ASSESSMENT OF RISKS POSED BY EXPOSURE TO LOW LEVELS OF ASBESTOS IN THE GENERAL ENVIRONMENT

Prepared by:

Marvin S. Schneiderman, Ph.D.
Ian C. T. Nisbet, Ph.D.
Susan M. Brett, M.P.H.

Clement Associates, Inc.
1010 Wisconsin Avenue, N.W.
Washington, D.C. 20007 USA

Prepared for:

Institut für Wasser-, Boden- und Lufthygiene
des Bundesgesundheitsantes

June 1981

00001

TABLE OF CONTENTS

[redacted]
00001

I. EXECUTIVE SUMMARY

Estimates of probable excess risks of lung cancer and mesothelioma are made for low levels of exposure to airborne asbestos under environmental conditions. This is done by extending to low doses the estimated risks observed for industrial workers who were exposed at substantially higher doses. An extensive review of the dose-response data for industrially exposed workers (extending an earlier review by Nicholson) leads to the conclusion that at an exposure of 1 fiber x years/ml the expected lifetime excess risk of lung cancer would lie in the following ranges:

	Men	Women
Smokers	10^{-3} to 10^{-2}	3×10^{-4} to 3×10^{-3}
Nonsmokers	10^{-4} to 10^{-3}	4×10^{-5} to 4×10^{-4}

There is some empirical evidence that these risks are not strongly dependent on the age when exposure starts.

For pleural and peritoneal mesotheliomas, the corresponding excess risk after half a lifetime's exposure (36-37 years) is estimated to be between 1 and 6×10^{-4}. This risk appears to be independent of smoking habits (and not clearly dependent on sex). However, it is strongly dependent on the elapsed time since first exposure.

These estimates are derived from five independent studies which yielded reasonably consistent results. Two studies which yielded lower estimates of risk per unit exposure are discounted because of methodological deficiencies. Two other studies of workers exposed during mining and milling operations yielded much lower estimates of risk per unit exposure, perhaps indicating lower biological activity of asbestos at early stages in processing.

These risk estimates are extended to environmental exposure levels, using a number of assumptions about relationships between response, dose, age, and timing of exposure. There is considerable empirical and theoretical evidence to support the assumption of linear, nonthreshold relationships between dose and response, for both lung cancer and mesotheliomas. Data for mesotheliomas fit reasonably well to a "quadratic residence time" model, in which cumulative risks depend approximately on the third power of elapsed time since exposure. Response-time relationships for lung cancers are less consistent, so that environmental risk estimates are more uncertain.

Lifetime risk estimates for the general population are presented in Table 11 in Section V. For all categories except male cigarette smokers, lifetime risks for mesothelioma are predicted to be higher than those for lung cancer. For mesotheliomas, the most important period of exposure is expected to be the first 20 years of life, but most effects are expected after age 55. "Virtually safe" concentrations (i.e., exposure

levels corresponding to excess lifetime risks of 10^{-6}) are predicted to be in the range 10^{-5} to 10^{-4} fibers/ml for outdoor exposure, and 10^{-6} to 10^{-5} fibers/ml for indoor exposure. These concentrations are well below current detection limits. These estimates cannot be expressed reliably in units of ng/ml, because of wide variability in measured conversion factors.

These estimates are subject to considerable uncertainties. The 10-fold range in the estimates that are presented reflects the variability in the results of occupational studies, and probably reflects the variability in the properties of asbestos. However, the estimates of risk may be much too high to apply to asbestos at an early stage in processing. They would also be much too high if the assumption of a linear, nonthreshold dose-response relationship proves incorrect.

Risks of gastrointestinal and other cancers resulting from exposure to airborne asbestos have not been considered in detail in this report, but probably would add a small fraction (20-30%) to the estimates of excess risk that are presented.

[redacted] 00005

II. INTRODUCTION

This report has been prepared for the Institut für Wasser,- Boden- und Lufthygiene des Bundesgesundheitsantes. It presents estimates of health risks, specifically risks of cancer, posed to the general population by low concentrations of asbestos present in the general environment. This report is part of the development of health criteria for airborne asbestos, on which ambient standards may be based. Accordingly, we have developed estimates of "virtually safe" airborne concentrations of asbestos. These are the concentrations of asbestos which, if inhaled throughout life, would be expected to give rise to an excess risk of cancer of about 10^{-6} (1 in a million). Separate estimates are provided for indoor and outdoor exposure, the sole difference being the difference in the length of time which the average person spends indoors and outdoors.

The basis for the risk assessments presented in this report is the extensive information on excess frequency of cancers (primarily lung cancers and pleural and peritoneal mesotheliomas) observed in workers exposed to relatively high levels of asbestos in the workplace. These data have recently been reviewed by Nicholson (1981), who derived a number of estimates of dose-response relationships for lung cancer. In this report, we have extended Nicholson's review, primarily by deriving estimates of dose-response relationships for mesotheliomas, and by making

a preliminary analysis of relationships between response, age, and elapsed time.

The results of these analyses are then used to derive estimates of risks likely to be experienced by the general population, exposed to much lower levels of asbestos from birth onwards. The extrapolation involves a number of assumptions about dose-time-response relationships. These assumptions are based on substantial empirical and theoretical evidence, but nevertheless introduce a number of uncertainties into the final estimates of general population risks. Uncertainties are also introduced by variability in the results of the epidemiological studies, which reflect variability in the properties of asbestos. The final estimates are presented to order of magnitude only.

In preparing this report, we have greatly benefited from the pioneering efforts of Dr. William Nicholson in constructing dose-response relationships. We also acknowledge helpful advice from Dr. Nicholson and from Dr. Charles C. Brown of the National Cancer Institute.

We emphasize that our analysis of dose-time-response relationships is preliminary, and that we have probably not extracted all the information that is available in published and unpublished studies. We recommend that a more formal and complete mathematical analysis of the available data should be conducted, to serve as the basis for improved estimates of general population risk.

