

Epidemiology of Asbestos-Related Diseases

2.1 Introduction

Forecasts of asbestos-related diseases typically rely on epidemiological studies that establish the connection between asbestos exposure in the workplace and disease. These studies report increased risks of cancer among workers who have been exposed to asbestos. In particular, lung cancer and mesothelioma risks are increased. Asbestos workers are also at risk of contracting noncancer diseases such as asbestosis, a pulmonary disease characterized by fibrosis and caused by protracted inhalation of asbestos particles. Experimental animal studies have described the physiological mechanisms that account for the relationship between asbestos exposure and these illnesses (Roggli and Brody, 1992).

The Occupational Safety and Health Administration (OSHA) began setting permissible exposure limits (PELs) on the amount of asbestos in the workplace environment in 1971. In May 1971, the PEL was set at 12 fibers per milliliter (f/ml). In December 1971, this was reduced to 10 f/ml, with an 8-hour time-weighted average (TWA) PEL of 5 f/ml. In July 1976, the 8-hour TWA PEL was reduced to 2 f/ml; in July 1986, to 0.2 f/ml; and in October 1995, to 0.1 f/ml – the current PEL. In conducting air monitoring under these standards, OSHA (e.g., 1986, p. 22,739) mandated that asbestos exposure samples must be collected on mixed cellulose ester filter membranes, that fiber counts must be made by positive phase-contrast optical microscopy at a total magnification of 400 \times , and that the count must include fibers with a length of 5 μ m or greater and an aspect ratio (length-to-width ratio) of 3:1 or greater.

Environmental studies have established that historical workplace exposure concentrations of airborne asbestos fibers for many workers exposed to asbestos were 1000-100,000 times higher than the nonoccupational or environmental exposures faced by the general population (EPA, 1986, p. 162). This differential explains why most epidemiological studies of asbestos-related diseases focus on or identify workers with high levels of asbestos exposure and

why most claims against the Manville Trust and other asbestos defendants are based on occupational exposures. Such claims are generally limited to occupational exposures because the proof of claim must identify exposure to the defendant's asbestos products and this is most easily done for the workplace environment where specific brand-name asbestos products were well known to the workers. In contrast, in the case of disease due to environmental exposures to low levels of asbestos in the ambient air, it would be difficult to identify Johns-Manville or any other asbestos defendant as the source, and the low levels of asbestos fiber content in the lungs following such exposures would make it difficult to confirm that asbestos was the causal agent.

These considerations lead us to expect occupational exposures to account for virtually all of the claims against the Manville Trust. Thus, forecasting the number, timing, and nature of future claims against the Trust requires that we can forecast these same factors for persons who were exposed to asbestos in the workplace, and this requires a firm understanding of the epidemiology of asbestos-related diseases.

In this chapter, we examine a range of epidemiological studies, including those used by Walker (1982) and Selikoff (1981, reissued in 1982) in their projections. This review will be conducted in five parts. First, we discuss design and data quality issues that are specific to epidemiological studies of the occupational health hazards of asbestos. Second, we review studies of health risks of occupational exposures to asbestos. Third, we examine the variation in estimates of the relation of disease to the level of asbestos exposure produced in different studies. Fourth, we consider evidence on the effects of different types of asbestos fiber on different disease risks. Fifth, we consider evidence on the potential role of simian virus 40 as a causative agent and cocarcinogen with asbestos in inducing human mesothelioma.

2.2 Design Issues in Studying Occupational Exposure

There are two main types of epidemiological study: the prospective cohort study and the retrospective case-control study. The interpretation of the results of a specific study requires that we know whether the study is of the cohort or case-control type and are aware of issues in applying each type of design to the health outcomes, exposure factors, and populations of interest (Liddell et al., 1977). The use of epidemiologic data in projections must be consistent with the properties of data determined by the study design and the particular characteristics of the study population and its exposure.

The first design involves collecting data prospectively on a cohort of workers followed over a period of time. The essential characteristic of this design is that a group of persons (the "cohort") is identified on the basis of some exposure of interest and followed to determine when and how many of them become ill.

In the retrospective case-control design, the researcher starts with a group of people who are afflicted by the disease (the “cases”). A second independent group is also selected from the population of persons who do not manifest the disease. This second group is selected to match certain characteristics of the cases. Consequently, it is referred to as the “control” population. Typically, cases and controls are “matched” on the basis of selected factors (e.g., age, sex, and smoking) to account for the effects of the variables used in matching. The goal is to identify differences in the distribution of exposure factors between those with and without the disease. People who do and do not have the disease are compared to see if the group with the disease has a higher exposure to a suspected cause even when other factors are taken into account.

2.2.1 Measures of Risk

The underlying logic of the two approaches can be clarified with a simple numerical example. Consider the following two-way table generated from prospective follow-up of two cohorts:

Cohort	Outcome		Total
	Disease	No Disease	
High Risk	100	10,000	10,100
Low Risk	10	100,000	100,010
Total	110	110,000	110,110

The probabilities of the disease in the two cohorts are estimated as

$$\begin{aligned} \Pr_H(D) &= 100/10,100 = 0.009901, \\ \Pr_L(D) &= 10/100,010 = 0.000100, \end{aligned}$$

and the relative risk as

$$RR = \Pr_H(D)/\Pr_L(D) = 99.01,$$

or 99.01 to 1. Relative risks are often approximated by the odds (cross-product) ratio:

$$OR = \frac{100 \times 100,000}{10 \times 10,000} = 100,$$

or 100 to 1. The odds ratio provides the essential link between the two study designs. Consider the following two-way table generated from retrospective case-control sampling of the outcomes above:

Cohort	Outcome		Total
	Case=Disease	Control=No Disease	
High Risk	100	10	110
Low Risk	10	100	110
Total	110	110	220

Here, 100% of the cases are retained, but only 0.1% of the controls (people with no diseases). For simplicity, we assumed that the relative distribution of the controls in the sample was identical to the original table, so that the selection of controls is independent of the indicator of high-low risk. In addition, we assumed that each case was matched with one control. We compute the odds ratio as

$$\text{OR} = \frac{100 \times 100}{10 \times 10} = 100,$$

which is the same as earlier. The odds ratio is the same no matter how many controls are sampled if controls are sampled independently of the indicator of risk. Cases may also be sampled independently of the indicator of high-low risk without changing the odds ratio.

The case-control design does not permit calculation of the disease probabilities $\Pr_H(D)$ or $\Pr_L(D)$, because the row totals are arbitrary functions of the number of controls selected to match each case. For example, with two controls for each case the above table becomes

Cohort	Outcome		Total
	Case=Disease	Control=No Disease	
High Risk	100	20	120
Low Risk	10	200	210
Total	110	220	330

Here, the row total depends on the sampling fraction. However the odds ratio,

$$\text{OR} = \frac{100 \times 200}{10 \times 20} = 100,$$

is the same as earlier. The odds ratio approximates the relative risk if the disease outcome is rare; however this cannot be confirmed from the case-control data.

A related concept is that of the attributable risk – the fraction of the disease that can be uniquely attributed to the risk factor. Fleiss (1981) defined this fraction as

$$\begin{aligned} \text{AR} &= [\Pr_H(D) \cdot \Pr(H) - \Pr_L(D) \cdot \Pr(H)] / \Pr(D) \\ &= \frac{\Pr(H) [\text{RR} - 1]}{1 + \Pr(H) [\text{RR} - 1]}. \end{aligned}$$

The second expression derives from Fleiss (1981, p. 76, Eq. 5.76). Here, $\Pr(H)$ is the marginal probability of exposure to the “high risk,” and $\Pr(D)$ is the marginal probability of manifesting the selected disease. Continuing the above numerical example,

$$\begin{aligned} \Pr(H) &= 10,100/110,110 = 0.09173, \\ \Pr(D) &= 110/110,110 = 0.0009990, \end{aligned}$$

and

$$\text{AR} = \frac{0.09173 \times 98.01}{1 + 0.9173 \times 98.01} = 0.900.$$

Fleiss (1981, p. 94) provided an alternative expression for retrospective data:

$$\text{AR} = \frac{\text{Pr}_D(H) - \text{Pr}_{ND}(H)}{1 - \text{Pr}_{ND}(H)},$$

where $\text{Pr}_{ND}(H)$ is the probability of “high-risk” exposure in the No-Disease group, where it is assumed that (a) $\text{Pr}(D)$ is low enough that $\text{OR} \approx \text{RR}$ and (b) the control group (ND = No Disease) is a random sample of the ND population.

Continuing the above numerical example,

$$\text{AR} = \frac{\frac{100}{110} - \frac{10}{110}}{1 - \frac{10}{110}} = 0.900.$$

The identical result obtains in the example with two controls per case. In these examples, 90.0% of the disease outcomes are attributable to the risk factor associated with the high-risk cohort. This may be compared with estimates that 85-90% of lung cancers are attributable to cigarette smoking (Roggli et al., 1992b, p. 325) and that 85% of mesotheliomas among men (23% among women) are attributable to asbestos exposure (Spirtas et al., 1994).

Two other calculations are important. First, the attributable risk in the high-risk cohort is the fraction of the disease in that cohort uniquely attributed to the risk factor:

$$\begin{aligned} \text{AR}_H &= [\text{Pr}_H(D) - \text{Pr}_L(D)] / \text{Pr}_H(D) \\ &= [\text{RR} - 1] / \text{RR}, \end{aligned}$$

so that based on the above example,

$$\text{AR}_H = 98.01/99.01 = 0.990,$$

which shows that virtually all disease in the high-risk cohort is due to the risk factor. Later, the assumption that all mesotheliomas among asbestos workers is due to asbestos exposure will be justified as an approximation based on AR_H values close to unity.

Second, the relationship between AR and AR_H is

$$\begin{aligned} \text{AR} &= \text{AR}_H \cdot \text{Pr}_H(D) \cdot \text{Pr}(H) / \text{Pr}(D) \\ &= \text{AR}_H \cdot \text{Pr}_D(H) \\ &\approx \text{Pr}_D(H) \end{aligned}$$

when AR_H is close to unity, where $\text{Pr}_D(H)$ is the probability of high-risk exposure among persons manifesting the disease. In the above example,

$$\Pr_D(H) = \frac{100}{110} = 0.909,$$

which is just 1% higher than the above AR estimates. This approximation can be used in retrospective analyses of occupational exposure to asbestos among mesothelioma cases to estimate the risk fraction attributable to this exposure route.

The distinction between AR and AR_H is important when reviewing epidemiological analyses in the context of product liability modeling. The population focus of epidemiology leads to consideration of AR (and RR) to measure risk and to guide primary prevention activities. The targeted subpopulation focus of product liability modeling leads to consideration of AR_H as a fundamental risk measure for the cohort or group designated by “ H ”. The inequality $AR < AR_H$ may yield vastly different estimates of attributable risk. For example, Roggli et al. (1992b, p. 325) indicated an AR of about 2% for lung cancer in the United States attributable to asbestos exposure. In contrast, results from Hammond et al. (1979; see Section 2.3.1c) imply an AR_H of about 80% for insulation workers, with no differences between smokers and nonsmokers. Other occupations with lower levels of asbestos exposure would have AR_H values in the range 2-80%. McDonald et al. (1980; see Section 2.3.4) found differences in relative risks of smokers among chrysotile miners and millers in Quebec that implied AR_H values ranging from 50% to 90% for smokers and nonsmokers, respectively, supporting arguments that the lower compensation offered to smokers by the Manville Trust for lung cancer injuries among asbestos-exposed workers is justified (Weinstein, 1994).

2.2.2 Design Issues

Each type of study has its advantages. The cohort design is not subject to conscious or unconscious biases in criteria for participation in the study to the same degree as the case-control design because disease outcomes are not known ahead of time in cohort studies. The results of cohort studies can be expressed in terms of population incidence rates and the absolute risk attributed to a given level of exposure can be evaluated for a target population.

The effects of competing risks on the duration of exposure must be considered in cohort studies because termination of exposure may be associated with the diseases under study (Liddell et al., 1977). An inaccurate assessment of the risk of an exposure may result precisely where those risks are highest. If the risks from exposure are high, no one may live long enough to achieve a long duration of exposure. As a consequence, there may be little evidence of an increase in risk with longer exposure. Furthermore, the total duration and intensity of exposure are often not known until the exposure has ended.

The case-control method has several advantages over the cohort approach, perhaps the most important being its lower cost. This is because the cohort design may require a very large cohort to get adequate numbers of affected

persons. The case-control method can also explicitly control for sources of variation such as age or sex through matching on the appropriate variables. A disadvantage of the case-control method is that incidence rates and dose-response functions cannot be estimated.

Liddell et al. (1977) identified six design issues for prospective cohort studies:

First, is the cohort grouped into appropriate exposure categories?

