure (1940–75). Br J Ind Med 34:174–180.

Enterline P, Henderson V. 1987. Geographic patterns for pleural mesothelioma deaths in the United States 1968–81. JNCI 79:31–37.

Environmental Protection Agency, U.S. 1986. (See Nicholson WJ. 1986.)

Ernst P, Zejda J. 1991. Pleural and airway disease associated with mineral fibers (Chapter 10). In: Mineral Fibers and Health (Liddell D, Miller K, eds.) pp. 117–130. CRC Press, Boca Raton, FL.

Ferguson D. 1989. Malignant mesothelioma: The rising epidemic. Med J Aust 150:233–235.

Ferguson D, Berry G, Jelihovsky T, Andreas SB, Rogers AJ, Fung SC, Grimwood A, Thompson R. 1987. The Australian mesothelioma surveillance program 1979–1985. Med J Aust 147:166–172.

Finkelstein MM. 1983. Mortality among long term employees of an Ontario asbestos-cement factory. Br J Ind Med 40:138–144.

Fleury-Feith J, Nebut M, Saint-Etienne L, Laurent P, Pinchon MC, Kheuang L, Renier A, Jaurand MC. 1989. Occurrence and morphology of tumors induced in nude mice transplanted with chrysotile-transformed rat pleural mesothelial cells. Biol Cell 65:45-50.

Fornace AJ Jr, Lechner JF, Grafstrom RC, Harris CC. 1982. DNA repair in human bronchial epithelial cells. Carcinogenesis 3:1373–1377.

Gabrielson EW, Rosen GM, Grafstrom RC, Strauss KE, Harris CC. 1986. Studies on the role of oxygen radicals in asbestos-induced cytopathology of cultured human lung mesothelial cells. Carcinogenesis 7:1161–1164.

Gaensler EA, Kaplan AL. 1971. Asbestos pleural effusion. Ann Intern Med 74:178–191.

Gamsu G, Aberle DR, Lynch D. 1989. Computed tomography in the diagnosis of asbestos-related thoracic disease. J Thorac Imaging 4:61.

Garcia JGN, Dodson RF, Callahan KS. 1989. Effect of environmental particulates on cultured human and bovine endothelium. Lab Invest 61:53–61.

Gardner MJ, Acheson E, Winter P. 1982. Mortality from mesothelioma of the pleura during 1968–78 in England and Wales. Br J Cancer 46:81–88.

Gardner MJ, Jones R, Pippard E, Saito N. 1985. Mesothelioma of the peritoneum during 1967–82 in England and Wales. Br J Cancer 51:121–126.

Gardner MJ, Saracci R. 1989. Effects on health of nonoccupational exposure to airborne mineral fibers. In: Non-occupational Exposure to Mineral Fibers (Bignon J, Peto J, Saracci R, eds.) pp. 375–397. IARC Scientific Publications No. 90. International Agency for Research on Cancer, Lyon, France.

Gardner MJ, Winter PD, Pannett B, Powell CA. 1986. Follow-up study of workers manufacturing chrysotile asbestos cement products. Br J Ind Med 43:726–732.

Gaudichet A, Sébastien P, Clark NJ, Pooley FD. 1980. Identification and quantification of asbestos fibres in human tissues. In: Biological Effects of Mineral Fibres (Wagner JC, Davis W, eds.) pp. 61–68. IARC Scientific Publications No. 30. International Agency for Research on Cancer, Lyon, France.

Gerde P, Scholander P. 1988. Adsorption of benzo[*a*]pyrene on to asbestos and manmade mineral fibres in an aqueous solution and in a biological model solution. Br J Ind Med 45:682–688.

Gibas Z, Li FP, Antman KH, Bernal S, Stahel R, Sandberg AA. 1986. Chromosome changes in malignant mesothelioma. Cancer Genet Cytogenet 20(3–4):191–201.

Gibbs AR, Jones JSP, Pooley FD, Griffiths DM, Wagner JC. 1989. Non-occupational malignant mesotheliomas. In: Non-occupational Exposure to Mineral Fibres (Bignon J, Peto J, Saracci R, eds.) pp. 219–228. IARC Scientific Publications No. 90. International Agency for Research on Cancer, Lyon, France.

Gold C. 1967. A simple method for detecting asbestos in tissue. J Clin Pathol 20:674.

Goodglick LA, Kane AB. 1986. Role of reactive oxygen metabolites in crocidolite asbestos toxicity to mouse macrophages. Cancer Res 46:5558–5566.

Goodglick LA, Kane AB. 1990. Cytotoxicity of long and short crocidolite asbestos fibers in vitro and in vivo. Cancer Res 50:5153–5163.

Greenberg M, Lloyd-Davies T. 1974. Mesothelioma register 1967–68. Br J Ind Med 31:91–104.

Gulumian M, Kilroe-Smith TA. 1987. Crocidolite-induced lipid peroxidation. Environ Res 44:254–259.

Gylseth B, Mowe G, Wannag A. 1983 Fiber type and concentration in the lungs of workers in an asbestos cement factory. Br J Ind Med 40:375

Hansen K, Mossman BT. 1987. Generation of superoxide from alveolar macrophages exposed to asbestiform and nonfibrous particles. Cancer Res 47:1681–1686.

Harvey G, Page M, Dumas L. 1984. Binding of environmental carcinogens to asbestos and mineral fibres. Br J Ind Med 41:396–400.

Hedenborg M, Klockars M. 1987. Production of reactive oxygen metabolites induced by asbestos fibres in human polymorphonuclear leucocytes. J Clin Pathol 40:1189–1193.

Hei TK, Geard CR, Osmak RS, Travisano M. 1985. Correlation of in vitro genotoxicity and oncogenicity induced by radiation and asbestos fibres. Br J Cancer 52:591–597.

Hei TK, He ZY, Piao CQ, Waldren C. 1991. The mutagenicity of mineral fibers. In: Proceedings of the NATO Workshop: Mechanisms of Mineral Fiber Carcinogeneis (Brown RC, Hoskins J, eds.). In press.

Henderson VL, Enterline PE. 1979. Asbestos exposure: Factors associated with excess cancer and respiratory disease mortality. Ann NY Acad Sci 330:117–126.

Hesterberg TW, Barrett JC. 1984. Dependence of asbestos and mineral dust-induced transformation of mammalian cells in culture on fiber dimension. Cancer Res 44:2170–2180.

Hesterberg TW, Barrett JC. 1985. Induction by asbestos fibers of anaphase abnormalities: mechanism for aneuploidy induction and possibly carcinogenesis. Carcinogenesis 6:473–475.

Hesterberg TW, Butterick CJ, Oshimura M, Brody AR, Barrett JC. 1986. Role of phagocytosis in syrian hamster cell transformation and cytogenetic effects induced by asbestos and short and long glass fibers. Cancer Res 46:5795–5802.

Hillerdal G. 1983. Malignant mesothelioma: 1982. Review of 4710 published cases. Br J Dis Chest 77:321–342.

Hillerdal G. 1989. Rounded atalectasis: Clinical experience with 74 patients. Chest 95:836.

Hillerdal G, Özesmi M. 1987. Benign asbestos pleural effusion: 73 exudates in 60 patients. Eur J Respir Dis 71:113–121.

Hinds M. 1982. Mesothelioma in the United States: Incidence in the 1970s. J Occ Med 20:469–471.

Hirsch A, Brochard P, De Cremoux H, Erkan L, Sébastien P, Di Menza L, Bignon J. 1982. Features of asbestos exposed and unexposed mesothelioma. Am J Ind Med 3:413–422.

Hobbs MST, Woodward SD, Murphy B, Musk AW, Elder JE. 1980. The incidence of pneumoconiosis, mesothelioma and other respiratory cancer in men engaged in mining and milling crocidolite in Western Australia. In: Biological Effects of Mineral Fibres, Vol. 2 (Wagner JC, Davis W, ed.) pp. 615–625. IARC Scientific Publications No. 30. International Agency for Research on Cancer, Lyon, France.

Hobson J, Gilks B, Wright J, Churg A. 1988. Direct enhancement by cigarette smoke of asbestos fiber penetration and asbestos-induced epithelial proliferation in rat tracheal explants. JNCI 80:518–521.

Hoel D. 1990. National Institute of Environmental Health Sciences, personal communication.

Huang SL. 1979. Amosite, chrysotile and crocidolite asbestos are mutagenic in Chinese hamster lung cells. Mutat Res 68:265–274.

Hughes JM, Weill H. 1986. Asbestos exposure: Quantitative assessment of risk. Am Rev Respir Dis 133:5–15.

Hughes JM, Weill H, Hammad YY. 1987. Mortality of workers employed in two asbestos cement manufacturing plants. Br J Ind Med 44:161–174.

Ilgren EB. 1989. Mesothelioma threshold. In: Effects of Mineral Dusts on Cells, NATO Series H. Cell Biology, Vol. 30 (Mossman BT, Begin RO, eds.) pp. 455–464. Springer-Verlag, New York, NY.

Ilgren EB, Browne K. 1991. Asbestos-related mesothelioma: evidence for e threshold in animals and humans. Reg Toxicol Pharmacol 13:116–132.

Ilgren EB, Wagner CJ. 1991. Background incidence of mesothelioma: animal and human evidence. Reg Toxicol Pharmacol 13:133–149.

International Agency for Research on Cancer. 1982. IARC Monograph: Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 1–29, Suppl 4. World Health Organization, Geneva, Switzerland.

International Agency for Research on Cancer. 1988. Man-made mineral fibres and radon. IARC Monograph: The Evaluation of Carcinogenic Risks to Humans, Vol. 43. World Health Organization, Geneva Switzerland.

Jackson JH, Schraufstatter IU, Hyslop PA, Vosbeck K, Sauerheber R, Weitzman SA, Cochrane CG. 1987. Role of oxidants in DNA damage: Hydroxyl radical mediates the synergistic DNA damaging effects of asbestos and cigarette smoke. J Clin Invest 80:1090–1095.

Jaurand MC, Gaudichet A, Halpern S, Bignon J. 1984. In vitro biodegradation of chrysotile fibres by alveolar macrophages and mesothelial cells in culture: Comparison with a pH effect. Br J Ind Med 41:389–395.

Jaurand MC, Kheuang L, Magne L, Bignon J. 1986. Chromosome changes induced by chrysotile fibers and benzo-3,4-pyrene in rat pleural mesothelial cells. Mutat Res 169:141–148.

Jones JSP, Smith PG, Pooley FD, Berry G, Sawle GW, Wignall BK, Madeley RJ, Aggarwal A. 1980. The consequences of exposure to asbestos dust in a wartime gas-mask factory. In: Biological Effects of Mineral Fibres, Vol. 2 (Wagner JC, Davis W, eds.) pp. 637–653. IARC Scientific Publications No. 30. International Agency for Research on Cancer, Lyon, France.

Jones RN, McLoud T, Rockoff SD. 1988a. The radiographic pleural abnormalities in asbestos exposure: Relationship to physiologic abnormalities. J Thorac Imaging 3:57.

Jones JSP, Smith D, Thomas P. 1988b. Mesothelioma in Great Britain in 1968–1983. Scand J Work Environ Health 14:145–152.

King EJ, Glegg JW, Rae VM. 1946. Effect of asbestos and asbestos and aluminium on the lungs of rabbits. Thorax 1:188

Kleinfeld M, Messite J, Kooyman O. 1967. Mortality experience in a group of asbestos workers. Arch Environ Health 15:177–180.

Kleinfeld M, Messite J, Zaki MH. 1974. Mortality experience among talc workers: A follow-up study. J Occup Med 16:345–349.

Klosterkötter W. 1968. Experimentelle Untersuchunger über die Bedeutung der Faserlange für die Asbest-Fibrose sowie Untersuchungen über die Beeinflussung der Fibrose durch Polyvinylyridin-*n*-oxid. In: Biologische Wirkungen des Asbestos, p. 47. Proceedings of the International Conference, Dresden, Germany. Deutches Zenralinstitut für Arbeitsmedizin, Berlin, Germany.

Kolev K. 1982. Experimentally-induced mesothelioma in white rats in response to intraperitoneal administration of amorphous crocidolite asbestos. Environ Res 29:123.

Kolonel LN, Hirohata T, Chappell BV, Viola FV, Harris DE. 1980. Cancer mortality in a cohort of naval shipyard workers in Hawaii: Early findings. JNCI 64:739–743.

Kouzan S, Brody AR, Nettesheim P, Eling T. 1985. Production of arachidonic acid metabolites by macrophages exposed in vitro to asbestos, carbonyl iron particles, or calcium ionophore. Am Rev Respir Dis 131:624–632.

Kühn J. 1941. Ultramicroscopic investigations on asbestos dust and asbestosis lungs. Arch f Gewerbepath u Gewerbehyg 10(5):473–485.

Kuschner M. 1987. The effects of MMMF on animal systems: Some reflections on their pathogenesis. Ann Occup Hyg 31:791–798.

Lacquet LM, van der Linden L, Lepoutre J. 1980. Roentgenographic lung changes, asbestosis and mortality in a Belgian asbestos cement factory. In: Biological Effects of Mineral Fibers, Vol. 2 (Wagner JC, Davis W, eds.) pp. 783–793. IARC Scientific Publication No. 30. International Agency for Research on Cancer, Lyon, France.

Lamm SH, Levine MS, et al. 1988. Analysis of excess lung cancer risk in short term employees. Am J Epidemiol 127:1202–1209.

Landesman JM, Mossman BT. 1982. Induction of ornithine decarboxylase in hamster tracheal epithelial cells exposed to asbestos and 12-O-tetradecanoylphorbol-13-acetate. Cancer Res 42:3669–3675.

Langer AM. 1972. Chemical characterization of uncoated asbestos fibers from the lungs of asbestos workers by electron microprobe analysis. J Histochem Cytochem 20:735–740.

Langer AM. 1978. Crystal faces and cleavage planes in quartz as templates in biological processes. Q Rev Biophys 11:543–575.

Langer AM, Ashley R, Baden V, Berkley C, Hammond EC, Mackler AD, Maggiore CJ, Nicholson WJ, Rohl AN, Rubin IB, Sastre A, Selikoff IJ. 1973. Identification of asbestos in human tissues. J Occup Med 15:287–295.

Langer AM, Baden V, Hammond EC, Selikoff IJ. 1971a. Inorganic fibers, including chrysotile, in lung at autopsy: Preliminary report. In: Inhaled Particles, **Vol. 3** (Walton WH, ed.) pp. 683–694. Proceedings of the International British Occupational Hygiene Society Symposium, London, England, 1970. Unwin Brothers, London, England.

Langer AM, Nolan RP. 1985. Physio-chemcial properties of minerals relevant to biological activities. In: In Vitro Effects of Mineral Dusts (Beck EG, Bignon J, eds.) pp. 9–25. Nato Advanced Science Institutes Series. Springer-Verlag, New York, NY.

Langer AM, Nolan RP. 1986. The properties of chrysotile asbestos as determinants of biological activity. Accompl Oncol 1:30–51.

Langer AM, Nolan RP. 1989a. Fiber type and mesothelioma risk. In: Proceedings of the Symposium of Health Aspects of Exposure to Asbestos in Buildings, Cambridge, MA, December 14–16, 1988, pp. 91–140. Harvard University Energy and Environmental Policy Center, Cambridge, MA.

Langer AM, Nolan RP. 1989b. Fibre type and burden in parenchymal tissues of workers occupationally exposed to asbestos in the United States. In: Non-occupational Exposure to Mineral Fibres. (Bignon J, Peto J, Saracci R, eds.) pp. 330–335. IARC Scientific Publications No. 90. International Agency for Research on Cancer, Lyon, France.

Langer AM, Nolan RP. 1990. Pleural mesothelioma resulting from exposure to amosite asbestos in a building: Letter to the editor. Respir Med 84:509–510.

Langer AM, Nolan RP, Constantopoulos SH, Moutsopoulos HM. 1987. Association of Metsovo lung and pleural mesothelioma with exposure to tremolite-containing whitewash. Lancet 1:965–967.

Langer AM, Pooley FD. 1973. Identification of single asbestos fibers in human tissue. In: Proceedings of the International Conference on the Biological Effects of Asbestos, October 2–6, 1972. IARC No. 19. International Agency for Research on Cancer, Lyon, France.

Langer AM, Rohl AN, Wolff MS, Selikoff IJ. 1979. Asbestos, fibrous minerals and acicular cleavage fragments: Nomenclature and biological properties. In: Dusts and Disease (Lemen R, Dement JM, eds.) pp. 1–22. Proceedings of the Conference on Occupational Exposures to Fibrous and Particulate Dusts and Their Extension into the Environment. Pathotox Publishers, Forest Park, IL.

Langer AM, Rubin IB, Selikoff IJ. 1970. Electron microprobe analysis of asbestos bodies. In: Proceedings of the Pneumoconiosis Conference Johannesburg, 1969 (Shapiro HA, ed.) pp. 57–69. Oxford University Press, Cape Town, South Africa.

Langer AM, Rubin IB, Selikoff IJ. 1972a. Chemical characterization of asbestos body cores by electron microprobe analysis. J Histochem Cytochem 20:723–735.

Langer AM, Rubin IB, Selikoff IJ, Pooley FD. 1972b. Chemical characterization of uncoated asbestos fibers from the lungs of asbestos workers by electron microprobe analysis. J Histochem Cytochem 20:735-740.

Langer AM, Selikoff IJ, Rosenberg C. 1979. Defining new asbestos high-risk groups. In: Proceedings of International Conference on the Critical Current Issues in Environmental

Health Hazards (abstract) (Chwat M, Drow K, eds.) p. 50. Tel Aviv, Israel, March 4–7, 1979. Israel Medical Association, Society of Occupational Health, Haifa, Israel.

Langer AM, Selikoff IJ, Sastre A. 1971b. Chrysotile asbestos in the lungs of persons in New York City. Arch Environ Health 22:348–361.

Langer AM, Wolff MS, Rohl AN, Selikoff IJ. 1978. Variation of properties of chrysotile asbestos, subjected to prolonged milling. J. Toxicol Environ Sci 4:173–188.

Law MR, Ward FG, Hodson ME, Heard BE. 1983. Evidence for longer survival of patients with pleural mesothelioma without asbestos exposure. Thorax 38:744–746.

Le Bouffant L. 1974. Investigation and analysis of asbestos fibers and accompaning minerals in biological materials. Environ Health Perspect 9:149–154.

Le Bouffant L, Daniel H, Henin JP, Martin JC. 1985. Carcinogenic potency of chrysotile fibers of the length <5m. Cahiers de Notes Documentaires 118:83–90.

Lechner JF, Tokiwa T, LaVeck M, Benedict WF, Banks-Schlegel S, Yeager H Jr, Banerjee A, Harris CC. 1985. Asbestos-associated chromosomal changes in human mesothelial cells. Proc Natl Acad Sci USA 82:3884–3888.

Lee KP, Kelly DP, O'Neal FO, Slader JC, Kennedy GL. 1988. Lung response to ultrafine kevlar aramid synthetic fibrils following 2-year inhalation exposure in rats. Fundam Appl Toxicol 11:1.

Lemaire I, Gingras D, Lemaire S. 1986. Effects of chrysotile asbestos on DNA synthesis and growth of human embryonic lung fibroblasts. J Environ Path Toxicol Oncol 6:169–180.

Liddell FDK, Hanley JA. 1985 Relations between asbestos exposure and lung cancer SMRs in occupational cohort studies. Br J Ind Med 42 389–396.

Lippmann M. 1988. Asbestos exposure indices. Environ Res 46:86–106.

Lippmann M. 1990. Effects of fiber characteristics on lung deposition, retention, and clearance. Environ Health Perspect 88:311–317.

Lippmann M, Timbrell V. 1991. Particle loading in the human lung-human experience and implications for exposure limits. J Aerosol Med (in press).

Lu YP, Lasne C, Lowy R, Chouroulinkov I. 1988. Synergistic effects of asbestos fibres and 12-O-tetradecanoylphorbol-13-acetate in the BALB/3T3 cell transformation system. Mutagenesis 3:355–362.

Lynch DA, Gamsu G, Ray CS, Aberle DR. 1988. Asbestos-related focal lung masses: Manifestation on conventional and high-resolution CT scans. Radiology 169:603.

Mancuso TF, El-Attar AA. 1967. Mortality pattern in a cohort of asbestos workers. J Occup Med 9:147–162.

Marsh JP, Mossman BT. 1988. Mechanisms of induction of ornithine decarboxylase activity in tracheal epithelial cells by asbestiform minerals. Cancer Res 48:709–714.

McConnochie K, Simonato J, Mavrides P, Christofides P, Mitha R, Griffiths DM, Wagner JC. 1989. Mesothelioma in Cyprus. In: Non-occupational Exposure to Mineral Fibres. IARC Scientific Publications No. 90 (Bignon J, Peto J, Saracci R, eds.) pp. 411–419. International Agency for Research on Cancer, Lyon, France.

McDonald AD. 1980. Malignant mesothelioma in Quebec. In: Biological Effects of Mineral Fibres, Vol. 2 (Wagner JC, Davis W, eds.) pp. 673–680. IARC Scientific Publications No. 30. International Agency for Research on Cancer, Lyon, France.

McDonald AD, Fry JS, Woolley AJ, McDonald JC. 1983a. Dust exposure and mortality in an American chrysotile textile plant. Br J Ind Med 40:361–367.

McDonald AD, Fry JS, Woolley AJ, McDonald JC. 1983b. Dust exposure and mortality in an American factory using chrysotile, amosite and crocidolite in mainly textile manufacturing. Br J Ind Med 40:368–374.

McDonald AD, Fry JS, Woolley AJ, McDonald JC. 1984. Dust exposure and mortality in an Americal chrysotile asbestos friction products plant. Br J Ind Med 41 151–157

McDonald AD, McDonald JC. 1978. Mesothelioma after crocidolite exposure during gas mask manufacture. Environ Res 17:340–346.

McDonald AD, McDonald JC. 1980. Malignant mesothelioma in North America. Cancer 46:1650–1656.

McDonald AD, McDonald JC. 1987a. Epidemiology of malignant mesothelioma. In: Asbestos-Related Malignancy (Antman K, Aisner J, eds.) pp 31–56. Grune & Stratton, Orlando, FL.

McDonald JC. 1985. Health implications of environmental exposure to asbestos. Environ Health Perspect 62:319–328.

McDonald JC, Armstrong B, Case B, Doell D, McCaughey WTE, McDonald AD, Sébastien P. 1989a. Mesothelioma and asbestos fiber type: Evidence from lung tissue. Cancer 63:1544–1547.

McDonald JC, Liddell FDK, Gibbs GW, Eyssen GE, McDonald AD. 1980. Dust exposure and mortality in chrysotile mining, 1910–75. Br J Ind Med 37:11–24.

McDonald JC, McDonald AD. 1977. Epidemiology of mesothelioma from estimated incidence. Prev Med 6:426–446.

McDonald JC, McDonald AD. 1987b. Epidemiology of asbestos-related lung cancer. In: Asbestos-Related Malignancy (Antman K, Aisner J, eds.) pp. 57–79. Grune & Stratton, Orlando, FL.

McDonald JC, McDonald AD. 1990. Asbestos and carcinogenicity (letter); comment on Science 1990; 248(4957):795–802. Science 249(4971):844.

McDonald JC, Sébastien P, McDonald AD, Case B. 1989b. Epidemiological observations on mesothelioma and their implications for non-occupational exposure. In: Non-occupational Exposure to Mineral Fibres (Bignon J, Peto J, Saracci R, eds.) pp. 420–427. IARC Scientific Publications No. 90. International Agency for Research on Cancer, Lyon, France.

McLoud T, Woods BO, Carrington CB, Epler GR, Gaensler EA. 1985. Diffuse pleural thickening in an asbestos exposed population: Prevalence and causes. AJR 144:9.

Meijers JMM, Planteydt HT, Slangen JJM, Swaen GMH, Van Vliet C, Strumans F. 1990. Trends and geographic patterns of pleural mesotheliomas in the Netherlands 1970–1987. Br J Ind Med 47:775–781.

Meurman LO, Kiviluoto R, Hakama M. 1974. Mortality and morbidity among the working population of anthophyllite asbestos miners in Finland. Br J Ind Med 31:105–112.

Mikalsen SO, Rivedal E, Sanner T. 1988. Morphological transformation of syrian hamster embryo cells induced by mineral fibres and the alleged enhancement of benzo[*a*]pyrene. Carcinogenesis 9:891–899.

Morgan A. 1979. Fiber dimensions: Their significance in the deposition and clearance of inhaled fibrous dusts. In: Dusts and Disease (Lemen R, Dement JM, eds.) pp. 87–96. Proceedings of the Conference on Occupational Exposures to Fibrous and Particulate Dusts and Their Extension into the Environment. Pathotox Publishers, Forest Park, IL.

Morgan A, Holmes A. 1986. Solubility of asbestos and man-made mineral fibers in vitro and in vivo: Its significance in lung disease. Environ Res 39(2):475–484.

Morrow PE. 1988. Possible mechanisms to explain dust overloading of the lungs. Fundam Appl Toxicol 10(3):369–384.

Mossman BT, Begin RO, eds. 1989. Effects of Mineral Dusts on Cells. Series H: Cell Biology, Vol. 30. Springer-Verlag, New York, NY.

Mossman BT, Bignon J, Corn M, Seaton A, Gee JBL. 1990. Asbestos: scientific developments and implications for public policy. Science 247:294–301.

Mossman BT, Craighead JE. 1982. Comparative cocarcinogenic effects of crocidolite asbestos, hematite, kaolin and carbon in implanted tracheal organ cultures. Ann Occup Hyg 26:553–567.

Mossman BT, Gee JB. 1989. Medical Progress: Asbestos-related diseases. N Engl J Med 320:1721–1730.

Mossman BT, Marsh JP, Shatos MA. 1986. Alteration of superoxide dismutase activity in tracheal epithelial cells by asbestos and inhibition of cytotoxicity by antioxidants. Lab Invest 54:204–212.

Mowe G. 1982. Time trend in the incidence of malignant mesothelioma in Norway: 1970–1979. In: Prevention of Occupational Cancer, pp. 213–219. International Symposium on Occupational Safety and Health, Series No. 46. International Labour Office, Geneva, Switzerland.

Mowe G, Gylseth B. 1986. Occupational exposure and regional variation of malignant mesothelioma in Norway, 1970–1979. Am J Ind Med 9:323–332.

Murray M. 1907. Departmental Committee for Compensation for Industrial Diseases. Cmd 3495 and 3496. Her Majesty's Stationery Office, London, England.

Musk A, Dolin P, Armstrong B, Ford J, de Klerk N, Hobbs M. 1989. The incidence of malignant mesothelioma in Australia, 1947–1980. Med J Aust 150:242–246.

Nagelschmidt JG. 1965. Some observations of the dust content and composition in lungs with asbestosis made during work on coal miners pneumoconiosis. Ann NY Acad Sci 132:64–76.

National Institute of Occupational Safety and Health (NIOSH). 1990. The incidence of mesothelioma, Australia, 1986–1988. The Australian Mesothelioma Register, AGPS, Canberra, Australia.

National Research Council (NRC). 1984. Asbestiform Fibers: Non-occupational Health Risks Committee on Non-occupational Health Risks of Asbestiform Fibers, National Research Council, National Academy Press, Washington, DC.

Newhouse ML, Berry G. 1979. Patterns of mortality in asbestos factory workers in London. Ann NY Acad Sci 330:53–60.

Newhouse ML, Berry G, Wagner JC. 1985. Mortality of factory workers in east London 1933–80. Br J Ind Med 42:4–11.

Newhouse ML, Sullivan KR. 1989. A mortality study of workers manufacturing friction materials: 1941–86. Br J Ind Med 46:176–179.

Nicholson WJ. 1976. Case study 1: Asbestos: The TLV approach. Ann NY Acad Sci 271:152–169.

Nicholson WJ. 1986. Airborne Asbestos Health Assessment Update. U.S. Environmental Protection Agency, EPA-600/8-84/003F. Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC.

