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Asbestos Health Assessment Update

Review Draft

(Do Not Cite or Quote)

NOTICE

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

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Asbestos Health Assessment Update

by

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ABSTRACT

Data developed since the early 1970's from large population studies with long follow-up have added to our knowledge of asbestos disease. These data strengthen the association of asbestos with disease. Lung cancer and mesothelioma are the most important asbestos-related causes of death among exposed individuals. Cancer at other sites also has been associated with asbestos exposure in some studies. The accumulated data suggest that the excess risk of lung cancer from asbestos exposure is proportional to the cumulative exposure (the duration times the intensity) and the underlying risk of lung cancer in the absence of exposure. The risk of death from mesothelioma appears to be proportional to the cumulative exposure to asbestos in a given period. Animal studies confirm the human epidemiological results. All major asbestos varieties produce lung cancer and mesothelioma with only limited differences in carcinogenic potency. Some measurements demonstrate that significant asbestos exposure, exceeding 100 times the background, occurs to individuals in non-occupational environments. Currently, the most important of these non-occupational exposures is from the release of fibers from asbestos-containing surfacing materials in schools, auditoriums, and other public buildings or from asbestos fireproofing sprayed in high-rise office buildings. Extrapolations of risks of asbestos cancers from occupational circumstances can be made, although any numerical estimates have a large (approximately tenfold) uncertainty. These calculations of unit risk values for asbestos must be viewed with caution as they are uncertain and aspects of them are necessarily based on estimates that are subjective to some extent because of the following limitations in data: (1) one is extrapolating from high occupational levels to much lower ambient levels, (2) the mass to fiber conversion is uncertain, (3) statistical uncertainties are involved, (4) various biases and confounding aspects of the medical data exist, and (5) very importantly, the exposure estimates are nonrepresentative.

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1. SUMMARY

Data developed since the early 1970's from large population studies with long follow-up have added to our knowledge of asbestos disease. These data strengthen the association of asbestos exposure with disease. Lung cancer and mesothelioma are the most important asbestos-related causes of death among exposed individuals. Cancer at other sites also has been associated with asbestos exposure in some studies.

Data from the extensive study of insulators allow models to be developed for the time and age dependence of lung cancer and mesothelioma risk. Other studies have provided exposure-response information. The accumulated data suggest that the excess risk of lung cancer from asbestos exposure is proportional to the cumulative exposure (the duration times the intensity) and the underlying risk of lung cancer in the absence of exposure. The time course of lung cancer is determined primarily by the time course of the underlying risk. However, the risk of death from mesothelioma increases very rapidly after the onset of exposure. The risk is independent of age and other factors, such as cigarette smoking. As with lung cancer, the risk appears to be proportional to the cumulative exposure to asbestos in a given period. The dose and time relationships for other asbestos cancers are uncertain.

Eleven studies provide data for estimates of the fractional increased risk of lung cancer per unit exposure. The values obtained from different studies vary widely, but a range of fractional unit risks that encompass the results of most studies can be specified. Four studies indicate similar variability for the unit exposure risks developed for the observed incidence of mesothelioma.

The variability in the unit risks cannot be attributed to differences in exposures to different fiber types. All major commercial asbestos varieties (chrysotile, amosite, and crocidolite) appear to be equally capable of producing pleural mesothelioma and lung cancer. Peritoneal mesothelioma appears to be associated with exposure to amphibole asbestos rather than chrysotile, but this suggestion is tempered by the possibility of severe misdiagnosis of the disease.

Animal studies confirm the human epidemiological results. All major asbestos varieties produce lung cancer and mesothelioma with only limited differences in carcinogenic potency. Implantation and injection studies show

that fiber dimensionality, not chemistry, is the most important factor in fiber-induced carcinogenicity. Long (>4 μm) and thin (≤4 μm) fibers are the most carcinogenic at a cancer-inducible site. However, the size dependence of the deposition and migration of fibers also affects their carcinogenic action.

Some measurements demonstrate that significant asbestos exposure, exceeding 100 times the background, occurs to individuals in non-occupational environments. Currently, the most important of these non-occupational exposures is from the release of fibers from asbestos-containing surfacing materials in schools, auditoriums, and other public buildings or from asbestos-sprayed fireproofing in high-rise office buildings. A high potential exists for future exposure from the maintenance, repair, and removal of these materials and those previously applied as thermal insulation.

Extrapolations of risks of asbestos cancers from occupational circumstances can be made, although any numerical estimates have a large (approximately tenfold) uncertainty. These calculations of unit risk values for asbestos must be viewed with caution as they are uncertain and aspects of them are necessarily based on estimates that are subjective to some extent because of the following limitations in data: 1) variability in the exposure-response relationship at high exposures; 2) uncertainty in extrapolating to exposures 100 times lower, and 3) uncertainties in conversion of optical fiber counts to electron microscopic mass determinations.

2. INTRODUCTION

The purpose of this health effects review is to evaluate the information that has been developed since 1972 on human disease from asbestos exposure. The review examines the substantial amount of new health research that has been reported in the last decade to help evaluate the current standard promulgated by the U.S. Environmental Protection Agency (EPA) for asbestos emissions. Thus, emphasis will be placed on the literature published after 1972 and on those papers that provide information on the risk from low-level exposures such as those encountered in the non-occupational environment. Specifically, this report will address the following issues:

1. Are there models that illustrate the age, time, and exposure dependence of asbestos diseases that can be used satisfactorily in a quantitative risk assessment?

2. Is there consistency among studies and sufficiently good estimates of exposure in occupational circumstances so that useful exposure-response relationships can be established?

3. Do these studies indicate any significant differences in the carcinogenic potency of the different asbestos minerals or of fibers of different dimensionality?

4. What additional or confirmatory information relating to human carcinogenicity is provided by animal studies?

5. What are the non-occupational concentrations of asbestos to which populations are exposed?

6. Is there a basis for estimating numerical risks of asbestos disease that results from environmental exposure.

Two documents provide a good review of the status of knowledge of the health effects of asbestos in the early 1970s. One source is the criteria document for occupational exposure to asbestos produced by the National Insti-

tute of Occupational Safety and Health as part of the Occupational Safety and Health Administration's consideration of an asbestos standard in early 1972 (NIOSH, 1972). The second document is the proceedings of a conference sponsored by the International Agency for Research on Cancer (IARC), which was convened in October 1972 with the stated purpose of reviewing the knowledge of the biological effects of asbestos at that time (IARC, 1973). This latter document included a report by an Advisory Committee on Asbestos Cancers appointed by the IARC to review evidence relating exposures to asbestos dust to cancers.

2.1 SUMMARY OF ASBESTOS HEALTH EFFECTS THROUGH 1972

This summary relies heavily on review articles that are in the proceedings of the October 1972 IARC meeting and in the report of the IARC Advisory Committee published therein (IARC, 1973) for the summary of health effects knowledge in 1973.

2.1.1 Occupational Exposure

Diseases considered to be associated with asbestos exposure in 1972 included asbestosis, mesothelioma, bronchogenic carcinoma, and cancers of the GI tract, including the esophagus, stomach, colon, and rectum. Lung cancer was associated with exposure to all principal commercial varieties of asbestos fiber: amosite, anthophyllite, crocidolite, and chrysotile. Excess risks of bronchogenic carcinoma were documented in mining and milling, manufacturing, and end product use (application of insulation materials). Mesothelioma was a cause of death among factory employees, insulation applicators, and workmen employed in the mining and milling of crocidolite. A much lower risk of death from mesothelioma was observed among chrysotile or amosite mine and mill employees, and no cases were associated with anthophyllite exposure. The IARC Advisory Committee suggested that the risk of death from mesothelioma was greatest with crocidolite, less with amosite, and still less with chrysotile. This suggestion was based on the association of disease with exposures. No unit exposure risk information existed.

Information on exposure-response relationships for lung cancer risk among various exposed groups was scanty. Data from Canadian mine and mill employees clearly indicated an increasing risk with increasing exposure measured in terms of millions of particles per cubic foot-years (mppcf-yr), but data on

the risk at minimal exposure were uncertain because the number of expected deaths calculated using adjacent county rates suggested that all exposure categories were at elevated risk (McDonald et al., 1971). A study of retirees of the largest U.S. asbestos manufacturer showed lung cancer risks ranging from 1.7 times that expected in the lowest exposure category to 5.6 times that expected in the highest (Enterline and Henderson, 1973). Again, exposures were expressed in mppcf-yr and information on conversion of mppcf to fibers per milliter was available only for textile production. Despite the paucity of data, the report of the Advisory Committee on Asbestos Cancers to the IARC (1973) stated, "The evidence ... suggests that an excess lung carcinoma risk is not detectable when the occupational exposure has been low. These low occupational exposures have almost certainly been much greater than that to the public from general air pollution." Limited data existed on the association of GI cancer with asbestos exposure, but the "excess is relatively small compared with that for bronchial cancer."

The prevalence of asbestosis, particularly as manifest by X-ray abnormalities of the pleura or parenchymal tissue, had more extensive documentation than the risk of the asbestos-related malignancies. In part, this documentation was the result of knowledge of this disease extending back to the turn of the century, whereas the malignant potential of asbestos was not suggested until 1935 (Lynch and Smith, 1935; Gloyne, 1936) and not widely appreciated until the 1940s (Merewether, 1947). Such asbestosis had been documented in a wide variety of work circumstances and associated with all commercial types of asbestos fiber. Among some exposed groups, 50 to 80% of individuals employed for 20 or more years were found to have abnormal X-rays characteristic of asbestos exposure (Selikoff et al., 1965; Lewinsohn, 1972). Company data supplied to the British Occupational Hygiene Society (BOHS, 1968) on X-ray and clinical abnormalities among 290 employees of a large textile production facility in Great Britain were analyzed by Berry (1973) in terms of a fiber exposure-response relationship. The results were utilized in establishing the 1969 British regulation on asbestos. These data, shown in Figure 2-1, suggested that the risk of developing the earliest signs of asbestosis (rales) was less than 1% for accumulated fiber exposure of 100 fibers-yr/ml (e.g., 2 fibers/milliliter (f/ml) for 50 years). However, shortly after the establishment of the British Standard, additional data from the same factory population suggested a much greater prevalance of X-ray abnormalities than was believed

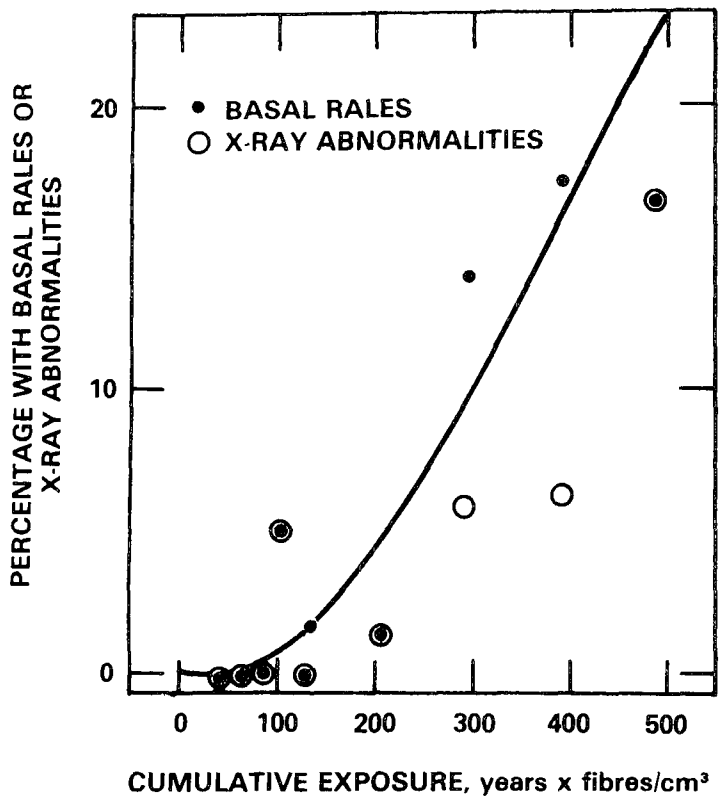

Figure 2-1. Dose-response relationship for prevalance of basal rales in a chrysotile asbestos factory.

Source: Berry (1973); x-ray data added from BOHS (1968).

to exist at the time the British Standard was set (Lewinsohn, 1972). These data resulted from use of the new International Labour Office (ILO) U/C standard classification of X-rays (ILO, 1971) and the longer time from onset of employment. Of the 290 employees, only 13 had been employed for 30 or more years; 172 had less than 20 years of employment. The progression of asbestosis depends on both cumulative exposure and time from exposure; therefore, analysis in terms of only one variable (as in Figure 2-1) can be misleading.

2.1.2 Environmental and Indirect Occupational Exposure Circumstances.

Four research groups had shown that asbestos disease risk could exist in circumstances other than direct occupational circumstances. In 1960, Wagner, Sleggs, and Marchand (1960) showed that a mesothelioma risk in environmental circumstances existed in the mining areas of the Northwest Cape Province of South Africa. Of 33 mesotheliomas reported over a 5-year period, roughly half were from occupational exposure. However, all but one of the remainder resulted from exposure occasioned by living or working in the area of the mining activity. A second study that showed an extra-occupational risk was that of Newhouse and Thompson (1965), who investigated the occupational and residential background of 76 individuals deceased of mesothelioma in the London hospital. Forty-five of the decedents had been employed in an asbestos industry; of the remaining 31, 9 lived with someone employed in asbestos work and 11 were individuals who resided within half a mile of an asbestos factory. Bohlig and Hain (1973) further defined the residential risk by documenting environmental asbestos exposure near a factory in 38 cases in Hamburg. The final study, which is particularly important because of the size of the population implied to be at risk, is that of Harries (1968), who pointed to a risk of asbestos disease from indirect occupational exposure in the shipbuilding industry. He described the presence of asbestosis in 13 individuals and mesothelioma in 5 others who were employed in a shipyard, but were not members of trades that regularly used asbestos. Rather, their work took place where other employees were placing or removing insulation.

Evidence of ubiquitous general population exposure and environmental contamination from the spraying of asbestos on the steel-work of high rise buildings was established by 1972. Data by Nicholson and Pundsack (1973) showed that asbestos was commonly found at concentrations of nanograms per cubic meter (ng/m^3) in virtually all United States cities and at concentra-

tions of micrograms per liter (μg/l) in river systems of the United States. Concentrations of hundreds of nanograms per cubic meter were documented at distances up to one quarter of a mile from fireproofing sites. Mesothelioma was acknowledged by the Advisory Committee to be associated with environmental exposures but "the evidence relates to conditions many years ago .... There is no evidence of a risk to the general public at present." Further, their report stated that, "There is at present no evidence of lung damage by asbestos to the general public," and "Such evidence as there is does not indicate any risk" from asbestos fibers in water, beverages, food, or parenteral drugs. No mention was made in the report of risks from indirect occupational asbestos exposures.

2.1.3 Analytical Methodology

During the late 1960s and early 1970s, significantly improved methods were developed for assessing asbestos disease and the quantifying of asbestos in the environment. In 1971, a standardized methodology was established for the identification of pneumoconiosis: the ILO U/C Classification of Pneumoconioses (ILO, 1971). This methodology provided a uniform criteria for assessing the prevalence of asbestos-related X-ray abnormalities. Further, significant advances were achieved in the quantification of asbestos aerosols. In the late 1960s, the membrane filter technique was developed for the measurement of asbestos fibers in workplace aerosols. While this procedure had some limitations, it established a standardized method, using simple instrumentation, that was far superior to any that existed previously. This method subsequently allowed epidemiological studies that based exposure estimates on a standardized criterion. Additionally, experimental techniques in the quantification of asbestos at concentrations of tenths of ng/m^3 of air and tenths of μg/l of water were developed. These techniques extended the sensitivity of exposure estimates approximately three orders below those of occupational aerosols and allowed assessment of general population exposures. Finally, techniques for the analysis of asbestos in lung and other body tissues were developed. Both digestion techniques, use of electron microscopy to analyze fibers contained in the digest, and to analyze thin sections of lung tissue showed that asbestos fibers were commonly present in the lung tissue of general population residents, as well as in that of individuals exposed in occupational circumstances.

2.1.4 Animal Studies

Experimental animal studies using asbestos fibers confirmed the risks of lung cancer and mesothelioma from amosite, crocidolite, and chrysotile. In each case, the establishment of a risk in animals followed the association of the malignancy with human exposure. For example, a causal relationship between lung cancer and asbestos exposure in humans was suggested in 1935, but was not described in the open literature in animals until 1967 (Gross et al., 1967). Mesothelioma, reported in an asbestos worker in 1953 (Weiss, 1953), was produced in animal experimentation in 1965 (Smith et al., 1965). Other animal experimentation showed that combinations of asbestos and other carcinogenic materials produced an enhanced risk of asbestos cancer. Asbestos exposure combined with exposure to benz(a)pyrene was demonstrably more toxic than exposure to either agent alone. Additionally, organic and metal compounds associated with asbestos fibers were ruled out as an important factor in the carcinogenicity of fibers. Lastly, animal experimentation involving the application of fibers onto the pleura of animals indicated that the important factor in the carcinogenicity was the dimensionality of the fibers rather than their chemical properties (Stanton, 1973). The greatest carcinogenicity was related to fibers that were less than 2.5 μm in diameter and longer than 10 μm.

2.2 CURRENT ASBESTOS STANDARDS

The current Occupational Safety and Health Administration (OSHA) standards for an 8-hour time-weighted average (TWA) occupational exposure to asbestos is 2 fibers longer than 5 μm in length per milliliter of air (2 f/ml or 2,000,000 f/m^3). Peak exposures of up to 10 f/ml are permitted for no more than 10 min. (29 CFR 1910.001). This standard has been in effect since July 1, 1976, when it replaced an earlier one of 5 f/ml (TWA). In Great Britain, a value of 1 f/ml is now the accepted level for chrysotile. This standard resulted from recommendations made in 1979 by the Advisory Committee (1979a), which also recommended a TWA of 0.5 f/ml for amosite and 0.2 f/ml for crocidolite. From 1969 to 1983, 2 f/ml (TWA) was the standard for chrysotile (BOSH, 1968). This earlier British standard served as a guide for the OSHA standard (NIOSH, 1972).

The British standard was developed specifically to prevent asbestosis among working populations; data that would allow a determination of a standard

for cancer (BOHS, 1968) were felt to be lacking. Unfortunately, among occupational groups, cancer is the primary cause of excess death among workers (see Chapter 3). Three-fourths or more of asbestos-related deaths are from malignancy. This fact has led OSHA to propose a lower TWA standard to 0.5 f/ml (500,000 f/m^3) in October, 1975 (29 CFR 1910.001). The National Institute for Occupational Safety and Health anticipated hearings on a new standard and proposed a value of 0.1 f/ml (NIOSH, 1976) in an update of their 1972 criteria document. In the discussion of the NIOSH proposal, it was stated that the value was selected on the basis of the practical limitations of analytical techniques using optical microscopy and that 0.1 f/ml may not necessarily protect against cancer. The preamble to the OSHA proposal acknowledges that no information exists to define a threshold for asbestos carcinogenesis. The OSHA proposal has been withdrawn, and a new proposal is anticipated. NIOSH has reaffirmed its position on an 0.1 f/ml standard (1980).

The existing Federal national emission standards for asbestos are published in Part 61, Title 40, Code of Federal Regulations. In summary, these apply to milling, manufacturing, and fabrication sources and to demolition, renovation, and waste disposal, and include other limitations. In general, the standards allow compliance alternatives, either (1) no visible emissions, or (2) employment of specified control techniques. The standards do not include any mass or fiber count emission limitations. However, some local governmental agencies have numerical standards (e.g., New York: 27 ng/m^3).

3. HUMAN HEALTH EFFECTS ASSOCIATED WITH OCCUPATIONAL EXPOSURE TO ASBESTOS

3.1 INTRODUCTION

This review of human health effects associated with occupational exposure to asbestos is concerned with those studies that aid in the development of an exposure-response relationship for lung cancer and mesothelioma. While lung cancer and mesothelioma are the most dominant asbestos-related malignancies, the strength of the evidence and the relative excess of cancers at extra-thoracic sites are discussed. Models for assessment of the risk of lung cancer and mesothelioma are reviewed. Unit exposure risks are estimated from 11 studies that provide information on exposure-response relationships. These estimates illustrate that considerable variation exists in the unit exposure risks found for mesothelioma and lung cancer in the different studies. The possible sources of these different unit risks are also considered. An important question is whether the variation is the result of methodological uncertainties (i.e., on the estimates of exposure or of the magnitude of disease) or whether differences are real and must be reconciled on the basis of the character of the exposure in terms of fiber size and chemistry.

3.2 MORTALITY ASSOCIATED WITH ASBESTOS EXPOSURE

The study of U.S. and Canadian insulators by Selikoff et al. (1979) contains the largest excess of asbestos-related deaths among any group of asbestos workers studied. Thus, this study best demonstrates the full spectrum of disease from asbestos exposure. The mortality experience of 17,800 asbestos insulation workers was studied prospectively from January 1, 1967, through December 31, 1976. These workers were exposed primarily to chrysotile prior to 1940, to chrysotile and amosite from 1940 through 1965, and primarily to chrysotile thereafter. No crocidolite is known to have been used in the U.S. insulation material (Selikoff et al., 1970). The workers' main activity was applying new insulation; removal of old materials constituted less than 5% of their work.

In this group, 2,271 deaths occurred, and their analysis provides important insights into the nature of asbestos disease. Table 3-1 lists the expected and observed deaths by cause and includes data on tumors found less frequently. Lung tumors were common and accounted for approximately 21% of the deaths; 8% were from mesothelioma of the pleura or peritoneum, and 7% resulted

TABLE 3-1. DEATHS AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES AND CANADA JANUARY 1, 1967 - DECEMBER 31, 1976
NUMBER OF MEN 17,800
MAN-YEARS OF OBSERVATION 166,853

Underlying cause of death	Number of Deaths			Ratio of observed to expected	
	Expected[a]	Observed BE	Observed DC	BE	DC
Total deaths, all causes	1658.9	2271	2271	1.37	1.37
Total cancer, all sites	319.7	995	922	3.11	2.88
Cancer of lung	105.6	486	429	4.60	4.06
Pleural mesothelioma	-[b]	63	25	-[b]	-[b]
Peritoneal mesothelioma	-[b]	112	24	-[b]	-[b]
Mesothelioma, n.o.s.	-[b]	0	55	-[b]	-[b]
Cancer of esophagus	7.1	18	18	2.53	2.53
Cancer of stomach	14.2	22	18	1.54	1.26
Cancer of colon-rectum	38.1	59	58	1.55	1.52
Cancer of larynx	4.7	11	9	2.34	1.91
Cancer of pharynx, buccal	10.1	21	16	2.08	1.59
Cancer of kidney	8.1	19	18	2.36	2.23
All other cancer	131.8	184	252	1.40	1.91
Noninfectious pulmonary diseases, total	59.0	212	188	3.59	3.19
Asbestosis	-[b]	168	78	-[b]	-[b]
All other causes	1280.2	1064	1161	0.83	0.91

BE = best evidence. Number of deaths categorizes after review of best available information (autopsy, surgical, clinical).

DC = Number of deaths as recorded from death certificate information only.

[a]Expected deaths are based upon white male age-specific U.S. death rates of the U.S. National Center for Health Statistics, 1967-1976. (NCHS, Annually: 1967-1977)

[b]Rates and thus ratios are not available, but these have been rare causes of death in the general population.

Source: Selikoff et al. (1979)

from asbestosis. Considering all cancers, 675 excess malignancies occurred, constituting 30% of all deaths. In addition to the usual asbestos malignancies, lung cancer, mesothelioma, and gastrointestinal cancer, the incidences of cancers of the larynx, pharynx and buccal cavity, and kidney were significantly elevated. Other tumors were also increased, but not to a statistically significant degree for individual sites. However, as a group, these other cancers were significantly in excess, 184 observed deaths (using best available evidence for classification) versus 131.8 expected deaths ($p<0.001$). However, some of this observed excess may be the result of misclassification of asbestos-related lung cancer or peritoneal mesothelioma. Rather than 184 deaths, certificate of death classification attributed 252 deaths to cancer at these other sites. Pancreatic, liver, and unspecified abdominal cancers were commonly misclassified. Pancreatic and abdominal cancers were often found to be peritoneal mesotheliomas, and several liver cancers were the result of a primary malignancy in the lung. Because all cases could not be reviewed, some additional misclassification may still exist. However, the magnitude would not be great compared to the remaining excess of 52 cases. The excess at extrathoracic sites may reflect mortality from the dissemination of asbestos fibers to various organs (Langer, 1974). Alternatively, this trend could represent a systemic effect of asbestos, perhaps on the immune system, that leads to a general increased risk of cancer (Goldsmith, 1982).

3.2.1 Accuracy of Cause of Death Ascertainment

Table 3-1 lists the observed deaths according to the cause recorded on the death certificate (DC) and according to the best evidence (BE) available from medical records, surgical specimens, and autopsy protocols. In comparing occupational mortality with that of the general population, information recorded on death certificates is usually used because such information, without verification, serves as the basis for "expected rates." However, mesothelioma and asbestosis are virtually unseen in the general population; therefore, their misdiagnosis (which is common) is of little importance. In contrast, their misdiagnosis among asbestos workers can cause serious distortions in assessing mortality. Not only are asbestos-related causes understated, but others, such as pancreatic cancer, might wrongly appear to be significantly elevated (Selikoff and Seidman, 1981). While substantial differences exist in the DC and BE characterization of deaths from mesothelioma and asbestosis, the

BE and DC deaths from cancer of all sites and lung cancer agree reasonably well.

Mesothelioma is best described by an absolute risk model and lung cancer by a relative risk model. Thus, risks for mesothelioma will be expressed in absolute rates (e.g., deaths/ 1,000 person-years), and the best medical evidence will be used, when available, to establish the number of cases. Risks for lung cancer will be quantified by the ratio of observed to expected deaths. In this document, it is assumed that misclassification of lung cancer deaths would occur as frequently in asbestos workers as in the general population (in terms of the percentage of lung cancer cases). Therefore, the certificate of death cause will be used for establishing the relative risks of lung cancer in asbestos-exposed groups.

3.3 LINEARITY OF EXPOSURE-RESPONSE RELATIONSHIPS

Some limited direct evidence for linearity of response with asbestos exposure is available from three studies that compared lung cancer mortality to the cumulative total dust exposure in asbestos workplaces (Henderson and Enterline, 1979; Liddell et al., 1977; Dement et al., 1982). Figure 3-1 shows the exposure-response data in these studies in which the ratio of observed to expected lung cancer mortality is plotted against the measured cumulative dust exposure. While different exposure-response relationships appear to exist for the three circumstances, each demonstrates a linear relationship over the entire range of observation. The differences in the slopes of the three relationships may relate to differences in the quantity of other dust present, the fiber size distribution, the age of the population under observation, and the representativeness of the dust sampling program. These factors will be discussed later when the exposure-response relationships of all available studies are compared (Section 3.7). Further, when exposure-response relationships are analyzed according to duration and intensity of exposure (McDonald et al., 1980), the results are far less dramatic than those shown in Figure 3-1. However, this may be the result of small numbers; only 46 excess lung cancer deaths are reported in all exposure categories.

Fewer data are available on the exposure-response relationship for mesothelioma. Table 3-2 lists the mesothelioma mortality from three studies (Seidman et al., 1979; Hobbs et al., 1980; Jones et al., 1980) in terms of cases per 1,000 person-years of observation beginning 10 years after first

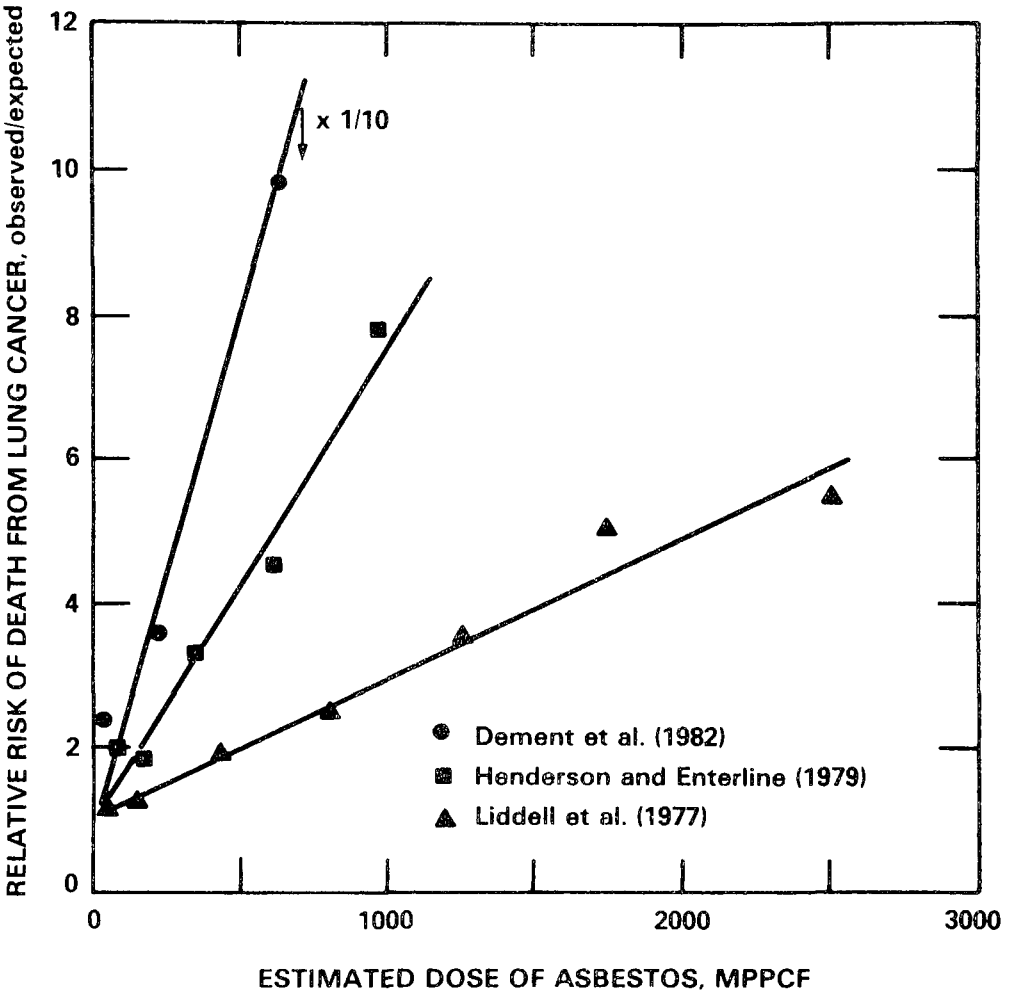

Figure 3-1. Exposure-response relationship for lung cancer observed in three studies. The cumulative exposures are measured in terms of millions of particles per cubic foot-years (MPPCF). Note that the exposure values for the circles are to be multiplied by 1/10.

TABLE 3-2. THE RISK OF DEATH FROM MESOTHELIOMA ACCORDING TO THE TIME OF ASBESTOS EXPOSURE IN THREE STUDIES

Study	Exposure period, months	Number of deaths	Estimated person-years 10+ years from first exposure	Deaths/ 1000 Person-years	Number exposed	Percent of deaths
Hobbs et al. (1980)						
	< 3	0	21,213	0		
	3 - 11	10	19,548	0.5		
	12+	16	14,833	1.1		
Seidman et al. (1979)						
	2.2	0	6,640	0		
	7.1	3	2,000	1.5		
	15.4	4	2,290	1.7		
	57	7	2,480	2.8		
Jones et al. (1980)						
	< 5	0			314	0
	5 - 10	3			116	2.6
	10 - 20	4			145	2.8
	20 - 30	4			101	4.0
	30+	5			51	9.8

exposure. While few deaths are available for analysis, the data for exposure periods longer than 3 to 5 months are consistent with a linear relationship. No deaths from mesothelioma were observed in any of the lowest exposure categories, whereas 1 to 2 would have been expected in each study on the basis of a linear dose-response relationship. Similarly, data of Newhouse and Berry (1979) (Table 3-3) show an increasing risk of mesothelioma with increasing duration and intensity of exposure. However, a quantitative relationship cannot be determined.