Second, has one selected an appropriate population for comparison as a standard? Such “standard” populations may be either external (e.g., state or national populations) or internal (e.g., groups of nonexposed workers).

Third, is the duration of exposure appropriately measured? The study interval over which duration of exposure is measured should start at the same point relative to entry to employment for each subject in the study. The definition of study interval becomes problematic when follow-up is continuous and the duration of exposure for a worker changes over the course of the study.

Fourth, is the measure of health outcome appropriate (e.g., is the rate of onset or the frequency of death from the disease of interest assessed against some index of the size of the population at risk)? The measure most generally accepted is based on person-years of observation (i.e., the number of years each person in the study remains disease-free). The number of cases of disease expected if there is no effect of exposure is calculated by applying incidence/death rates specific to age, year, and disease from the standard population to the corresponding numbers of person-years lived, by age and year, in the study cohort, where person-years for individual cohort members are accumulated from the start of the study to the point at which incidence/death, loss from follow-up, or the end of the study occurs.

Fifth, has one selected an appropriate summary measure of the cohort morbidity/mortality experience and an appropriate statistical model to determine the quantitative relation between the duration of exposure and the measure of morbidity/mortality? The summary measure most often employed is the standardized mortality ratio (SMR). The SMR is the ratio of two quantities. The first is the observed number of deaths at all ages in the study population. The second is the number of deaths expected to occur if their age-specific mortality rates were the same as those in the standard or unexposed population. Thus, the ratio of the observed to the expected number of deaths indicates whether the exposure has increased the risks of the study population (i.e., $SMR > 1.0$), whether it has no effect ($SMR = 1.0$), or whether the frequency of death is smaller in the exposed population ($SMR < 1.0$). The SMR is frequently multiplied by 100 to express the observed number of deaths as a percentage of the expected number. When the SMR is less than 100%, epidemiologists often search for factors which might cause only healthy persons to be drawn into the exposed population. This actually happened in Selikoff et al.’s (1979) study of asbestos insulation workers.

Sixth, are subcohorts properly defined? They should be as follows:

- Mutually exclusive and comprehensive
- Approximately equal in size
- Large enough to produce stable estimates of morbidity/mortality
- Small enough to be fairly homogeneous
- Detailed enough to provide estimates of a dose-response relationship (usually at least three categories of exposure are required)

Liddell et al. (1977) raised a different set of design issues for retrospective case-control studies. The most critical issue is whether an appropriate non-exposed control group has been selected. For example, in studying exposure characteristics of persons with mesothelioma, it would be inappropriate to select a control group of farmers (i.e., a population with little or no exposure to industrial concentrations of chemical dusts or vapors in a closed work environment). In the McDonald and McDonald (1980) study of mesothelioma deaths (to be reviewed in Section 2.3.2), the control group consisted of persons who died in the same hospital as the mesothelioma cases and who had pulmonary metastases from nonpulmonary primary tumors (i.e., the primary site of their disease was not the lung, but the disease had spread secondarily to the lung). Controls should be as similar as possible to cases except for manifestations of the disease under study.

After selecting an appropriate control group, two further issues must be addressed. First, a strategy is needed for matching cases and controls. Once the control population is identified on the basis of some characteristic which all controls must possess, each case must be paired with a control so that they are matched as closely as possible on factors that may be relevant to disease risks (e.g., age and sex). Because it is difficult to find an exact match on certain variables, auxiliary analyses may be required to make the matches as similar as possible.

Second, there can be gains in relative efficiency when more than one control is selected for each case. This may be necessary when the number of cases is small, and, in general, is a way of increasing statistical power.

Finally, one may select one of two basic approaches to analyzing case-control data. The first approach (e.g., Miettinen, 1969) analyzes the data in tabular form. Alternately, hazard-rate regression strategies have been developed for analyzing case-control data (e.g., Prentice and Breslow, 1978). An important difference between the two strategies is that hazard-rate regression permits the use of continuous variables in the analysis.

2.3 Studies of Health Risks of Occupational Exposures

In this section, we review studies of the health risks of occupational exposures to asbestos that can be used in developing projections.

2.3.1 Health Risks of a Cohort of Insulation Workers Occupationally Exposed to Asbestos

The first study, described by Selikoff et al. (1979) and extended by Selikoff and Seidman (1991), contains what Walker (1982, p. 18) argued to be the most extensive and complete data on the health risks of high levels of occupational exposure to asbestos. This study is based on the mortality experience of two groups of U.S. and Canadian insulation workers:

- A cohort of 632 asbestos insulation workers in the New York-New Jersey metropolitan area registered as members of the International Association of Heat and Frost Insulators and Asbestos Workers as of January 1, 1943, who were followed from January 1, 1943 to December 31, 1962
- A cohort of 17,800 members of the International Association of Heat and Frost Insulators and Asbestos Workers union who were listed as members on January 1, 1967, who were followed from January 1, 1967 to December 31, 1976.

The 17,800 insulation workers followed from 1967 to 1976 yielded the most extensive data on the health implications of occupational exposure to asbestos. That cohort suffered 995 cancer deaths, including 486 from lung cancer and 175 from mesothelioma, and 168 deaths from asbestosis. Selikoff and Seidman (1991) extended the follow-up to December 31, 1986, with a 20-year total of 2295 cancer deaths (1168 lung; 458 mesothelioma) and 427 asbestosis deaths. The extended follow-up data are used in Chapter 7 in our sensitivity analysis of the updated forecasts.

All workers in both cohorts were on the active union enrollment list on the date of start of follow-up. Thus, the onset of exposure to asbestos occurred at some earlier date, and this date was recorded and included in the calculation of time from first exposure to onset of asbestos-related disease. The duration of employment in an asbestos-related job was not reported for these cohorts. In the following, we will describe the experience of the 17,800 member cohort over the periods 1967-1976 and 1977-1986. The results are summarized in Table 2.1.

2.3.1a Basic health effects

Selikoff et al. (1979) found a considerable delay between the start of the exposure and the time at which the disease was diagnosed. They concluded that a person would have to be observed for at least 20 years before the adverse health effects of exposure could be reasonably expected to be manifest.

They further argued that for up to 20 years after the first occupational exposure to asbestos, a “healthy worker” effect kept any adverse health effects from being noticed. Persons who were accepted for employment were selected for good health. They did not find significant excesses in total mortality until 20-34 years after the start of occupational exposure to asbestos. For this

Table 2.1: Observed and Expected Deaths Among 17,800 North American Insulation Workers, 1967-1976 and 1977-1986

Cause of Death	Number of Deaths					
	1967-1976			1977-1986		
	Observed Best Evidence	Death Certificate	Expected ¹	Observed Best Evidence	Death Certificate	Expected ¹
Total deaths, all causes	2,271	2,271	1,658.9	2,680	2,680	1,794.6
Total deaths, all cancers	995	922	319.7	1,300	1,205	441.7
Lung cancer	486	429	105.6	682	579	163.1
Mesothelioma	175	104	—	283	77	—
Colon/rectum	59	58	38.1	62	67	50.4
Larynx/buccal-cavity/oropharynx/esophagus	50	43	21.9	46	41	28.5
All other cancers	225	288	154.1	227	441	199.8
Total deaths, all noncancer causes	1,276	1,349	1,339.2	1,380	1,475	1,352.9
Noninfectious respiratory diseases	212	188	59.0	295	277	85.8
Asbestosis	168	78	—	259	123	—
All other noncancer causes	1,064	1,161	1,280.2	1,085	1,198	1,267.1

Note 1: Expected deaths are based on U.S. white male age-specific death rates, 1967-1976 or 1977-1986.

(Continued)

Table 2.1 (Continued)

Cause of Death	Standardized Mortality Ratios (SMR) and z-Score Statistics ²											
	1967-1976				1977-1986							
	SMR (%)		z-Score		SMR (%)		z-Score		SMR (%)		z-Score	
	Best Evidence	Death Certificate	Best Evidence	Death Certificate	Best Evidence	Death Certificate	Best Evidence	Death Certificate	Best Evidence	Death Certificate	Best Evidence	Death Certificate
Total deaths, all causes	137	137	15.03	15.03	149	149	20.90	20.90	149	149	20.90	20.90
Total deaths, all cancers	311	288	37.77	33.69	294	273	40.84	36.32	294	273	40.84	36.32
Lung cancer	460	406	37.02	31.47	418	355	40.64	32.57	418	355	40.64	32.57
Mesothelioma	—	—	—	—	—	—	—	—	—	—	—	—
Colon/rectum	155	152	3.39	3.22	123	133	1.64	2.34	123	133	1.64	2.34
Larynx/buccal-cavity/oropharynx/esophagus	228	196	6.00	4.51	161	144	3.28	2.34	161	144	3.28	2.34
All other cancers	146	187	5.71	10.79	114	221	1.93	17.07	114	221	1.93	17.07
Total deaths, all noncancer causes	95	101	-1.73	0.27	102	109	0.74	3.32	102	109	0.74	3.32
Noninfectious respiratory diseases	359	319	19.92	16.79	344	323	22.58	20.64	344	323	22.58	20.64
Asbestosis	—	—	—	—	—	—	—	—	—	—	—	—
All other noncancer causes	83	91	-6.04	-3.33	86	95	-5.11	-1.94	86	95	-5.11	-1.94

Note 2: z-Score = (Observed - Expected)/Expected^{0.5}.

Source: Derived from Seilkoff et al. (1979, Table 12) and Seilkoff and Seidman (1991, Tables 2 and 3).

time interval from first exposure, they calculated that there were increased relative risks of death for all types of cancer ($SMR > 1$), except mesothelioma. The reason for not calculating relative risks for mesothelioma deaths was that Selikoff viewed mesothelioma as a “signal” disease (Selikoff, 1981, p. 26) whose presence is *prima facie* evidence for asbestos exposure. Thus, no mesothelioma would be expected in an unexposed population, and the SMR would be undefined.

Selikoff et al. (1979) also argued that the expected number of mesothelioma deaths cannot be computed for the general population because mesothelioma is not a distinct category in the various revisions of the International Classification of Diseases (ICD). However, it would have been possible to calculate an expected value from either the Third National Cancer Survey (TNCS), 1969-1971, or from the Surveillance, Epidemiology, and End Results Program (SEER), 1973 onward (see Hinds, 1978).

Selikoff et al. (1979) also found that, except for mesothelioma and asbestosis, the death certificate diagnoses of asbestos-related diseases were reasonably accurate. Death certificate diagnoses in the study cohort were generally consistent with diagnoses based on the “best available” evidence (i.e., in order of preference: autopsy findings, pathological information derived from surgical evidence, and clinical and roentgenological observations made during life). In the absence of any additional medical evidence, findings were based only on death certificates. This occurred in only 28 of 995 cancer deaths.

All 175 diagnoses of mesothelioma were supported by autopsy or surgical findings. This was particularly important because only 104 of the 175 mesothelioma cases were correctly diagnosed on the death certificate. Mesothelioma was so poorly reported on the death certificate because it was not an explicit diagnostic entry in the ICD. Many cases of mesothelioma were also diagnosed as other types of neoplasia; in particular, 15 of 49 pancreatic cancer cases were reassigned to mesothelioma upon review of the best medical evidence.

Asbestosis also was not well diagnosed on the death certificate. Only 78 cases were identified on the death certificate; 168 cases were identified from the “best evidence.”

The primary substantive result from this study was the determination of the risk of a wide range of diseases for a heavily exposed occupational cohort. The results for 1977-1986 were based on 134,740 person-years of observation for the 15,529 survivors over the second 10-year period.

The results for 1967-1976 were based on 166,853 person-years of observation for the 17,800 asbestos insulation workers over the first 10-year period. At the onset of observation in 1967, most men were below age 40 (10,101 of 17,800) and most had not yet been followed for 20 years from the time of their first occupational exposure to asbestos (12,683 of 17,800). By the end of the first observation period in 1976, 12,051 men had been observed for 20 or more years after their first exposure. Over the first observation period, there were 89,462 person-years of exposure at less than 20 years after the start of insulation employment (presumed onset of asbestos exposure) and

77,391 person-years of exposure 20 or more years after the start of insulation employment. Significant numbers of excess deaths were noted for total mortality, asbestosis, total cancer mortality, mesothelioma, lung cancer, esophageal cancer, cancer of colon and rectum, cancer of the larynx, oropharynx, and buccal cavity, and kidney cancer. Stomach cancer had marginally significant elevation in the first 10-year period but not in the full 20-year period (Selikoff and Seidman, 1991). Cancers of the pancreas and gallbladder/bile ducts had significant elevations in the full 20-year period but not in the first 10-year period (Selikoff and Seidman, 1991).