Nicholson WJ. 1989. Airborne mineral fibre levels in non-occupational environments. In: Non-occupational Exposure to Mineral Fibres (Bignon J, Peto J, Sarracci R, eds.) pp. 239–261. IARC Scientific Publications No. 90. International Agency for Research on Cancer, Lyon, France.

Nicholson WJ, Perkel G, Selikoff IJ. 1982. Occupational exposure to asbestos: Population at risk and projected mortality: 1980–2030. Am J Ind Med 8:259–312.

Nicholson WJ, Selikoff IJ, Seidman H, Lilis R, Formby P. 1979. Long-term mortality experience of chrysotile miners and millers in Thetford Mines, Quebec. Ann NY Acad Sci 330:11–21.

Nishizuka Y. 1986. Studies and perspectives of protein kinase C. Science 233:305–312.

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

Oberdörster G, Ferin J, Finkelstein J, Soderholm S, Gelein R. 1990. Mechanistic studies on particle-induced acute and chronic lung injury. In: Aerosols: Science, Industry, Health and Environment, Vol. 2 (Masuda S, Takahashi K, eds.) pp. 1229–1233. Pergamon Press, New York, NY.

Oberdörster G, Morrow PE, Spurny K. 1988. Size-dependent lymphatic short-term clearance of amosite fibers in the lung. Ann Occup Hyg 32(Suppl 1):149–156.

Ohlson CG, Hogstedt C. 1985. Lung cancer among asbestos cement workers. A Swedish cohort study and a review. Br J Ind Med 42:397–402.

Oldham PD. 1973. A trial of techniques for counting asbestos bodies in tissue. In: Biological Effects of Asbestos (Bogovski P, et al.) pp. 45–49. IARC Scientific Publications No. 8. International Agency for Research on Cancer, Lyon, France.

Ontario Royal Commission (ORC). 1984. Report of the Royal Commission on Matters of Health and Safety Arising from the Use of Asbestos in Ontario (3 Vols.). Ontario Ministry of the Attorney General, Toronto, Ontario, Canada.

Oshimura M, Hesterberg TW, Tsutsui T, Barrett JC. 1984. Correlation of asbestos-induced cytogenetic effects with cell transformation of Syrian hamster embryo cells in culture. Cancer Res 44:5017–5022.

Palekar LD, Most BM, Coffin DL. 1988. Significance of mass and number of fibers in the correlation of V79 cytotoxicity with tumorigenic potential of mineral fibers. Environ Res 46:142–152.

Palekar LD, Eyre JF, Most BM, Coffin DL. 1987. Metaphase and anaphase analysis of V79 cells exposed to erionite, UICC chrysotile and UICC crocidolite. Carcinogenesis 8:553–560.

Pampalon R, Siemiatycki J, Blanchet M. 1982. Pollution environnementale par l'amiante et santé publique au Québec. Union Méd 3:1–9.

Pancoast HK, Miller TG, Landris HRM. 1917. A roentgenologic study of the effects of dust inhalation on the lung. Trans Soc Am Physician 32:97.

Paterour MJ, Bignon J, Jaurand MC. 1985. In vitro transformation of rat pleural mesothelial cells by chrysotile fibres and/or benzo[*a*]pyrene. Carcinogenesis 6:523–529.

Pathology Working Group. 1965. Report and recommendations of the working group on asbestos and cancer. In: Biological Effects of Asbestos, Appendix 1 (Selikoff IJ, Churg S, eds.) Geographical Pathology Section. International Union Against Cancer (UICC). Ann NY Acad Sci 132:706–720.

Peterson JT, Greenberg SC, Buffler PA. 1984. Non-asbestos-related malignant mesothelioma: A review. Cancer 5:951–960.

Peto J. 1978. The hygiene standard for chrysotile asbestos. Lancet 1:484–489.

Peto J. 1979. Dose-response relationships for asbestos-related disease: Implications for hygiene standards. Part II: Mortality. Ann NY Acad Sci 330:195–204.

Peto J. 1980. Lung cancer mortality in relation to measured dust levels in an asbestos textile factory. In: Biological Effects of Mineral Fibers, Vol. 2 (Wagner JC, Davis W, eds.) pp. 829–836. IARC Scientific Publication No. 30. International Agency for Research on Cancer, Lyon, France.

Peto J. 1989. Fibre carcinogenesis and environmental hazards In: Non-occupational Exposure to Mineral Fibres (Bignon J, Peto J, Saracci R, eds.) pp. 457–470. IARC Scientific Publications No. 90. International Agency for Research on Cancer, Lyon, France.

Peto J, Doll R, Hermon C, Binns W, Clayton R, Goffe T. 1985. Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. Ann Occup Hyg 29:305–355.

Peto J, Henderson BE, Pike MC. 1981. Trends in mesothelioma incidence in the United States and the forecast epidemic due to asbestos exposure during World War II. In: Occupational Cancer 51–69. Banbury Report 9. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Peto J, Seidman H, Selikoff IJ. 1982. Mesothelioma mortality in asbestos workers: implications for models of carcinogenesis and risk assessment. Br J Cancer 45:124–135.

Piolatto G, Negri E, LaVecchia C, Pira E, Decarli A, Peto J. 1990. An update of cancer mortality among chrysotile asbestos mining in Balangero, northern Italy. Br J Ind Med 47:810–814.

Pooley FD. 1972a. Asbestos bodies, their formation, composition, and character. Environ Res 5:363.

Pooley FD. 1972b. Electron microscope characteristics of inhaled chrysotile asbestos fiber. Br J Ind Med 29:363.

Pooley FD. 1976. An examination of the fibrous mineral content of asbestos lung tissue from the Canadian chrysotile mining industry. Environ Res 12:281–298.

Pooley FD, Clark NJ. 1979. Quantitative assessment of inorganic fibrous particles in dust samples with an analytical electron microscope. Ann Occup Hyg 22:253–271.

Pooley FD, Mitha R. 1986. Fibre types, concentrations and characteristics found in lung tissues of chrysotile exposed cases and controls. Accompl Oncol 1:1–11.

Pooley FD, Wagner JC. 1988. The significance of the selective retention of mineral dusts. Ann Occup Hyg 32(Suppl 1):187–194.

Popescu NC, Chahinian AP, di Paolo JA. 1988. Nonrandom chromosome alterations in human malignant mesothelioma. Cancer Res 48:142-147.

Pott F. 1978. Some aspects on the dosimetry of the carcinogenic potency of asbestos and other fibrous dusts. Staub-Reinholt Luft 38:486–490.

Pott F, Friedrichs KH. 1972. Tumours in rats after intraperitoneal injection of asbestos dusts. Naturwissenschaften 59:318.

Pott F. 1978. Some aspects on the doseometry of the carcinogenic potency of asbestos and other fibrous dusts. Staub-Reinholt Luft. 38:486.

Pott F, Ziem V, Reiffer FJ, Huth F, Ernst H, Mohr L. 1987. Carcinogenicity studies on fibers, metal compounds and some other dusts in rats. Exp Pathol 32:129.

Price-Jones MJ, Gubbings G, Chamberlain M. 1980. The genetic effects of crocidolite asbestos; comparison of chromosome abnormalities and sister-chromatid exchanges. Mutat Res 79:331–336.

Puntoni R, Vercelli M, Merlo F, Valerio F, Santi L. 1979. Mortality among shipyard workers in Genoa, Italy. Ann NY Acad Sci 330:353–377.

Pushkin JS, Nelson CB. 1989. EPA's perspective on risks from residential radon exposure. JAPCA 39:915–920.

Raffu E, Lynge E, Juel K, Korsgaard B. 1989. Incidence of cancer and mortality among employees in the asbestos cement industry in Denmark. Br J Ind Med 46:90–96.

Reiss B, Tong C, Telany S, Williams GM. 1983. Enhancement of benzo[*a*]pyrene mutagenicity by chrysotile asbestos in rat liver epithelial cells. Environ Res 31(1):100–104.

Robinson BW, Rose AH, James A, Whitaker D, Musk AW. 1986. Alveolitis of pulmonary asbestosis: Brochoalveolar lavage studies in crocidolite- and chrysotile-exposed individuals. Chest 90:396.

Robinson C, Lemen R, Wagner JK. 1979. Mortality patterns, 1940–75, among workers employed in an asbestos textile friction and packing products manufacturing facility. In: Dusts and Disease: Proceedings of the Conference on Occupational Exposures to Fibrous and Particulate Dust and Their Extension into the Environment (Lemen R, Dement JM, eds.) pp. 131–143. Pathotox Publishers, Forest Park, IL.

Roggli VL. 1989. Pathology of human asbestosis: A critical review. Adv Pathobiol 2:31–60.

Rohl AN, Langer AM, Selikofff IJ. 1978. Airborne asbestos in the vicinity of a freeway: Discussion. Atmos Environ 12:2030–2031.

Rom WN, Travis WD, Brody AR. 1991. Cellular and molecular basis of the asbestos-related diseases. Am Rev Respir Dis 143:408-422.

Rossiter CE, Coles RM. 1980. HM Dockyard, Devonport: 1947 mortality study. In: Biological Effects of Mineral Fibres, Vol. 2 (Wagner JC, Davis W, eds.) pp. 713–721. IARC Scientific Publications No. 30. International Agency for Research on Cancer, Lyon, France.

Rowlands N, Gibbs GW, McDonald AD. 1982 Asbestos fibers in the lungs of chrysotile miners and millers. Ann Occup. Hyg 26(1–4):411–415.

Rubino GF, Piolatto G, Newhouse ML, Scansetti G, Aresini GA, Murray R. 1979. Mortality of chrysotile asbestos workers at the Balangero Mine, northern Italy. Br J Ind Med 36:187–194.

Samet JM, Marburg MC, Spengler JD. 1988. Health effects and sources of indoor air pollution: Part I. Am Rev Respir Dis 137:221–242.

Saracci R. 1977. Asbestos and lung cancer: An analysis of the epidemiological evidence on the asbestos-smoking interaction. Int J Cancer 20:323.

Sargent EN, Boswell WD Jr, Ralls WP, Markovitz A. 1984. Subpleural fat pads in patients exposed to asbestos: Distinction from non-calcified pleural plaques. Radiology 152(2):273–277.

Scholze H, Conradt R. 1987. An in vitro study of the chemical durability of siliceous fibers. Ann Occup Hyg 31:683–692.

Schwartz DA. 1991. New developments in asbestos-induced pleural disease. Chest 99:191–198.

Schwartz DA, Fuortes LJ, Galvin JR, Burmeister LF, Schmidt LE, Leistikow BN, Lamarte FP, Merchant JA. 1990. Asbestos-induced pleural fibrosis and impaired lung function. Am Rev Respir Dis 141:321.

Scymczykiewicz K, Wiecek E. 1960. The effect of fibrous and amorphous asbestos on the collagen content in the lungs of guinea pigs. In: Proceedings of the 13th International Congress on Occupational Hygiene, New York, NY. Excerpta Medica Foundation, New York, NY.

Sébastien P, Janson X, Bonnand G, Riba G, Masse R, Bignon J. 1979. Translocation of asbestos fibers through respiratory tract and gastrointestinal tract according to fiber type and size. In: Dusts and Disease (Lemon R, Dement JM, eds.) pp. 65–68. Proceedings of the Conference on Occupational Exposures to Fibrous and Particulate Dust and Their Extension into the Environment. Pathotox Publishers, Forest Park, IL.

Sébastien P, McDonald JC, McDonald AD, Case B, Harley R. 1989. Respiratory cancer in chrysotile textile and mining industries: Exposure inferences from lung analysis. Br J Ind Med 46:180–187.

Seidman H, Selikoff IJ, Hammond EC. 1979. Short term asbestos work exposure and long term observation. Ann NY Acad Sci 330:61–90.

Seidman H. 1984. Short-term asbestos work exposure and long-term observation. In: docket of current rulemaking for revision of the asbestos (dust) standard. U.S. Department of Labor, Occupational Safety and Health Administration, Washington, DC. Summarized in Nicholson (1986).

Selikoff IJ, Hammond EC. 1970. Asbestos bodies in the New York City population in two periods of time. In: Pneumoconiosis: Proceedings of the International Conference Johannesburg, 1969 (Shapiro HA, ed.) pp. 99–105. Oxford University Press, Cape Town, South Africa.

Selikoff IJ, Hammond EC, Churg J. 1968. Asbestos exposure, smoking, and neoplasia. JAMA 204:106–112.

Selikoff IJ, Hammond EC, Seidman H. 1979. Mortality experience of insulation workers in the United States and Canada, 1943–1976. Ann NY Acad Sci 330:91–116.

Selikoff IJ, Lee DHK, eds. 1978. Asbestos and Disease. Academic Press, Orlando, FL.

Sesko AM, Cabot M, Mossman BT. 1990. Hydrolysis of inositol phospholipids precedes cellular proliferation in asbestos-stimulated tracheobronchia epithelial cells. Proc Natl Acad Sci USA 87:7385–7389.

Sesko AM, Mossman BT. 1989. Sensitivity of hamster tracheal epithelial cells of asbestiform minerals modulated by serum and by transforming growth factor beta 1. Cancer Res 49(10):2743–2749.

Shatos MA, Doherty JM, Marsh JP, Mossman BT. 1987. Prevention of asbestos-induced cell death in rat lung fibroblasts and alveolar macrophages by scavengers of active oxygen species. Environ Res 44(1):103–116.

Shelby MD. 1988. The genetic toxicity of human carcinogens and its implications. Mutat Res 204(1):3–15.

Skidmore JW, Dufficy BL. 1983. Environmental history of a factory producing friction material. Br J Ind Med 40:8–12.

Smith WE, Hubert DD, Miller L, Badollet MS, Churg J. 1968. Tests for levels of carcinogenicity of asbestos. In: Biologische Wirkungen des Asbestos, p. 240. Proceedings of the International Conference, Dresden, Germany. Deutches Zentralinstitut für Arbeitsmedizin, Berlin, Germany.

Spirtas R, Beebe GW, Connelly RR, Wright WE, Peters JM, Sherwin RP, Henderson BE, Stark A, Kovasznay BM, Davies JND, Vianna N, Keehn RN, Ortega LG, Hochholzer L, Wagner JC. 1986. Recent trends in mesothelioma incidence in the United States. Am J Ind Med 9:397–407.

Stanton MF, Layard M. 1978. The carcinogenicity of fibrous minerals. Proceedings of the Workshop as Asbestos, Gaithersburg, MD. NBS special publication 506, (National Bureau of Standards) National Institute of Standards and Technology, Gaithersburg, MD.

Stanton MF, Layard M, Tegeris A, Miller M, Kent E. 1977. Carcinogenicity of fibrous glass: Pleural response in the rat in relation to fiber dimension. JNCI 58:587.

Stanton MF, Layard M, Tegeris A, Miller E, May M, Morgan E, Smith A. 1981. The relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. JNCI 67:965–975.

Stanton MF, Wrench C. 1972. Mechanisms of mesothelioma induction with asbestos and fibrous glass. JNCI 48:797.

Staples CA, Gamsu G, Ray CS, Webb WR. 1989. High resolution computed tomography and lung function in asbestos-exposed workers with normal chest radiographs. Am Rev Respir Dis 139:1502.

Stein RC, Kitajewska JY, Kirkham JB, Tait N, Sinha G, Rudd RM. 1989. Pleural mesothelioma resulting from exposure to amosite asbestos in a building. Respir Med 83:237–239.

Stephens M, Gibbs AR, Pooley FD, Wagner JC. 1987. Asbestos-induced diffuse pleural fibrosis: Pathology and mineralogy. Thorax 42:583.

Stöber W. 1972. Dynamic shape factors of nonspherical aerosol particles. In: Assessment of Airborne Particles (Mercer TT, Morrow PE, Stöber W, eds.) pp. 249–289. Charles C. Thomas, Springfield, IL.

Sundius N, Bygden A. 1938. Der Staubinhalt einer Asbestosis Lunge und die Beschaffenheit der sogennannter Asbestosis-Korperchen. Arch Gewerbepath u. Gewerbehyg 8:26.

Sussman RG, Cohen BS, Lippmann M. 1991. Asbestos fiber deposition in a human tracheobronchial cast. Part I: Experimental. Inhal Toxicol 3:145–160.

Suzuki Y, Kohyama N. 1984. Malignant mesotheliomata induced by asbestos and zeolite in the mouse peritoneal cavity. Environ Res 35:277.

Thomas HF, Benjamin IT, Elwood PC, Sweetnam PM. 1982. Further follow-up study of workers from an asbestos cement factory. Br J Ind Med 39:273–276.

Thomson JG, Kaschula ROC, McDonald RR. 1963. Asbestos as a modern urban hazard. S Afr Med J 37:77–81.

Tiainen M, Tammilehto L, Mattson K, Knuutila S. 1988. Nonrandom chromosomal abnormalities in malignant pleural mesothelioma. Cancer Genet Cytogenet 33(2):251–274.

Timbrell V. 1972. An aerosol spectrometer and its applications. In: Assessment of Airborne Particles (Mercer TT, Morrow PE, Stöber W, eds.) pp. 249–289. Charles C Thomas, Springfield, IL.

Timbrell V. 1982. Deposition and retention of fibers in the human lung. Ann Occup Hyg 26:347–369.

Timbrell V, Ashcroft T, Goldstein B, Heyworth F, Meurman L, Rendall R, et al. 1987. Relationships between amphibole fibers and fibrosis in human lung tissue specimens. In: Inhaled Particles VI (Walton, WH, ed.). Pergamon Press, Oxford, England.

Turver CJ, Brown RC. 1987. The role of catalytic iron in asbestos induced lipid peroxidation an DNA-strand breakage in C3H10T1/2 cells. Br J Cancer 56(2):133–136.

U.K. Health and Safety Commission. 1985. (See Doll R, Peto J. 1985.)

Vorwald AJ, Durkan TM, Pratt PC. 1951. Experimental studies of asbestosis. AMA Arch Ind Hyg Occup Med 3:1.

Voytek P, Anver M, Thorslund T, Conley J, Anderson E. 1990. Mechanisms of asbestos carcinogenicity. J Am Coll Toxicol 9:541–550.

Wagner JC. 1985. Introduction: The biological effects of chrysotile. In: Accomplishments in Oncology (Wagner J, ed) p. 1. J.B. Lippincott Company, Philadelphia, PA.

Wagner JC. 1986. Mesotheliomata and mineral fibres. Cancer 57:1905–1911.

Wagner JC. 1990. Biological effects of short fibers. Proceedings of the VII International Pneumoconiosis Conference, Pittsburgh, PA, August 1988. NIOSH 90-108, Vol. 2, pp. 835–840. National Institute of Occupational Safety and Health, Washington, DC.

Wagner JC, Berry G, Pooley FD. 1982. Mesotheliomas and asbestos type in asbestos textile workers: A study of lung contents. Br Med J 285:603–606.

Wagner JC, Berry G, Skidmore JW, Pooley FD. 1980. The comparative effects of three chrysotiles by injection and inhalation in rats. In: Biological Effects of Mineral Fibres, Vol. 1 (Wagner JC, Davis W, eds.) pp. 363–372. IARC Scientific Publications No. 30. International Agency for Research on Cancer, Lyon, France.

Wagner JC, Berry G, Skidmore JW, Timbrell V. 1974. The effects of the inhalation of asbestos in rats. Br J Cancer 29:252–269.

Wagner JC, Berry G, Timbrell V. 1973. Mesotheliomata in rats after inoculation with asbestos and other minerals. Br J Cancer 28:173.

Wagner JC, Griffiths DM, Hill RJ. 1984. The effect of fibre size on the in vivo activity of UICC crocidolite. Br J Cancer 49:455-458.

Wagner JC, Moncrieff CB, Coles R, Griffiths DM, Munday DE. 1986. Correlation between fibre content of the lungs and disease in naval dockyard workers. Br J Ind Med 43:391–395.

Wagner JC, Newhouse ML, Corrin B, Rossiter CE, Griffiths DM. 1988. The correlation between fibre content of the lung and disease in East London asbestos factory workers. Br J Ind Med 45:305–308.

Wagner JC, Skidmore JW, Hill RJ, Griffiths DM. 1985. Erionite exposure and malignant mesothelioma in rats. Br J Cancer 51:727–730.

Wagner JC, Sleggs CA, Marchand P. 1960. Diffuse pleural mesothelioma and asbestos exposure in the north western Cape Province. Br J Ind Med 17:260–267.

Walker AM. 1984. Declining relative risks for lung cancer after cessation of asbestos exposure. J Occup Med 26 422–425.

Walton WH. 1982. The nature, hazards and assessment of occupational exposure to airborne asbestos dust: A review. Ann Occup Hyg 25:117–247.

Warnock ML, Isenberg W. 1986. Asbestos burden and the pathology of lung cancer. Chest 89:20.

Wehner AP, ed. 1989. Biological interaction of inhaled mineral fibers and cigarette smoke. Proceedings of the Biological Interaction of Inhaled Mineral Fibers and Cigarette Smoke Conference, Seattle, WA, April 1988. Battelle Press, Columbus, OH.

Weibel ER. 1984. The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System, p. 249. Harvard University Press, Cambridge, MA.

Weill H, Abraham JL, Balmes JR, Case B, Churo AM, Hughes J, Schenker M, Sébastien P. 1990. Health effects of tremolite. Am Rev Respir Dis 142:1453–1458.

Weill H, Hughes J, Waggenspack C. 1979. Influence of dose and fiber type on respiratory malignancy risk in asbestos cement manufacturing. Am Rev Respir Dis 120:(2)345–354.

Weill H, Rossiter C, Waggenspack C, Jones R, Ziskind M. 1979. Differences in lung effects resulting from chrysotile and crocidolite exposure. In: Inhaled Particles IV, Vol. 2 (Walton W, ed.) p. 789–796. Pergamon Press, Oxford, England.

Weiss W. 1977. Mortality of a cohort exposed to chrysotile asbestos. J Occup Med 19:737–740.

Whitwell F, Scott J, Grimshaw M. 1977. Relationship between occupations and asbestos fiber content of the lungs in patients with pleural mesothelioma lung cancer, and other diseases. Thorax 32:377.

Wignall BK, Fox AJ. 1982. Mortality of female gas mask assemblers. Br J Ind Med 39:34–38.

Woodworth CD, Mossman BT, Craighead JE. 1983. Induction of squamous metaplasia in organ cultures of hamster trachea by naturally occurring and synthetic fibers. Cancer Res 43(10):4906–4912.

Wright A, Cowie H, Gormley IP, Davis JMG. 1986. The in vitro cytotoxicity of asbestos fibers: I. P388D1 cells. Am J Ind Med 9(4):371–384.

Wright GW, Kuschner M. 1977. The influence of varying lengths of glass and asbestos fibres on tissue response in guinea pigs. In: Inhaled Particles, Vol. IV (Walton WH, ed.) pp. 455–474. Pergamon Press, Oxford, England.

Yazicioglu S, Ikayto R, Balci K, Sayli BS, Yorulmaz B. 1980. Pleural calcification, pleural mesotheliomas and bronchial cancers caused by tremolite dust. Thorax 35:564.

Yu CP, Asgharian B, Abraham JL. 1990. Mathematical modeling of alveolar clearance of chrysotile asbestos fibers from rat lungs. J Aerosol Sci 21:587–594.

Zalma R, Bonneau L, Guignard J, Pezerat H. 1987. Formations of oxy-radicals by oxygen reduction arising from the surface activity of asbestos. Can J Chem 65:2338–2341.

Zwi A, Reid G, Landau S, Kielowski D, Sitas F, Becklake MR. 1989. Mesothelioma in South Africa, 1976–84; incidence and case characteristics. Int J Epidemiol 18(2):320–329.

7

Man-Made Mineral Fibers

Many types of man-made mineral fibers (MMMF) have been used in buildings as substitutes for asbestos (see section 4.1.4, Types of Asbestos Products in Buildings). Such fibers are of interest insofar as their biological properties and health implications resemble, or differ from, those of asbestos fibers. This chapter is a very brief survey of the topic.

7.1 Description of Man-Made Mineral Fibers

Man-made mineral fibers is a generic term applied to fibrous inorganic substances made primarily from rock, clay, slag, or glass. Such fibers can be classified into three general groups: glass fibers (comprising glass wool and glass filaments); rock wool; and slag wool and ceramic fibers. The term "wool" is used synonymously with fiber when describing vitreous or glass material that has been attenuated without the use of a nozzle. Fibers that are drawn through nozzles are referred to as filamentous or continuous fibers.

According to the International Agency for Research on Cancer (IARC 1988):

> "More than five million tons of man-made mineral fibers are produced annually in more than 100 factories located throughout the world. Glass filaments are used mainly as textiles and as reinforcement materials in plastics. Ceramic fibers are being produced in increasingly large quantities for high-temperature insulation and in specialty products. Man-made mineral fibers release airborne respirable fibers during their production and use. In general, as the nominal diameter of man-made mineral fiber products decreases, both the concentration of mineral fibers and the ratio of respirable fibers increase. Exposure levels in glasswool production have generally been 0.1 respirable f/cm^3 or less; in rockwool and slagwool production, exposures may occur when man-made mineral fiber products are used in confined spaces, such as in the application of loose insulation. Concentrations of man-made mineral fibers have been measured in outdoor air and in nonoccupational settings indoors and found to be much lower than those associated with occupational settings."

7.1.1 Fibrous Glasses

Fiberglass and glass wool are names for silica-based vitreous fibers manufactured by either die extrusion or mechanical drawing, by steam-, air-, and flame-blowing, or by chemical alteration of preexisting fibers with attendant thermal treatment. If they are manufactured as continuous filament glass fibers, the chemistry and diameter are closely controlled, depending on their intended application. Continuous filament fibers display uniform diameter along most of their length. For example, soda-lime glasses melt at low temperatures and are easily die-extruded. Boron glasses are also easily extruded, and both these glasses make high-quality long-filament, strong fibers. Low-alkali glasses possess good dielectric properties and surface resistivity to local "environmental" conditions (the glasses are stable under conditions of high humidity). Alumina and magnesia added to the borate glasses increase their chemical stabilities. The chemical compositions of common glasses are given in Table 7-1. It should be noted that many fibrous glasses today are formulated from silica, sand, limestone, and soda ash, mixed in predetermined proportions.

Table 7-1. Approximate Chemical Composition of Some Representive Vitreous Fibers[a]

Chemical	Soda-Lime Borosilicate	Soda-Lime Glass	Lime-Alumina Borosilicate	Soda-Lime Borosilicate	Soda Borosilicate, Refractory Glass	Lead Silicate Glass	Average Fibrous Glass	Vitreous Wool From Blast Furnace Slag[b]
SiO_2	59.0	73.0	54.5	65.0	59.5	34.0	52 – 54	60.24
ZrO_2	—	—	—	—	4.0	—	—	—
TiO_2	—	—	—	—	8.0	—	—	—
Al_2O_3	4.5	2.0	14.5	4.0	5.0	3.0	13 – 16	6.54
B_2O_3	3.5	—	8.5	5.5	7.0	—	—	—
CaO	16.0	5.5	22.0	14.0	—	—	16 – 18	25.15
BaO	—	—	—	—	—	—	6 – 10	—
PbO	—	—	—	—	—	59.0	—	—
MgO	5.5	3.5	—	3.0	—	—	3 – 5	1.83
FeO	—	—	—	—	—	—	0.3 – 0.5	—
MnO	—	—	—	—	—	—	—	1.08
Na_2O	11.0	16.0	0.5	8.0	14.5	0.5	0.5 – 1.0	5.16
K_2O	0.5	—	—	0.5	—	3.5	0.3 – 0.5	—
F_2	—	—	—	—	2.0	—	—	—
H_2O	—	—	—	—	—	—	0.5 – 1.0	—
Total	100.0	100.0	100.0	100.0	100.0	100.0	*E* = 100.0	100.0

[a] Glasses (soda-lime borosilicate, soda-lime glass, lime-alumina borosilicate, soda borosilicate, lead silicate), Phillips 1960; average glass (average fibrous glass), Schepers 1976; slag wool (vitreous wool from blast furnace slag), Pavlushkin and Beletskii 1973.