This document uses a linear exposure-response relationship for estimating unit exposure risks and for calculating risks at cumulative exposures 10 to 100 times less than those of the occupational circumstances of past years. This relationship is plausible and no evidence contradicts it, although the strength of the evidence supporting it is limited. The method has three

TABLE 3-3. INCREASING RISK OF MESOTHELIOMA WITH INCREASING DURATION AND INTENSITY OF EXPOSURE

	Duration of exposure	Intensity of exposure	
		Low-moderate	Severe
Males	< 2 yrs	33	104
	> 2 yrs	93	243
Females	< 2 yrs	{48}	136
	> 2 yrs		360

Source: Newhouse and Berry (1979).

distinct advantages: 1) point estimates of exposure-response can be made without knowledge of individual exposures, i.e., the excess mortality of an entire group can be related to the average exposure of the group, 2) extrapolation (or interpolation) to various exposure circumstances can be made easily, and 3) this procedure is probably conservative from the point of view of human health. Linearity of exposure-response applies only for similar times of exposure and observation, among similarly aged individuals, with similar personal habits.

3.4 TIME AND AGE DEPENDENCE OF LUNG CANCER

A relative risk model has long been assumed to be applicable for the description of the incidence of lung cancer induced by occupational asbestos exposure. Such a model is tacitly assumed in the descriptions of mortality in terms of observed and expected deaths. Virtually every study of asbestos workers is described in these terms. Early suggestive evidence supporting this model is found in the synergistic action between asbestos exposure and cigarette smoking (Selikoff et al., 1968) in which the lung cancer risk from asbestos exposure depended on the underlying risk in the absence of exposure. Relative risk models have been discussed by Enterline (1976), Peto (1977), and Nicholson (1982) and have been utilized in projections of lung cancer from past asbestos exposure by Nicholson et al. (1982). Information on lung cancer risk from exposures at different ages is available from two studies (Selikoff et al., 1979; Seidman et al., 1979). The analyses of these data provide substantial support for the use of such a formulation for lung cancer.

Information from the insulation workers study on the time course of asbestos cancer risk is given in Figure 3-2, which shows the relative risk of death from lung cancer (the ratio of observed deaths to expected deaths) according to age for individuals first employed between ages 15 and 24 and for those employed between ages 25 and 34. The two curves in Figure 3-2 rise with the same slope and are separated by the 10 years of difference in age at first exposure. This result suggests that the relative risk of developing asbestos-related lung cancer according to time from onset of exposure is independent of age and of the pre-existing risk at the time of exposure. In contrast, both the slope and the value of the excess risk of lung cancer are two to four times greater for the group first exposed at older ages compared to those exposed at younger ages. The similarity of the data for each group in Figure 3-2 suggests that the data be combined and plotted according to time from the onset of exposure. The result is shown in Figure 3-3. The data of Figure 3-3 are plotted according to years from the onset of exposure. However, because of the great stability of union insulation work, the curve also reflects effects according to the duration of exposure up to at least 25 years from the onset of exposure. A linear increase with time from the onset of exposure is seen for about 35 years (to about the time when many insulators would have terminated employment), after which the relative risk falls substantially rather than remain constant as would be expected from the linear increase with continued exposure. The decrease is partially the result of the earlier deaths of smokers from the group under study because of their higher mortality from lung cancer and cardiovascular disease. However, the decrease is not solely the result of the deaths of smokers; a similar rise and fall occurs among those individuals who were smokers at the start of the study compared to smokers in the general population. Part of the decrease may relate to the elimination of asbestos, particularly chrysotile, from the lung; from selection processes, such as differing exposure patterns (e.g., the survivors may have avoided intense exposures); from cohort effects; or from differing individual biological susceptibilities. While the exact reason for the effect is not understood, it is a general phenomenon seen in other mortality studies of asbestos workers (Nicholson et al., 1979; 1983).

The early portions of the curves of Figures 3-2 and 3-3 have three important features. First, after a short delay, the curves show a linear increase in the relative risk of asbestos lung cancer according to time from onset of exposure. Second, Figure 3-3 shows that this increased relative risk is

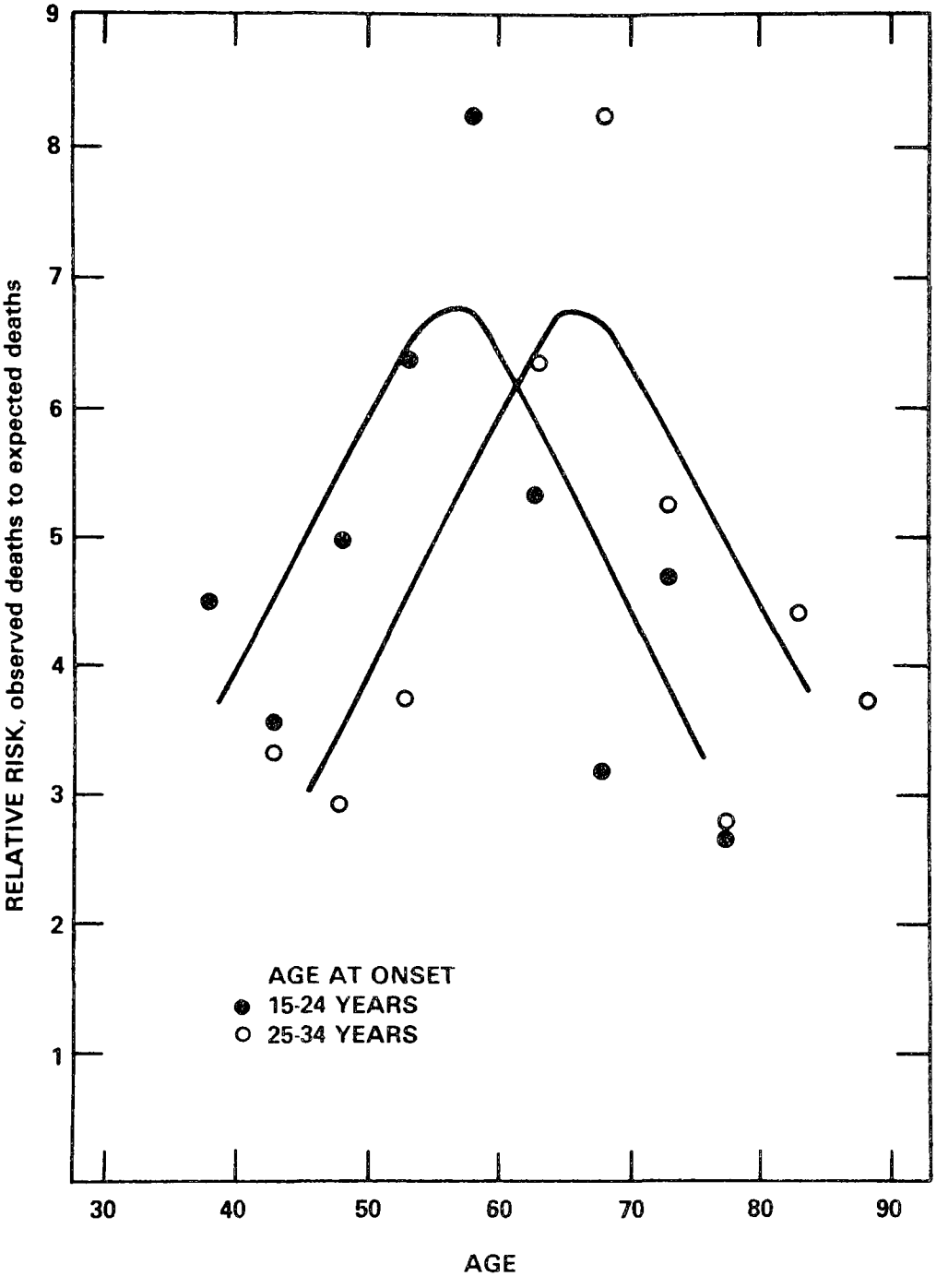

Figure 3-2. The relative risk of death from lung cancer among insulation workers according to age. Data supplied by I.J. Selikoff and H. Seidman.
Source: Nicholson (1982).

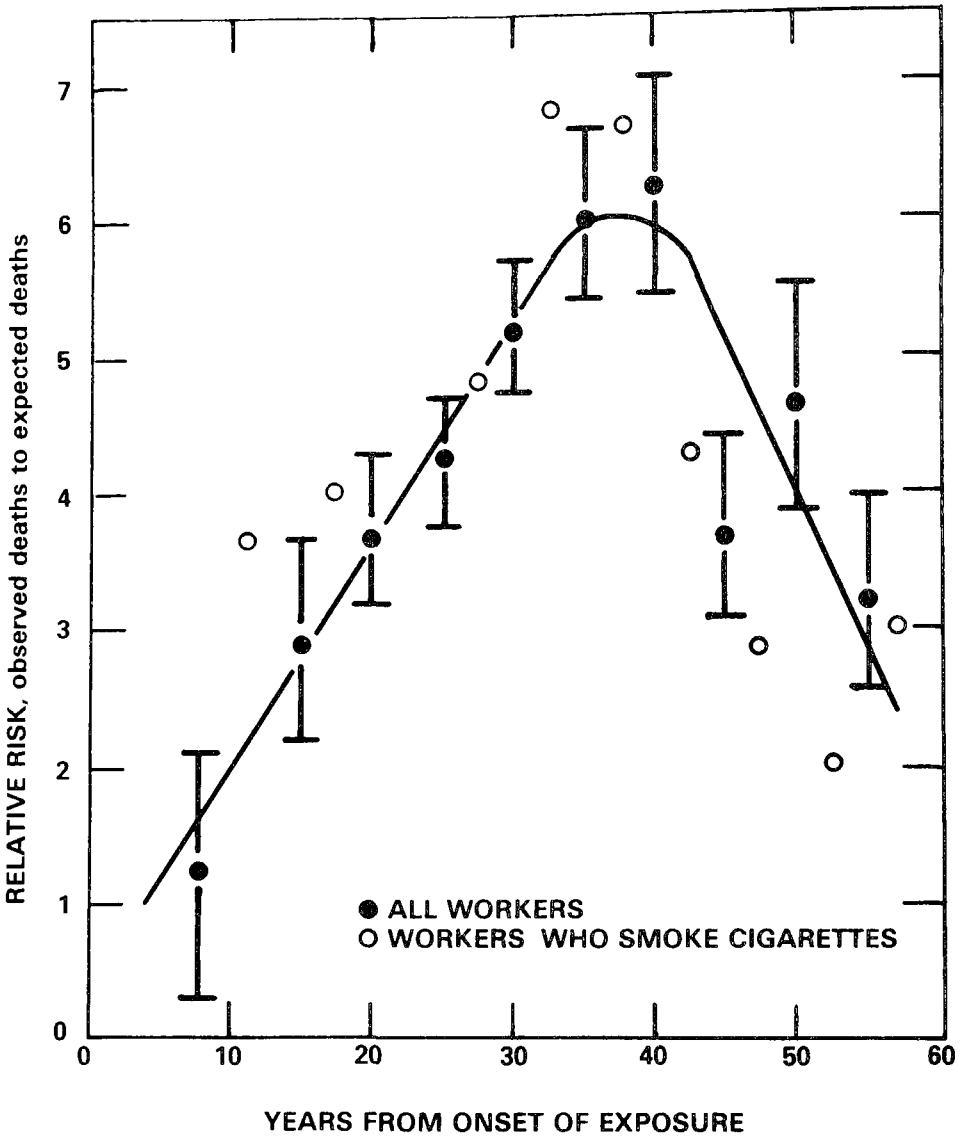

Figure 3-3. The relative risk of death from lung cancer among insulation workers according to time from onset of exposure (● all insulators; ○ indicates insulators who were smoking cigarettes at the start of follow-up in 1967.) Data supplied by I.J. Selikoff and H. Seidman.
Source: Nicholson (1982).

proportional to the time worked, and, thus, to the cumulative asbestos exposure. However, the linear rise can occur only if the increased relative risk that is created by a given cumulative exposure of asbestos continues to multiply the underlying risk for several decades thereafter. Finally, an extrapolated linear line through the observed data points crosses the line of relative risk equal to one (that expected in an unexposed population) at about 5 years from the onset of exposure. This result shows that the increased relative risk appropriate to a given exposure is achieved soon after the exposure takes place. However, if there is a low underlying risk at the time of the asbestos exposure (e.g., for individuals aged 20 to 30), most of the cancers that will arise from any increased risk attributable to asbestos will not occur for many years or even decades until the underlying risk becomes substantially greater

The data of Seidman et al. (1979) also show that exposure to asbestos multiplies the pre-existing risk of lung cancer and that the multiplied risk becomes manifest in a relatively short time. Figure 3-4 depicts the time course of lung cancer mortality beginning 5 years after the onset of exposure of a group exposed for short periods of time. The average duration of exposure was 1.46 years; 77% of the population was employed for less than 2 years. Thus, exposure had largely ceased prior to the beginning of the follow-up period. Figure 3-4 indicates that a rise to a significantly elevated relative risk occurred within 10 years, and that the increased relative risk remained constant throughout the observation period of the study Furthermore, the relative risk from a specific exposure was independent of the age at which the exposure began, whereas the excess risk would have increased considerably with the age of exposure. Seidman et al. (1979) studied the relative risk of death from lung cancer for individuals exposed for less than and greater than 9 months. Table 3-4 lists their data according to the individual's age at the time of entrance into a 10-year observation period. Within a given age category, the relative risk was similar during different decades from onset of exposure, as indicated in Figure 3-4 with the overall data. However, the relative risk also was independent of the age decade at entry into a 10-year observation period (see lines labeled "All" in each exposure category). There was some reduction in the oldest groups. This decrease may be attributed to the same effects manifest at older ages in insulators and to relatively fewer cigarette smokers who might be present in the older groups because of selective mortality.

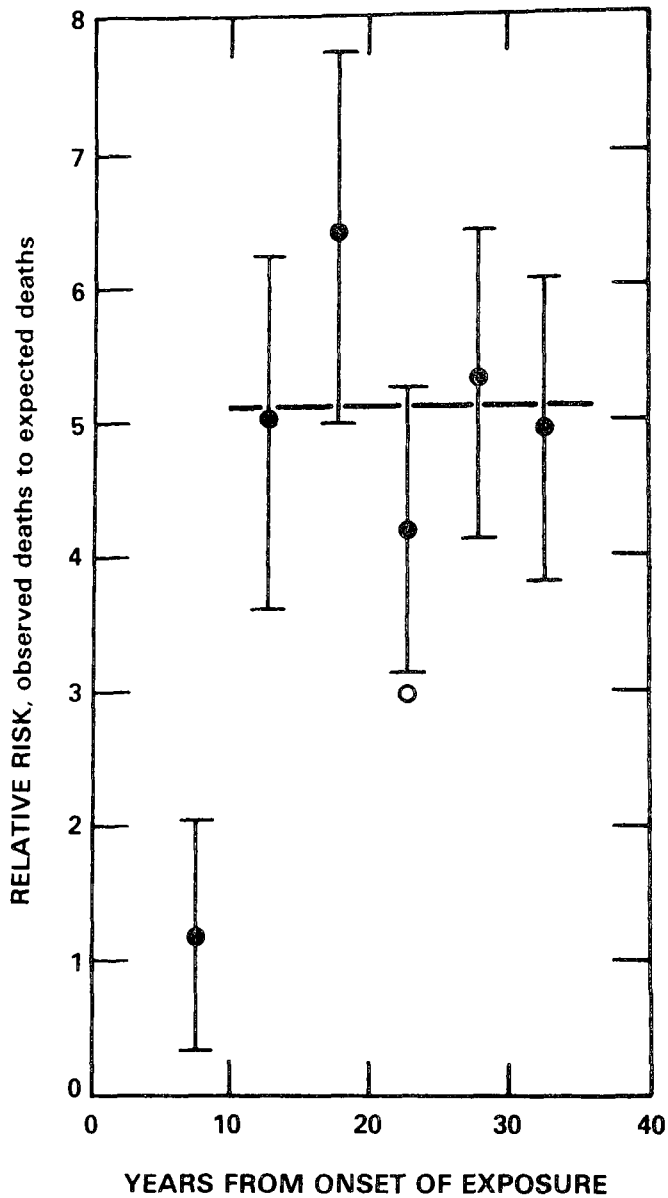

Figure 3-4. The relative risk of death from lung cancer among amosite factory workers according to time from onset of exposure.

Source: Seidman et al. (1979).

TABLE 3-4. RELATIVE RISK OF LUNG CANCER DURING 10-YEAR INTERVALS AT DIFFERENT TIMES FROM ONSET OF EXPOSURE

Years from onset of exposure	Age at start of period, years		
	30-39	40-49	50-59
Lower exposure (<9 months)			
5	0.00 [0.35][a]	3.75 (2)[b]	0.00 [3.04]
15	6.85 (1)	4.27 (3)	2.91 (4)
25	--	2.73 (2)	4.03 (6)
All	3.71 (1)	3.52 (7)	2.58 (10)
Higher exposure (>9 months)			
5	0.00 [0.66]	11.94 (4)	9.93 (8)
15	19.07 (2)	11.45 (5)	5.62 (5)
25	--	13.13 (6)	7.41 (8)
All	11.12 (2)	12.32 (16)	7.48 (21)

[a] [] = No cases seen. Number of cases expected on the basis of the average relative risk in the overall exposure category.

[b] () = Number of cases.

Source: Seidman et al. (1979).

In terms of carcinogenic mechanisms, asbestos appears to act like a lung cancer promoting agent. However, because of the continued residence of the fibers in the lung, the promotional effect does not diminish with time after cessation of exposure, as it may with chemical or tobacco promoters. Further, inhalation of the fibers can precede initiating events because the fibers remain continuously available in the lung to act after other necessary carcinogenic processes occur.

A feature of Figure 3-3 that is important in the assessment of asbestos carcinogenic risk is the decrease in relative risk after 40 years from the onset of exposure or 60 years of age. As mentioned previously, this decrease is not completely understood but it has generality. A virtually identical time course of lung cancer risk occurs in asbestos factory employees (Nicholson et al., 1983) and in Canadian chrysotile miners and millers (Nicholson et al., 1979). Because of the significant decrease at long times from the onset of exposure and older ages, observations on retiree populations can seriously

understate the actual risk of asbestos-related death during earlier years. To the extent that time periods between 25 and 40 years from the onset of exposure are omitted from observation, a study will underestimate the full impact of asbestos exposure on death.

To appreciate the effect of the observed lung cancer time-dependence upon the results of an epidemiological study, the excess risk of lung cancer was calculated for different observation periods for a hypothetical group that was exposed for 25 years beginning at age 20. The time course of the risk was set proportional to that of Figure 3-3, and 1977 general population rates were used (NCHS, Annually: 1967-1977). Table 3-5 lists the percent excess lung cancer mortality observed for three follow-up periods, 10 years, 20 years, and lifetime, beginning at different ages. The table indicates that the percent excess risk from start of exposure at age 20 to the complete death of all cohort members is 55% of the maximum that would be achieved 32.5 years after onset of exposure. The percent excess risk rises up to age 50 because the follow-up period starts later, reflecting the increased relative risk concomitant with increased exposure. For observations starting after age 50, it falls substantially, such that follow-up begun at age 65 observes only 38% of the full risk.

To the extent that a group under observation has an age distribution that is similar to the number alive in each quinquennium in a lifetime follow-up, an observation for any period of time would reflect the same mortality ratio

TABLE 3-5. ESTIMATES OF THE PERCENTAGE OF THE MAXIMUM EXPRESSED EXCESS RISK OF DEATH FROM LUNG CANCER FOR A 25-YEAR EXPOSURE TO ASBESTOS BEGINNING AT AGE 20[a]

Age at start of observation, years	Period of follow-up, years			Years from onset of exposure
	10	20	Lifetime	
20	02	32	55	0
30	34	65	55	10
40	69	91	56	20
50	97	81	55	30
60	73	55	46	40
65	55	41	38	45
70	37	29	29	50

[a]The maximum expressed risk is that manifest 7.5 years after the conclusion of the 25-year exposure.

as an observation from the onset of exposure to the death of the entire cohort. To some extent, this situation applies to insulation workers, although they have fewer older individuals than would occur had their mortality been governed by general population data. (Their higher risk leads to an earlier death and there is some loss due to lapse in cohort membership.) Since very old groups are underrepresented, the excess relative risk of 3.60 (4.60-1) (BE) documented by Selikoff et al. (1979) overestimates the age 20 to 85+ risk, calculated in this document as 2.53: [excess relative risk at 32.5 years (5.6-1) (Figure 3.3) X reduction for lifetime exposure (0.55) (Table 3-5)].

The data in Table 3-4 came from observations of long-term exposures to high concentrations of asbestos (>10 f/ml), where preferential death of susceptible individuals occurred. Thus, appropriate comparisons between heavily exposed groups could be made on the basis of lifetime risk (i.e., 55% of the maximum). However, in groups exposed to low levels (<0.1 f/ml), even for many years, selection effects may be much less important. A minimal excess risk would barely affect the pool of susceptibles. A lesser effect would also be expected from short-term exposures (to less than extreme concentrations). For such lower exposures, a relative risk unaffected by selection effects probably would best represent the exposure circumstances. Such risks (at high exposure) are seen in the rising slope of Figure 3-3 and the relative risk in Figure 3-4. Other studies will likely be affected by selection effects to some extent.

The above discussion supports a general model for lung cancer in which the excess risk that occurs t years from the onset of exposure is proportional to the cumulative exposure to asbestos at time t-10 years times the age and calendar year risk of lung cancer in the absence of exposure. The incidence of lung cancer can be formally expressed by

$$I_L(a,y,t,d,f) = I_E(a,y)\,[1 + K_L \cdot f \cdot d(t-10)] \qquad (3\text{-}1)$$

Here, $I_L(a,y,t,d,f)$ is the lung cancer mortality observed or projected in a population of age a, observed in calendar period y, at t years from the onset of an asbestos exposure of duration d, and intensity f. $I_E(a,y)$ is the age and calendar year lung cancer mortality expected in the absence of exposure. If smoking data are available, I_L and I_E can be smoking-specific incidences. In this case, f is the intensity of asbestos exposure in fibers

longer than 5 μm/ml (f/ml), d is the duration of exposure up to 10 years from observation, and K_L is a proportionality constant, which is a measure of the carcinogenic potency of the asbestos exposure. Alternatively, (f·d) is the cumulative exposure (to 10 years prior to observation) and K_L is the slope of the exposure-response relationship. A delay in manifestation of risk is based on the data of Seidman et al. (1979) and Selikoff et al. (1979). Equation 3-1 illustrates that the relative risk of lung cancer, I_L/I_E, is independent of age and depends only on the cumulative exposure to asbestos.

Different asbestos varieties have different size distributions and the fraction greater than 5 μm depends on fiber type and the production process (Nicholson et al., 1972; Gibbs and Hwang, 1975). Animal data demonstrate that dimensionality is an important variable in fiber carcinogenicity. Thus, K_L would be expected to depend, to some extent, on fiber type and dimension. In practice, however, uncertainties in establishing quantitative dose-response relations, through the application of Equation 3-1 to observed data, may preclude the determination of K_L by fiber type.

3.5 MULTIPLE FACTOR INTERACTION WITH CIGARETTE SMOKING

The multiplicative interaction between asbestos and the underlying risk of lung cancer is seen in the synergism between cigarette smoking and asbestos exposure, which was first identified by Selikoff et al. (1968). Recent data on U.S. insulation workers confirm and greatly extend the initial findings (Hammond et al., 1979a). In this extensive study, 12,051 asbestos workers, 20 or more years from the onset of their exposure, were followed from 1967 through 1976. At the outset, 6,841 workers volunteered a history of cigarette smoking while 1,379 said they had not smoked cigarettes. By January 1, 1977, 299 deaths had occurred among the cigarette smokers, and 8 deaths occurred among workers who had not smoked cigarettes.

This experience was compared on an age- and calendar-year-specific basis with that of comparable workers who had the same smoking habits and were a part of the American Cancer Society's prospective Cancer Prevention Study (Hammond, 1966). A total of 73,763 white males who had only a high school education and were exposed to dusts, fumes, gases, or chemicals during non-farming work were selected for the control group. The age standardized rates per 100,000 person-years for each group are shown in Table 3-6. The results show that both the smoking and non-smoking lung cancer risk is multiplied five times by the insulator's asbestos exposure. However, the risk is low for

TABLE 3-6. AGE-STANDARDIZED LUNG CANCER DEATH RATES FOR CIGARETTE SMOKING AND/OR OCCUPATIONAL EXPOSURE TO ASBESTOS DUST COMPARED WITH NO SMOKING AND NO OCCUPATIONAL EXPOSURE TO ASBESTOS DUST

Group	Exposure to asbestos?	History cigarette smoking?	Death rate[a]	Mortality difference	Mortality ratio
Control	No	No	11.3	0.0	1.00
Asbestos Workers	Yes	No	58.4	+47.1	5.17
Control	No	Yes	122.6	+111.3	10.85
Asbestos Workers	Yes	Yes	601.6	+590.3	53.24

[a]Rate per 100,000 person-years standardized for age on the distribution of the person-years of all the asbestos workers. Number of lung cancer deaths based on death certificate information.

Source: Hammond et al. (1979a).

non-smokers; therefore, multiplying it five times does not result in many cases, although any excess is undesirable. On the other hand, smoking by itself causes a major increase and when that high risk is multiplied five times, an immense increase is found. Corroborative data on the multiplicative smoking-asbestos interaction are seen in studies by Berry et al. (1979) and McDonald et al. (1980).

The study by Hammond et al. (1979a) carried the asbestos-smoking interaction a step further, to show increased risk of death of asbestosis. As noted previously, insulation work carried a risk of fatal progressive pulmonary fibrosis, and some workers who never smoked cigarettes died of asbestosis. Nevertheless, asbestosis mortality for workers who smoked 20 or more cigarettes a day was 2.8 times higher than that for workers who never smoked regularly. Cigarette smoking, with resulting bronchitis and emphysema, adds an undesirable and sometimes unsupportable burden to the asbestos-induced pneumoconiosis. Interactive effects between cigarette smoking and the prevalence of X-ray abnormalities have been reported previously (Weiss, 1971). However, no relationship between cigarette smoking and the risk of death from mesothelioma or gastrointestinal cancer was found in the Hammond et al. study (Seidman, quoted in Frank, 1979).

3.6 METHODOLOGICAL LIMITATIONS IN ESTABLISHING DOSE-RESPONSE RELATIONSHIPS

Establishing dose-response relationships for human exposure to asbestos is associated with substantial difficulties. Perhaps the most important consideration is that current health effects are the result of exposures to dust in previous decades when few and imperfect measurements of fiber concentrations were made. Current estimates of those concentrations can be inaccurate because individual exposures were highly variable. Further, while disease response now can be established through epidemiological studies, these also can be misleading because of methodological limitations. Despite this possible inaccuracy, useful estimates of risk can be made to provide an approximate measure of asbestos disease potential in environmental circumstances. Limitations of existing data can be taken into account and their recognition can stimulate appropriate research to fill identified gaps.

One limitation on the accuracy of exposure-response data for asbestos disease is the lack of information concerning past fiber exposures of those populations whose mortality or morbidity have been evaluated. Relatively few measurements were made in facilities that used asbestos fibers before 1965. Further, those measurements quantified all dust (both fibers and particles) present in the workplace air Current techniques, which use membrane filters and phase contrast microscopy for the enumeration of fibers longer than 5 μm, have been utilized in Great Britain and the United States only since 1964 (Ayer et al., 1965; Holmes, 1965) and have been standardized in the United States only since 1972 (NIOSH, 1972; 1979) and even later in Great Britain (Advisory Committee on Asbestos, 1979a, b).

Modern counting techniques may be used to evaluate work practices and ventilation conditions believed to be typical of earlier activities. However, it is always difficult to duplicate materials and conditions of earlier decades and such retrospective estimates are necessarily uncertain. Alternatively, fiber counting techniques and the particle counting instrumentation of earlier years can be used together to simultaneously evaluate a variety of asbestos-containing aerosols. The comparative readings serve as a "calibration" of the historic instrument in terms of fiber concentrations. Unfortunately, the calibration depends on the type and size distribution of the asbestos used in the process under evaluation and the quantity of other dust present in the aerosol. Thus, no universal conversion has been found between earlier dust measurements and current fiber counts.

In the United States and Canada, those few data that were obtained on asbestos workers' exposures before 1965 were based primarily upon total dust concentrations that were measured using a midget impinger. Fibers were inefficiently counted with this instrument because bright field microscopy was used. Attempts to compare fiber concentrations with midget impinger particle counts generally showed poor correlations (Ayer et al., 1965; Gibbs and LaChance, 1974). Figure 3-5 provides an illustration of these correlations. In the United Kingdom, the thermal precipitator was used from 1951 through 1964 in one plant for which environmental data have been published. This instrument does not allow accurate evaluation of fiber concentrations and the variability in the correlation between fiber measurements and thermal precipitator data is reported to be large (Advisory Committee, 1979b) but no specific data were given.

Even with the advances in fiber counting techniques, significant errors may be introduced into attempts to formulate general fiber exposure-response relationships. The current convention of counting only fibers longer than 5 μm was chosen solely for the convenience of optical microscopic evaluation (surveillance agencies are generally limited to such instrumentation). This method does not necessarily correspond to any sharp demarcation of effect for asbestosis, lung cancer, or mesothelioma. While it is readily understood that counting only fibers longer than 5 μm enumerates but a fraction of the total number of fibers present, there is incomplete awareness that the fraction counted is highly variable. The results depend upon the fiber type, the process or products used, and the past history of the asbestos material (e.g., old vs. new insulation material), and other factors. For example, the fraction of chrysotile fibers longer than 5 μm in an aerosol can vary by a factor of 10 (from as little as 0.5% of the total number to more than 5%). When amosite aerosols are counted, the fraction longer than 5 μm may be 30%, extending the variability of the fraction counted to two orders of magnitude (Nicholson et al., 1972; Nicholson, 1976a; Winer and Cossete, 1979).