For our analyses, we retabulated Selikoff's detailed tables to show the relative risks for lung cancer, mesothelioma, colon/rectum cancer, and a combined category representing the larynx and upper digestive tract (buccal cavity and oropharynx, and esophagus). These four specific cancer categories corresponded to the compensable categories recognized by the Manville Trust during 1995-2002, except that the Trust dropped buccal cavity but accepted all types of pharyngeal cancer, not just the oropharynx site (Weinstein, 1994); additionally, the Trust began paying for stomach cancer claims in January 2003 (Weinstein, 2002). A residual category was defined for all other cancers, including cancers of the stomach, pancreas, kidney, and gallbladder/bile ducts.

Table 2.1 presents the retabulated summary counts for observed and expected deaths for the major cancer and noncancer diseases associated with asbestos exposure, stratified by observation period. For 1967-1976, almost half (46.4%) of the person-years of observation were 20 or more years after first exposure; for 1977-1986, most (81.5%) were 20 or more years after first exposure.

The SMRs for the second observation period reflect the joint impact of longer times since first exposure and older attained ages. The SMRs (best evidence) increased for all causes of death and for all noncancer causes, decreased slightly for lung cancer, and dropped sharply for colon/rectum cancer, cancer of the larynx and upper digestive tract, and all other cancers. The absolute death counts increased sharply for mesothelioma and asbestosis, diseases for which an SMR was not defined. The SMRs for noncancer causes other than respiratory diseases (primarily asbestosis) were 83% and 86%, respectively, indicating that these workers were generally healthier than the standard reference population of U.S. white males over the period 1967-1986. The impact of lung cancer, mesothelioma, and asbestosis is evident in both observation periods. The impact of cancer of the larynx and upper digestive tract is relatively much lower, although still significant.

For the second period (but not the first), under the best evidence criterion, the SMRs for colon/rectum cancer and all other cancers were not significantly elevated. This loss of significance was not noticed by Selikoff and Seidman (1991) but it is consistent with Greenberg and Roggli's (1992) conclusion that the evidence for increased risk is inconclusive for colon/rectum cancer and several other cancer sites (i.e., pancreas, stomach, and kidney). Nonetheless,

claims for colon/rectum cancer are compensable under the Trust Distribution Process (TDP) (Weinstein, 1994).

2.3.1b Time to onset of disease

The 10-year follow-up data for 1967-1976 were evaluated in a second article (Selikoff et al., 1980). A more detailed examination of the increase in incidence of asbestosis, mesothelioma, and lung cancer with time since onset of occupational exposure to asbestos confirmed that there was little increase in deaths before 15 years from onset of exposure. Beginning at 15-19 years from onset of exposure, there was a superlinear (i.e., accelerating) increase in the absolute risks of death from mesothelioma, asbestosis, and lung cancer. The lung cancer risks turned to sublinear (i.e., decelerating) increases at 30-35 years, a point at which their relative risks (i.e., compared to the expected risks in the U.S. white male population) peaked at a ratio of 6.1 to 1.0. Asbestosis risks exhibited a downturn at 45-59 years after onset of exposure, but this was reversed at 50+ years (with 73 deaths) in the 20-year follow-up data of Selikoff and Seidman (1991). Mesothelioma risks turned to sublinear increases at 40-44 years, but this also was reversed in Selikoff and Seidman (1991), where a peak was found at 45-49 years and a decline at 50+ years.

These reversals in the trends at the longest time intervals from first exposure suggest that there may be an interaction between date of initiation of exposure and time since onset of exposure. This could result if the type or amount of exposure changed over time. For example, Selikoff et al. (1979, p. 92) noted that only one type of asbestos (chrysotile) was used in the United States until the early 1940s, when a second type (amosite) became much more common. This could account for anomalies in the risk functions above 40 years since first exposure in the 1967-1976 follow-up. In addition, with 10 or 20 years follow-up, person-years of exposure at the longest durations are about one-tenth those of the shorter durations and are not for the same people. Selection effects may be operating on these groups (e.g., effects of cohort differences in cigarette smoking).

These results indicate that data for at least 40 years after first exposure are necessary for the full health implications of asbestos exposure to become manifest.

2.3.1c Impact of cigarette smoking on asbestos-related disease

A third study of the 1967-1976 follow-up data (Hammond et al., 1979) is the primary source of our current understanding of the effects of smoking on asbestos-related mortality. In this study, attention was restricted to the 12,051 men who, by 1976, had at least 20 years elapsed since onset of occupational exposure. This provided 77,391 person-years of observation. The average age during observation was 53.8 and the number of deaths observed was 1946.

Of the 12,051 men in the study, 8220 answered the smoking questionnaire, of whom 83% were current or ex-smokers.

This study had data that allowed the authors to select a control group where smoking history was available. Because smoking was not recorded on death certificates, national vital statistics were not suitable for this task. Fortunately, data from a prospective American Cancer Society (ACS) study, begun in 1959, of over one million persons were available. These persons were traced through September 30, 1972. Smoking information was recorded. From this group, a subset of 73,763 male subjects was selected as a comparison population who were white, not farmers, had no more than a high school education, and had a history of occupational exposure to dust, fumes, vapors, gases, chemicals, or radiation. It was expected that this group was likely to be physically active (to match the physical activity required by insulation work). Because deaths were observed for the control group only through 1972, the experience of the controls was extrapolated from cause-specific mortality changes observed in the national population over the period 1972-1976.

The number of deaths expected in the study population based on the mortality experience of the control group was calculated in two ways. First, the mortality rates from the ACS study were applied to the person-years of insulation workers to calculate an expected number of deaths. Second, the mortality rates of the U.S. white male population were applied to the person-years of insulation workers to calculate another expected number of deaths. The calculation of the expected number of deaths using the ACS study was the preferred method because education, work activity, and smoking could be controlled in those computations.

Hammond et al. (1979) found significant excess mortality among insulation workers for all causes of death and for cancer from all sites when compared to the mortality expected using either standard population. Among deaths due to specific types of cancer determined from the best medical evidence, cancers of the lung, larynx, buccal cavity and oropharynx, esophagus, and colon/rectum were found to be significantly elevated, with smoking controlled, when compared to the mortality experience of the ACS population.

Another comparison was between smoking and nonsmoking insulation workers. For insulation workers, smoking elevated both the risk of total mortality and the risk of lung cancer. Insulation workers who were current heavy smokers had a lung cancer mortality risk 10.4 times greater than expected on the basis of the nonsmoker insulation worker mortality rates. The level of risk was lower if a person had quit smoking more than 5 years previously. Thus, the lung cancer risk was greatly increased among insulation workers who smoked.

Fewer data were available to assess risks of death from other diseases among insulation workers who smoked, so only a few general observations were made. First, the risk of asbestosis mortality was 2.8 times higher among smoking insulation workers than expected from the mortality experience of nonsmoking insulation workers. Of the insulation workers who never smoked

regularly, none died of cancer of the esophagus, larynx, or buccal cavity and oropharynx. This was interpreted as evidence that asbestos exposure, in the absence of smoking, may have no effect on the risks of these diseases.

Next, insulation workers who were smokers were compared with nonsmokers from the control group. The observed number of lung cancer deaths among insulation workers who were smokers was 46.2 times higher than expected for nonsmokers in the ACS subpopulation (for current heavy smokers, the ratio was 87.4; for ex-smokers, it was 36.6).

The conclusion was that a strong interaction existed between asbestos exposure and smoking for lung cancer risks. Specifically, if the lung cancer risks of nonsmokers in the control group were taken as a baseline, then nonsmoking insulation workers had a risk 5.2 times greater. Among smokers in the control population, the relative risk was higher (10.9) than for nonsmoking insulation workers. For smoking insulation workers, the relative risk was 53.2 to 1 compared with nonsmoking insulation workers, and 4.9 to 1 compared with smokers (i.e., $53.2/10.9$). The nearly equal estimates of asbestos relative risk for smokers and nonsmokers (4.9 vs. 5.2) is consistent with a multihit/multistage model of carcinogenesis, with asbestos and smoking affecting different “hits” or “stages” of the process (see Section 2.3.1d). In this case, the attributable risk (AR_H) for asbestos induced lung cancer among insulation workers is approximately 80%, compared to 2% for the general population. This suggests that much of the total excess lung cancer mortality among insulation workers who smoked cigarettes was attributable to the interaction of asbestos with smoking.

There was no evidence of an elevation of mesothelioma risks among smokers, in distinct contrast to the strong elevation of lung cancer risks. This finding has been confirmed in other studies (Lemen et al., 1980; McDonald and McDonald, 1980; Peto et al., 1982; Tagnon et al., 1980; Muscat and Wynder, 1991).

2.3.1d Biologically motivated models of mesothelioma risks

A fourth study of the 1967-1976 follow-up data (Peto et al., 1982) estimated the parameters of a mathematical model of the increase of the risk of mesothelioma with the time since first exposure. Important findings were established by Peto et al. (1982) through the application of this model to the experience of the insulation workers. First, it was demonstrated that the *absolute* risk of mesothelioma was dependent on time since first exposure but independent of age. Similarly, Nicholson et al. (1981a), using the same data, showed that the *relative* (but not absolute) risk of lung cancer was dependent on time since first exposure but independent of age.

Peto et al. (1982) had to demonstrate that the incidence of mesothelioma was dependent upon the time since the onset of asbestos exposure but not age before they could legitimately apply a multihit/multistage model of carcinogenesis to the exposure experience over the period 1922-1946 for the insulation

workers. The multihit/multistage model of carcinogenesis is a model of the biology of tumor initiation developed by Armitage and Doll (1954, 1961). The model suggests that a tumor initiates when $k + 1$ errors occur in the genetic code of a single cell, leading to the loss of the mechanisms regulating cell reproduction. The model is a widely accepted model of carcinogenesis for the following reasons: (Whittemore and Keller, 1978)

- It is based on a plausible biological mechanism.
- It leads to a very simple computational form for predicting the increase in the risk of tumor onset as a function of time since the initiation of exposure to agents that might cause the genetic errors.
- It fits a wide range of data (e.g., Cook et al., 1969).

The mathematical form of the multihit/multistage model is

$$I_t = bt^k,$$

where I_t is the incidence rate (equivalently, hazard rate) of the tumor (in this case, mesothelioma) t years after initiation of exposure to the risk factor (asbestos), b is a proportionality constant, and $k + 1$ is the number of cellular errors that are required for a tumor to start. Mathematically, this expression for the incidence rate is identical to the hazard rate of the Weibull distribution – a distribution frequently used in reliability analysis in engineering applications. This distribution also arises in extreme value theory as the distribution of the smallest extreme of a set of independent and identically distributed times to failure of independent components of a multicomponent system. In a biological system, individual cells are the components and the transformation of any one of up to a billion or more cells in a given organ (pleura or peritoneum, in the case of mesothelioma) is sufficient to generate the disease. The multihit/multistage model explains the parameter $m = k + 1$ as either the number of stages or hits, depending on whether or not a specific fixed order of cellular errors is required. The choice of hit versus stage affects the interpretation of the parameter b , but not its estimated value.

This model was fitted to mesothelioma mortality data from the insulation workers by Peto et al. (1982), who obtained estimates of 3.20 for k and 4.37×10^{-8} for b . Mortality data, rather than incidence data, were used because the time from diagnosis to death for mesothelioma is typically under 1 year and because incidence data were unavailable. The parameter estimates were obtained by minimizing the chi-squared statistic used to measure the goodness-of-fit of the observed and expected deaths under the model. The parameters were reestimated using the maximum likelihood method and the results were virtually identical (e.g., $k = 3.17$ vs. 3.20 under the minimum chi-squared method).

To assess the generalizability of the model, it was also fitted to data from four studies with different levels of asbestos dust exposure and fiber types (i.e., Newhouse and Berry, 1976; Peto, 1980; Hobbs et al., 1980; Seidman et

al., 1979). The value of k was fixed at 3.20 for each of these studies, but b was allowed to vary (yielding estimates of 4.95×10^{-8} , 2.94×10^{-8} , 5.15×10^{-8} , and 4.91×10^{-8} , respectively). In each case, the model fits reasonably well to the mesothelioma mortality data. Thus, the increase of mesothelioma mortality could be well described by the 3.2 power of the time since first exposure (i.e., $I_t = bt^{3.2}$), over variations in asbestos fiber type, site [different mixes of pleural (lung) and peritoneal (abdominal) tumors were observed across the studies], and exposure levels. Variation in all of these factors could be modeled by changes in b .