[b] Soviet Union.

7.1.2 Mineral, Rock, and Slag Wools

Mineral, rock, and slag wool are terms used for vitreous products made from the precursor materials' names, by remelting the slag and then processing it in a manner as described for the glasses. These processes produce *discontinuous* fiber, so that the resulting materials are short in length and generally not spinnable. Feldspar and kaolinite, now confined principally to use in ceramic manufacture, were once used to make mineral wool; argillaceous (high clay) limestone has been used for the production of rock wool; slags, by-products from many sources including iron and steel making and base-metal and copper-metal smelting, have been used as the precursor material in the production of slag wools. The use of these products in the United States is currently decreasing because of the retrenchment in steel making and mineral processing.

Mineral wool is the generic name for any discontinuous vitreous fiber made from a melt, of any origin. It must be stressed that often the wool nomenclature does not connote origin.

The bulk chemistry and trace metal chemistry of slag wools range greatly, with relation to slag source: Calcium-rich vitreous fibers, with low arsenic, sulfur, and phosphorus, generally reflect slags derived from the iron- and steel-making processes; chromium-, manganese-, and nickel-containing vitreous fibers are by-products of steel making; trace-metal-rich vitreous fibers, with detectable amounts of arsenic, antimony, sulfur, etc., reflect origin from copper- and base-metal smelting slags.

7.1.3 Ceramic Fiber

The principal ceramic fibers in commerce in the United States are of alumina-silica composition. These fibers have great stability, thought to be imparted by the structural match of the aluminum and silicon tetrahedral units.

Vitreous fiber displays a range of physical-chemical properties. One of the more important properties is that of diameter, which is thought to control biological potential (see Table 7-2).

7.2 Properties of Vitreous Fibers

7.2.1 Crystalline Domains

Man-made mineral (vitreous) fibers (MMVF) are used widely as asbestos substitutes. Vitreous materials are macroscopically isotropic, unable to maintain periodic, atomic order over long distances (hundreds of angstrom units). However short-range order is present with local structures formed in clusters (see discussion in Hoare 1976; Turnbull 1976). High-silica glasses have been observed to contain short-range structures, ranging from open silica tetrahedra (cristobalite) to Si_4O_{11} chains (an anhydrous amphibole), as reported by Galakhov and Varshal (1973).

Table 7-2. Diameters of Some Representative Vitreous Fibers[a]

Fiber Description		Diameter (range of average in μm)
Owens-Corning		
DE		5.3 – 8.9
C		3.6 – 5.8
Beta		2.5 – 4.6
Extra coarse	#12	Avg.[b] ~ 38.0
Coarse	#37	18.0 – 19.0
Medium	#150	8.9 – 10.2
Fine	#333	Avg. ~ 0.8
Glass fiber		
Spinning quality		4.0 – 6.0
Reinforcing fiber		9.0 – 11.0
Standard insulating fiber		0.5 – 16.0; Avg. ~ 4.3
Johns Manville		
Fibrous glass	AAA	0.06 – 3.0
	100	0.05 – 0.12
	104	0.20 – 0.50; Avg. ~ 0.33
	110	Avg. ~ 1.9

[a] Data from Heisel (1976); Pundsack (1976).
[b] Avg. = the stated average diameter for the product.

If different cationic metals are present in silica melts, they may coordinate oxygens differently, as related to cation charge (Z) and ionic radius (r). Patches of orderliness will form following the general principles of crystal chemistry. However, if unlike polyhedra form during quenching, they have a tendency to unmix. The immiscibility regions in glass melts are compositionally dependent, a function of Z/r^2 (the determining factor in influencing cation field strength).

7.2.2 Stability in Biological Hosts

Because of their different chemistries, MMVF behave differently in biological hosts. The aluminum-silicon ceramic fibers are stable (similar Z/r^2 values) and are therefore long-lived in vivo (durable). Slag wools, rich in exotic metals, are for the most part neither stable nor durable in biological hosts. High-soda glasses are soluble in vivo.

The issue of fiber durability may be of extreme biological importance. Because MMVF are generally not stable in vivo, they appear to carry less risk of producing disease (Lippmann 1990). It is crucial to stress that these vitreous fibers exhibit a range of properties (Dunnigan 1990).

7.2.3 Fiber Diameter

The wool products used in thermal or acoustic insulation or in fireproofing material are generally larger than 3 μm in diameter, although a small proportion of the fibers are thinner and, thus, are respirable (Table 7-2). Special products for high-temperature aircraft insulation are much thinner, with most fibers being less than 3 μm in diameter. The wool or filament fibers used for reinforcement also usually have nominal diameters in excess of

3 μm. However, the distribution of diameters may include some respirable fibers, and special products may use mostly respirable fibers.

7.2.4 Other Properties of Man-Made Vitreous Fibers

Insulating glasses may be coated with binders, for example, phenol formaldehyde resins, with mineral oil lubricant, in a range of concentrations. The biological significance of these coating materials for long-term, chronic diseases is unknown.

Specialty glasses, for specific applications, may require the formation of glass fibers with very small diameters (significantly less than 1 μm). These are infrequently encountered in building environments.

7.3 Levels of Human Exposure to Man-Made Mineral Fibers

Respirable fiber concentrations have been measured in U.S. plants manufacturing various glass and mineral wool products (Esman et al. 1979a,b; Enterline et al. 1987). Exposures in plants using respirable fibers longer than 5 μm for mineral wool were estimated to be 1.5 f/mL prior to 1945, 0.3 f/mL for the years 1945 to 1960, and 0.03 f/mL thereafter. Fibrous glass plants appeared to have concentrations about 10 times lower. Higher concentrations were present in the 1977 to 1980 period in European glass and rock-wool plants, averaging about 1 f/mL (IARC 1988). Recent measurements in the workplace suggest that the emission of respirable glass fibers is limited because few fibers become airborne (National Academy of Sciences [NAS] 1984). During the installation of glass and mineral wool products, primarily as insulation, concentrations of from less than 0.01 to 20 f/mL were found in individual samples; mean concentrations of respirable fibers for most activities were less than 1 f/mL (Esman et al. 1982; IARC 1988).

7.3.1 Levels of Man-Made Mineral Fibers in Public Buildings

A number of studies have been carried out to monitor levels of airborne MMMF outside and in building environments. Only the vitreous types of MMMF—glass, rock, and slag wools—have been widely used in public buildings, and no data for the ceramic types of fibers are available, mostly because of the unlikely occurrence of any of these materials in significant amounts.

Analyses by phase contrast microscopy (PCM), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) have been used to monitor MMMF both outside and inside buildings. Some authors found much higher fiber levels by PCM than by electron microscopy (Dodgson et al. 1987), but if the microscope is used with crossed-polars and a sensitive red plate, the isotropic nature of the vitreous wools can be used to separate vitreous MMMF from other mineral and organic fibers and nonMMMF (Schneider 1986). This is possible because many of the vitreous wools have large diameters and are easily visible and analyzed by optical microscopy. Some fibers may have a refractive index similar to the filter and mount and are thus rendered invisible (Rooker et al. 1982), but this is not thought to be a problem with routine MMMF commonly used in buildings. When direct comparisons have been made between methods (Schneider 1986; Gaudichet et al. 1989; Jaffrey 1990; Jaffrey et al. 1990), there is often a good degree of correlation, and for most purposes the analytical methods can be considered to be equivalent if the correct optical method has been used.

Gaudichet and coworkers (1989) found that outdoor locations in Paris gave very low average levels of 2×10^{-6} f/mL for MMMF in comparison with results reported by Friedrichs (1979) for Dusseldorf of 0.00082 f/mL and by Balzer (1976) for various towns in California of 0.0086 f/mL for glass fibers and 0.0022 for all MMMF. Jaffrey (1990) recently reported values of less than 0.0001 f/mL outside buildings in England.

Inside buildings Balzer and associates (1971), Esman and coworkers (1980), and Schneider (1986) showed that air conditioners and their transmission systems did not make any significant contribution to ambient air pollution. Rindel and colleagues (1987) estimated that concentrations in buildings were some 100 to 1,000 times lower than in industry, and Schneider (1986) made measurements in schools and other public buildings and reported airborne levels ranging from undetected to 0.084 f/mL by PCM. Skov and Valbjorn (1987) found only one of 14 Danish town halls had a concentration above the analytical sensitivity of 0.00007 f/mL. The more recent measurements in buildings are summarized in Table 7-3, along with any results taken in control buildings or outside. Even during installation or disturbance of the MMMF materials in lofts, the concentrations in the living areas of homes were only moderately raised (Dodgson et al. 1987; Jaffrey 1990; Jaffrey et al. 1990) showing how difficult it is to produce high fiber levels for normal occupants in buildings. Persons installing vitreous fiber products will be exposed to much higher concentrations, but exposures will rarely exceed 1 f/mL, with most commercial products. Fiber concentrations of MMMF decay rapidly because of their large dimensions, resulting in increased settling velocity, and as a result are below the limit of detection (Dodgson et al. 1987; Jaffrey 1990; Jaffrey et al. 1990).

Table 7-3. Respirable Man-Made Mineral Fiber Concentrations in the Indoor-Air Environment

Reference	Site	Number of Samples	Mean[a] (f/mL)	Range[a] (f/mL)	Analytical Method
Schneider 1986	Random sample of schools	11	0.00006	0 – 0.0024	PCM
Rindel et al. 1987	Random sample of kindergartens with MMMF ceiling boards	5	0.00011	0.00006 – 0.00016	PCM
Rindel et al. 1987	Random sample of kindergartens with resin binder ceiling board	3	0.0001	0.000043 – 0.00015	PCM
Rindel et al. 1987	Random sample of kindergartens with ceiling boards with no MMMF	4	0.00004	0.00001 – 0.00007	PCM
Schneider et al. 1990	Random selection of day-care centers and schools with ceiling boards with MMMF	210 (105 rooms)	0.00008	0 – 0.00166	PCM
Schneider et al. 1990	Random selection of day-care centers and schools with ceiling boards with no MMMF	24 (12 rooms)	0.00006	0 – 0.000195	PCM
Schneider 1986	Sites with reported problems	6		0.00023 – 0.0029	PCM

Table 7-3 (Continued). Respirable Man-Made Mineral Fiber Concentrations in the Indoor-Air Environment

Reference	Site	Number of Samples	Mean[a] (f/mL)	Range[a] (f/mL)	Analytical Method
Gaudichet et al. 1989	Buildings (79) in various locations, with sprayed surfacing wall panel, etc. with MMMF	79	Inside 0.000225	0 – 0.0062	PCM
		18	Outside 0.000002	0 – 0.000015	Indirect
TUV 1989	University buildings	3		0.00041 – 0.003	
Dodgson et al. 1987	Old houses (5) with MMMF	5	0.00005	0 – 0.00025	SEM
Dodgson et al. 1987	New houses (5) without MMMF	5	0.00018	0 – 0.00065	SEM
Dodgson et al. 1987	New houses (5), insulation installed	5			
	• 1 day later		0.00011	0 – 0.00059	SEM
	• 7 days later		0.00033	0.0007 – 0.00095	SEM
Jaffrey 1990	Living space of 12 homes during installation of MMMF insulation (blown and blanket)	39	0.0092	0.0015 – 0.049	TEM
Jaffrey 1990	Buildings (10) before insulation:				
	• outside	10	< 0.0001	—	TEM
	• living space	10	< 0.00005	—	TEM
	• loft	10	0.00005	0 – 0.0005	TEM
Jaffrey 1990	Buildings (10) after insulation	10		0.002 – 0.0005	TEM

[a] Longer than 5 μm, greater than 3 μm in diameter, aspect ratio greater than 3:1.

7.4 Epidemiologic Studies of Effects of Man-Made Mineral Fibers on Human Health

For the reasons discussed above, and because most MMMF during production are encapsulated, incorporated into matrices, or manufactured in the presence of binders, MMMF have not been regulated historically in the workplace (Krantz and Remaeus 1987). In comparison to the many reports on asbestos-exposed cohorts, few epidemiologic studies exist on MMMF workers (reviewed in Mossman 1988; Enterline 1991). Two large epidemiologic studies of fibrous glass and mineral wool production workers have been performed in the United States (Enterline et al. 1987; updated in Marsh et al. 1990) and in Europe, under the auspices of the IARC (Simonato et al. 1987). In the U.S. study of 16,661 MMMF workers in 17 plants, there was a small, statistically significant increase in all

malignant neoplasms (standard mortality ratio [SMR] = 108.3) and in respiratory cancer (SMR = 112.1). The latter excess was greater in mineral wool workers. The development of lung cancer was not related to the duration of exposure or to time since first exposure. Among approximately 25,000 workers in 13 European MMMF plants, there were 2,719 deaths (SMR = 111), of which 189 were from lung cancer (SMR = 125). Lung cancer mortality in working producing rock and slag wool increased with time of first exposure. However, this increase was associated with an early technological phase of fiber production causing high levels of airborne fibers in the workplace. No excess in lung cancer was observed after the introduction of dust-suppressing agents such as oils and other binders. Only one mesothelioma occurred, with a latency period of 13 years since the time of first exposure. No increases in malignancies at other sites were reported. On the basis of these data the IARC (1988) deemed that evidence for the carcinogenicity of rock wool and slag wool in humans was limited.

7.5 Experimental Studies on the Biological Effects of Man-Made Mineral Fibers

Most experimental studies on the harmful effects of mineral fibers have concentrated on the different varieties of asbestos; however, many authors have also reported studies using a wide variety of MMMF. This work has been extensively reviewed (World Health Organization [WHO] 1984; Saracci [IARC] 1986; Walton and Coppock 1987; IARC 1988). Inhalation studies using vitreous fibers (glass wool, rock wool, and slag wool) have uniformly failed to demonstrate harmful effects in experimental animals. When pulmonary tumors have been found, their numbers have not been significantly greater than in control groups. This finding probably relates to the high solubility in lung tissue of the fibers tested. Two very durable MMMF types (ceramic fiber and aramid fiber) have, however, produced pulmonary fibrosis and pulmonary tumors following inhalation in experimental animals (Davis et al. 1984; Lee et al. 1988).

Injection studies using MMMF show that these materials are highly carcinogenic if the injected materials contain large numbers of long, thin fibers. Differences between these results and the results of inhalation studies probably occur because massive doses have been injected and, even with relatively soluble fibers, sufficient fiber burden in lung remains throughout the life span of laboratory rodents to exert carcinogenic effects. As recorded in section 6.3 (Data from Experiments with Laboratory Animals and Cultured Cells), MMMF, when used in experiments in vitro, in general, produce results similar to those produced by asbestos fibers of similar dimensions. In these short-term tests, differences in long-term fiber solubility cannot be demonstrated.

7.6 Summary

There is limited evidence to suggest that exposures to rock wool and slag wool have produced an increased incidence of carcinoma of the lung in humans. Whether this increase is due to the actual mineral wools, to contaminants such as trace metals, or to other factors is uncertain.

In experimental studies in rats, only very fine glass and ceramic wools with a diameter of less than 1.0 μm have produced mesotheliomas by inhalation and by implantation. These tumors have not been observed after exposure to the coarser glass wools, and no studies have been undertaken on the effects of the coarser ceramic fibers. These results should be viewed with caution as the data are still accumulating.

7.7 References

Balzer LJ, Cooper WC, Fowler DP. 1971. Fibrous glass-lined air transmission systems: an assessment of their environmental effects. Am Ind Hyg Assoc J 32:512–518.

Balzer JL. 1976. Environmental data: Airborne concentrations of fibrous glass found in various operations. In: Proceedings of a Symposium on Occupational Exposure to Fibrous Glass, College Park, Maryland, pp. 82–90. U.S. Department of Health, Education, and Welfare, Washington, DC.

Davis JMG, Addison J, Bolton RE, Donaldson K, Jones AD, Wright A. 1984. The pathogenic effects of fibrous ceramic aluminum silicate glass administered to rats by inhalation and ingestion. In: The Biological Effects of Man-Made Mineral Fibres, pp. 303–322. Report of a WHO/IARC meeting, Copenhagen, Denmark. World Health Organization, Geneva, Switzerland.

Dodgson J, Harrison GE, Cherrie J, Sneddon F. 1987. Assessment of Airborne Mineral Wool in Domestic Houses. BP. 31051/3-525, Institute of Occupational Medicine, Edingburgh, Scotland.

Dunnigan J. 1990. Author's reply: Comparing biological effects of mineral fibres. Br J Ind Med 47:287.

Enterline PE, Marsh GM, Henderson V, Callahan C. 1987. Mortality update of a cohort of U.S. man-made mineral fibre workers. Ann Occup Hyg 31:625–656.

Enterline PE. 1991. Carcinogenic effects of man-made mineral fibers. Annu Rev Pub Health 12:459–80.

Esman NA, Corn M, Hammad Y, Whittier D, Kotsko N. 1979a. Summary of measurements of employee exposures to airborne dust and fibers in 16 facilities producing man-made mineral fibers. Am Ind Hyg Assoc J 40:108–117.

Esman NA, Corn M, Hammad Y, Whittier D, Kotsko N, Haller M, Kahn RA. 1979b. Exposure of employees to man-made mineral fibers: Ceramic fiber production. Environ Res 19:265–278.

Esman NA, Sheehan MJ, Corn M, Engel M, Kotsko N. 1982. Exposure of employees to man-made vitreous fibers: Installation of insulation materials. Environ Res 28:386–398.

Esman NA, Whittier D, Kahn RA, Lee TC, Sheehan MJ, Kotsko N. 1980. Entrainment of fibers from air filters. Environ Res 22:450–465.

Friedrichs KH. 1979. Morphological aspects of fibers. In: Dust and Disease (Lemen R, Dement JM, eds) pp. 51–64. Pathotox Publishers, Forest Park, IL.

Galakhov FY, Varshal BG. 1973. Causes of phase separation in glasses. In: The Structure of Glass, 8, Phase Separation Phenomenon in Glasses (Porai-Koshits EA, ed.) pp. 7–11. Consultants Bureau, New York, NY.

Gaudichet A, Petit G, Billon-Gallard MA, Dufour G. 1989. Levels of atmospheric pollution by man-made mineral fibers in buildings. In: Non-occupational Exposure to Mineral Fibers (Bignon J, Peto J, Saracci R, eds.). IARC Scientific Publication 90. International Agency for Research on Cancer, Lyon, France.

Heisel EB. 1976. Some cutaneous effects of fiber glass exposure. In: Occupational Exposure to Fibrous Glass. Proceedings of a Symposium, College Park, MD, June 26–27, 1974. National Institute for Occupational Safety and Health, U.S. Government Printing Office, Washington, DC.

Hoare M. 1976. Stability and local order in simple amorphous packings. Ann NY Acad Sci 279:186–207.

Hohr D. 1985. Fasserformige Staube in der Aussenluft. Staub Reinhalt Luft 45:171–174.

International Agency for Research on Cancer (IARC). 1988. Man-made mineral fibres and radon. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 43. International Agency for Research on Cancer, Lyon, France.

Jaffrey SAMT 1990. Levels of airborne man-made mineral fibres in U.K. dwellings. I: Fibre levels during and after installation of insulation. Atmos Environ 24A(1):133–141.

Jaffrey SAMT, Rood AP, Llewellyn JW, Wilson AJ. 1990. Levels of airborne man-made mineral fibres in U.K. dwellings. II: Fibre levels during and after some disturbance of loft insulation. Atmos Environ 24A(1):143–146.

Krantz S, Remaeus B. 1987. Current regulations and guidelines for MMMF production and use. Ann Occup Hyg 31:523–528.

Lee KP, Kelly DP, O'Neal FO, Slader JC, Kennedy GL. 1988 Lung response to ultrafine kevlar aramid synthetic fibrils following 2-year inhalation exposure in rats. Fundam Appl Toxicol 11:1.

Lippmann M. 1990. Man-made mineral fibers (MMMF): Human exposures and health risk assessment. Toxicol Ind Health 6:(2)225–246.

Marsh GM, Enterline PE, Stone RA, Henderson VL. 1990. Mortality among a cohort of US man-made mineral fiber workers: 1985 follow-up. J Occup Med 32(7):594–604.

Mossman BT. 1988. Carcinogenic potential of asbestos and nonasbestos fibers. J Environ Sci Health C6(2):151–195.

National Academy of Sciences (NAS). 1984. Asbestiform Fibers: Non-occupational Health Risks. National Research Council, National Academy Press, Washington, DC.

Pavlushkin NM, Beletskii BI. 1973. Differentiation of structural groups in slag glasses. In: The Structure of Glass, 8, Phase-Separation Phenomenon in Glasses (Porai-Koshits EA, ed.) pp. 196–199. Consultants Bureau, New York, NY.

Phillips CP. 1960. Glass: Its Industrial Applications. Rheinhold Publishing Co., New York, NY.

Pundsack FL. 1976. Fibrous-glass manufacture, use, and physical properties. In: Proceedings of the Symposium on Occupational Exposure to Fibrous Glass, University of Maryland, June 26–27, 1974, pp. 11–18. CDC-NIOSH. U.S. Government Printing Office, Washington, DC.

Rindel A, Bach E, Breum NO, Hugod C, Scheider T. 1987. Correlating health effect with indoor air quality in kindergartens. Int Arch Occup Health 59:363–373.

Rooker SJ, Vaughan NP, Le Guen JM. 1982. On the visibility of fibers by phase contrast microscopy. Am Ind Hyg Assoc J 43:505–515.

Saracci R (International Agency for Research on Cancer). 1986. Contributions to the IARC study on mortality and cancer incidence among man-made mineral fiber production workers. Scand J Work Environ Health 12(Suppl 1).

Schepers GWH. 1976. The comparative pathogenicity of inhaled fibrous dusts. In: Occupational Exposure to Fibrous Glass. HEW-(NIOSH)76-151, pp. 265–341. U.S. Department HEW-CDC-NIOSH, Division of Criteria Documentation and Standards Development, Washington, DC.

Schneider T. 1986. Man-made mineral fibers and other fibers in the air and in settled dust. Environ Int 12:61–65.

Schneider T, Nielson O, Bredsdorff P, Linde P. 1990. Dust in buildings with man-made mineral fibre ceiling boards. Scand J Work Environ Health 16.

Schneider T, Skotte J, Nissen P. 1985. Man-made mineral fiber size fractions and their interrelation. Scand J Work Environ Health 11:117–122.

Simonato L, Fletcher AC, Cherrie JW, Andersen A, Bertazzi P, Charnay N, Claude J, Dodgson J, Esteve J, Frentzel-Beyme R, Gardner MJ, Jensen O, Olsen J, Teppo L, Winkelmann R, Westerholm P, Winter PD, Zocchetti C, Saracci R. 1987. The International Agency for Research on Cancer historical cohort study of MMMF production workers in seven European countries: Extension of the follow-up. Ann Occup Hyg 31:603–624.

Skov P, Valbjørn O. 1987. The "sick" building syndrome in the office environment: The Danish town hall study. Environ Int 13:339–349.

Turnbull D. 1976. Relation of crystallization behavior to structure in amorphous systems. Ann NY Acad Sci (abstract) 279:185.

Technischer Uberwachungs-Verein Berlin (TUV). 1989. Technischer Bericht Nr. D-89/704. Nov. 11, 1989, Berlin, Germany.

Walton WH, Coppock SM, eds. 1987. Man-made mineral fibres in the working environment. Ann Occup Hyg 31:523–822.

World Health Organization (WHO). 1984. The Biological Effects of Man-Made Mineral Fibres. Report of a WHO/IARC meeting, Copenhagen, Denmark. World Health Organization, Geneva, Switzerland.

8

Estimation of Risks to the Health of Building Occupants

An assessment of the risks to the health of building occupants from exposure to asbestos involves many uncertainties, most notably the poor understanding of the dose-response relationships for different diseases, and the lack of systematically-collected data on exposure. It is uncertain whether or not the low ambient levels of airborne asbestos fibers that have usually been found to exist in today's well-maintained public and commercial buildings pose any risks to building occupants. However, if a linear dose-response relationship is assumed, it is possible to estimate the risks to building occupants based on the current knowledge of cancer-risk models and such exposure data as are available. For some types of building workers, such as those involved in custodial, maintenance, renovation, or asbestos remediation activities, the levels of exposure may be high enough at times to pose a more substantial health risk. It is essential, therefore, to distinguish among the different categories of building occupants in attempting to assess the risks in question.

8.1 Exposure-Response Relationship

For each of the two major neoplastic diseases in which asbestos has been implicated as a causal factor—namely, lung cancer and mesothelioma—the incidence of disease has been observed to increase with increasing dose in occupationally exposed human populations and in experimentally exposed laboratory animals. Data on the biological effects of asbestos on cells in vitro, while demonstrating the dose-dependent induction of chromosome abnormalities, disturbances in growth factors, and neoplastic transformation under certain experimental conditions, do not suffice to define the complete mechanism of carcinogenesis or to clarify the relevant dose-incidence relationships. Estimates of average lung cancer and mesothelioma risk, derived from different occupational studies, vary widely (see section 6.2.2, Exposure-Response Relationships for Lung Cancer and Mesothelioma). At the much lower levels of exposure in buildings, the uncertainty is even greater, because of the added uncertainty of extrapolation from high to low levels of exposure.

The major epidemiologic studies that have provided relevant data are broadly consistent with linear nonthreshold relationships between the relative risk of lung cancer and cumulative exposure to asbestos, and between the absolute risk of mesothelioma and cumulative exposure to asbestos. While the mortality rate in the low exposure categories in some of the studies have not been statistically different from those in comparison populations, the observed numbers are not inconsistent with the linear dose-response relationship suggested at higher levels of exposure. However, because of the statistical uncertainty of the data at low levels of exposure, neither the presence nor the absence of a threshold can be demonstrated with certainty. Thus, the shape of the dose-response curve at exposures below today's U.S. occupational standards cannot be defined by standard epidemiologic methods.

While a linear dose-incidence model for lung cancer has been found to be consistent with the existing human data, differences in slope are observed among various exposed populations. These differences (as discussed in section 6.2.2, Exposure-Response Relationships for Lung Cancer and Mesothelioma) remain to be fully explained but may result from differences in fiber size distribution or fiber types, errors in the estimates of exposure, conversion of one exposure index to another, or statistical uncertainties in the vital statistics.

8.2 Health Outcome

Observing and monitoring building occupants and workers for adverse health effects due to asbestos exposure presents enormous problems. First, because of the long clinical latency time between inhalation of asbestos fibers and detectable disease, some individuals exposed today may not manifest any ill effects for 20 years or longer. Similarly, workers showing effects today may have been exposed to asbestos at a much earlier time during their lives when exposure conditions and work practices were different than they are today.

A second consideration is the specificity of the abnormalities that may be detected. Some of the nonmalignant diseases produced by asbestos inhalation, particularly pleural plaques and pleural calcification, are quite characteristic of the fibrous agent. However, diffuse pleural effusions are not specific, and can be caused by other agents.

The two major malignancies that are caused by asbestos exposure are lung cancer and mesothelioma. Lung cancer is currently the most common fatal malignancy in both men and women, with about 160,000 deaths a year in the United States (American Cancer Society [ACS] 1991). It is impossible to recognize those individuals whose lung cancers may have resulted from asbestos exposure, as opposed to other causes. As noted below, it is almost certain that the overall excess of cases that could be attributed to asbestos exposure in buildings will be relatively small and probably undetectable (see also Table 6-3).

Mesothelioma, on the other hand, has a strong relationship to asbestos exposure, and is almost universally fatal. A majority of the cases now occurring each year in the United States can be shown to occur in workers occupationally exposed to asbestos or in their household members. The latency from exposure to manifestation of disease is usually 20 years or more. There has been a great reduction in such exposures in recent years, and we can anticipate that by the year 2030 or so, the cases from occupational exposure prior to 1970 will have virtually ceased to exist. The prevalence of the disease may then fall to about 400 cases a year, a number representing the background prevalence in the United States. The risk estimates discussed in section 6.2 (Exposure-Risk Relationships: Human Data) imply that the excess deaths that may occur from exposure in buildings will not cause a sufficient increase in the mesothelioma rate to be readily detected (Table 6-3).

