Asbestiform Fibers
Nonoccupational Health Risks

Committee on Nonoccupational Health Risks
of Asbestiform Fibers

Board on Toxicology and Environmental Health Hazards
Commission on Life Sciences
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Risk Assessment

Exposure, laboratory, and epidemiological data provided earlier in this report are used in this chapter to make quantitative and qualitative (or comparative) assessments of risks from exposure to asbestiform fibers. To place the discussion in context, the chapter begins with a brief general discussion of risk assessment and a few special considerations concerning asbestos and related fibrous materials.

Various difficulties often limit the accuracy and precision with which risk to human health can be estimated. Nevertheless, when the data base is good, the risk estimates can be sufficiently informative to aid policy judgments. Some of the factors that enhance the usefulness of the data include dose-response information based on several accurately known exposure levels; knowledge of physiologic and metabolic factors that affect exposure of body tissues; an understanding of the mechanism by which the substance results in toxicity; knowledge of the extent to which experimental systems mimic the human response; and an understanding of the properties of a complex and variable substance that account for its toxicity.

Many of these issues apply in the assessment of risk from asbestiform fibers, which have varying physical and chemical properties. Some members of the class, the commonly used naturally occurring forms of asbestos, have been clearly shown to cause fibrosis of the lung and pleura as well as cancer of the lung, mesothelium, and possibly the gastrointestinal tract in humans. Some occupational data on other fibers are also available, and considerable numbers of experimental studies have been conducted. It is reasonable from a biological viewpoint to use data from occupational studies to derive estimates of risk from nonoccupational exposure. However, differences in route of exposure, type and characteristics of fiber, exposure levels, and time patterns must be considered. Moreover, because working populations are generally healthier than the public at large, the latter may contain a higher proportion of more susceptible individuals.

THE PROCESS OF RISK ASSESSMENT

The principles guiding the assessment of health risks from environmental substances were recently reviewed by a committee of the

National Research Council (1983). These principles are summarized here to provide a framework for assessing the health risks from exposure to asbestiform fibers.

The numerous terms used to describe different aspects of risk assessment include "hazard assessment," "hazard identification," "risk assessment," "qualitative risk assessment," "dose-response assessment," "comparative risk assessment," "quantitative risk assessment," and "risk characterization." The use of these terms has not been standardized.

Three concepts are generally incorporated into the risk assessment process. First is the identification of the kinds of harmful health effects, e.g., anemia, birth defects, or cancer, that can result from sufficient exposure to a substance. Second is the dose-response curve for a particular effect, i.e., the severity of damage and/or the percentage of people or animals likely to be at various exposure levels. Third is the number of people in a particular population, e.g., residents of the United States or workers in a particular industry, likely to be harmed under past, present, or projected levels and conditions of exposure.

In this report, the committee has used "risk assessment" as a broad term encompassing all three of these concepts. "Hazard identification" refers to the first concept, "dose-response" curves or relationships are used in discussions of particular sets of data, and "quantitative risk assessment" refers to the estimates of risk to humans derived by mathematical extrapolations from these data. "Population risk estimates" describe the expected frequency or incidence of a harmful effect in a specific group of humans under defined conditions of exposure.

The amount and complexity of information needed increase as we progress from hazard identification to dose-response assessment to population risk estimation, although each step builds on the preceding one. Hazard identification characterizes the nature of toxic effects that a substance is capable of causing in laboratory animals or humans. Dose-response curves based on experimental or epidemiological observations define the frequency and sometimes the severity of these toxic effects at several levels of exposure.

The dose-response information is used in quantitative risk estimation. Through mathematical modeling and application of known biological principles, attempts are often made to estimate risk for dose levels, exposure conditions, or species other than those for which dose-response data have been obtained. For example, quantitative risk assessments often rely on dose-response data from studies of laboratory animals exposed to relatively high exposure levels in order to estimate the risk to humans exposed to lower levels. Assumptions and uncertainties involved in the application of quantitative risk assessment to cancer induction have been discussed extensively (Food

Safety Council, 1980; International Regulatory Liaison Group, 1979; Office of Technology Assessment, 1981). Population risk estimates bring together quantitative risk estimates and data on exposure of a specific group of humans to identify their risk under actual or anticipated exposure conditions.

The most relevant information for categorizing the hazard or the dose-response for humans is derived from studies of exposed humans. Unfortunately, evidence from this source is often unavailable or inconclusive at times when decisions about acceptable exposure must be made. Humans are exposed to so many different substances through food, medicines, air, water, household materials, and occupational environments that sorting out the causes of harmful effects on health is often difficult. Perhaps of most importance is the fact that evidence of human health hazards from substances introduced into our environment cannot be obtained directly from observations in humans until people have been harmed.

For these reasons, evidence from laboratory animals or from other biological test systems is often used as an alternative or as a supplement to data on humans. A substantial body of evidence has demonstrated the utility of these experimental systems (Doull et al., 1980; National Research Council, 1977; Richmond et al., 1981). A variety of mathematical models have been developed for using data at high doses, usually only available from studies in animals, to estimate risks for humans at low doses (Armitage, 1982; Cornfield et al., 1978; Crump et al., 1976; Fishbein, 1980; Food Safety Council, 1980; Krewski and Van Ryzin, 1981; Van Ryzin, 1980). Because there are extensive data on the effects of asbestos and some other fibers in humans, the quantitative risk assessments in this chapter are based exclusively on data from epidemiological studies in humans, whereas the comparative risk assessments also take into consideration data from laboratory studies.

Every scientific study or technique has some lower limit to its sensitivity. A sensitive method in analytical chemistry may be capable of detecting a few molecules of a particular chemical among a billion other kinds of molecules but incapable of detecting a few among a trillion. The sensitivity of an animal test for toxicity is limited by many factors, such as the number of animals that it is practical to study, the subtlety of the effect of interest, the occurrence of similar effects in animals not exposed to the material under test, and limitations on the amounts of material that can be administered and on the methods used to administer them.

Other difficulties limit the power of epidemiological studies. For example, it is often difficult to select appropriate control groups, estimate exposure, or detect health effects from the exposures of concern, especially if the exposures are much lower than those that occur among occupational groups.

Several kinds of information are useful for estimating risks at low exposure levels on the basis of observations at higher exposures. These include the shape of the dose-response curve in the range of exposures studied, knowledge of the mechanism by which the type of toxic effect occurs, and information on dose-related changes in the uptake, distribution, chemical or physical modification, and excretion of the substance, i.e., pharmacokinetics.

Substances vary markedly both in the quantity required to produce a toxic effect and in the rapidity with which the incidence of toxic effects decreases with decreasing dose, i.e., the shape of the dose-response curve. In an experiment covering a sufficiently wide range of exposure levels, it is possible to find some levels that are toxic and some lower levels at which no toxicity is observed. The highest dose at which no toxicity is seen is often called the "no-observed-effect level," or NOEL (Klaassen and Doull, 1980). However, any experiment will have some limit in its sensitivity to small effects, and the true no-effect-level, if any, may be below the NOEL in a particular experiment.

The fundamental assumption underlying the NOEL safety factor approach is that some minimal level of a toxic substance is required to cause damage and that the substance is not toxic below that level. The NOEL type of experiment is used to find that level.

The maximum dose at which no toxicity would occur is called the "threshold" for that substance. However, several mathematical models for quantitative estimation of cancer risk assume that there is no threshold; risk diminishes with decreasing dose, but some risk is assumed to remain as long as there is any exposure.

The determination of which of these two assumptions is correct will probably depend on the nature of the toxic effect. Thus, understanding the mechanism of toxicity can provide guidance in setting acceptable exposure levels. For a substance that exerts its toxic effect by inactivating an enzyme present in abundance in each cell, it is reasonable to assume that a threshold would exist. Inactivation of a few molecules of the enzyme is unlikely to damage the cell. On the other hand, a chemical that is mutagenic or carcinogenic because it damages some critical site on a DNA molecule that starts the carcinogenic process can reasonably be assumed not to have a threshold. The likelihood that a critical site would be damaged would decrease with decreasing dose, but the possibility that this damage could occur remains at any exposure above zero.

For many effects, the severity of the toxic effect, as well as the probability that it will occur, also decreases with dose. For example, a dose that damages a high proportion of cells in the liver may be lethal; one that damages a moderate number may cause severe illness but not death; a small dose that causes damage to a few cells may not lead

to any clinical symptoms. The error in assuming a threshold if none truly existed would generally not be expected to lead to serious cases of disease in this situation.

By contrast, the severity of cancer and of mutations is not related to the dose of the substance causing them. Low dose exposure to x-rays or cigarette smoke causes fewer cancers than does high dose exposure, but the resulting cancers are just as lethal. Thus, although there may be some substances that show a threshold for cancer induction (Hoel et al., 1983), an error in assuming a threshold when none really exists would severely harm those persons who got the disease despite a low exposure.

Accurate documentation of exposure is important for determining the dose-response curves for toxicity in animals or humans and also for estimating population risks. Errors in the estimation of exposure will lead to errors in defining the dose-response curve and in making quantitative risk estimates for individuals or specific populations. The amount of a toxic substance or its active metabolite that reaches the body site that is susceptible to its effect is the exposure that accounts for toxicity, but such measures are almost never available (Hoel et al., 1983). Other measurements, such as amounts in the blood, amounts entering the body, or concentrations in the air or water of a community, are often useful surrogates, but as noted earlier in this report, they are also often unavailable.