The estimate of k obtained from the insulation worker data had a very broad confidence interval (standard error of 0.36) so that any value between 2.5 and 4.0 would provide an adequate fit. Peto et al. (1982) suggested that lack of precision of k would not greatly alter predictions of future mortality trends. However, if one employs a value of 4.0 instead of 3.2, the predicted lifelong mesothelioma risk for men first exposed at age 20 (with b reestimated to account for the change in k – a necessary step due to a correlation of the sample estimates of k and b on the order of -0.998) would be 19% instead of 15%, a relative difference of 27%. If one uses $k = 2.5$, then the lifelong risk would be 12% instead of 15%. The overall uncertainty (i.e., going from $k = 2.5$ to 4.0) is 58% (i.e., with estimates of lifelong mesothelioma risks ranging from 12% to 19%). For the purposes of projecting future mesothelioma mortality, this degree of uncertainty is noteworthy.

Peto et al. (1982) warned against attributing spurious precision to the estimate of k and recommended that a value of 3.5 be used to imply a value between 3 and 4. The lack of precision in the estimate of k cited by Peto et al. (1982) and the large effect that the variation in k has on the projection of mesothelioma mortality suggest that long-term projections will be sensitive to this parameter.

Peto et al. (1982) examined the risk of the two subtypes of mesothelioma – peritoneal and pleural mesothelioma – and concluded that fiber type was a primary determinant of anatomical site. Amphiboles (i.e., amosite or crocidolite) were argued to be largely responsible for peritoneal tumors. They also showed that the lifelong risk of mesothelioma was very sensitive to the assumed distribution of age at first exposure. For example, for the insulation worker data, the lifelong mesothelioma risk was 15% for persons first exposed at age 20, 7% for persons first exposed at age 30, and only 3% for persons first exposed at age 40. This suggests that projections will be sensitive to variations in the distribution of age at first exposure.

Peto et al. (1982) considered that the low mortality 10-15 years after first exposure could be a result of a lengthy tumor growth time; that is, under the multihit/multistage assumptions, the Weibull incidence rate is actually the rate at which a single cell gains status as a bona fide cancer cell. However, a tumor does not generally become detectable until about a billion or more daughter cells have been generated by mitosis from the original transformed cell, and this takes time. Peto et al. (1982) tested a modified model,

$$I_t = b(t - w)^k$$

with $k = 2$ and $w = 10$ years, and found, with suitable adjustment to b , that this model fit better than the first model for the first 15 years since first exposure and fit equally well thereafter.

This modified form of the model was adopted by both the Occupational Safety and Health Administration and the U.S. Environmental Protection Agency in their risk assessment models (OSHA, 1983, 1986; EPA, 1986). These agencies made additional adjustments, however, to account for the fact that union insulation workers tended to have continuous career-long exposure histories (35 years or more), whereas other workers typically had shorter durations of exposures at lower intensities. We discuss these modifications in Section 2.4.

2.3.2 A Case-Control Study of Asbestos Risks in the United States and Canada

McDonald and McDonald (1980) conducted a large and frequently cited retrospective case-control study of occupational exposure to asbestos. This study provided Walker's (1982) projections with the proportion of the total number of mesothelioma deaths that were likely to result in lawsuits. The study also provided Selikoff's (1981) projections with occupation-specific measures of relative risks that could be multiplied by estimates of the number of workers in each occupational category to produce the projected number of mesothelioma cases.

McDonald and McDonald (1980) identified groups of diseased and non-diseased persons and examined retrospectively their differences in exposure. The retrospective design differs from Selikoff et al.'s (1979) study of insulation workers where the population was defined on the basis of exposure and prospectively followed to determine who got the disease. The retrospective design allows for better control of confounding factors by closely matching cases with controls. However, it cannot be used to produce estimates of the incidence rate of mesothelioma. The results of the retrospective and prospective studies complement each other.

McDonald and McDonald (1980) contacted nearly all U.S. and Canadian pathologists (7400 in number) to determine how many cases of mesothelioma they had observed. For the period 1960-1975 in Canada and for the year 1972 in the United States, the pathologists contacted reported a total of 668 cases (557 recorded through the end of 1972 and selected for detailed analysis). For each mesothelioma case, a staff physician visited the hospital where the case was recorded, reviewed the diagnostic evidence, and selected a control matched for sex, age, and year of death, and in which pulmonary (lung) metastases were present from a nonpulmonary malignant tumor. After the selection of cases

and matched controls, interviews were conducted (generally with relatives) to determine occupational and residential histories and smoking habits. For each occupation recorded, respondents were questioned about occupational dust exposure.

For the 557 cases selected for detailed analysis, 71% (395) were male and 29% (162) were female. Among males, 78% of cases were pleural and 22% peritoneal mesotheliomas. Among females, the corresponding figures were 61% and 39%, respectively.

Occupation coding was conducted for 344 male cases and 344 controls using a list of occupations associated with asbestos exposure provided by Selikoff. Jobs were independently assessed for the likelihood of asbestos exposure by four research centers specializing in occupational health studies. The agreement among the four centers was quite good for exposures categorized as “definite” and “unlikely,” and for the cases of “possible” and “probable” exposure taken together. In the United States, on average, 73.6% of male cases were classified as possibly-definitely exposed; in Canada, the corresponding average was 58.3%.

For females, only 2 of 162 cases had worked with asbestos, so it was not possible to carry out a similar analysis. However, six additional cases were spouses of an asbestos worker, suggesting that about 5% of female cases could be linked to occupational exposures.

From the 344 male cases and 344 controls, it was also possible to calculate the relative risks of asbestos exposure for five occupational groups with an established association with mesothelioma. Recall that the relative risk is the ratio of the probability of dying from mesothelioma in one of the occupational categories with identified exposure to asbestos to the probability of dying from mesothelioma in occupational categories without identified exposure to asbestos (in this case, all occupations other than the five selected groups). The relative risks were calculated using the odds ratio approximation described in Section 2.2.1. The odds ratios were as follows:

- 46.0 for insulation workers
- 6.1 for asbestos production and manufacturing
- 4.4 for heating trades (excluding insulators)
- 2.8 for shipyard workers
- 2.6 for construction workers

These were evaluated for consistency with risk estimates made from prospective cohort studies and found to be in substantial agreement (Selikoff, 1981; see Section 3.3, Task 3 and Table 3.1).

In the United States, 64.8% of cases had worked in one of the five occupations; in Canada, the corresponding figure was 45.9%. These figures are 8.8% and 12.4% lower, respectively, than the figures based on the possible-definite exposure classifications.

In evaluating the two methods of analysis, McDonald and McDonald concluded that:

The list of occupations provided by the Environmental Sciences Laboratory, Mount Sinai School of Medicine, proved a satisfactory method of classifying occupations thought to entail asbestos exposure. With minor modifications, the list could improve the comparability of case-control surveys in different regions and countries. Greater discrimination was achieved between case and controls by selecting occupations reported to have been associated with mesothelioma than by assigning probabilities of asbestos exposure to all occupations listed. (McDonald and McDonald, 1980, pp. 1654-1655)

In addition, McDonald and McDonald (1980) indicated that the likelihood of asbestos exposure for an occupation may be underestimated by both methods because it was determined from interviews conducted after the subject had died. They noted that interview data, especially from secondary sources such as relatives, may not yield complete occupational or exposure histories.

McDonald and McDonald (1980) noted a tendency for male workers in higher-risk occupations to have relatively more peritoneal (abdominal) mesothelioma. Combined with the results of Peto et al. (1982; see Section 2.3.1d), this finding suggested that asbestos fiber exposures in high-risk occupations may include greater relative amounts of amphiboles than in low risk occupations. This interpretation would also be consistent with the finding that females have relatively more peritoneal mesotheliomas than do males, even though their asbestos exposure is much lower. Moreover, the finding of no association of mesothelioma risk with smoking was confirmed for males (see Section 2.3.1c).

Walker (1982) used the data provided by McDonald and McDonald (1980) to divide the total projected number of mesothelioma cases (see Section 4.4, Task 1b):

- Into a group with a plausible (i.e., “definite” or “probable”) occupational exposure history and a group without such a history
- For workers with a plausible occupational exposure history, into subgroups that were heavily and less heavily exposed

2.3.3 Short-Term Amosite Exposure Among Factory Workers in New Jersey

Seidman et al. (1979) considered the long-term effects of short-term exposures: 933 men employed in an amosite asbestos factory during the period 1941-1945 were followed in cohort studies for 35 years. As Seidman et al. (1979, p. 62) state, “This resulted in a unique experience; men with a very limited duration of intense work exposure to amosite asbestos followed by long observation.” Thus, it was possible to determine if very limited exposures (e.g., 1 month) increased the risk of cancer, whether cancer risks increased with greater exposure duration, and if the exposure duration was correlated with the length

of the latency period. There were no direct observations of dust counts for this cohort, although measurements made in 1971 suggested average exposure levels as high as 23 fibers/ml, for fibers longer than 5 μm .

One hundred thirteen men were eliminated from the original 933 men, 20 because of prior asbestos work experience, 14 because during the first 5 years after employment, they took up asbestos work elsewhere, 41 died, and 38 were lost to follow-up. This left 61 workers who worked less than 1 month, 90 for 1 month, 82 for 2 months, 149 for 3-5 months, 125 for 6-11 months, and 313 for 12 or more months. The mortality experience of these workers was compared on an age- and date-specific basis for the period 1946-1977 with the mortality experience of New Jersey white males (New Jersey having some of the highest cancer rates in the United States). Total mortality, mortality from specific causes, lung cancer, and an "all-asbestos" disease category were analyzed. The "all-asbestos" disease category represented asbestosis, chronic pulmonary disease, lung cancer, mesothelioma, and cancers of the esophagus, stomach, colon, rectum, larynx, buccal cavity, pharynx, and kidney.

The study yielded several conclusions. First, the lower the dose the longer it took for excess mortality to become evident and the smaller the magnitude of the effect. Second, the length of the latency period decreased with increasing age at exposure. It had been suggested that if asbestos-related diseases had long latent periods, then older workers, because of their age, would not live long enough to manifest those diseases. Unfortunately, Seidman et al. (1979) found that high levels of exposure for older persons (e.g., aged 50 to 59) produced increased mortality very quickly (i.e., within 5 to 14 years). Third, it was demonstrated that mortality risks increased with time, even after exposure had ceased, apparently due to the effects of permanently retained asbestos in lung tissue and other sites. Fourth, for light exposure, it was determined that the follow-up period would have to be lengthy to identify health effects.

2.3.4 Effects of Chrysotile Exposure Among Miners and Millers in Quebec

McDonald et al. (1980) followed until 1975 a cohort of 11,379 workers (10,939 men and 440 women) born 1891-1920 and exposed to chrysotile in the mines and mills of Asbestos and Thetford, Quebec. Data were analyzed using two cohort methods, using male mortality in Quebec as a standard, and a case-control method employing internal controls. Cumulative measures of exposure to asbestos were available.

In the first cohort analysis, the male cohort was subdivided into four groups on the basis of length of service (i.e., less than 1 year, 1-4 years, 5-19 years, and 20 or more years). The workers in each length of service category were further divided into four subgroups on the basis of cumulated dust concentrations for all kinds of airborne particles, not just airborne asbestos, measured as the number of millions of particles per cubic foot (mppcf) to which the worker

was exposed weighted by the number of years he was exposed at that level (mppcf-yr). The subgroups were defined so that there was little variation in the average daily level of exposure in each of the four sets of four accumulated exposure categories (i.e., “low” accumulated exposure groups had been exposed to a concentration of 2.5 to 4.2 mppcf on average, “medium” accumulated exposure groups experienced dust concentrations that varied from 4.3 to 9.4 mppcf, “high” exposure groups experienced dust concentrations that varied from 14.4 to 23.6 mppcf, and “very high” groups varied from 46.8 to 82.6 mppcf).

There was little association between exposure level and cause of death for gross service of less than 5 years. For service of 5-19 years, there were consistent trends across exposure levels for total mortality, asbestosis (pneumoconiosis), heart disease, and stroke. SMRs were elevated in the highest-exposure group for lung cancer and other respiratory diseases. For workers with 20 or more years service, the most severely exposed category had the highest SMRs for total mortality and for all listed causes other than laryngeal cancer and accidents. Furthermore, there was a relatively consistent gradient for asbestosis, heart disease, total mortality, lung cancer, respiratory tuberculosis, and other respiratory diseases.

McDonald et al. (1980) conducted a second analysis using exposure categories based on the dose accumulated by age 45 (three categories: less than 30 mppcf-yr, 30-299 mppcf-yr, and 300+ mppcf-yr). There were clear trends in the SMRs for total mortality, asbestosis, lung cancer, cancer of the colon and rectum, respiratory tuberculosis, other respiratory diseases, and stroke. At age 45, lung cancer risks increased linearly at a rate of 0.16% per mppcf-yr accumulated exposure to asbestos (with exposure of 30 mppcf-yr or more divided into four categories).