8.3 Exposure Measurements

In order to assess the asbestos-related cancer risk for building occupants, an estimate of the distribution (for example, mean and range) of long-term average exposures encountered in buildings is necessary. This section summarizes the data described in Chapter 4, most of which relate to exposures of general building (C1) occupants, and discusses the strengths and weaknesses of the exposure estimates.

8.3.1 Summary of Air Concentration Data

Direct transmission electron microscopy (TEM) concentration measurements of asbestos fibers longer than 5 μm in 198 ACM-containing buildings not involved in litigation have been summarized in Chapter 4 (Table 4-10). Building averages have been computed for each of these buildings as described in Chapter 4 and Appendix 1. Summary statistics, by study, are given in Figure 8-1 and Table 8-1. The mean concentrations in the various studies range from 0.00004 to 0.00243 f/mL. The 90th percentiles of building averages in the various studies range from 0 to 0.008 f/mL. Table 8-2 and Figure 8-2 present the data

from the same studies with the results combined according to building categories: schools, residences, and public and commercial buildings. The mean concentrations are 0.00051, 0.00019, and 0.00020 f/mL in schools, residences, and public and commercial buildings, respectively. The 90th percentiles are 0.0016, 0.0005, and 0.0004, respectively. When all data are pooled, this data set represents 1,377 samples in 198 different buildings containing ACM (108 buildings from the United States, 26 from Canada, and 64 from the United Kingdom). For the pooled data, the mean exposure value is 0.00027 f/mL, with 90th and 95th percentiles of 0.0007 and 0.0014 f/mL.

Table 8-1. Distribution of Building Average Airborne Asbestos Concentrations for Nonlitigation Data by Study[a]

Study	No. of Buildings	Building Types[b]	Minimum	10th Percentile	Median	Mean	90th Percentile	Maximum
Burdett and Jaffrey 1986[c]	39	5S,8PC,26 R	0	0	0.0001	0.00026	0.0009	0.0017
Chatfield 1986	7	5S,2PC	0	0	0.0005	0.00243	0.0080	0.0080
Gazzi and Crockford 1987[c]	25	R	0	0	0	0.00030	0.0008	0.0025
Hatfield et al. 1988; Chesson et al. 1990b; Crump and Farrar 1989	43	PC	0	0	0	0.00005	0.0003	0.0006
Pinchin 1982	19	S	0	0	0	0.00042	0.0020	0.0030
CPSC 1987	45	R	0	0	0	0.00010	0	0.0020
McCrone 1991 (unpublished) schools	19	S	0	0	0.0002	0.00022	0.0005	0.0016
McCrone 1991 (unpublished) office	1	PC	—	—	—	0.00004	—	—

[a] Fibers greater than 5 μm.

[b] S = schools, PC = public and commercial buildings, R = residences.

[c] Only including buildings with asbestos.

With respect to the public and commercial buildings, the average value is particularly influenced by the General Services Administration (GSA) building study, since 43 of the 54 buildings are from this study (Hatfield et al. 1988; Crump and Farrar 1989; Chesson et al. 1990). Hence, the caveats and uncertainties with respect to this study (section 4.6.3.1; Table 4-10; Appendix 1) should be kept in mind when interpreting the data for public and commercial buildings. It should also be noted that the average for this building category is strongly influenced by a single observation from the Chatfield (1986) study. One sample in an office building in this study was found to have a value of 0.042 f/mL, the highest among the samples collected in public and commercial buildings. The author described this

sample as having been collected in an area where cable was being installed (Chatfield 1991, personal communication). If this single sample value were to be excluded from calculation of the average for all public and commercial buildings, the average value would be reduced from 0.00020 to 0.00008 f/mL for fibers longer than 5 μm.

Table 8-2. Distribution of Building Average Airborne Asbestos Concentrations for Nonlitigation Data by Building Type[a]

Building Type	No. of Buildings	Minimum	10th Percentile	Median	Mean	90th Percentile	Maximum
School	48	0	0	0	0.00051	0.0016	0.0080
Residence	96	0	0	0	0.00019	0.0005	0.0025
Public and commercial	54	0	0	0	0.00020	0.0004	0.0065
All buildings	198	0	0	0	0.00027	0.0007	0.0080

[a] Fibers greater than 5 μm.

With respect to the data from schools (including a few colleges), the average value (0.00051 f/mL) is strongly affected by a sample collected in a mechanical room/closet (Chatfield 1986); if this high value (0.02 f/mL) were to be excluded, the average would be reduced to 0.00038 f/mL.

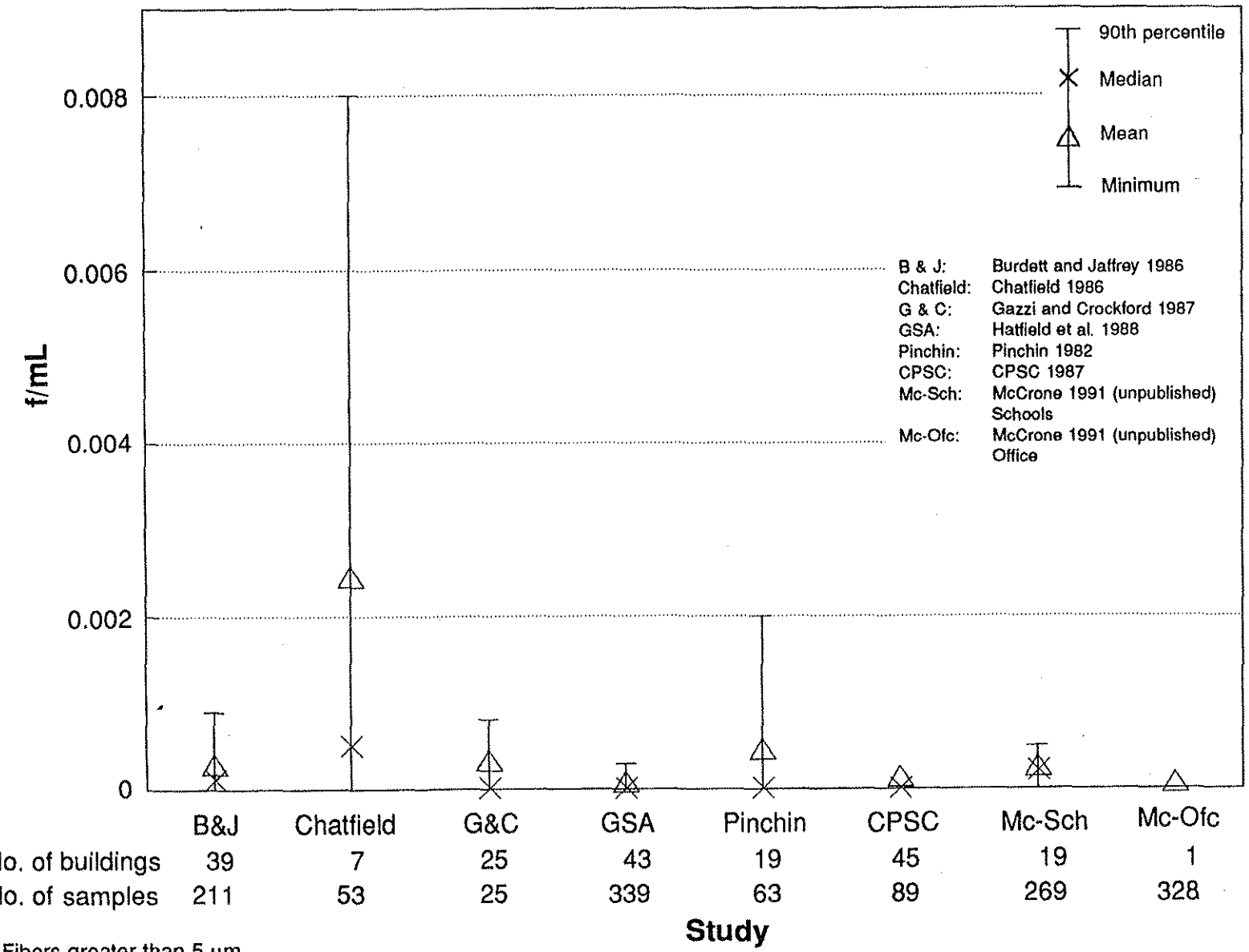
An extensive amount of data on airborne asbestos concentrations exists in the files of commercial laboratories. In response to a public request from the HEI-AR (see Chapter 3), several organizations made such data available to the Literature Review Panel. The unpublished data from U.S. Consumer Product Safety Commission (CPSC 1987) and McCrone Environmental Services are included as part of Tables 8-1 and 8-2, and Figures 8-1 and 8-2 (these data were not collected in support of litigation, to the best of the Panel's knowledge). A few organizations provided data that they acknowledged to be in support of litigation; the information from one such large data set—from 231 buildings—is summarized in Chapter 4.

8.3.2 Issues in the Interpretation of Exposure Data

8.3.2.1 Representativeness of the Data

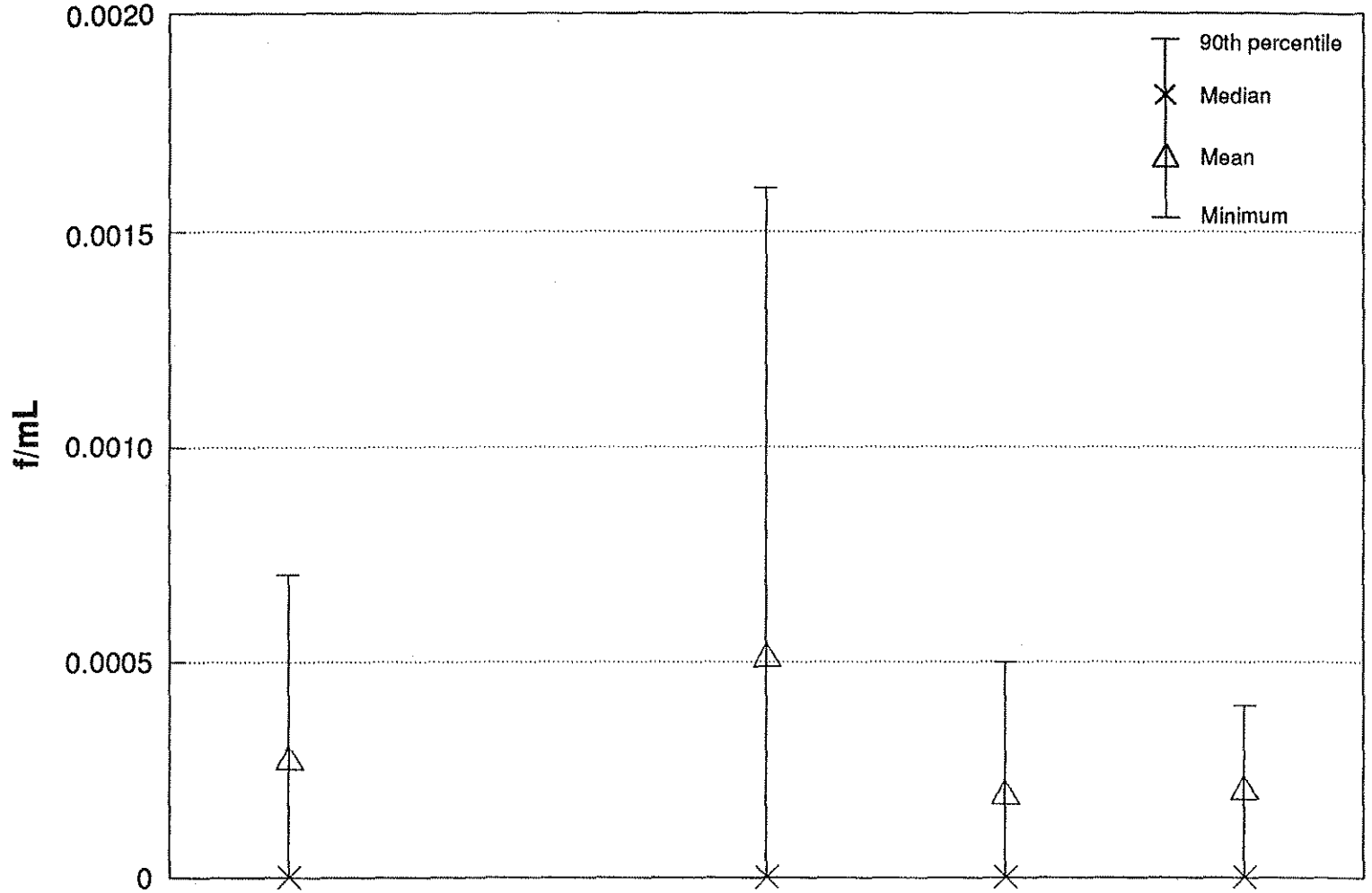
In order to evaluate the validity of the nonlitigation data for the purposes of risk estimation, a number of issues must be considered. These include questions related to the representativeness of the sampled data with respect to the reference population of all U.S. public and commercial and school buildings. The issues include the types of buildings sampled, building selection strategy, sampling location within buildings, types of asbestos-containing materials (ACM) present, extent of ACM damage, level of building activity, whether an O&M program was established, and the level of maintenance activity observed. In addition, there are issues related to analytical methods and sample sensitivity which must be considered.

Figure 8-1. Distribution of Building Average Airborne Concentrations for Nonlitigation Data by Study[a]



[a] Fibers greater than 5 µm.

Figure 8-2. Distribution of Building Average Airborne Concentrations for Nonlitigation Data by Building Type[a]



[a] Fibers greater than 5 μm.

As described in Chapter 4, individual studies that have reported ambient airborne asbestos levels in buildings were evaluated with regard to their representativeness for purposes of average exposure estimation. The results of this evaluation (Table 4-13) indicated that:

- Friable sprayed surface treatments, such as an ACM type, may be over-represented in the available database.

- Samplers tended to be located in direct proximity to ACM, rather than in building areas thought to be most representative of C1-occupant areas.

- Few buildings were sampled in which significantly damaged ACM was present. While damaged ACM was present in 37 buildings in the GSA study, of the remaining published studies, little or no damage was reported. Old, poorly maintained buildings are likely to have been under-represented in the available database.

- Nearly all measurements have been made under conditions of normal building occupation; however, it is not known to what degree normal levels of building maintenance or custodial activities are represented.

- At least partial O&M programs were in place at some of the GSA buildings and all of the McCrone school and office buildings.

- With the exception of a few small studies, the buildings investigated were not randomly selected, and it is not known how representative the studied buildings are of the total population of U.S. buildings. The available studies have focused on office buildings, school and university buildings, and single family or multiple unit residences; other building categories such as shopping centers, theaters, churches, hospitals, factories, etc., are very poorly represented in the available data.

- For the most part, the data represent the results of sampling at one time or over a relatively short period of time; thus it is not known how well the available database reflects the long-term building exposures.

When all of these issues were considered together, some members of the Panel concluded that, with respect to all U.S. buildings, a net positive bias may exist in the available data, while others concluded that a net negative bias may exist. It did not appear that the data possess any systematic bias with respect to the buildings sampled. For the purposes of this report, it was decided to use the data as they are, with a note of caution that it was not possible to ascertain from the available information whether or not the sampled buildings and sampling conditions are truly representative of U.S. public and commercial buildings as a whole.

If no systematic bias is assumed to exist in the sampling studies with respect to the buildings sampled, average concentrations measured in individual buildings can be taken to represent the long-term averages in those buildings. There is only one study currently available, however, in which extensive repeated measurements were made over time in a building; this is the unpublished longitudinal study of some 328 samples taken in one building subject to an O&M program (McCrone Environmental Services 1991). In that study, 95 percent of the sample concentrations were below the limit of detection and 99 percent were below 0.001 f/mL. The average level over all samples was 0.00004 f/mL. The ratio of peak to mean levels, taking the 99th percentile as the peak level, was 25:1.

8.3.2.2 Direct Versus Indirect Sample Preparation

The available data on airborne asbestos concentrations in buildings presented in this report are based on two analytical TEM measurement techniques: indirect and direct preparation. Most of the indirect TEM data currently available are mass concentration data collected in the past. A very limited amount of recent fiber count data using indirect preparation are also available. Most of the recent fiber count data have been obtained using direct preparation techniques.

The historic, indirectly prepared mass data have been reviewed thoroughly in a previous report (National Research Council [NRC] 1984), and no further indirect mass survey data have become available to alter the report's conclusions that, converting mass to fiber concentrations, the median exposures in the buildings sampled were 0.00007 f/mL outdoors, 0.00054 f/mL inside rooms without asbestos, and 0.0006 f/mL in rooms with asbestos.

All historical occupational exposure data and epidemiologic risk estimates are based on counts (or, in most cases, estimates calculated from particle counts) of the concentration of fibers longer than 5 μm as determined by optical microscopy. In addition, it has been shown in experimental animals that fibers longer than 5 μm have the greatest carcinogenic potential. These factors dictated the Panel's decision to base its conclusions only on measurement of conventional (> 5 μm) fibers, on the premise that, for the purposes of risk assessment, environmental measurements need to be specified in units that can be compared with the historical industrial measurements on which the dose-response, and hence the risk assessment, are based. At the present time, the direct TEM measurements of fibers longer than 5 μm are the most extensive data available to the Panel to assess exposure and risk.

However, the decision to consider only direct TEM counts of fibers longer than 5 μm introduces three unavoidable but potentially serious uncertainties in the resulting risk estimates:

1. At a given conventional (> 5 μm) fiber count, the proportion of long fibers (for example, greater than 20 μm) tends to be lower in buildings than in historical industrial environments. Conversely, however, the ratio of short (< 5 μm) fibers to measured (> 5 μm) fibers is higher in buildings, and these short fibers are completely ignored in the conventional fiber count.

2. There was considerable discussion in the Panel over the most appropriate protocol for TEM sample preparation. A measurement made by the direct preparation method is an attempt, insofar as possible, to examine the airborne particulate matter as it exists in the air. A measurement made by an indirect sample preparation method is an attempt to optimize the detection limit and to detect all airborne asbestos present in the sample, some of which may be contained in larger nonthoracic particles or aggregates of fibers.

   Indirect TEM measurements usually give higher fiber counts than direct measurements. The reasons for this difference are not well established. If the cause of such a difference is related to factors that lead to a failure to count a proportion of airborne fibers on directly prepared filters, then indirect measurements would be more appropriate. Conversely, if the difference is due mainly to the release of particles from aggregations which would not have been counted by historical fiber counting methods (and which may not even be respirable), the direct measurement would be preferable as a basis for risk assessment.

3. Another potential bias in the risk assessment is the difference between TEM and optical fiber counts. TEM counts on occupational samples are usually higher because of increased visibility of thin fibers, often by a factor of two or more (for fibers longer than 5 μm) depending on fiber type and degree of manipulation. At the same time, optical fiber counts include both asbestos and nonasbestos fibers, while TEM counts are specific for asbestos. It is impossible to select any specific adjustment factor to account for these differences.

8.3.2.3 Sensitivity of Reported Measurements

Finally, most of the available direct TEM data were obtained using sampling and analytical protocols that had varying sensitivities, with individual samples having sensitivities an order of magnitude above the building mean. In computing building averages, individual samples have been pooled for each building, achieving an increased sensitivity. As compared to a single measurement in a given building, a building average derived from multiple samples represents a better estimate of the average exposure for C1 occupants; however, information on individual sample maxima is lost in such an averaging process. When reviewing the overall average data presented here, one should remember that there can be areas in some buildings with concentrations substantially higher than the building average, and that some buildings may have average concentrations in order of magnitude above the group average.

8.4 Derivation of Risk Estimates

On the basis of the available exposure information, and assuming linear nonthreshold risk models for lung cancer and mesothelioma, tentative estimates of the risks of such cancers to different types of building occupants may be formulated. These data, together with data on the exposure of insulation workers and their disease outcomes, can be used to make estimates of risks for different scenarios of exposure to asbestos in buildings. Thus, according to the linear risk assessment models for mesothelioma and lung cancer developed in Chapter 6, the overall cancer risk to an exposed population can be calculated by assuming that all individuals are exposed to the mean long-term average exposure of the whole group. The estimates of this average, shown in Table 8-3, can therefore be used, along with the risk estimates table in Chapter 6 (Table 6-3), to compute overall population risks to occupants in the buildings sampled.

The risk assessment calculations of this sort are "best estimates" in the sense that we have no direct evidence that they are too high or too low. However, no meaningful upper confidence limits can be assigned to them, due to the many uncertainties in the reliability and representativeness of the exposure data, as well as the scientific uncertainties relating to the model itself, which are discussed in Chapter 6.

Category 1: General occupants of buildings, such as office workers, comprise by far the largest population group considered in this report. The risk estimates, shown in Table 8-3, indicate that the lifetime cancer risk is about 4 per million for adults who work for 20 years in asbestos-containing public and commercial buildings where the average concentration of airborne asbestos is 0.00020 f/mL (> 5 μm fibers). (If the single highest sample value were excluded from calculation of the average indoor asbestos concentrations in public and commercial buildings, or if the average of the litigation data were used, the lifetime risk would be about halved.) For children who attend asbestos-containing schools from age 5 to age 18, the lifetime cancer risk is about 6 per million. The relative impact of the public health consequences can be judged by comparing this assessment with lifetime risks of lung cancer that have been projected to occur as a result of exposure to indoor radon and

environmental tobacco smoke, which are in the range of 5,000 to 20,000 per million (Pushkin and Nelson 1989) and 2,000 to 5,000 per million (Repace and Lowrey 1990), respectively.

Categories 2 and 3: Category 2 consists of custodians and janitors who are generally not involved directly with disturbing or handling ACM, but may cause brief increased levels of airborne material as a result of their housekeeping duties. Category 3 includes maintenance workers who may actively damage or disturb ACM during their work, and, without appropriate respiratory protection and work practices, may be exposed to relatively high levels of asbestos fibers; such exposures would generally be in the form of intermittent peaks over a prolonged period of working life. We consider these two categories together here because sufficient information is not available on the exposure levels and patterns of workers in either category. Also, the job titles suggested by these categories are very broad, and are differently interpreted in different places.

Table 8-3. Estimated Lifetime Cancer Risks for Different Scenarios of Exposure to Airborne Asbestos Fibers[a]

Conditions	Premature Cancer Deaths (Lifetime Risks) per Million Exposed Persons
Lifetime, continuous outdoor exposure	
• 0.00001 f/mL from birth (rural)	4
• 0.0001 f/mL from birth (high urban)	40
Exposure in a school containing ACM, from age 5 to 18 years (180 days/year, 5 hours/day)	
• 0.0005 f/mL (average)[b]	6
• 0.005 f/mL (high)[b]	60
Exposure in a public building containing ACM age 25 to 45 years (240 days/year, 8 hours/day)	
• 0.0002 f/mL (average)[b]	4
• 0.002 f/mL (high)[b]	40
Occupational exposure from age 25 to 45	
• 0.1 f/mL (current occupational levels)[c]	2,000
• 10 f/mL (historical industrial exposures)	200,000

[a] This table represents the combined risk (average for males and females) estimated for lung cancer and mesothelioma for building occupants exposed to airborne asbestos fibers under the circumstances specified. These estimates should be interpreted with caution because of the reservations concerning the reliability of the estimates of average levels and of the risk assessment models summarized in Chapter 8.

[b] The "average" levels for the sampled schools and buildings represent the means of building averages for the buildings reviewed herein (Figure 8.2; Table 8-2). The "high" levels for schools and public buildings, shown as 10 times the average, are approximately equal to the average airborne levels of asbestos recorded in approximately 5 percent of schools and buildings with asbestos-containing materials (ACM) (see Chapters 4 and 8). If the single highest sample value were excluded from calculation of the average indoor asbestos concentration in public and commercial buildings, the average value is reduced from 0.00020 to 0.00008 f/mL, and the lifetime risk is approximately halved.

[c] The concentration shown (0.1 f/mL) represents the permissible exposure limit (PEL) proposed by the U.S. Occupational Safety and Health Administration. Actual worker exposure, expected to be lower, will depend on a variety of factors including work practices, and use and efficiency of respiratory protective equipment.

Because of the lack of any reliable average estimates of exposure of such workers, the Panel has based its risk assessment on the recently proposed permissible exposure limit of 0.1 f/mL, shown in Table 4-17 (OSHA 1990). Actual average exposures of C2 and C3 workers in real life should be lower than the proposed 0.1 f/mL permissible exposure limit provided that the provisions of the proposed regulations, including appropriate work practices and respiratory protection equipment, are employed. However, no information was available to the Panel to assess how widely the requirements of OSHA will be met. Thus, the anticipated real life exposures and the risks to C2 and C3 workers could not be calculated. For comparison, Table 8-3 presents the historical risk from exposure to much higher levels of asbestos in past industrial occupations.

Although the risk estimates in Table 8-3 are at best imprecise, it can be concluded that while C2 and C3 workers in today's buildings are not at as high a risk as past industrial workers, they are at a higher risk for mesothelioma and lung cancer than the general building occupant (C1). In addition, recent studies indicate that exposure in these groups of workers can produce a significant incidence of nonmalignant thoracic scarring (pleura and lung) that can interfere with lung function. There is a serious concern that because of the lack of oversight and education, these workers are not being protected by the regulations that should govern their work environments. These workers should be targeted as the most important group with the potential for significant asbestos exposure.

Category 4: Control of exposure to asbestos for workers responsible for remediation of damaged ACM or asbestos removal is now covered under OSHA regulations; however, there is a serious possibility that unless regulations are strictly enforced, a substantial group of individuals (if they work for a prolonged time in this occupation) could be exposed to levels of asbestos that not only allow manifestation of some nonmalignant effects, including pleural and parenchymal scarring due to asbestos inhalation, but also cause an excess of cancer deaths.

Category 5: At this time, the asbestos exposure level of fire fighters and other emergency personnel who enter buildings during or after catastrophic damage is entirely unknown. It is, however, doubtful that in the emergent situation, asbestos exposure is important compared with other hazards that will exist. Following extensive damage, the removal and repair of disrupted ACM should be conducted under appropriately protective working conditions.

8.5 References

American Cancer Society (ACS). 1991. Cancer Facts and Figures. Atlanta, GA.

Burdett GJ, Jaffrey SAMT. 1986. Airborne asbestos concentrations in public buildings. Ann Occup Hyg 30:(2)185-190.

Chatfield EJ. 1986. Airborne asbestos levels in Canadian public buildings. In: Proceedings: Asbestos Fibers Measurements in Building Atmospheres, pp. 177–207. Ontario Research Foundation, Mississauga, Ontario, Canada.

Chesson J, Hatfield J, Schultz B, Dutrow E, Blake J. 1990. Airborne asbestos in public buildings. Environ Res 51:100–107.

Consumer Products Safety Commission, U.S. (CSPC). 1987. Report on the first round of air sampling of asbestos in home study. Memorandum by AM Rock. U.S. Consumer Product Safety Commission, Washington, DC.

Crump KS, Farrar DB. 1989. Statistical analysis of data on airborne asbestos levels collected in an EPA survey of public buildings. Reg Toxicol Pharmacol 10:51–62.

Gazzi D, Crockford GW. 1987. Indoor asbestos levels on a housing estate: Determined by TEM. Ann Occup Hyg 31(4A):429–439.

Hatfield J, Ogden J, Stockrahm J, Leczynski B, Price B, Chesson J, Russell J, Ford P, Thomas J, Fitzgerald J, Roat R, Lee R, Van Orden D, Dunmyre G, Constant P, McHugh J. 1988. Assessing Asbestos Exposure in Public Buildings. EPA-560/5-88-002, May 1988. U.S. Environmental Protection Agency, Washington, DC.

National Research Council (NRC). 1984. Asbestiform Fibers: Nonoccupational Health Risks. National Academy Press, Washington, DC.