III. BACKGROUND

A. Nature of Asbestos

Asbestos is the generic term for the fibrous forms of a group of naturally occurring mineral silicates of the amphibole or serpentine series. Asbestos occurs naturally in the seams and veins of many igneous or metamorphic rocks, with fibers generally 1-20 millimeters in width and having length-to-width ratios of 100:1 and higher (NCI 1978, Advisory Committee Report 1979). Currently six fibrous silicates are generally classified as asbestos: the fibrous amphiboles--actinolite, amosite, anthophyllite, crocidolite, and tremolite; and the fibrous serpentine mineral--chrysotile ("white asbestos"). Chrysotile is the form of asbestos used most commercially.

The chemical form of each type of asbestos is different as indicated below:

Amphiboles

Actinolite	Anthophyllite	Crocidolite
$2CaO.4MgO.FeO.8SiO_2.H_2O$	$7MgO.8SiO_2.H_2O$	$Na_2O.Fe_2O_3.FeO.8SiO_2.H_2O$

Tremolite	Amosite
$2CaO.5MgO.8SiO_2.H_2O$	$5.5FeO.1.5MgO.8SiO_2.H_2O$

Serpentine

Chrysotile
$3MgO.2SiO_2.2H_2O$

SOURCE: Advisory Committee Report 1979, citing Hodgson 1965

Although each asbestos mineral is generally considered as a single chemical and physical entity, the fibers themselves belong to more complex crystal chemical systems, so that they may range in both chemical and physical properties (Langer 1974).

Chrysotile fibers are generally of a smooth, silky texture and whitish in color; crocidolite fibers are straighter, shorter, and less silky than chrysotile and bluish in color; amosite fibers are more brittle than either crocidolite or chrysotile and brownish in color. It should be noted, however, that color is not a reliable indicator for the identification of asbestos type in any particular product. These minerals may all occur in the nonfibrous form and in such cases are not considered as asbestos.

Asbestos fibers are flexible, possess high tensile strength, and are easily separated into filamentous strands. The properties which give asbestos its major commercial value are insolubility, noncombustibility, strength, ability to be woven, and efficacy as a binding or reinforcing agent when combined with other materials such as plastic or cement. In varying degrees, the different types of asbestos are also efficient at absorbing sound and resistant to electric currents, high temperatures, and alkalis. In addition, the amphibole fibers are resistant to acids.

B. Uses

Asbestos fibers can be adapted to a large number of uses due to their high tensile strength, flexibility, chemical and

heat resistance, and favorable frictional properties. Dependent upon the properties of the fibers, asbestos can be spun, carded or woven; used for structural reinforcement of materials such as cement, plastic, and asphalt; or laid and pressed to form paper. The Asbestos Information Association suggests that there are more than 3,000 uses.

Longer asbestos fibers tend to be used in textiles, electrical insulation, filtration media, and maximum-strength asbestos products. Medium length fibers are used as reinforcing fillers in asbestos cement products, in friction materials such as brake linings, in pipe covering, and in paper. Shorter fibers tend to be used as reinforcing fibers in plastics, asphalt, and floor tiles, as well as in oil-well drilling muds and paints (NCI 1978).

C. Occurrence

Asbestos formation occurs as a result of several stages of geologic processes in which parent rocks (ultramafic, dolomitic, or limestone) are transformed into the substance. Transformation of parent rock may occur under localized conditions of temperature and pressure or as a result of the action of hot mineral solutions that can alter some minerals to form others.

In addition to commercial mining and milling, the occurrence of asbestos in the environment may result from the inadvertent disturbance of asbestos deposits by activities as road building or farming; from the manufacture, use, repair and demolition of asbestos-containing products; from the transportation of

asbestos ore, milled fiber, products, and wastes; and from the disposal of asbestos waste.

Individuals can be occupationally exposed to the substance during processing, including mining, milling, factory production, and handling of asbestos-containing products. Contamination of air with asbestos can result from the spraying of the material for fire protection or acoustical purposes. Workers may also be exposed during end-product use such as brake maintenance or application of insulation. Other examples of workers potentially exposed to asbestos include those in ship-building, general construction, demolition, building inspection, repair and maintenance (of asbestos-containing structures), waste disposal, and cleaning operations. Workers' family members may be exposed to asbestos from dusts brought home on clothing, shoes and hair.

People can be exposed in the home as a result of performing construction and repairs using asbestos containing materials. Such materials include asbestos plastic-fillers, cement sheets, and furnace and heating equipment cements.

Finally, asbestos can be present in the general environment in air, water, food, and beverages. Asbestos concentrations in the range of 10-100 ng/m^3 have been reported in the general urban atmosphere. Near some factories using asbestos, asbestos concentrations have been reported to be as high as 5,000 ng/m^3. The air inside buildings can be contaminated due to working with or damage or erosion of asbestos material. In addition, asbestos has been detected in some samples of drinking water,

food, beverages, and pharmaceutical preparations (NCI 1978, Advisory Committee Report 1979).

D. Routes of Exposure

The most important route of exposure of asbestos fibers is by inhalation into the respiratory tract. The disposition of fibers entering the respiratory tract is not fully understood. Some fibers can be conveyed to the gastrointestinal tract by airway clearance mechanisms and others to the pleural and peritoneal cavities by lymphatic drainage. The physical characteristics of asbestos fibers which favor penetration of asbestos fibers to the bronchi, lungs, and pleura are briefly discussed in Section III.F below.

Ingestion is another potential route of exposure. It may be secondary to inhalation of fibers wherein the individual swallows nasal and bronchial secretions containing inhaled asbestos fibers. It is assumed that this is the form of ingestion which accounts for the excesses of gastrointestinal cancers which have been observed in some groups of asbestos workers. Ingestion of asbestos can also occur by the consumption of contaminated water, food, or beverages. It should be noted, however, that most asbestos fibers entering the gastrointestinal tract are probably excreted with the feces.

Asbestos may be injected inadvertently through the use of asbestos-containing syringes or through the use of fluids containing pharmaceutical agents which were filtered through asbestos pads during manufacture. After injection into the

bloodstream, asbestos is rapidly removed and deposited into various tissues, with the highest concentrations observed in lungs, liver and spleen (NCI 1978).