McDonald et al. (1980) also analyzed their data retrospectively, using the case-control method. Multiple controls and four exposure categories (i.e., less than 30 mppcf-yr, 30-299 mppcf-yr, 300-999 mppcf-yr, and 1000+ mppcf-yr) were employed with persons with less than 30 mppcf-yr exposure used as internal controls. Clear increases in risk were found for asbestosis, lung cancer, esophageal and stomach cancer, and colon/rectum cancer. For these four diseases persons who had accumulated 1000+ mppcf-yr asbestos exposure had risks respectively 30.6, 3.16, 4.69, and 5.26 times greater than expected based on the mortality experience of persons with less than 30 mppcf-yr accumulated exposure.

When the analysis was stratified by smoking status, lung cancer risk increased 10-fold for nonsmokers with the highest level of accumulated exposure, compared to internal controls (i.e., nonsmokers with the lowest level of accumulated exposure). For persons with undifferentiated (i.e., unknown or doubtful) smoking habits, the risk ratio for persons with high levels of asbestos exposure compared to those with low levels was nearly 14-fold but only 2-fold for definite smokers. In this case, the attributable risk (AR_H) for asbestos-induced lung cancer at the highest levels of exposure were 90% for

nonsmokers versus 50% for smokers – compared to estimates of 80% for both groups in Hammond et al. (1979).

In summary, both retrospective and prospective analyses of the data showed the following:

- There was essentially a linear response to dose of risk for lung cancer, asbestosis, and total deaths based on accumulated exposure.
- Both an additive model of smoking interaction with asbestos exposure and a multiplicative model (found in Hammond et al., 1979) are consistent with the data.
- Because of the difficulty in identifying excess risks at lower exposure levels, the fitting of linear dose-response forms are essential to the task of setting standards for acceptable environmental exposure levels.

Perhaps the most important conclusion from this study is that chrysotile asbestos fibers appeared to be less potent in increasing mesothelioma risks than amphiboles (amosite or crocidolite):

The incidence of malignant mesothelial tumors, especially of the peritoneum, is so very much higher after exposure to amphiboles (and amphibole-rich mixtures) than after exposure to chrysotile alone, that differences in dust concentrations are unlikely to explain it. (McDonald et al., 1980, p. 22).

Nonetheless, McDonald et al. (1980) suggested that the available evidence on the aggregate health implications of fiber type was not conclusive because (a) no comparable (i.e., as statistically reliable) studies had been made of crocidolite or amosite production and (b) for the available reports on single-fiber exposure, exposure was expressed only in terms of duration [e.g., no direct exposure measures were available in Seidman et al. (1979)].

2.3.5 Mesothelioma Risks Among World War II Shipyard Workers

Important evidence about the health implications of asbestos was provided by studies of mesothelioma and lung cancer risks among World War II shipyard workers. Because this workforce was so large (i.e., 4-5 million workers), a significant elevation of risk in this group served to raise concern for the magnitude of the total health effect of occupational exposure to asbestos. Early evidence of this effect was derived from cancer maps for the period 1950-1969 (Mason et al., 1975). Several areas of excess lung cancer mortality risk were noted in coastal counties. One hypothesis to explain this elevation was that increased lung cancer mortality risk was due to shipyard exposure to asbestos. Eventually, case-control studies were conducted in a number of areas observed to have elevated lung cancer mortality risks on the maps (e.g., Blot et al., 1978, Georgia; Tagnon et al., 1980, Virginia; Blot et al., 1982, Florida; see also Blot and Fraumeni, 1981). The study by Tagnon et al. (1980) of coastal Virginia illustrates the general design and results of those case-control studies.

Sixty-one cases of mesothelioma diagnosed 1972-1978 were identified among white males from discharge diagnoses, pathology files, and tumor registries at major hospitals in coastal Virginia and from records of the Virginia Tumor Registry. Pathological specimens were sought for all cases for independent review. Mesothelioma incidence rates were calculated for each sex, race, and age group. The observed numbers of cases were compared to the numbers expected based on national estimates of mesothelioma derived from the Surveillance, Epidemiology, and End Results Program (SEER) results (Hinds, 1978). The case-control study was limited to white males – the only group with elevated rates. Controls consisted of 320 local residents who died from 1972 to 1976 from causes other than chronic respiratory diseases and were similar with respect to age at death and county of residence. Personal interviews of 4 surviving cases and the next-of-kin of 52 deceased cases and 236 controls were conducted using a standard questionnaire to obtain data on (a) place, type, and length of employment for all jobs held for more than 6 months and (b) information on smoking habits and residential history.

The mesothelioma incidence rates were four times the national estimates from SEER, with the excess concentrated among white males. Shipyard employment was reported for 77% of the cases. The risk of mesothelioma was 15.7 times higher for shipyard workers who had reported contact with asbestos than for the controls – implying that $AR_H = 93.6\%$. Among shipyard workers reporting no contact with asbestos, the risk of mesothelioma was 4.9 times higher than among controls. Because mesothelioma risks were significantly elevated among shipyard workers who were not identified as having contact with asbestos, it was suggested that the determination of asbestos exposure from the interviews may have been incomplete. Cigarette smoking was not associated with an increased risk of mesothelioma.

Tagnon et al. (1980) also reported results from a parallel study of the same population in which lung cancer risks of shipyard workers were 1.7 times greater than those of the controls. Furthermore, shipyard workers developing lung cancer tended to have shorter durations of exposure to asbestos than those developing mesothelioma.

Because latencies of 35 years were often noted for mesothelioma, it was suggested that the full impact of mesothelioma had not yet been felt. The authors concluded:

Assuming that the Tidewater rate of 10 cases/year/100,000 white males ages 50 to 70 years ... is composed of a 15-fold increased risk among 12% (the percentage of the 236 controls) of this population who worked in shipbuilding prior to 1950 and either handled asbestos or were career employees, and assuming that the risk was usual among the remaining 88%, then the annual incidence of mesothelioma among former shipyard employees would be 56/100,000. This rate exceeds that for all cancers except those of the lung, prostate, colon, and bladder. Furthermore, since survival is poorer for mesothelioma than

for the other neoplasms, mesothelioma may claim as many or more deaths among shipyard workers than does any cancer except lung cancer. (Tagnon et al., 1980, p. 3878).

2.3.6 Effects of Asbestos Exposure Among a Cohort of Retired Factory Workers

Henderson and Enterline (1979) reported the mortality experience of 1348 men aged 65+ who had “completed their working life times as production or maintenance-service employees with a U.S. asbestos company and retired with a company pension” (p. 117). Of the 1348 men, 273 were excluded whose only known employment was in Canada. For the remaining 1075 men, 781 deaths were recorded. For these 781 deaths, death certificates could be located for 749. The cohort was composed of three types of retiree for the period 1941-1967:

- Normal retirees at age 65
- Those who retired before age 65 for nonmedical reasons but who lived to 65
- Those who retired due to disability before age 65 but who lived to 65

The mortality experience of this cohort was compared with that expected assuming that U.S. white male mortality rates for the same ages and dates applied to the study population. Although this is a cohort study, one must be aware of the implications of selecting a group of persons who must survive to age 65 and who must have adequate service to qualify for a pension. The health effects of intense exposure to asbestos may have already been manifest before age 65. Therefore, workers who succumbed to asbestos-related diseases before age 65 were excluded from consideration by the study design.

Despite the selectivity of their cohort, Henderson and Enterline (1979) found that total mortality, cancer mortality, and mortality from chronic respiratory diseases were elevated, although perhaps not as high as in other studies. The authors calculated cumulative dosages and studied the dose-response relations. Previously, with Canadian data and 4 fewer years of follow-up, it was speculated that the mathematical function describing the dose-response relation was nonlinear. The later data (with 4 more years of follow-up and with the Canadian data excluded) were found by Henderson and Enterline (1979) to be consistent with a linear dose-response form. The estimated dose-response equation for respiratory cancer was $SMR = 100.0 + 0.658 \times mppcf\text{-yr}$, where the SMR is the standardized mortality ratio (percent form) based on U.S. white male respiratory cancer mortality and the dust levels were estimated by job and time period.

The authors obtained information on the type of asbestos fiber to which each worker was exposed (i.e., amosite, chrysotile, crocidolite, or some combination thereof). The effect of exposure to specific types of asbestos fibers

on disease risk could be adjusted for cumulative dose. Although the numbers were small, the 112 men exposed to both chrysotile and crocidolite asbestos had an SMR that was 94.3% higher than expected on the basis of cumulative dust exposure alone. In contrast, the 754 men exposed only to chrysotile had an SMR that was 5.3% lower than expected on the basis of cumulative dust exposure alone. Taken together, these results imply that the excess risk induced by the chrysotile-crocidolite mixture could be 99.6% higher than that of chrysotile alone. Because the majority of the men who had mixed exposures worked in asbestos cement pipe manufacturing, it was difficult to draw firm conclusions about the different effects of chrysotile and crocidolite. The SMRs for amosite were elevated, but the sample sizes were too small for those SMRs to achieve statistical significance.

Although useful information was generated from the study, the study design made it impossible to draw meaningful conclusions about the relation of asbestos exposure and mesothelioma. The authors had previously reported only 1 mesothelioma death during 1941-1969 for the 1348 men in the study. This was surprising given that the study summarized the experience of a group with typically long durations of employment (3-51 years; 25 year average), high exposure levels, and lengthy times since onset of exposure.

As noted by Henderson and Enterline (1979), this finding is frequently compared with a study conducted near the Manville, NJ plant, where 72 cases of mesothelioma were identified (Borow et al., 1973). Henderson and Enterline (1979) provided a table to indicate the status of 58 of 72 of Borow's cases. No explanation was given by Henderson and Enterline for the difference between the 58 cases reviewed and Borow's total of 72. Furthermore, as Henderson and Enterline (1979, p. 124) explain:

Of the 58 cases, there were records of work at the plant for 41. Thirty-one of these men were not included in our cohort, however. That is, they did not, according to our records, retire during the period 1941-1967. Most of these men were too young or had too little service to retire. Of the 10 on whom we did have records, seven died at ages under 65 and were not part of our study, because we studied deaths only at ages 65 and over.

Thus, a major portion of the effect of asbestos exposure on health (i.e., deaths due to mesothelioma) was lost because of the requirement of the study design that persons be over age 65 and have adequate service to retire.

Since a major portion of the total health consequences of occupational exposure to asbestos was excluded by the study design, the data from this study cannot be directly employed in projections of the total health consequences of occupational exposure to asbestos. Using these data in such projections could grossly understate future mesothelioma incidence. It seems likely that the same limitations of the study design that caused mesothelioma mortality to be grossly underestimated could also lead to underestimation of other health consequences of asbestos exposure.

2.4 Increases in Disease Risk Associated with Exposure to Asbestos

In all of the above-cited studies, the risks of certain diseases and causes of mortality increased for persons with significant occupational exposure to asbestos. However, it was not possible in all studies to estimate a dose-response function because the level of asbestos exposure was not measured in all studies. The dose-response function is a mathematical expression indicating the exact magnitude of the increase in risk associated with a unit dose increase in exposure to asbestos. The coefficient applied to the measured level of asbestos exposure is called the “dose-response coefficient.” In this section, we will examine dose-response coefficients estimated for studies where asbestos exposure was measured (Selikoff, 1981; EPA 1986).

In addition to quantitative measures of asbestos exposure, a second requirement must be satisfied before a dose-response function can be estimated. This requirement is that the mathematical form of the dose-response function be known. In general, one lacks adequate data to prove that a dose-response function is of a particular form. Consequently, one is required to (a) specify a theoretically acceptable dose-response function and (b) make sure that the form specified is consistent with the data. The specification of a particular dose-response function is important in projections because it determines the level of disease risk that can be expected for persons exposed to a given level of asbestos.

The most common type of dose-response function used in the analysis of the risks of asbestos exposure is the linear dose-response function, a function that derives from the multihit/multistage model under the assumption that asbestos affects only one “hit” or “stage” of the process of carcinogenesis (Whittemore and Keller, 1978). This function has the property that the increase in risk associated with a unit increase in asbestos exposure is the same at all levels of asbestos exposure. The EPA found this assumption to be plausible for mesothelioma and strongly indicated by the evidence for lung cancer (EPA, 1986, p. 30). Both Walker (1982) and Selikoff (1981) assumed that the dose-response function is linear. This assumption was important for both of their projection strategies in that it permitted them to treat the duration of exposure as equivalent to dose. Thus, exposing 2000 persons to a given level of asbestos for 1 year would produce the same amount of disease as exposing 1000 persons to the same level of asbestos for 2 years. This equivalence holds only for the linear form of the dose-response function and only for moderate variations of the exposure duration.