Occupational Safety and Health Administration, U.S. (OSHA). 1990. Notice of Proposed Rulemaking for Occupational Exposure to Asbestos, Tremolite, Anthophyllite and Actinolite. Docket no. H-033-D. 55 Fed Reg, p. 29. Occupational Safety and Health Administration, Washington, DC.

Pinchin DJ. 1982. Asbestos in Buildings. Study No. 8. Ontario Ministry of Government Services, Publications Services Branch, Toronto, Ontario, Canada.

Pushkin JS, Nelson CB. 1989. EPA's perspective on risks from residential radon exposure. JAPCA 39:915–920.

Repace JL, Lowrey AH. 1990. Risk assessment methodologies for passive smoking-induced lung cancer. Risk Anal (1):27–37.

Statements

STATEMENT BY DR. WILLIAM NICHOLSON
CONCERNING SOME OF THE CONCLUSIONS OF THE
LITERATURE REVIEW PANEL[1]

August 6, 1991

Dr. Arthur C. Upton, Chairman
Literature Review Panel
Health Effects Institute/Asbestos Research
141 Portland Street
Cambridge, MA 02139

Dear Arthur:

I have reviewed the final draft of the HEI/AR Literature Review Panel report and, while there is much that is meritorious in the document, some aspects of the report are such that I cannot sign-off on it. My major concerns follow.

Asbestos concentrations in buildings

One of the mandates to HEI-AR was to review and synthesize the state of knowledge on the concentrations of airborne asbestos fibers found in public and commercial buildings. It is unfortunate, but there are very few published studies of asbestos fiber concentrations in non-school public and commercial buildings. They are represented by studies of:

1. 43 US federal buildings controlled by the General Services Administration (GSA) [1,2]
2. 2 buildings in Canada [3]
3. 8 British buildings [4]
4. 6 Swiss buildings [5], a study that was not included in the HEI-AR summary data because the sample analysis involved an indirect technique.

Also included in the HEI-AR report are data on a single US building periodically sampled as part of an operations and maintenance (O&M) program [6], and data from samples collected at the request of defendants in buildings litigation suits.

Are these studies representative of US buildings? I strongly believe they are not and this feature should have received more emphasis in the report. Further, data from such a small and unrepresentative sample should not be used as an estimate of the US

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[1] Statement individually prepared by Dr. Nicholson has not been subjected to review or editing by other members of the Panel or by HEI-AR staff; the statement appears exactly as prepared by Dr. Nicholson. The Panel neither endorses nor takes responsibility for the content of the statement.

population risk from exposure to asbestos in buildings, as is done in Chapter 8, the Executive Summary and Table 1-1.

If we consider the non-litigation US data, it is dominated by the GSA set, which shows a low average fiber concentration. The use of GSA buildings in this EPA sponsored study came about because, at the time the study was being planned, the GSA was implementing a national asbestos management program and assessing the condition of asbestos in buildings under its jurisdiction. This information was available and saved significant time and money in building selection. Additionally, building access was assured by GSA cooperation. However, the O & M programs that were in place or being implemented could have substantially altered the likelihood of exposure compared to buildings without such programs, in which maintenance workers still may be unaware of the presence of asbestos or of how to carry out their tasks in a way that would minimize exposure. Chesson [1] noted that the concentrations of all asbestos structures in this study was about 10 times lower than other studies and suggested that the asbestos management program of GSA may have contributed to this difference.

Secondly, there is no information presented in any report of the GSA study that would indicate if any activities that could release fibers were taking place during the sampling phase of this study. Parenthetically, if I were the manager of a government building that is about to have government sponsored asbestos air sampling, I don't think I would schedule maintenance or repair work that might release fibers. Samplers were placed near damaged asbestos materials, but 75% of such locations were in non-public areas such as boiler rooms, electrical closets and fan rooms. Information was not presented on the extent to which these areas were occupied at any time during sampling. The public areas sampled were largely damage free. Only one sample of all taken in 54 public and commercial buildings mentioned an activity (installation of a computer cable) that might have disturbed building asbestos (see section on peak exposures below).

Finally, the GSA set consisted only of office buildings. Different exposure circumstance can exist for people employed in or using post offices, hospitals, recreation buildings, stores, shopping centers, etc.

Thus, it would appear that the studied buildings are not a representative sample of the total building population and that the short-term and localized sampling was not representative of long-term building conditions, including consideration of the full effect of custodial and maintenance work. In short, Table 1-1 and 8-3 should not have been presented with the impression that these are the asbestos-related risks common to all US buildings. They are not. They may apply to buildings in which no disturbance of asbestos is taking place, to buildings with intact, well maintained asbestos material or to buildings with an effective O & M program. They do not apply to buildings which have ongoing disturbances of asbestos materials in public areas or to buildings with uncontrolled maintenance work.

Analytical techniques

The HEI report focussed on samples analyzed by direct TEM methods. Of concern is the dramatic differences seen in the analysis of samples when using an indirect grid preparation technique compared to the direct one used in the sample analyses presented in Table 4-10. In reanalyses of 30 of the GSA samples by an indirect technique fiber concentrations were 9 to 18 times greater [7]. These two techniques are discussed in the report, but it is not clear which method best represents the lung fiber exposure of an individual. Fibers dispersed into the air come in contact with other particles to which they adhere. These are unlikely to be counted as fibers in the direct method of analysis, but are in the indirect, which redisperses the material. Since the fiber-particle combination may also be redispersed by lung surfactants when inhaled, the indirect method may better reflect the lung dose. This agglomeration feature is not a factor in the analysis of samples from past occupational exposures, where the time from fiber release to collection is short and fibers, rather than particles, are the dominant material in workplace air.

A second issue of concern is the possibility of loss in the direct technique using cellulose ester filters. Mention is made of this in the report and it is stated that the problem is corrected by a plasma-etch technique. However, the success of the method depends on the degree of plasma-etch. Unfortunately, at this time, there are no published data on the quality assurance results of US laboratories.

Peak exposure episodes

Peak exposure episodes occur in buildings from both occupant and maintenance activities. We have no data that accurately describe their contribution to long term exposures of building occupants. The effect of maintenance on general building occupants will depend on the work involved, its location and duration, and the control measures utilized. The report notes that the removal of a single sample from the 769 taken in the 54 public and commercial buildings reviewed in Chapter 4 reduces the average concentration from 0.00021 f/mL to 0.0008 f/mL, the implication being that the lower value is the more representative of building occupant (C1) exposure. On the contrary, I would suggest that this indicates that even the higher value is an underestimate of C1 exposure. The only maintenance activity noted in any of the public and commercial building studies was a computer cable installation. This was mentioned by Chatfield as taking place in occupied offices in one building, where a concentration of 0.042 f/mL was measured. The 769 samples represent at least the 1067 days of building operation. [596 days in GSA buildings (two-day samples), 328 in the McCrone building (assuming one-day samples) and at least 143 in the other buildings]. I don't believe that maintenance or repair work occurs in a building area at a frequency of only once every four years. Thus, I feel that the effect of peak exposures are substantially under-represented in the limited data set we have. If removal of a single sample reduces the average by 0.00013 f/ml or 60%, inclusion of the samples required to reflect actual frequency and varieties of maintenance and repair work would raise the average by 0.00013 f/ml for each sample that has a value equal to that of the Chatfield sample.

Building maintenance and custodial workers

I feel the potential effects of inadequate control of asbestos exposures on maintenance workers are inadequately addressed in the report. Granted there are limited data on these exposures, but that which is available indicates the magnitude of the potential problem. Mention is made in text of exposures of several f/mL in particular circumstances. Table 4-19 lists results of 61 samples of various maintenance activities. Sixty-nine percent of the samples exceed the current OSHA TWA asbestos permissible exposure limit of 0.2 f/mL and 20% exceeded 2 f/mL, the standard in effect during 1976-1986. Even with O & M programs in place and using available control technology, personal air samples averaged 0.11 f/mL. In buildings with no O & M programs in place the higher concentrations are likely to occur and average concentrations in excess of the 0.1 f/mL assumed in Table 1-1 may occur for workers in such buildings.

Unfortunately, the effects of asbestos exposure on building maintenance workers are described only in an appendix describing pleural plaques (Appendix 2, Table A2-2). In the three available studies of school custodian or maintenance employees having no other occupational exposure to asbestos, the prevalence X-ray abnormalities (parenchymal 1/0 or greater, pleural plaques or pleural thickening) ranged from 11.4% in one study of current workers with 10+ years of employment to 36.0% in a group of workers 20+ years from first exposure. These X-ray changes were often accompanied by decreases in pulmonary function, particularly FVC.

This prevalence of abnormalities among long term maintenance workers is characteristic of a significant past asbestos exposure. Based on a comparison with one factory group [8], it is likely that the past average group exposure for those with 16% parenchymal abnormality exceeded 1 f/ml. This is far in excess of the current (0.2 f/mL) or proposed (0.1 f/mL) asbestos standard. However, even these standards may not serve to protect current building maintenance workers. Such workers are rarely monitored by OSHA personnel. The workers and even the building manager may be unaware of the presence of asbestos and its potential risks. An effective O & M program would provide the appropriate information on risks and how to prevent them.

Short fibers

The role of short fibers is given short shrift in the document. It is stated that the rate of tumor induction increases sharply as fiber length increases above 5 μm. What is not stated is the number of fibers increase sharply as the length decreases below 5 μm. In occupational exposures to chrysotile the percentage shorter than 5 μm can range from 95 - 99.5%. In a building environment the number shorter than 5 μm may even exceed 99.9% as measured by direct TEM techniques. There is no question that longer fibers are more carcinogenic than shorter fibers. However, because of their greater number, the fibers shorter than 5 μm could be a more important cause of a tumor such as mesothelioma than longer fibers. To the extent that this is true, the finding that in some building exposure circumstances the percentage of fibers shorter than 5 μm is much

greater than in the work environment is not a cause for dismissal of concern, but one of greater concern, because there is an increase in the short fiber risk with no concomitant increase in the measure of that risk from the number of counted fibers greater than 5 μm.

Remediation exposures

It is emphasized at several places in the report that removal of asbestos can lead to increased levels of asbestos that can persist for some time. Burdett has shown that dry removal and inadequate clean-up can lead to increased levels for weeks. Increases could also result from abatement action other than removal. The point is an important one, but it emphasizes not that abatement should never be done, but that it be done properly. When ongoing disturbance of asbestos is present in a building and fiber concentrations are increased, proper abatement will reduce the long term average concentrations of both the maintenance workers and building occupants.

Summary

Asbestos is a carcinogen for which we have no knowledge of a level below which there is no risk. The estimated risks from exposures in some buildings are comparable to risks for which regulations have been promulgated in other environmental or occupational circumstances. The primary issue of asbestos in buildings is how to prevent, to the extent feasible, asbestos exposure to building occupants, building workers and employees of outside contractors, including abatement workers. This will not be done by ignoring the presence of asbestos in buildings, but by putting in place a proper O & M control program and taking action commensurate with the building circumstances. Chapter 5 well describes the appropriate control processes. Removal of well maintained, intact asbestos is not necessary for health reasons. However, elimination of continuing releases of asbestos fibers in a building and prevention of high episodic exposures during maintenance work is.

Very truly yours,

William J. Nicholson, Ph. D.
Professor of Community Medicine

References

1. Chesson J, Hatfield J, Schultz B, Dutrow E, Blake J. Airborne asbestos in public buildings. Environ Res 1990; 51:100-107

2. U.S. Environmental Protection Agency. Assessing Asbestos Exposure in Public Buildings, EPA 560/5-88-002. Washington DC: Office of Toxic Substances. May 1988.

3. Chatfield EJ. Airborne asbestos levels in Canadian public buildings. In: Asbestos Fibers Measurements in Building Atmospheres: Proceedings. Mississauga, Ontario, Canada: Ontario Research Foundation. 1986. pp. 177-207.

4. Burdett GJ, Jaffrey SAMT. Airborne asbestos concentrations in public buildings. Ann Occup Hyg 1986; 30:185-190.

5. Guillemin MP, Madelaine P, Litzistorf G, Buffat P, Iselin F. Asbestos in buildings. Aerosol Sci Tech 1989; 11:221-43.

6. McCrone Environmental Services Inc. Data furnished to HEI/AR, 1991.

7. Chesson J, Hatfield J, Leczynski B. A Comparison of Airborne Asbestos Levels Determined by Transmission Electron Microscopy (TEM) Using Direct and Indirect Transfer Techniques, EPA 560/5-89-004. Washington, DC: Office of Toxic Substances. March 1990.

8. Berry G, Gilson JC, Holmes S, Lewisohn HC, Roach S. Asbestosis: a study of dose-response relationships in an asbestos textile factory. Br J Ind Med 1979; 36:98-112.

STATEMENT BY DR. J. CHRISTOPHER WAGNER
CONCERNING SOME OF THE CONCLUSIONS OF THE
LITERATURE REVIEW PANEL[1]

August 27th 1991

While agreeing with most of the conclusions of the Report, I decided to make a statement covering four major issues on which I disagree. These are tremolite asbestos, lung burden, the possibility of threshold, and Table of Life-Time Cancer Risks.

Both tremolite asbestos and threshold have been discussed. The section on threshold was 6.1.2.3 in the September 1990 version, but there is no mention of it in the final draft.

Chrysotile and Tremolite Asbestos

1. Pure Chrysotile. I do not accept the fact that pure chrysotile will cause mesotheliomas. There is the possible exception of excessive exposure i.e. for more than 20 years to very high dosage, which might account for some of the Quebec tumours.

2. I agree with the workers on lung tissue burden who have demonstrated that certain tremolite asbestos fibres of the right length and diameter, because of their durability, are the cause of mesotheliomas in the majority of cases in Quebec. The exception here is the gas-mask workers who were exposed to crocidolite (McDonald and McDonald 1978).

Tremolite asbestos, elsewhere, has been shown to be associated with mesotheliomas in Turkey, Greece, and Cyprus, and with pleural plaques in Turkey, Greece, Yugoslavia, Czechoslovakia and Montana.

3. Comparisons of two workplaces (such as Acheson et al. 1978, Berry and Newhouse 1983, and Newhouse and Sullivan 1989) show the lack of disease caused by chrysotile, when compared with crocidolite. This does not confirm the theory (see 6-40) that it is the initial high level of chrysotile fibres (later cleared) that cause the disease, and does confirm the importance of the final lung burden.

4. Short chrysotile fibres found at the pleura (see page 6-60). There is a tendency for all small inorganic dust particles to drift or be carried to the pleura. It is unlikely that short chrysotile fibres are carried there preferentially, and the main body of opinion is that they are unlikely to contribute to the formation of mesotheliomas.

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[1] Statement individually prepared by Dr. Wagner has not been subjected to review or editing by other members of the Panel or by HEI-AR staff; the statement appears exactly as prepared by Dr. Wagner. The Panel neither endorses nor takes responsibility for the content of the statement.

Threshold

1. I consider that there is a background incidence of mesotheliomas of pleura and peritoneum which are "spontaneous", or are not related to exposure to mineral fibres (Gardiner and Saracci 1989; Ilgren and Wagner 1991).

2. It is likely that threshold will be established for various diseases associated with asbestos dusts (Gibbs et al. 1989). A threshold for asbestos-related lung cancer, especially in chrysotile-exposed individuals is suggested by several studies. First the marked difference in lung cancer rate between the high exposure group and the rest of the cohort of Quebec miners and millers (see page 6-24 and Table 6-6). Secondly, an increased incidence of lung cancer rate is not observed in Thetford, Quebec where airborne concentrations of chrysotile are 200-300-fold higher than in most urban environments (Churg 1986). Lastly, some evidence of a threshold of cumulative exposure below which the risk of lung cancer does not appear to be elevated exists in asbestos workers (with data on duration and intensity of exposure) (Browne 1986).

Tables of Life-time Cancer Risks

Considering the Tables of Life-time Cancer Risks (1-1 and 8-3). In these the maximum risk life-time risks have been calculated. With all of the doubts expressed in sections 6 and 8, and including my opinions stated above, and if consideration is given to the fact that a large proportion of the dust calculations include chrysotile, and that litigation data is to be included, it would seen at this stage the estimated life-time risks should not have been stated, as they are probably far too high. Also, the risks from passive smoking and radon should be carefully considered in relation to these Tables, especially in the Executive Summary.

Finally it is of interest that the fibre content of the lungs of the cases of peritoneal mesotheliomas from the London factory, which was investigated by Newhouse, show a higher level of crocidolite fibres than amosite fibres on tissue analysis (see page 6-19), reference Wagner, Newhouse et al. 1988.

I have therefore not signed off, at present. Signed J.C. Wagner

Additional References

1. Ilgren E.B. and Wagner, J.C.: Background incidence of mesothelioma: Animal and human evidence. Regulatory Toxicology and Pharmacology 13: 13-149, 1991.

2. Ilgren E.B. and Browne, K.: Asbestos-related mesotheliomas: Evidence for a threshold in animals and humans. Regulatory and Pharmacology 13: 116-132, 1991.

3. Browne K.: A threshold for asbestos-related lung cancer: Br. J. Indust. Med. 43: 550-558, 1986.

4. Churg A.: Lung asbestos content in long-term residents of a chrysotile mining town: Am. Rev. Resp. Dis. 134: 125-128, 1986.

COMMENTS BY DR. ARTHUR C. UPTON,
CHAIRMAN
LITERATURE REVIEW PANEL,
IN RESPONSE TO THE STATEMENTS BY
DRS. WILLIAM J. NICHOLSON AND J. CHRISTOPHER WAGNER

The statements by Drs. Nicholson and Wagner reiterate limitations in the existing exposure and toxicity data, which have restricted the Panel's ability to resolve adequately a number of critical issues, as discussed in the Report. The Panel has strived to summarize, interpret and integrate the data that are available at this time. Pending the availability of more-adequate data, however, uncertainty will continue to cloud some of the issues in question.

A major source of uncertainty, identified in the Report and re-emphasized by Dr. Nicholson, is the degree to which the available data on the concentrations of airborne fibers in public and commercial buildings are representative of the concentrations in U.S. buildings in general. Individual members of the Panel differed somewhat in their opinions on this question, but all agreed that the issue cannot be resolved adequately without a more comprehensive database, including larger numbers and types of buildings, a wider range of building operating conditions, and additional research to validate the methodology for assessing the relevant levels of exposure actually experienced by building occupants. Further research on analytical techniques as well as the effectiveness of various remediation methods is also important.

Further research on the exposure and long-term heath status of custodial and maintenance workers, whose activities may expose them recurrently to elevated airborne asbestos fiber concentrations, also are needed, as Dr. Nicholson has stressed. Such limited information as now exists, which is reviewed in the Report and its appendices, suggests that the risks for these workers may be increased, but the data are insufficient to establish or quantify the level of risk.

Also calling for further study, as re-emphasized by Dr. Nicholson, is the extent to which the inhalation of asbestos fibers shorter than 5 μm may contribute to the total risks to building occupants. This is an important question since, although such fibers are much less hazardous individually than longer fibers, they are relatively more numerous in the air of buildings.

Whether the numbers of asbestos fibers in the lung must exceed some critical threshold before causing any increase in the risk of cancer, as suggested by Dr. Wagner, is another issue about which opinions on the Panel were divided. This issue, as emphasized in the report, cannot be resolved on the basis of existing knowledge. Further studies to clarify the exposure-risk relationship are among the types of research recommended most strongly by the Panel.

Dr. Wagner is not alone in the view that it was the tremolite, rather than the chrysotile, that was responsible for the increased risks of cancer experienced by some cohorts of workers exposed to mixtures of both types of asbestos fibers. As indicated

in the report, however, this issue cannot be resolved with certainty from the available data.

In summary, the statements by Drs. Nicholson and Wagner are helpful in reiterating a few of the many caveats with which the Panel's conclusions have been, and must be, qualified. The Panel was pleased to learn that HEI-AR has already taken steps to initiate research in several of these areas of uncertainty. In the meantime, it is clear, as emphasized both by the Panel and by Dr. Nicholson, that close attention should be paid to the activities of workers in buildings who are engaged in custodial, maintenance, abatement, and emergency work. As discussed in the Report, strategies for preventing the exposure of these and other building occupants constitute a subject calling for further study.

TOPICS DISCUSSED IN STATEMENTS BY DRS. NICHOLSON AND WAGNER: LOCATIONS IN MAIN TEXT

Building Maintenance and Custodial Workers

Executive Summary: pages 4, 6, 7, 10, 11
Chapter 4: sections 4.3, 4.6.3.4, 4.6.4 (see also section 4.5)
Chapter 5: sections 5.3, 5.4
Chapter 6: section 6.4.4
Chapter 8: sections 8.3.2.1, 8.3.2.3, 8.4

Fiber Types, Differences in Toxicity

Executive Summary: pages 8, 11
Chapter 6: sections 6.2.2 (especially 6.2.2.4), 6.3.1.1

Peak Exposure Episodes

Executive Summary: pages 4, 6, 7, 10, 11
Chapter 4: sections 4.3, 4.6.3.4, 4.6.4 (see also section 4.5)
Chapter 5: sections 5.3, 5.4
Chapter 6: section 6.4.4
Chapter 8: sections 8.3.2.1, 8.3.2.3, 8.4

Remediation

Executive Summary: pages 6-8, 10, 11
Chapter 5: particularly section 5.4

Representativeness of the Sampled Buildings

Executive Summary: pages 4-6, 9, 11

Chapter 4:
Building concentrations; mass measurements: section 4.6.2
Building concentrations; numerical measurements: section 4.6.3, Appendix 1
Evaluation of biases in the data: section 4.6.3.2
GSA buildings' study: section 4.6.3.1
Types of ACM in buildings: section 4.1.4

See also sections 4.8 and 4.9

Chapter 8: sections 8.3.2.1, 8.3.2.3

Risk Estimation

Executive Summary: pages 9-10, 11
Chapter 6: section 6.2.2.4
Chapter 8: section 8.4

Short Fibers

Executive Summary: pages 3-4, 8, 11
Chapter 4: sections 4.1.2, 4.2, 4.6.3
Chapter 6: sections 6.3, 6.4
Chapter 8: section 8.3.2.2

TEM Analytical Techniques

Executive Summary: pages 3-4, 5, 9, 11
Chapter 4: sections 4.4.2.4, 4.6.3.1
Chapter 8: section 8.3.2.2

Threshold

Executive Summary: pages 8-9, 11
Chapter 6: sections 6.2.2.4, 6.3.1.1

Appendix 1

Review of Measurements in Buildings

A1.1 Introduction

The published results for measurements in buildings are reviewed in this appendix and summarized in Tables 4-10, 4-14, and 4-15 in the main text of this report. The purpose of this appendix is to extract building averages based on the individual sample measurements and, where appropriate, to obtain averages from multiple sites. This would make the results more compatible with the procedures used in the U.S. Environmental Protection Agency (EPA) survey of public buildings (Hatfield et al. 1988) and address the limitations of data comparison commented on in a recent EPA review (Chesson et al. 1989).

In the past, the normal scientific practice of using a statistically valid limit of quantification, that is, where a recount has a 95 percent confidence of equalling or exceeding the limit of detection (or analytical sensitivity, in the case of fiber counting) of one fiber or structure, has been used as the approach for interpretation. However, because many of the environmental asbestos samples collected are below the analytical sensitivity, it has become a common practice to rely on and report concentrations down to the analytical sensitivity. Given the nature of the available data, this practice has been followed for the measurements below.

Ideally, the number and type of all asbestos fibers, and the number of nonasbestos fibers longer than 5 μm have been reported, along with the volume of air analyzed and the calculated concentrations. The volume of air analyzed is usually calculated by summing the volume of air sampled and multiplying by the fractional area of the filter examined. Each publication has been reviewed and the data reworked, sometimes extensively, to give results down to the analytical sensitivity (one fiber or structure counted). Where detailed information was available, the arithmetic mean concentration in a given building was computed by dividing the total number of fibers (or structures) detected on filters collected in the building by the total volume of air analyzed in all the samples collected in that building. This approach yielded building average concentrations that had improved analytical sensitivities compared with the individual samples. Where all the data were not presented in the publications, the Panel relied on the averages reported by the authors. For a group of buildings, the mean was calculated by averaging the building means; any building mean reported as below the analytical sensitivity (that is, where no fibers were detected) was considered to be zero for the purpose of this calculation. Concentrations of asbestos fibers longer than 5 μm are reported in units of fibers per milliliter (f/mL), and all sizes of asbestos fibers are reported as structures per liter (s/L) (see also section 4.2, Units of Measurement). The data are presented in chronological order of publication, although they may span several years of study.

A1.2 Review of Reported Data

A1.2.1 Nineteen Canadian Buildings with Sprayed Friable Asbestos

These data were first published as Study 8, Asbestos in Buildings, by the Royal Commission on Matters of Health and Safety Arising from the Use of Asbestos in Ontario (Pinchin 1982). The buildings (thought to be schools) all contained friable asbestos, and from their hazard ratings most of the buildings had friable (dry applied) asbestos-containing spray insulation on ceilings with varying amounts of damage.

The results (presented in Table A1-1) in the original publication showed that asbestos fibers longer than 5 μm were found at only 5 of the 19 sites. Building average concentrations

ranged from not detected (ND) to 0.003 f/mL, with a mean of 0.00042 f/mL. For structures of all sizes, the building averages ranged from ND to 202 s/L, with a mean of 22.1 s/L.

Table A1-1. Airborne Asbestos Concentrations in Nineteen Ontario Buildings[a]

Building No.	Number of Samples	Asbestos Fibers of All Lengths (f/L)	Asbestos Fibers > 5.0 µm (f/mL)
1	4	0.7	0.001
2	5	6	ND[b]
3	1	4	ND
4	3	3	ND
5	5	ND	ND
6	3	15	0.001
7	5	10	ND
8	3	4	ND
9	2	202	ND
10	4	10	ND
11	7	9	0.001
12	3	23	0.003
13	2	10	ND
14	4	16	0.002
15	1	59	ND
16	2	3	ND
17	4	27	ND
18	1	10	ND
19	4	1	ND
Total	63	22.1	0.00042

[a] Source: Adapted from Pinchin (1982).
[b] ND = Not Detected.

A1.2.2 Ontario Office and School Buildings

This study, published by Chatfield (1986), gives detailed information on seven buildings in normal use, and some data on maintenance activities in buildings. The number of asbestos fibers both longer than 5 µm and of all lengths are given in the report, but there is no information on the volume of air sampled. However, an analytical sensitivity is reported for each sample, and by taking the reciprocal of the quoted analytical sensitivity, the volume of air analyzed was calculated. The total volume of air for all samples and the total number of fibers for all samples were obtained for each building, and the building averages calculated are shown in Table A1-2. The average results from a 44-floor office

building with sprayed chrysotile asbestos and mineral wool in the return air plenum, sampled in 1977 and 1982, were 0.0002 f/mL and 5.5 s/L. In another high-rise building, the average concentrations were 0.0065 f/mL and 48.4 s/L. The average concentration in the two buildings was thus 0.0034 f/mL (27.0 s/L). The sample with the highest value (0.042 f/mL) was taken in the 55-floor building while cable installation was in progress, with office workers working in the vicinity (Chatfield 1991, personal communication). If this single sample were to be excluded from the calculations, the average concentration in the two buildings would change to 0.0001 f/mL (7.6 s/L). Four outdoor samples taken at these two sites yielded no asbestos fibers.

Table A1-2. Average Building Airborne Asbestos Concentrations in Ontario Office and School Buildings Measured by Transmission Electron Microscopy[a]

Sample Site	No. of Samples	Volume of Air Analyzed (mL)	No. of Fibers > 5 µm Long	Concentration (f/mL)	No. of Structures All Sizes	Concentration (s/L)
Office buildings						
44-Floor office building	28	9,746	2	0.0002	54	5.5
55-Floor office building	5	1,693	11	0.0065	82	48.4
Total indoors[b]	33			0.0034		27.0
Outdoors	4	322	0	< 0.003	0	< 3.1
Schools						
High school	6	2,514	1	0.0004	138	54.9
Middle school	3	1,452	2	0.0014	37	25.5
Secondary school	5	1,884	0	< 0.0005	7	3.7
Total indoors[b]	14			0.0006		28.0
Outdoors	1	625	0	< 0.0016	0	< 1.6
Colleges						
College	4	1,952	1	0.0005	55	28.2
College	3	882	7	0.008	51	57.8
Total indoors[b]	7			0.0043		43.0
Outdoors	1	294	0	< 0.0034	5	17.0

[a] Data from Chatfield (1986).