E. Problems in Identification of Asbestos Fibers

The identification of asbestos fibers requires structural, morphological, and chemical information. Due to the variability in the characteristic properties of asbestos fibers, their detection and identification can often be difficult. Several methods have been proposed for the identification and quantitation of asbestos in air, water, and biologic materials. These include optical and electron microscopy, X-ray diffraction, differential thermal analysis, and infrared, emission and atomic absorption spectroscopy. A number of factors contribute to the difficulty in the analysis of asbestiform materials. The problems which can be encountered in such analyses include: complexity of sample preparation of the differing media; level of fiber exposure (contamination); presence (kind and amount) of other particles; variations in reactions of tissue types to different preparation techniques; improper choice of instrumental technique; and the great amount of time required for analysis and quantitation (Langer 1974).

F. Identification of Biologically Active Fractions

The information available about the disposition of asbestos fibers following inhalation or ingestion is relatively limited due to the difficulties involved in the assay of biological

tissues for the substance. The factors which have been considered to influence fiber deposition and the occurrence of human disease include fiber length, fiber diameter, fiber number, stability of fiber in vivo, fiber translocation and migration, fiber type, and overall dose.

It has been suggested that fibers less than 5 microns in length may be completely phagocytosed in vivo whereas those longer than 25 microns generally are not (Allison 1973). Those fibers in the 20 micron range may be only partially phagocytosed or may cause thinning of the phagosomal membrane (Langer et al. 1979). The predominant fibers found in the lung parenchyma and in extrapulmonary organs are those shorter than 5 microns in length. However, in cases of asbestosis, peribronchial and perivascular lesions generally contain both long and short fibers. The interaction of short and long fibers has also been considered as an aspect of biological activity. In summary, current data suggest that both long and short fibers are biologically active and suspect in producing human disease.

The diameter of asbestos fibers appears to play an important part in determining biological activity. The diameters considered most important range from 0.5-2.5 microns (Langer et al. 1974). When compared with "thin" fibers, "thick" (and long) fibers tend to produce less biological response. Reduction in fiber diameter tends to reflect an increase in particle number and surface area per unit mass of material. This suggests that when evaluating environmental samples, any diameter under several

microns should be considered in the active respirable range (Langer et al. 1979).

An increase in asbestos fiber number may in some cases increase and in others greatly decrease biological activity. A correlation of activity and absolute number is probably not equal for all fiber types. Furthermore, such a correlation is probably not equal for all disease entities.

It has been proposed that fiber retention may be partially related to fiber stability in vivo. Resistance to degradation has been considered to be of prime importance in the induction of cancer (Pott 1978). However, fiber degradation and dissolution in vivo may also increase the activity of the fiber (Langer et al. 1979).

Approximately 10-30% of asbestos fibers retained by human lungs become coated with hemosiderin and mucopolysaccaride to form yellow-to-brown rod-shaped structures called asbestos bodies (NCI 1978). The effects of asbestos fibers and bodies are not limited to one target organ; they have been found in almost every extrapulmonary tissue. In certain cases removal of fibers from the lung may result in translocation to another site. Short fibers tend to be translocated more readily than long fibers and should therefore be expected to lodge in organs other than the lungs.

It has been difficult to assign a scale of relative pathogenicity to various asbestos types. This is related to many factors, including differences in physical characteristics within

fibers of a particular asbestos type; changes in fiber characteristics during processing; and contamination of one type of asbestos with another type. It has been suggested that chrysotile is less hazardous than other asbestos types. However, high rates of lung cancer in asbestos workers have been related to all types of asbestos (see Section IV below). In addition, pleural and peritoneal mesotheliomas have been observed in workers exposed primarily to chrysotile, as well as to crocidolite and amosite.

G. Health Effects

The following discussions of carcinogenic and noncarcinogenic health effects are based upon data presented in the following reviews on asbestos: NCI 1978, NIOSH 1976, and Advisory Committee Report 1979.

1. Carcinogenic effects--human studies

There is extensive evidence that asbestos is a cause of lung cancer in humans. The majority of this evidence is derived from occupational epidemiological studies. It should be noted, however, that the lung tumors which occur in persons exposed to asbestos have no special diagnostic feature. It is usually impossible, therefore, to determine to what extent any specific lung tumor is related to asbestos, rather than to other agents such as cigarette smoke or polluted air to which the individual may have been exposed. The combined effect of smoking and asbestos exposure has been found to produce a risk of lung cancer that exceeds the sum of their separate risks.

Asbestos exposure has also been strongly correlated with pleural and peritoneal mesothelioma. The disease is one of the rarest malignancies and occurs mainly in workers in heavy industry, as in shipbuilding. Mesothelioma rarely occurs in the absence of exposure to asbestos dust. It is therefore much easier to distinguish its relationship to asbestos than is the case with lung cancer, due to the strong association of the latter with tobacco smoking.

Several epidemiological studies have suggested that an excess risk of cancer of the digestive system is associated with occupational asbestos exposure. A problem with some of these studies has been sketchy clinical and pathological data and the possible inclusion of peritoneal mesothelioma cases among all observed cases. This can make it difficult to document an increased risk of any one digestive system cancer independent of that for mesothelioma. It must be stated, however, that the excesses are larger than can be reasonably explained away in this manner, so that a true increase in gastrointestinal cancer seems more probable.

Highly suggestive but limited evidence exists suggesting a casual link between asbestos and laryngeal cancer. The risk, in absolute terms, however, is much smaller than for the cancers already described. There are currently insufficient data available to permit adequate study of possible synergism between the effect of smoking and asbestos exposure on laryngeal cancer incidence.