Although such an assumption has not been proven, most findings are consistent with a linear dose-response form. Furthermore, none of the supporting data suggest the existence of a threshold level required for disease response. As a result, a linear dose-response form is usually accepted for practical reasons and because no epidemiological study can give accurate risk estimates at the lower dosage levels (McDonald et al., 1980).

Given the linear form of the dose-response relation, a number of technical issues remain. First, what measure of cumulative dosage should be employed? A common measure is the number of asbestos fibers greater than $5\ \mu\text{m}$ in length found in 1 ml of air to which a worker is exposed, for 40 hours per week, over some standard time unit like a year. This measure is frequently abbreviated as f-yr/ml. An alternate cumulative measure, the mppcf-yr (see Section 2.3.4), may be related to this measure by the simple approximation $1\ \text{mppcf-yr} = 3\ \text{f-yr/ml}$ (Selikoff, 1981, p. 211; or Selikoff, 1982, p. 124).

Actually, this conversion is more complex than it appears. Direct conversion from U.S. customary units to metric units yields $1\ \text{mppcf-yr} = 35.3\ \text{f-yr/ml}$ assuming that 1 fiber = 1 particle. The discrepancy occurs because the mppcf measure was typically used to measure the total dust concentration for all kinds of airborne particle – not just airborne asbestos fibers. Selikoff's approximation is equivalent to the assumption that 1 asbestos fiber = 11.8 airborne particles. Selikoff warned that the conversion factor for 1 mppcf could plausibly range from 1 to 8 f/ml, so that the assumed conversion factor 3 f/ml may be grossly in error. For additional discussion, see Dement et al. (1983a) and EPA (1986, pp. 42-46).

A second technical issue to consider is what measure of response to use. In Table 2.2, the dose-response coefficients from a range of studies are presented for two measures: (a) the change in lung cancer deaths due to each 1 f-yr/ml change in exposure, as a percent of the expected lung cancer deaths, and (b) the change of all asbestos-related deaths due to each 1 f-yr/ml change in exposure, as a percent of observed deaths. Selikoff (1981) summarized these studies to show how the estimates changed with study design and condition. To maximize comparability, the asbestos-related deaths were restricted to include only deaths from asbestosis, lung cancer, mesothelioma, and gastrointestinal cancer [defined by Selikoff (1981) to include cancers of the esophagus, stomach, and colon/rectum].

According to Table 2.2, in the study of Seidman et al. (1979), where factory workers were exposed to amosite fibers, there was a 9.1% increase in lung cancer risk for each f-yr/ml. The lowest estimate was 0.06% (McDonald and Liddell, 1979) where miners and millers were exposed to chrysotile fibers. The ratio of the largest dose-response coefficient to the smallest coefficient was 151 to 1 (i.e., $9.1/0.06$). This variation is large and probably reflects unidentified systematic differences in study design, study population, and study conditions, or combinations of these factors. For example, amosite fibers may be more toxic than chrysotile fibers. Thus, one might expect the dose-response coefficient to be higher in studies where the primary fiber type is amosite, as in Seidman et al. (1979). The ratio of the largest and smallest dose-response coefficients relating the risk of all asbestos-related deaths to asbestos exposure was also large: 108 to 1 (i.e., $0.65/0.006$).

The ranges of dose-response estimates for both lung cancer and all-asbestos-related diseases are so broad that it may be hazardous to pool such estimates. Instead, Selikoff (1981) recommended that one examine the esti-

Table 2.2: Estimated Risk Increases Associated with Asbestos Exposure

Study Group	Asbestos Type	Increase in Risk per f-yr/ml of Cumulative Exposure		Reference
		Lung Cancer as a % of Expected Lung Cancer Deaths	All Asbestos-Related Deaths as a % of Observed Deaths	
Factory Employment Insulation Manuf. – Paterson, N.J. Asbestos Products Manuf. – London, U.K.	Amosite	9.10	0.650	Seidman et al., 1979
Males	Crocidolite, chrysotile, and amosite	1.30	0.140	Newhouse and Berry, 1979
Females	Crocidolite, chrysotile, and amosite	8.40	0.140	Newhouse and Berry, 1979
Asbestos Manuf. Retirees – U.S.	Amosite and chrysotile; some crocidolite	0.30	0.020	Henderson and Enterline, 1979
Asbestos Products Manuf. – Manville, N.J.	Chrysotile; some amosite and crocidolite	1.10	0.080	Nicholson et al., 1981b
Insulation Application Textile Production U.S.	Chrysotile and amosite	1.70	0.170	Selikoff et al., 1979
Rochdale, U.K. Before 1951	Chrysotile	5.30	0.290	Dement et al., 1982
After 1950	Chrysotile	0.07	0.020	Peto, 1980
Chrysotile Mining and Milling Quebec	Chrysotile	0.80	0.080	Peto, 1980
	Chrysotile	0.06	0.006	McDonald and Liddell, 1979; McDonald et al., 1980
Theftord Mines, Quebec	Chrysotile	0.15	0.030	Nicholson et al., 1979

Source: Selikoff (1981, Table 3-14) and NRC (1984, Table 7-3).

mates in terms of data quality and systematic differences in the exposure and setting in order to select plausible dose-response estimates for specific forecasting or risk assessment applications.

Selikoff pointed out that the three highest estimates (5.3%, 8.4%, and 9.1%) suggested that even very low exposures (e.g., 0.5 f/ml for workers employed for 40 years = 20 f-yr/ml) may produce twice the risk of lung cancer and 4-13% higher total mortality. The six highest estimates implied that an exposure of 2.5 f/ml would produce, after 40 years, at least a doubling of lung cancer risk and 10% higher total mortality. This exposure level is half the U.S. standard permissible exposure limit of 5.0 f/ml existing in 1972-1976 and is just above the 2.0-f/ml standard existing in 1976-1986 (OSHA, 1986).

Despite Selikoff's (1981, p. 219; 1982, p. 134) admonition that "it is not appropriate to average or otherwise combine the data from the various investigations," this is precisely what was done in the National Research Council (NRC) (1984) study which relied on the same set of nine estimates for lung cancer as reported in Table 2.2. The NRC (1984, p. 214) computed the median dose-response coefficient (1.1%) and rounded the result upward to 2.0% for computing lifetime risks of lung cancer for nonoccupational environmental exposures.

Likewise, the EPA (1986) used an averaging of the risk coefficients obtained in their review of 14 studies that permitted estimation of the OSHA (1983) form of the lung cancer model. This model extended previously developed SMR models to explicitly introduce a 10-year latency period during which asbestos exposure would have no observable impact. The SMR (percent form) at age a , exposure level f , duration d , and time since first exposure t , is represented as

$$\text{SMR}(f, d, t) = 100 + K_L \times f \times d_{t-10},$$

which is independent of age; and where K_L is the dose-response coefficient (percent form), f is the exposure intensity in f/ml, and d_{t-10} is the completed duration of exposure 10 years in the past (i.e., as of age $a - 10$), where

$$d_{t-10} = \begin{cases} d & (t \geq d + 10) \\ t - 10 & (d + 10 \geq t \geq 10) \\ 0 & (t < 10). \end{cases}$$

The EPA (1986) evaluated 14 studies that allowed the estimation of dose-response coefficients and confidence intervals for the OSHA (1983) lung cancer model. The results in Table 2.3 indicate that there were significant differences among the estimates.

The EPA (1986, p. 82) computed the geometric mean K_L of the 14 studies as 0.65%. However, for assessing the impact of environmental exposures, they excluded the three studies of mining and milling workers and recomputed the geometric mean as 1.0% – nearly identical to the initial result of 1.1% in the NRC (1984) study. A 95% confidence interval from 0.4% to 2.7% was derived from an analysis of variance of the 11 separate estimates.

Table 2.3: Estimates of Dose-Response Coefficients for Asbestos-Related Lung Cancer in 14 Epidemiologic Cohort Studies

Industrial Process / Location	Asbestos Type	Estimated Dose-Response Coefficient K_L (%)	95%-Confidence Interval (%)		Reference
			Low	High	
Textile Production					
Charleston, SC	Chrysotile	2.80	1.70	5.60	Dement et al., 1983b
Charleston, SC	Chrysotile	2.50	1.00	3.70	McDonald et al., 1983a
Rochdale, U.K.	Chrysotile	1.10	0.30	2.40	Peto, 1980
Lancaster, PA	Chrysotile; some amosite and crocidolite	1.40	0.36	1.70	McDonald et al., 1983b
Friction Products					
U.K.	Chrysotile	0.06	0.01	0.80	Berry and Newhouse, 1983
Connecticut	Chrysotile	0.01	0.01	0.55	McDonald et al., 1984
Mining and Milling					
Quebec	Chrysotile	0.06	0.02	0.11	McDonald et al., 1980
Theftord Mines, Quebec	Chrysotile	0.17	0.06	0.32	Nicholson et al., 1979
Turin, Italy	Chrysotile	0.08	0.01	0.89	Rubino et al., 1979
Insulation Manufacturing					
Paterson, NJ	Amosite	4.30	0.84	7.40	Seidman, 1984
Insulation Workers					
U.S. and Canada	Chrysotile and amosite	0.75	0.60	1.10	Selikoff et al., 1979
Mixed Products					
U.S.	Amosite and chrysotile; some crocidolite	0.49	0.24	0.91	Henderson and Enterline, 1979
Cement Products					
U.S.	Chrysotile, crocidolite, and amosite	0.53	0.14	1.10	Weill et al., 1979
Ontario, Canada	Chrysotile and crocidolite	6.70	3.50	11.20	Finkelstein, 1983

Source: EPA (1986, Table 3-10 and Figure 3-7).

Following essentially the same logic, OSHA (1986, p. 22,637) derived an identical estimate of K_L (1.0%) with an uncertainty interval of 0.3-3.0%. Neither confidence interval includes the three estimates in Table 2.3 for mining and milling (0.06%, 0.17%, and 0.75%), whose geometric mean is 0.091% – smaller than the 1.0% pooled estimate by a factor of 11.0. To deal with this, the EPA recommended an uncertainty factor of 10 in applications to new exposure situations.

Part of Selikoff's (1981) concern about pooling the risk coefficients was that it may lead to underestimation of the risk faced by certain classes of workers. Conversely, it may lead to overestimation of the risk faced by others. For example, Camus et al. (1998) evaluated the EPA parameterization of the OSHA lung cancer model using mortality data for women from two chrysotile mining areas of Quebec for the period 1970-1989. The estimated average cumulative exposure was 25 f-yr/ml, which was relatively high given that 95% of the exposure was nonoccupational. The predicted relative risk was 2.05 to 1. The observed relative risk was 0.994 or 1.101, depending on the method used in the calculation. On this basis, Camus et al. (1998, p. 1568) concluded that "the EPA's risk-assessment model overestimated the mortality attributable to asbestos by a factor of at least 10."

The authors offered six possible reasons for overestimation by the EPA's model:

- Overestimation of risk at low doses
- Inadequacy of cumulative exposure in measuring risk
- Overestimation of the exposure-risk gradient
- Lower risk for chrysotile versus amphibole asbestos
- Lower relative risk of lung cancer due to asbestos among nonsmokers than smokers
- Overestimation of the dose-response gradient

These reasons included no mention of the uncertainty of the dose-response coefficient due to pooling, nor of the large confidence intervals recommended by the EPA (1986). The EPA (1986, p. 82) stated that application of their model to new exposure situations should allow for a risk differential as large as a factor of 10 from their 1% dose-response coefficient. This would include the risk level found by Camus et al. (1998) at its lower bound.

Alternatively, the results of Camus et al. (1998) may be reinterpreted as providing validation of the EPA (1986) model. This requires that we view the Quebec exposures not as a new exposure situation, but as one similar to the mining and milling exposures in the three studies (including Quebec) excluded from EPA's pooled estimate (see Table 2.3). The pooled dose-response coefficient for these three studies is 0.091%, which implies a predicted relative risk of 1.096 – a value in-between the two observed values 0.994 and 1.101 provided by Camus et al. (1998). [*Note:* $1.096 = 1 + (2.05 - 1) \times 0.091$.]

This explanation is more plausible than any of the six explanations proposed by the authors and it provides additional support for the OSHA (1983)

form of the lung cancer model used by the EPA (1986). The question remains: Why is the lung cancer risk coefficient for the mining and milling of chrysotile so much lower than for other asbestos processing activities, especially for textile production in the United States and the United Kingdom?