[b] Concentrations represent the direct means of the individual building means. Building means reported as less than the analytical sensitivity are counted as zero.

Airborne asbestos concentrations in two college buildings were measured, and the combined averages were 0.0043 f/mL for fibers longer than 5 μm and 43.0 s/L for all asbestos structures. One of the samples, described in the original report as having been taken in a "mechanical room" but later described by the author as being taken in a janitorial closet (Chatfield 1991, personal communication) had a concentration of 0.02 f/mL; excluding this one sample would reduce the average for the two college buildings to 0.0011 f/mL. Sampling in three schools yielded averages of 0.0006 f/mL and 28.0 s/L. Relatively high levels of fine chrysotile fibers were found in some areas in the schools and colleges, for which the author could find no obvious explanation. No fibers of any size were found in an outdoor sample taken at a school. In the one outdoor sample taken at a college, 5 fibers were found (for a concentration of 17 s/L), but none of them were longer than 5 μm.

A1.2.3 United Kingdom Buildings

For the Literature Review Panel's report, Burdett reviewed the measurements in United Kingdom (U.K.) buildings studied by Burdett and Jaffrey (1986). The purpose of this review was to recalculate the average concentrations of asbestos for each building, based on the actual number of fibers counted, rather than the limit of quantification of a count of four fibers. The number of samples and the volume of air analyzed varied from site to site, but in general approximately 10 liters of air were analyzed at each site, except for buildings with warm-air heaters. The resulting analytical sensitivities were about 0.0001 f/mL for the 100 grid openings examined at a magnification of 1,000 for fibers longer than 5 μm, and 1 s/L for the 10 grid openings examined at a magnification of 17,000 for all asbestos fibers.

The four mutually exclusive categories of sites from the published paper are retained: residential and nonresidential buildings containing asbestos, buildings with warm-air heaters and buildings without asbestos. In addition, one new category has been created from among the residential and nonresidential buildings containing asbestos: buildings with sprayed or trowel-applied asbestos. Outdoor results by site are also given. Details on the 43 individual sites are in the original publication.

A1.2.3.1 Twelve Nonresidential Buildings Containing Asbestos

Fifty fibers longer than 5 μm were found in 101 indoor air samples taken in 12 buildings, with a building average concentration of 0.00032 f/mL (Table A1-3). Just over half (26) the fibers were from site 7, and 15 of these fibers were in a single sample from a school darkroom with a damaged cementitious sprayed ceiling and little ventilation. All other sites had counts of 0 to 6 fibers, which have limited statistical significance. The average concentration for nonschool buildings (that is, excluding sites 7 to 10) was 0.00023 f/mL, and for school buildings was 0.0005 f/mL. The types of fibers longer than 5 μm found were in agreement with the known asbestos-containing material (ACM) types in the buildings, except at site 4, where a single crocidolite fiber was found. There were 33 chrysotile, 11 amosite and 6 crocidolite fibers longer than 5 μm found; as mentioned above, 26 chrysotile fibers were from one site (site 7).

The average concentrations for all sizes of asbestos fibers was 8.2 s/L (5.6 s/L excluding schools). The higher level in schools alone (13.2 s/L) was again influenced by site 7. Site 4, a shopping center with delaminated sprayed amosite in the return air plenum, had increased levels of chrysotile fibrils and clusters. The 10 remaining sites had counts of 0 to 7 fibers of all sizes, and again the types of asbestos detected in sampling were consistent with the types of ACM present, with the exception of chrysotile which was found at all but two of the sites. In total 106 chrysotile, 6 amosite and 7 crocidolite structures were found, but 80 of the chrysotile fibers were associated with sites 4 and 7. The average concentration

of all sizes of asbestos fibers was 25 times higher than the counts of fibers longer than 5 μm (that is, about 4 percent of the fibers were longer than 5 μm), which is in close agreement with size distribution measurements of chrysotile asbestos in industry (Berman and Chatfield 1989; Rood and Scott 1990).

Table A1-3. Airborne Asbestos Concentrations in the United Kingdom: Nonresidential Buildings Containing Asbestos[a]

	Fibers Longer than 5 μm				All Sizes			
Site No.	No. of Samples	No. of Asbestos (Non-asbestos) Fibers[b]	Volume of Air Analyzed (mL)	Concentration (f/mL)	No. of Samples	No. of Asbestos Fibers[b]	Volume of Air Analyzed (mL)	Concentration (s/L)
1	3	1C (3)	7,181	0.0001	3	4C	457	9
2	4	5K (10)	9,888	0.0005	4	7K	989	7
3	6	2C (58)	11,730	0.0002	5	7C	1,173	6
4	12	1K (175)	33,411	0.00003	10	25C +1A	2,463	10.6
5	16	1A (363)	21,707	0.00005	16	2C	4,156	0.5
6	26	4A (142)	49,272	0.00008	26	0	6,260	< 0.16
7	9	26C (98)	15,012	0.0017	7	2A+ 55C	1,263	45
8	6	0 (106)	12,297	< 0.00008	5	3C	596	5
9	5	2C +1A (84)	12,651	0.0002	5	1C	795	1
10	4	1C (81)	8,074	0.0001	4	2C	807	2
11	5	0 (1559)	9,656	< 0.0001	5	4C	1,212	3
12	5	1C+5A (95)	7,030	0.0009	5	3C +3A	703	9
Total[c]	101			0.00032	96			8.2

[a] Data from Burdett and Jaffrey (1986).

[b] C = chrysotile; A = amosite; K = crocidolite.

[c] Concentrations represent the direct means of the individual building means. Building means reported as less than the analytical sensitivity are counted as zero.

Fifteen outdoor samples (Table A1-7) taken simultaneously with the indoor samples yielded two amosite and one crocidolite fibers, with an average concentration of 0.00007 f/mL, showing that levels were significantly higher inside buildings. Six chrysotile and one amosite structures were found for all sizes of fibers with an average of 1.8 s/L, 4.5 times lower than the average indoor results from all buildings and 7.3 times lower than in schools.

A1.2.3.2 Residential Buildings Containing Asbestos

Two buildings with trowel-applied amosite and chrysotile coatings and one with a chrysotile based textured finish were investigated (Table A1-4). The average for all three sites (36 samples) was 0.0004 f/mL. Both of the sites with trowel-applied asbestos gave significant fiber counts. The average concentration of all fibers was 6.4 s/L. One outdoor sample (taken in a partially covered corridor with trowel applied asbestos) yielded 4 amosite fibers at site 15, which gave a concentration of 0.001 f/mL (see Table A1-7). There were no fibers longer than 5 μm found in the other outdoor sample, taken at site 14.

Table A1-4. Airborne Asbestos Concentrations in the United Kingdom: Residential Buildings Containing Asbestos[a]

	Fibers Longer than 5 μm				All Sizes			
Site No.	No. of Samples	No. of Asbestos (Non-asbestos) Fibers[b]	Volume of Air Analyzed (mL)	Concentration (f/mL)	No. of Samples	No. of Asbestos Fibers[b]	Volume of Air Analyzed (mL)	Concentration (s/L)
13	5	0 (25)	31,104	<0.00003	5	8C	3,101	2.6
14	15	4C+7A (260)	26,436	0.0004	3	3A	505	5.9
15	16	6C +14A (148)	30,075	0.0007	12	14C +11(A+K)	2,349	10.6
Total[c]	36			0.0004	20			6.4

[a] Data from Burdett and Jaffrey (1986).

[b] C = chrysotile; A = amosite; K = crocidolite.

[c] Concentrations represent the direct means of the individual building means. Building means reported as less than the analytical sensitivity are counted as zero.

A1.2.3.3 Buildings with Warm Air Heaters Containing Asbestos

Data from 24 individual sites are listed in Table A1-5. The averages for all warm-air heater sites were 0.00021 f/mL and 1.1 s/L. The highest concentrations were 0.0011 f/mL and 7 s/L. Outdoor concentrations measured at six of these sites (Table A1-7) averaged 0.0 f/mL (no fibers detected) and 1.7 s/L. No asbestos was detected from nine field blanks.

A1.2.3.4 Buildings Without Asbestos

Four buildings, two of them with warm-air heaters that (according to the manufacturers) did not contain asbestos, were investigated (Table A1-6). The group averages were 0.00018 f/mL (2 chrysotile fibers found at one site) and 0.3 s/L (one chrysotile fiber found).

Table A1-5. Airborne Asbestos Concentrations in the United Kingdom (U.K.): Buildings with Warm-Air Heaters Containing Asbestos[a]

	Fibers Longer than 5 μm				All Sizes			
Site No.	No. of Samples	No. of Asbestos (Non-asbestos) Fibers[b]	Volume of Air Analyzed (mL)	Concentration (f/mL)	No. of Samples	No. of Asbestos Fibers[b]	Volume of Air Analyzed (mL)	Concentration (s/L)
16	3	6C (60)	20,462	0.0003	2	2C	269	7
17	9	4C (24)	16,070	0.0002	3	0	399	< 2.5
18	4	0 (26)	26,345	< 0.00004	4	1C	2,636	0.4
19	5	0 (50)	39,425	< 0.000025	5	4C	3,942	1
20	4	2A+6C (10)	7,600	0.0011	4	1C	760	1
21	8	5C (94)	43,544	0.00011	8	12C	4,347	2.8
22	2	1C (41)	8,408	0.00012	2	0	841	< 1
23	2	1A (43)	7,584	0.00013	2	1C	758	1
24	3	0 (24)	3,213	< 0.0003	2	0	414	< 2
25	2	1A (19)	40,623	0.00002	2	0	3,982	< 0.3
26	2	0 (8)	2,874	< 0.0003	2	0	288	< 0.4
27	5	2A+1C (22)	6,667	0.0004	5	0	668	< 1.5
28	3	0 (22)	4,263	< 0.0002	3	0	426	< 2
29	2	0 (16)	2,794	< 0.0003	2	0	240	< 4
30	2	4A (24)	3,548	0.0011	2	1C	354	3
31	2	1A (28)	3,930	0.0003	2	1A	392	3
32	4	1A (102)	7,720	0.0001	4	1A+1C	760	3
33	3	3A (34)	5,661	0.0005	3	0	567	< 2
34	2	1A (120)	3,804	0.0003	2	0	380	< 3
35	2	0 (23)	3,710	< 0.0003	2	0	372	< 3
36	2	0 (25)	3,758	< 0.0003	2	2C	378	5
37	2	0 (68)	3,726	< 0.0003	2	0	372	< 3
38	2	0 (33)	3,710	< 0.0003	2	0	370	< 3
39	4	2A (135)	5,334	0.0004	4	0	1,118	< 1
Total[c]	79			0.00021	71			1.1

[a] Data from Burdett and Jaffrey (1986).

[b] C = chrysotile; A = amosite; K = crocidolite.

[c] Concentrations represent the direct means of the individual building means. Building means reported as less than the analytical sensitivity are counted as zero.

Table A1-6. Airborne Asbestos Concentrations in the United Kingdom: Buildings Without Asbestos[a]

	Fibers Longer than 5 µm				All Sizes			
Site No.	No. of Samples	No. of Asbestos (Non-asbestos) Fibers[b]	Volume of Air Analyzed (mL)	Concentration (f/mL)	No. of Samples	No. of Asbestos Fibers[b]	Volume of Air Analyzed (mL)	Concentration (s/L)
40	8	0 (64)	14,194	< 0.00007	8	0	1,227	< 0.8
41	4	0	7,760	< 0.0001	4	1C	776	1.3
42	3	0 (18)	4,287	< 0.0002	3	0	429	< 2.3
43	2	2C (26)	2,842	0.0007	2	0	284	< 3.5
Total[c]	17			0.00018	17			0.3

[a] Data from Burdett and Jaffrey (1986).

[b] C = chrysotile; A = amosite; K = crocidolite.

[c] Concentrations represent the direct means of the individual building means. Building means reported as less than the analytical sensitivity are counted as zero.

A1.2.3.5 Buildings with Sprayed or Trowel-Applied Asbestos Coatings

These buildings represent a subgroup of 11 buildings from among the 15 buildings discussed above under sections A1.2.3.1 and A1.2.3.2. The fiber data for this group of buildings are given in Tables A1-3 and A1-4 (building numbers 1, 3, 4, 5, 6, 7, 9, 10, 12, 14, 15). The indoor average of 0.00040 f/mL for fibers longer than 5 µm was approximately four times the average outdoor level for the whole study, and the average of 9.1 s/L for all structures was five times the outdoor study average. Four of the 11 sites exceeded the limit of quantification of four fibers longer than 5 µm.

A1.2.3.6 Nonasbestos Fibers

Nonasbestos fibers dominated the fiber types present. A comparison of the asbestos and nonasbestos fiber concentrations (and number of fibers counted) is presented in Table A1-8 for each of the site categories. Average concentrations of nonasbestos fibers were as high as 0.0198 f/mL for nonresidential buildings, with calcium sulphate (gypsum) and calcium silicate fibers being the most common fibers present. Ratios of nonasbestos to asbestos fibers as high as 62:1 were found inside buildings with asbestos, but this value was influenced by one site. The ratio for outdoor samples was 63:1.

A1.2.3.7 Outdoor and Blank Results

Table A1-7 summarizes the outdoor results for the four main site categories. The levels were reasonably consistent throughout the survey, except at site 15, where the ACM was present in the partially covered entrance corridor. Excluding this site as a representative outdoor concentration results in a reduction of the study average from 0.00009 to 0.00004 f/mL. It is interesting that no chrysotile fibers longer than 5 µm were present in the outdoor samples, and that amphibole fibers were usually due to a nearby source (Burdett, personal communication 1991). Blank sample results were reviewed; there was no evidence that filter or laboratory contamination exceeded the analytical sensitivity.

Table A1-7. Airborne Asbestos Concentrations in United Kingdom: Outdoor Measurements[a]

	Fibers Longer than 5 μm				All Sizes			
Site No.	No. of Samples	No. of Asbestos (Non-asbestos) Fibers[b]	Volume of Air Analyzed (mL)	Concentration (f/mL)	No. of Samples	No. of Asbestos Fibers[b]	Volume of Air Analyzed (mL)	Concentration (s/L)
Nonresidential buildings containing asbestos								
2	2	0 (0)	1,030	< 0.001	1	0	206	< 4.9
3	2	1K (12)	5,260	0.0002	2	1C	683	1.5
4	1	0 (43)	3,262	< 0.0003	1	0	326	< 3.1
5	3	0 (48)	7,873	< 0.0001	3	0	694	<1.4
6	3	0 (45)	13,368	< 0.00007	3	0	1,336	<0.7
7	1	0 (4)	3,947	< 0.0003	—	—	—	—
9	1	0 (26)	4,147	< 0.0002	1	3C	415	7.2
10	1	2A (94)	4,905	0.0004	1	2C+1A	380	7.9
11	1	0 (10)	2,453	< 0.0004	1	0	245	< 4.1
Total[c]	15			0.00007	13			1.8
Residential buildings containing asbestos								
14	1	0 (7)	2,536	< 0.0004				
15	1	4A (34)	3,895	0.0010				
Total[c]	2	4A (41)	6,431	0.0005				
Buildings with warm air heaters								
16	3	0 (101)	20,822	< 0.00005	1	1C	505	2
17	2	0 (32)	6,315	< 0.0002	2	0	1,138	< 0.9
22	1	0 (2)	1,308	< 0.0008	1	0	131	< 7.6
23	1	0 (28)	2,895	< 0.0004	1	0	289	< 3.5
24	1	0 (3)	3,000	< 0.0004	1	0	300	< 3.3
25	1	0 (16)	1,595	< 0.0007	1	2C	240	8
Total[c]	9			< 0.00003	7			1.7
Building with no asbestos								
40	2	0 (17)	4,196	< 0.0003	—	—	—	
Study average[c]								
	28			0.00009	20			1.9

[a] Data from Burdett and Jaffrey (1986).
[b] C = chrysotile; A = amosite; K = crocidolite.
[c] Concentrations represent the direct means of the individual building means. Building means reported as less than the analytical sensitivity are counted as zero.

Table A1-8. Comparison of Asbestos to Nonasbestos Fibers Longer than 5 µm in U.K. Buildings[a]

Building Category	Asbestos Fiber (f/mL) (No.)	Nonasbestos Fiber Concentration (f/mL) (No.)	Ratio
Nonresidential	0.00032 (50)	0.0198 (2,777)	62:1
Nonresidential[b]	0.00032 (50)	0.0070 (1,218)	22:1
Residential	0.0004 (31)	0.0052 (433)	13:1
Warm-air heaters	0.00021 (41)	0.0073 (1,051)	35:1
No asbestos	0.00018 (2)	0.0060 (108)	33:1
Ambient outdoor	0.00009 (3)	0.0057 (524)	63:1

[a] Data from Burdett and Jaffrey (1986).

[b] One nonasbestos sample had very high contamination with gypsum and has been removed from the analysis.

A1.2.4 U.K. Residential Apartments Containing Amosite Insulation Board

This study, published by Gazzi and Crockford (1987), used similar methods to Burdett and Jaffrey (1986) but chose buildings to sample from among a well-defined population of 1400 residential apartments in the United Kingdom. The apartments had amosite-containing insulation board in airing cupboards (heated cupboards in which linen is stored to prevent it from becoming damp) and over a service duct inside the apartment. The panels on the floor of the airing cupboard formed a return air plenum for the warm-air heating. Single samples were collected in 25 occupied apartments. Approximately 4 m^3 of air were sampled in each one, using a 25 mm to 0.8 µm pore size Millipore filter, for either an 8-hour period in the day or a 16-hour period at night, at rates of 10 and 5 L/minute, respectively.

Nineteen apartments were at or below the analytical sensitivity (one fiber counted), and the two highest values found were 0.0019 and 0.0025 f/mL. A total of 34.5 fibers longer than 5 µm were found, 24 of them amosite and 10 chrysotile fibers. The survey averages, calculated by the authors, were 0.00044 f/mL in the daytime and 0.00020 f/mL at night, with a combined average of 0.00028 f/mL. No asbestos fibers were found in five control apartments, at a level of less than 0.00014 f/mL. The authors found that the measurements just failed to reach the commonly accepted level of statistical significance, but felt that the percentage of amosite fibers found was indicative of releases above the background and would have been significant had the study population been larger. No measurements of all sizes of asbestos structures were made.

Average asbestos concentrations for fibers longer than 5 µm in each of the 25 apartments were not reported by Gazzi and Crockford. However, the authors did report the frequency distribution of the number of fibers longer than 5 µm counted in the various apartments. From this information, and the fact that 0.436 mm^2 was examined in a total sampled filter area of 385 mm^2 with a sample volume of 4 m^3 (yielding a volume examined of 4.5 liters), it is possible to estimate the frequency distribution of air concentrations in individual buildings. These data (Table A1-9) have been used to compute summary statistics reported elsewhere in this report. Note that the mean concentration, computed as the building-

weighted mean of the concentrations reported in Table A1-9, is 0.0003 f/mL, which is slightly higher than the mean (0.00028 f/mL) reported by the authors.

Table A1-9. Frequency Distribution of Airborne Asbestos Concentrations in 25 U.K. Residential Apartments with Amosite-Containing Board[a]

No. of Apartments	No. of Asbestos Fibers (> 5 μm)	Estimated Asbestos Concentrations (> 5 μm)
13	0	0
1	0.5	0.0001
5	1	0.0002
1	1.5	0.0003
2	2	0.0004
1	3.5	0.0008
1	8.5	0.0019
1	11.5	0.0025

[a] Data from Gazzi and Crockford (1987).

A1.2.5 U.S. Single-Family Homes

A study of U.S. single family homes with ACM, conducted by the Consumer Products Safety Commission (CPSC 1987), has not been published except as an internal memorandum, but is nevertheless a valuable data set, and the results have been widely discussed. The study did not use a random sampling scheme; sites were chosen on the basis of consumer complaints. The survey was carried out at three locations: San Francisco, Cleveland, and Philadelphia. Fifteen houses were sampled at each of these locations, generally with one sample at each house collected in close proximity to the asbestos, one sample collected in the main room where there was the highest level of activity and one sample collected outdoors. Approximately 3,000 liters of air were collected over three 8-hour, or two 12-hour days with the aim of sampling only during periods of activity. Samples were collected on Nuclepore filters for transmission electron microscopy (TEM) analysis and Millipore filters for phase contrast microscopic (PCM) analysis. The Nuclepore filters were carbon coated at a local facility before shipping to the Illinois Inhalation Technology Research Institute, where presumably Yamate Level II analysis was carried out (Yamate et al. 1984). All sizes of asbestos structures and fibers longer than 5 μm were evaluated. Nine buildings had asbestos throughout the house, so in these cases both indoor samples were classified as being near the source. Much of the asbestos was present in the form of thermal insulation on heating systems in the basements.

The results are summarized in Tables A1-10, A1-11, and A1-12 for all sizes of asbestos fibers; the averages for each city were calculated. Unfortunately, the numbers and types of fibers identified and volume of air sampled are not given in the CPSC summary, but relatively few structures were counted and the city averages can be calculated with reasonable accuracy. The results showed that there were no significant differences

according to whether samples were taken inside or outside the houses, type of ACM present, or city taken from. For all asbestos structures, the city averages ranged between 3.72 and 6.2 s/L (both of which are outdoor averages), and building averages between 0 and 17 s/L. The approximate study average (all cities) was 4.9 s/L indoors near sources of asbestos, 5.0 s/L in the main area of activity, and 4.9 s/L outdoors.

Table A1-10. Airborne Asbestos Concentrations in 15 Single-Family Houses in San Francisco with Sprayed Cementitious ACM on Ceilings or ACM in Heating Ducts[a,b]

Site No.[c]	Near Source (s/L)	Main Activity (s/L)	Outdoor (s/L)	Blank (s/L)
1	0	2.1	4.2	
2	2.4	5.9	0	
3	1.8	3.5	1.8	
4	1.8	1.8	1.9	
5	4.2	10.9	2.1	
6	0	0	9.0	
7	4.3	4.8	18.0	
8	10.1/3.8[d]	—	9.8	
9	3.6/1.8[d]	—	3.7	
10	6.0	5.9	3.8	
11	0/5.6	—	0	
12	17.0/7.3[d]	—	11.0	
13	5.6	3.7	0	
14	5.6	1.8	1.9	
15	13.0	1.9	3.4	
Total number of samples	19	11	15	4
Mean concentration	4.94	3.84	4.71	0

[a] All sizes.

[b] Data from Consumer Products Safety Commission (CPSC 1987).

[c] Site numbers are not the same as those in the original report.

[d] Both indoor samples taken near source of asbestos.

Table A1-11. Airborne Asbestos Concentrations in 15 Single-Family Houses in Cleveland with Preformed Asbestos Insulation or Asbestos Paper on Pipes in the Basement[a,b]

Site No.[c]	Near Source (s/L)	Main Activity (s/L)	Outdoor (s/L)	Blank (s/L)
1	4.2	4.0	5.9	
2	6.4	4.0	10.5	
3	4.3	6.5	5.9	
4	6.5	8.3	4.2	
5	2.1	6.5	2.1	
6	6.6	13.0	3.4	
7	3.9	3.8	0	
8	2.4	0	4.2	
9	6.1	4.3	2.1	
10	10.0	8.4	12.0	
11	5.2	3.6	1.9	
12	8.5	4.1	0	
13	3.9	3.8	5.9	
14	7.3	9.0	17.0	
15	10.9/0[d]	—	18.0	
Total number of samples	16	14	15	3
Mean concentration	5.5	5.7	6.2	0

[a] All sizes.

[b] Data from Consumer Products Safety Commission (CPSC 1987).

[c] Site numbers are not the same as those in the original report.

[d] Both indoor samples taken near source of asbestos.

Results for asbestos fibers longer than 5 μm are summarized in Table A1-13. Only four such fibers were counted in the whole survey, and all were single fibers at different indoor sites that resulted in individual sample concentrations ranging from 0.001 to 0.004 f/mL. This range shows that different volumes of air must have been collected on the samples because all were based on a count of one fiber. The average of the buildings in San Francisco, Cleveland, and Philadelphia were ND, 0.00023 f/mL, and 0.00007 f/mL, respectively. Averaging over all 45 buildings, the mean was 0.0001 f/mL. No long fibers were detected in the outdoor samples.

The values throughout the survey are close to contamination levels for Nuclepore filters (EPA 1986), but the nine blanks analyzed in this survey did not yield a single asbestos structure, suggesting that the asbestos fibers identified were airborne.

Table A1-12. Airborne Asbestos Concentrations in 15 Single-Family Houses in Philadephia with Asbestos Thermal Insulation in Basement and Other Asbestos-Containing Materials[a,b]

Site No.[c]	Near Source (s/L)	Main Activity (s/L)	Outdoor (s/L)	Blank (s/L)
1	0	1.6	0	
2	6.4	1.9	4.1	
3	4.2	4.3	9.7	
4	14.0	20.0	4.0	
5	4.6	5.2	3.6	
6	8.6	6.2	4.0	
7	0	0	5.6	
8	—	4.0	5.2	
9	3.7	7.8	7.4	
10	0	0	0	
11	7.0	8.1	1.8	
12	4.4	0	2.0	
13	4.4/0[d]	—	0	
14	2.3	10.9	2.1	
15	4.1	2.0	6.3	
Total number of samples	15	14	15	4
Mean concentration	4.25	5.14	3.72	0

[a] All sizes.

[b] Data from Consumer Products Safety Commission (CPSC 1987).

[c] Site numbers are not the same as those in the original report.

[d] Both indoor samples taken near source of asbestos.

Table A1-13. Airborne Asbestos Concentrations in Single-Family Houses, by City[a,b]

Site	No. of Houses	Indoors			Outdoors	
		No. of Samples	No. of Fibers Longer than 5 µm	Concentration (f/mL)	No. of Samples	No. of Fibers Longer than 5 µm
San Francisco	15	30	0	ND	15	0
Cleveland	15	30	3	0.00023	15	0
Philadelphia	15	29	1	0.00007	15	0
Average		89	4	0.0001	45	0

[a] Fibers longer than 5 µm.

[b] Data from Consumer Products Safety Commission (1987).

A1.2.6 EPA Study of Public Buildings

An EPA study of 49 U.S. General Services Administration buildings (often referred to as the GSA study) has been reported by a number of authors (Hatfield et al. 1988; Crump and Farrar 1989; Chesson et al. 1990).

Results for all asbestos fibers were 0.73 s/L for the buildings with damaged ACM, 0.59 s/L in buildings with undamaged ACM, and 0.99 s/L in the buildings with no asbestos. There is some discussion of whether there is a statistically significant increase inside buildings with damaged ACM, but of all the studies this one provides the weakest evidence for any increase in airborne levels due to the presence of ACM in a building.

Data from the GSA study were reanalyzed to derive building averages for structures longer than 5 µm. Structure counts and sample volumes were obtained from staff at EPA and RJ Lee Group, the laboratory that originally analyzed the filters. A total of seven structures longer than 5 µm were observed in the study, on seven separate samples. Five of these samples were collected inside buildings with ACM; the two remaining samples were collected outdoors. For each of the five buildings in which a structure longer than 5 µm was observed, the total volume (summed over all indoor samples in that building) of air examined in the TEM analysis was calculated (Table A1-14). Since only one long structure was detected in each of the five buildings, the reciprocal of the sampled air volume gives the average concentration in the building (Table A1-14). These values were then used to compute average concentrations of fibers longer than 5 µm in the various categories of buildings in the GSA study, as well as outdoors (Table A1-15). Note that the numbers reported here are different than those reported by Crump and Farrar (1989), who reported concentrations for fibers greater than or equal to 5 µm (Crump 1991, personal communication).