The sensitivity of the exposed population is another consideration in the risk estimation process. Some individuals may be more sensitive than others to specific environmental insults because of nutritional deficiencies, genetic predisposition, and for children, small body size, developmental immaturity, and increased metabolic and respiratory rates (Calabrese, 1978, 1980).

With their rapid metabolic rate, children consume proportionately more food and inhale greater volumes of air than an adult for a given body weight. Thus, they would also consume or inhale proportionately more of any contaminants that are present (Babich and Davis, 1981). Human infants do not have mature hepatic detoxification systems until they reach 2 to 3 months of age (Pelkonen et al., 1973; Rane and Ackerman, 1972). Serum immunoglobulin does not attain adult levels until children are 10 to 12 years old (Calabrese, 1978). Studies in animals have also demonstrated a greater sensitivity among the young after exposure to chemicals by a variety of routes (Goldenthal, 1971). Children's lungs may also be especially sensitive to environmental pollutants. Tager et al. (1983) have observed measurable differences in lung function between children of smoking mothers and children whose mothers did not smoke.

Population risk estimation is based on all the preceding steps. First, the exposure of the study population must be known. Heterogeneity of the population with respect to level of exposure or sensitivity to the toxic material should also be considered in the calculations. Exposure, dose-response curves, distribution of sensitivity factors, and the size of the population are then used to estimate the number of people likely to suffer toxic effects from the substance of interest. If the material causes more than one type of toxic effect, each effect requires separate calculations.

Ideally, calculation of risk is an objective, scientific activity devoid of policy judgments. The latter are made separately when deciding the acceptable level of exposure. However, policy decisions can seldom be divorced completely from the process of risk assessment. The reason for this lies in the uncertainty of many of the scientific judgments required. For example, if one experimental species is more susceptible to the toxicity of a material than another and data on humans are unavailable, which species should be used for estimating human risk? Which mathematical model should be applied to the data? These and many other questions of judgment were discussed in the recent National Research Council (1983) report.

In the following sections, the committee has used epidemiological data, mostly from occupational settings, to develop a quantitative model of the relationship between fiber dose and carcinogenic response for a generalized "asbestos" exposure resulting in either lung cancer or mesothelioma. That dose-response relationship is then applied to a hypothetical, but reasonable, exposure level to show potential population risk levels in populations of arbitrary size. In the final section, the committee assesses risks for other types of fibers and, in some cases, for other diseases by qualitative comparisons with the base case of a generalized asbestos exposure.

QUANTITATIVE RISK ASSESSMENT

In the previous chapters, the committee extensively reviewed information on the health effects of asbestos and other asbestiform fibers. In preparing this section, it also reviewed several risk assessments for asbestos in the open literature and in government documents. On the basis of its evaluation of the quality and coverage of the information and the assessment techniques, the committee decided that a quantitative assessment of the risks for mesothelioma and lung cancer from nonoccupational exposures to asbestos would be meaningful. It also concluded that the information base was insufficient for useful quantitative assessments for other fiber types and diseases, but that in some cases a qualitative, comparative assessment was feasible and useful. These decisions do not mean that the asbestos assessment is without major uncertainties nor does it mean that the comparative assessments are of poor quality. In both cases, the objective is to

present information useful for evaluating the health risks of asbestiform fibers in nonoccupational settings.

First, an overview of mathematical models for carcinogenic risk assessment is presented to provide a context for the assessments for lung cancer and mesothelioma, which are of principal interest. Next, there is a review of several assessments for asbestos that were based on such models. Finally, these assessments and the committee's own analyses are applied to the information presented in earlier chapters to produce quantitative risk estimates for nonoccupational exposures to asbestos in ambient air.

Mathematical Model for Carcinogenic Risk Estimate

As explained earlier, it is not necessary to use data on asbestos exposure from animal experiments to estimate risks for humans, but it is necessary to extrapolate from the health effects observed at high occupational levels of exposure to much lower nonoccupational exposures. Occupational epidemiology makes it possible to describe the probability of dying from a particular type of cancer as a function of age at first exposure, level and duration of exposure, and current age. Mathematical extrapolation models based on the multistage theory of carcinogenesis make it possible to estimate the probability of dying from that type of cancer for different ages at first exposure, different (lower) exposure levels, and different (often longer) duration of exposure, also as a function of current age. By considering the cumulative probability throughout a lifetime, the "lifetime risk" of cancer mortality can be computed.

At any age, an individual faces some probability of reaching an end point that is related to cancer in the next year, for example, dying of lung cancer. Suppose that at a given age, a, the probability is given by $p(a,d)$, where d is the dose of the carcinogen--in this case, asbestos. When $d = 0$, $p(a,0)$ is the probability of the end point for unexposed people. If t is some age of interest, then the cumulative probability $P(t,d)$ of reaching the end point before that age is given by the sum of the annual probabilities up to that age:

$$P(t,d) = \text{the sum of } p(a,d) \text{ over all ages, a, } \leq t. \qquad (1)$$

Reaching the end point by time t is analogous to the "failure time" for a generalized system that is no longer effective after time t. General mathematical analysis can be used to show that the probability of failure as a function of time can be written as follows:

$$P(t,d) = 1 - e^{-I(t,d)}, \qquad (2)$$

where $I(t,d)$ represents the cumulative incidence function (or cumulative hazard function) of occurrence of the observable failure prior to time t.

Armitage and Doll (1961), Peto et al. (1982), Kalbfleisch and Prentice (1980), Hartley and Sielken (1977), Hartley et al. (1981), and Kalbfleisch et al. (1983) have applied this model to carcinogenesis. If the cumulative incidence I(t,d) is small, then equation (2) may be simplified to

$$P(t,d) \doteq I(t,d), \tag{3}$$

where $\doteq$ means approximately.

In carcinogenic risk assessment, attention is usually focussed on the cumulative incidence function I(t,d) rather than on the probability function P(t,d). The Armitage-Doll (1961) multistage theory of carcinogenesis suggests that I(t,d) can be written as a product of two terms--g(d), depending only on dose, and h(t), depending only on time. That is,

$$I(t,d) = g(d)\, h(t). \tag{4}$$

If there are k dose-dependent stages in the process of carcinogenesis and the rate of transformation from one stage to the next is assumed to be a linear function of dose, the function g(d) would be a polynomial of degree k in the dose. The function h(t) depends only on time. This model and its generalization and justification have been discussed by Crump et al. (1976), Hartley et al. (1981), and Kalbfleisch et al. (1983).

To determine the values of the constants in the polynomial g(d) and the functional form for h(t), the cumulative incidence function must be fitted to data--preferably to data based on observations in human populations. The multistage model described above has been fitted successfully to many sets of cancer data, including data on asbestos, and appears at present to be a generally adequate model for assessing cancer risk. Fitting equation (4) to data involves estimating the constants in the model for some suitably determined function h(t). This model has been applied to both mesothelioma and lung cancer data on asbestos-exposed workers. The form of h(t) and the values of the constants from those studies will be discussed in the next section. The function g(d)--and thus the cumulative excess incidence function I(t,d)--can be approximated as a linear function of dose in the low-dose range that equals 0 when d = 0. This relationship can be used for extrapolating from high to low doses and has the following form:

$$I(t,d) = cdh(t). \tag{5}$$

This form assumes that there is at least one dose-dependent stage of cancer development. The argument for a linear (with respect to dose) approximation for low-dose exposures has been justified on the basis that the exposure dose d is added to a background level (Hoel, 1980; Peto, 1978). This assumption may not always be justified in application

(see Cornfield et al., 1978 and Van Ryzin, 1981), but it should lead to an appropriate upper bound for the committee's risk assessments for asbestos. Furthermore, and more importantly, ruling out a linear dose term for asbestos exposure does not seem justified by the data now available (Nicholson, 1983; Peto, 1982; Schneiderman et al., 1981). Thus, the model adopted for risk assessment in the next three sections of this chapter is based on the cancer mortality incidence calculated by equation (5).

PUBLISHED RISK ASSESSMENTS

This section reviews some published risk assessments for lung cancer and mesothelioma. These assessments helped the committee select a functional form for h(t) for the two diseases and to establish the value of the constant c in equation (5).

Lung Cancer Risk from Nonoccupational Environmental Exposures

The following summary of risk assessments for lung cancer from asbestos exposures is based on data on exposure of worker populations. These data suggest that the function I(t,d) in equation (5) becomes

$$I(t,d) = c^{*}T_{0}dI_{0}(t), \qquad (6)$$

where T_0 is the duration of exposure to asbestos at dose d, $I_0(t)$ is the cumulative mortality incidence for lung cancer up to age t for those who have not been exposed to asbestos, and c* is a constant that depends on the cohort under study, but not on dose or age. As used in equation (6) and in the remainder of this section, d is the concentration of fibers in the workplace air, usually measured in fibers/cm^3. Although d is referred to as dose, some authors would call it dose rate and would refer to the product T_0d as (cumulative) dose. Equation (6), derived by Peto (1982), is consistent with his earlier studies of chrysotile workers (Peto, 1978). This equation is also supported by four studies reviewed by Nicholson (1983), who noted that the relative risk of lung cancer deaths for asbestos workers compared to a similar population was linearly related to the accumulated dose years, i.e., fibers/cm^3 x years, or (fibers/cm^3)yr.

In equation (6), the underlying incidence rate $I_0(t)$ is considerably different for smokers and nonsmokers of each sex. Therefore, the risks for each of these groups must be assessed separately. Another consequence of equation (6) is that the relative risk of lung cancer due to asbestos exposure does not depend on age at first exposure.