2. Noncarcinogenic effects of asbestos

Asbestosis is a disease characterized by a diffuse interstitial fibrosis of the lung, which may or may not be associated with fibrosis of the outer or inner layer of the pleura. By definition, the disease is specifically related to asbestos exposure. The disease is difficult to diagnose because its onset is gradual, and the characteristic signs and symptoms may occur in other lung diseases and are somtimes difficult to detect. Symptoms rarely become apparent until after at least a decade of exposure. By the time the initial symptom of dyspnea on exertion appears, the underlying disease process is well established. At present, there appears to be no scientific evidence that asbestosis and lung cancer are interrelated, except that they are both causally associated with asbestos exposure.

Benign pleural effusion (fluid development in the space between the pleural membranes lining the lung and chest wall) is another manifestation of disease associated with asbestos exposure. It may occur in the presence of some degree of parenchymal asbestosis or with other asbestos-related lung diseases or as the only and most prominent process. Pleural plaques and calcification (thickening) are additional manifestations of asbestos exposure, which may occur alone or in association with fibrosis of the lung. The plaques do not generally alter pulmonary function to a significant extent; pleural thickening may be symptomless or associated with restriction of breathing and chest discomfort.

IV. DOSE-RESPONSE DATA DERIVED FROM STUDIES OF INDUSTRIAL WORKERS

A. Introduction

Ideally, one would like to base estimates of risks to a human population on dose-response data derived from studies in the same population. Unfortunately, this can rarely be done. The general population is usually exposed at very low doses, so that effects are likely to be small and hard to discern. Not only are members of the general population exposed to low doses of the material of concern, they are also likely to be exposed to many other things, usually also at low doses--which will also have some small effects--making the sorting out of the different effects nearly impossible. Because of these problems of low doses and of confounding with other exposures it becomes necessary to turn to populations that are more heavily exposed--usually worker populations, exposed on the job.

Worker populations often show clear-cut effects at the high doses to which they are exposed. From the dose-response curves observed it is then necessary to infer dose-response curves that are likely to be valid at the low levels of ambient exposure. There are difficulties with making such inferences. Industrial workers are usually men. They do not include the very young or the very old. They are usually healthier than the general population. They are often exposed to more than one toxic material in their working or personal lives. For example, many are cigarette smokers. Thus there are logical

and conceptual as well as biological problems in extrapolating data from young, healthy men to other categories of people, such as children, pregnant women, or older, not nearly so healthy retired persons.

Within these limitations, however, it is possible to make some reasonable use of the data that have been developed on industrial workers. Such data are useful when one can find workers exposed to clearly different levels of the material. Short-term exposures have occurred. High exposures lead to earlier illness and earlier recognition of health effects. Workers, at least male workers, are relatively easy to trace. However, in addition to the problems pointed out earlier, the major gap in the worker-derived data is that they do not give any direct measures of effects of exposures at young ages, especially under age 16. Rarely do industrial exposures begin before age 16. Thus there are assumptions that need to be made and some uncertainties associated with them.

Nicholson (1981) has brought together and reviewed all the published industrial epidemiology studies on workers exposed to asbestos. His review provides a basis for the analysis presented here. In the material that follows an attempt has been made to state all the assumptions that enter into the computations and, where important, to indicate the variation that would ensue from the use of other possible assumptions.

B. Measurement of Health Effects

This report deals largely, but not exclusively, with data on mortality--death from specific causes. This leads to some immediate problems. The major causes of (cancer) deaths associated with asbestos exposure have been cancer of the bronchus and lung (ICD 162), mesotheliomas, both pleural and peritoneal, and cancers of the esophagus (ICD 150), stomach (ICD 151), colon (ICD 153), and rectum (ICD 154). Some increases have also been reported in the frequency of cancers of the larynx (ICD 161), pharynx and buccal cavity (ICD 140-149), and cancer of the kidney (ICD 180). Selikoff et al. (1979) have reported that for all other cancers the ratio of observed to expected deaths, as reported on death certificates, was 1.91--a significant excess.

1. Ascertainment of cause of death

Two difficulties arise in using data on these causes of death. The first is that reports on death certificates can be substantially in error. In a detailed review of death certificate reporting compared to what they called "best estimates" from detailed hospital data, Selikoff et al. (1979) found that the death certificates substantially over-reported cancers of the pancreas (ICD 157), liver and biliary passages (ICD 155), and possibly brain (ICD 193). There was substantial under-reporting of mesotheliomas, and about a 10% under-reporting of cancer of the lung. Mesotheliomas, being rare causes of death, are usually not reported in national death statistics.

There have been reporting problems for mesotheliomas in the past. These are likely to continue in the future. Unless specified as "malignant," mesotheliomas were usually coded to ICD 228, "benign" tumors. In addition, most national data are not published in more detail than the basic 3-digit codes. Thus, data on mesotheliomas of the peritoneum, ICD 158.9, were not published in the United States. Similarly, data on mesotheliomas of the pleura were not published and, under certain circumstances, all mesotheliomas not otherwise specified were included under code 199 "malignant neoplasm without specification of site." Special tabulation of cause of death by 4-digit code can usually be made by national vital statistics centers.

When comparisons have been made of death certificate reporting and hospital diagnosis in the United States, lung cancers have been found generally to be properly reported (see Percy et al. 1981). In one study of about 50,000 cancer deaths, hospital records recorded 10,059 lung cancer deaths, and the death certificates recorded 10,178 lung cancer deaths. Several other sites, however, were not as well reported (see Table 1).

The second important point to recognize is that there appears to be a strong interaction with cigarette smoking in the development of lung cancer in asbestos-exposed workers. In typical circumstances, the frequency of lung cancer in cigarette smokers is about 10 times that in nonsmokers with similar exposure

TABLE 1

COMPARISON OF REPORTED FREQUENCIES OF CERTAIN TYPES OF CANCER FROM HOSPITAL RECORDS AND DEATH CERTIFICATES

Site (and ICD number)	Hospital Records	Death Certificates	Percent Difference
Buccal cavity (140-149)	1,397	1,187	-15
Colon (153)	4,546	5,131	+13
Rectum (154)	2,098	1,367	-35
Liver (155.0, 197.8)	462	687	+49
Kidney (189)	984	930	-5
Brain (191, 192)	1,074	1,171	+9

SOURCE: Percy et al. (1981)

to asbestos (Selikoff et al. 1979). For this reason, measures of excess risk of lung cancer in asbestos workers are likely to be variable unless account can be taken of the prevalence of smoking among them. No interaction with smoking has been reported for mesotheliomas, and as shown below, estimates of risks for mesotheliomas appear to be less variable than those for lung cancers.