Even if consideration is restricted to fibers longer than 5 μm, many fibers are missed by optical microscopy. Using electron microscopy, Rendall and Skikne (1980) have measured the percentage of fibers with a diameter less than or greater than 0.4 μm (the limit of resolution of an optical microscope) in various asbestos dust samples. In general, they found that more than 50% of the 5 μm or longer fibers were less than 0.4 μm in diameter and, thus,

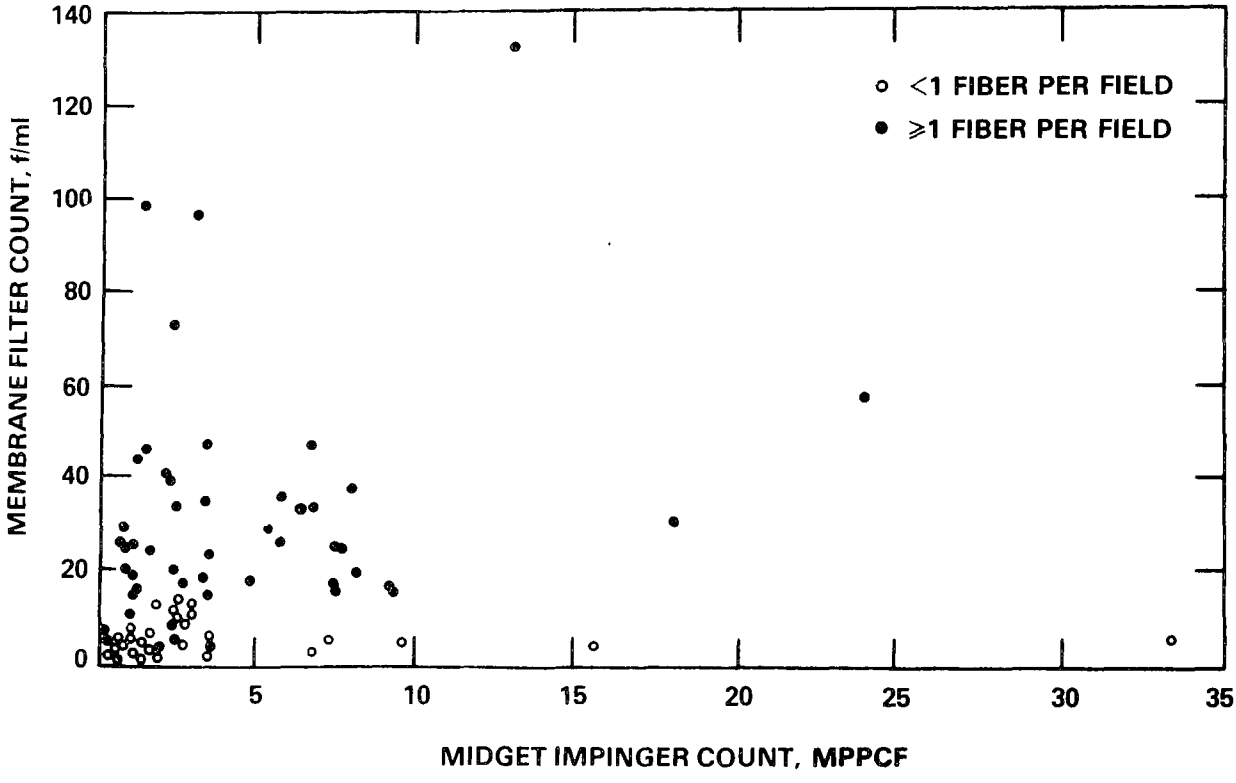

Figure 3-5. A plot of membrane filter and midget impinger counts; MPPCF represents millions of particles per cubic foot.

Source: Gibbs and LaChance (1974).

would not be visible using a standard phase contrast optical microscope. Moreover, the diameter distribution also varied with activity and fiber type. As a result, the fraction of fibers that was longer than 5 μm and visible by light microscopy varied from about 22% in chrysotile and crocidolite mining and amosite/chrysotile insulation manufacture to 53% in amosite mining. Intermediate values of 40% were measured in chrysotile brake lining manufacture and 33% in amosite mill operations. Thus, even perfect measurement of workplace air, with accurate enumeration of fibers according to currently accepted methods, would be expected to lead to different exposure-response relationships for any specific asbestos disease when different work environments are studied. Conversely, risks estimated for a given exposure circumstance must have a large range of uncertainty to allow for the variability resulting from fiber size effects.

Those uncertainties that exist in the physical determinations of past fiber concentrations and the difficulty in evaluating the most important exposure parameter in current measurements are exacerbated by the sampling limitations in determining individual or even average exposures of working populations; only a few workers at a worksite are monitored and then only occasionally. Variability in work practices, ventilation controls, use of protective equipment, personal habits, and sampling circumstances add considerable uncertainty to available information on exposure.

Variability in exposure-response relationships obtained in different studies can also be attributed to statistical variability associated with small numbers and to methodological difficulties in the estimation of disease. Studies can be significantly biased by inclusion of recently employed workers in study cohorts, use of short follow-up periods, and improper treatment of the various time factors that are important in defining asbestos cancer. Inadequacies of tracing can lead to significantly inaccurate estimates of disease. Generally, from 10 to 30% of an observation cohort will be deceased (sometimes even less). If 10% of the group is untraced and most are deceased, very large errors in the determination of mortality could result, even if no person-years are attributed to the lost-to-follow-up group. Finally, the choice of comparison mortality rates can introduce significant errors. Local rates are generally the most desirable to use, but these may be unstable because of small numbers, or they may be affected by special circumstances (e.g., other industry). Data on general population worker mortality rates are

not available, and existing general population rates may overstate the expected total mortality because of a "healthy worker effect" (Fox and Collier, 1976). Proper consideration of smoking habits is important in the determination of lung cancer risks. Unfortunately, full information on the smoking patterns of all individuals in a cohort often is not available.

Thus in summary, calculations of unit risk values for asbestos must be viewed with caution as they are uncertain and aspects of them are necessarily based on estimates that are subjective to some extent because of the following limitations in data: 1) statistical uncertainties and systematic biases in epidemiological studies, 2) conversions of particle counts to fiber exposures are uncertain, and 3) very importantly, the nonrepresentative nature of the exposure estimates.

3.7 QUANTITATIVE DOSE-RESPONSE RELATIONSHIPS FOR LUNG CANCER

In theory, exposure-response relationships can best be determined from studies in which individal exposures are estimated for each cohort member, subgroups are established according to cumulative exposure (with proper consideration of time factors), and an exposure-response relationship is determined from effects observed in all exposure categories. Consistencies in the observed exposure-response relationships strengthen the risk estimates made from such studies. In practice, however, the estimation of individual exposures involves considerable uncertainties. An exposure estimate for each worker must use historic data on particle counts and recent measurements of the ratio of fiber to particle concentrations. Unfortunately, complete job histories are not always available for each worker; often only employment departments are known. Second, relatively few dust counts were made before 1965 and exposure data may not exist for many plant jobs. Third, few fiber-particle comparison counts are made and these often demonstrate great variability (Figure 3-5). Finally, worker mobility may significantly alter his or her exposure from that estimated at a work station. Systematic and random biases that may occur from any of these uncertainties can lead to significant alteration of a measured exposure-response relationship, even in studies that demonstrate a near perfect linear relationship.

In some studies, individual exposures are not determined for each cohort member, but only for cancer cases of interest and a selected number of controls. Odds ratios are then calculated according to exposure, but they are limited by the uncertainties of small numbers and confounding effects in addition to all of the uncertainties discussed above.

Finally, two studies will be considered for which information is available only for the group as a whole. Both studies used recent determinations of fiber concentrations in work activities believed to represent those of previous years. While the studies are not affected by the uncertainties of fiber-particle conversions, they are uncertain because members of each group were exposed to highly variable asbestos concentrations. In one case (insulators), each worker experienced variable exposure, and in the other case (an amosite insulation factory), different workers experienced different exposures; however, a plant average exposure was estimated. Both estimates could be in error to the extent that all jobs were not properly weighted in the sampling program.

In the following analysis of 11 studies, all available exposure-response information will be used. When such data are inconsistent or possible biases are perceived, alternative analyses will also be undertaken (weighted regression analysis or use of averaged risk-exposure data). A value for K_L will be calculated for each study using either the slope of the observed dose response data, the odds ratios of case control analyses, or the ratio of excess lung cancer risk to average exposure. The calculations will generally use Equation 3-1, $I_L = I_E(1 + K_L \cdot f \cdot d)$. Rearranging one obtains

$$K_L = [(I_L - I_E)/I_E]/f \cdot d \qquad 3\text{-}2a$$

or

$$K_L = [(I_L/I_E) - 1]/f \cdot d \qquad 3\text{-}2b$$

The K_L values obtained are listed in Table 3-7 and displayed in Figure 3-6. The 95% confidence limits, calculated from the variance of the observed number of lung cancer cases are also shown in Table 3-7 For example, consider the study of Peto (1980). In a cohort exposed after 1950, 11 lung cancers were observed and 3.35 were expected in the group followed 15 years after first employment. From Equation 3-2a, K_L = (11 3.35)/3.35/250 f-yr/ml = 7.65/3.35/250 = 0.0091 [fiber-years/ml is abbreviated (f-yr/ml)]. [As discussed later, an appropriate exposure for the cohort is 250 f-yr/ml.] The 95% confidence limits on a Poisson variant of 11 are 5.4 and 19.7. Thus, the range of K_L will be from K_L = 0.0024, (5.4 - 3.35)/3.35/250 to K_L = 0.019, (19.7 3.35)/3.35/250. The same procedure will also be used in estimating

TABLE 3-7. COMPUTATIONAL DATA ON THE STATISTICAL VARIABILITY ASSOCIATED WITH K_L

	K_L	Deaths			Range of observed deaths	Range of K_L
		Expected	Observed	Excess		
Selikoff et al. (1979)	0.0091	105.6	429	324.4	388.4 - 469.6	0.0079 - 0.010
Seidman et al. (1979)	0.068	18.5	83	64.5	65.1 - 100.9	0.0049 - 0.0087
Henderson and Enterline (1979)	0.0044	23.3	62	39.7	46.6 - 77.4	0.0026 - 0.0060
Weill et al. (1979)	0.0051	(32.2)[a]	51	(17.8)[a]	37.0 - 65.0	0.0014 - 0.0094
Finkelstein (1983)	0.067	2.0	17	15.0	9.9 - 27.2	0.035 - 0.110
Peto (1980) (>1950)	0.0091	3.35	11	7.65	5.4 - 19.7	0.0024 - 0.019
Peto (1980) (<1950)	0.0009	16.83	26	9.17	17.0 - 38.0	0.00002 - 0.0021
Dement et al. (1983a, b)	0.042	9.8	33	23.2	22.7 - 46.3	0.023 - 0.066
Berry and Newhouse (1983)	0.0006	Case-control calculations				
Lidell et al. (1977)	0.0006	184	230	46	200.3 - 259.7	0.0002 - 0.001
Nicholson et al. (1979)	0.0030	7.5	20	13.9	12.2 - 30.8	0.0010 - 0.0083
Rubino et al. (1979)	0.0055	Case-control calculations				

[a]Adjusted for low trace.

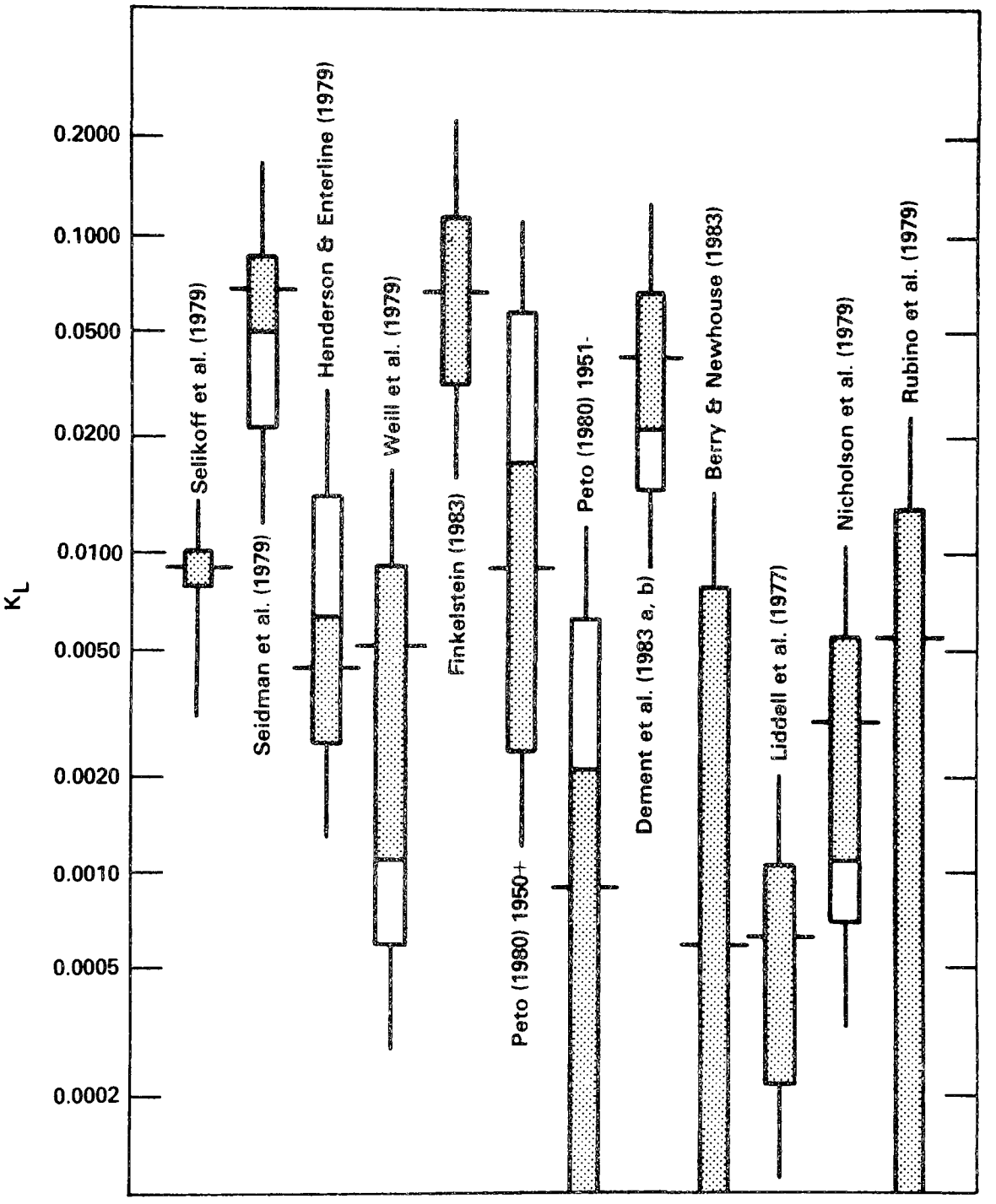

Figure 3-6. The values for K_L, the fractional increase in lung cancer per f-yr/ml exposure in 11 asbestos exposed cohorts. The shaded bar represents the 95% confidence limits on K_L associated with the statistical variability of number of cases observed. The open bar represents adjustments associated with possible biases. The line represents estimated uncertainties associated with exposure estimates.

the variability in studies that provide exposure-response data by cumulative exposure category. While the variation in K_L could be calculated from expected variances of the individual exposure categories, the above procedure will yield very similar results. In addition to statistical variations, possible systematic biases considered in the analysis of each study will be displayed in Figure 3-6. Finally, the effect of an additive ± two-fold range of uncertainty in cumulative exposure will be indicated in Figure 3-6. This two-fold range is a subjective choice, but it is felt to be a realistic estimate of the uncertainty of all the sampling problems mentioned previously.

3.7.1 Insulation Application; United States (Chrysotile and Amosite)

The previously discussed mortality study of Selikoff et al. (1979) can be combined with information on asbestos exposure to provide an exposure-risk estimate. The data on insulators' exposure have been reviewed by Nicholson (1976a) and are summarized in Table 3-8. Using the standard membrane filter

TABLE 3-8. SUMMARY OF AVERAGE ASBESTOS AIR CONCENTRATION DURING INSULATION WORK[a] Selikoff et al. (1979)

Research group	Average fiber concentration, f/ml	
	Light and heavy construction	Marine work
Nicholson (1975)	6.3	
Balzer and Cooper (1968)		
Cooper and Balzer (1968)	2.7	6.6
Ferris et al. (1971)		2.9
Harries (1971)		8.9
Average concentrations of all visible fibers counted with a konimeter and bright-field microscopy		
Murphy et al. (1971)		8.0
Fleisher et al. (1946)		30-40
Estimates of past exposure based on current membrane-filter data		
Nicholson (1976a)	10-15	

[a]Average concentrations of fibers longer than 5 μm evaluated by membrane filter techniques and phase-contrast microscopy.

Source: Nicholson (1976a).

technique of the U.S. Public Health Service for counting asbestos fibers (NIOSH, 1979), three different laboratories in the United States have found that the average fiber concentration of asbestos dust in insulation work between 1968 and 1971 ranged from about 3 to 6 f/ml. A similar study used the same technique in the Devonport Naval Dockyard in Great Britain, and obtained 8.9 f/ml for the average of long-term samples of asbestos concentrations measured during the application of insulation materials aboard ship (Harries, 1971). The research that led to these data indicated that peak exposures could be extremely high. For example, it was not uncommon for 2- to 5-minute concentrations of asbestos to exceed 100 f/ml during the mixing of cement. However, this mixing would be done perhaps once an hour. Thus, exposures measured during that hour, including the mixing, would seldom average more than 10 f/ml. Similar experiences were subsequently reported by Cooper and Miedema (1973), who stated that "peak concentrations may be high for brief periods, while time-weighted averages are often deceptively low."

Direct information on asbestos fiber concentration, measured by the currently prescribed analysis procedures, is available only after 1966. Insulation materials have changed from earlier years. Fibrous glass has found extensive use, and cork is used rarely. Moreover, the asbestos composition of insulation products has changed. Pipe covering and insulation block may have had twice the asbestos content in past years as in the period from 1968 to 1970. However, during this period work practices were virtually identical to those of previous years, and during the period of these measurements, few controls of consequence were used. Thus, dust concentrations measured under these conditions have relevance for the estimate of levels of past years. Considering the possible doubling of asbestos content of insulation materials, the data from the studies listed in Table 3-6 would suggest that the insulators' average exposures in the United States during past years could have ranged from 10 to 15 f/ml for commercial and industrial construction. In marine construction, it may have been between 15 and 20 f/ml A value of 15 f/ml is used in this document as an overall average. However, because of the great variability in work activities of this group, the range of uncertainty in the exposure is estimated to be 10 to 45 f/ml; this range is indicated in Figure 3-6.

This information and the data in Figure 3-3 allow the calculation of a lung cancer risk per cumulative unit asbestos exposure (in f-yr/ml) from the

linearly rising portion of the curve, the slope of which is 0.16 relative risk units per year or 0.0107 per f-yr/ml (divided by an average exposure intensity of 15 f/ml). However, the data of Figure 3-3 used BE in establishing lung cancer mortality. Adjusting to DC diagnosis reduces the value of K_L from 0.0107 to 0.0091; multiply by (3.06/3.60), the ratio of the DC to BE relative excess risk in Table 3-1.

3.7.2 Insulation Manufacturing; Paterson, NJ (Amosite), Seidman et al. (1979)

The study by Seidman et al. (1979) also can be used for quantitative risk estimates. While no data exist for air concentrations at the time the Paterson factory operated, information, in terms of fiber counts, exists for air concentrations in two other plants that manufactured the same products with the same fiber and machinery. One of these plants, located in Tyler, Texas, opened in 1954 and operated until 1971 and the other plant, located in Port Allegany, Pennsylvania, opened in 1964 and closed in 1972. Efforts to control dust were limited in all three facilities. One plant was housed in a low Quonset-type building where the confined space exacerbated dust conditions. During 1967, 1970, and 1971, asbestos fiber concentrations in these plants were measured by the U.S. Public Health Service, and the results were published in the Asbestos Criteria Document of the National Institute for Occupational Safety and Health (NIOSH, 1972). The arithmetic averages of these exposure measurements for Tyler (Plant X) and Port Allegany (Plant Y), obtained using current fiber counting techniques, were 39.1 and 28.9 f/ml, respectively, with an overall average of 34.9 f/ml. These two recently operating plants had very similar average exposures; therefore, the Paterson plant exposures probably did not differ significantly.

The mortality data presented by Seidman et al. (1979) are in a different format from that usually encountered in epidemiological studies. Seidman et al. compared the cumulative mortality, by cause, of a cohort of 820 asbestos-exposed workers with a similarly aged hypothetical control population followed over the same calendar years. Thus, the number of expected deaths in a time period is based on the number of individuals expected to be alive at the start of the period, rather than on the number alive in the exposed population at the start of the period. Because the mortality of the cohort is considerably above that expected, the number assumed alive at the start of later observation periods is much greater than the actual number. Table 3-9 lists the exposure groups of Seidman et al (1979), the average work period of

TABLE 3-9. OBSERVED AND EXPECTED CUMULATIVE PROBABILITY OF DEATH FROM LUNG CANCER 5 THROUGH 35 ELAPSED YEARS SINCE THE ONSET OF WORK IN AN AMOSITE ASBESTOS FACTORY, 1941-1951, BY LENGTH OF TIME WORKED

Length of time worked	Number of men at 5-year point	Average exposure time, years	Estimated average dose f-yr/ml	Expected percentage of deaths[a]	Observed percentage of deaths (DC)		Ratio
>1 mo.	61	0.04	1.4	2.95	6.07	(3)[b]	2.06
1-2 mo.	90	0.09	3.2	2.70	7.34	(5)	2.72
2-3 mo.	82	0.17	5.9	2.79	7.42	(6)	2.66
4-6 mo.	148	0.29	10.2	2.47	5.90	(8)	2.38
6-12 mo.	125	0.59	20.6	2.15	10.21	(12)	4.74
1-2 yr.	125	1.28	44.8	2.02	12.41	(15)	6.14
2+ yr.	188	4.77	166.9	2.34	18.51	(34)	7.91
All times	820	1.46	51.1[c]	2.40	10.71	(83)	4.46

[a]Adjusted to a person-years-at-risk basis.

[b]() = number of lung cancer deaths.

[c]Person-weighted average.

Source: Seidman et al. (1979).

each group, the estimated cumulative exposure using 35 f/ml as the average intensity of exposure for the group, the observed cumulative percentages of deaths (DC), and the expected cumulative percentages of death, adjusted to a person-years-at-risk basis.

A group average cumulative exposure of 51 f-yr/ml is calculated from the work duration of all cohort members. This average gives a value of 0.068 for K_L [(10.71 observed/2.40 expected -1)/51 f-yr/ml] (using Equation 3-2b and data from Table 3-7). The high Standard Mortality Ratios (SMR's) at low durations of exposure suggest that general population rates may be inappropriately low for the study group, because all of the short-term exposure categories are proportionately higher than expected (by extrapolating from the longer exposure period data). The underestimate of expected rates may be a factor of 2; this would correspondingly lower K_L in Figure 3-6.

3.7.3 Asbestos Products Manufacturing; United States (Chrysotile and Crocidolite), Henderson and Enterline (1979)

The data of Henderson and Enterline (1979) (Figure 3-1) can be used to establish fiber dose-response data even though their data were presented in terms of total dust concentrations measured in millions of particles per cubic foot (mppcf). No data exist on the conversion between mppcf and f/ml for most of the plants studied. Data do exist on the relationship between fiber and total dust concentrations in textile operations and asbestos cement production. Dement et al. (1982) found a conversion of 3 f/ml/mppcf was appropriate to most textile operations, although Ayer (1965) had earlier suggested a value of 6 f/ml/mppcf. In a plant making asbestos cement pipe and sheets, Hammad et al. (1979) determined the conversion value to be 1.4. The lower value probably would be most applicable to the Henderson and Enterline circumstance because of the extensive use of cement and other mineral particles in asbestos products manufacturing. The least squares regression line through the points in Figure 3-1 is SMR = 100 + 0.66 x mppcf. Using a value of 1.5 f/ml/mppcf to represent the conversion relationship, the estimate of K_L is 0.0044 (0.66/100/1.5). (Dividing by 100 to convert an increase in SMR to an increase in relative risk.)

As described previously, observing a cohort beginning at age 65 seriously understates the full impact of asbestos exposure. Most of the workers whose mortality experience was graphed in Figure 3-1 began employment before age 25.

It was estimated that a study of a retiree cohort could understate mortality by as much as 60% relative to the maximum observable risk (Table 3-3). A possible 2.5-fold increase in the value of K_L is indicated in Figure 3-6.

3.7.4 Asbestos Cement Products; United States (Chrysotile and Crocidolite), Weill et al. (1979), Hughes and Weill (1980)

A study of an asbestos cement production facility provides exposure-response information (Weill et al., 1979; Hughes and Weill, 1980). However, the data quality is limited because of uncertainties in the mortality data. While the experience of 5,645 individuals was reported, only 1,791 had been employed for longer than 2 years. Thus, exposures were limited for most cohort members. More significantly, tracing was accomplished through information supplied on vital status by the Social Security Administration. This method allowed the vital status of only 75% of the group to be determined. Those individuals untraced were considered alive in the analyses. This assumption can lead to serious misestimates of mortality because before 1970, many deaths, particularly of blacks, were not reported to the Social Security Administration. The percentage of unreported deaths of both sexes ranged from nearly 80% in 1950 to 15% in 1967 (Aziz and Buckler, 1980). Thus, many cohort members who were considered alive could be deceased. This inaccuracy is likely to be the source of the extraordinarily low overall reported mortality of the cohort, with deficits of about 40% commonly seen in several exposure categories. (The overall SMR is 68.)

Two methods can be used to adjust an incomplete trace. In one method, the overall SMR for lung cancer, 104, is divided by the SMR for non-asbestos related causes to give a corrected relative risk for lung cancer. This method yields a value for K_L of 0.0060, using a value of 64 mppcf for the group exposure and a fiber-particle conversion factor of 1.4 (Hammad et al., 1979) [(104/68) - 1]/64/1.4 (Cf. equation 3-2b). Alternatively, a regression of SMR on dose yields SMR = 77 + 0.46 x mppcf. The low value of SMR at zero exposure probably is the result of missing deaths. If the percent missing is similar in each category, then K_L = 0.0043, (0.46/100/1.4/0.77), where the 3 divisions account for conversion of SMR to relative risk, mppcf to f/ml, and to a SMR of 100 at zero dose. The average of these values, 0.0052, will be used for the point estimate of K_L. The assumption that there is an equal percentage of missing deaths in each category is uncertain. There are more untraced deaths

in the lowest category (J. Hughes, personal communication). However a greater percentage of those untraced in the most exposed group may be deceased (because of longer exposure and greater age). If all of the untraced deaths are assumed to be in the three lowest exposure categories and the regression line for SMR is forced through the origin, its slope is 0.040; (mppcf); K_L is 0.0029. This downward adjustment is indicated in Figure 3-6.

3.7.5 Asbestos Cement Products; Ontario, Canada (Chrysotile and Crocidolite), Finkelstein (1983)

A recent study by Finkelstein (1983) relates mortality in an asbestos cement products facility to measured exposures. He established a cohort of 241 production and maintenance employees from records of an Ontario asbestos cement factory. The cohort consisted of all individuals who had 9 or more years of employment beginning before 1960. Their mortality experience was followed through October 1980. (An expanded cohort of 751 workers who had 1 or more years of employment has also been reported by Finkelstein (1982b), but is not yet published. This cohort yields virtually identical unit risk values.) Impinger particle counts of varying degrees of comprehensiveness were available from various sources (government, insurance company, employer) from 1949 until the 1970's. After 1973, membrane fiber counts were taken. Individual exposure estimates were constructed, based on recent fiber concentrations at a particular job, and modified for earlier years by changes in dustiness of that job, as determined by the impinger particle counts. For example, exposure estimates for the years 1948 to 1954 for willow operators, forming machine operators, and lathe operators were 40 f/ml, 16 f/ml, and 8 f/ml, respectively.

The average cumulative 18-year exposure for the production group in the asbestos cement work was 112.5 f-yr/ml. Seventeen lung cancer deaths were observed versus 2.0 expected deaths from Ontario rates for an SMR of 850 or a relative risk of 8.5. Three deaths versus 2.3 expected occurred in an unexposed group. This result yields a value of $K_L = 0.067$ [(8.5-1)/112.5]. Data also are presented on the lung cancer SMRs for separate cumulative exposure categories, but they are so variable because of the few deaths in each exposure category that no exposure-response relationship can be obtained. The first two exposure categories show risk increasing steeply with exposure, but the last falls significantly, although an extreme mesothelioma and GI cancer risk occurs in the category.

The reasons for the very significant difference in risk seen in two plants (of the same company) producing the same product are unknown. The point estimate of risk from Finkelstein (1983) (K_L = 0.067) is 13 times that of Weill et al. (1979) (K_L = 0.0052) even after an attempt to correct for the incomplete trace of the latter study. The exposure estimates of Finkelstein would appear reasonable. In a study of asbestosis in the Ontario plant (Finkelstein, 1982a), data comparable to that of Berry et al. (1979) were obtained. Finkelstein observed prevalence rates of asbestosis of 4% at 50 to 99 f-yr/ml and 6% at 100 to 149 f-yr/ml versus Berry et al.'s 2.5% and 8.5%, respectively. Henderson and Enterline (1979) observed SMR's of 231 and 522, respectively, among retirees of cement sheet and shingle work and cement pipe work. These values are more consistent with the higher risk of Finkelstein than the lower one of Weill et al.

3.7.6 Textile Products Manufacturing; Rochdale, England (Chrysotile), Peto (1980)

The mortality experience from an oft-studied British textile plant (BOHS, 1968; Berry et al., 1979; Knox et al., 1968; Peto, 1980) is difficult to interpret. First, dust concentrations have changed fairly dramatically over the past 5 decades of plant operations. Subsequent estimates of those concentrations have changed also. No measurements of dust concentrations were made before 1951. Between 1951 and 1964 thermal precipitators were used to evaluate total dust levels, and thereafter, filter techniques similar, but not identical to those in the United States, were used. Average fiber concentrations have been published for earlier years, based on a comparison of fiber counting with thermal precipitator techniques (Berry, 1973). Unfortunately, no published data exist on the variability of the correlation between these two techniques, although they are stated to correlate "relatively poorly" (Advisory Comm., 1979b). Earlier published estimates have been stated to be inaccurate; Berry et al. (1979) reported that a re-evaluation of the work histories indicated that some men had spent more time in less dusty jobs than previously believed and that previous average cumulative doses to 1966 had been overestimated by 50%. Recently, coincident with the finding of considerable asbestos-related disease among recent (post-1951) employees and the British Government's review of its asbestos standard, the hygiene officers of the plant have re-evaluated previously reported exposure data. Data now

suggest that earlier static sampling methods underestimated personal exposures by a factor of about 2 and that whole field, rather than graticule field, microscopic counting understated fiber concentrations by another factor of 2 to 2.5 (Steel, 1979). Unfortunately, the data on which such revised estimates were made were not provided in the text of the British Advisory Committee Reports when the Advisory Committee accepted them (Advisory Comm. 1979a). The comparative fiber concentration estimates are provided by Peto (1980) and listed in Table 3-10. However, no background data are available.

TABLE 3-10. PREVIOUS AND REVISED ESTIMATES OF MEAN DUST LEVELS IN FIBERS/ML (WEIGHTED BY THE NUMBER OF WORKERS AT EACH LEVEL IN SELECTED YEARS)

	1936	1941	1946	1951	1956	1961	1966	1971	1974
Previous estimates corresponding to early fiber counts (Peto et al., 1977)	13.3	14.5	13.2	10.8	5.3	5.2	5.4	3.4	-
Revised estimates corresponding to modern counting of static samples[a]	No measurements prior to 1951			32.4	23.9	12.2	12.7	4.7	1.1

[a]These estimates are based on preliminary data on 126 workers, first employed between 1951 and 1955, and should be regarded as provisional.