Thus, lifelong risk of lung cancer resulting from exposure to asbestos can be calculated quite simply by using equation (6). As an example, consider the following calculation given by Peto (1982).

Consider the effect of 10 years of exposure at 1 fiber/cm^3. If we assume that the relative risk for lung cancer among insulation workers increased approximately fourfold [Hammond et al. (1979) reported 4.2 for nonsmokers and 3.9 for smokers] and that this risk is based on a cumulative dose of 600 fibers/cm^3 (20 years at 30 fibers/cm^3), then 10 years of exposure to 1 fiber/cm^3 will increase the relative risk by 4.0 x 10/600 = 0.067. Since approximately 15% of lifelong smokers die of lung cancer, this mortality rate will increase to 0.15 x 1.067 x 100, or 16%. Thus, the difference (1%) is the excess due to asbestos as predicted by the equation. Since only 0.5% of nonsmokers die of lung cancer, this would become 0.533% (0.005 x 1.067 x 100) for an added risk of 0.033% due to asbestos exposure.

Mesothelioma Risk from Nonoccupational Environmental Exposures

The committee reviewed two estimations of mesothelioma risk, one by Peto and his colleagues (Peto, 1982; Peto et al., 1982) and the other by Nicholson (1983). These analyses and their consequences are summarized in this section.

Using the data of Selikoff et al. (1979) on mortality among 17,800 members of the International Association of Heat and Frost Insulators and Asbestos Workers, Peto et al. (1982) showed that the mortality rate from mesothelioma in these workers was dependent on the time since first exposure, but did not depend on the age at first exposure. From this finding, and the application of the multistage theory of carcinogenesis through equation (5), the cumulative incidence function becomes:

$$I(t,d) = cd(t - t_0)^k, \qquad (7)$$

where $t - t_0$ represents time since first exposure at age t_0. For any group of workers exposed at the same dose level d, the product cd = b is a constant depending on the type of asbestos exposure. Equation (7) suggests that the risk for mesothelioma is primarily dependent on the time since first exposure ($t - t_0$). This same phenomenon was noted by Schneiderman et al. (1981) and Nicholson (1983). Fitting equation (7) with b = cd to the data of Selikoff et al. (1979) for men up to age 80 by the method of maximum likelihood estimation resulted in an estimate of k = 3.2 with a standard error of $\pm$ 0.36 and b = 4.37 x 10^{-8}. Using this calculation, Peto et al. (1982) estimated the lifelong mesothelioma risk for this worker group to be 15%, 7%, and 3% for age at first exposures of 20, 30, and 40 years, respectively. These figures have been adjusted for other competing causes of death.

Using equation (7) with k = 3.2, Peto and colleagues determined that b x 10^8 ranges in value from 2.94 to 5.15 for four other sets of data (see Table 7-1). Using k = 3.5, Peto (1982) computed a lifetime mesothelioma rate of 1 in 100,000 children exposed from age 12 to age 18

TABLE 7-1. Mesothelioma Death Rates in Various Studies and Predictions of Risk[a]

Study Population and Reference	Relative Risk ($b \times 10^8$)	Corresponding Lifetime Risk (%)[b] by Age at First Exposure (yrs)		
		20	30	40
North American insulation workers (mixed exposure) Selikoff et al., 1979	4.37	15	7	3
Factory workers (mixed exposure) Newhouse and Berry, 1976	4.95	17	8	3
Chrysotile textile factory workers Peto, 1980b	2.94	10	5	2
Australian crocidolite miners Hobbs et al., 1980	5.15	17	8	3
U.S. amosite factory workers Seidman et al., 1979	4.91	17	8	3

[a]Adapted from Peto et al. (1982). The death rate at time $t - t_0$ since first exposure at age t_0 is proportional to b, obtained by fitting equation (7) with $k = 3.2$.

[b]The calculation of "lifetime risk," i.e., the percentage of similarly exposed men who would die of mesothelioma before age 80, is based on an actuarial calculation using 1977 U.S. rates for white males for all causes of death other than mesothelioma inflated by a factor of 1.26, the observed relative risk among insulation workers (Selikoff et al., 1979).

(i.e., 6 years of school age), assuming the fiber level was 0.003 fiber/cm^3 (1/1,000 of the exposure of the insulation workers).

A second risk assessment was done by Nicholson (1983), who criticized the Peto et al. (1982) analysis for fitting equation (7) to only those men who died of mesothelioma up to age 80. By including all insulation workers, he estimated k to be 5.0.

QUANTITATIVE RISK ASSESSMENT FOR NONOCCUPATIONAL ENVIRONMENTAL EXPOSURES

As a starting point for assessing the risk from nonoccupational environmental exposure to asbestiform fibers, the committee adopted equation (6) as representing the cumulative mortality up to age t, which is appropriate for lung cancer induced by a continuous exposure of T_0 years at dose level d in fibers/cm^3. This model implies that any given total dose before time t would have the same effect on the relative risk at time t, regardless of the time at which exposure started or its duration. The model thus ignores a minimum latency period, which might cause the model to overestimate effects, but also ignores the difference between exposures at earlier and later ages, which might cause the model to underestimate effects.

Equation (7) was assumed to be a reasonable representation of the cumulative mortality from mesothelioma up to age t for continuous exposure to asbestos at dose level d in fibers/cm^3 from age t_0 until age t. In this case, latency is implicitly included in the dependence on $(t-t_0)$, because k is greater than 1, but no minimum latency is assumed. These assumptions are supported by the work of Peto (1982), Peto et al. (1982), Nicholson (1983), and Schneiderman et al. (1981), who extensively reviewed the basis for these assumptions by examining the models and their consistency for several observed worker cohorts exposed to ambient concentrations of asbestos fibers. These authors have suggested that asbestos acts as a late-stage carcinogen in producing lung cancer but acts at earlier stages in the development of mesothelioma. Using these models, the committee developed lifetime estimates of risk for lung cancer and mesothelioma mortality from continuous nonoccupational exposures to 0.0004 fibers/cm^3 and for 0.002 fibers/cm^3.

For lung cancer, the committee assessed the risk for four exposure subgroups: male smokers, female smokers, male nonsmokers, and female nonsmokers. For mesothelioma, only one calculation was made, since equation (7) and the supporting data in the papers cited above suggest that mesothelioma mortality does not depend on sex or smoking history, but does depend strongly on age at first exposure.

Lifetime Risk Estimates for Lung Cancer and Mesothelioma

Table 7-2 summarizes lifetime risk estimates for lung cancer and mesothelioma for nonoccupational environmental exposures to 0.0004 fibers/cm^3 (a median level) and 0.002 fibers/cm^3 (a high level). It is assumed this exposure is continuous from birth through a lifetime of 73 years, an approximate average lifetime in the United States. Thus, in equations (6) and (7), t = 73 years and d = 0.0004 or 0.002. In equation (6), T_0 = 73 and in equation (7), t_0 = 0 to account for continuous exposure. Because equations (6) and (7) are linear in the dose unit d, one can immediately obtain from Table 7-2 lifetime risks at other continuous (from birth) environmental exposures by multiplying by the appropriate dose factor. For example, lifetime risk estimates at 0.02 fibers/cm^3 are 10 times higher than the estimates at 0.002 fibers/cm^3.

TABLE 7-2. Estimated Individual Lifetime Risks from a Continuous Exposure to Asbestos at 0.0004 Fibers/cm^3 (a Median Dose) or 0.002 Fibers/cm^3 (a High Dose)[a]

Disease	Exposure Group	Estimated Individual Lifetime Risk x 10^6 Median Exposure (0.0004 fibers/cm^3)	High Exposure (0.002 fibers/cm^3
Lung cancer[b]	Male smoker	64 (0 to 290)[c]	320 (0 to 1,500)
Lung cancer	Female smoker	23 (0 to 110)	120 (0 to 530)
Lung cancer	Male nonsmoker	6 (0 to 22)	29 (0 to 130)
Lung cancer	Female nonsmoker	3 (0 to 13)	15 (0 to 66)
Mesothelioma	All	9 (0 to 350)	46 (0 to 1,700)

[a]Lifetime assumed to be 73 years; exposure occurs from birth. Lung cancer risks are calculated with $c^* = 1.02$ or an excess risk of 2% per (fiber/cm^3)yr, estimated from nine studies with varied results. Mesothelioma risks are calculated with $c = 2.53 \times 10^{-8}$ and $k = 3.2$, estimated from five studies with varied results. See also explanations in text.

[b]Sex differences for lung cancer risk are due to differences in lung cancer background rates associated with smoking patterns, occupational exposures, and other factors.

[c]Range of estimates. The lower limit of 0 is always possible if linear extrapolation overestimates risk. See also text below.

The estimates in Table 7-2 were based on the following five considerations:

- Exposure levels. A mix of indoor and outdoor measured exposure levels was used to select the median value of 0.0004 fibers/cm^3 and the high value of 0.002 fibers/cm^3 as the reference levels.

- Use of the linear model. The models used by the committee all assume low-dose linearity and, as such, produce higher estimates of risk at low doses than would be obtained with other models. However, because the occupational data do not rule out low-dose linearity, the committee believes that these estimates do not unduly overstate the risks.

- Count-mass conversion. The conversion of ambient fiber mass measurements to an equivalent number of fibers was based on measurements

of mass and numbers of fibers in the workplace. The committee realized, however, that the number of fibers in ambient air would be much greater because these fibers tend to be smaller than those in the workplace (see Chapter 4). Depending on the toxicity of small fibers, the risks could be greater or less than those calculated in this chapter. If the presence of long fibers is necessary for a toxic response, risks would be lower.