2. Dependence of disease frequency on age and elapsed time since first exposure

Cancer is clearly a disease of older ages, with roughly half of all cancer deaths occurring ir persons over 65. It is also a disease of long delay; there is a long time from initial exposure in a working population to the diagnosis of cancer,

or to death from cancer. (Median time from diagnosis to death is about 2 years, for the totality of cancers.)

Selikoff et al. (1979) have reported on deaths from lung cancer and mesotheliomas among insulation workers in the United States and Canada as a function of the number of years following initial exposure. For lung cancers, the median time to death (from first exposure) was about 32 years. For mesotheliomas, the median time was somewhat longer--36 years. It has been suggested that the effect of the interaction of cigarette smoking with asbestos exposure is to move forward in time the appearance of the lung cancers. Under this hypothesis, nonsmoking asbestos workers might eventually develop as much cancer as the smokers, but, on the average, the disease might appear several years later. Mesotheliomas, which appear to be unaffected by cigarette smoke, lead to later deaths than do the lung cancers.

Seidman et al. (1979) examined the effects of the age at which the men started working in an amosite factory on their subsequent development of lung cancer. Their conclusion was that

> ...heavy direct exposure to men who are already at "cancer ages" [i.e., men 50 and over] can result in a very large increase in mortality in a surprisingly short period of time, 5-14 years after onset of work. With lighter direct exposures, even to men already at "cancer ages" there is a latency period of a number of years before significant increases in mortality are seen and these increases are smaller than those of the more heavily dosed men. Regardless of the level of exposure, there were few deaths in younger men, those in their 20's at the 5 year point after onset [of exposure].

> The length of the latency period depends not only on the dosage but also on the age at which exposure takes place.

This latter observation is consistent with the hypothesis that asbestos may act at a middle or late stage in the development of cancer, leading to the clinical development of cancers initiated earlier in life.

The manner in which asbestos leads to cancer has also been considered by Day and Brown (1980). Analyzing the data of Seidman et al. referred to above, they came to the conclusion that asbestos operates as an early-stage, rather than a late-stage carcinogen for workers employed for less than 2 years. However, they qualified this conclusion by pointing out the unusual manner of "residence" of asbestos.

> ...there is some ambiguity in interpreting the evolution of risk after the external exposure has stopped, because asbestos bodies remain in the lungs. It might be more appropriate to consider exposure as being continuous but at a decreasing level as the asbestos bodies are either excreted or their carcinogenic ability is reduced. However, the mechanism of action of asbestos carcinogenesis is unknown, and it is not clear that its carcinogenic effect remains with the asbestos bodies that remain in the lungs. The observed increasing excess cancer incidence is thus consistent either with an early-stage effect or with a late-stage effect resulting from the asbestos remaining in the lungs.

Seidman et al. did not analyze the age-at-first-exposure effect for mesotheliomas, but Day and Brown, examining other data, concluded

> ...the quadratic residence time model as described by Peto appears to fit the observed data reasonably well. Under this model, the incidence at time T, e.g., I(T), is proportional to $\int_0^T (T-t)^2 c(t)dt$, where c(t) is the exposure level at time t. It should

be noted that this quadratic residence time model is mathematically equivalent to a model derived from the assumption of a first-stage effect in a four-stage carcinogenic process. As with the risk for lung cancer following asbestos exposure, we can interpret these data as describing either the effect of a continuous exposure due to the inhaled fibers or the effect of short-term exposure to an early-stage carcinogen.

We shall deal with the quadratic residence time model later, when we attempt to estimate lifetime risks of mesotheliomas following exposure to asbestos. Thus, while it is clear that age at first exposure is of considerable consequence, few of the industrial data reported assemble the information in this manner. For problems of ambient exposure, it is most important to attempt to make estimates of the effects of life-time exposures, beginning at birth, if that is when first exposure occurs.

3. Measures of excess risk

There are three questions in the measurement of excess risk that must be considered.

a. Excess over what? What comparison population is appropriate? If we deal with exposed workers, should they be compared with other unexposed workers, or the general population, or people in the same region or city, or some ideal, low-risk population?

Usually comparisons are made with a general, country-wide population, at least as a first step. This usually leads to an understatement of risks for a working population, because working populations are often healthier than nonworking populations. When deaths in workers are compared

to expected deaths in the total population, one often finds that the workers show about 80% of the expected deaths computed from general population rates for persons of the same age and sex.

b. Excess among all causes of death, or only certain causes of death? If earlier work or if animal studies have shown excess deaths from certain specific causes, should these be the only ones considered? Are excess deaths from one cause made up for by reduced deaths from other causes?

It is most common to look both at total causes of death and at specific causes that are likely to be associated with the exposure. Biological plausibility is often invoked to justify examining one cause and not another. Thus, in asbestos exposure, it looks most reasonable to look at respiratory disease and probably noninfectious diseases of the digestive tract. It would be suprising to find increased leukemias, or increased diabetes, but not surprising to find increased pneumonias or bronchitis, or even cancers of the colon and rectum.

c. What specific measures of excess should be used? Relative risks (or Standard Mortality Ratios, SMR) or absolute increases? Average years of life lost because of premature death?

The relative risk or Standard Mortality Ratio is a commonly used measure. It compares observed deaths with expected deaths, where "expected" deaths are usually calculated

from general population data. Thus for the average cigarette smoker (about 20 cigarettes per day), the relative risk of death from lung cancer is about 10 or 11 compared to a nonsmoker. (The SMR would then be 1,000 or 1,100. A SMR of 100 means observed equals expected.) The SMR is a useful measure for excesses among total deaths and for relatively common causes of death such as lung cancer. For causes of death that are rare in the general population, such as mesotheliomas, the SMRs would approach infinity and would convey little information. For mesotheliomas, therefore, absolute increases in death rates due to this cause are used as the appropriate measure. Because mesotheliomas appear to be a disease that appears later in life, on the average, than lung cancer, it is important that the ages of the exposed populations be well defined, so that various populations may be compared on an equal basis.