The EPA (1986) used 4 of the 14 studies to estimate risk coefficients for mesothelioma using the OSHA (1983) form of the mesothelioma model. This model extended the latency form of the multihit/multistage model used by Peto et al. (1982; see Section 2.3.1d) to explicitly represent (a) the permanent increase in risk associated with each fiber that is inhaled and retained and (b) the reduced rate of increase in risk following the cessation of exposure. The absolute mortality risk at exposure level f , duration d , and time since first exposure t , for $t \geq 10$, is represented as

$$\text{AMR}(f, t, d) = K_M \times 10^{-8} \times f \times \left[(t - 10)^3 - (t - 10 - d_t)^3 \right],$$

where

$$d_t = \begin{cases} d & (t \geq d + 10) \\ t - 10 & (t < d + 10), \end{cases}$$

where the final condition is set to zero out the second term in brackets in the expression for $\text{AMR}(f, d, t)$ during the 10-year latency period following cessation of exposure. The constant 10^{-8} is extracted from the constant K_M to simplify the scaling. The 10-year latency assumption is implemented by setting $\text{AMR}(f, d, t) = 0$ for $t < 10$.

The EPA's (1986) estimates of dose-response coefficients for mesothelioma are presented in rows 2, 3, 4, and 6 of Table 2.4. These estimates range from 1.0 to 12.0 with a geometric mean of 2.75. However, when the two OSHA (1986) estimates are included, the geometric mean drops to 0.98. The EPA (1986) was concerned about bias in their estimates, noting that two of the four studies included the two highest lung cancer dose-response estimates. To deal with this concern, the EPA evaluated the ratios of the mesothelioma and lung cancer coefficients, noting that the ratios for the four selected studies were in much closer agreement, ranging from 0.74 to 2.00, with a geometric mean of 1.25. Following this, the EPA (1986, p. 95) developed a series of adjustments that incorporated mesothelioma death counts from the other 10 studies listed in Table 2.3 and concluded that the best estimate of the dose-response ratio was 1.00, so that $K_M = K_L = 1.0$, with an approximate 95% confidence interval from 0.2 to 5.0 and an uncertainty factor of 20 in applications to new exposure situations.

This estimate of K_M is almost identical to the geometric mean (0.98) of the six studies in Table 2.4. However, the EPA's uncertainty bounds are large, suggesting that use of the OSHA-EPA model may lead to serious errors of underestimation of the risk faced by some workers and overestimation of the risk faced by others.

OSHA (1986, p. 22,640) followed a similar logic in their assessment of the four studies in Table 2.4, arriving at the same final estimate: $K_M = 1.0$. They

Table 2.4: Estimates of Dose-Response Coefficients for Asbestos-Related Mesothelioma in Six Epidemiologic Cohort Studies

Industrial Process/Location	Asbestos Type	Mesothelioma		Lung Cancer		Mesothelioma-Lung Cancer Ratio	Reference
		Dose-Response Coefficient	K_M (10^{-6})	Dose-Response Coefficient	K_L (%)		
Textile Production Charleston, SC Rochdale, U.K.	Chrysotile	0.22		2.80		8	Dement et al., 1983b
	Chrysotile	1.00		1.10		91	Peto, 1980
Insulation Manufacturing Paterson, NJ	Amosite	3.20		4.30		74	Seidman, 1984
	Chrysotile and amosite	1.50		0.75		200	Selikoff et al., 1979; Peto et al., 1982
Cement Products U.S. Ontario, Canada	Chrysotile, crocidolite, and amosite	0.07		0.53		13	Weill et al., 1979
	Chrysotile and crocidolite	12.00		6.70		179	Finkelstein, 1983

Source: Mesothelioma parameters in rows 2, 3, 4, and 6 are from EPA (1986, Table 3-30); mesothelioma parameters in rows 1 and 5 are from OSHA (1986, p. 22640-22641). Lung cancer parameters are from EPA (1986, Table 3-10).

also reported the K_M estimates for the data of Dement et al. (1983b) and Weill et al. (1979) included in rows 1 and 5 of Table 2.4. In our model development in Section 8.4, we used the updated insulation worker data in Selikoff and Seidman (1991) to obtain a K_M value of 1.45, 45% higher than the EPA (1986) value, but only 3.3% lower than the insulation worker value in Table 2.4. The uncertainty in these estimates motivated us to develop additional constraints on our forecasting model that will be discussed in Chapters 6-10.

2.5 Effects of Fiber Type on Disease Risks

Two aspects of the OSHA (1983) mesothelioma model are important to our modeling applications. First, the fact that the absolute risk is proportional to the asbestos exposure level, f , means that no nonasbestos-related causes of mesothelioma are represented. In the general population, where 80-90% of mesotheliomas are attributable to asbestos exposure, this assumption is clearly only an approximation, and the approximation could be improved by better accounting of the rate for the remaining 10-20% not due to asbestos exposure. In the exposed worker population, however, where the attributable risk (AR_H) is on the order of 99% or higher, the approximation is much better and there would be little gain in modeling the nonasbestos-related risk.

Second, the exponent $k = 3$ in the formula for absolute risk implies a four-stage or four-hit multistage/multihit model, consistent with the mechanisms proposed by Hahn et al. (1999; see Section 2.6 for discussion). This is 1 unit higher than the estimate $k = 2$ obtained by Peto et al. (1982) for the fitted model with a 10-year latency (see Section 2.3.1d). However, when we re-fitted that model to the updated data in Selikoff and Seidman (1991), we found that $k = 3$ was the best integer estimate for the exponent, and $k = 2.8$ was the best overall estimate (see Table 8.7). Thus, the fixed parameters of the OSHA model are consistent with the mesothelioma experience of the insulation worker cohorts and with the biological evidence on the mechanisms underlying the disease.

The variability in risk coefficient estimates from the various cohort studies of workers exposed to asbestos has yet to be fully explained. At several points in the preceding sections, it was suggested that there may be a gradient in carcinogenicity across the different types of asbestos fiber, with the lowest risks for chrysotile, increased risks for amosite, and the highest risks for crocidolite. However, the variability in risk coefficients for chrysotile in Tables 2.3 and 2.4 indicates that consideration should also be given to risk gradients according to the type of industrial process.

OSHA reviewed evidence on risk differentials by asbestos fiber type and concluded “that epidemiological and animal evidence, taken together, fail to establish a definitive risk differential for the various types of asbestos fiber”

(OSHA, 1986, p. 22,628). OSHA further stated that there exists “a clear relationship between fiber dimension and disease potential” (1986, p. 22,629). OSHA (1994) reviewed additional evidence relating to its earlier analysis and determined that it would stand by that analysis. Three reasons were offered:

1. Similar risk potencies for chrysotile and amphiboles were found for both lung cancer and asbestosis; evidence for lower chrysotile risk was presented only for mesothelioma.
2. Chrysotile presents a significant risk of cancer, even if it is accepted that its risk is lower than for amphiboles.
3. Most occupational exposures involve mixed fiber types.

The EPA (1986, p. 106-117) reviewed evidence on the relative carcinogenicity of different asbestos fiber types. Based on the 14 epidemiological studies of lung cancer risk identified in Table 2.3, it concluded “that factors other than mineral types substantially influenced the studies reviewed” (EPA, 1986, p. 108). For example, it was pointed out that chrysotile textile production exhibited lung cancer risks significantly larger than chrysotile mining or friction products manufacturing. Based on the four epidemiological studies of mesothelioma risk identified in Table 2.4, it concluded “that the same factors affect the variability of mesothelioma risk as affect lung cancer risk” and “it appears impossible to separate the effect of mineral type from other factors contributing to the variability of potency” (EPA, 1986, p. 110).

Using a more extensive set of 41 epidemiological studies, the EPA developed a series of adjustments that allowed it to compute ratios of pleural and peritoneal mesothelioma to excess lung cancer incidence in each of the studies. Assuming that excess lung cancer incidence is a proxy for cumulative asbestos exposure, the mesothelioma ratios could be interpreted as measures of relative carcinogenicity of the asbestos fibers in a given study. Several conclusions were reached (EPA, 1986, p. 114-115):

1. Amphibole exposures produced comparable numbers of pleural and peritoneal mesothelioma; chrysotile exposures rarely produced peritoneal mesothelioma.
2. For pleural mesothelioma, the ratios for chrysotile, amosite, and mixed exposures were roughly comparable, whereas the ratios for crocidolite were two to three times greater.
3. For peritoneal mesothelioma, the ratios for pure chrysotile exposures were significantly lower than for amphiboles or mixed exposures.
4. On average, pure amosite exposure has a risk about twice that of pure chrysotile exposure, whereas pure crocidolite exposure has a risk about four times that of pure chrysotile exposure.
5. Within fiber type, significant differences appear to be related to the type of processing conducted (e.g., chrysotile mining versus textile production; amosite mining versus insulation manufacturing).

The EPA (1986, p. 116) considered differences in fiber size distributions and industrial processes in different work environments to be major factors in accounting for risk differentials in the various epidemiological studies. This is consistent with Stanton and Wrench (1972), who evaluated the carcinogenicity of amosite, chrysotile, crocidolite, and other fibers by direct application to the pleura of 1200 Osborne-Mendel rats and concluded that the carcinogenicity of asbestos was primarily related to its structural shape rather than to its physicochemical properties. In contrast to the human epidemiological results obtained by the EPA (1986), Stanton and Wrench (1972) found that the incidence of pleural mesothelioma in their experiments on rats did not differ significantly among the three types of asbestos fiber.

The EPA's findings (conclusions 1 and 3) that chrysotile exposure rarely produces peritoneal mesothelioma may explain an anomalous result that is often cited but never adequately explained – that peritoneal mesothelioma appears to be associated with heavier cumulative exposure intensities (e.g., Lemen et al., 1980; Antman, 1980; Walker, 1982; Browne and Smither, 1983; Roggli et al., 1987, 1992c). Roggli et al. (1987, 1992c, p. 112) noted that about 50% of peritoneal cases had concurrent asbestosis compared with 20% of pleural cases; whereas Roggli et al. (1992b, p. 312) reported a correlation of 0.46 between asbestosis scores and the lung fiber burden in 36 autopsied cases. Walker (1982) cited results from 11 epidemiological studies to support the association of peritoneal mesotheliomas with heavier exposure. Given both epidemiological and tissue burden evidence, the anomaly is that the relative amount of peritoneal versus pleural mesothelioma is significantly higher among females than among males (McDonald and McDonald, 1980; SEER, 2000) – exactly the opposite of what one would expect if the association were real.

We review Walker's (1982) evidence in Section 4.4.1, Task 1b where we find an alternative interpretation of no association to be more plausible. Roggli et al.'s (1992c) finding of a correlation with asbestosis was based on autopsied cases and is subject to three important limitations (Stayner et al., 1996): (1) Asbestosis is indicative of heavy fiber concentration in the lungs, not the mesothelium; (2) chrysotile asbestos is cleared more rapidly than the amphiboles from the lungs – it differentially migrates to the pleura, frequently leaving tremolite contaminants in the lungs as the only persistent evidence of its presence; and (3) the lung tissue fiber distribution at the time of death may not be representative of the distribution at the time of exposure 20-50 years earlier. Combined with the finding of higher relative frequencies of peritoneal mesothelioma for females, these considerations suggest that the alternative explanation of no association is more plausible.

Evidence in favor of this explanation is provided by comparing the ratios of male to female counts of peritoneal versus pleural mesothelioma in the SEER data for 1973-1997 (SEER, 2000): 1.19 versus 4.50. Given that chrysotile accounts for 90-95% of asbestos consumption in the United States, and that chrysotile rarely produces peritoneal mesothelioma, one would expect only

a modest increase in peritoneal cases for males (with $AR_H \approx 16\%$) and a substantial increase for pleural cases (with $AR_H \approx 78\%$), where the “ H ” factor is associated with being male.

Lippmann (1988, 1990) reviewed the literature relating fiber characteristics to disease in animals and humans in an attempt to establish critical fiber parameters for the three main asbestos-related diseases: asbestosis, lung cancer, and mesothelioma. He concluded the following:

1. Asbestosis risk is related to the surface area of asbestos fibers longer than $2 \mu\text{m}$ with diameters in the range $0.15\text{-}2.0 \mu\text{m}$.
2. Lung cancer risk is related to the number of asbestos fibers with lengths in the range $10\text{-}100 \mu\text{m}$ with diameters greater than $0.15 \mu\text{m}$, especially diameters in the range $0.3\text{-}0.8 \mu\text{m}$.
3. Mesothelioma risk is related to the number of asbestos fibers with lengths in the range $5\text{-}10 \mu\text{m}$ and diameters less than $0.1 \mu\text{m}$.