- Model dependence. The results of the mesothelioma model depend very heavily on the value of k. This accounts for the large range of estimates for mesothelioma. It is assumed that this dependence on k among workers holds for the entire population throughout a lifetime. If the dependence is not as strong (i.e., a lower k value), the lower end of the range would apply. If this dependence is as strong (i.e., a higher k value), the upper bound may be more appropriate.

- Childhood exposure. The models used for extrapolation for both lung cancer and mesothelioma are based on the assumption that a unit dose of exposure (measured as fibers/cm^3 > 5 μm long) in early life is equivalent in its intrinsic carcinogenic potential to a unit dose in later life. If children are more biologically sensitive than the worker group, the risk per unit dose would be increased. Results from studies of exposure to other materials indicate that children are often more sensitive than adults to a given dose, even when expressed as dose/body weight.

The risk estimates and ranges shown in Table 7-2 are those the committee considers most reasonable. Because of the uncertain value of k and the sensitivity of equation (7) to its value, the range of estimates is much larger for mesothelioma than for lung cancer. Two conclusions can be drawn from the estimates in Table 7-2:

- For nonsmokers, the lifetime risk for mesothelioma from nonoccupational environmental exposure to asbestos is higher than for lung cancer. For smokers, however, the risks of lung cancer are substantially higher than for mesothelioma, because of the multiplicative interaction of smoking and asbestos exposures.

- Individual lifetime risk estimates for lung cancer from nonoccupational environmental exposures to 0.0004 fibers/cm^3 are much lower than the risks observed for smoking.

The basis for the calculations in Table 7-2 is discussed in detail in the following two subsections.

Calculation of the Lung Cancer Risk Estimates in Table 7-2. Calculating lifetime risk estimates from equation (6) involves the notion of relative risk up to time t, designated here as RR. From equation (6), the RR for lung cancer by age t can be shown as follows:

$$\frac{I(t,d)}{I_0(t)} \tag{8}$$

$$= \frac{\text{cumulative lung cancer mortality by age t at dose d}}{\text{baseline cumulative lung cancer mortality by age t}}$$

$$= c^*(T_0d),$$

where (T_0d) = total dose-years for the exposed group and c^* is a constant that depends on the cohort.

For a given study showing an increased relative risk for lung cancer,

$$c^* = (1 + P/100), \tag{9}$$

where P is the percentage increase in lung cancer risk per unit dose [% per (fibers/cm^3)yr]. Schneiderman et al. (1981) presented the values of P for nine different worker cohorts. The results are summarized in Table 7-3.

Values for P in Table 7-3 range from 0.06 (Study 8) to 9.1 (Study 1). The higher value establishes the upper end of the range given in Table 7-2. The zero value for the lower end of the range indicates that the low-dose linear approximation in equation (5) may overstate risk.

The median value for P in the studies shown in Table 7-3 is P = 1.1 (Study 7). This value, rounded upward to 2, was used in obtaining the estimates for lifetime lung cancer risk in Table 7-2. To calculate these estimates, it was necessary to know only the baseline absolute risks for the appropriate subpopulations. The baseline cumulative incidence rates of lung cancer for the four subgroups in Table 7-2 have been estimated by Schneiderman et al. (1981) as follows: male smokers = 0.11; female smokers = 0.04; male nonsmokers = 0.01; and female nonsmokers = 0.005.

Thus, using 2% as a value for P, the lifetime risk of lung cancer for a male smoker is

$$(0.11)(1 + P/100) = (0.11)(1 + 0.02) = 0.1122. \tag{10}$$

The increased lifetime risk attributable to asbestos exposure at 1 fiber/cm^3 for 1 year is 0.0022, i.e., 0.1122 - 0.1100. At the ambient exposure of 0.0004 fibers/cm^3 assumed in Table 7-2 and for a 73-year lifetime exposure, the increased lifetime risk of lung cancer is 6.42×10^{-5}, i.e., 0.0022 x 0.0004 x 73. Rounding to two significant figures gives the estimate in Table 7-2 for male smokers. The other calculations in that table were derived in a similar fashion.

When describing the use of the percentages given in Table 7-3, Schneiderman et al. (1981) commented that the low percentage increases in risk in Studies 3, 6, 8, and 9 probably resulted from several factors. In Study 3, for example, the subjects were retirees older than 65.

TABLE 7-3. Estimated Increase in Lung Cancer Risk per Unit of Exposure to Asbestos[a]

Study No.	Occupation of Worker Cohort	Asbestos Type	Percent Increase in Lung Cancer Risk per (fibers/cm^3)yr	Reference
1	Insulation manufacturing	Amosite	9.1	Seidman et al., 1979
2	Asbestos product manufacturing	Crocidolite, chrysotile, and amosite	1.3 males 8.4 females	Newhouse and Berry, 1979
3	Asbestos manufacturing	Amosite and chrysotile; some crocidolite	0.3	Henderson and Enterline, 1979
4	Asbestos product manufacturing	Chrysotile; some amosite and crocidolite	1.1	Nicholson et al., 1979
5	Textile production	Chrysotile	5.3	Dement et al., 1982
6	Textile production	Chrysotile	0.07 early employees[b] 0.8 later employees[b]	Peto, 1980
7	Insulation manufacturing	Chrysotile and amosite	1.7	Selikoff et al., 1979
8	Mining and milling	Chrysotile	0.06	McDonald and Liddell, 1979
9	Mining and milling	Chrysotile	0.15	Nicholson et al., 1979

[a]Adapted from Table 4 in Schneiderman et al., 1981.
[b]Early employees began work before or during 1950. Later employees began work after 1950.

Schneiderman et al. stated that the investigators may thus have missed asbestos-related deaths occurring at earlier ages. In Study 6, the disease rates for workers employed earlier were lower than those employed later who were followed for shorter periods. The discrepancy has diminished as more data have accumulated. The subjects in Studies 8 and 9 were mining and milling workers whose exposure patterns were quite different from environmental ambient air exposures. There is also some evidence that many lung cancer cases were missed in Studies 8 and 9 because of competing causes of death at earlier ages. Thus, Schneiderman et al. (1981) concluded that the range from 1.1 (Study 4) to 9.1 (Study 1) is the most representative of true values. The value of P = 2 used in the calculations in Table 7-2 falls near the bottom of this range, but is within a factor of 5 of the top of the range. If we use P = 5, which is the middle of the range, the lung cancer risk estimates in Table 7-2 would be multiplied by a factor of 2.5.

Calculation of Mesothelioma Risk Estimates. To calculate the lifetime risk with equation (7), the numbers c and k must be determined. Then the lifetime risk L at d = 0.0004 fibers/cm^3, assuming t = 73 and t_0 = 0 (continuous exposure from birth to age 73), is

$$L = c(0.0004)(73)^k. \qquad (11)$$

To apply this equation, c and k must be estimated from epidemiological studies of occupational exposures to asbestos. Each study must be stratified by duration of exposure $(t-t_0)$ to estimate these parameters. Most of the following analysis is similar to that of Peto et al. (1982).

First, let us consider the choice of k. As noted earlier, when Peto et al. (1982) fitted equation (7) to the data of Selikoff et al. (1979), they obtained the equation $I(t,d) = b(t - t_0)^{3.2}$, with b = 4.37 and k = 3.2 ± 0.36 (standard error). In equation (11), therefore, we initially use k = 3.2. Modifications using different values for k will give the range of estimates for d = 0.0004 fibers/cm^3 in Table 7-2. For d = 0.002 fibers/cm^3, we replace 0.0004 with 0.002 in equation (11). With k = 3.2, Peto et al. (1982) also fitted four other data sets to obtain four values of b in the equation $I(t,d) = b(t - t_0)^{3.2}$. The value of b is specific to each worker cohort and depends on three numbers: d (the average fiber/cm^3 exposure), ℓ (the average length of exposure), and $t - t_0$ (the average time since first exposure). These values are given in Table 7-4. In addition, Table 7-4 contains the estimates of c that are appropriate for equation (7), based on the corresponding estimate of b given by Peto et al. (1982). When exposure is not continuous from time of first exposure (t_0) to the age of observation (t) for these studies, the relationship between b and c changes from c = b/d to

$$\frac{4.56\ b/d}{1 - [1 - \ell/(t-t_0)]^{3.2}}. \qquad (12)$$

TABLE 7-4. Estimated Constants for Equations (11) and (12) for Five Studies

Study	$b \times 10^8$	d^a	ℓ^a	$t - t_0{}^a$	$c \times 10^8$
Selikoff et al., 1979	4.37	15	15	24	1.39
Newhouse and Berry, 1976	4.95	12.5	6	31.5	3.67
Peto, 1980a,b	2.94	16.5	14	22.5	0.85
Hobbs et al., 1980	5.15	NA[b]	NA	NA	NA
Seidman et al., 1979	4.91	35	1	35	7.22

[a]Estimated from data given in Tables 4 and 10 of Schneiderman et al. (1981), using estimated median values. The product $d\ell$ from columns 3 and 4 above is the estimated cumulative exposure in (fiber/cm^3)yr of their Table 10.
[b]NA = not available.

The factor 4.56 adjusts from occupational exposures at about 1,920 hours per year to environmental exposures at 8,760 hours per year. Appendix G provides the mathematical basis for equation (12). Table 7-4 gives the values of the constants for each study in which Peto et al. (1982) estimated b.