Source: Peto (1980)

Evaluation of the new estimates is further clouded by questions concerning the appropriateness of multiplying static sampler concentrations by two. This approach is directly contradicted by published factory data (Table 3-11) on the comparison of static and personal sampling results by job (Smither and Lewinsohn, 1973). Dr. Lewinsohn (personal communication) confirmed these results. He stated that the static sampler concentrations were generally higher than those of the personal samplers of men workers at the monitored job. The company placed the static samplers to best reflect the breathing zone dust concentrations of operators while they tended machines. Dr. Lewinsohn stated that if the machines were running smoothly, the worker would often leave the site (e.g., to talk with fellow workers, go to the rest room) and experience a lower dust concentration. The difference between static and personal sampling data was greatest in the dustier jobs (compare

TABLE 3-11. DUST LEVELS: ROCHDALE ASBESTOS TEXTILE FACTORY, 1971

Department	Process	Sampler	
		Static	Personal
Fiberising	Bag slitting	3	1
	Mechanical bagging	4	1
Carding	Fine cards	3.5	2
	Medium cards	4.5	3.5
	Coarse cards	8	6
	Electrical sliver cards	1.5	1
Spinning	Fine spinning	2.5	3
	Roving frames	6	3
	Intermediate frames	5.5	3
Weaving	Beaming	0.5	0.5
	Pirn weaving	1.5	1
	Cloth weaving	2	1
	Listing weaving	0.5	0.5
Plaiting	Medium plaiting	4	2

Source: Smither and Lewinsohn, 1973.

weaving vs. carding) because workers tended to leave a dusty area more frequently In the Rochdale factory, the average of the ratios of static to personal sample concentrations at the same work station is 1.8 (1.5 if the fiberizing operation is not considered). Thus, the fiber estimates published by Peto (1980) reflect what is believed to be an improper adjustment and the range of uncertainty in K_L will reflect this.

A second difficulty of the British textile factory study is that the dose-response data calculated from groups exposed before and after 1950 differ considerably. The published fiber concentrations (Peto, 1980) suggest that the pre-1951 group was exposed to about 30 to 40 f/ml prior to 1965 and that the post-1950 group was exposed to about 15 to 20 f/ml. In the pre-1951 group, 26 lung cancers occurred vs. 16.85 expected; in the post-1950 group eleven occurred vs. 3.35 expected. It is anomalous that proportionally more incidents of disease were seen in the latter group. An analysis by Peto (1980) suggests that the cumulative exposure of the post-1950 group is 250 (200 to 300) f-yr/ml. This dose and mortality data 15 years after the onset of exposure yields a value of K_L = 0.0091, [(11-3.35)/3.35/250] (using Equation 3-2a). The corresponding estimate for the pre-1951 group, using

600 f-yr/ml for the cumulative exposure, is 0.0009. The values for the older group suffer from uncertainties in exposure estimates and those of the younger group suffer from few deaths in the cohort. Both sets of data are negatively influenced by the relatively short time since first exposure for many of the cohort members. As indicated above, uncertainties in exposure estimates could raise these estimates by a factor of 3.

The differences between the two subcohorts employed in this facility are difficult to reconcile. The data are severely limited by the relatively small size of the cohort and the few deaths available for analysis. Nevertheless, the nearly 10-fold difference in the estimated risk of death from lung cancer suggests the possible existence of some unidentified bias in the pre-1951 group. The finding of only a 50% increase in lung cancer in exposure circumstances where 5.3% of deaths were from asbestosis is certainly unusual, as is the finding that virtually as many deaths occurred from mesothelioma as lung cancer

3.7.7 Textile Products Manufacturing; United States (Chrysotile), Dement et al. (1982, 1983a, 1983b)

Mortality data from a chrysotile textile plant studied by Dement et al. (1982, 1983a, 1983b) allow a direct estimate of lung cancer risk per fiber exposure. In this study, data from impinger measurements of total dust, in terms of mppcf were available, characterizing dust concentrations since 1930. Further, 1,106 paired and concurrent impinger-membrane filter measurements allowed conversion of earlier dust measurements to fiber concentrations. These conversions showed that 3 f/ml were equivalent to 1 mppcf for all operations except fiber preparation. (The 95% confidence interval was 2 to 3.5 f/ml/mppcf.) A value of 8 f/ml/mppcf characterized fiber preparation work (95% confidence interval: 5 to 9). After 1940, average fiber concentrations in most operations were estimated to range from 5 to 10 f/ml with the exception of fiber preparation and waste recovery, where mean concentrations were from 10 to 80 f/ml. A weighted regression line through all data plotted according to cumulative fiber exposure yields SMR = 150 + 4.20 x f-yr/ml for a K_L of 0.042 (4.20/100).

Dement et al. (1982) used U.S. rates for calculating expected deaths. County rates were 75% higher. Dement et al.'s arguments for the use of national rates are persuasive. (Local rates were probably influenced by

nearby shipyard employment and the smoking habits of the study population reflected those of the U.S. general population.) However, a value of K_L reduced by 33% will be indicated in Figure 3-7 This value will bring the SMR at zero exposure to 100 and allow for some consideration of unusually high local rates.

3.7.8 Friction Products Manufacturing; Great Britain (Chrysotile and Crocidolite), Berry and Newhouse (1983)

Newhouse and Berry (1983) analyzed the mortality of a large workforce employed to manufacture friction products. All individuals employed after 1940 were included in the study and the mortality experience through 1979 was determined. Exposure estimates were made by reconstructing work and ventilation conditions of earlier years. Fiber measurements from these reconstructed conditions suggested that exposures before 1931 exceeded 20 f/ml but those afterwards seldom exceeded 5 f/ml. From 1970, exposures were less than 1 f/ml. These relatively low intensities of exposure kept the average cumulative exposure for the group to less than 50 f-yr/ml.

The overall mortality of all study participants, 10 years and more after the onset of exposure, was no greater than expected for all causes. The number of deaths from cancer of the lung and pleura was slightly elevated in men (151 observed vs. 139.5 expected) but the excess was largely accounted for by eight mesothelioma deaths. No unusual mortality was found in study participants employed 10 or more years. Using a case-control analysis according to cumulative exposure, Newhouse and Berry estimated that the lung cancer increased risk was 0.06% per f-yr/ml (K_L = 0.0006) with an upper 90% confidence limit of 0.8% per f-yr/ml.

3.7.9 Mining and Milling; Quebec, Canada (Chrysotile), Liddell et al. (1977), McDonald et al. (1980)

The results reported by Liddell et al. (1977) on mortality with respect to total dust exposure in Canadian mines and mills can be converted to relationships expressed in terms of fiber exposures. Using a slope of 0.0019 mppcf-yr as indicated in Figure 3-1, and a value of 3 f/ml/mppcf for the particle fiber conversion factor, K_L = 0.00063. The factor of 3 f/ml/mppcf is the midpoint of the range of 1 to 5 f/ml/mppcf suggested by McDonald et al. (1980) as applicable to most jobs in mining and milling.

These studies of the Canadian miners are highly anomalous and indicate a lung cancer risk lower than virtually any other study of asbestos workers. First, the overall risk of lung cancer mortality in all miners is 1.25 times that expected for the general population. Yet in studies of the mortality of male residents of Thetford, in the midst of the Canadian asbestos mining area (Toft et al., 1981; Wigle, 1977), an excess risk of 1.84 is seen in lung cancer and 2.30 in cancer of the stomach. No corresponding increases were seen in female cancer rates, therefore, Toft et al. (1981) and Wigle (1977) attributed the excesses to occupational exposure in the mines. Siemiatycki (1982) recently showed data from Asbestos and Thetford Mines, Québec, which indicated an SMR for lung cancer in males of 148 compared to Québec rates [which may be high by a factor of 1.5 compared to local rates (McDonald et al., 1971). Second, internal inconsistencies exist in the McDonald et al. (1980) analysis of the combined effect of asbestos exposure and cigarette smoking. In the lower cumulative asbestos exposure category, the relative risk of death of smokers compared to that of non-smokers is 11.8, as expected. However, in the medium and high cumulative asbestos exposure categories, the relative mortality risks of smokers to non-smokers are 6.6 and 3.6, respectively. This result suggests the possibility of some misclassification of asbestos exposure or of smoking. A final uncertainty of the studies is the large percentage (10%) of untraced cohort members. The bias introduced by such a large proportion of individuals is unknown. The studies do not indicate how the untraced individuals were treated.

3.7.10 Mining and Milling; Thetford Mines, Canada (Chrysotile), Nicholson et al. (1976b, 1979)

Higher risks were obtained by Nicholson et al. (1976b, 1979) from the mortality experience of a smaller group of miners and millers employed 20 or more years at Thetford Mines, Québec. The 1979 publication indicates that 178 deaths occurred among 544 men who were employed during 1961 in one of four mining companies. In the ensuing 16 years of follow-up, 26 deaths resulted from asbestosis, 28 (25 on DC) resulted from lung cancer (11.1 expected), and 1 resulted from mesothelioma.

In this study, fiber measurements were made during 1974 in five mines and mills, and data on particle counts were supplied by the Canadian Government. From these data, exposure estimates were made for each of the 544 individuals

according to their job history. Fiber exposures for earlier years were estimated by adjusting current measurements by changes in particle counts observed since 1950.

The mortality experience of the whole group has been reported by two exposure categories (Nicholson, 1976b). The first exposure category corresponded to a 20-year cumulative dust exposure of 560 f-yr/ml. The lung cancer SMR in this group was 1.55 (7 observed, 4.52 expected). In the second category, with a cumulative exposure of 1,760 f-yr/ml, the SMR was 4.33 (13 observed, 3.00 expected). The ratio of the difference in excess risk to the difference in cumulative exposure suggests that K_L = 0.0023, (3.33 - 0.55)/(1760 - 560). However, Québec rates were used to estimate expected deaths, and these may overestimate mortality. McDonald et al. (1971) stated that the local rates of five contiguous counties are two-thirds those of the Province. Thus, K_L should be increased by a factor of 1.5 to 0.0034, or 0.0030 on the basis of DC lung cancer diagnosis. Such an adjustment also makes a straight line through the two SMR's that pass close to the value of 100. The effect of not adjusting K_L is indicated in Figure 3-6.

3.7.11 Mining and Milling; Italy (Chrysotile), Rubino et al. (1979)

A final study of chrysotile mining and milling is that of Rubino et al. (1979) of the Balangero Mine and Mill, northwest of Turin. A cohort was established of 952 workers, each with at least 30 calendar days of employment between January 1, 1930, and December 31, 1965, who were alive on January 1, 1946. Ninety-eight percent of the cohort was traced and their mortality experience through 1975 was ascertained. Overall, an exceptionally high mortality was seen compared to that expected; 332 deaths were observed versus 214.4 expected. However, the excess mortality was largely confined to non-malignant respiratory disease, cardiovascular diseases, and accidents. The overall SMR for all malignant neoplasms was 106, with only cancer of the larynx found to be significantly in excess in the whole group. While the overall data were relatively unremarkable, the age standardized rates of lung cancer according to cumulative dust exposure showed the relative risk for a high exposure group (376 f-yr/ml) was 2.54 times that of a low exposure group (75 f-yr/ml) [K_L = 0.0051, (2.54-1)/(376-75)]. A case-control analysis of the lung cancer according to cumulative dust exposure showed a relative risk of 2.89.

Thus, K_L lies between 0.005 and 0.006 from the analyses according to dust exposure. However, the relatively low overall risk for lung cancer in the entire group (11 cases observed and 10.4 expected) suggests that the excess risk could be zero.

3.7.12 Summary Dose-Response Relationships for Lung Cancer

The results of all the determinations of K_L, the fractional increases in lung cancer risk per f-yr/ml exposure are displayed in Figure 3-6, along with estimates of statistical variation, adjustments for possible biases, and estimates of uncertainties associated with exposure determinations. The details of the calculations of statistical uncertainty are provided in Table 3-7. The range of individual values of K_L is large, and many of the differences may be the result of statistical variation associated with small numbers. Several studies have 95% statistical confidence limits exceeding an order of magnitude. While the study of insulators could have the widest uncertainty in exposure estimates, its low statistical variance gives it considerable strength. Considering the statistical variability and other uncertainties in the data, the agreement is fairly good. The ranges of all but one estimate of K_L lie between 0.005 and 0.03. The only estimate of K_L that lies outside this range is that made from the study of Liddell et al. (1977). An average for K_L, weighted by the reciprocol of the variance of the value of each study (with a lower cutoff at 0.0001), is 0.0095. No evidence in this analysis suggests that a special carcinogenic potency is ascribable to an individual type of fiber. Some of the highest and lowest values for K_L are obtained from pure chrysotile exposures. Exposures involving a mixture of fibers, including amosite and crocidolite, also span a large range of values for K_L. Wide differences occur in the results of separate epidemiological studies of nearly identical work conditions. This difference suggests a midpoint estimate for K_L of about 0.01, but with an uncertainty of about three-fold.

3.8 TIME AND AGE DEPENDENCE OF MESOTHELIOMA

In contrast to lung cancer, for which a relative risk model accurately explains the data, mesothelioma is best described by an absolute risk model, in which the incidence of death is independent of the age at first exposure and increases according to a power of time from the onset of exposure. The rationale for such a model describing human carcinogenesis has been discussed by several authors (e.g., Armitage and Doll, 1960; Pike, 1966; Cook et al.,

1969). Such a model was utilized by Newhouse and Berry (1976) to predict mesothelioma mortality among a cohort of factory workers in England. Specifically, they matched the incidence of mesothelioma to the relationship $I_M = c(t - d)^k$, where I_M is the mesothelioma incidence at a time t from onset of exposure, d is a delay in the expression of the risk, and k is an empirically derived constant. Additionally, the incidence of asbestos-induced mesothelioma in rats (Berry and Wagner, 1969) followed this time course. In the case of the analysis of Newhouse and Berry, the data suggested that the value of k was between 1.4 and 2 and d was between 9 and 11 years. However, the relatively small number of cases available for analysis led to a large uncertainty in the values estimated for either k or d. Peto et al (1982) have recently analyzed mesothelioma incidence in five groups of asbestos-exposed workers. In one analyzed study, by Selikoff et al. (1979), the number of cases of mesothelioma was sufficiently large that the age dependence of the mesothelioma risk could be investigated. Peto et al. (1982) showed that the absolute incidence of mesothelioma was independent of the age at first exposure and that a function, $I_M = ct^{3.2}$, accurately represented the data for individuals between 20 and 45 years from the onset of exposure. However, observed incidence rates for earlier times were less than those projected, and the authors suggested that an expression proportional to $(t - 10)^2$ better fit the data up to 45 years from the onset of exposure. The analysis of Peto et al. (1982) was confined primarily to individuals who were first employed between 1922 and 1946; the fit to the mortality of the entire group (including those exposed before and after that span) suggests a value of k greater than 3.2.

Figure 3-7 shows the risk of death from mesothelioma according to age for individuals exposed first between ages 15 and 24 and between ages 25 and 34. Although these data are somewhat uncertain because of small numbers, they roughly parallel one another by 10 years as did the increased relative risk for lung cancers. Thus, the absolute risk of death from mesothelioma appears to be directly related to onset of exposure and is independent of the age at which the exposure occurs. The risk of death from mesothelioma among the insulation workers is plotted according to time from the onset of exposure on the right side of Figure 3-7 The risk increases at about 45 or 50 years from the onset of exposure and then appears to decrease. Whether the decrease is real or simply the result of misdiagnosis of the disease in individuals age 70 and older or the result of statistical fluctuations associated with small numbers is not certain.

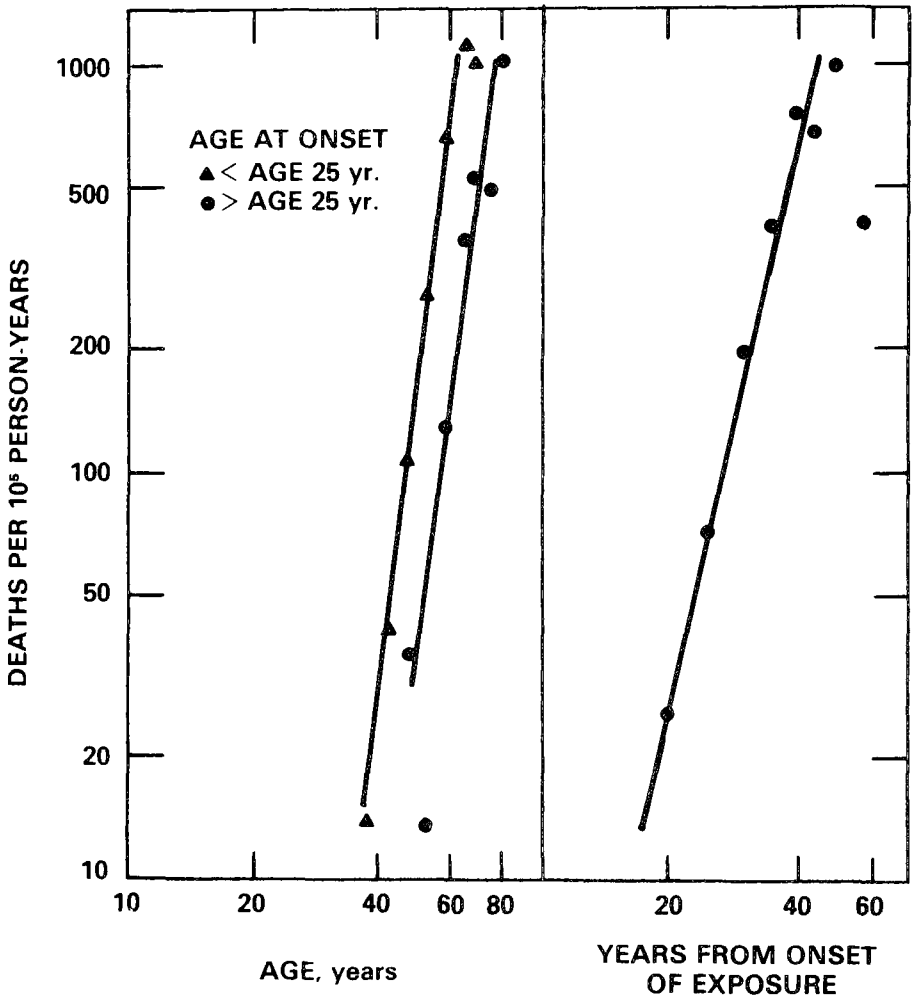

Figure 3-7. The risk of death from mesothelioma among insulation workers according to age and years from onset of exposure. The risk of death according to age is shown separately for insulators first employed before age 25 and after age 25. Data supplied by I.J. Selikoff and H. Seidman.

Source: Nicholson et al. (1982).

Mesothelioma risk from a short-term exposure can be considered to increase at $c(t - 10)^k$, where k is between 2 and 4 and c is proportional to the short-term cumulative exposure. Using a value of k = 3 (which best fits the data for insulators) leads to the following relations for varying times of exposure.

$$I_M(t,d,f) = K_M\, f[(t-10)^3 - (t-10-d)^3] \qquad t > 10+d \qquad (3\text{-}3a)$$

$$= K_M\, f(t-10)^3 \qquad 10+d > t > 10 \qquad (3\text{-}3b)$$

$$= 0 \qquad 10 > t \qquad (3\text{-}3c)$$

I_M is the mesothelioma mortality at t years from the onset of exposure to asbestos for duration d at a concentration f K_M represents the carcinogenic potency and may depend on fiber type and dimensionality. I_M depends only upon exposure variables and not upon age or calendar year period.

Mesothelioma incidence is better represented by a model with a delay period versus one that rises as t^k First, the delay period model fits the full time course of insulator data better. Second, after 45 years from onset, this model rises less rapidly than a function with no delay. The evidence from two studies (Selikoff et al., 1979 - See Figure 3-7; Nicholson et al., 1983) shows that mesothelioma risk after 45 years from the onset of exposure ceases to rise and perhaps falls. Thus, a function with a 10-year delay is less likely to overstate the lifetime risk of mesothelioma in individuals who were exposed early in life.

3.9 QUANTITATIVE DOSE-RESPONSE RELATIONSHIPS FOR MESOTHELIOMA

Four of the above studies provide information on the incidence of mesothelioma (pleural and peritoneal combined) according to time from the onset of exposure and data that would allow estimates to be made of the duration and intensity of asbestos exposure. Thus, values for K_M, the potency factor for mesothelioma risk in Equations 3-3a to 3-3c, can be estimated. Other studies have reported cases of mesothelioma, but incidence data are lacking. In some of these other studies, the incidence data are not provided. In others, data were not given because very few mesothelioma deaths were seen. Thus, some studies with missing data could be those in which a lower value of K_M is obtained and values of K_M were estimated from a biased sample of those studies in which K_L was estimated. A measure of the bias can be estimated by compari-

son of the values of K_M and K_L obtained in each analysis. The estimate of K_M for each of the four studies was made by calculating a relative mesothelioma incidence using Equation 3-3 and data on duration and intensity of asbestos exposure. The relative incidence curves were then superimposed on the observed incidence data in each study and a value for K_M established. These fits are depicted on Figures 3-8 and 3-9. The four studies are described below and summary data are listed in Table 3-12.

3.9.1 Insulation Application; Selikoff et al. (1979), Peto et al. (1982)

A follow-up through 1979 of the cohort of insulators provides data on the incidence of mesothelioma with time from the onset of exposure (Peto et al., 1982). Their time-weighted average exposure was estimated to be 15 f/ml (Nicholson, 1976a). Using these data and 25 years for their average duration of exposure, a value of $K_M = 1.5 \times 10^{-8}$ is estimated.

3.9.2 Amosite Insulation Manufacturing; Seidman et al. (1979)

The average employment time of all individuals in this factory was 1.46 years. This value and the previously used value of 35 f/ml for the average exposure yields an estimate for K_M of 5.7×10^{-8}.

3.9.3 Textile Products Manufacturing; Peto (1980), Peto et al. (1982)

A value of 30 f/ml is suggested by the data presented by Peto (1980). However, this value is uncertain because discrepancies exist in the relative exposures measured using personal samplers and static samplers (see above). If the exposure measured by personal samplers are less than those from static samplers, as suggested by the data of Smither and Lewinsohn (1973), the average exposure could be about 15 f/ml. Using 30 f/ml and an employment period of 25 years, a value of $K_M = 0.7 \times 10^{-8}$ is estimated.

3.9.4 Asbestos Cement Products; Ontario, Canada, Finkelstein (1983)

The cumulative exposure of the cohort over 18 years was 112 f/yr. Only men with 9 or more years of employment were included in the cohort. When data on the exact duration and intensity of exposure are unavailable, a value of 12 years for duration of exposure and 9 f/ml for the intensity of exposure were used. These figures yield a value of $K_M = 1.2 \times 10^{-7}$.

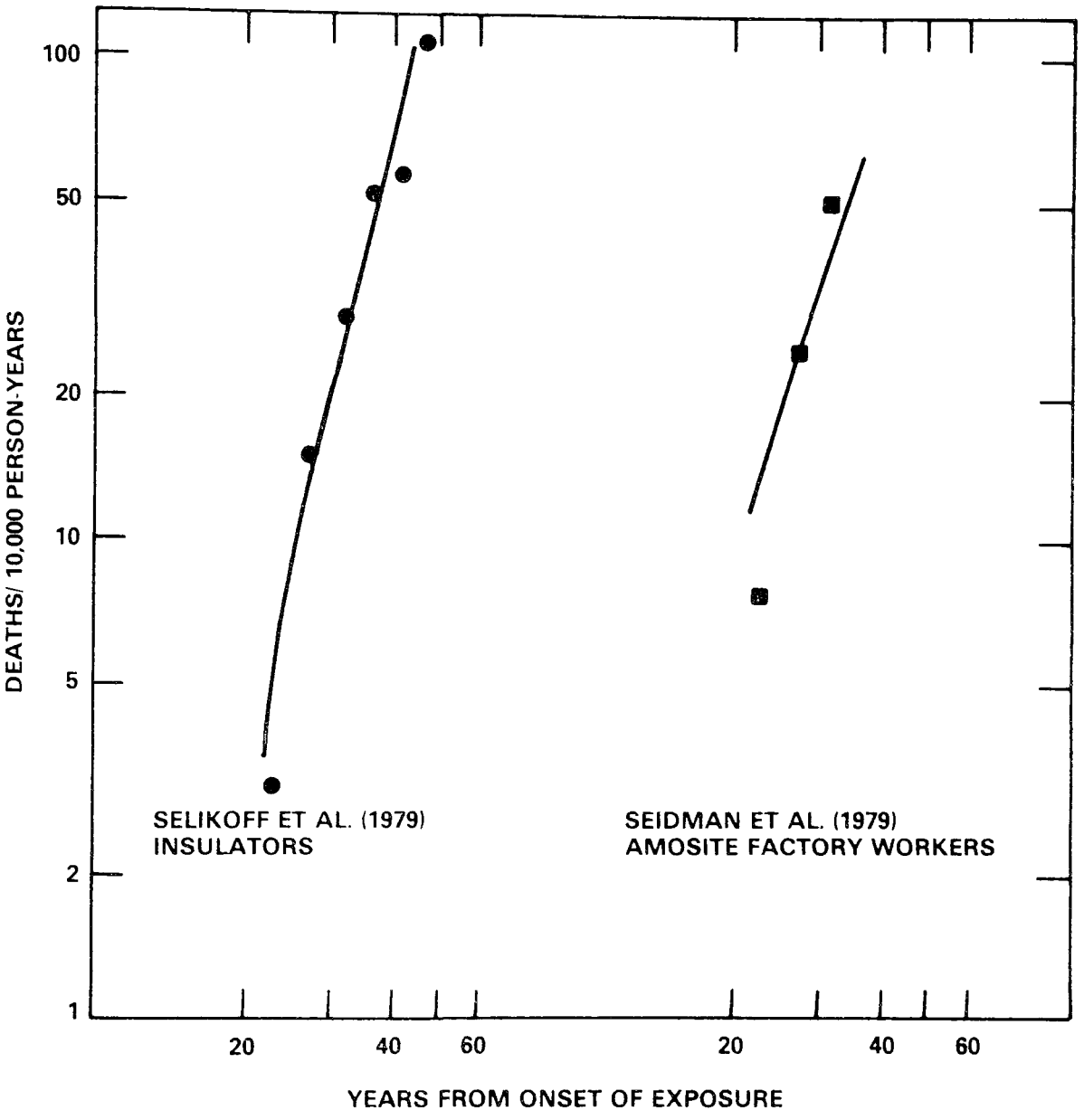

Figure 3-8. The match of curves calculated using Equation 3-3 to data on the incidence of mesothelioma in two studies. The fit is achieved for $K_M = 1.5 \times 10^{-8}$ for insulators data and $K_M = 5.7 \times 10^{-8}$ for the amosite workers data.
Source: Peto et al. (1982); Selikoff et al. (1979); Seidman et al. (1979).

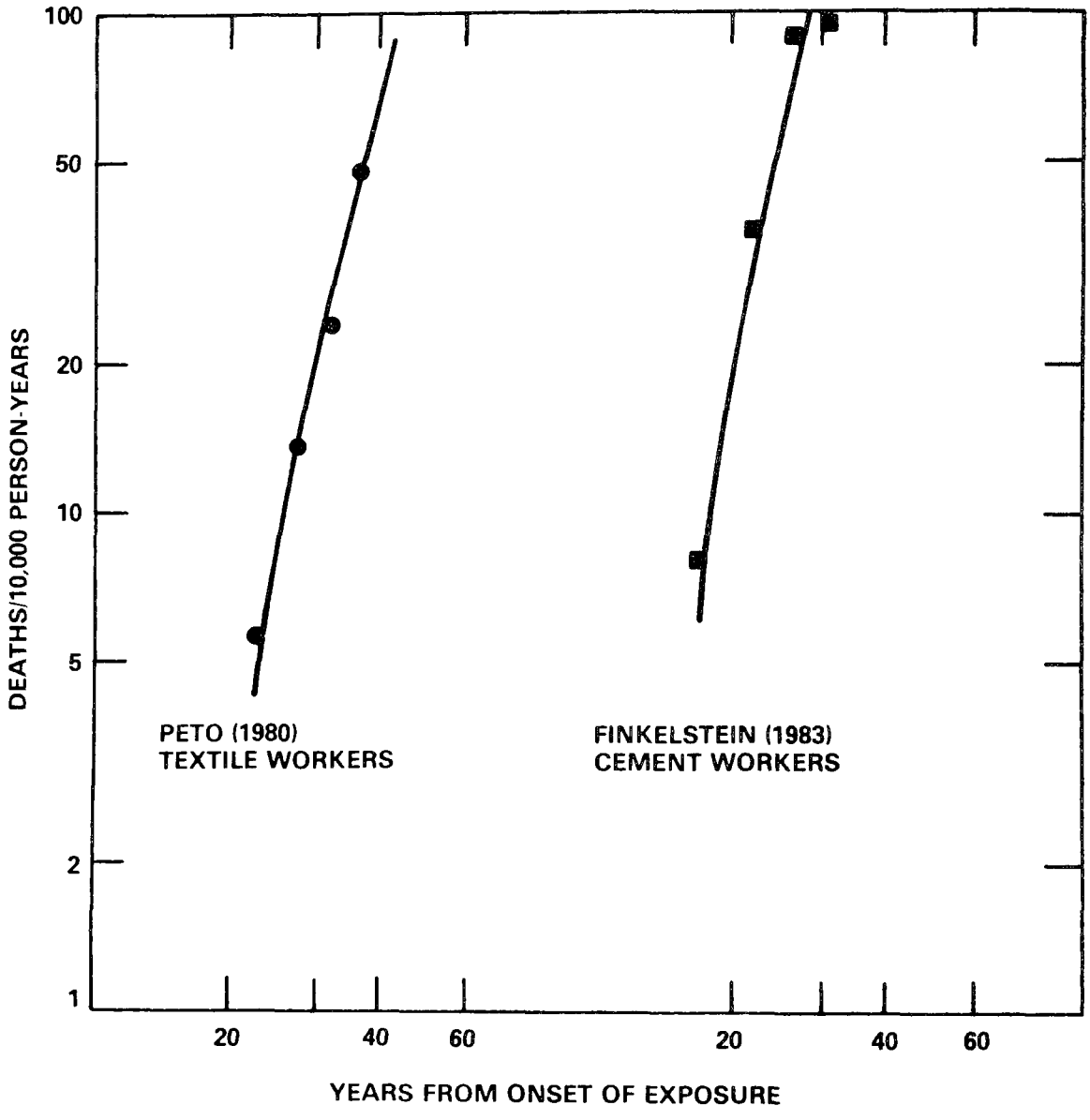

Figure 3-9. The match of curves calculated using Equation 3-3 to data on the incidence of mesothelioma in two studies. The fit is achieved for $K_M = 0.7 \times 10^{-8}$ for the textile workers data and $K_M = 1.2 \times 10^{-7}$ for the cement workers data.

Source: Peto (1980); Finkelstein (1983).

TABLE 3-12. SUMMARY OF THE DATA ON K_M, THE MEASURE OF MESOTHELIOMA RISK PER FIBER EXPOSURE IN FOUR STUDIES OF ASBESTOS WORKERS

Study	Average employment duration	Average exposure, f/ml	K_M	K_M/K_L
Insulators (Selikoff et al., 1979; Peto et al., 1982)	25	15	1.5×10^{-8}	1.6×10^{-6}
Textile workers (Peto, 1980; Peto et al., 1982)	25	30	0.7×10^{-8}	0.8×10^{-6}
Amosite factory workers (Seidman et al., 1979)	1.5	35	5.7×10^{-8}	0.8×10^{-6}
Cement factory workers (Finkelstein, 1983)	12	9	1.2×10^{-7}	1.7×10^{-6}

3.9.5 Summary of Quantitative Dose-Response Relationships for Mesothelioma

These data for these four studies are plotted in Table 3-12 and show remarkable consistency between the ratio of K_M/K_L. The four studies suggest that a ratio of K_M/K_L of 10^{-6} is appropriate and that a range of 3×10^{-9} to 3×10^{-8} for K_M would appear to represent most exposure situations, but several studies suggest values outside this range.