4. Biases and confounding factors

There are four major possibilities for distorting estimates of excess risk through problems of confounding (with other exposures) or statistical bias through the use of unrepresentative samples of the exposed or comparison populations.

a. "Healthy worker effect." This effect has already been mentioned. Several suggestions have been made to minimize or avoid this effect, but none seems fully satisfactory. These suggestions range from arguing that no adjustment

need be made, to suggestions that all individual SMRs be inflated by the inverse of the SMR for all causes, for example, by multiplying cause-specific SMRs, such as that for lung cancer, by 1/SMR for the total deaths. Thus, if the SMR for total deaths were 0.8 and the SMR for lung cancer was 1.2, the "adjusted" lung cancer SMR would be 1.2 x 1/0.8 = 1.50. Another suggestion is that the SMR for a cause of death thought very unlikely to be related to exposure (such as diabetes) be used as a "normalizing" divider for the cause-specific SMR. In the example above, say the SMR for diabetics was 0.75. The adjusted SMR for lung cancer would be 1.2 x 1/0.75 = 1.6.

b. Other characteristics of the workers. Most workers are urban dwellers. Urban residents have, in general, higher cancer rates than rural persons. The differential increases with the density of urban populations, although there is no reason to believe that population density, in itself, should be cancer-causing. Similarly, social class has been associated with increased cancer rates. Social class, however, is difficult to disentangle from occupation, since occupation often determines social class. Long-time patterns of diet, recreational activity (or lack of it) and other disease-related factors are associated with social class. In general, when generalizing from industrially exposed populations to more generally exposed populations, issues of urbanization, population density,

social class, etc., are usually set aside with the assumption that the industrial worker is nearly representative of the general population with respect to these issues.

c. Cigarette smoking. This is particularly important with respect to asbestos-related disease. There is some evidence of excesses in cigarette smoking among asbestos workers compared to the general population (Hammond et al. 1979, Seidman et al. 1979). Patterns of cigarette smoking in FDR appear to be similar to those of the United States (Erben 1979, Tobacco International 1980) so that computations based on American experience should be applicable to FDR. Overall, in 1979 in FDR approximately 41% of men and 34% of women were reported as cigarette smokers. (Tobacco International reported higher rates in men and lower rates in women.) The proportion of adults smoking cigarettes fell off with increasing age, as in the United States. In FDR, the age group with the highest proportion of persons smoking was under 30 and the lowest proportion was in persons over 60. In part the low proportion of smokers in persons over 60 is due to the higher death rates in smokers, particularly among the older age groups.

d. Competing causes of death. The smoking effect--particularly in older persons--leads to deaths from causes that may not usually be associated with asbestos exposure. This has two effects on the data that are examined for asbestos effects. First, there is an artificial increase

in so-called "natural" (unassociated) deaths, and a consequent underestimate of the associated deaths. Second, there is evidence of a "saturation" effect with increasing dose. For example, after some effective dose level, further exposure may not lead to deaths from lung cancer, but may lead to earlier deaths from asbestosis. For this reason, the dose-response curve would flatten or even turn down at very high doses, because persons died early of other causes. This saturation effect, due to competing causes of death, is also seen when followup proceeds for a long time. Nicholson (1981), in considering relative risks for asbestos workers for all causes of death, found the maximum relative risk after about 25-30 years of followup and then a slow decline in relative risk with continuing followup. Thus, a followup period of 25-30 years appeared to provide the best measure of the excess risks of lung cancer. Shorter followup periods yield underestimates of risk because the latency period has not been reached; longer followup periods also yield underestimates of risk because of competing causes of death. The latter phenomenon has not been discussed extensively in the epidemiological literature.

5. Conversion of risk measures to estimates of lifetime risks.

Epidemiologic studies rarely measure lifetime risks. To do so would require following a population to extinction which,

of course, is rarely done. To estimate lifetime risks, two principal approaches can be used.

a. The first approach is useful when the agent increases the frequency of a disease which is fairly frequent in the general population. Then, if the relative risk R (frequency in exposed population/frequency in general population) can be assumed to be constant (independent of age), the lifetime risk in the exposed population can be estimated from the lifetime frequency of the disease in the general population. Specifically, if the lifetime probability of developing the disease in the general population is

$$P_B = 1 - e^{-\lambda},$$

then the lifetime probability of developing the disease in the exposed population is

$$P_E = 1 - e^{-R\lambda}.$$

For low values of R, $P_E \simeq RP_B$. This method of estimating lifetime risk is appropriate for asbestos-induced lung cancer, for which there is empirical evidence that R is approximately constant (see Section IV.E below).

b. In cases in which the relative risk varies with age, or cannot be calculated because the disease is rare in the general population, lifetime risks can only be calculated by assuming a specific model for the dependence of risk on age and duration of exposure. For many cancers, there is empirical evidence that frequency depends on the k'th power of age (and/or elapsed time since exposure), where k is usually between 3 and 6 (Armitage

and Doll 1961). This is the basis for a number of models from which lifetime risks can be calculated (Armitage and Doll 1961, Day and Brown 1980). This approach is necessary for asbestos-induced mesotheliomas, which are rare in unexposed individuals. A general problem with the approach is that the results are strongly dependent on the value assumed for k, because most of the lifetime risk falls in the last quarter of life for which direct observations are often scanty. However, this problem is not very serious for asbestos-induced mesotheliomas, for which there are good data on frequency up to 35-40 years after exposure, and for which k can be estimated empirically (Peto 1979, Day and Brown 1980).