To obtain the estimates for mesothelioma at the dose of 0.0004 fibers/cm^3 in Table 7-2, equation (11) is used with values for c from Table 7-4 and k = 3.2. In Table 7-2 the lifetime risk for mesothelioma at d = 0.0004 fibers/cm^3 is 9 per million. This is calculated from equation (11) with $c = 2.53 \times 10^{-8}$, the median of the range of the c values in Table 7-4, and k = 3.2. The highest value of the range in Table 7-2 at d = 0.0004 uses equation (11) with $c = 7.22 \times 10^{-8}$, the upper value of c in Table 7-4, and k = 3.8, obtained from $3.2 + 1.65 \times 0.36$. The selection of 3.8 as the value for k is based on an approximate upper 95% confidence limit for the estimate of k. The lower limit is taken as 0, which is always a possible lower limit, especially if the low-dose linear assumption in equation (5) overestimates the individual lifetime risk.

Peto (1982) recommended using a k value of 3.5 for risk assessment purposes. As an example, he estimated that the risk of mesothelioma for children exposed for a 6-year period (ages 12 to 18) at 0.003 fibers/cm^3 would be one in 100,000. Nicholson reviewed additional data, including data on older workers up to age 80, and determined that a k value would be 5. Schneiderman et al. (1981) used k = 3.0. For this study, the committee used a value of 3.2. Although neither existing data nor biological theory can provide very much guidance on the value of k, its value is very important in projecting the lifetime risks of mesothelioma from asbestos exposures. Table 7-5 shows how lifetime risk varies from the value of 9 per million for several values of k. Also shown are risk estimates for other values of c. The reader can easily calculate the results for other values of exposure.

Other authors have also estimated the risks of mesotheliomas. Enterline (1983) derived a lifetime risk of 100 per million by using current reported rates of mesothelioma, an assumption about the relative contributions of nonoccupational and occupational asbestos exposures, and other factors. This estimate clearly relates to past exposure to varying levels of asbestos. Schneiderman et al. (1981) estimated lifetime risks for mesothelioma to be between 800 and 5,000 per million for a cumulative exposure of 1 (fiber/cm^3)yr. These estimates correspond to lifetime risks of 23 to 150 per million for 0.0004 fibers/cm^3 for 73 years. As mentioned above, these investigators effectively assumed k = 3, but their equivalent c was higher than that used for the corresponding estimates in Tables 7-2 and 7-5.

TABLE 7-5. Sensitivity of Estimates for Lifetime Risks[a] of Mesothelioma to Values of k and c

	Lifetime Risk Estimates x 10^6, Using k Values from Various Studies						
	This Study (low)	Schneiderman et al., 1981	This Study (middle)	Peto et al., 1982 (middle)	This Study (high)	Peto et al., 1982 (high)	Nicholson, 1983
c \ k	2.6	3.0	3.2	3.5	3.8	4.0	5.0
0.85 x 10^{-8}	0.2	1.3	3	11	41	97	7,000
2.53 x 10^{-8}	0.7	4	9	34	120	290	21,000
7.22 x 10^{-8}	2	11	26	96	350	820	60,000

[a]All estimates are derived from equation (11), $L = c(0.0004)(73)^k$, where L = lifetime risk at a continuous exposure to 0.0004 fibers/cm^3 for a lifetime of 73 years.

Note: This table demonstrates that the risk estimates are extremely sensitive to changes in the value of k.

The Use of 0.0004 Fibers/cm^3 and 0.002 Fibers/cm^3 as the Median and High Nonoccupational Environmental Exposure Levels. The lifetime risk estimates given in Table 7-2 are based on an assumed continuous environmental ambient exposure equivalent to either 0.0004 or 0.002 fibers longer than 5 μm per cm^3 of air breathed. The committee believes that 0.0004 fibers/cm^3 is a reasonable assumption for a median population exposure level and that 0.002 fibers/cm^3 is a reasonable high exposure level (considering only exposures from breathing ambient air continuously). These assumptions are discussed below. The effects of noncontinuous high exposures are discussed later in this chapter.

Table 7-6 summarizes some environmental asbestos sampling data provided by Nicholson (1983). To convert from mass measurements (ng/m^3) of airborne exposures to fiber counts (fibers/cm^3), the committee used the conversion factor of 30 μg/m^3 for 1 fiber/cm^3. (See Chapter 4 of this report, Schneiderman et al., 1981, and Consumer Product Safety Commission, 1983 for further explanation.)

The dose-response data used in the committee's risk estimate were taken from measurements of exposures in the workplace, where the fibers tend to be longer than those in ambient environments not close to major sources of asbestos. As discussed in Chapter 4, there would typically be approximately 2,000 fibers per nanogram in workplace air; in remote areas, however, there would be approximately 70,000 ambient fibers in a nanogram. To convert mass in the workplace to ambient air, the committee used the number of fibers longer than 5 μm that would be found in the workplace when the workplace mass equaled the remote ambient fiber mass. The dose estimate in numbers of fibers would be approximately 35 times greater (70,000/2,000) if the actual sizes of fibers in ambient air were considered. If we assume that all fibers are equally potent, then the risk estimates would be correspondingly higher. On the other hand, fiber size apparently affects fiber potency, but the appropriate adjustment factors for fiber size are not known.

Table 7-6 indicates that median concentrations in outdoor air have ranged from 0.00002 to 0.00075 fibers/cm^3 in several studies (sample sets 1 to 8); their median is approximately 0.00007 fibers/cm^3. The observed median inside rooms without asbestos is 0.00054 (sample set 9). In rooms with asbestos surfaces, the median is 0.0006 fibers/cm^3 (range of medians for sample sets 10 through 14, 0.00006 to 0.00405 fibers/cm^3). If these three medians are weighted by assuming persons spend approximately one-fourth of their time outdoors, five-eighths of their time indoors in uncontaminated rooms, and one-eighth of their time in asbestos-contaminated rooms, a reasonable estimate for a median population exposure is 0.0004 fibers/cm^3.

The committee also used 0.002 fibers/cm^3 for a high value of continuous exposure in its calculations for Table 7-2. This value was obtained by using the median of the 90th percentiles in Table 7-6 for each exposure subcategory. For outdoor air, the median is 0.0003

TABLE 7-6. Summary of Environmental Asbestos Exposure Samples[a]

Sample Sets	No. of Samples	Measured Concentration (ng/m^3) Median	Measured Concentration (ng/m^3) 90th Percentile	Equivalent Concentration (fibers/cm^3)[b] Median	Equivalent Concentration (fibers/cm^3)[b] 90th Percentile	Reference
1. Paris air	161	0.7	3.2	0.00002	0.00011	Sebastien et al., 1980
2. Paris (outdoor control)	19	0.7	5.2	0.00002	0.00017	Sebastien et al., 1980
3. Outdoor control samples, for U.S. schools	31	0.9	9.8	0.00003	0.00033	Constant et al., 1982
4. Air of 48 U.S. cities	187	1.6	6.8	0.00005	0.00023	Nicholson, 1971
5. Air of U.S. cities	127	2.3	7.8	0.00008	0.00026	U.S. Environmental Protection Agency, 1974
6. Air of five U.S. cities (outdoor control sample)	34	6.7	31.9	0.00022	0.00106	Nicholson et al., 1975, 1976
7. New York City air	22	13.7	42.9	0.00046	0.00143	Nicholson et al., 1971
8. Air 0.5 mile (0.8 km) from asbestos spraying	17	22.5	82.6	0.00075	0.00275	Nicholson et al., 1971
9. Air in U.S. schoolrooms without asbestos	31	16.3	72.7	0.00054	0.00242	Constant et al., 1982
10. Air in Paris buildings with asbestos surfaces	135	1.8	32.2	0.00006	0.00107	Sebastien et al., 1980
11. Air in U.S. buildings with cementitious asbestos	28	7.9	19.1	0.00026	0.00064	Nicholson et al., 1975, 1976
12. Air in U.S. buildings with friable asbestos	54	19.2	96.2	0.00064	0.00321	Nicholson et al., 1975, 1976
13. Air in U.S. schoolrooms with asbestos surfaces	54	62.5	550	0.00208	0.01833	Constant et al., 1982
14. Air in U.S. schools with damaged asbestos surfacing materials	27	121.5	465	0.00405	0.01550	Nicholson et al., 1978

[a]Adapted from Nicholson, 1983.
[b]Based on conversion factor of 30 μg/m^3 = 1 fiber/cm^3.

fibers/cm^3; for indoor uncontaminated air, it is 0.002 fibers/cm^3; and for indoor asbestos-contaminated air, it is 0.003 fibers/cm^3. The same distribution of occupancy over time was used to arrive at the 0.002 fibers/cm^3 figure for a high exposure level.

Risk Assessments for Special Subpopulations

Table 7-2 shows lifetime risk estimates for people who are exposed throughout their lives to levels of either 0.0004 or 0.002 fibers/cm^3 in ambient air. The predominant risk is from mesothelioma, but lung cancers also contribute to the risk, especially for male smokers. For exposure patterns that are different from those assumed, lifetime risks could be higher or lower. The following are three illustrations of how lifetime risks could be derived for such special populations.