3.10 ASBESTOS CANCERS AT EXTRATHORACIC SITES

The consistency of an increased cancer risk at extrathoracic sites and its magnitude, either in absolute (observed-expected deaths) or relative (observed/expected deaths) terms, is less for cancer at other sites than for lung cancer. Nevertheless, many studies document significant cancer risks at various GI sites. Cancer of the kidney has also been found to be significantly elevated in two large studies (Selikoff et al., 1979; Puntoni et al., 1979). Among female workers, ovarian cancer has been found in excess (Newhouse et al., 1972). While no other specific sites have been shown to be elevated at the 0.05 level of significance, the category of all cancers other than lung, GI tract or mesothelial is significantly elevated (e.g., Selikoff et al., 1979)

Table 3-13 lists all studies in which more than 10 GI cancers were expected or observed and in which the overall lung cancer risk was elevated at the 0.05 level of significance. This choice eliminated many small studies, which have statistically uncertain data, from consideration, as well as several large studies that demonstrated a low risk of lung cancer, either because of exposure or follow-up circumstances. Because the excess risk of GI cancer is less than that of the lung, significantly elevated risks are unlikely to be seen in studies that demonstrate little lung cancer risk. Negative data in such studies do not carry great significance. Data in Table 3-13, show that all but one of the listed studies has an excess GI cancer risk, albeit in three studies, the risk is small. However, five of the 13 studies demonstrate the risk at a 0.05 level of significance. Figure 3-10 displays the relationship between the relative risk of lung cancer and relative risk of GI cancer in the 12 studies with excess GI cancer risk. A consistent relationship exists between a greater GI cancer risk and an increased lung cancer risk. The GI tract obviously is exposed to fibers because the majority of inhaled fibers are brought up from the respiratory tract and swallowed (Morgan et al., 1975). Additionally, some fibers may become entrapped within the gut wall (Storeygard and Brown, 1977). Nevertheless, the magnitude of the excess fibers at GI sites is much less than that for the lung. In recent studies, the GI excess is about 10 to 15% of the lung excess.

Table 3-13 also lists the observed and expected mortality for cancers other than mesothelioma and the GI or respiratory tract. The elevation is not as consistent as that for GI cancer. Only three studies have elevated risks that are significant at the 0.05 level and deficits are observed in four. The analysis is further complicated by the possibility that misattribution of lung cancer or mesothelioma may have occurred for some cases. For example, brain or liver cancers could be metastatic lung cancers in which the primary cancer was not properly identified. In the study of insulators, Selikoff et al. (1979) found that 26 of 49 pancreatic cancers were misclassified; most of the misclassified were peritoneal mesotheliomas. As with GI cancer, the excess at other sites is much less than the excess for lung cancer and generally less than that for GI cancer.

TABLE 3-13. OBSERVED AND EXPECTED DEATHS FOR VARIOUS CAUSES IN SELECTED MORTALITY STUDIES

		Respiratory cancer ICD 162-164			Digestive cancer ICD 150-159				Other cancers ICD except 150-49, 162-4, meso			
		O	E	O-E	O	E	O-E	$\frac{(O-E)}{(O-E)_r}$ d	O	E	O-E	$\frac{(O-E)}{(O-E)_r}$ o
1.	Henderson and Enterline (1979)	63	23.3	39.7	55	39.9	15.1	0.380	55	45.6	9.4	0.237
2.	McDonald et al. (1980)	230	184.0	46.0	276	272.4	3.6	0.078	237	217.4	19.6	0.426
3.	Newhouse and Berry (1979) (male)	103	43.2	59.8	40	34.0	6.0	0.100	38	27.4	10.6	0.177
4.	Newhouse and Berry (1979) (female)	27	3.2	23.8	20	10.2	9.8	0.412	33	20.4	12.6	0.529
5.	Selikoff et al. (1979) (NY-NJ)	93	13.3	79.7	43	15.0	28.0	0.351	28	24.5	3.5	0.044
6.	Selikoff et al. (1979) (U.S.)	429	105.6	381.4	122	84.1	37.9	0.099	184	131.8	52.2	0.137
7.	Nicholson et al. (1979)	28	11.0	17.0	10	9.5	0.5	0.029	10	16.1	(6.1)	def.
8.	Peto (1977)	51	23.8	17.2	16	15.7	0.3	0.019	18	24.8	(6.8)	def.
9.	Mancuso and El-attar (1967)	30	9.8	20.2	15	7.1	7.9	0.527	20	6.8	13.2	0.653
10.	Puntoni et al. (1979)	123	54.9	68.1	94	76.6	17.4	0.255	88	81.3	6.7	0.098
11.	Seidman et al. (1979)	83	21.9	61.1	28	22.7	5.3	0.087	39	35.9	3.1	0.037
12.	Dement et al. (1983b)	33	9.8	23.2	10	8.1	1.9	0.082	11	14.1	(3.1)	def.
13.	Jones et al. (1980)	12	3.8	8.2	10	20.3	(10.3)	def.	35	39.5	(4.5)	def.

O = observed deaths.

E = expected deaths.

D = digestive cancer

R = respiratory cancer

o = other cancer

def. = no ratio when deficient in O-E

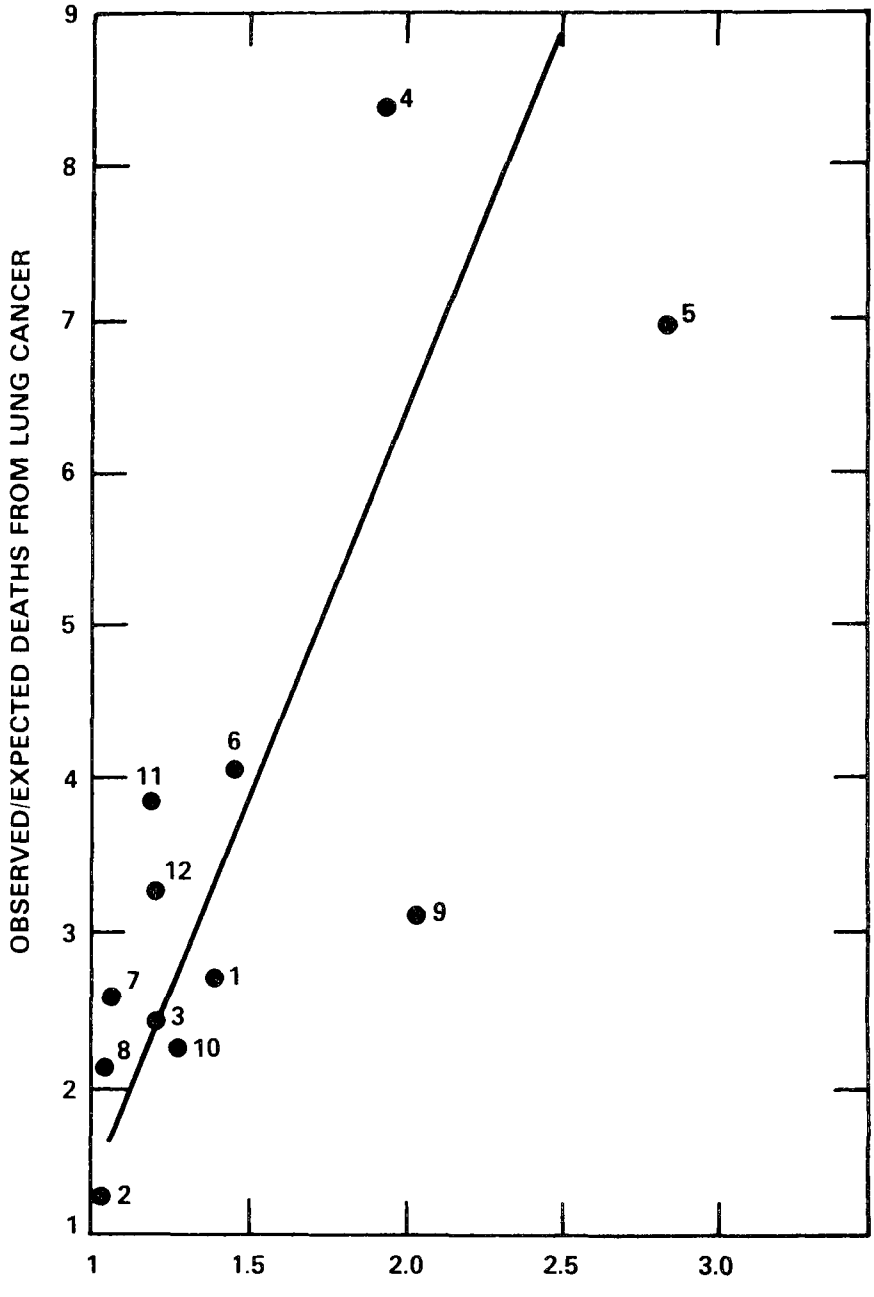

Figure 3-10. The ratio of observed to expected mortality from lung cancer versus the ratio of observed to expected mortality from gastrointestinal cancer. See Table 3-13 for study reference number 1-12. The point of Jones et. al. (1980) with an SMR of 0.49 for digestive cancer is not plotted.

3.11 ASBESTOSIS

Asbestosis, the long-term disease entity resulting from the inhalation of asbestos fibers, is a chronic, progressive pneumoconiosis. The disease is characterized by fibrosis of the lung parenchyma, usually radiologically evident only after 10 years from first exposure, although changes can occur earlier following more severe exposures. Shortness of breath is the primary symptom; coughing is a less common symptom; and signs such as rales, finger clubbing, and, in later stages of the disease, weight loss appear in a proportion of cases. The disease was first reported 8 decades ago (Murray, 1907) and has occurred frequently among workers occupationally exposed to asbestos fibers in ensuing years. Characteristic X-ray changes are small, irregular opacities, usually in the lower and middle lung fields, often accompanied by evidence of pleural fibrosis or thickening and/or pleural calcification. Both the visceral and, more commonly, parietal pleura may be involved.

Currently, 50 to 80% of individuals in some occupational groups with exposures beginning more than 20 years earlier have been found to have abnormal X-rays. These individuals include asbestos insulation workers (Selikoff et al., 1965), miners and millers (Nicholson, 1976b), and asbestos factory employees (Lewinsohn, 1972). In many circumstances, the disease progresses following cessation of exposure. In a group of workers employed in an asbestos factory for various periods of time between 1941 and 1954, X-ray changes were observed years following exposure in individuals having exposures as short as 1 week (Personal communication, I.J. Selikoff).

In addition to disease and disablement during life, asbestosis accounts for a large proportion of deaths among workers. The first reports of the disease (Auribault, 1906; Murray, 1907) described complete eradication of working groups. Much improvement in dust control has taken place in the industry since the turn of the century, but even recently, those exposed in extremely dusty environments, such as textile mills, may have up to 40% of their deaths attributed to asbestos (Nicholson, 1976a). Groups experiencing less severe exposures for 20 or more years, such as occurs in mining and milling (Nicholson, 1976b) or insulation work (Selikoff et al , 1979) may have from 5 to 20% of their deaths attributed to pneumoconiosis. All varieties of asbestos appear equally capable of producing asbestosis (Irwig et al., 1979). In groups exposed at lower concentrations, such as the families of workers, there is less incapacitation, and death from asbestosis has not been reported.

3.12 MANIFESTATIONS OF OTHER OCCUPATIONAL EXPOSURE TO ASBESTOS

In the past decade, considerable evidence has been developed on the prevalence of asbestos disease in workers who were exposed to a variety of work activities. Shipyard trades (other than insulation work), were shown to have particularly significant exposure. By 1975, Harries (1976) had identified 55 mesothelial cases in the Devonport Dockyard, only two of which were in asbestos workers. In a case-control study of four Atlantic Coast areas, an average relative risk for lung cancer of 1.4 was determined (Blot et al., 1978). The study population had an average employment time of 3 years. However, no exposure data are available. X-ray abnormalities among non-insulator shipyard employees also are common. Among long-term (mostly 30+ years) shipyard workers, 86% were found to have X-ray abnormalities characteristic of asbestos exposure (Selikoff et al., 1981). Maintenance personnel have also been shown to be at risk from asbestos disease. Lilis et al. (1979) reported the finding of X-ray abnormalities among 55% of X-rays of 20+ year chemical plant workers.

These findings are important because they point to future sources of asbestos emission to the environment. The removal of asbestos from friable products, including insulation material, and the installation of engineering controls in factories have significantly reduced the exposure and emissions from primary manufacturing or primary using sources. However, over one million tons of asbestos is contained in friable materials in ships, buildings, power plants, chemical plants, refineries, and other locations of high temperature equipment (Nicholson, 1976a). The maintenance, repair, and removal of this material will account for the principal exposures to workers and emissions into the environment (both in and out of buildings) in the future.

3.13 DEPOSITION AND CLEARANCE

Some limited data are available on the quantity of asbestos fibers in lungs of individuals with and without known exposures to asbestos (Sebastien et al., 1979; Jones et al., 1980; Wagner et al., 1982). Most of the analyzed cases were selected because of death from mesothelioma, often coupled with an investigation of a specific work group (Wagner et al., 1982; Berry and Newhouse, 1983). However, the cases have not been correlated with known cumulative exposures. Generally, amphibole burdens of individuals who were heavily exposed range from 10^7 to 19^8 f/g dry weight; general population controls (in

Great Britain) are usually less than 10^6 f/g dry weight (Jones et al , 1980). Similar concentrations of chrysotile are seen in exposed workers (Wagner et al., 1982) and unexposed controls (Jones et al., 1980).

Very few data are available to provide a basis for establishing a model for the deposition and clearance of fibers in humans. Both short- and long-term clearance mechanisms are expected to exist in humans as in animals (See Chapter 4). If only long-term processes are considered (characterized by months or years), the simplest model is one in which the change in lung burden (N) is proportional to the rate of deposition of fibers (A) (assuming continuous exposure) diminished by a clearance that is proportional to (by factor β) the number of fibers present.

$$\frac{dN}{dt} = A - \beta N \tag{3-4}$$

For the number of fibers present after a constant exposure of duration t_1, Equation 3-4 yields,

$$N = \frac{A}{\beta}(1-e^{-\beta t_1}) \tag{3-5}$$

and at a time t_2 after cessation of a constant exposure of duration t_1,

$$N = \frac{A}{\beta}(1-e^{-\beta t_1})e^{-\beta t_2} \tag{3-6}$$

Such a model would be applicable at times t_1 and t_2, which are long compared to any short-term clearance mechanisms. This model is clearly very simplistic in that it considers only one characteristic time for long-term removal processes. Nevertheless, the model illustrates the difficulty of applying even the simplest model. In order to systematize lung burdens, information on the duration and intensity of the exposure and the time from last exposure is required to obtain a measure of the characteristic removal time for a given fiber type. Such information is not yet available for the individuals whose lungs have been analyzed.

Data have been presented by Bignon et al. (1978) on the number of amphibole fibers detected in lung washings of seven asbestos insulation workers. All workers were exposed between 10 and 16 years. While data on the individual exposure times were unknown, fewer fibers were found in the lung washings of those workers who were removed from exposure for the longest period. The data are consistent with a decrease of 50% in the number of washable fibers at 5 to 7 years after cessation of exposure. However, washable fibers may not be proportional to the residual lung burden or to the number of fibers trapped within lung tissue. The lung washings were largely amphibole; no corresponding data are available for chrysotile fibers.

Data on the fiber dimensionality from these studies show a decrease in the average length and diameter of fibers found in the pleura compared with those found in the parenchyma. However, no distinction was made between amphiboles and chrysotile in this analysis, and the different length-width data could simply be a reflection of the predominance of chrysotile in the pleura.

3.13.1 Models of Deposition and Clearance

The Task Group on Lung Dynamics of the International Commission on Radiological Protection has proposed a model for the deposition and retention of particles (See Brain and Valberg, 1974). The results of this model are shown in Figure 3-11, which depicts the percentages of particles of different sizes deposited in the various compartments of the respiratory tract. Alveolar deposition is dominant for particles with a mass median diameter of less than 0.1 μm. As the particle size increases, deposition in this area decreases, falling to 25% at 1 μm and to 0 at 10 μm or above. Nasal and pharyngeal surface deposition becomes important above 1 μm and rises rapidly to be the dominant deposition site for particles 10 μm in diameter or greater. The above model was developed for spherical particles. Timbrell (1965) has shown that the settling velocities of particles and their aerodynamics are such that fibers with aspect ratios greater than three behave like particles with a diameter three times as great, independent of the length of the fiber. This finding has been corroborated by calculations of Harris and Fraser (1976). Thus, few fibers with diameters as large as 2 μm are likely to deposit in the alveolar spaces, although finer fibers, even as long as 200 μm, may do so.

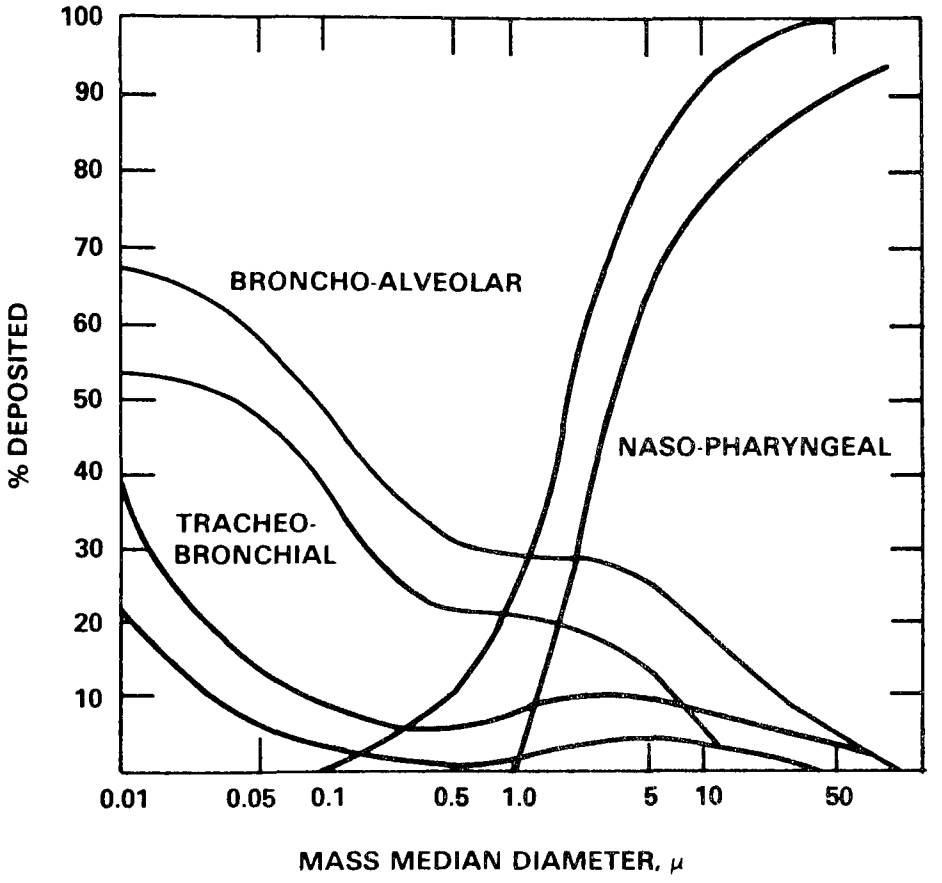

Figure 3-11. Aerosol deposition in the respiratory tract. Tidal volume is 1,450 ml; frequency, 15 breaths per minute. Variability introduced by change of sigma, geometric standard deviation, from 1.2 to 4.5. Particle size equals diameter of mass median size.

Source: Brain and Valberg (1974).

3.14 EFFECTS OF INTERMITTENT EXPOSURE VERSUS CONTINUOUS EXPOSURE

Two distinct kinds of exposure occurred to workers in the studies reviewed above. On the one hand, workers in some production operations (e.g., textiles) would be exposed to a relatively constant concentration of asbestos fiber throughout their work day. On the other hand, insulators, maintenance mechanics, and some production workers were exposed to extremely variable concentrations of asbestos, with most of their cumulative exposure being the result of intense exposures of short duration. Implicit in the use of a linear dose-response relationship and average exposures is the concept that the risk of cancer is directly related to the cumulative asbestos exposure received in a period of time, i.e., the effect of an exposure to 100 f/ml for 1 hour is the same as that of 1 f/ml for 100 hours. (This equivalence applies for only short time periods. Because of the time dependence of mesothelioma risk, 100 f/ml for 1 year is not equivalent to 2 f/ml for 50 years.) Short, intense exposures could have an effect different from longer, lower exposure if clearance mechanisms are altered by very high concentrations of inspired asbestos. There are no data that directly address this question. However, indirect information suggests that the magnitude of the effect is less than the variability between studies with continuous exposure. First, Henderson and Enterline (1979) found that the excess lung cancer risk for plant wide maintenance mechanics was only slightly higher (21%) than that for production workers, on a unit exposure basis. The risk of pneumoconiosis was much less per unit cumulative exposure among maintenance workers. Second, the similarity of unit exposure risks of insulators compared to that for groups with continuous exposure would suggest that the character of their exposure is not important. However, both comparisons depend upon the exposure estimates of these groups. Clearly, average exposures are difficult to estimate from episodic exposures and the above numerical similarities may be fortuitous. The unusually low pneumoconiosis risk among the mechanics in the Henderson and Enterline study may be the results of exposure misestimates.

3.15 RELATIVE CARCINOGENICITY OF DIFFERENT ASBESTOS VARIETIES

Information on the effect of specific asbestos varieties in different exposure circumstances is limited. Considerable controversy has developed as to whether one variety of asbestos (crocidolite) or mineral class (amphibole) is more carcinogenic than another (the serpentine mineral, chrysotile). Both

Great Britain and Sweden have imposed far more rigid standards for crocidolite than for other varieties of asbestos. In contrast, the United States has no special standard for any specific asbestos mineral.

A special role has been attributed to crocidolite by some investigators, perhaps because the first environmental mesotheliomas were found in an area where crocidolite exposure was likely (Wagner et al., 1960). Subsequently, in Great Britain, where crocidolite was often used, many individuals who developed mesotheliomas were found to have had opportunities, for exposure to this fiber, although such association was not unique. In fact, equal opportunity for exposure to chrysotile was demonstrated (Greenberg and Lloyd-Davies, 1974). While crocidolite is a factor in an increased risk of death from mesothelioma in some circumstances, in others this cannot be demonstrated. Considerable data indicate that significant risks of mesothelioma exist in particular circumstances from exposure to other asbestos varieties.

Enterline and Henderson (1973) and Weill et al. (1979) suggested that workers who were exposed to chrysotile and crocidolite may have had a greater lung cancer risk than those exposed to only chrysotile. These suggestions were based on air concentrations of total particles in the respective work environments, and they included much other dust, such as cement. A significantly added crocidolite exposure could have been present in the combined exposure work circumstances without significantly affecting the total particle count.

The manufacture of amosite insulation has been shown to be associated with a high risk of mesothelioma (Table 3-12), while amosite mining has demonstrated little excess risk of death from mesothelioma (Webster, 1970). Similarly, data on chrysotile use is ambiguous. Exposures in the British factory studied by Peto (1980), which predominently used chrysotile, carried a high risk of mesothelioma, but recently questions were raised over the use of some crocidolite in the facility. No data are available on the relative amounts used of each fiber. Over 4% (4.3%) of the deaths were caused by mesothelioma in a long-term follow-up of a facility that used 5000 to 6000 tons of chrysotile, 50 tons of amosite, and 4 tons of crocidolite annually (except for 3 years when 375 tons of amosite were used) (Robinson et al., 1979). In contrast, only one mesothelioma occurred in 175 deaths in the factory studied by Dement et al. (1982).

Much of these differences in risk may be accounted for by the differences in fiber size distributions in the three work environments rather than fiber type. The greatest percentage of longer and thicker fibers would occur in the work environment of miners and millers. When asbestos is used in manufacturing processes, it is broken apart as it is incorporated in finished products. During application or removal of insulation products, asbestos is further manipulated and the fibers become reduced in length and diameter. As these smaller fibers can readily be carried to the periphery of the lung, penetrate the visceral pleura, and lodge in the visceral or parietal pleura, they may be important to the etiology of mesothelioma. Bignon, Sebastien, and their colleagues (1978) have reported data from a study of lungs and pleura of shipyard workers. Larger fibers, often amphibole, were usually found in lung tissue. In the pleura, the fibers were generally chrysotile, but finer and smaller. The early association of mesothelioma with crocidolite occurred because, even in mining, crocidolite is readily broken apart and its extensive use in Great Britain in extremely dusty circumstances (e.g., spray insulation) created high exposures for many individuals with a concomitant high risk of death from mesothelioma. On the other hand, the mining and milling of chrysotile involved exposure to long and curly fibers, which are easily counted but not easily inspired.

In Turkey, recent exposure to the fibrous zeolite mineral erionite has been associated with mesothelioma. Results reported by Baris et al. (1979) demonstrate an extraordinary risk. Annual incidence rates for mesothelioma of nearly 1% exist. In 1974, 11 of 18 deaths in Karain, Turkey were from mesothelioma. Seventy-five percent of the fiber diameters are reported to be less than 0.25 μm. The lengths were highly variable, but most fibers were shorter than 5 μm. Asbestos minerals in identified geological deposits are not reported to occur in the area.

3.16 SUMMARY

Data are available that allow a unit risk to be made for lung cancer and allow such risks to be made for mesothelioma. The values for K_L, the fractional risk per f-yr/ml, vary widely among the studies, largely because of the statistical variability associated with smaller numbers, but also because of uncertainties associated with methodology and exposure estimates. Nevertheless, even with this variability, a ten-fold range of K_L from 0.003 to 0.03 overlaps the ranges of K_L observed in all studies but one.

Data on K_M, the potency coefficient for mesothelioma risk, suggests a range between 3×10^{-9} and 3×10^{-8}. However, the data available to establish K_M are much more limited than that for K_L Differences in asbestos type cannot explain the variation seen in K_L and K_M in different studies. However, lower risk values found in chrysotile mining suggest that fiber dimensionality may be important.

Thus in summary, calculations of unit risk values for asbestos must be viewed with caution as they are uncertain and aspects of them are necessarily based on estimates that are subjective to some extent because of the following limitations in the data: 1) statistical uncertainties and systematic biases in epidemiological studies, 2) conversions of particle counts to fiber exposures are uncertain, and 3) very importantly, the nonrepresentative nature of the exposure estimates.

4. ANIMAL STUDIES

4.1 INTRODUCTION

Most animal studies of asbestos health effects have been used to confirm previously established human data rather than to predict human disease. This situation has occurred in part because asbestos usage predated the use of animal studies for ascertainment of risk; in part because some animal models used were relatively resistant to the human diseases of concern; and finally because the principal carcinogenic risk from asbestos, lung cancer, is the result of a multifactorial interaction between other agents, principally cigarette smoking, and asbestos exposure and is difficult to elicit in a single exposure circumstance. All of the asbestos-related malignancies were first identified in humans. Nevertheless, the experimental studies have confirmed the identification of disease and provided important information not available from human studies on the deposition, clearance, and retention of fibers, as well as on cellular changes at short times after exposure. Unfortunately, one of the most important questions raised by human studies, that of the role of fiber type and size, is only partially answered by animal research. Injection and implantation studies have shown longer and thinner fibers to be more carcinogenic once in place at a potential site of cancer. However, the size dependence of the movement of fibers to mesothelial and other tissues is not fully elucidated, and the questions raised in the human studies concerning the relative carcinogenicity of different asbestos varieties still remains.

4.2 FIBER DEPOSITION AND CLEARANCE

The deposition and clearance of fibers from the respiratory tract of rats has been studied directly by Morgan and his colleagues (Morgan et al., 1975; Evans et al., 1973) using radioactive asbestos samples. Following 30-minute inhalation exposures in a nose breathing apparatus, the deposition and clearance from the respiratory tract were followed. At the conclusion of the inhalation, the distribution of fibers in various organ systems was determined. Thirty-one to 68% of the inspired fibrous material was deposited in the respiratory tract. The distributions of that deposited material are shown in Table 4-1. Rapid clearance, primarily from the upper respiratory tract (airways above the trachea), occurred within 30 minutes; up to two-thirds of the fibers were swallowed and found in the GI tract.

TABLE 4-1. DISTRIBUTION OF FIBER AT THE TERMINATION OF 30-MINUTE EXPOSURES (PERCENT OF TOTAL DEPOSITED)

Fiber	Nasal passages[a]	Esophagus	Gastro-intestinal tract	Lower respiratory tract	Percent deposited[b]
Chrysotile A	9 ± 3	2 ± 1	51 ± 9	38 ± 8	31 ± 6
Chrysotile B	8 ± 2	2 ± 1	54 ± 5	36 ± 4	43 ± 14
Amosite	6 ± 1	2 ± 1	57 ± 4	35 ± 5	42 ± 14
Crocidolite	8 ± 3	2 ± 1	51 ± 9	39 ± 5	41 ± 11
Anthophyllite	7 ± 2	2 ± 1	61 ± 8	30 ± 8	64 ± 24
Fluoramphibole	3 ± 2	1 ± 1	67 ± 5	29 ± 4	68 ± 17

[a]Mean and standard deviation

[b]Percent of total inspired.

Source: Morgan et al., 1975

Clearance from the lower respiratory tract (trachea to alveoli) proceeds slower; two distinct components were observed. The first component, believed to be caused by macrophage movement, leads to the elimination of a considerable portion of the material deposited in the lower respiratory tract with a half life of 6 to 10 hours. The slower phase that follows has a half life of 60 to 80 days and involves the clearance from alveolar spaces. Data for a synthetic fluoramphibole (Figure 4-1) show one short and two long-term components for the clearance of fibers. Other data on the lung content of animals sacrificed at various times after exposure show only a single long-term clearance component (Morgan et al., 1978). However, the ratio of fibers in the feces to those in the lung at the time of sacrifice is not a constant as would be expected from a single exponential clearance mechanism.