Corn and associates (1991) recently published a study of 71 school buildings sampled for litigation purposes. The sites were selected from a database of 2,000 samples, primarily because they had at least 5 indoor and 1 outdoor sample taken. Some additional analysis of 130 samples was required to meet this criterion for all but three sites. The average sampling volume was 1,900 liters with 90 percent between 1,267 and 2,500 liters. Sampling was conducted during normal workday occupation over a two-day period at flow rates of 2 to 3 L/minute.

Table A1-14. Indoor Airborne Asbestos Concentrations of Fibers Longer than 5 μm in U.S. General Services Administration (GSA) Buildings

Building No.[a]	Condition of ACM	Total Volume Examined by TEM (mL)	No. of Structures Longer than 5 μm	Building Average Concentrations (f/mL)
8	Undamaged	3,600.8	1	0.00028
16	Damaged	2,797.4	1	0.00036
23	Damaged	1,780.5	1	0.00056
30	Damaged	2,007.3	1	0.00050
37	Damaged	2,829.3	1	0.00035

[a] Building numbers are those given in Appendix G of Hatfield and associates (1988).

Table A1-15. Indoor Airborne Asbestos Concentrations of Fibers Longer than 5 μm in U.S. General Services Administration (GSA) Buildings, by Building Category

Building Category	No. of Buildings (Samples)	No. of Structures Longer than 5 μm	Building Average Concentrations (f/mL)
No ACM	6	0	ND[a]
Undamaged ACM	6	1	0.00005
Damaged ACM	37	4	0.00005
Outdoors	(48)	2	0.00010

[a] ND = not detected.

A1.2.7 U.S. School Buildings

Data were analyzed from a total of 473 air samples (328 indoor, 51 personal, and 94 outdoor samples) taken in the 71 schools. The average concentration of fibers longer than 5 μm across all the schools was 0.00024 f/mL. Personal samples gave averages of 0.00012 f/mL and 11 s/L. The highest concentrations were found in gymnasiums (16 samples in 15 schools) with averages of 0.00060 f/mL and 27 s/L, closely followed by classrooms, which presumably reflect the level of activity and resuspension of surface dust. The maximum building average was 0.0023 f/mL, and the 95th percentile of building averages was 0.0014 f/mL. The highest single sample was 0.012 f/mL. This data set included samples from Houston schools which were first monitored in the study by Constant and colleagues (1983) for mass and were reported to have significant levels of airborne asbestos.

The authors found a significant difference between the average indoor and outdoor concentrations of asbestos and between the personal and outdoor samples. No significant difference was found between area and personal samples, or for several other factors (such

as presence, accessibility and condition of ACM in sampled areas, and where sweeping was carried out), except for the state in which the school was located.

One important finding of this study is that the measurement of both asbestos mass and fibers longer than 5 μm allows a relevant conversion factor to be calculated and applied to the mass levels reported in previous studies. For the average of 328 indoor samples a concentration of 0.00017 f/mL was equivalent to 4.3 ng/m^3 (1 f/mL = 25,294 ng/m^3), which is similar to the conversion factor of 1 f/mL = 30,000 ng/m^3 used in the National Research Council review (NRC 1984).

The problem still remains as to why there are increased airborne levels in schools. The degree of pedestrian traffic causing resuspension of settled dust and abrasion of any ACM that may be on the floor appears to be the most likely explanation at present.

A1.2.8 Minnesota University Buildings and Maryland Public Buildings

The study averages were reported by Crump (1990), but no other documentation was available for review. The buildings, however, do form part of the database of results summarized for this report (see Table 4-12).

A1.2.9 Twelve Swiss Buildings

The only study to use indirect preparation methods was that of Guillemin and coworkers (1989). Air samples were collected during normal building daytime activity over periods of one to four days. The analytical sensitivity varied from 0.00006 to 0.008 f/mL. Results for asbestos fibers longer than 5 μm ranged from ND to 0.0048 f/mL in nonschool buildings, and 0.00012 to 0.00859 f/mL in school buildings. Concentrations of all asbestos fibers were 15.6 to 54.3 s/L in nonschool buildings, and 229 and 1,599 s/L in 2 school buildings; these numbers are higher than those reported in other studies reviewed here, probably due to the use of the indirect preparation method. This study was excluded from Table 4-10 because of the use of the indirect method of sample preparation.

A1.3 Discussion

One of the main features of the data discussed here is that many of the measurements are below the analytical sensitivity; that is, no asbestos structures or fibers are detected in the TEM analysis. This has several important implications for the interpretation of the data.

When operating at the analytical sensitivity, there is no way of knowing whether the presence of an asbestos fiber or structure is due to the collection of an airborne fiber, or filter or laboratory contamination. The analysis of field and laboratory blanks parallel to the exposed filters provides each study with an idea of the contamination levels, but these blank analyses are fewer in number, and therefore restrict interpretation of the data. For example, the CPSC (1987) study reported no asbestos structures in the 10 blanks, and found that only 20 of the 134 airborne samples were zero, giving some reassurance that the structures found were airborne asbestos structures. However, only 4 asbestos fibers longer than 5 μm were seen in these 134 airborne samples, which makes it impossible to say whether these fibers represent an airborne concentration or contamination.

Data analysis is also affected by the large number of samples below the limit of detection. Ideally, the data should be analyzed for their central tendency and the shape of the distribution. This distribution can be expressed as the arithmetic mean, median or

geometric mean, with the range, standard deviation, upper quartile and 95th percentile of data points identified to show the spread of data. However, the median is often zero, and the same can happen for the upper quartile when using individual sample data. In an effort to address this problem, the Panel pooled samples to calculate building averages with better analytical sensitivity. It is also possible to improve analytical sensitivity by analyzing more of the sample deposit, but this is both expensive and time consuming, and often multi-point averages are preferable for building surveys if the ACM is present over a large area.

Again, the rationale behind the averaging of groups of buildings is to provide data above the limit of detection. In some situations this seems justified, as in the case when a homogeneous set of buildings with similar types and/or uses of ACMs has been identified (for example, Gazzi and Crockford 1987). The EPA survey of public buildings, in particular, set a trend for grouping buildings by use rather than any other criteria. Although this may represent the actual experience of the EPA in not being able to correlate algorithm or other assessment techniques with air measurements, it does remove all possibility that some patterns will emerge as the database grows. There is also a concern that by averaging results across a large number of dissimilar buildings to achieve an order of magnitude reduction in the sensitivity, the buildings which have higher airborne concentrations (between 0.0001 and 0.001 f/mL) are not detected and are lost in the averaging process.

A1.4 References

Berman DW, Chatfield EJ. 1989. Interim Superfund Method for the Determination of Asbestos in Ambient Air. Part 2: Technical background document. EPA-68-01-7290. U.S. Environmental Protection Agency, Washington, DC.

Burdett GJ, Jaffrey SAMT. 1986. Airborne asbestos concentrations in buildings. Ann Occup Hyg 30:185–189.

Chatfield EJ. 1986. Airborne asbestos levels in Canadian public buildings. In: Proceedings: Asbestos Fibers Measurements in Building Atmospheres, pp. 177–207. Ontario Research Foundation, Mississauga, Ontario, Canada.

Chesson J, Rench J, Schultz B, Milne K. 1989. Interpretation of Airborne Asbestos Measurements, pp. 1–45. Draft report. Chesson Consulting, Washington, DC. (In press).

Chesson J, Hatfield J, Schultz B, Dutrow E, Blake J. 1990. Airborne asbestos in public buildings. Environ Res 51:100–107.

Constant PC, Bergman FJ, Atkinson GR, Rose DR, Watts DL, Logue EE, Hartwell TD, Price BP, Ogden JS. 1983. Airborne Asbestos Levels in Schools. EPA-560/5-83-003, June 1983. Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC.

Corn M, Crump K, Farrar DB, Lee RJ, McFee DR. 1991. Airborne concentrations of asbestos in 71 school buildings. Reg Toxicol Pharmacol 13:99–114.

Consumer Products Safety Commission, U.S. (CPSC). 1987. Report on the First Round of Air Sampling of Asbestos in Home Study. Memorandum by AM Rock. U.S. Consumer Products Safety Commission, Washington, DC.

Crump KS. 1990. Letter. Science 248:799.

Crump KS, Farrar DB. 1989. Statistical analysis of data on airborne asbestos levels collected in an EPA survey of public buildings. Reg Toxicol Pharmacol 10:51–62.

Environmental Protection Agency, U.S. (EPA) 1986. Filter Blank Contamination in Asbestos Abatement Monitoring Procedures. Proceedings of a peer review workshop. EPA-68-03-3264. Water Engineering Research Laboratory, Cincinnati, OH.

Gazzi D, Crockford GW. 1987. Indoor asbestos levels on a housing estate: Determined by TEM. Ann Occup Hyg 31(4A):429–439.

Guillemin MP, Madelaine P, Litzistorf G, Buffat P, Iselin F. 1989. Asbestos in buildings. Aerosol Sci Tech 11:221–243.

Hatfield J, Ogden J, Stockrahm J, Leczynski B, Price B, Chesson J, Russell J, Ford P, Thomas J, Fitzgerald J, Roat R, Lee R, Van Orden D, Dunmyre G, Constant P, McHugh J. 1988. Assessing Asbestos Exposure in Public Buildings. EPA-560/5-88-002, May 1988. U.S. Environmental Protection Agency, Washington, DC.

National Research Council (NRC). 1984. Asbestiform Fibers: Nonoccupational Health Risks. National Academy Press, Washington, DC.

Pinchin DJ. 1982. Asbestos in buildings. Study No. 8. Ontario Ministry of Government Services, Publications Services Branch, Toronto, Ontario, Canada.

Rood AP, Scott R. 1990. Size distribution of chrysotile asbestos in a friction products factory determined by transmission electron microscopy. Ann Occup Hyg 34:583–590.

Yamate G, Agarwal SC, Gibbons RD. 1984. Methodology for the Measurement of Airborne Asbestos by Electron Microscopy. Draft report. Environmental Monitoring Systems Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC.

Appendix 2

Nonmalignant Asbestos-Related Pleural Conditions

A2.1 Nonmalignant Pleural Conditions Associated with Asbestos Exposure

Benign and malignant conditions of the pleura can result from inhalation of asbestos fibers (Craighead and Mossman 1982; Churg 1983; Schwartz 1991). Malignant mesothelioma is considered in Chapter 6 of this report. Benign diseases of the pleura may be the only manifestation of exposure, and are of importance as they are likely to be the most common way in which building occupants, who are occupationally and even nonoccupationally exposed and who may be affected by asbestos exposures, are identified. The following distinct diseases are recognized as manifestations of asbestos exposure.

A2.1.1 Pleural Plaques

Pleural plaques are discrete hyaline fibrous lesions that involve predominantly the submesothelial layer of the parietal pleura of the costal margins, hemidiaphragms, and paraspinous regions (Meurman 1966). Plaques also occur in the pleura over the pericardium, but not usually on the remainder of the mediastinal pleura. Visceral pleural plaques may involve the interlobular fissures, but are much less common than parietal pleural plaques (Lynch et al. 1988). Pleural calcification invariably occurs within preexisting hyaline plaques and is dystrophic in nature (Gibbs 1979). The pathophysiologic mechanism of pleural plaque formation is speculative (Hillerdal 1980; Stephens et al. 1987).

A2.1.2 Diffuse Pleural Thickening

Diffuse thickening of the pleura (Stephens et al. 1987) can be from three causes. In one series (Jones et al. 1988), the following three accounted respectively for 10 to 20 percent, 10 to 30 percent, and 40 to 60 percent of the cases.

1. Extensive pleural plaques can become confluent, producing a sheet of pleural thickening.

2. Lung fibrosis can extend to the subvisceral pleural interstitium and produce diffuse visceral pleural thickening. This form of pleural thickening is often not visible on conventional chest radiographs given the presence of interstitial pulmonary fibrosis, and it may only be imaged with computed tomography (CT) (McLoud et al. 1985).

3. Benign pleural effusion due to an inflammatory pleuritis (see below) can resolve leaving an adhesive fibrothorax (McLoud et al. 1985; Hillerdal and Ozesmi 1987).

In 20 to 40 percent of cases of apparent pleural thickening, pseudo-pleural thickening, caused by extrapleural fat, mimics pleural thickening on chest radiographs and produces a false impression of diffuse pleural fibrosis. Unless strict criteria are used for defining pleural thickening and fibrosis, this normal variant can falsely increase the prevalence of described pleural thickening (Sargent et al. 1984).

A2.1.3 Pleuritis

An acute exudative pleuritis with effusion occurs in an estimated 5 percent of occupationally exposed individuals (Epler et al. 1984). The effusion can be silent or associated with symptoms, can be transient or recurrent, and unilateral or bilateral (Epler et al. 1984). The latency period, usually less than 20 years, is shorter than for most other

asbestos-related lung or pleural disorders (Epler et al. 1984). Such effusions may also result in an adhesive fibrothorax, sometimes with the development of areas of rounded atelectasis that may resemble peripheral lung tumors (Hillerdal 1989). Obliteration of the costophrenic angles is a common sequela (McLoud et al. 1985). Diffuse fibrothorax from pleuritis is readily distinguished from pleural plaques on CT and high-resolution CT (Aberle et al. 1988).

A2.1.4 Rounded Atelectasis

This term describes atelectasis of the peripheral part of the lung, the consequence of pleural adhesions and fibrosis, which in turn cause deformation of the lung including the bronchial tree, and may on occasion resemble lung cancer (Hillerdal 1989).

A2.2 Methods of Detecting Nonmalignant Pleural Disease

A2.2.1 Autopsy and Thoracotomy

The most accurate method for detecting pleural plaques is direct observation of the pleural surfaces at autopsy or thoracotomy. The prevalence of disease detected by imaging modalities should be validated by autopsy studies (Hourihane et al. 1966; Svener et al. 1986).

A2.2.2 Radiographic Imaging Techniques

Conventional chest radiographs are the most commonly used method for surveillance and detection of pleural plaques, pleural thickening, and pleural calcification. The sensitivity for detecting pleural plaques is, however, probably only 20 to 50 percent, even with modern high-kilovoltage x-ray techniques and the use of multiple projections (Svener et al. 1986). The specificity is likewise low. The interobserver and intraobserver error for detecting pleural disease is high (Bourbeau and Ernst 1988; Staples et al. 1989).

A2.2.3 Computed Tomography and High-Resolution Computed Tomography

Computed tomography and high-resolution CT are both considerably more sensitive than chest radiographs for detecting asbestos-related pleural abnormalities of all types (Fiedman et al. 1988; Gamsu et al. 1989). Although their specificity has not been investigated, it is probably high, and experience indicates that CT has greater specificity for pleural abnormalities than chest radiographs.

A2.3 Epidemiology: Distribution and Determinants in Populations

A2.3.1 Occupational Exposures

A2.3.1.1 Prevalence in Different Workforces

The prevalence rates of pleural and parenchymal diseases detected from radiographs vary considerably from workforce to workforce (Murphy et al. 1971; Rossiter et al. 1972; Weill et al. 1975, 1979; Berry et al. 1979; Irwig et al. 1979, 1984; Becklake et al. 1980a,b; Finkelstein 1982; British Occupational Hygiene Society 1983; Sepulveda and Merchant 1983; Viallat et al. 1983; Cordier et al. 1984; Baker et al. 1985; Oliver et al. 1985; Cookson et al. 1986; Lilis et al. 1986; Hilt 1987; Marcus et al. 1987; Michaels et al. 1987; Bourbeau et al. 1988, 1990; Enarson et al. 1988; Rosenstock et al. 1988; Schwartz et al. 1990a; see Table A2-1). These

depend, among other things, on the industry and process, or both; on exposure level, duration, and profile (Copes et al. 1985); and probably also on fiber type, size, and chemical composition (see footnote to Table A2-1). Table A2-1 presents data from studies of workers engaged in mining and milling (Rossiter et al. 1972; Irwig et al. 1979, 1984; Viallat et al. 1983; Cordier et al. 1984; Cookson et al. 1986; Enarson et al. 1988) and in the manufacture of asbestos products (Weill et al. 1975, 1979; Berry et al. 1979; Becklake et al. 1980a,b; Finkelstein 1982; British Occupational Hygiene Society 1983). Most of these studies were conducted in the late 1960s and 1970s, many before workplace controls had been implemented. By contrast, reports published in the 1980s have generally been on workers in occupations requiring the use or application of asbestos, in which exposure is often intermittent and to high levels of asbestos, but for which quantitative measurements are not available (Murphy et al. 1971; Sepulveda and Merchant 1983; Baker et al. 1985; Oliver et al. 1985; Lilis et al. 1986; Hilt 1987; Marcus et al. 1987; Michaels et al. 1987; Bourbeau et al. 1988, 1990; Rosenstock et al. 1988; Schwartz et al. 1990a). As a result, in such studies, the only exposure index available as an independent variable for the analysis of exposure-response relationships is either latency (time since first exposure) and/or duration of exposure, which is often self-reported rather than job records. In addition, many of these studies are based on data gathered in voluntary surveillance programs, in which participation may be under 50 percent or is not known; therefore, their results should be interpreted with caution. Nevertheless, there are some interesting trends that deserve comment.

A2.3.1.2 Relationships to Exposure

In general, the data suggest that fibrotic lesions of the pleura detected by chest radiograph tend to develop after a long latent period, usually more than 20 years after first exposure, and their prevalence is related to duration of exposure (Irwig et al. 1979, 1984; Baker et al. 1985; Michaels et al. 1987; Rosenstock et al. 1988; Bourbeau et al. 1988, 1990), and/or to latency (Murphy et al. 1971; Marcus et al. 1987) (probably a measure of residence time of fibers in the lung), and possibly to peaks of exposure (Rossiter et al. 1972; Copes et al. 1985). By contrast, fibrotic lesions of the parenchyma detected from chest radiographs may develop after relatively short periods of exposure if exposure levels are high (Gibbs and Lachance 1972; Copes et al. 1985; Becklake 1991b; Ernst and Zejda 1991). Their prevalence is related to cumulative exposure, based on job history, and is calculated as the product of exposure level and duration of exposure at that level, cumulated over time, for each job or exposure held by the worker (Gibbs and Lachance 1972).

A2.3.1.3 Ratio of Prevalence Rates of Pleural to Parenchymal Disease

Of interest is the prevalence of radiologic pleural lesions relative to that of parenchymal lesions within the same workforce (see ratio in the last column of Table A2-1). For mining and milling and for manufacturing, prevalence rates for parenchymal changes tend to be either higher than those for pleural changes (ratio greater than 1), or if the rates for pleural changes exceed those for parenchymal changes, they are not more than double. By contrast, studies of several occupations involving disturbance, use, or removal of asbestos-containing materials (ACM) show either more pleural diseases than parenchymal diseases, or close to equal frequencies. For instance, in one study of sheet metal workers (Baker et al. 1985), the pleural to parenchymal ratio was as high as 12.8. However, in other studies of sheet metal workers, lower ratios of 0.8 and 1.6 were reported (Michaels et al. 1987; Schwartz et al. 1990a). In insulation workers (Bourbeau et al. 1990) and railcar workers (Sepulveda and Merchant 1983; Oliver et al. 1985) pleural to parenchymal disease ratios were higher than one. These differences may be from intermittent exposure and also partially explained by the increased sensitivity for pleural diseases with the newer radiographic techniques that

Table A2-1. Prevalence Percent of Radiologic Abnormality in Selected Workforce-Based Studies[a]

Study and Location	Fiber Mined, Product, or Job	No. in Study	Age (years)	Exposure		Prevalence Percent		
				Years	Level	SIO[b] 1/0 or More	Pleural Change (Any)	Ratio Pleural Change to SIO
Mining and milling:								
Enarson et al. 1988 Canada	Chrysotile	63	46	14	0.7 to 88 f/mL	9.5	1.5	0.2
Viallat et al. 1983 Corsica, France	Chrysotile	133	58	16	20 to 282 f/mL	15.8	6.5	0.4
Rossiter et al. 1972 Canada	Chrysotile	6,127	35 to 65	20.2	13 mppcf[c]	7.2	12.9	1.8
Cordier et al. 1984 Canada	Chrysotile	342	45	20+	10 f/mL[d]	2.1	2.7	1.3
Irwig et al. 1979, 1984 S. Africa	Crocidolite	1,692	33	5	5.2 f/mL	7.3	7.6	1.0
Cookson et al. 1986 W. Australia	Crocidolite	280	NA[h]	~ 3[d]	~ 30 f/mL[d]	12.2[d,e]	NA[h]	NA[h]
Manufacturing processes:								
Berry et al. 1979, BOHS 1983 United Kingdom	Textiles	379	54	20.1	6.4 f/mL[d]	21.2	4.6[f]	0.2
Becklake et al. 1980[e,b] Canada	Textiles	118	42	12.6	> 2 f/mL[d]	16.2	14.6	0.9
Rossiter et al. 1972 Canada	Textiles, cement products	398	35 to 65	19.4	4.4 mppcf	7.5	10.3	1.4
Weill 1975 U.S., LA	Cement products	589	45	17.4	12.9 mppcf	8.3	10.0	1.2

Table A2-1 (Continued). Prevalence Percent of Radiologic Abnormality in Selected Workforce-Based Studies[a]

Study and Location	Fiber Mined, Product, or Job	No. in Study	Age (years)	Exposure		Prevalence Percent		
				Years	Level	SIO[b] 1/0 or More	Pleural Change (Any)	Ratio Pleural Change to SIO
Finkelstein 1982 Canada	Cement products	201	NA[h]	18+	5.8 F/mL[d]	39[g]	NA[h]	NA[h]
Use and/or removal of asbestos-containing materials:								
Hilt 1987 Norway	Maintenance of electro-chemical plant	153	63	11.6	NA[h]	20.3	12.4	0.6
Michaels et al. 1987 U.S., NY	Sheet metal workers	707	40	19.0	NA[h]	10.9	9.2	1.8
Lilis et al. 1986 U.S., NY	Insulators	1,117	All	19.1	NA[h]	11.5	17.5	1.5
Schwartz et al. 1990a U.S.	Sheet metal workers	1,211	57	32.7	NA[h]	17.0	27.3	1.6
Rosenstock et al. 1988 U.S., WA	Plumbers, pipe fitters	681	42	17.1	NA[h]	19.4	29.4	1.5
Marcus et al. 1987 Sweden	Auto mechanics	925	35	NA[h]	NA[h]	0.8	4.4	5.5
Bourbeau et al. 1988 Canada	Insulators	110	35 to 55	17.8	NA[h]	10.0	58.2	5.8
Sepulveda and Merchant 1983 U.S., PA	Rail car repair	266	All	9.2	NA[h]	1.9	18.4	9.6
Baker et al. 1985 U.S., MA	Sheet metal workers	299	47	18.0	NA[h]	4.0	51.0	12.8

Table A2-1 (Continued). Prevalence Percent of Radiologic Abnormality in Selected Workforce-Based Studies[a]

Study and Location	Fiber Mined, Product, or Job	No. in Study	Age (years)	Exposure		Prevalence Percent		
				Years	Level	SIO[b] 1/0 or More	Pleural Change (Any)	Ratio Pleural Change to SIO
Murphy et al. 1971 U.S., MA	Pipe coverers	101	42	17.4	5.2 mppcf	30.7	NA[h]	—
Oliver et al. 1985 U.S., PA	Rail car construction	377	57	29.3	NA[h]	1.6	22.9	14.3

[a] Adapted from Becklake (1991a,b), and Ernst and Zejda (1991). Table shows results of selected studies, chosen to illustrate various occupational exposures. Determinants of prevalence of small irregular opacities (SIO) included cumulative exposure (Murphy et al. 1971; Rossiter et al. 1972; Weill et al. 1975, 1979; Berry et al. 1979; Irwig et al. 1979, 1984; British Occupational Hygiene Society [BOHS] 1983); exposure duration (Michaels et al. 1987); exposure level (Rossiter et al. 1972; Irwig et al. 1979, 1984); fiber type (Weill et al. 1975, 1979); process (Becklake et al. 1980a,b; Enarson et al. 1988); and age (Rossiter et al. 1972). Determinants of pleural abnormality include duration of exposure (Irwig et al. 1979, 1984; Baker et al. 1985; Michaels et al. 1987; Bourbeau et al. 1988, 1990; Rosenstock et al. 1988); cumulative exposure (Murphy et al. 1971); exposure level (Hilt 1987); latency (Oliver et al. 1985; Marcus et al. 1987); age (Sepulveda and Merchant 1983; Rosenstock et al. 1988); and sometimes smoking (Baker et al. 1985; Rosenstock et al. 1988).

[b] SIO = small irregular opacities.

[c] mppcf = millions of particles per cubic foot.

[d] Derived from information supplied in the text.

[e] Represents the cumulative prevalence in subjects followed between 1947 and 1983.

[f] Refers to bilateral pleural thickening.

[g] Cases certified as asbestosis by a compensation board.

[h] NA = not available in the report.

have evolved over the last decade, and use more penetrating radiation and multiple projections. Greater prevalence ratios of pleural over parenchymal abnormalities are also found in subjects with nonoccupational exposure. In these individuals the exposure is infrequently measured but probably is lower and more intermittent than occupational exposures.

A2.3.1.4 Potential Role of Intermittent Exposure

Exposure in occupations using or removing asbestos (Table A2-1; Murphy et al. 1971; Sepulveda and Merchant 1983; Baker et al. 1985; Oliver et al. 1985; Lilis et al. 1986; Hilt 1987; Marcus et al. 1987; Michaels et al. 1987; Bourbeau et al. 1988, 1990; Rosenstock et al. 1988; Schwartz et al. 1990a) is characteristically intermittent and may attain high levels. This exposure profile may favor the development of pleural as opposed to parenchymal abnormality (Copes et al. 1985). For the categories of exposure in buildings considered in this report (see Chapter 4), exposure in C3 workers (maintenance or skilled workers who may disturb ACM in the course of repairs, new installations, and minor renovations) is likely to be intermittent and possibly reach high levels. Exposures, however, probably will be lower than those encountered in, for instance, maintenance workers in electrical or chemical plants (Hilt 1987) or in foundries and other industrial buildings.

Detectable disease in the pleura is likely to be a more common manifestation of building-related exposures than abnormalities involving the lung parenchyma, hence their pertinence for the present report.

A2.3.1.5 Prevalence in Building Custodians and Maintenance Workers

The reports from several surveys conducted in maintenance workers (C3) and custodial workers (C2) in nonindustrial buildings have become available recently; their results are summarized in Table A2-2. Balmes and associates (1991) and Selikoff and Levin (1990) studied maintenance and custodial workers employed by school boards; in both studies a substantial proportion of men were in trades or performed tasks likely to require direct contact with asbestos; and in both studies a substantial proportion of men reported asbestos exposure, or had been engaged in occupations likely to have exposure, prior to their employment by the school boards. In addition, custodians in both studies undertook maintenance duties, and in the New York study, custodians also assisted in asbestos abatement work (Selikoff and Levin 1990). In both studies, a significant proportion of custodians, without known asbestos exposure prior to their employment with the school board, had radiographic abnormalities (parenchymal, pleural, or both) consistent with the presence of asbestos-related disease: 11.4 percent in the California study (Balmes et al. 1991) and 27.5 percent in the New York study (Selikoff and Levin 1990).

A third study (Oliver et al. 1990) reports on 120 New England public school custodians. Pleural plaques occurred in 33 percent, and parenchymal opacities in 2.5 percent, giving a pleural-to-parenchymal-disease ratio of 13.3:1. Of 57 custodians without previous asbestos exposure, 26 percent showed pleural plaques. Slightly lower overall rates were reported by Anderson and colleagues (1990) from the State of Wisconsin in a survey of 457 school maintenance workers. In that study (notes from an oral presentation were made available to the Panel for review), the prevalence of parenchymal (small irregular opacities [SIO] of 1/0 or greater) or pleural disease was 8.1 percent, ranging from 2.3 percent for those with less than 10 years of employment, to 42.3 percent for those employed for 30 years or longer.