Peto (1979) has applied the first approach to asbestos-induced lung cancer and the second to asbestos-induced mesotheliomas. For mesotheliomas, Peto utilized a "quadratic residence time" model (see footnote to Table 3); this is equivalent to assuming k = 3. Tables 2 and 3 present the results of Peto's calculations, modified to present lifetime risks as a function of age at first exposure and duration of exposure. (Note that the calculations are designed only to illustrate the functional form of these relationships; the exposure level required to cause this response is hypothetical.)

In the case of lung cancer (Table 2), the calculations assume a linear dependence of lifetime risk on duration of exposure (i.e., on cumulative dose), but predict that lifetime risks are independent of age at first exposure. In the case of

mesotheliomas (Table 3), however, the calculations predict that lifetime risk depends very strongly on the age at first exposure, and that only the first 20 years of exposure contribute significantly to the lifetime risk. The models on which these results are based are equivalent to assuming that asbestos acts at a middle or late stage in the development of lung cancer, but at an early stage in the development of mesothelioma. As discussed elsewhere in this report, there is substantial empirical basis for the functional forms of the dependence of risk on age and duration of exposure (Nicholson 1981), but there is ambiguity about the stages at which asbestos acts (Day and Brown 1980). Accordingly, although we will use assumptions equivalent to Peto's in calculating lifetime risks, it should be recognized that these assumptions may exaggerate the differences in age-dependent frequency between lung cancers and mesotheliomas.

An important result in Table 3 is that the lifetime risk for mesotheliomas is 2-7 times higher in persons exposed from birth than in persons starting exposure at ages 15-35. This is important because all the data used in Section IV are derived from workers whose exposure started after age 16. Hence a multiplying factor is needed when these data are used in Section V to estimate risks to persons in the general population, whose exposure to ambient asbestos starts at birth. The figures in Table 2 would indicate that no such multiplying factor is needed for lung cancer, but this conclusion would be wrong if asbestos actually acts at an early stage in development of lung cancer.

TABLE 2

THEORETICAL DEPENDENCE OF LIFETIME RISK (%) OF LUNG CANCER ON DURATION OF ASBESTOS EXPOSURE AND AGE AT FIRST EXPOSURE

Duration of Exposure (yr)	Age at First Exposure					
	0	15	25	35	45	55
1	0.04	0.04	0.04	0.04	0.04	0.04
2	0.08	0.08	0.08	0.08	0.08	0.08
5	0.19	0.19	0.19	0.20	0.20	0.18
10	0.38	0.38	0.39	0.39	0.38	0.33
20	0.76	0.76	0.77	0.76	0.69	
30	1.1	1.1	1.1	1.1		
40	1.5	1.5	1.4			
50	1.9	1.8				
60	2.2					

SOURCE: Modified from Peto (1979)

Assumptions: relative risk independent of age, but propor-tional to exposure level x duration; lifetime = 73 yrs. Peto presented these risks as hypothetically resulting from continuous exposure to 2 fibers/ml.

TABLE 3

THEORETICAL DEPENDENCE OF LIFETIME RISK (%) OF MESOTHELIOMA ON DURATION OF ASBESTOS EXPOSURE AND AGE AT FIRST EXPOSURE

Duration of Exposure (yr)	Age at First Exposure					
	0	15	25	35	45	55
1	0.42	0.21	0.12	0.06	0.03	0.01
2	0.82	0.41	0.23	0.12	0.05	0.02
5	1.90	0.93	0.52	0.26	0.11	0.03
10	3.21	1.6	0.89	0.43	0.17	0.05
20	5.0	2.5	1.3	0.59	0.21	
30	5.8	2.9	1.5	0.63		
40	6.0	3.0	1.5			
50	6.0	3.0				
60	6.0					

SOURCE: modified from Peto (1979)

Assumptions: contribution of exposure at time t to risk at time T is proportional to $(T-t)^2$ ("quadratic residence time model"); lifetime = 73 yrs. Peto presented these risks as hypothetically resulting from continuous exposure to 2 fibers/ml.

C. Measurement of exposure

Problems in measuring exposure to asbestos have been reviewed recently by Nicholson (1981), whose comments are reproduced here in their entirety.

1. Importance of past estimates

The accuracy of judgements on dose-response relationships for asbestos is largely limited by our knowledge of past fiber exposures of those populations whose mortality or morbidity were later evaluated. Few measurements were made in facilities using asbestos fibers prior to 1970. Further, those measurements that were done usually quantified all dust (both fibers and particles) present in the workplace air. Current techniques, using membrane filters and phase contrast microscopy for the enumeration of fibers longer than 5 micrometers, have been utilized in Great Britain and the United States only since 1964 (Holmes, 1965; Ayer et al., 1965) and have been standardized in the United States only since 1972 [National Institute for Occupational Safety and Health (NIOSH), 1972; 1979].

These techniques may be utilized to evaluate work practices and conditions believed to be typical of earlier activities. However, it is always difficult to duplicate materials and conditions of earlier decades and such retrospective estimates are necessarily uncertain. Alternatively, fiber counting techniques and the instrumentation of earlier years can be used together to simultaneously evaluate a

variety of asbestos-containing aerosols. The comparative readings then serve as a "calibration" of the historic instrument in terms of fiber concentrations. Unfortunately, the calibration depends on the type and size distribution of the asbestos used in the process under evaluation and the quantity of other dust present in the aerosol. Thus, no universal conversion has been found between earlier dust measurements and current fiber counts.

In the United States and Canada those few data that were obtained on asbestos workers' exposures prior to 1965 were based upon total dust concentrations using a midget impinger. Fibers were inefficiently counted with this instrument because of the use of bright field microscopy. Attempts to compare fiber concentrations with midget impinger particle counts generally showed poor correlations (Ayer et al., 1965; Gibbs and Lachance, 1974). In the United Kingdom the thermal precipitator was used from 1951 through 1964 in one plant for which environmental data have been published. This instrument, too, does not allow accurate evaluation of fiber concentrations and the variability in the correlation between fiber measurements and thermal precipitator data is reported to be large (Sykes, 1977, quoted in Advisory Committee, 1979b), but no specific data are available.