Children Exposed in Asbestos-Contaminated Schools. The committee estimated the risk for persons exposed from birth to age 73 years to environmental levels of 0.002 fibers/cm^3 (as assumed in Table 7-2) plus an additional risk from a 10-year exposure (from ages 6 to 16) in an asbestos-contaminated schoolroom for 6 hours daily, 200 days per year, to 0.02 fibers/cm^3 (550 ng/m^3, the 90th percentile in Table 7-6). The equivalent continuous daily 10-year exposure is approximately 0.003 fibers/cm^3, i.e., 0.02 x (200 x 6)/(365 x 24). Using equation (6), the lifetime risk of lung cancer for a male who eventually becomes a smoker is 0.003 x 10 x 0.0022, or 66 in a million. This risk represents an approximately 20% addition to his ambient lifetime risk of 320 in a million (0.002 x 73 x 0.0022), for a total of about 390 in a million. For such an individual, the schoolroom exposure adds relatively more to the risk of mesothelioma, as shown below. Using equations (G4) and (G5) in Appendix G for the lifetime mesothelioma risk, L, at t = 73 for an exposure of ℓ = 10 years starting at age t_0 = 6 at the dose level d, this risk can be calculated from the formula:

$$L = cd\{1-[1-\ell/(t-t_0)]^k\}(t-t_0)^k,$$

with d = 0.003, ℓ = 10, $t - t_0 = 73 - 6 = 67$, and k = 3.2. This lifetime mesothelioma risk becomes

$$L = c(0.003)\{1-[1-(10/67)]^{3.2}\}(67)^{3.2} = 845c.$$

If c is the median value of Table 7-4 (i.e., $c = 2.53 \times 10^{-8}$), the estimated lifetime mesothelioma risk, L, from the 10-year exposure is 21×10^{-6}.

This risk is then added to the background risk of 46×10^{-6} in Table 7-2, giving a lifetime mesothelioma risk for this subpopulation of 67×10^{-6}. If a million people had received such a pattern of exposures, about 67 might be expected to die of mesothelioma. In this example, the contribution to total risk from the schoolrooms is less than that of the lifetime exposure to the lower concentrations of asbestos estimated for the ambient air. However, if the value for k in Equation (7) were higher than 3.2, the significance of the schoolroom exposures

would increase because of the stronger dependence on time since first exposure. For example, if k = 3.8, the highest value used in Table 7-2, the lifetime mesothelioma risk would be 910 x 10^{-6}. If k were less than 3.2, the corresponding lifetime risk for mesothelioma would be less than 67 x 10^{-6}. These calculations show that childhood exposures to asbestiform fibers might contribute noticeable lifetime mesothelioma risks to those so exposed.

A Female Nonsmoker in a Relatively Asbestos-Free Environment. An example of a person in a low-risk group is a female nonsmoker exposed to an average level of 0.0001 fibers/cm^3. This exposure level would not be too unlikely for a person exposed primarily to rural indoor and outdoor air, since 0.00002 fibers/cm^3 is the lowest median value for all the outdoor city readings in Table 7-6. Then, the calculations in Table 7-2 would lead to a mesothelioma lifetime risk of 2.25 x 10^{-6} (9 x 10^{-6} divided by 4) plus a lung cancer lifetime risk of 0.73 x 10^{-6}. The lifetime individual risk for such a person would be 3 x 10^{-6} for both types of cancer.

A Male Smoker Living in an Area Contaminated with High Levels of Asbestos Who is Also Exposed to High Indoor Concentrations. As an example of a high-risk person, consider an urban male smoker exposed to 0.003 fibers/cm^3 for one-half the time and 0.018 fibers/cm^3 for the other half. This pattern is based on the assumption that the subject spends one-half of his time in indoor environments with a high asbestos concentration (see sample sets 13 and 14 of Table 7-6) and one-half either in highly contaminated outdoor environments (see sample sets 7 and 8 of Table 7-6) or in indoor environments at the high end of the distribution for rooms that are normally not contaminated with asbestos (see sample set 9 of Table 7-6). Thus, his continuous average exposure would be approximately 0.01 fibers/cm^3, i.e., 0.5(0.003) + 0.5(0.018). Therefore, multiplying the second column of Table 7-2 by a factor of 5 (0.01 = 5 x 0.002) would give the individual lifetime risks for such a person as 1.8 x 10^{-3} for the two forms of cancer taken together (230 x 10^{-6} for mesothelioma and 1,600 x 10^{-6} for lung cancer). This lifetime risk is the additional incurred risk attributable to the nonoccupational environmental exposure to asbestos and does not include the risk incurred by the smoking itself. The portion of the additional risk attributable to lung cancer is considerably higher than it would be for a nonsmoker experiencing identical asbestos exposures.

COMPARATIVE RISK ASSESSMENT

Methods

The goal of comparative risk assessments is to determine whether the fiber exposure in question presents risks--in terms of total number and severity of effects per year in the United States--that are about the same, considerably more, or considerably less than those assessed

quantitatively above. The quantitative assessments made in the earlier part of this chapter were based on exposure to a generalized "asbestos" fiber. Because future exposures to asbestos in the United States will be dominated by chrysotile, risks of lung cancer and mesothelioma from chrysotile inhalation are assumed to be approximately the same as those attributed in the quantitative assessment to "asbestos." However, if at equal doses chrysotile is less hazardous than the other kinds of asbestos, the assumption of equal potency may lead to overstated risk estimates.

These comparative risks are population risks, which combine information about the inherent risks that a given exposure to fibers could pose to an individual and information about the current and projected distribution of exposures over the U.S. population. Unlike the quantitative risk estimates for particular assumed exposure levels, the population risk estimates can easily change along with changing patterns of production and use. Even at a known population risk level, some individuals will receive higher than average exposures and stand at correspondingly greater individual risk, whereas the majority of the population will usually have lower risks.

General Methodological Considerations

The comparative risk assessments in this chapter are based on several factors, such as:

- fiber type
  - asbestos
  - other fibers with some similar properties
- type of effect[1]
  - lung cancer
  - mesothelioma
- route of exposure
  - inhalation
  - ingestion
- source of exposure
- population at risk
  - smokers
  - other special groups (such as schoolchildren)

[1]The committee did not assess fibrosis or nonmalignant pleural disease because functional impairment resulting from such effects would occur much less often than would the cancers at nonoccupational levels of exposures.

Taking the first three of these factors as examples, risk assessment can be visualized as a three-dimensional matrix. As shown in Figure 7-1, the best understood combinations (inhaled chrysotile and crocidolite asbestos for lung cancer and mesothelioma) are in the upper right "cells" of the matrix, and the less understood combinations are successively further from that position to emphasize their "distance" from the state of knowledge necessary for quantitative risk assessment. Additional cells could be added for other combinations.

The following combinations of fiber type, effect, and route of exposure were considered for comparative risk assessments:

chrysotile/gastrointestinal cancer/ingestion
chrysotile/mesothelioma/ingestion
crocidolite/lung cancer/inhalation
crocidolite/mesothelioma/inhalation
other asbestos/all cancers/both routes
fibrous glass/lung cancer/inhalation
fibrous glass/mesothelioma/inhalation
attapulgite/lung cancer/inhalation
attapulgite/mesothelioma/inhalation
mineral wool/lung cancer/inhalation
mineral wool/mesothelioma/inhalation
ceramic fiber/lung cancer/inhalation
ceramic fiber/mesothelioma/inhalation
carbon fiber/lung cancer/inhalation
carbon fiber/mesothelioma/inhalation

The committee's results are expressed in comparison with the chrysotile/lung cancer/inhalation cell, hereafter called the prime cell. Its designation as the prime cell does not imply that it is the cell corresponding to greatest population risk. According to the calculations in the preceding section, if environmental exposures to asbestos in early life are frequent, mesothelioma may prove to be the dominant effect.

Both the comparative scores and the evaluation of the uncertainty in them were made qualitatively rather than quantitatively; the entries are symbols (+, 0, -, a, b, c) rather than numeric. Appendix H describes how the committee went about assigning, combining, and assessing the symbolic codes.

A score sheet for recording judgments about comparative risks is shown in Figure 7-2. Completed sheets for scored cells are included in Appendix H. These sheets are supplied to allow the reader to evaluate the individual judgments or the committee's subjective combination of them.

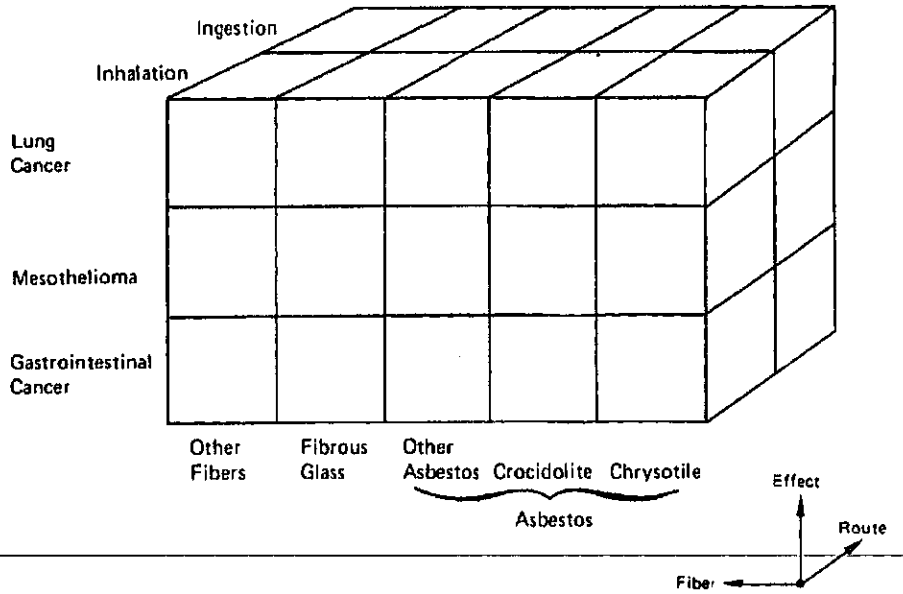

FIGURE 7-1. Three-dimensional matrix for conceptualizing the risk assessment problem.