Table A2-2. Prevalence Percent of Radiologic Abnormality in Workers with Maintenance and Custodial Duties in Nonindustrial Buildings

Study; Location; Population	No. in Study (Percent Response)	Exposure Years	Prevalence Percent		Ratio Pleural change to SIO	Determinants of SIO and Pleural Change
			SIO[a] 1/0 or More	Pleural Change (Any)		
Balmes (1991); U.S., CA; Maintenance employees in a large urban school district, includes plumbers, sheet metal and construction workers, and custodian and maintenance workers	422[b,c] (61%)	~ 12.9[d]	5.9	14.6	2.5	SIO[e] and/or pleural change related to latency, age, smoking, and job
	315[f]	10+	7.3	5.7	0.8	
Selikoff et al. (1990); U.S., NY; Custodians, cleaners and firemen (who tended boiler equipment) working for New York City public schools	660[g] (86%)	20+ for 73% of men	15.9	16.2	1.0	SIO and/or pleural change[h] related to latency, smoking, not to direct contact with asbestos reported by the worker
	247[e]	20+ for 55% of men	17.4	7.2	0.4	
Oliver et al. (1990); U.S., MA; Boston school custodians with more than 15 years service	63	27.7	4.7	33.0	7.0	Pleural plaques increased with latency and duration of exposure
	57[f]	30.9	0.0	26.0	∞	

[a] SIO = small irregular opacities.

[b] ACM present in approximately 80 percent of the buildings.

[c] 693 of approximately 900 workers likely to have been exposed at work, of whom 422 reported no exposure prior to working for the school board.

[d] Estimated exposure level of 217 $\mu g/m^3$ based on an EPA survey of 10 schools evaluated because of friable ACM; custodial activity in an urban school with an exposed ceiling containing 15 percent chrysotile was associated with a mean airborne level of 643 $\mu g/m^3$.

[e] Median of three readers.

[f] Custodians with no previous asbestos exposure and greater than or equal to 10 years employment.

[g] Denominator (the total number employed by the Board of Education) not given; study subjects were selected by the Union and the Board.

[h] Number of readers not given.

A2.3.2 Nonoccupational Exposures

Several studies have documented the existence of asbestos-related abnormalities in individuals not occupationally exposed to asbestos. Several types of nonoccupational exposures have been identified:

1. Household exposures of those living with an asbestos worker (Sider et al. 1987). The prevalence of pleural plaques in household contacts of asbestos workers has been reported to be as high as 20 percent, with about 25 percent of these having calcified plaques. In the past, exposure was attributed to work clothes brought to the home.

2. Environmental exposures related to commercial exploitation of asbestos. These involve people living close to asbestos mines (Pampalon et al. 1982; Case and Sébastien 1987; Churg and de Paoli 1988) or to plants manufacturing asbestos products. Lung dust burden in individuals with this type of environmental exposure has been shown to be higher than the lung dust burden without this type of environmental exposure (Case and Sébastien 1987).

3. Environmental exposures unrelated to commercial exploitation of asbestos. Numbers of locations around the world have asbestos within the soil or in soil products, such as plaster; this can be released into the atmosphere, resulting in the development of asbestos pleural plaques and calcification (Kiviluoto 1960; Burilkov and Babadjov 1970; Yazicioglu 1976; Neuburger et al. 1984; Boutin et al. 1986; Constantopolous et al. 1987).

A2.3.3 General Population Studies

The prevalence of pleural plaques in the general population is estimated to be about 5 percent (Hillerdal 1978; Hilt et al. 1986; Rogan et al. 1987). In general, rates are higher in men than in women, and in urban than in rural areas. This figure may represent a false-positive rate for the radiographic detection of these lesions or may represent the results of other processes, such as infection or trauma. However, in most studies exposure to asbestos is reported by a substantial proportion of those with pleural plaques, ranging from 80 percent in a Swedish community-based study (with overall rates of pleural plaques from 0.5 to 3.0 percent in men over 40 surveyed from six municipalities), to 44 percent in a survey of subjects admitted to a Philadelphia hospital (with overall rates for pleural plaques of from 16.7 percent in men to 0.5 percent in women) (Albeda et al. 1982). When strict criteria are used for the interpretation of radiographs, the prevalence rates are lower (Greene et al. 1984).

A2.4 Effects of Asbestos-Related Pleural Disease on Lung Function

Pleural diseases associated with asbestos exposure vary, ranging from localized lesions to diffuse thickening. Thus, the functional abnormalities associated with asbestos-induced pleural disease are also variable. Cases of asbestos pleurisy leading to frank respiratory failure have been reported (Miller et al. 1983), but more often involve small decrements in function. In most individuals, the presence of pleural plaques without lung disease is not associated with symptoms or significant functional abnormalities.

The functional consequences of asbestos-related pleural disease have been addressed in a number of epidemiologic studies, summarized in Table A2-3 (Becklake et al. 1970; Fridrikson et al. 1981; Baker et al. 1985; McLoud et al. 1985; Oliver et al. 1985; Järvholm and

Table A2-3. Relationship of Lung Function to Pleural Abnormality in Asbestos-Exposed Workers[a]

Study and Location	Subjects Studied	Exposure Years	Prevalence Percent: SIO[b] 1/0 or More[c]	Prevalence Percent: Pleural Change[c] (Any)	Effect on FVC[d] (% pre)	Criteria for Pleural Abnormality[e]
Fridrikson et al. 1981 Sweden	45 men from a population survey	22	None	All	–16[f]	PP, used 4 grades[g]
Baker et al. 1985 U.S., MA	229 men in a sheet metal union	18	4.0	51.0	–4	PP or PL-TH
Oliver et al. 1985 U.S., PA	377 men in rail car construction	29	1.6	22.9	–7	PL-TH (2 mm+) scored for extent
Järvholm and Sanden 1986 Sweden	202 workers in shipyards, NS	20+	None	43.0	–7	PP (PA, lat), 40 x 40 cm films
Järvholm and Larsson 1988 Sweden	242 with PP, 1,103 without detected in a screening program	20+	None	11.5	–2 to –6	See above
Rosenstock et al. 1988 U.S., WA	684 members of a plumber/pipe-fitters union	17	19.4	29.4	–12	PL-TH (cir or dif)
Staples et al. 1989 U.S., CA	76 of over 400 men screened for asbestos effects	20	None	57.0	No effect	HRCT used to exclude SIO, and to detect PL-TH
Schwartz et al. 1990a U.S., IA	1,211 members of a sheet metal workers union	33	17.0	27.3	–3[h] –7	PL-TH (cir) PL-TH (dif)
Bourbeau et al. 1990 Canada	110 members of an insulators union	18	10.0	58.2	–12	PL-TH (2 mm) cir/dif/CP angle

[a] Adapted from Ernst and Zejda (1991).

[b] SIO = small irregular opacities.

[c] In all but two studies, full-size chest radiographs were read into the International Labor Organization (1980) classification, and pleural abnormality was usually graded for extent.

[d] In all studies but one (Staples et al. 1989) the effect was significant ($p < 0.05$) in the analyses carried out by the authors.

[e] Abbreviations describing radiologic pleural abnormality are: Pleural plaque (PP); pleural thickening (PL-TH), which may be circumscribed (cir) or diffuse (dif). In some studies (Bourbeau et al. 1990; Schwartz et al. 1990a), PL-TH (dif) was only diagnosed if the costophrenic angle was blunted.

[f] Refers to total lung capacity: Effects on vital capacity not significant.

[g] Effect related to grade of pleural abnormality.

[h] Calculated from data supplied in the report.

Sanden 1986; Marcus et al. 1987; Bourbeau et al. 1988, 1990; Rosenstock et al. 1988; Staples et al. 1989; Schwartz et al. 1990a). The methods employed in these studies for assessing pleural abnormalities have varied. In most studies, the radiographic classification system of the International Labor Organization (ILO) was used, and in many, pleural abnormality was graded for extent and severity. In most studies, persons with parenchymal abnormalities suggestive of asbestosis were excluded or the degree of abnormality (for example, the profusion of small opacities) was taken into account. In some studies (Becklake et al. 1970; Baker et al. 1985; Oliver et al. 1985; Schwartz et al. 1990a), the effects of pleural disease on lung function were assessed after taking into account exposure (using years of exposure or years since exposure as an index).

In spite of the varied methodology, and differences in the prevalences of parenchymal and pleural change in the various study populations, in all but one study (Staples et al. 1989, in which CT was used to assess presence or parenchymal disease) the presence of asbestos-related pleural abnormalities was associated with reduction in the forced vital capacity (FVC), and other measures of lung function. Depending on the population studied, the magnitude of the effect of pleural abnormalities on FVC ranged from a few percent to over 10 percent of the predicted value. More severe grades of pleural plaques were usually associated with increased impairment in lung function. In addition, progression of pleural disease over time is likely to be associated with concomitant decrease in pulmonary function. For any grade of severity of parenchymal disease, the presence of pleural disease was associated with more severe impairment of lung function (Rosenstock et al. 1988).

Diffuse pleural thickening of the type caused by an adhesive pleuritis is likely to cause lung restriction, as much as any fibrothorax can reduce lung volume. Computed tomography studies have shown that this type of pleural fibrosis is frequently associated with selective reduction in volume of the lower lobes and frequently with lung scarring.

The reduction in FVC in persons with pleural plaques has several interpretations. The functional loss might directly reflect restriction of lung size or a change in the mechanical properties of the lung (Schwartz et al. 1990b). Alternatively, the presence of pleural disease might be a marker of subtle asbestosis, not detected on conventional chest radiographs (Fridrikson et al. 1981; Staples et al. 1989). These explanations need not be considered exclusive. Furthermore, in several studies (Oliver et al. 1985; Rosenstock et al. 1988; Bourbeau et al. 1990; Schwartz et al. 1990a), effects of pleural plaques have persisted with control for exposure or profusion of parenchymal opacities. The average reduction of FVC is small and by itself might be of little functional consequence to the individual; nevertheless, in several studies (Järvholm and Sanden 1986; Bourbeau et al. 1990; Schwartz et al. 1990b), the presence of pleural abnormality was associated with the complaint of shortness of breath. In addition, the range of loss of function (as opposed to the mean) among individuals attributable to asbestos-related pleural disease has not been well characterized, and could be considerable in certain individuals.

A2.5 Progression

Pleural thickening may progress, in extent and in thickness, with time. In a study by de Klerk and coworkers (1989) the rate of progression was greater for those individuals with the shortest latency. The rate of progression also decreased with time up to 15 years. The long latency for the development of pleural plaques and the likelihood of calcification occurring later in the disease indicate that radiographic techniques may not assess the true biological activity of these lesions.

A2.6 Significance of Pleural Plaques

Pleural plaques and the less common diffuse pleural fibrosis had in the past been relegated to a "marker" of asbestos exposure with no functional or prognostic significance (Sargent et al. 1977). It now appears that view does not adequately acknowledge the importance of pleural plaques. Patients with pleural plaques have a higher lung burden of amosite, crocidolite, and probably chrysotile than the general population. These fibrotic pleural lesions are frequently progressive and are associated with a significant incidence of underlying lung fibrosis and reduced lung function.

In some studies, the presence of pleural plaques is also associated with a higher incidence of lung and larynx cancer, and probably mesothelioma (Edge 1973; Selikoff and Hammond 1978; Hillerdal and Lindholm 1980). These results are not confirmed by other studies (Harber et al. 1987; Edelman 1988). Both pleural plaques and the possible increased cancer risk may be related to the dose of asbestos. In populations exposed to low levels of asbestos, pleural plaques are likely to be the only detectable abnormality on chest radiographs or CT scans that is specific for asbestos exposure, and hence pleural plaques will be an important marker for surveillance studies of low-dose exposure. Currently CT and high-resolution CT are the most sensitive and specific methods for the detection of pleural plaques.

In summary, there is now persuasive evidence implicating asbestos-related pleural disease as an independent cause or indicator of functional impairment and possibly even disability. The underlying mechanism remains to be clarified: Neither parenchymal fibrosis visible on the chest radiograph (Rosenstock et al. 1988; Bourbeau et al. 1990), nor alveolitis by gallium scan (Bourbeau et al. 1990) appear to be the explanation; while fibrosis detectable only on high-resolution CT scans (Staples et al. 1989) might be implicated. On the individual level, pleural disease may be the only indication of asbestos exposure, may explain symptoms and functional impairment, and may predict future deterioration in lung function.

A2.7 References

Aberle DR, Gamsu G, Ray CS, Feuerstein IR. 1988. Asbestos-related pleural and parenchymal fibrosis: Detection with high-resolution CT. Radiology 166:729.

Albeda SM, Epstien DM, Gefter WB, Miller WT. 1982. Pleural thickening: Its significance and relationship to asbestos dust exposure. Am Rev Respir Dis 126:621-624.

Anderson HA, Hanrahan LP, Schirmer J, Higgins D, Sarow P. 1990. Mesothelioma among employees in public buildings. Presented at the Collegium Ramazzini Conference, "The Third Wave of Asbestos Disease: Exposure to Asbestos in Place," New York, NY, June 7-8, 1990.

Baker EL, Dagg TD, Greene RE. 1985. Respiratory illness in the construction trade: 1. The significance of asbestos-associated pleural disease among sheet metal workers. J Occup Med 27:483.

Balmes JR, Daporte A, Cone JE. 1991. Asbestos-related disease in custodial and building maintenance workers from a large municipal school district. The proceedings of the conference: The Third Wave of Asbestos Disease: Exposure to Asbestos in Place: Public Health Control, June 1990, New York, NY (Landrigan PJ, Kazemi H, eds.). Annals of the

New York Academy of Sciences Series. New York Academy of Sciences, New York, NY. In press.

Becklake MR. 1991a. Asbestos and other fiber-related interstitial lung diseases: Distribution and determinants in exposed populations. Chest (in press).

Becklake MR. 1991b. The epidemiology of asbestosis. In: Monograph: Mineral Fibers and Health (Liddell FDK, Miller K, eds.) pp. 99-115. CRC Press, Boca Raton, FL.

Becklake MR, Arhirii M, Gibbs GW, Hurwitz S. 1980a. Exposure to asbestos and respiratory abnormality: The influence of fiber type and nature of exposure. In: Biological Effects of Mineral Fibers (Wagner JC, ed.) pp. 763. IARC Scientific Publication No. 30. World Health Organization, Geneva, Switzerland.

Becklake MR, Fournier-Massey G, McDonald JC, Siemiatycki J, Rossiter CE. 1970. Lung function in relation to chest radiographic changes in Quebec asbestos workers: I. Methods, results and conclusions. Bull Physiopathol Respir 6:637.

Becklake MR, Gibbs GW, Arhirii M, Hurwitz S. 1980b. Respiratory changes in relation to asbestos exposure in manufacturing processes (abstract). Am Rev Respir Dis 121(4)(part 2):223.

Berry G, Gilson JC, Holmes S, Lewinsohn HC, Roach SA. 1979. Asbestosis: A study of dose-response relationships in an asbestos textile factory. Br J Ind Med 36:98.

Bourbeau J, Ernst P. 1988. Between- and within-reader variability in the assessment of pleural abnormality using the ILO 1980 International Classification of Pneumoconioses. Am J Ind Med 14:537.

Bourbeau J, Ernst P, Chrome J, Armstrong B, Becklake MR. 1990. The relationship between respiratory impairment and asbestos-related pleural abnormality in an active workforce. Am Rev Respir Dis 142:837-842.

Bourbeau J, Ernst P, Chrome J, Nunes F, Armstrong B, Blanchet Y, Becklake MR. 1988. The relationship between respiratory impairment and asbestos-related pleural abnormality in an active workforce (abstract). Am Rev Respir Dir 137(4)(part 2):82.

Boutin C, Viallat JR, Steinbauer J, Massey DG, Charpin D, Mouries JC. 1986. Bilateral pleural plaques in Corsica: A nonoccupation asbestos exposure marker. Eur J Respir Dis 69:4.

British Occupational Hygiene Society. 1983. Report from the Committee on Asbestos: A study of the health experience in two UK asbestos factories. Ann Occup Hyg 27:1.

Burilkov T, Babadjov L. 1970. Beitrag zum endemischen Auftreten doppelsiitiger Pleuraverkalkungen. Prax Pneumol 24:433.

Case B, Sébastien P. 1987. Environmental and occupational exposures to chrysotile asbestos: A comparative microanalutic study. Arch Environ Health 42:185.

Churg A. 1983. Current issues in the pathologic and mineralogic findings in asbestos-induced disease. Chest 84:275.

Churg A, de Paoli L. 1988. Environmental pleural plaques in residents of a Quebec chrysotile mining town. Chest 94:59.

Constantopoulos SH, Saratzis NA, Kontagiannis D, Karantanas A, Goudevenous JA, Katsiotis P. 1987. Tremolite whitewashing and pleural calcifications. Chest 2:709.

Cookson W, de Klerk N, Musk AW, Glancy JJ, Armstrong B, Hobbs M. 1986. The natural history of asbestosis in former crocidolite workers of Wittenoom Gorge. Am Rev Respir Dis 133:994.

Copes R, Thomas D, Becklake MR. 1985. Temporal patterns of exposure and nonmalignant respiratory abnormality in Quebec chrysotile workers. Arch Environ Health 40:80.

Cordier S, Theriault G, Provencher S. 1984. Radiographic changes in a group of chrysotile miners and millers exposed to low asbestos dust concentrations. Br J Ind Med 41:384.

Craighead JE, Mossman BT. 1982. The pathogenesis of asbestos-associated disease. N Engl J Med 306:1446.

de Klerk V, Cookson WOC, Musk AW, Armstrong BK, Glancy JJ. 1989. Natural history of pleural thickening after exposure to crocidolite. Br J Ind Med 46:461.

Edelman DA. 1988. Asbestos exposure, pleural plaques and the risk of lung cancer. Int Arch Occup Environ Health 60:389.

Edge JR. 1973. Incidence of bronchial carcinoma in shipyard workers with pleural plaques. Am J Clin Pathol 60:608.

Enarson, DA, Embree V, MacLean L, Grzybowski S. 1988. Respiratory health in chrysotile asbestos miners in British Columbia: A longitudinal study. Br J Ind Med 45:459.

Epler GR, McLoud TC, Gaensler EA. 1984. Prevalence and incidence of benign asbestos pleural effusion in a working population. JAMA 247:617.

Ernst PE, Zejda J. 1991. Pleural and airway disease associated with mineral fibers. In: Monograph: Mineral Fibers and Health (Liddell FDK, Miller K, eds.) pp. 121-133. CRC Press, Boca Raton, FL.

Fiedman AC, Fiel SB, Fisher MS, Radecki PD, Lev-Toaff AS, Caroline DF. 1988. Asbestos-related pleural disease and asbestosis: A comparison of CT and chest radiography. AJR 150:269.

Finkelstein MA. 1982. Asbestosis in long term employees of an Ontario asbestos-cement factory. Am Rev Respir Dis 124:496.

Fridrikson HV, Hedenstrom H, Hillderdal G, Malmberg P. 1981. Increased lung stiffness in persons with pleural plaques. Eur J Respir Dis 62:412.

Gamsu G, Aberle DR, Lynch D. 1989. Computed tomography in the diagnosis of asbestos-related thoracic disease. J Thorac Imaging 4:61.

Gibbs GW. 1979. Etiology of pleural calcification: A study of chrysotile asbestos miners and millers. Arch Environ Health 34:76.

Gibbs GW, Lachance M. 1972. Dust exposure in the chrysotile-asbestos mines and mills of Quebec. Arch Environ Health 24:189-190.

Greene R, Boggis C, Jantsch H. 1984. Asbestos-related pleural thickening: Effect of threshold criteria on interpretation. Radiology 152:569.

Harber P, Mohsenifar Z, Oren A, Lew M. 1987. Pleural plaques and asbestos-associated malignancy. J Occup Med 29:641.

Hillerdal G. 1978. Pleural plaques in a health survey material: Frequency, development and exposure to asbestos. Scand J Respir Dis 59:257.

Hillerdal G. 1980. The pathogenesis of pleural plaques and pulmonary asbestosis: Possibilities and impossibilities. Eur J Respir Dis 61:129.

Hillerdal G. 1989. Rounded atelectasis: Clinical experience with 74 patients. Chest 95:836.

Hillerdal G, Lindholm CE. 1980. Laryngeal cancer and asbestos. J Oto Relat Spec 42:233.

Hillerdal G, Ozesmi M. 1987. Benign asbestos pleural effusion. 73 exudates in 60 patients. Eur J Respir Dis 71:113-121.

Hilt B. 1987. Nonmalignant asbestos diseases in workers in an electrochemical plant. Br J Ind Med 44:621.

Hilt B, Lied JT, Lund-Larsen Pg, Lund K, Langard S. 1986. Asbestos-related findings in chest radiographs of the male population of the county of Telemark, Norway: A cross-sectional study. Scand J Work Environ Health 12:567.

Hourihane DOB, Lessof L, Richardson PC. 1966. Hyaline and calcified pleural plaques as an index of exposure to asbestos: A study of radiological and pathological features of 100 cases with a consideration of epidemiology. Br Med J 1:1069.

Irwig LM, du Toit RSJ, Sluis-Cremer GK, Thomas RG. 1984. Risk of asbestosis in crocidolite and amosite mines in South Africa: An erratum. Am J Ind Med 5:479.

Irwig LM, Sluis-Cremer GK, Solomon A, Thomas RG, Hamel PPH, Webster I, Hostie T. 1979. Risk of asbestosis in crocidolite and amosite mines in South Africa. Ann NY Acad Sci 330:35.

Järvholm B, Larsson S. 1988. Do pleural plaques produce symptoms? A brief report. J Occup Med 30:345.

Järvholm B, Sanden A. 1986. Pleural plaques and respiratory function. Am J Ind Med 10:419-426.

Jones RN, McLoud T, Rockoff SD. 1988. The radiographic pleural abnormalities in asbestos exposure: Relationship to physiologic abnormalities. J Thorac Imaging 3:57.

Kiviluoto R. 1960. Pleural calcification as a roetgenelogic sign of nonoccupational endemic anthophyllite-asbestosis. Acta Radiol 194:1.

Lilis R, Selikoff IJ, Lerman Y, Seidman H, Gelb SK. 1986. Asbestosis: Interstitial pulmonary fibrosis and pleural fibrosis in a cohort of asbestos insulation workers: Influence of cigarette smoking. Am J Ind Med 10:459.

Lynch DA, Gamsu G, Ray CS, Aberle DR. 1988. Asbestos-related focal lung masses: Manifestations on conventional and high-resolution CT scans. Radiology 129:603.

Marcus K, Jarvholm BG, Larsson S. 1987. Asbestos-associated lung effects in car mechanics. Scand J Work Environ Health 13:252.

McLoud T, Woods BO, Carrington CB, Epler GR, Gaensler EA. 1985. Diffuse pleural thickening in an asbestos-exposed population: Prevalence and causes. AJR 144:9.

Meurman L. 1966. Asbestos bodies in pleural plaques in a Finnish series of cases. Acta Pathol Microbiol Scand 181:8.

Michaels D, Zoloth S, Lacher M, Holstein E, Lilis R, Drucker E. 1987. Asbestos disease in sheet metal workers: II. Radiologic signs of asbestosis among active workers. Am J Ind Med 12:595.

Miller A, Teirstein AS, Selikoff IJ. 1983. Ventilatory failure due to asbestos pleurisy. Am J Med 75:911.

Murphy RLH, Ferris BG, Burgess WA, Worcester J, Gaensler EA. 1971. Effects of low concentrations of asbestos: clinical, environmental, radiologic, and epidemiologic observations in shipyard pipecoverers and controls. N Engl J Med 285:1271.

Neuburger M, Kundi M, Firedl HP. 1984. Environmental asbestos exposure and cancer mortality. Arch Environ Health 39:261.

Oliver LC, Eisen EA, Greene RE, Sprince NL. 1985. Asbestos-related disease in railroad workers. Am Rev Respir Dis 131:499.

Oliver LC, Sprince NL, Greene RE. 1990. Asbestos related radiographic abnormalities in public school custodians. Toxicol Ind Health 6:629.

Pampalon R, Siemiatycki J, Blanchet M. 1982. Pollution environmentale par l'amiante et santé publique au Québec. L'Union Med 3:1.

Rogan WJ, Gladen BC, Ragan NB, Anderson HA. 1987. US prevalence of occupational pleural thickening: A look at chest x-rays from the first National Health and Nutrition Examination Survey. Am J Epidemiol 126:893.

Rosenstock L, Barnhart S, Heyer NJ, Pierson DJ, Hudson LD. 1988. The relation among pulmonary function, chest roentgenographic abnormalities, and smoking status in an asbestos-exposed cohort. Am Rev Respir Dis 136:272.

Rossiter CE, Bristol LJ, Cartier PH, Gilson JC, Grainger TR, Sluis-Cremer GK, McDonald JC. 1972. Radiographic changes in chrysotile asbestos mine and mill workers of Quebec. Arch Environ Health 24:388.

Sargent EN, Boswell WD Jr, Ralls WP, Markovitz A. 1984. Subpleural fat pads in patients exposed to asbestos: Distinction from non-calcified pleural plaques. Diagn Radiol 152(2):273-277.

Sargent EN, Jacobson G, Gordonson JS. 1977. Pleural plaques: A signpost of asbestos dust inhalation. Semin Roentgenol 4:287.

Schwartz DA. 1991. New developments in asbestos-induced pleural disease. Chest 99:191-198.

Schwartz DA, Fuortes LJ, Galvin JR, Burmeister LF, Schmidt LE, Leistikow BN, Lamarte FP, Merchant JA. 1990a. Asbestos-induced pleural fibrosis and impaired lung function. Am Rev Respir Dis 141:321.

Schwartz DA, Galvin JR, Dayton CS, Stanford W, Merchant JA, Hunninghake GW. 1990b. Determinants of restrictive lung function in asbestos-induced pleural fibrosis. J Appl Physiol 68(5):1932-1937.

Selikoff IR, Hammond EC. 1978. Asbestos-associated disease in United States shipyards. CA 28:87.

Selikoff IJ, Levin SM. 1990. Radiologic abnormalities and asbestos exposure among custodians of the New York Board of Education. Report to the New York City Board of Education, March 10, 1990. Environmental Sciences Laboratory, Mt. Sinai School of Medicine of the City, University of New York, New York, NY.

Sepulveda M-J, Merchant JA. 1983. Roentgenographic evidence of asbestos exposure in a select population of railroad workers. Am J Ind Med 4:631.

Sider L, Holland EA, Davis TM, Cugell DW. 1987. Changes on radiographs of wives of workers exposed to asbestos. Radiology 164:723.

Staples CA, Gamsu G, Ray CS, Webb WR. 1989. High resolution computed tomography and lung function in asbestos-exposed workers with normal chest radiographs. Am Rev Respir Dis 139:1502.

Stephens M, Gibbs AR, Pooley FD, Wagner JC. 1987. Asbestos-induced diffuse pleural fibrosis: Pathology and mineralogy. Thorax 42:583.

Svener KB, Borgersen AM, Haaversen O, Holten K. 1986. Parietal pleural plaques: A comparison between autopsy and X-ray findings. Eur J Respir Dis 69:10.

Viallat JR, Boutin C, Pietri JF, Fondarai J. 1983. Late progression of radiographic changes in Canari chrysotile mine and mill ex-workers. Arch Environ Health 38:54.

Weill H, Rossiter CE, Waggenspack C, Jones RN, Ziskind MM. 1979. Differences in lung effects resulting from chrysotile and crocidolite exposure. In: Inhaled Particles IV, Vol. 2 (Walton W, ed.) pp. 798. Pergamon Press, New York, NY.

Weill H, Ziskind MM, Waggenspack C, Rossiter CE. 1975. Lung function consequences of dust exposure in asbestos-cement manufacturing plants. Arch Environ Health 30:88.

Yazicioglu S. 1976. Pleural calcification associated with exposure to chrysotile asbestos in Southeast Turkey. Chest 70:43.

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