By extrapolating curves like that of Figure 4-1 to zero-time for a variety of fibers, it is possible to ascertain the relative amounts of fibers deposited in the bronchiolar-alveolar spaces. These data are shown for different fibers in Figure 4-2, along with estimates of the percentage of material deposited in the upper respiratory tract. The relative similarity of the

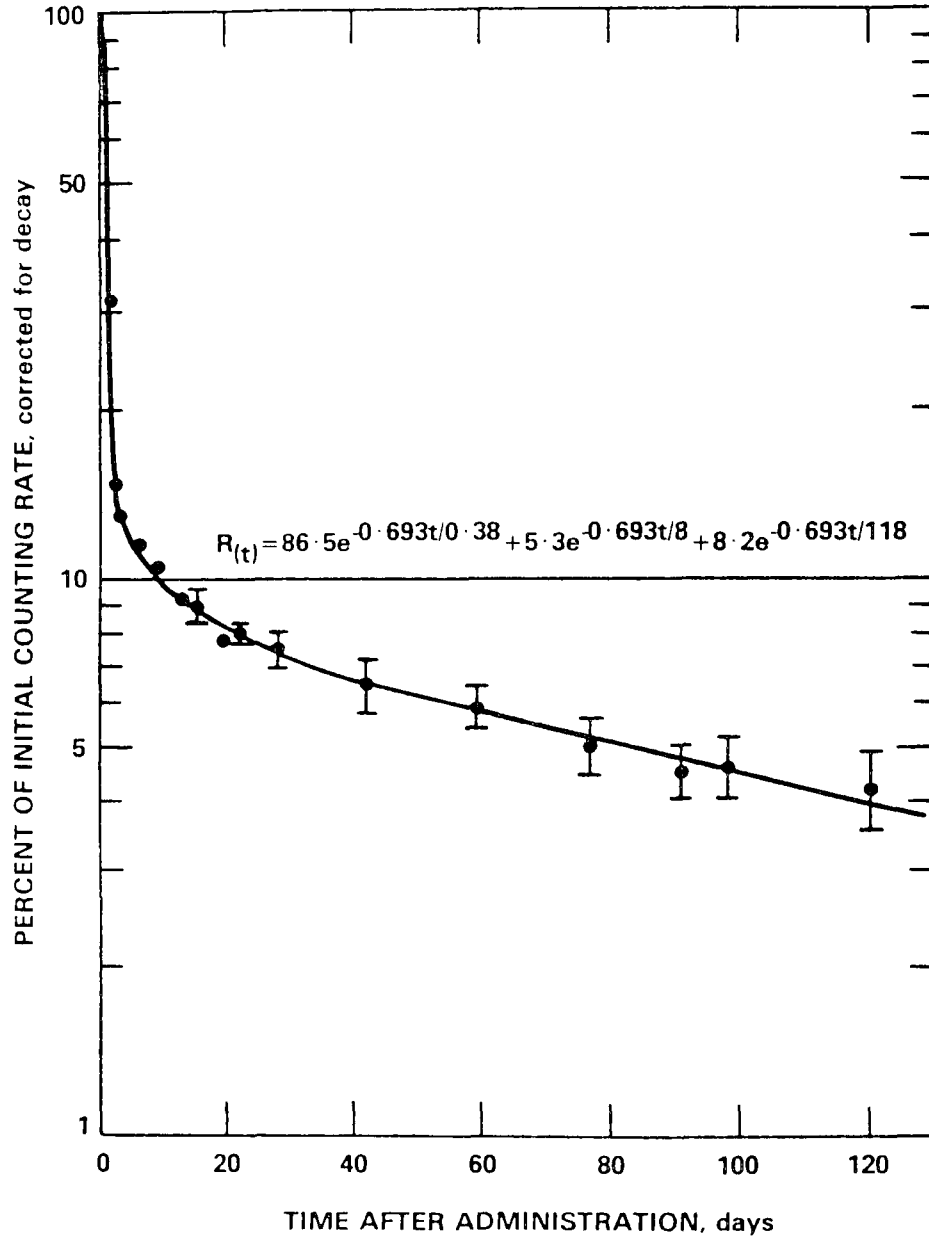

Figure 4-1. Measurements of animal radioactivity (corrected for decay) at various times after inhalation exposure to synthetic fluoramphibole. Mean result for three animals expressed as a percentage of the counting rate measured immediately after exposure.

Source: Morgan et al. (1977).

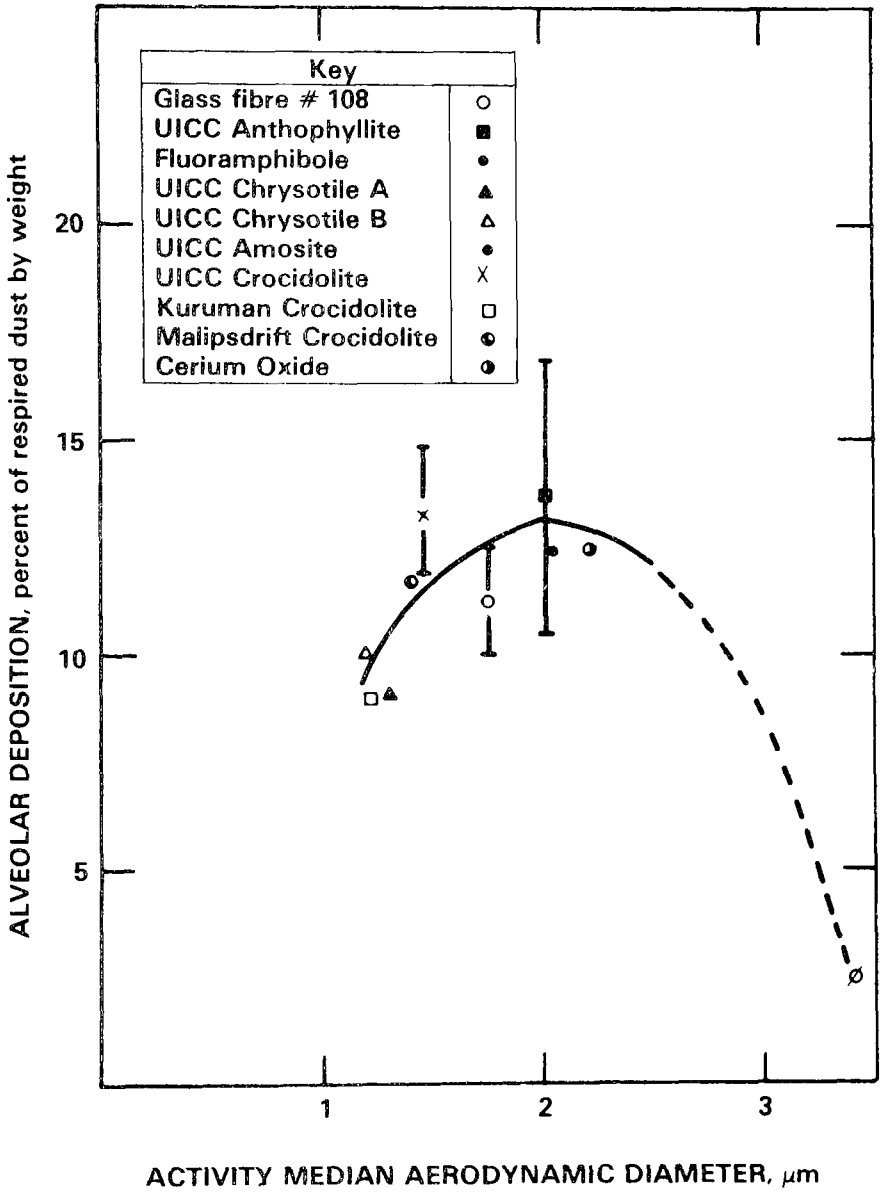

Figure 4-2. Correlation between the alveolar deposition of a range of fibrous and non-fibrous particles inhaled by the rat and the corresponding activity median aerodynamic diameters. Source: Morgan (1979).

percentage deposited in the lower bronchioles or alveoli for different fiber diameters is a reflection of two competing processes. At lower fiber diameters, fibers can be inspired and then expired without impaction in the lower respiratory tract. As the fiber diameter increases, impaction in the upper respiratory tract becomes important; this leads to a lower percentage being carried to the alveolar spaces.

Morgan et al. (1978) have also studied the length distribution of fibers that remain in the lungs of rats to determine the significance of fiber length on clearance. They found that the shorter fibers are preferentially removed after one week following inhalation and suggested that longer fibers reaching the alveolar spaces are trapped.

The radioactive chrysotile used in the clearance experiments allows autoradiography to demonstrate the location of fibers at different times after exposure. At 48 hours after exposure, the distribution of fibers in the lung was relatively uniform. However, at later times, there was a movement of fibers to the periphery of the lung where they accumulated in subpleural foci consisting of alveoli filled with fiber-contained cells.

Other data on the deposition and retention of inhaled asbestos have been reported by Wagner et al (1974). Figure 4-3 shows the dust content of rat lungs following exposures to different asbestos varieties. In the case of amphibole exposures, a linear increase in the amount of retained fiber was seen, whereas for chrysotile, the content of the lung rapidly reached an equilibrium between removal or dissolution processes and deposition and did not increase thereafter The long-term build-up of the amphiboles indicates that, in addition to the clearance processes observed by Morgan, Evans, and Holmes (1977), there is a virtual permanent retention of some fibers. Using a minute volume for the rat of 100 ml, it would appear that about 1% of the total crocidolite or amosite inhaled is permanently in the lung.

The finding of a rapid movement from the upper respiratory tract and a slower clearance from the lower respiratory tract to the GI tract demonstrates a route of exposure that may be important for GI cancer. The observation in humans of peritoneal mesothelioma, excess cancer of the stomach, colon, and rectum, and possibly cancers at other non-respiratory sites, such as the kidney, could result from the migration of such fibers to and across the

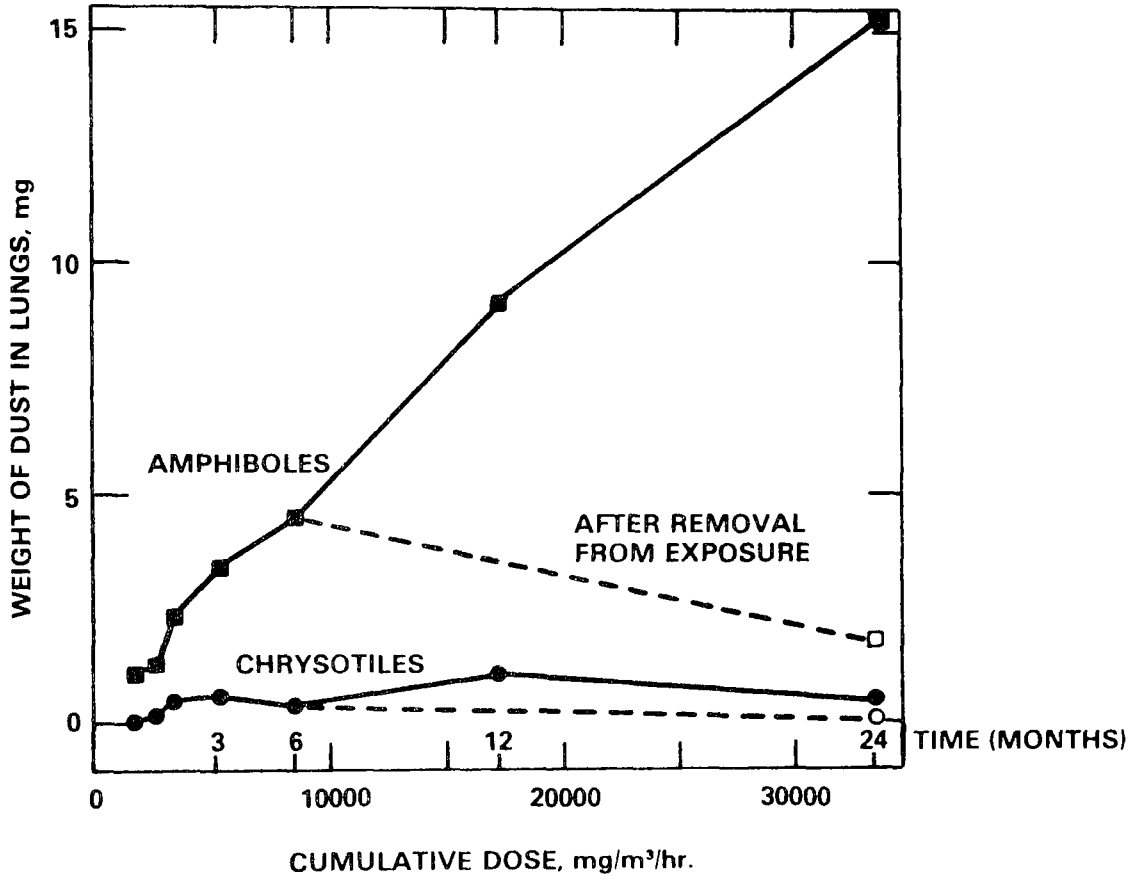

Figure 4-3. Mean weight of dust in lungs of rats in relation to dose and time.

Source: Wagner et al. (1974).

gastrointestinal mucosa. Additionally, fibers may reach organs in the peritoneal cavity by transdiaphragmatic migration or lymphatic-hematogenous transport.

4.3 CELLULAR ALTERATIONS

Several studies describe cellular changes in animals following exposure to asbestos. Holt et al. (1964) described early (14-day) local inflammatory lesions found in the terminal bronchioles of rats following inhalation of asbestos fibers. These lesions consisted of multinucleated giant cells, lymphocytes, and fibroblasts. Progressive fibrosis followed within a few weeks of the first exposure to dust. Davis et al. (1978) described similar early lesions that were found in rats and consisted of a proliferation of macrophages and cell debris in the terminal bronchioles and alveolae.

Jacobs et al. (1978) fed rats 0.5 mg or 50 mg of chrysotile daily for 1 week or 14 months and subsequently examined GI tract tissue by light and electron microscopy. No effects were noted in esophagus, stomach, or cecum tissue, but structural changes in the ileum were seen, particularly of the villi. Considerable cellular debris was detected by light microscopy in the ileum, colon, and rectum tissue. The electron microscopic data confirmed the light microscopy data and indicated that the observed changes were consistent with a mineral-induced cytotoxicity.

A single oral administration of from 5 to 100 mg/kg of chrysotile to rats has produced a subsequent increase in thymidine in the stomach, duodenum, and jejunum (Amacher et al., 1975). This result suggests that an immediate response of cellular proliferation and DNA synthesis may be stimulated by chrysotile ingestion.

4.4 MUTAGENICITY

Asbestos has not been shown to be mutagenic in Escherichia coli or Salmonella typhimurium tester strains (Chamberlain and Tarmy, 1977). Newman et al. (1980) reported that asbestos has no mutagenic ability in Syrian hamster embryo cells, but may increase cell permeability and allow other mutagens into the cell. However, Sincock (1977) used several chrysotile, amosite, and crocidolite samples to show that an increased frequency of polyploids and cells with fragments resulted from passive inclusion of asbestos in the culture media of Chinese hamster ovary (CHO)-K1 cells. Similarly, Lavappa et al. (1975) showed that chrysotile induced a significant and exposure-related

increase in chromosome aberrations in cultured Syrian hamster embryo cells. Amosite, chrysotile, and crocidolite have been found to be weakly mutagenic in Chinese hamster lung cells in the 6-thioguanine-resistance assay (Huang, 1979). Finally, Livingston et al. (1980) have shown that exposure to crocidolite and amosite can increase the sister chromatid exchange rate in Chinese hamster ovarian fibroblasts.

4.5 INHALATION STUDIES

The first unequivocal data that showed a relationship between asbestos inhalation and lung malignancy in laboratory animals was that of Gross et al. (1967), who observed carcinomas in rats exposed to a mean concentration of 86 mg/m^3 chrysotile for 30 hr/wk from the age of 6 weeks. Of 72 rats surviving for 16 months or longer, 19 developed adenocarcinomas, 4 developed squamous cell carcinomas, and 1 developed a mesothelioma. No malignant tumors were found in 39 control animals. A search was made for primaries at other sites which could have metastasized and none were found. These and other data are summarized in Table 4-2.

Reeves et al. (1971) found two squamous cell carcinomas in 31 rats sacrificed after 2 years following exposure to about 48 mg/m^3 of crocidolite. No malignant tumors were reported in rabbits, guinea pigs, or hamsters or in animals exposed to similar concentrations of chrysotile or amosite. No details of the pathological examinations were given.

In a later study (Reeves et al., 1974), malignant tumors developed in 5 to 14% of the rats that survived 18 months after exposure. Lung cancer and mesothelioma were produced by exposures to amosite and chrysotile and lung cancer was produced by crocidolite inhalation. Again, significant experimental details were lacking; information on survival times and times of sacrifice would have been useful. Available details of the exposures and results are given in Table 4-3. While the relative carcinogenicity of the fiber types was similar, the fibrogenic potential of chrysotile, which had been substantially reduced in length and possibly altered (Langer et al., 1978) by milling, was much less than that of the amphiboles. These results were also discussed in a later paper by Reeves (1976).

The most important series of animal inhalation studies is that of Wagner et al. (1974, 1977b). Wagner exposed 849 Wistar SPF rats to the five UICC (Union Intranationale Contra le Cancer) asbestos samples at concentrations from 10.1 to 14.7 mg/m^3 for times ranging from 1 day to 24 months. These

TABLE 4-2. SUMMARY OF EXPERIMENTS ON THE EFFECTS OF INHALATION OF ASBESTOS

Study	Animal species	Material administered	Dosage	Animals Examined for tumors	Findings (malignant tumors)	verage survival time
Gross et al. (1967)	132 male white rats	Ball- and hammer-milled Canadian chrysotile with/without 0.05 ml intratracheal 5 percent NaOH	42-146 mg/ml (mean concentration, 86 mg/m^3) for 30 hrs/week	72	17 adenocarcinomas 4 squamous-cell sarcomas 7 fibrosarcomas 1 mesothelioma	not available
	55 male white rats	Controls with/without 5 percent NaOH	control	39	none	not available
Reeves et al. (1971)	206 rats 106 rabbits 139 guinea pigs 214 hamsters	Ball-milled chrysotile, amosite, and crocidolite	48±2 mg/m^3 for 16 hours/week up to 2 years	not available	2 squamous-cell carcinomas in 31 animals from crocidolite exposure	no information periodic sacrifices were made
Reeves et al. (1974)	219 rats 216 gerbils 100 mice 72 rabbits 108 guinea pigs	Ball- and hammer-milled chrysotile, amosite and crocidolite	48±2 mg/m^3 for 16 hours/week up to 2 years	120 rats 116 gerbils 10 mice 30 rabbits 43 guinea pigs	10 malignant tumors in rats, 2 in mice (Table 4-3)	no information periodic sacrifices were made
Wagner et al. (1974)	13 groups of approximately 50 and 15 of about 25 Wistar SPF rats	Amosite, anthophyllite, crocidolite, Canadian chrysotile, Rhodesian chrysotile (UICC samples)	10.1 to 14.7 mg/m^3 for 1 day to 24 months, 35 hours/week	849	(See Tables 4-4 and 4-5) All asbestos varieties produced mesothelioma and lung cancer, some from exposure as short as 1 day	669 to 857 days versus 754 to 803 for controls. Survival times not significantly affected by exposure.
Wagner et al. (1977a)	CO Wistar male and female rats	Superfine chrysotile	10.8 mg/m^3 37.5 hours/week for 3, 6, or 12 months		1 adenocarcinoma of the lung in 24 animals exposed for 12 months	
	CO Wistar male and female rats	Nonfibrous cosmetic talc			none	
Davis et al. (1978)	46 groups of approximately Han SPF rats and 20 Han SFP rats	UICC samples of amosite, chrysotile, and crocidolite	2 mg/m^3 and 10 mg/m^3 35 hours/week for 224 days	208	7 adenocarcinomas 3 squamous-cell sarcomas, 1 pleural mesothelioma, 1 peritoneal mesothelioma	not available sacrificed at 29 months
	20 Han SPF rats	control	control	20	none	

TABLE 4-3. EXPERIMENTAL INHALATION CARCINOGENESIS

Fiber	Exposure[a]		Rats		Mice	
	Mass mg/m^3	Fiber, f/ml	Animals examined	Malignant tumors	Animals examined	Malignant tumors
Chrysotile	47.9	54	43	1 lung papillary carcinoma 1 lung squamous-cell carcinoma 1 pleural mesothelioma	19	None
Amosite	48.6	864	46	2 pleural mesotheliomas	17	None
Crocidolite	50.2	1,105	46	3 squamous-cell carcinomas 1 adenocarcinoma 1 papillary carcinoma - all of the lung	18	2 papillary carcinomas of bronchus
Controls			5	None	6	1 papillary carcinoma of bronchus

[a]The asbestos was comminuted by vigorous milling, after which 0.08 to 1.82% of the airborne mass was of fibrous morphology (3:1 aspect ratio) by light microscopy.

Source: Reeves et al. (1974).

concentrations are typically 10 times those measured in dusty asbestos workplaces during earlier decades. For all the exposure times, 50 adenocarcinomas, 40 squamous-cell carcinomas, and 11 mesotheliomas were produced. All varieties of asbestos produced mesothelioma and lung malignancies, in some cases from exposures as short as 1 day. Data from these experiments are presented in Tables 4-4 and 4-5. These tumors follow a reasonably good linear relationship for exposure times of 3 months or greater. However, the incidence in the 1-day exposure group is considerably greater than expected. Exposure had a limited effect on length of life. Average survival times varied from 669 to 857 days for exposed animals versus 754 to 803 days for controls. The development of asbestosis was also documented. There were 17 lung tumors, 6 in rats with no evidence of asbestosis and 11 in rats with minimal or slight asbestosis. Cancers at extrapulmonary sites were listed. Seven malignancies of ovaries and eight malignancies of male genitourinary organs were observed in the exposed groups of approximately 350 male and female rats. No malignancies were observed in control groups of 60 males and females. The incidence of malignancy at other sites varied little from that of the controls. However, the authors note that if controls from other experiments in which ovarian and genitourinary tumors were present are included, the comparative incidence in the exposed groups in the first study lacks statistical significance. However, no data were provided on the variation of tumor incidence at extrapulmonary sites with asbestos dosage.

Wagner et al. (1977a) also compared the effects of inhalation of a superfine chrysotile to those of inhalation of a pure nonfibrous talc. One adenocarcinoma was found in 24 rats exposed to 10.8 mg/m^3 of chrysotile for 37.5 hr/wk for 12 months.

In a study similar to Wagner's, Davis et al. (1978) exposed rats to 2.0 or 10.0 mg/m^3 of chrysotile, crocidolite, and amosite (equivalent to 430 to 1950 f/ml). Adeno- and squamous cell carcinomas were observed in chrysotile exposures, but not in crocidolite or amosite exposures (Table 4-6). One pleural mesothelioma was observed with crocidolite exposure, and extrapulmonary neoplasms included a peritoneal mesothelioma. A relatively large number of peritoneal connective tissue malgnancies also were observed; these included a leimyofibroma on the wall of the small intestine. The meaning of these tumors is unclear.

TABLE 4-4. NUMBER OF RATS WITH LUNG TUMORS OR MESOTHELIOMAS AFTER EXPOSURE TO VARIOUS FORMS OF ASBESTOS THROUGH INHALATION

Form of Asbestos	Number of animals	Adenocarcinomas	Squamous-cell carcinomas	Mesothelioma
Amosite	146	5	6	1
Anthophyllite	145	8	8	2
Crocidolite	141	7	9	4
Chrysotile (Canadian)	137	11	6	4
Chrysotile (Rhodesian)	144	19	11	0
None	126	0	0	0

Source: Wagner et al. (1974)

TABLE 4-5. NUMBER OF RATS WITH LUNG TUMORS OR MESOTHELIOMAS AFTER VARIOUS LENGTHS OF EXPOSURE TO VARIOUS FORMS OF ASBESTOS THROUGH INHALATION

Length of exposure	Number of Animals Tested	Number of Animals with lung carcinomas	Number of Animals With pleural mesotheliomas	Percent of animals with tumors
None	126	0	0	0.0
1 day	219	3[a]	2[b]	2.3
3 months	180	8	1	5.0
6 months	90	7	0	7.8
12 months	129	35	6	31.8
24 months	95	37	2	41.0

[a]Two rats exposed to chrysotile and one to crocidolite.

[b]One rat exposed to amosite and one to crocidolite.

Source: Wagner et al. (1974).

TABLE 4-6. EXPERIMENTAL INHALATION CARCINOGENESIS IN RATS

	Exposure		Number of animals examined	Malignant tumors
	Mass mg/m^3	Fiber, f>5μ/ml		
Chrysotile	10	1,950	40	6 adenocarcinomas 2 squamous-cell carcinomas
Chrysotile	2	390	42	1 squamous-cell carcinoma 1 peritoneal mesothelioma
Amosite	10	550	43	None
Crocidolite	10	860	40	None
Crocidolite	5	430	43	1 pleural mesothelioma
Control			20	None

Source: Davis et al. (1978)

Inhalation exposures result in concomitant GI exposures from the asbestos that is swallowed after clearance from the bronchial tree. While all inhalation experiments focus on thoracic tumors, those of Wagner et al. (1974), Davis et al. (1978) and, to a limited extent, Gross et al. (1967) also included a search for tumors at extrathoracic sites. A limited number of these tumors were found, but no association can be made with asbestos exposure.

One important aspect of the inhalation experiments is the number of pulmonary neoplasms that can be produced by inhalation in the rat as compared to other species (Reeves et al., 1971, 1974). This phenomenon illustrates the variability of species response to asbestos and the need for an appropriate model before extrapolations to man can be made with confidence. The absence of significant GI malignancy from asbestos exposure in animals, in contrast to that found in humans, may be the result of the use of inappropriate animal models.

4.6 INTRAPLEURAL ADMINISTRATION

Evidence that intrapleural administration of asbestos would result in mesothelioma was forthcoming in 1970 when Donna (1970) produced mesotheliomas

in Sprague-Dawley rats treated with a single dose of 67 mg of chrysotile, amosite, or crocidolite. Reeves et al (1971) produced mesothelial tumors in rats (1 of 3 with crocidolite and 2 of 12 with chrysotile) by intrapleural injection of 10 mg of asbestos. Two of 13 rabbits injected with 16 mg of crocidolite developed mesotheliomas.

In a series of experiments, Stanton and Wrench (1972) demonstrated that major commercial varieties of asbestos, as well as various other fibers, produce mesotheliomas in as many as 75% of animals into which material had been surgically implanted onto the pleural surface. The authors concluded that the carcinogenicity of asbestos and other fibers is strongly related to their physical size; fibers that have a diameter of less than 3 μm would be carcinogenic and those that have a larger diameter would not be carcinogenic. Further, samples treated by grinding in a ball mill to produce shorter length fibers were less likely to produce tumors. While the authors attributed the reduced carcinogenicity to a shorter fiber length, the question has been raised as to the effect of the destruction of crystallinity and perhaps other changes in the fibers occasioned by the extensive ball milling (Langer et al., 1978).

Since 1972, Stanton and his co-workers (Stanton et al., 1977; 1981) have continued these investigations of the carcinogenic action of durable fibers. Table 4-7 summarizes the results of 72 different experiments. In their analyses, Stanton et al. (1981) suggest that the best measure of carcinogenic potential is the number of fibers that measure ≤ 0.25 μm in diameter and ≥ 8 μm in length, although a good correlation of carcinogenicity is also obtained for fibers ≤ 1.5 μm in diameter and ≥ 4 μm in length. The logit distribution of tumor incidence against the log of the number of particles ≤ 0.25 μm x ≥ 8 μm is shown in Figure 4-4. The regression equation for the dotted line is:

$$\ln[p/(1-p)] = -2.62 + 0.93 \log x, \qquad (4\text{-}1)$$

where p is the tumor probability and x the number of particles ≤ 0.25 μm x ≥ 8 μm. A reasonable relationship exists for the equation results and available data, but substantial discrepancies occur, suggesting the possibility that other relationships may better fit the data. Bertrand and Pézerat (1980) have suggested that carcinogenicity may correlate as well with the ratio of length to width (aspect ratio).

TABLE 4-7. SUMMARY OF 72 EXPERIMENTS WITH DIFFERENT FIBROUS MATERIALS

Experiment	Compound	Actual tumor incidence	Percent tumor probability ± SD	Common log fibers/μg ≤0.25 μm x >8 μm	Experiment	Compound	Actual tumor incidence	Percent tumor probability ± SD	Common log fibers/μg ≤0.25 μm x >8 μm
1	Titanate 1	21/29	95±4.7	4.94	37	Halloy 1	4/25	20±9.0	0
2	Titanate 2	20/29	100	4.70	38	Halloy 2	5/28	23±9.3	0
3	Silcarbide	17/26	100	5.15	39	Glass 8	3/26	19±10.3	3.01
4	Dawson 5	26/29	100	4.94	40	Crocid 11	4/29	19±8.5	0
5	Tremolite 1	22/28	100	3.14	41	Glass 19	2/28	15±9.0	0
6	Tremolite 2	21/28	100	2.84	42	Glass 9	2/28	14±9.4	1.84
7	Dawson 1	20/25	95±4.8	4.66	43	Alumin 6	2/28	13±8.8	0.82
8	Crocid 1	18/27	94±6.0	5.21	44	Dawson 6	3/30	13±6.9	0
9	Crocid 2	17/24	93±6.5	4.30	45	Dawson 2	2/27	12±7.9	0
10	Crocid 3	15/23	93±6.9	5.01	46	Wollaston 2	2/25	12±8.0	0
11	Amosite	14/25	93±7.1	3.53	47	Crocid 12	2/27	10±7.0	3.73
12	Crocid 4	15/24	86±9.0	5.13	48	Attapul 2	2/29	11±7.5	0
13	Glass 1	9/17	85±13.2	5.16	49	Glass 10	2/27	8±5.6	0
14	Crocid 5	14/29	78±10.8	3.29	50	Glass 11	1/27	8±5.5	0
15	Glass 2	12/31	77±16.6	4.29	51	Titanate 3	1/28	8±8.0	0
16	Glass 3	20/29	74±8.5	3.59	52	Attapul 1	2/29	8±5.3	0
17	Glass 4	18/29	71±9.1	4.02	53	Talc 1	1/26	7±6.9	0
18	Alumin 1	15/24	70±10.2	3.63	54	Glass 12	1/25	7±5.4	0
19	Glass 5	16/25	69±9.6	3.00	55	Glass 13	1/27	6±5.7	0
20	Dawson 7	16/30	68±9.8	4.71	56	Glass 14	1/25	6±5.5	0
21	Dawson 4	11/26	66±12.2	4.01	57	Glass 15	1/24	6±5.9	1.30
22	Dawson 3	9/24	66±13.4	5.73	58	Alumin 7	1/25	5±5.1	0
23	Glass 6	7/22	64±17.7	4.01	59	Glass 16	1/29	5±4.4	0
24	Crocid 6	9/27	63±13.9	4.60	60	Talc 3	1/29	4±4.3	0
25	Crocid 7	11/26	56±11.7	2.65	61	Talc 2	1/30	4±3.8	0
26	Crocid 8	8/25	53±12.9	0	62	Talc 4	1/29	5±4.9	0
27	Alumin 2	8/27	44±11.7	2.95	63	Alumin 8	1/28	3±3.4	0
28	Alumin 3	9/27	41±10.5	2.47	64	Glass 21	2/47	6±4.4	0
29	Crocid 9	8/27	33±9.8	4.25	65	Glass 22	1/45	2±2.3	0
30	Wollaston 1	5/20	31±12.5	0	66	Glass 17	0/28	0	0
31	Alumin 4	4/25	28±12.0	2.60	67	Glass 18	0/115	0	0
32	Crocid 10	6/29	37±13.5	3.09	68	Crocid 13	0/29	0	0
33	Alumin 5	4/22	22±9.8	3.73	69	Wollaston 4	0/24	0	0
34	Glass 20	4/25	22±10.0	0	70	Talc 5	0/30	0	0
35	Glass 7	5/28	21±8.7	2.50	71	Talc 6	0/30	0	3.30
36	Wollaston 3	3/21	19±10.5	0	72	Talc 7	0/29	0	0

SD = Standard deviation.