COMPARATIVE RISK ASSESSMENT SCORESHEET

Cell Scored _____ / _____ / _____
Fiber Effect Route

Scores Comparative with Cell _____ / _____ / _____
Fiber Effect Route

Exposure Score	Score	Biodisposition		Effects	Score
Production	____	Fiber Size	____	Human Studies	____
Use Pattern	____	Morphology	____	Animal Studies	____
Geography	____	Chemistry	____	In-Vitro Studies	____
Population	____	Penetration	____	Synergism	____
Trends	____	Stability	____	Other	____

Overall risk compared with cell above _____
Overall risk compared with prime cell _____
Quality of comparative risk assessment _____

Remarks:

FIGURE 7-2. Score sheet for recording judgments about comparative risks.

Scoring Considerations

Production. If all other factors were equivalent, a greater production volume (or U.S. consumption level, if that is significantly different) would result in a greater level of exposure and a correspondingly greater population risk. If natural occurrence is important, it can be used here as another surrogate for exposure.

Use Pattern. Several concepts are embodied here. All have to do with the degree to which production, consumption, or natural occurrence will lead to actual human exposures. If the fibers are used only in products where they are tightly bound into a matrix, relatively little exposure will occur at least until final disposal, whereas loose fiber use in consumer applications would lead to relatively heavy and immediate exposures. Products such as talcum powder, which are intended for direct human use, will lead to higher exposures per unit production than those that are not.

Geography. This score applies to the spatial distribution of sources including natural deposits, mills or production facilities, fiber product manufacturing sites, use sites, and disposal sites. Concentrated sources tend to imply higher exposures of fewer people. This classification can also be used as a basis for evaluating such factors as the likelihood of fibers reaching drinking water.

Population. The size of the population at risk determines the extent of the hazard for a given level of individual risk. A type of fiber that yields exposures to many people, such as a constituent of a common consumer product, has more potential for producing adverse health effects than one that affects only a few people, such as a naturally occurring but noncommercial fiber that is present only in selected, sparsely populated regions.

Trends. Exposure is a dynamic process that changes with changes in total production volume, production processes, use patterns, population distribution and habits, and many other factors that do not remain static. Thus, the risk that would apply to a steady state of exposure at current levels can be misleading both for currently observed effects or for future occurrence of effects. The sharp downtrend in asbestos exposures tends to ameliorate the population risks that might otherwise be assessed, whereas new fiber types may present enormously higher exposures in the future than they do at present.

Fiber Size. Two counteracting influences are at work with fiber size. The clearest is their respirability, which declines markedly as fiber diameter increases, becoming essentially zero above 3 or 4 μm. It is likely that length also eventually affects respirability and, especially, transport potential within the body. On the other hand, short fibers are probably more easily removed from the body by phagocytes; thinner ones may be more easily dissolved, coated, or gelled

by body fluids; and small fibers in general may not act biologically the same as large fibers, which can disturb many cells at once. Furthermore, small fibers may be more likely to be exhaled with the tidal volume and, thus, not retained in the lung. The overall significance of fiber size may therefore be represented as a potency that is greatest for fibers around 0.2 μm diameter and 20 μm in length (Pott, 1978).

Morphology. Whatever the response to fiber size, it seems likely that long, thin fibers that have strength, durability, flexibility, and a high aspect ratio are more likely to cause adverse health effects than are fibers without these characteristics. The curliness of chrysotile fiber bundles may increase their effective aerodynamic diameter, thus decreasing their respirability below that expected on the basis of fiber diameter alone.

Chemistry. Although little is known about the influence of fiber chemistry on potential for health effects, it seems possible that the chemical properties of fibers play some role, especially with respect to surface chemistry. Another feature of surface chemistry, i.e., the ability to adsorb carcinogenic substances, is included under "synergism."

Penetration. The ability of a fiber to penetrate to the site where effects are developed, for example, to the pleura or peritoneum in the development of mesothelioma, is clearly important to its potential for causing disease. This category includes all fiber properties that facilitate such penetration. It is closely related to fiber size, morphology, and stability.

Stability. Some experimental evidence suggests that the longer a fiber remains in a tissue, the greater is its opportunity for inducing its biological effects, for example, stimulating cell hyperplasia when a transformed cell is present. In this case, the important factor is not the resistance to translocation but the resistance to chemical or physical degradation such as dissolution or gelling.

Human Studies. This category includes both clinical and epidemiological observations in human populations.

Animal Studies. The demonstration of significant biological effects in a well-designed animal experiment is considered evidence that the test substance has a potential for causing similar effects in humans.

In Vitro Studies. Although the meaningfulness of short-term, in vitro experiments with respect to the effects of fibers is questionable, it is known that asbestos and some other fibers demonstrate some cellular-level effects such as hemolysis. The ability to cause such effects is considered a weak, but not entirely worthless, argument for health effects potential.

Synergism. Information on synergistic effects would markedly affect assessment of comparative risk. The only such information available involves asbestos and cigarette smoking.

Other. This catchall category could be applied to any influence on overall risk, including exposure, biodisposition, and effects. For example, if a particular fiber is found to be more likely than the others to reach young children and if the effect in question is most prevalent in children or if it increases in incidence with time after first exposure as with mesothelioma, then the comparative risk estimate would be increased.

Discussion of Comparative Risks

Table 7-7 summarizes from a different perspective the information in Appendix H.

No cell of the fiber/effect/route matrix approaches the population risk levels associated with the prime cell (chrysotile/lung cancer/inhalation). As noted in the quantitative assessment, the mesothelioma risk from lifetime exposure to asbestos is potentially much greater than the lung cancer risk. Although some researchers question whether chrysotile is as potent as other asbestos varieties in causing mesothelioma, the committee has assumed that even exposure only to chrysotile continously since birth would cause more mesothelioma than lung cancer. Chrysotile has been extensively used in the past and thus also provides a source of in-place exposure. Of the other combinations, the committee believes the ones most worth watching in the near term are fibrous glass and attapulgite for lung cancer by inhalation. The risks for effects of crocidolite and other asbestos varieties are reasonably well understood, and measures taken to reduce occupational exposures in the future may also keep the nonoccupational exposures to a mininum. However, general population exposures to crocidolite already in place could be substantial, especially in connection with its disposal.

The other cells seem to entail significantly less population risk (more than 10 times less) than the prime cell. In several cases, this judgment is based principally on current exposure or biodisposition rather than on definitive evidence that the fibers have low intrinsic health effects potential. For example, both ceramic and carbon fibers can be found in respirable size ranges and may well have biological properties similar to those of asbestos. However, they are produced in low volumes and are used in limited, generally contained applications. Population risks could become substantial if these facts changed. Most fibrous glass and mineral wool is produced in nonrespirable sizes, and some evidence from epidemiological and animal studies suggests that their biological toxicity is low. Thus, risk levels for these substances are rated low despite the substantial potential for exposure.

TABLE 7-7. Summary of Comparative Risk Assessment

Factor	Compared with Chrysotile/Lung Cancer/Inhalation, Data on the Factor Suggest that Population Risk Should be			
	Higher	Similar	Lower	Much Lower
Production	Fibrous glass Attapulgite		Mineral wool	Crocidolite Other asbestos Carbon fiber Ceramic fiber
Use pattern	Fibrous glass Attapulgite	Other asbestos	Crocidolite Carbon fiber Mineral wool Chrysotile/ingestion	Ceramic fiber
Geography	Fibrous glass	Other asbestos Mineral wool Carbon fiber	Crocidolite Attapulgite Ceramic fiber Chrysotile/ingestion	
Population	Fibrous glass Attapulgite	Crocidolite Other asbestos Mineral wool	Carbon fiber Ceramic fiber	
Trends	Fibrous glass Attapulgite Mineral wool Carbon fiber Ceramic fiber	Other asbestos	Crocidolite	
Fiber size		Crocidolite Other asbestos Carbon fiber Ceramic fiber	Mineral wool	Fibrous glass Attapulgite
Morphology	Crocidolite	All others		
Chemistry	No clear effect of chemistry evident			
Penetration	Crocidolite Other asbestos Attapulgite	Carbon fiber Ceramic fiber	Mineral wool Chrysotile/ingestion	Fibrous glass
Stability	Crocidolite Other asbestos	All others	Fibrous glass	

(continued on next page)

TABLE 7-7 (cont.)

Factor	Compared with Chrysotile/Lung Cancer/Inhalation, Data on the Factor Suggest that Population Risk Should be			
	Higher	Similar	Lower	Much Lower
Epidemiological studies	Crocidolite/ mesothelioma	Crocidolite/ lung cancer Mineral wool	Fibrous glass Ceramic fiber Mineral wool	
Animal studies		Crocidolite Other asbestos	All others	
In vitro studies[a]	--	--	--	--
Synergism		All others	Fibrous glass	
Other[b]	--	--	--	--
Overall population risk			Chrysotile/ mesothelioma/ ingestion Crocidolite Attapulgite/ lung cancer Fibrous glass	Carbon fiber Ceramic fiber Attapulgite/ mesothelioma Other asbestos/ other cancer

[a]Quantitative differences in activity not apparent.
[b]No other factor was sufficiently striking for inclusion.