Interestingly, there is no overlap between the mesothelioma and lung cancer fiber parameters, with respect to either length or diameter, nor between mesothelioma and asbestosis, with respect to diameter. These results could account for variability in the ratios of mesothelioma to excess lung cancer incidence in the studies reviewed by the EPA (1986). These results could also account for the variability of risk associated with different industrial processes, if those processes changed the lengths, diameters, or surface areas of asbestos fibers. Lippmann (1988, p. 103) noted that the phase-contrast optical method was recommended for counting fibers with diameters between 0.25 and $3 \mu\text{m}$. However, Mossman et al. (1990, p. 299) and Gaensler (1992, p. 234) commented that the phase-contrast microscopy mandated by OSHA (1986, 1994) actually has a resolution only to $0.5 \mu\text{m}$, more than three times the lower bound for diameters of fibers causing asbestosis and lung cancer and more than five times the upper bound for diameters of fibers causing mesothelioma. Lippmann (1988, p. 103) noted that fibers with diameters below the resolution limit cannot be counted using the methods mandated by OSHA (1986, 1994); he recommended electron microscopy or magnetic alignment and light scattering techniques.

The role of chrysotile asbestos as a causal agent in human mesothelioma has been challenged. Churg (1988) surveyed the literature on chrysotile-induced mesotheliomas and concluded that at most 53 cases could be accepted as valid, and he argued that the causal agent in most chrysotile-induced mesothelioma was actually tremolite asbestos contaminants. Mossman et al. (1990, p. 247) argued that the lower carcinogenicity of chrysotile combined with the high proportion of chrysotile in asbestos-containing materials in buildings and schools suggest that most environmental exposures to asbestos will not lead to asbestos-associated malignancy or functional impairment. Furthermore, they suggested that “exposure to chrysotile at current

occupational standards does not increase the risk of asbestos-associated diseases” (Mossman et al., 1990, p. 247).

Counterarguments to Mossman et al. (1990) were provided by Nicholson (1991) and Dement (1991). Nicholson (1991, p. 82) concluded that there was “no difference in the potency of chrysotile and amosite for producing mesothelioma.” He accepted that there was two to three times greater risk for crocidolite. Dement (1991) compared data on asbestos fiber distributions in human lung tissues from Quebec chrysotile miners and millers with South Carolina chrysotile textile workers. These two groups exhibited the largest risk differentials for lung cancer in Table 2.3. Dement (1991, p. 18) noted that the South Carolina workers had lower total fiber deposition rates and lower proportions of tremolite, leading to the conclusion that tremolite was not the principal causal agent for lung cancer among these chrysotile workers. Rall (1994a, 1994b) and Mossman (1994) continued the debate with a series of points and counterpoints. Stayner et al. (1996) reviewed lung burden studies, epidemiologic studies, toxicologic studies, and mechanism studies that provided evidence on the relative carcinogenicity of chrysotile and amphibole fibers and concluded that tremolite contamination is not the explanation of mesothelioma incidence among chrysotile asbestos workers. Smith and Wright (1996) reviewed evidence from animal and human studies of pleural mesothelioma, including analyses of the asbestos fiber content of pleural tissue, and concluded that the potency of chrysotile was comparable to that of amosite, with crocidolite 2-4 times more potent. However, given that chrysotile accounted for about 95% of asbestos usage, they also concluded that chrysotile was the main cause of pleural mesothelioma in the United States.

Liddell et al. (1997, 1998) and McDonald et al. (1997) completed follow-up on the cohort of 11,000 Quebec chrysotile miners and millers discussed in Section 2.3.5. For overall mortality, they concluded that exposure to less than 1000 f-yr/ml was essentially innocuous. For lung cancer and mesothelioma, analysis of the geographical variation in risk correlated with the geographical distribution of fibrous tremolite as a contaminant in chrysotile asbestos. This correlation was investigated further by McDonald and McDonald (1997), who suggested that the greater durability and biopersistence of amphiboles in lung tissue may be of critical importance. McDonald (1998) noted that the very high risk of lung cancer, but not of mesothelioma, among chrysotile textile workers remains unexplained.

Cullen (1998) attempted to provide some perspective to these divergent findings. In particular, he noted that the high lung cancer rates among South Carolina chrysotile textile workers were not explained by the tremolite contamination hypothesis, but, instead, required additional explanation and explication of the risks associated with fiber length, diameter, and other physical characteristics.

2.6 Simian Virus 40 and Mesothelioma

Bocchetta et al. (2000) noted that (1) 5-10% of asbestos workers get mesothelioma, (2) 10-20% of mesotheliomas are not associated with asbestos exposure, and (3) 60% of human mesotheliomas contain simian virus 40 (SV40 – a macaque polyomavirus that is tumorigenic in rodents and inactivates p53 and pRb tumor suppressor proteins) DNA fragments. The first point suggested to them that additional factors may be involved; the second point suggested that alternative factors may cause mesothelioma; and the third point suggested a potential causative role for SV40 in mesothelioma development. To test this latter hypothesis, Bocchetta et al. (2000) conducted a series of in vitro experiments that established that SV40 infection of human mesothelial cells was different from the lytic pattern seen in almost all other types of cells, that the difference was related to increased levels of p53 in mesothelial cells, and that infected mesothelial cells underwent tumorigenic transformation to immortal phenotype. In addition, they demonstrated that the rate of transformation increased when the cells were exposed to increasing concentrations of crocidolite asbestos. This led Bocchetta et al. (2000) to conclude that asbestos and SV40 are cocarcinogens in vitro and may be cocarcinogens in vivo. One anomalous result, however, was the finding that crocidolite alone, without SV40, did not produce tumorigenic transformations of mesothelial cells in vitro.

Several comments are in order. First, the fact that only 5-10% of asbestos workers get mesothelioma does not mean that additional factors must be involved. Under the multistage model of carcinogenesis, the tumor develops only after several tumorigenic transformations have occurred. Hahn et al. (1999) argued that changes are needed in at least four distinct intracellular signaling pathways and cited SV40 large tumor antigen, oncogenic *ras*, and the catalytic subunit of human telomerase as candidates for study. The identity of the fourth pathway was left unspecified, except that it was related to some fundamental difference in the biology of rodent and human cells. The plausibility of this conjecture was boosted by Killian et al. (2001), who found that primates have two functional copies of the IGF2R tumor suppressor gene, whereas virtually all nonprimate mammals (including rodents) have only one functional copy due to a process of “genomic imprinting.” Damage to the IGF2R gene is associated with cancer development at multiple sites. Humans, however, would need one additional tumorigenic transformation (to the second copy of the IGF2R gene) to reach an equivalent stage to that of rodents undergoing tumor development. Thus, Hahn et al.’s (1999) argument appears credible. Furthermore, the identification of four stages in the process of carcinogenesis is significant for our modeling effort because that number exactly matches the number of stages implied by the OSHA model of mesothelioma mortality in Section 2.3 (assuming a 10-year latency period).

Nonetheless, this does not mean that Hahn’s model is the only mechanism underlying mesothelioma. Murthy and Testa (1999) identified a range of possible pathways to mesothelioma, including mutational deletions on chro-

mosomes 1p, 3p, 6q, 9p, 13q, 15q, and 22q. Gene IGF2R is on chromosome 6q at a site adjacent to the deletions noted by Murthy and Testa (1999). Murthy and Testa (1999) concluded that multiple tumor suppressor genes are lost or inactivated in mesothelioma but that it was not currently possible to determine their identity or sequence.

Second, the fact that 10-20% of mesotheliomas are not associated with asbestos exposure means that the attributable risk (AR) for asbestos is in the range 80-90%. The attributable risk among exposed workers (AR_H) could be substantially higher (e.g., 99% or more). Thus, the fraction of cases among exposed workers not due to asbestos must be on the order of 1% or less and it would be difficult to segregate these cases for separate treatment in our models.

In addition, the meaning of the term “asbestos exposure” varies from one study to the next. Generally, the term includes occupational exposures; it may also include environmental exposures, some of which are known and documentable, with others unknown and undocumentable. Roggli et al. (1992b, p. 316) estimated the distribution of asbestos-body (coated asbestos fibers) counts from the lungs of 100 mesothelioma patients and found a bimodal distribution, with about 25% of cases overlapping the general population with a mean value approximately 1/1000 that of the high-count group. The ratio 1/1000 is consistent with estimates of environmental exposures for the general population (EPA, 1986, p. 162). The distribution for the general population had a mean of about 1.6 asbestos-bodies per gram of wet lung tissue, suggesting that there is a significant amount of asbestos fibers in the lungs of “nonexposed” persons. Consequently, it may be impossible to rule out asbestos as a causative agent in any mesothelioma.

Third, the finding that 60% of human mesotheliomas contain SV40 DNA fragments is somewhat tentative. Butel and Lednicky (1999, p. 128) noted that the 60% figure is the median of seven published estimates ranging from 0% to 86%, with a pooled mean of 48% ($= 95/196$). However, the 0% estimate was obtained in the largest data series with 50 tumors tested. Pilatte et al. (2000) tested six mesothelioma cell lines and found no evidence of SV40 DNA. However, they did find that commercially available mouse monoclonal antibodies are contaminated with a 90kDa protein of similar size to SV40 large tumor antigen and this may lead to false-positive results in some test series.

Butel and Lednicky (1999) reviewed the evidence on the cellular and molecular biology of SV40, noting that it is tumorigenic in rodents, that it is potentially tumorigenic in humans, and that it may have been a contaminant in polio vaccines given to 10-30 million children vaccinated in the United States between 1955 and 1963.

Strickler et al. (1998) used SEER data 1973-1993, Connecticut Tumor Registry data 1950-1969, and national mortality statistics 1947-1973 to evaluate cohort differentials in relative risks for three types of cancers linked to SV40 – mesothelioma, osteosarcoma, and ependymomas. No evidence of increased risk for cohorts exposed to SV40 via polio vaccinations was found. The pos-

sibility of effects becoming manifest in future years was recognized, but at least through 1993, no effect was detected. More recent data for 1994-1997 (SEER, 2000) indicate that the annual numbers of mesothelioma deaths have plateaued or declined slightly since reaching a peak in 1992, a pattern consistent with the diminution of asbestos exposure beginning in the early 1970s. To indicate the potential size of the effect, we considered the SEER (2000) report of the number of mesotheliomas in 1997 for the age group 45-49, the cohort identified by Strickler et al. (1998) as the group at highest risk of SV40 exposure. In total, there were seven mesothelioma cases (three males, four females) in the SEER data approximately 34-42 years after SV40 exposure. Five years earlier, there were four mesothelioma cases in the SEER data for this cohort. SEER represents about 10% of the U.S. cases, so that the national incidence in 1992 and 1997 was about 40 and 70 cases, respectively. These estimates do not support the hypothesis that SV40 exposure will result in large numbers of new mesothelioma cases.

The SEER (2000) data indicate that the male/female ratio of mesothelioma cases continues at about 3.5 to 1 – consistent with the hypothesis that the main cause is occupational exposure to asbestos. This ratio is consistent with attributable risks (AR) of 80% for males and 30% for females for asbestos-induced mesothelioma, which compares well with estimates of 85% and 23%, respectively, from Spirtas et al. (1994).

Fourth, the finding that crocidolite asbestos does not produce tumorigenic transformations of mesothelial cells *in vitro*, combined with the strong *in vitro* effect of SV40, must be interpreted in the context of the overwhelming amount of epidemiologic evidence in support of an asbestos effect and the lack of similar evidence for an SV40 effect on human mesothelioma incidence. Bocchetta et al. (2000) speculated that asbestos, *in vivo*, may act as an immunosuppressant that permits the SV40 infection to proceed without cell lysis in mesothelioma cells. Alternatively, asbestos may induce the production of oxygen free radicals that lead to gene alterations and carcinogenesis *in vivo*. Klein (2000) commented that both alternatives are possible mechanisms that should be further studied, but that the results to date do not prove that SV40 has a causative role in human mesothelioma.

We observe that neither mechanism nor the *in vitro* experiments conducted by Bocchetta et al. (2000) is consistent with the hypothesis that the simple physical presence of asbestos fibers in contact with mesothelial cells is sufficient to induce tumorigenic transformations. There is a large and growing literature on the molecular biology of asbestos-induced fibrogenesis and carcinogenesis that suggests a complex series of pathways through which the health effects of asbestos are mediated. Kamp and Weitzman (1999) reviewed this literature and concluded that free radicals, especially the iron-catalyzed hydroxyl radical and reactive nitrogen species, are important mediators of asbestos genotoxicity. They noted, however, that the precise mechanisms by which asbestos leads to DNA damage, disrupted signaling mechanisms, al-

tered gene expression, mutagenicity, apoptosis, and altered immune responses are not firmly established.

Jaurand (1997) reviewed the literature on asbestos-induced genotoxicity and concluded that the mechanisms depended jointly on the fiber dimensions (length, diameter, and aspect ratio), its chemical composition, and the cell environment, with a critical role assigned to the process of phagocytosis.

Mossman and Churg (1998) reviewed the literature on asbestos-induced fibrogenesis, including lung burden studies, again finding a critical role for phagocytosis, with the fiber dimensions and chemical composition governing the cellular reactions. Additional details are provided in Robeldo and Mossman (1999).