Source: Stanton et al. (1981)

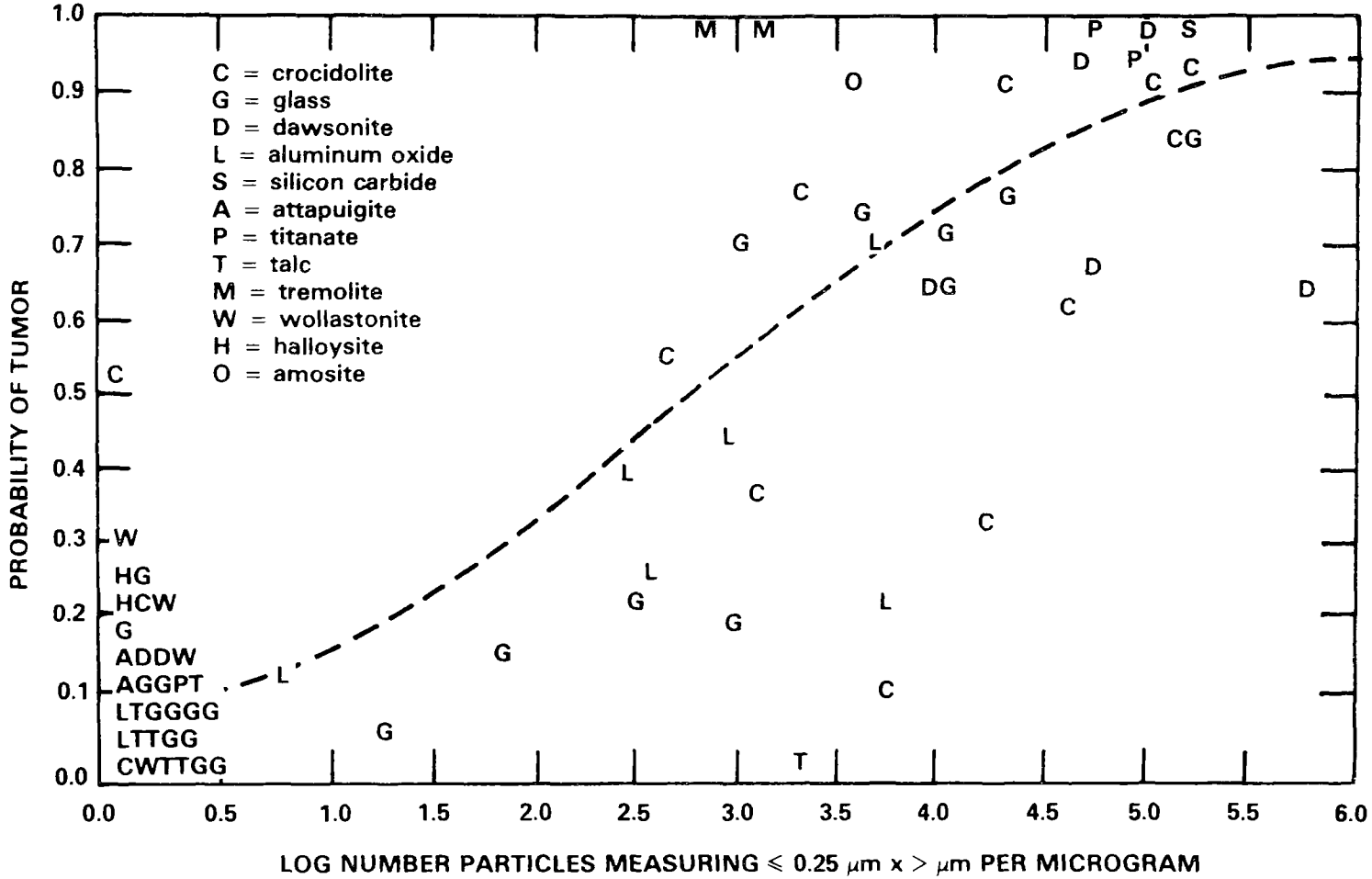

Figure 4.4 Regression curve relating probability of tumor to logarithm of number of particles per μg with diameter ⩽ 0.25 μm and length >8 μm.

Source: Stanton et al. (1981).

Another comprehensive set of experiments was conducted by Wagner (Wagner et al., 1973; 1977b). Wagner also produced mesothelioma from intrapleural administration of asbestos to CD Wistar rats and demonstrated a strong dose-response relationship. Tables 4-8 and 4-9 list the results of these experiments.

Pylev and Shabad (1973) and Shabad et al. (1974) reported mesotheliomas in 18 of 48 rats and in 31 of 67 rats injected with three doses of 20 mg of Russian chrysotile. Other experiments by Smith and Hubert (1974) produced mesotheliomas in hamsters injected with 10 to 25 mg of chrysotile, 10 mg of amosite or anthophyllite, and 1 to 10 mg of crocidolite.

Various suggestions have been made that natural oils and waxes contaminating asbestos fibers might be related to their carcinogenicity (Harington, 1962; Harington and Roe, 1965; Commins and Gibbs, 1969). However, this theory was not borne out in the previously mentioned experiments by Wagner et al. (1973) or Stanton and Wrench (1972).

4.7 INTRATRACHEAL INJECTION

Intratracheal injection has been used to study the combined effect of the administration of chrysotile with benzo(a)pyrene in rats or hamsters. In rats given three doses of 2 mg of chrysotile (Shabad et al., 1974) or in hamsters given 12 mg of chrysotile (Smith et al., 1970), no lung tumors were observed. However, the coadministration of benzo(a)pyrene resulted in lung tumors, and this suggests a cocarcinogenic or synergistic effect.

4.8 INTRAPERITONEAL ADMINISTRATION

Intraperitoneal injections of 20 mg of crocidolite or chrysotile produced three peritoneal mesotheliomas in 13 Charles River CD rats. Twenty mg of amosite produced no tumors in a group of 11 rats (Maltoni and Annoscia, 1974). Malton and Annoscia also injected 25 mg of crocidolite into 50 male and 50 female 17-week-old Sprague-Dawley rats and observed 31 mesothelial tumors in males and 34 in females.

In an extensive series of experiments, Pott and Friedrichs (1972) and Pott et al. (1976) produced peritoneal mesotheliomas in mice and rats that were injected with various commercial varieties of asbestos and other fibrous material. These results are shown in Table 4-10. Using experiments with intrapleural administration, the malignant response was altered by ball-

TABLE 4-8. PERCENTAGE OF RATS DEVELOPING MESOTHELIOMAS AFTER INTRAPLEURAL ADMINISTRATION OF VARIOUS MATERIALS

Material	Percent of Rats with Mesotheliomas
SFA chrysotile (superfine Canadian sample)	66
UICC crocidolite	61
UICC amosite	36
UICC anthophyllite	34
UICC chrysotile (Canadian)	30
UICC chrysotile (Rhodesian)	19
Fine glass fiber (code 100), median diameter, 0.12 μm	12
Ceramic fiber, diameter, 0.5-1 μm[a]	10
Glass powder	3
Coarse glass fiber (code 110), median diameter, 1.8 μm	0

[a]From Wagner et al. (1973).

Source: Wagner (1977b)

TABLE 4-9. DOSE-RESPONSE DATA FOLLOWING INTRAPLEURAL ADMINISTRATION OF ASBESTOS TO RATS

Material	Dose mg	Number of rats with mesothelioma	Total number of rats	Percent of rats with tumors
SFA chrysotile	0.5	1	12	8
	1	3	11	27
	2	5	12	42
	4	4	12	33
	8	8	12	62
Crocidolite	0.5	1	11	9
	1	0	12	0
	2	3	12	25
	4	2	13	15
	8	5	11	45

Source: Wagner et al. (1973)

TABLE 4-10. TUMORS IN ABDOMEN AND/OR THORAX AFTER INTRAPERITONEAL INJECTION OF GLASS FIBERS, CROCIDOLITE, OR CORUNDUM IN RATS

Dust	Form[a]	Intraperitoneal dose	Effective number of dissected rats	Number of days before first tumor	Average survival time of rats with tumors, days after injection	Rats with tumors, percent	Tumor/type[b]					
							1	2	3	4	5	6
Glass fibers MN 104	f	2	73	421	703	27.4	17	3	-	-	1	1
Glass fibers MN 104	f	10	77	210	632	53.2	36	4	-	1	3	-
Glass fibers MN 104	f	2 x 25	77	194	367	71.4	47	6	2	-	-	-
Crocidolite	f	2	39	452	761	38.5	12	3	-	-	2	1
Corundum	g	2 x 25	37	545	799	8.1	1	-	-	2	2	2
UICC Rhodesian chrysotile	f	2	37	431	651	16.2	4	2	-	-	1	-
UICC Rhodesian chrysotile	f	6.25	35	343	501	77.1	24	3	-	-	-	-
UICC Rhodesian chrysotile	f	25	31	276	419	00.6	21	2	1	1	-	-
UICC Rhodesian chrysotile	f	4 x 25	33	323	361	54.5	16	2	-	-	-	-
UICC Rhodesian chrysotile	f	3 x 25 s.c.	33	449	449	3.0	-	-	1 s.c.	-	-	-
UICC Rhodesian milled	f	4 x 25	37	400	509	32.4	9	3	-	-	-	-
Palygoescite	f	3 x 25	34	257	348	76.5	24	2	-	-	-	-

TABLE 4-10. (continued)

Dust	Form[a]	Intraperitoneal dose	Effective number of dissected rats	Number of days before first tumor	Average survival time of rats with tumors, days after injection	Rats with tumors, percent	Tumor/type[b] 1	2	3	4	5	6
Glass fibers s + s 106	f	2	34	692	692	2.9	1	-	-	-	-	-
Glass fibers S + S 106	f	10	36	350	530	11.1	2	2	-	-	1	-
Glass fibers S + S 106	f	4 x 25	32	197	325	71.9	20	3	-	-	-	-
Gypsum	f	4 x 25	35	579	583	5.7	-	-	1	1	1	-
Henalite	f	4 x 25	34	249	315	73.5	17	8	-	-	-	-
Actinolite	g	4 x 25	39	-	-	-	-	-	-	-	-	-
Biotite	g	4 x 25	37	-	-	-	-	-	-	-	-	-
Haematite (precipitation)	g	4 x 25	34	-	-	-	-	-	-	-	-	-
Haematite (mineral)	g	4 x 25	38	-	-	-	-	-	-	-	-	-
Pectolite	g	4 x 25	40	569	569	2.5	-	-	-	1	1	1
Sanidine	g	4 x 25	39	579	579	2.6	-	1	-	-	-	-
Talc	g	4 x 25	36	587	587	2.8	1	-	-	-	-	-
NaCl (control)	-	4 x 2 ml	72	-	-	-	-	-	-	-	-	-

[a] f = fibrous; g = granular.

[b] Tumor Types are: 1 Mesothelioma; 2 Spindle cell sarcoma; 3 Polym-cell sarcoma; 4 Carcinoma; 5 Reticulum cell sarcoma; 6 Benign -- not evaluated in tumor rates.

Sources: Pott and Friedrichs (1972); Pott et al. (1976).

milling fibers for 4 hours. The rate of tumor production was reduced from 55 to 32% and the time from the onset of exposure to the first tumor was lengthened from 323 to 400 days following administration of four doses of 25 mg of UICC Rhodesian chrysotile. In the case of the ball-milled fibers, 99% of the fibers were reported to be smaller than 3 μm, 93% were less than 1 μm, and 60% were less than 0.3 μm.

Pott (1980) has proposed a model for the relative carcinogenicity of mineral fibers according to their dimensionality using the results of injection and implantation data. Figure 4-5 shows the schematic features of this model. The greatest carcinogenicity is attributed to fiber lengths between 5 and 40 μm with diameters between 0.05 and 1 μm.

A strong conclusion that can be drawn from the above experimental data is that long (4 μm) and fine diameter (<1 μm) fibers are more carcinogenic than short, thick fibers when they are implanted on the pleura or injected into the peritoneum of animals. The origin of a reduced carcinogenicity for shorter, ball-milled fibers is less clear because the relative contributions of shorter fiber length and the significant alteration of the crystal structure by input of physical energy are not yet defined. However, the extrapolation of data developed on size-dependent effects, from intrapleural or intraperitoneal administration to inhalation (where movement of the fibers in airways and subsequently through body tissues is strongly size-dependent), presents significant difficulties. Moreover, the number of shorter (<5 μm) fibers in an exposure circumstance may be 100 times greater than the number of longer fibers; therefore, their carcinogenicity must be 100 times less before their contribution can be neglected.

4.9 TERATOGENICITY

There is no evidence that asbestos is teratogenic. Schneider and Maurer (1977) fed pregnant CD-1 mice doses of 4 to 400 mg/kg body weight (1.43 to 143) for days 1 to 15 of gestation. They also administered 1, 10, or 100 μg of asbestos to day 4 blastocysts, which were transferred to pseudopregnant mice. No positive effects were noted in either experiment.

4.10 SUMMARY

The animal data on the carcinogenicity of asbestos fibers confirm and extend epidemiological human data. Mesothelioma and lung cancer have been

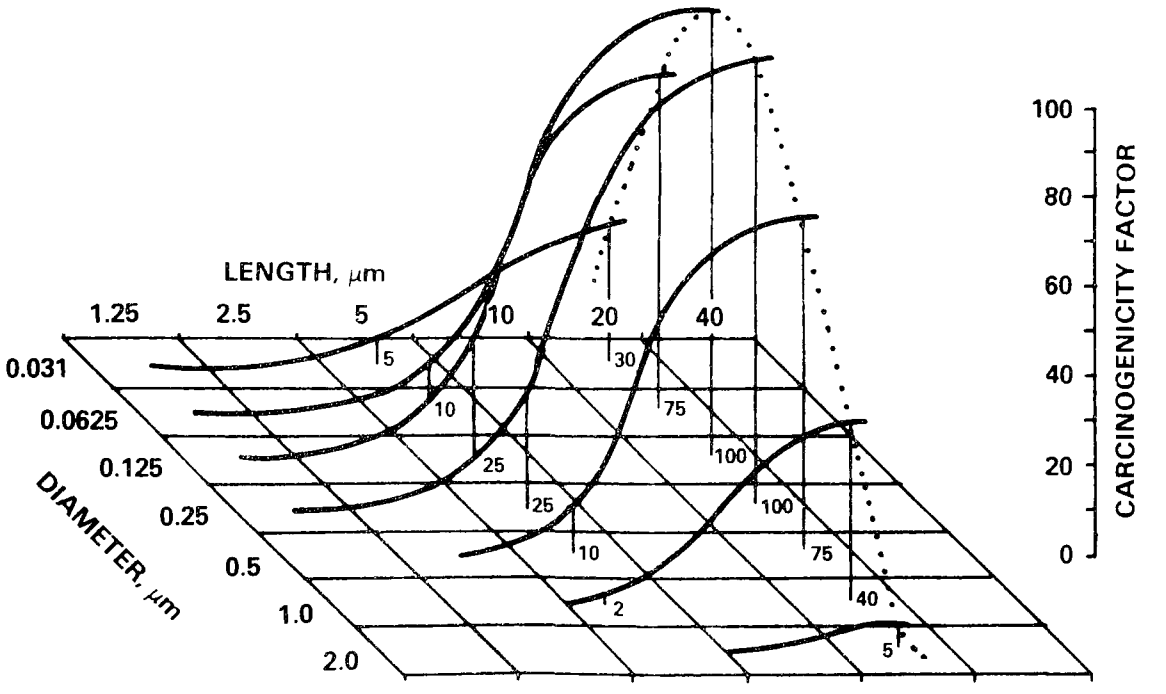

Figure 4-5. Hypothesis concerning the carcinogenic potency of a fiber as a function of its length and width using data on tumor incidence from injection and implantation studies.

Source: Pott (1980).

produced by all the principal commercial asbestos varieties, chrysotile, amosite, crocidolite and anthophyllite, even by exposures as short as 1 day. The deposition and clearance of fibers from the lung suggest that most inhaled fibers (~99%) are eventually cleared from the lung by ciliary or phagocytic action. Chrysotile appears to be more readily removed, and dissolution of the fibers occurs in addition to other clearance processes. Implantation and injection studies suggest that the carcinogenicity of durable mineral fibers is related to their dimensionality and not to their chemical composition. Long ($\geq$4 μm) and thin ($\leq$1 μm) fibers are most carcinogenic when they are in place at a potential tumor site. However, deposition, clearance, and migration of fibers is also size dependent, and the importance of all size-dependent effects in the carcinogenicity of inhaled fibers is not fully established.

5. ENVIRONMENTAL EXPOSURES TO ASBESTOS

5.1 INTRODUCTION

The analysis of ambient air samples for asbestos has utilized techniques different from those used in occupational circumstances. This situation occurred because typical urban air may contain up to 100 $\mu g/m^3$ of particulate matter in which the researcher is attempting to quantify asbestos concentrations from about 0.1 ng/m^3 to perhaps 1000 ng/m^3. Thus, asbestos may constitute only 0.0001 to 1% of the particulate matter in a given air sample. Moreover, the asbestos found in the ambient air had a size distribution in which the vast majority of the fibers were too short or thin to be seen in an optical microscope. In many cases, these fibers and fibrils will be agglomerated with a variety of other materials present in the air samples.

The only effective method of analysis has used the electron microscope to enumerate and size all asbestos fibers (Nicholson and Pundsack, 1973; Samudra et al., 1978). Samples from such analysis were collected on Millipore filters, usually with a nominal pore size of 0.8 μm and in some cases, backed by a nylon mesh. To prepare a sample for analysis, a portion of the filter was ashed in a low temperature oxygen furnace, which removed the membrane filter material and all organic material collected in the sample. The residue was recovered in a liquid phase, dispersed by ultrasonification, and filtered on a Nuclepore filter. The refiltered material was coated by carbon to entrap the collected particles. A segment of the coated filter was then mounted on an electron microscope grid, which was placed on a filter paper saturated with chloroform, the vapors of which serve to dissolve the filter material Earlier electron microscopic analysis utilized a rub-out technique in which the ash residue was dispersed in a nitrocellulose film on a microscope slide and a portion of that film was mounted on an electron microscope grid for scanning. Chrysotile asbestos was identified on the basis of its morphology in the electron microscope and amphiboles were identified by their selected area electron diffraction patterns, supplemented by energy dispersive X-ray analysis. Because of the dispersal of the fibers and their disruption by ultrasonification, no information was obtained on the size distribution of the original aerosol. Air concentrations were recorded only in terms of the total mass of asbestos present in a given air volume, usually in nanograms per cubic meter. (See Section 5-9 for data on the interconvertibility of optical fiber

counts and electron microscopic mass determinations.) Environmental measurements can also be made by using Nuclepore filters and eliminating the ashing and refiltration steps mentioned above. However, great care must be taken to assure that fibers are not lost from the filter prior to processing.

An analysis of 25 samples collected in buildings with asbestos surfacing material, some of which showed evidence of contamination, demonstrated the inadequacy of phase contrast optical microscopic techniques for the quantification of asbestos (Nicholson et al., 1975). Figure 5-1 shows the correlation of optical fiber counts determined using NIOSH prescribed techniques (1972) and asbestos mass measurements obtained on the same sample. In determining the fiber concentrations, all objects with an aspect ratio of three or greater were enumerated using phase contrast microscopy. Petrographic techniques were not utilized to verify whether an object was an asbestos fiber because the study was designed to evaluate phase contrast microscopy. Figure 5-1 shows that the optical microscopic data do not reflect the mass concentrations of asbestos determined by electron microscopy, largely because of a considerable number of nonasbestos fibers that were in the ambient air and were counted in the optical microscopic analysis.

5.2 GENERAL ENVIRONMENT

Asbestos of the chrysotile variety has been found to be a ubiquitous contaminant of ambient air. A study of 187 quarterly samples collected in 48 U.S. cities from 1969 to 1970 showed chrysotile asbestos to be present in virtually all metropolitan areas (Nicholson, 1971; Nicholson and Pundsack, 1973). Table 5.1 lists the distribution of values obtained in that study along with similar data obtained by the Battelle Memorial Institute (EPA, 1974). Each value represents the chrysotile concentration in a composite of from five to seven 24-hour samples and, thus, averages over possible peak concentrations, which could occur periodically or randomly. Of the three samples greater than 20 ng/m^3 analyzed by Mount Sinai, one sample was in a city that had a major shipyard and another was in a city that had four brake manufacturing facilities. Thus, these samples may have included a contribution from a specific source in addition to that of the general ambient air. Also shown in Table 5-1 is the distribution of chrysotile concentrations from five day samples of the air of Paris (Sebastien et al., 1980). These values were obtained during 1974 and 1975 and were generally lower than those measured in

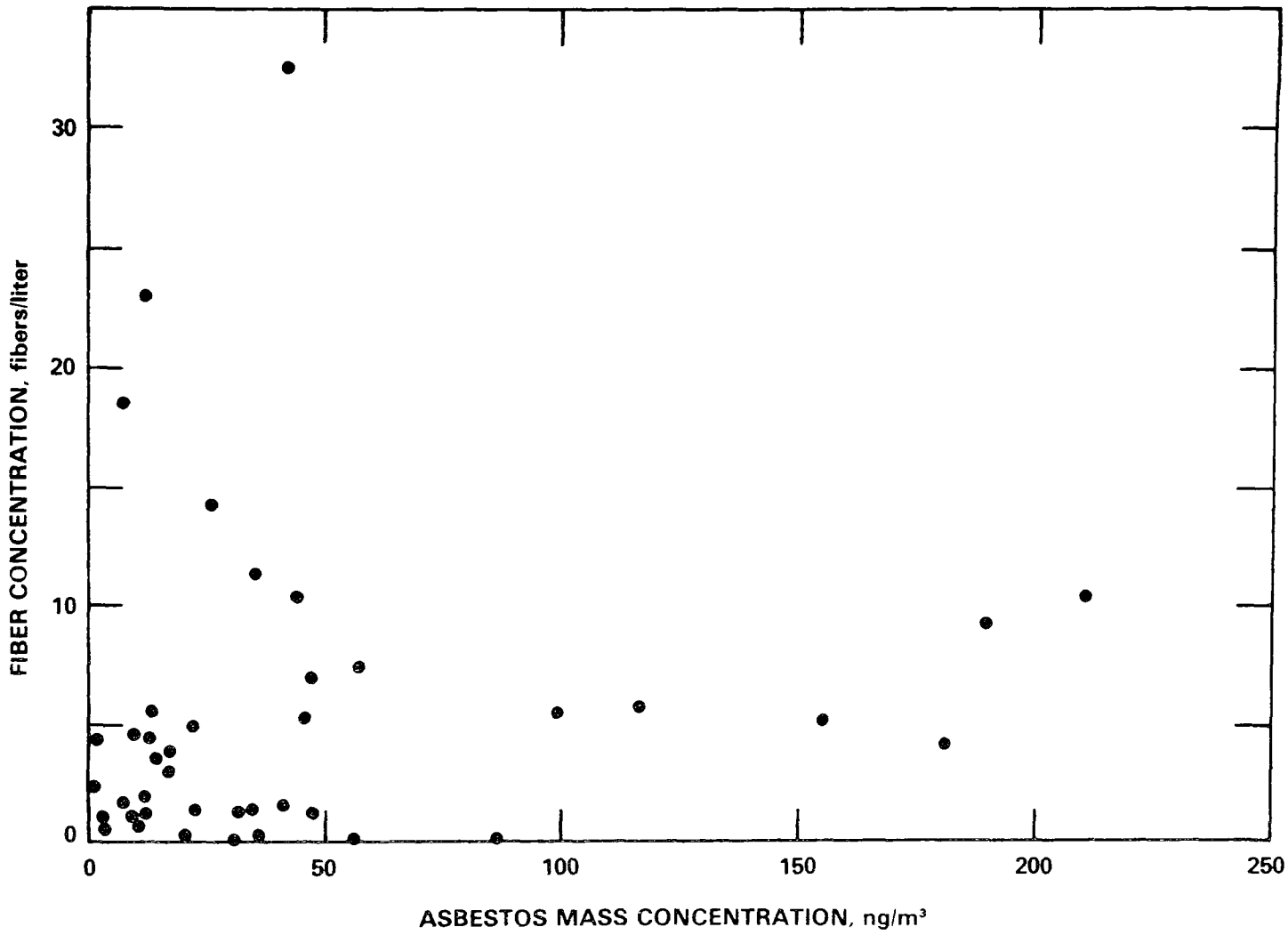

Figure 5-1. Fiber concentrations by optical microscopy versus asbestos mass concentrations by electron microscopy.

Source: NIOSH (1972).

TABLE 5-1. THE CUMULATIVE DISTRIBUTION OF 24-HOUR CHRYSOTILE ASBESTOS CONCENTRATIONS IN THE AMBIENT AIR OF U.S. CITIES AND PARIS, FRANCE

	Electron Microscopic Analysis				
	Mount Sinai School of Medicine[a]		Battelle Memorial Institute[b]		Paris, France[c]
Concentration (ng/m^3) less than	Number of samples	Percentage of samples	Number of samples	Percentage of samples	Percentage of samples
1.0	61	32.6	27	21.3	70
2.0	119	63.6	60	47.2	85
5.0	164	87.7	102	80.1	98
10.0	176	94.2	124	97.6	100
20.0	184	98.5	125	98.5	
50.0	185	99.0	127	100.0	
100.0	187	100.0	127	100.0	

Sources: [a]Nicholson (1971); [b]EPA (1974); [c]Sebastien et al. (1980).

the United States, perhaps reflecting a diminished use of asbestos in construction compared to that of the United States during 1969-1970.

In a study of the ambient air of New York City, in which samples were taken only during daytime working hours, higher values than those mentioned above were obtained (Nicholson et al., 1971). These 6-to 8-hour samples were collected between 8:00 A.M. and 5:00 P.M., and they reflect what could be intermittently higher concentrations during those hours compared to night time periods, for example. Table 5-2 records the chrysotile content of 22 samples collected in the five boroughs of New York and their overall cumulative distribution. The samples analyzed in all the studies discussed above were taken during a period when fireproofing of high rise buildings by spraying asbestos-containing materials was permitted. The practice was especially common in New York City. While no sampling station was known to be located adjacent to an active construction site, unusually high levels could nevertheless have resulted from the procedure. Other sources that may have contributed to these air concentrations include automobile braking, other construction activities, consumer use of asbestos products, and maintenance or repair of asbestos-containing materials (e.g., thermal insulation).

TABLE 5-2. DISTRIBUTION OF 4- TO 8-HOUR DAYTIME CHRYSOTILE ASBESTOS CONCENTRATIONS IN THE AMBIENT AIR OF NEW YORK CITY 1969-1970

Asbestos concentration (ng/m^3) less than	Cumulative number of samples	Cumulative percentage of samples
1	0	0.0
2	1	4.5
5	4	18.1
10	8	36.4
20	16	72.7
50	21	95.4
100	22	100.0

Distribution by borough

Sampling locations	Number of samples	Asbestos air level, ng/m^3	
		Range	Average
Manhattan	7	8-65	30
Brooklyn	3	6-39	19
Bronx	4	2-25	12
Queens	4	3-18	9
Staten Island	4	5-14	8

Source: Nicholson et al. (1971).

5.3 CHRYSOTILE ASBESTOS CONCENTRATIONS ABOUT CONSTRUCTION SITES

To determine if construction activities could be a significant source of chrysotile fiber in the ambient air, 6- to 8-hour daytime sampling was conducted in lower Manhattan in 1969 about sites where extensive spraying of asbestos-containing fireproofing material was taking place. Eight sampling sites were established about the World Trade Center construction site during the period when asbestos material was sprayed on the steelwork of the first tower. Table 5-3 shows the results of building-top air samples located at sites within one-half mile of the Trade Center site and demonstrates that spray fireproofing did contribute significantly to asbestos air pollution (Nicholson et al., 1971; Nicholson and Pundsack, 1973). In some instances, chrysotile asbestos levels approximately 100 times the concentrations typically found in the ambient air were observed.

TABLE 5-3. DISTRIBUTION OF 6- TO 8-HOUR CHRYSOTILE ASBESTOS CONCENTRATIONS WITHIN ONE-HALF MILE OF THE SPRAYING OF ASBESTOS MATERIALS ON BUILDING STEELWORK 1969-1970

Asbestos concentration (ng/m^3) less than	Cumulative number of samples	Cumulative percentage of samples
5	0	0.0
10	3	17.6
20	8	47.1
50	14	82.3
100	16	94.1
200	16	94.1
500	17	100.0

Distribution of chrysotile air levels according to distance from spray fireproofing sites

Sampling locations	Number of samples	Asbestos air level, ng/m^3	
		Range	Average
1/8-1/4 mile	11	9 - 375	60
1/4-1/2 mile	6	8 - 54	25
1/2-1 mile	5	3.5 - 36	18

Source: Nicholson et al (1971).

5.4 ASBESTOS CONCENTRATIONS IN BUILDINGS IN THE UNITED STATES AND FRANCE

During 1974, 116 samples of indoor and outdoor air were collected in 19 buildings in five U.S. cities to assess whether contamination of the building air resulted from the presence of asbestos-containing surfacing material in rooms or return air plenums (Nicholson et al., 1975). The asbestos material in the buildings was of two main types: 1) a cementitious or plaster-like material that had been sprayed as a slurry onto steelwork or building surfaces and 2) a loosely bonded fibrous mat that had been applied by blowing a dry mixture of fibers and binders through a water spray onto the desired surface. The friability of the two types of materials differed considerably; the cementitious spray surfaces were relatively impervious to damage while the fibrous sprays were highly friable. The results of the air sampling in these buildings (Table 5-4) provide evidence that the air of buildings with fibrous asbestos-containing materials may often be contaminated.

TABLE 5-4. THE CUMULATIVE DISTRIBUTION OF 8- TO 16-HOUR CHRYSOTILE ASBESTOS CONCENTRATIONS IN BUILDING WITH ASBESTOS-CONTAINING SURFACING MATERIAL IN ROOMS OF AIR PLENUMS

Asbestos concentration ng/m^3 less than	Friable spray		Cementitious spray		Control samples	
	Number of samples	Percentage of samples	Number of samples	Percentage of samples	Number	Percentage
1	5	9.3	3	10.7	5	14.7
2	6	11.1	6	21.4	6	17.6
5	8	14.8	10	35.7	15	44.1
10	15	27.8	17	60.7	21	61.8
20	28	51.9	26	92.9	29	85.3
50	44	81.5	27	96.4	33	97.1
100	49	90.7	27	96.4	34	100.0
200	52	96.3	28	100.0		
500	53	98.1				
1000	54	100.0				
Arithmetic average concentration		48 ng/m^3		14.5 ng/m^3		12.7 ng/m^3

Source: Nicholson et al. (1975; 1976).

Similar data were obtained by Sebastien et al. (1980) in a survey of asbestos concentration in buildings in Paris, France. Sebastien surveyed 21 asbestos insulated buildings, 12 of which had at least one measurement higher than 7 ng/m^3, the upper limit of the outdoor asbestos concentrations measured by these workers. The distribution of the 5-day asbestos concentrations in these buildings, along with 19 outdoor samples taken at the same time is shown in Table 5-5. One particularly disturbing set of data of Sebastien et al. is the concentrations of asbestos measured after surfacing material was removed or repaired. The average of 22 such samples was 22.3 ng/m^3. However, in two highly contaminated areas, significant reductions were measured (500 to 750 ng/m^3 decreased to less than 1 ng/m^3). The importance of proper removal techniques and cleanup cannot be overemphasized.

Additionally, Sebastien et al. (1982), measured concentrations of indoor airborne asbestos up to 170 ng/m^3 in a building with weathered asbestos floor tiles. Asbestos flooring is used in a large number of buildings and is the third largest use of asbestos fibers.

5.5 ASBESTOS CONCENTRATIONS IN U.S. SCHOOL BUILDINGS

A recent concern was the discovery of extensive asbestos use in public school buildings (Nicholson, 1978b). Asbestos surfaces were found in more than 10% of pupil use areas in schools of New Jersey, with two-thirds of these surfaces having some evidence of damage. Because these values appear to be typical of conditions in many other states, it has been estimated that from 2 to 6 million pupils and 100,000 to 300,000 teachers may be exposed to released asbestos fibers in schools across the nation. To obtain a measure of contamination for this use of asbestos, 10 schools were sampled in the urban centers of New York and New Jersey and suburban areas of Massachusetts and New Jersey. Schools were selected for sampling because of visible damage, in some cases extensive, and thus are not typical of all schools.