For any combination of fiber type, effect, and route of exposure not assessed, even for comparative risk, the committee believes either that risks are at most of marginal significance or that there is insufficient information on which to base such a comparison. Most of the combinations fall into the former category. Carcinogenic effects other than lung cancer or mesothelioma constitute examples of the insufficient information category for several fibers.

SUMMARY AND RECOMMENDATIONS

The committee has made quantitative risk assessments for nonoccupational exposures to asbestos and qualitative (or comparative) risk assessments for a variety of asbestiform fibers. Lung cancer and mesothelioma from inhaled materials received the greatest consideration.

For the quantitative risk assessment, a linear model for low dose extrapolation was used. When quantifying risk from nonoccupational exposures, uncertainties are introduced not only by the selection of mathematical models but also because the characteristics of fibrous materials in the ambient environment differ from those in the workplace. By converting mass concentrations measured in the environment to equivalent numbers of fibers in the workplace, the committee assumed a median population exposure of 0.0004 fibers/cm^3 air throughout a 73-year lifetime. Based on this and various other assumptions, the individual lifetime risk for lung cancer was estimated to be between 3 in a million for female nonsmokers and 64 in a million for male smokers, and for mesothelioma it was approximately nine in a million, regardless of smoking habits or sex. However, other assumptions could decrease the risks essentially to zero, or could increase them.

The finding that the risk for mesothelioma is greater than that for lung cancer among nonsmokers is due to the strong dependence of mesothelioma risk on time since first exposure. Thus, a given exposure in childhood markedly increases the lifetime risk of mesothelioma compared with an equivalent dose later. It should be remembered that these risk estimates were based on data obtained from worker cohorts.

Smokers runs a substantially higher risk of malignant disease from asbestos than do nonsmokers; for smokers, lung cancer is a greater risk than mesothelioma.

Studies should be conducted to learn more precisely the dependence of mesothelioma and lung cancer mortality on time since first exposure and on the characteristics of the exposure. Such efforts should include studies in animal models and follow-up studies of occupationally exposed cohorts.

For the comparative risk assessment, population risks (as opposed to individual risks) were considered. The risks were based on three major factors: exposure levels, biodisposition, and evidence of adverse health effects. The potential for exposure was a dominant factor. Thus, risk estimates for substances of equal biological potency may be widely divergent if the populations exposed to them differ greatly. Two points follow from this. First, some individuals may be exposed to high levels of a fiber for which the overall population exposure is low. Second, the overall population risk would change if use patterns change.

Current population risk from exposures to the various substances considered, including fibrous glass, attapulgite, and carbon fibers, appears to be much less than for the risk from asbestos, especially chrysotile. However, further information is needed to evaluate the possible adverse effects of exposures to fine fibrous glass and attapulgite.

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A. No, sir, I did not. I thought that the panel of stains that he prepared was adequate.
There were a few remaining unstained sections, but I did not see it necessary to have any other stains done.
Q. All right. Was there a discrepancy in the Calretinin stain done from the original hospital as to the one done here?
A. The original hospital read it as positive. I read it in my report as negative and Dr. Legier in his report also read it as negative. So, yes, sir, that would be a discrepancy.
Q. Does that in any way effect your diagnosis in the case?
A. Not in this particular case. I felt that given all the other information that I have about this case, this patient that it still was a sarcomatoid malignant mesothelioma.
Q. Today, do you feel that there is any differential diagnosis with that?
A. Well, not really. I believe that this is a sarcomatoid malignant mesothelioma.
Q. And you attribute it to what?
A. To the presentation of the case, to the distribution of the tumor, to the progression of the

disease, to the general histologic opinions -- to the general histologic appearance on the H & E sections and to the finding of many --
(There was a pause in the proceedings.)
THE WITNESS: I've turned the volume down. What do you guys want me to do?
MR. SWEENEY: Hey, can you all hear him on the phone?
Hello?
We may need to call back in.
Anybody there?
MR. ORNDORFF: Sounds like everybody hung up.
UNIDENTIFIED SPEAKER: I think it's clear now.
MR. SWEENEY: There are people on the phone?
UNIDENTIFIED SPEAKER: Actually, I stayed on throughout. I hear people hanging out, but I don't know what just happened.
MR. ORNDORFF: It sounded to me like there was somebody on a telephone.
MR. SWEENEY: Well, whoever you two guys, that's enough for us. We'll keep moving.
UNIDENTIFIED SPEAKER: I was on a cell

phone and causing that.
MR. SWEENEY: We're going to keep going since there's two of you on.
MR. WITTE: They will call back in.
BY MR. WELCH:
Q. We were discussing your attribution?
A. Yes, sir. And I had mentioned that the presentation of the disease, the natural history of the disease, the gross distribution of the disease in the patient, the general appearance on the H & E slides, the presence of keratin positivity, many cells two-plus positive in my report, the negative stains for other things like S100 and CD34 convinced me that this was, in fact, a sarcomatoid malignant mesothelioma.
Q. Did you prepare controls for -- or did someone here at Riverside prepare controls for the stains that were done here?
A. Yes, sir.
Q. And did they test appropriately?
A. Yes, sir, they did.
Q. You did not find any histological proof of an asbestos burden in Mr. Sartin's lungs, did you?
A. Well, I did not have any of his lungs to examine for that, so I could not evaluate that.

That's not a negative result; it's just that I didn't have anything to evaluate for that.
Q. And although you did have some pleural tissue, you did not find pleural plaque?
A. That's correct.
Q. In your report you have included a section which was absent from Dr. Legier's report concerning the Helsinki criteria for the attribution of mesothelioma to asbestos exposure.
Were you asked by anyone to include that portion of your report after Dr. Legier issued his?
A. No, sir. It's just my custom to include the criteria that I would use for making a statement with reasonable medical certainty.
If this were a lung cancer, for example, I would include a different set of criteria taken from Dr. Roggli's textbook probably. If this is a mesothelioma, I generally take the Helsinki criteria. Sometimes I'll list criteria from several sources that are the basis of making a causation statement.
Q. All right. Do you require any particular exposure in terms of fiber per cc years for the attribution of mesothelioma to asbestos?
A. Well, no, sir, I generally don't quantify it that precisely. I require that there be either --

well. basically what the Helsinki criteria asks for. either demonstrative increase in tissue burden or other asbestos-related lesions or a history of asbestos exposure, occupational, domestic, or environmental above background.

Q. What do you consider to be background?

A. There is a table on page 220 of the book, "Asbestiform Fibers: Nonoccupational Exposures," written by the national science --

MR. DeLUCA: National Academy of Sciences.

THE WITNESS: Excuse me, National Academy of Sciences, published in 1984, that details background or environmental exposure levels in a whole variety of different situations. There must be 15 or 20 references on that page.

In general, I regard an environmental level for ambient air of 0.0003 or less to be an environmental level. Some of the measurements given in that table are even less than that, some are higher than that. But as a -- what's the word? As a general -- it's not exactly an average, but as a reasonable --

BY MR. WELCH:

Q. Estimate?

A. -- estimate of background, that would be about right in my opinion.

Q. Would you feel that an exposure of .0003 or less capable of producing mesothelioma?

A. Well, I'm afraid that my answer to that question will be a little complicated.

If you have a group of people and that's the only exposure they had, a background environmental type exposure at that level, you would not be able to prove that their mesotheliomas were due to that exposure because you would not be able to construct a comparative -- a group for comparison, a control group you would not be able to construct because on this planet, that's background exposure level.

However, the other way to look at it is that if a person develops a mesothelioma, that person's body has no idea what fiber it's coming from. The body that's reacting by developing a mesothelioma cannot distinguish whether a -- any particular fiber or group of fibers is from an environmental source or an occupational source.

Q. But based upon the estimates you mentioned from the National Academy of Sciences, you would not expect an exposure of that level to produce mesothelioma?

A. At exposures of that level, that is to say, .0003 or less there will be some people that have mesothelioma. That number will be relatively low. Those would, I suppose, be the true idiopathic mesotheliomas.

Q. You agree that there are idiopathic mesotheliomas?

A. Yes, sir, according to the current medical literature. I've seen numbers that range from about six percent in the German mesothelioma registry up to about 20 percent in the Helsinki criteria paper.

Q. I believe Dr. Roggli listed it as 10 to 20 percent of males in United States.

A. Yes. In his book I believe he uses that figure. And as a convenient figure, I will use 10 percent in my discussions because it's very easy to do the mathematics that way. I certainly agree, however, that the medical literature has a variety of estimates somewhere around that.

Q. Doctor, let me ask you one question I didn't cover earlier. Have you issued any report on Mr. Sartin other than the one dated 11/22/2006?

A. No, sir, I have not.

Q. To your knowledge, has Dr. Legier issued any report other than his dated 11/9/06?

A. Not that I know of.

Q. Do you believe you would be aware of it if he had?

A. Probably. And I'd certainly be happy to check our information system, our pathology information system if we have a break at some time to see if there's anything out there.

MR. WELCH: Let me ask Mr. DeLuca. Are you aware of anything additional by Dr. Legier?

MR. DeLUCA: No, sir, I'm not.

MR. WELCH: All right.

MR. DeLUCA: Off the record?

MR. WELCH: Yeah.

(Recess: 9:59 - 10:17 a.m.)

BY MR. WELCH:

Q. Dr. Maddox, while we were taking a little break there, I understand you checked your computer system and discovered there were additional working drafts that were made on the two reports that we have discussed, yours and Dr. Legier's?

A. Yes, sir, that's correct. As far as I've been able to tell, there have been no changes or additions to either one of the final reports since they were issued. The working draft is simply a different format for presenting the typing, the