Table 5-6 lists the distribution of chrysotile concentrations found in samples taken over 4 to 8 hours in these 10 schools. Chrysotile asbestos concentrations ranged from 9 ng/m^3 to 1950 ng/m^3, with an average of 217 ng/m^3. Outside air samples at three of the schools varied from 3 ng/m^3, with an average of 14 ng/m^3. In all samples but two (which measured 320 ng/m^3) no asbestos was visible on the floor of the sampled area, although surface damage was generally present near this area. The highest value (1950 ng/m^3) was in a

TABLE 5-5. THE CUMULATIVE DISTRIBUTION OF 5-DAY ASBESTOS CONCENTRATIONS IN PARIS BUILDINGS WITH ASBESTOS-CONTAINING SURFACING MATERIALS

Asbestos concentration (ng/m^3) less than	Building samples		Outdoor control samples	
	Number	Percentage	Number	Percentage
		Chrysotile		
1	57	42.2	14	73.7
2	70	51.9	16	84.2
5	92	68.1	17	89.5
10	104	77.0	19	100.0
20	117	86.7		
50	128	94.8		
100	129	95.6		
200	130	96.3		
500	132	97.8		
1000	135	100.0		
Arithmetic average concentration		25 ng/m^3		1 ng/m^3
		Amphiboles[a]		
1	112	83.0	19	100.0
2	115	85.2		
5	122	90.4		
10	125	92.6		
20	129	95.6		
50	131	97.0		
100	132	97.8		
200	133	98.5		
500	135	100.0		
Arithmetic average concentration		10 ng/m^3		0.1 ng/m^3

[a]No value reported for 104 building samples. Some materials would have contained no amphibole asbestos.

Source: Sebastien et al. (1980).

TABLE 5-6. DISTRIBUTION OF CHRYSOTILE ASBESTOS CONCENTRATIONS IN 4- to 8-HOUR SAMPLES TAKEN IN PUBLIC SCHOOLS WITH DAMAGED ASBESTOS SURFACES

Asbestos concentration (ng/m^3) less than	Number of samples	Percentage of samples
5	0	0.0
10	1	3.7
20	1	3.7
50	6	22.2
100	12	44.4
200	19	70.4
500	25	92.6
1000	26	96.3
2000	27	100.0

Source: Nicholson, 1978b

sample that followed routine sweeping of a hallway in a school with water damage to the asbestos surface. However, no visible asbestos was seen on the hallway floor. Because the schools were selected on the basis of visible damage, these results cannot be considered typical of all schools with asbestos surfaces. However, the results illustrate the extensive contamination that can occur.

A recent study suggests that the above New Jersey samples in schools may not be atypical (Constant, Jr et al., 1983). Concentrations identical to those indicated above were found in the analysis of samples collected during a 5-day period in 25 schools that had asbestos surfacing materials. The schools were in a single district and were selected by a random procedure, not because of the presence or absence of damaged material. An arithmetic mean concentration of 237 ng/m^3 was measured in 54 samples collected in rooms or areas that had asbestos surfacing material In contrast, a concentration of 8 ng/m^3 was measured in 31 samples of outdoor air taken at the same time. Of special concern are 31 samples that were collected in the schools that used asbestos, but in areas where asbestos was not used. These data showed an average concentration of 54 ng/m^3, indicating the dispersal of asbestos from the source. The data are summarized in Table 5-7.

Finally, Sawyer (1977; 1979) has reviewed a variety of data on air concentrations, measured by optical microscopy, that have been observed in

TABLE 5-7. CUMULATIVE DISTRIBUTION OF 5-DAY CHRYSOTILE ASBESTOS CONCENTRATIONS IN 25 SCHOOLS WITH ASBESTOS SURFACING MATERIALS, 1980-1981

Asbestos concentration ng/m^3 less than	Rooms with asbestos		Rooms without asbestos		Outdoor controls	
	Number of samples	Percentage of samples	Number of samples	Percentage of samples	Number of samples	Percentage of samples
			Chrysotile			
1	4	7.4	6	19.3	18	58.1
2	6	11.1	7	22.6	21	67 7
5	7	13.0	10	38.7	26	83.9
10	10	18.5	12	41.9	28	90.3
20	16	29.6	13	54.8	29	93.5
50	25	46.3	17	87.1	30	96.8
100	33	61.1	27	93.5	31	100.0
200	43	79.6	29	96.8		
500	48	88.9	31	100.0		
1000	54	100.0				
Arithmetic average concentration		231 ng/m^3		54 ng/m^3		8 ng/m^3
			Amphiboles			
1	44	81.5	21	67 7	26	83.9
2	45	83.3	22	71.0	29	93.5
10	48	88.9	26	83.9	30	96.8
20	50	92.6	27	87.1	30	96.8
50	52	96.3	27	87 1	31	100.0
100	52	96.3	29	93.5		
200	53	98.1	31	100.0		
500	54	100.0				
Arithmetic average concentration		6.1 ng/m^3		8.7 ng/m^3		0.7 ng/m^3

Source: Constant, Jr et al. (1983).

circumstances where asbestos materials in schools and other buildings are disturbed by routine or abnormal activity. These results are shown in Table 5-8, demonstrate that a wide variety of activities can lead to high asbestos concentrations during disturbance of asbestos surfacing material. Maintenance and renovation work, particularly if performed improperly, can lead to substantially elevated asbestos levels.

TABLE 5-8. AIRBORNE ASBESTOS IN BUILDINGS

Friable asbestos material

Classification	Main mode of contamination	Activity description	Mean count of fibers per cm^3	n	Range or SD
Quiet, non-specific, routine	Fallout	None	0.0	32	0.0
	Reentrainment	Dormitory	0.1	NA	0.0-0.8
		University, schools	0.1	47	0.1
		offices	0.2	14	0.1-0.6
Maintenance	Contact	Relamping	1.4	2	0.1
		plumbing	1.2	6	0.1-2.4
		cable movement	0.9	4	0.2-3.2
Custodial	Mixed: contact reentrainment	Cleaning	15.5	3	6.7
		dry sweeping	1.6	5	0.7
		dry dusting	4.0	6	1.3
		by stander	0.3	3	0.3
		heavy dusting	2.8	8	1.6
Renovation	Mixed: contact reentrainment	Ceiling repair	17.7	3	8.2
		track light	7.7	6	2.9
		hanging light	1.1	5	0.8
		partition	3.1	4	1.1
		pipe lagging	4.1	8	1.8-5.8
Vandalism	Contact	Ceiling damage	12.8	5	8.0

Source: Sawyer, 1979.

5.6 CHRYSOTILE CONCENTRATIONS IN THE HOMES OF WORKERS

The finding of asbestos disease in family contacts of individuals occupationally-exposed to the fiber directs attention to air concentrations in the homes of such workers. Thirteen samples have been collected in the homes of asbestos mine and mill employees and analyzed for chryostile (Nicholson et al., 1980). The workers were employed at mine operations in California and Newfoundland and at the time of sampling (1973 and 1976), they did not have

access to shower facilities nor did they commonly change clothes before going home. Table 5-9 lists the concentrations range of the home samples. Three samples taken in homes of non-miners in Newfoundland yielded concentrations of 32, 45, and 65 ng/m^3 In contrast, the concentrations in workers' homes were much higher, pointing to the need for appropriate shower and change facilities at asbestos workplaces. Because as asbestos cancers have been documented in

TABLE 5-9. DISTRIBUTION OF 4-HOUR CHRYSOTILE ASBESTOS CONCENTRATIONS IN THE AIR OF HOMES OF ASBESTOS MINE AND MILL EMPLOYEES

Asbestos concentration (ng/m^3) less than	Number of samples	Percentage of samples
50	0	0.0
100	4	30.8
200	8	61.5
500	10	76.9
1000	12	92.3
2000	12	92.3
5000	13	100.0

Source: Nicholson et al (1980).

family contacts of workers, concentrations such as those described in this document should be viewed with particular concern.

5.7 SUMMARY OF ENVIRONMENTAL SAMPLING

Table 5-10 summarizes those studies of the general ambient air or of specific pollution circumstances that have a sufficient number of samples for comparative analysis. The data are remarkably consistent. Average 24-hour samples of general ambient air indicate asbestos concentrations of 1 to 2 ng/m^3 (two U.S. samples that may have been affected by specific sources were not included). Short-term daytime samples are generally higher; this reflects the possible contributions of traffic, construction, and other human activities. Of buildings with asbestos-surfacing materials, average concentrations 100 times those of the ambient air are seen in some schools. Concentrations of 5 to 30 times background are seen in some other building circumstances.

5.8 OTHER EMISSION SOURCES

The weathering of asbestos cement wall and roofing materials has been shown to be a source of asbestos air pollution in the analysis of air samples

TABLE 5-10. SUMMARY OF ENVIRONMENTAL ASBESTOS SAMPLING

Sample set	Collection period	Number of samples	Mean concentration, ng/m^3
Quarterly composites of 5 to 7 24-hour U.S. samples (Nicholson, 1971; Nicholson and Pundsack, 1973)	1969-70	187	3.3 C[a]
5 day samples of Paris, France (Sebastien et al., 1980)	1974-75	161	0.96 C
6- to 8-hour samples of New York City (Nicholson et al., 1971)	1969	22	16 C
5 day, 7 hour control samples for U.S. school study (Constant, Jr. et al , 1982)	1980-81	31	9 (8C,1A[b])
16-hour samples of five U.S. cites (EPA, 1974)	1974	34	13 C
New Jersey schools with damaged asbestos surfacing materials in pupil use areas (Nicholson, 1978b)	1977	27	217 C
U.S. school rooms/areas with asbestos surfacing material (Constant, Jr et al., 1983)	1980-81	54	237 (231C,6A)
U.S. school room/areas in building with asbestos surfacing material (Constant, Jr et al , 1983)	1980-81	31	63 (54C,9A)
Buildings with asbestos materials in Paris, France (Sebastien et al., 1980)	1976-77	135	35 (25C,10A)
U.S. buildings with friable asbestos in plenus or as surfacing material (Nicholson et al., 1975, 1976)	1974	54	48 C
U.S. buildings with cementitious asbestos material in plenum or as surfacing material (Nicholson et al , 1975, 1976)	1974	28	15 C

[a] C = chrysotile.

[b] A = amphibole.

taken in buildings constructed of such material (Nicholson, 1978a). Seven samples taken in a school after a heavy rainfall showed asbestos concentrations from 20 to 4500 ng/m^3 (arithmetic mean = 780 ng/m^3 -- all but two samples exceeded 100 ng/m^3). The source was attributed to asbestos washed from asbestos cement walkways and asbestos cement roof panels. No significantly elevated concentrations were observed in a concurrent study of houses constructed of asbestos cement materials. Roof water runoff from the homes landed on the ground and was not reentrained, while that of the schools fell to a smooth walkway, which allowed easy reentrainment, when dry. Contamination from asbestos cement siding has also been documented by Spurny et al. (1980).

One of the more significant remaining contributions to environmental asbestos concentrations may be emissions from braking by automobiles and other vehicles. Measurements of brake and clutch emissions revealed that, annually, 2.5 tons of unaltered asbestos are released to the atmosphere and an additional 68 tons fall to roadways, where some of the asbestos is dispersed by passing traffic (Jacko et al., 1973).

5.9 INTERCONVERTIBILITY OF FIBER AND MASS CONCENTRATIONS

The limited data that relate asbestos disease to exposure are derived from studies of workers exposed in occupational environments. In these studies, concentrations of fibers that are longer than 5 μm were determined using optical microscopy or were estimated from optical microscopic measurements of total particulate matter. On the other hand, all current measurements of low-level environmental pollution utilize electron microscopic techniques, which determine the total mass of asbestos present in a given volume of air. To extrapolate dose-response data obtained in studies of working groups to environmental exposures, it is necessary to establish a relationship between optical fiber counts and the mass of asbestos determined by electron microscopy.

Some data relate optical fiber counts (longer than 5 μm) to the total mass of asbestos as determined by electron microscopic techniques or other weight determinations. These relationships (Table 5-11) provide crude estimates of a conversion factor relating fiber concentrations fibers per milliliter to airborne asbestos mass micrograms per cubic meter. The proposed standards for asbestos in Great Britain set by the British Occupational

TABLE 5-11. MEASURED RELATIONSHIPS BETWEEN OPTICAL FIBER COUNTS AND MASS AIRBORNE CHRYSOTILE

Sampling situation	Fiber[a] counts f/ml	Mass concentration µg/m³	Conversion factors µg/m³ / f/ml or µg / 10⁶f	10³ f/mg
Textile factory British Occupational Hygiene Society (1968) (weight vs. fiber count)	2	120	60	16
Air chamber monitoring Davis, et al. (1978)	1950	10,000	5	200
Monitoring brake repair work Rohl et al. (1976) Electron Microscopy (E.M. mass vs. fiber count)	0.1 to 4.7 (7 samples)	0.1 to 6.6	0.7 to 24[b] mean = 6	170
Textile mill Lynch et al. (1970)			150[c]	6.7
Friction products manufacturing Lynch et al. (1970)			70[c]	13.9
Pipe manufacturing Lynch et al. (1970)			45[c]	22.5

[a]All fiber counts used phase-contrast microscopy and enumerated fibers longer than 5 µm.

[b]Conversion factor may be low due to losses in electron microscopy processing.

[c]Conversion factor may be high because of overestimate of asbestos mass on the basis of total magnesium.

Hygiene Society (BOHS) stated that a "respirable" mass of 0.12 mg of asbestos per cubic meter was equivalent to 2 f/ml (BOHS, 1968). The standard did not state how this relationship was determined. However, if the relationship was obtained from magnesium determinations in an aerosol, the weight determination would likely be high because of the presence of other nonfibrous, magnesium-containing compounds in the aerosol. Such was the case in the work of Lynch et al. (1970), and their values for the conversion factor are undoubtedly overestimates. The data of Rohl et al. (1976) are likely to be underestimates

because of possible losses in the determination of mass by electron microscopy. No information exists on the procedures used to determine the mass of chrysotile in the data presented by Davis et al. (1978).

The range of 5 to 150 for the conversion factor relating mass concentration to optical fiber concentration is large and any average value derived from it has a large uncertainty. However, for the purpose of extrapolating to low mass concentrations from fiber count, the geometric mean of the above range of conversion factors, 30 $\mu g/m^3/f/ml$, will be used. The geometric standard deviation of this value is 4, and this uncertainty severely limits any extrapolation in which it is used. In the case of amosite, the data of Davis et al. (1978) suggest that a conversion factor of 18 is appropriate. However, these data yielded lower chrysotile values than all other chrysotile estimates; therefore, they may also be low for amosite.

5.10 SUMMARY

Measurements using electron microscopic techniques have established the presence of asbestos in the urban ambient air, usually at concentrations less than 10 ng/m^3. Concentrations of 100 ng/m^3 to 1000 ng/m^3 have been measured near specific asbestos emission sources, in schools where asbestos-containing materials are used for sound control, and in office buildings where similar materials are used for fire control. Most ambient measurements were taken over ten years ago. More current data would be informative.

6. RISK EXTRAPOLATIONS AND HUMAN EFFECTS OF LOW EXPOSURES

6.1 RISK EXTRAPOLATIONS FOR LUNG CANCER AND MESOTHELIOMA

To obtain dose-response estimates at current or projected environmental asbestos concentrations, it is necessary to extrapolate from epidemiological data on deaths that have resulted from exposures to the considerably higher concentrations extant in occupational circumstances. As mentioned previously, the available data are compatible with a linear exposure-response relationship, with no evidence of a threshold. However, the limited data that indicate the validity of this relationship are for exposures two or three orders of magnitude higher than those of concern for environmental exposures.

The range of values determined for K_L and K_M in Chapter 3 will be used to calculate a range of risks from daytime exposure to 0.01 f/ml. This concentration corresponds to about 300 ng/m^3, a concentration previously found in several environmental exposure circumstances.

Tables 6-1, 6-2, and 6-3 list a range of calculated lifetime risks of mesothelioma and lung cancer for a 40 hr/wk exposure to 0.01 f/ml for various time periods. The risks from longer or shorter exposures/week can be estimated by directly scaling the data in the tables. Values of $K_L = 0.3$ to 3×10^{-2} and of $K_M = 0.3$ to 3.0×10^{-8} were used in these calculations. U.S. 1977 mortality rates (NCHS, Annually: 1967-1977) were utilized as the basic data for the calculation. The tables utilized both smoking specific (Tables 6-1 and 6-2) and general population (Table 6-3) rates. We will assume that current U.S. male mortality rates reflect the experience of 67% smokers (many, however, are now exsmokers) and current female rates reflect the experience of 33% smokers. Using these percentages and the data of Hammond (1966) on the mortality ratio of smokers to nonsmokers, smoking-specific total mortality rates were calculated. Current lung cancer rates for males will be multiplied by 1.5 to represent the rates for smoking males. This factor comes from the fact that current male rates largely result from the 67% of men who are smokers or exsmokers. Correspondengly, current female lung cancer rates will be multiplied by 3 to to reflect the fact that approximately 33% of women are current or exsmokers. This factor for women may, in fact, be low because the current rapid increase in female rates may not yet fully reflect the full impact of women's smoking. However, they should not exceed the male smoker's rates. Nonsmoking lung cancer rates for both males and females were taken from

TABLE 6-1. THE RANGE OF LIFETIME RISKS PER 100,000 FEMALES OF DEATH FROM MESOTHELIOMA AND LUNG CANCER FROM AN ASBESTOS EXPOSURE OF 0.01 F/ML FOR 40 HR/WK ACCORDING TO AGE AT FIRST EXPOSURE, DURATION OF EXPOSURE, AND SMOKING

Age at onset of exposure	Years of exposure									
	1		5		10		20		Lifetime	
Mesothelioma in Female Smokers										
0	1.0	9.9	4.6	45.7	8.2	82.2	13.3	133.0	18.0	180.0
10	0.6	6.4	2.9	28.8	5.1	51.0	8.0	80.0	10.2	102.0
20	0.4	3.8	1.7	16.8	2.9	29.1	4.4	43.8	5.2	52.0
30	0.2	2.0	0.9	8.8	1.5	14.7	2.1	21.0	2.3	23.4
50	0.04	0.4	0.1	1.4	0.2	2.1	0.3	2.5	0.3	2.5
Lung Cancer in Female Smokers										
0	0.2	2.0	1.0	9.6	1.9	19.1	3.8	38.1	10.7	107 1
10	0.2	2.0	1.0	9.6	1.9	19.1	3.8	38.1	8.8	88.2
20	0.2	2.0	1.0	9.6	1.9	19.1	3.8	37.5	7 0	69.2
30	0.2	2.0	1.0	9.5	1.9	18.5	3.4	34.2	5.1	50.7
50	0.1	1.4	0.6	6.3	1.1	11.1	1.6	16.2	1.7	17 4
Mesothelioma in Female Nonsmokers										
0	1.1	10.6	4.8	48.7	8.8	87 7	14.2	142.4	19.4	194.4
10	0.7	6.8	3.1	31.0	5.8	58.0	8.7	86.6	11.1	111.3
20	0.4	4.1	1.8	18.3	3.2	31.7	4.8	48.0	5.7	57.6
30	0.2	2.2	1.0	9.7	1.6	16.4	2.4	23.5	2.6	26.3
50	0.04	0.4	0.2	1.6	0.2	2.4	0.3	2.9	0.3	2.9
Lung Cancer in Female Nonsmokers										
0	0.02	0.2	0.09	0.9	0.2	1.9	0.4	3.7	1.2	11.7
10	0.02	0.2	0.09	0.9	0.2	1.9	0.4	3.8	1.0	9.9
20	0.02	0.2	0.09	0.9	0.2	1.9	0.4	3.7	0.8	8.1
30	0.02	0.2	0.09	0.9	0.2	1.9	0.4	3.6	0.6	6.2
50	0.02	0.2	0.08	0.8	0.2	1.5	0.3	2.5	0.3	2.8

TABLE 6-3. THE RANGE OF LIFETIME RISKS PER 100,000 PERSONS OF DEATH FROM MESOTHELIOMA AND LUNG CANCER FROM AN ASBESTOS EXPOSURE OF 0.01 F/ML FOR 40 HR/WK ACCORDING TO AGE AND DURATION OF EXPOSURE. U.S. GENERAL POPULATION DEATH RATES WERE USED AND SMOKING HABITS WERE NOT CONSIDERED

Age at onset of exposure	Years of exposure				
	1	5	10	20	Lifetime
			Mesothelioma in Females		
0	1.0 - 10.4	4.8 - 47.9	8.7 - 86.3	14.0 - 140.0	19.7 - 196.6
10	0.7 - 6.7	3.0 - 30.4	5.4 - 53.9	8.5 - 84.8	10.9 - 108.9
20	0.4 - 4.0	1.8 - 17 9	3.1 - 31.1	4.7 - 46.9	5.6 - 56.3
30	0.2 - 2.2	1.0 - 9.5	1.6 - 16.0	2.3 - 22.8	2.6 - 25.5
50	0.04 - 0.4	0.2 - 1.5	0.2 - 2.3	0.3 - 2.8	0.3 - 2.8
			Lung Cancer in Females		
0	0.07 - 0.7	0.3 - 3.3	0.7 - 6.6	1.3 - 13.2	3.8 - 37.5
10	0.07 - 0.7	0.3 - 3.3	0.7 - 6.6	1.3 - 13.3	3.1 - 31.0
20	0.07 - 0.7	0.3 - 3.3	0.7 - 6.6	1.3 - 13.0	2.5 - 24.5
30	0.07 - 0.7	0.3 - 3.3	0.6 - 6.4	1.2 - 11.9	1.8 - 17.9
50	0.05 - 0.5	0.2 - 2.2	0.4 - 3.9	0.6 - 5.8	0.6 - 6.3
			Mesothelioma in Males		
0	0.8 - 8.0	3.6 - 36.4	6.5 - 65.1	10.4 - 104.1	13.8 - 137.7
10	0.5 - 5.0	2.2 - 22.3	4.2 - 41.6	6.1 - 60.5	7.5 - 76.3
20	0.3 - 2.9	1.3 - 12.5	2.2 - 21.5	3.2 - 31.8	3.7 - 36.9
30	0.2 - 1.5	0.6 - 6.3	1.0 - 10.4	1.5 - 14.6	1.6 - 15.9
50	0.02 - 0.2	0.1 - 0.8	0.1 - 1.3	0.1 - 1.4	0.1 - 1.5
			Lung Cancer in Males		
0	0.2 - 2.1	1.1 - 10.6	2.1 - 21.2	4.2 - 42.3	12.2 - 121.8
10	0.2 - 2.1	1.1 - 10.6	2.1 - 21.3	4.3 - 42.5	10.1 - 101.4
20	0.2 - 2.2	1.1 - 10.7	2.1 - 21.4	4.2 - 42.4	8.1 - 80.7
30	0.2 - 2.2	1.1 - 10.7	2.1 - 21.3	4.0 - 40.4	6.1 - 60.6
50	0.2 - 1.8	0.8 - 8.2	1.5 - 14.5	2.1 - 20.8	2.2 - 21.6

TABLE 6-2. THE RANGE OF LIFETIME RISKS PER 100,000 MALES OF DEATH FROM MESOTHELIOMA AND LUNG CANCER FROM AN ASBESTOS EXPOSURE OF 0.01 F/ML FOR 40 HR/WK ACCORDING TO AGE AT FIRST EXPOSURE, DURATION OF EXPOSURE, AND SMOKING

Age at onset of exposure	Years of exposure								Lifetime
	1		5		10		20		
				Mesothelioma in Male Smokers					
0	0.8 -	7.6	3.5	34.5	6.2	61.1	9.8	98.2	12.9 - 129.3
10	0.5 -	4.7	2.1	21.0	3.7	36.8	5.6	55.6	7.0 - 70.2
20	0.3 -	2.6	1.2	11.7	2.0	20.0	2.9	29.4	3.4 - 34.2
30	0.1 -	1.4	0.6	5.8	1.0 -	9.6	1.3 -	13.2	1.4 - 14.4
50	0.02	0.2	0.08	0.8	0.1	1.1	0.1	1.3	0.1 - 1.3
				Lung Cancer in Male Smokers					
0	0.3	3.0	1.5	14.9	3.0	29.9	6.0	59.6	17.0 - 170.1
10	0.3	3.0	1.5	15.0	3.0	30.0	6.0	59.9	14.1 - 141.3
20	0.3	3.0	1.5	15.2	3.0	30.2	5.0	59.6	11.3 - 112.5
30	0.3	3.0	1.5 -	15.2	3.0	30.0	5.7 -	56.6	8.4 - 84.0
50	0.3 -	2.6	1.2 -	11.6	2.0	20.3	2.9	28.8	3.0 - 30.0
				Mesothelioma in Male Nonsmokers					
0	0.9	8.9	4.1	40.7	7.3 -	73.1	11.8	117.5	15.7 - 157.2
10	0.6	5.6	2.5	25.2	4.5	44.7	7.0	69.5	8.8 - 87 6
20	0.3	3.2	1.5	14.6	2.5 -	25.1	3.7	37.4	4.4 - 44.1
30	0.2	1.7	0.8	7.5	1.3 -	12.5	1.8	17.6	1.9 - 19.2
50	0.03	0.3	0.1	1.1	0.2 -	1.6	0.2	1.9	0.2 - 1.9
				Lung Cancer in Male Nonsmokers					
0	0.02 -	2.1	0.1	1.1	0.2 -	2.1	0.4	4.2	1.3 - 13.2
10	0.02 -	2.1	0.1	1.1	0.2	2.1	0.4	4.2	1.1 - 11.1
20	0.02 -	2.1	0.1 -	1.1	0.2	2.1	0.4	4.2	0.9 - 9.0
30	0.02	2.2	0.1 -	1.1	0.2	2.1	0.4	4.1	0.7 6.9
50	0.02	2.0	0.1 -	0.9	0.2 -	1.6	0.3	2.8	0.3 - 3.0

Garfinkel (1981). The results show the importance of the time course of mesothelioma. Children exposed at younger ages are especially susceptible because of their long life expectancy. The time of exposure plays little role in the lifetime excess risk of lung cancer; any exposure before the age of 45 or 50 contributes equally to the lifetime risk. The risk estimates are uncertain because of the variability of the data from which values of K_L were calculated and from uncertainties in extrapolating from risks estimated at high occupational exposures to concentrations more than 100 times lower. Thus, actual risks in a given environmental exposure could be outside the listed ranges.

6.2 OBSERVED ENVIRONMENTAL ASBESTOS DISEASE

Asbestos-related disease in persons who had not been directly exposed at the workplace has been known since 1960. In that year, Wagner et al. (1960) published a review of 47 cases of mesothelioma found in the Northwest Cape Province of South Africa in the previous 5 years. Approximately half of the cases described were in individuals who decades before, had lived or worked near an area of asbestos mining. The hazard from environmental asbestos exposure was further documented in the findings of Newhouse and Thomson (1965), who showed that mesothelioma could occur among individuals whose potential asbestos exposure consisted of having resided near an asbestos factory or in the household of an asbestos worker. Twenty of 76 cases from the files of the London Hospital were the result of such exposures.

Of considerable importance are the forthcoming data on the prevalence of X-ray abnormalities and the incidence of mesothelioma in family contacts of the amosite factory employees in Paterson, New Jersey. Anderson and Selikoff (1979) have shown that 35% of 685 family contacts of former asbestos factory workers had abnormalities that were characteristic of asbestos exposure, when they were x-rayed 30 or so years after their first household contact. The data are shown in Tables 6-4 and 6-5, which compares the household group with 326 New Jersey urban residents. The overall difference in the percentage of abnormalities between the two groups is highly significant. Of special concern was the finding that the difference in the prevalence of abnormalities in a group of children born into a worker's household <u>after</u> his employment ceased was also significant.

TABLE 6-4. PREVALENCE OF RADIOGRAPHIC ABNORMALITIES ASSOCIATED WITH ASBESTOS EXPOSURE AMONG HOUSEHOLD MEMBERS OF AMOSITE ASBESTOS WORKERS

Exposure group	Total examined	One or more radiographic abnormalities present*	
New Jersey urban residents**	326	15 (5%)	
Entered household after active worker employment ceased†	40	6 (15%)	$\chi^2 = 7.1$ $p < .01$
Household resident during active worker employment†	685	240 (35%)	$\chi^2 = 114$ $p < .001$
Household resident and personal occupational asbestos exposure	51	23 (45%)	

*ILO U/C Pneumoconiosis Classification categories; irregular opacities 1/0 or greater; pleural thickening; pleural calcification; pleural plaques.

**No known direct occupational or household exposure to asbestos.

†No known direct occupational exposure to asbestos.

Source: Anderson and Selikoff (1979)

TABLE 6-5. A MATCHED COMPARISON GROUP: CHEST X-RAY ABNORMALITIES AMONG 685 HOUSEHOLD CONTACTS OF AMOSITE ASBESTOS WORKERS AND 326 INDIVIDUAL RESIDENTS IN URBAN NEW JERSEY

Group	Total examined	Pleural thickening present	Pleural calcification present	Pleural plaques present	Irregular* opacities present
Household contacts of asbestos workers	685	146 (18.8%)	66 (8.5%)	61 (7.9%)	114 (16.6%)
Urban New Jersey residents	326	4 (1.2%)	0 (8.5%)	2 (0.6%)	11 (3.4%)

*ILO U/C Pneumoconioses Classification irregular opacities 1/0 or greater.

Source: Anderson and Selikoff (1979).

TABLE 6-6. MESOTHELIOMA FOLLOWING ONSET OF FACTORY ASBESTOS EXPOSURE, 1941-1945*

Years from onset	Factory workers (933)		Household contacts (2205)	
	Total deaths	Mesothelioma	Total deaths	Mesothelioma
<20 years	270	0	280	0
20-24 years	102	2	93	0
25-29 years	113	5	111	0
30-34 years	84	7	124	3
35+ years	5	0	56	1
Total >20 years	304	14	384	4
Total all years	574	14	664	4

*Data of Selikoff and Anderson

Source: Nicholson (1981)

Through 1977, four deaths from mesothelioma occurred among the family contacts of these same factory workers. Table 6-6 lists the cases by time from onset of exposure along with the number of deaths from other causes in the same time period (1961-1977; one death occurred subsequent to 1977). One percent of the deaths after 20 years from first exposure were from mesothelioma; however, further observations will be necessary to fully establish the incidence of this neoplasm among family contacts. An additional contribution of asbestos-related lung cancer could also exist, but studies in this regard have not yet been completed.

A second population-based mortality study of mesothelioma and other cancer risks in environmental circumstances is that of Hammond et al. (1979b). The study compared the mortality of a group of 1,779 residents within 0.5 mile of the Paterson amosite asbestos plant with 3,771 controls in a different, but economically similar section of town. No differences in the relative mortality experiences were seen, except for one mesothelioma in the neighborhood group. This one case was in an electrician and occupational exposure may have contributed to the disease.

6.3 COMPARISON OF OBSERVED MORTALITY WITH EXTRAPOLATED DATA

The mortality data in these two population-based studies can be compared with estimates from the data that led to Table 6-3 (but calculated for 35 years, rather than a lifetime) and adjusted to a continuous rather than daytime exposure. If the air concentration in both circumstances was 200 ng/m^3, approximately 2 mesothelioma deaths/100,000 would be expected in 35 years of observation. In both cases, the exposed population was about 2,000, so the expected number of mesotheliomas would be 0.04 (range: 0.004 to 0.4).

The higher numbers observed, particularly in the household group, would suggest that higher exposures (e.g., from shaking dusty overalls) may have occurred in workers' homes, or that the extrapolations based on occupational data may understate risks.

6.4 LIMITATIONS TO EXTRAPOLATIONS AND ESTIMATIONS

These calculations of unit risk values for asbestos must be viewed with caution as they are uncertain and aspects of them are necessarily based on estimates that are subjective to some extent because of the following limitations in data: 1) one is extrapolating from high occupational levels to much lower ambient levels, 2) the mass to fiber conversion is uncertain, 3) various confounding aspects of the medical data, and 4) very importantly the nonrepresentative nature of the exposure estimates.

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