2. Measurement techniques

Even with the advances in fiber counting techniques, significant errors may be introduced into attempts to formulate general fiber dose-response relationships. The convention now in use, that only fibers longer than 5 micrometers be counted, was chosen solely for the convenience of optical microscopic evaluation (since surveillance agencies have such instrumentation). It does not necessarily correspond to any parameter of biological importance for asbestosis, lung cancer, or mesothelioma. While it is readily understood that counting only fibers longer than 5 micrometers enumerates but a fraction of the total number of fibers present, there is incomplete awareness that the fraction counted is highly variable. It depends upon the fiber type, the process or products used, and even the past history of the asbestos material (old vs. new insulation material, e.g.), among other factors. For example, the fraction of chrysotile fibers longer than 5 micrometers in an aerosol can vary by a factor of ten (from as little as 0.5% of the total number to as many as approximately 5%). When amosite aerosols are counted, the fraction longer than 5 micrometers may be 30%, extending the variability of the fraction counted to two orders of magnitude (Nicholson et al., 1972; Nicholson, 1976; Winer and Cossette, 1979). Thus, even perfect measurement of workplace air, with accurate enumeration of fibers according to accepted methods,

may introduce a significant uncertainty in the dose-response relationships for any specific asbestos disease when different work environments are studied.

Those uncertainties that exist in the physical determinations of past fiber concentrations and our difficulty in evaluating the exposure parameter of importance in current measurements are exacerbated by the sampling limitations in determining individual or even average exposures of working populations; only few workmen at a worksite are monitored and then only occasionally. Variability in work activities, in personal habits, and in sampling circumstances add considerable uncertainty to our knowledge of dose.

This gloomy picture is not painted to suggest that one should throw up one's hands and say dose-response relationships are impossible to obtain or to require that any dose-response data be restricted only to those circumstances in which they were obtained. Rather, it is described to indicate how approximate any estimated dose-response relationship is likely to be and to emphasize that projections of health effects at low exposures, made on the basis of available information, may seriously mis-state these effects.

D. Relating dose to response

The usual procedure is to calculate cumulative dose in fibers/ml x years and then calculate response per unit of accumulated dose. This model of disease can be written as:

$$\text{Excess risk in period } (t_2 - t_1) = \text{constant} \int_{t_1}^{t_2} c(t)dt,$$

where c(t) is a function of the dose at time t. The model makes two important assumptions, which may or may not be true:

1. The dose-response relationship is linear. As dose increases, response increases, proportionately.

2. There is no dependence on the timing of exposure--that is, a fiber makes the same additive contribution to risk no matter whether it is inhaled early or late in life.

Several sets of data seem to support the assumption of linearity (see Nicholson 1981, and further discussion in Section IV.E below). However, some dose-response curves appear to flatten out at very high levels of exposure and at very long periods of followup. This may be due to dose saturation effects, to competing causes of mortality, or to both.

The second assumption is less plausible, for several reasons:

1. Cancer is known to have a latent period after exposure before clinical disease appears, so that exposures late in life make little or no contribution to risk.

2. Asbestos fibers are retained in the body for long periods, so that a fiber inhaled early in life has a much greater opportunity to cause biological effects than one inhaled late in life.

3. The multistage model of cancer provides theoretical support for the assumption that cancer risks depend strongly on age and on elapsed time since exposure (Armitage and Doll 1961, Peto 1979, Day and Brown 1980; see discussion above).

These considerations support several alternative formulations of the mathematical model given above:

(i) to take account of a latent period, L,

$$\text{Excess risk } \alpha \int_{t_1}^{t_2-L} c(t)dt;$$

(ii) to take into account retention of fibers,

$$\text{Excess risk } \alpha \int_{t_1}^{t_2} c(t)\,(t-t_1)dt,$$

or if fibers are cleared at a constant rate α,

$$\text{Excess risk } \alpha \int_{t_1}^{t_2}\int_{t_1}^{t} c(\tau)e^{-\alpha(t-\tau)}d\tau dt;$$

(iii) to take account dependence of risk on elapsed time since exposure,

$$\text{Excess risk } \alpha \int_{t_1}^{t_2} c(t)\,(t_2-t)^k dt.$$

The last model is the most general, and, by appropriate choice of k, can take account of all three of the considerations listed above. For example, it reduces to the first model where $k = 0$. For this reason, we apply this model to observed dose-response relationships. As described earlier, it is a good empirical fit to data on mesotheliomas, but empirical data on the age-dependence of lung cancer probably do not fit it so well.

For constant exposure (c(t) independent of t), this model has two important consequences:

(i) the cumulative risk after T years of continuous exposure is proportional to T^{k+1}. Empirical data on mesotheliomas fit this relationship, with k lying between 2 and 3.

(ii) the cumulative risk after T years of continuous exposure is proportional to 1/k+1. Hence, if the first model listed in this section (in which k=0) is used to estimate cumulative risks, these estimates will be too high by a factor (k+1). Another way of putting this result is that only a fraction 1/k+1 of the exposure period makes a significant contribution to the cumulative risk. For example, for lifetime exposure (T=73 years) and for k=2 or 3, the effective exposure period is only between 18 and 24 years; this result is illustrated in Table 3. For this reason, in this report we relate risks of mesothelioma to cumulative exposures during the first 25-30% of the exposure period.

It is less clear that this procedure is appropriate for lung cancer. The cumulative frequency of lung cancers in asbestos-exposed workers increases with age in parallel with that in the general population, suggesting that the above model is suitable, with k equal to about 3. On the other hand, the data of Seidman et al. (1979) on workers first exposed in middle age suggest that k should be much smaller than this, perhaps nearly zero (see discussion in Section IV.B and Table 2). However, other data, such as those in Table 5, indicate that exposures to asbestos make little or no contribution to lung cancer risk within the first 10-15 years. Recognizing that a different model may be required to fit the data on lung cancer, we will assume conservatively that the effective exposure period is

equal to about half of the actual exposure period (equivalent to assuming k=1 for this specific calculation), except that we will exclude from the effective period the last 10-15 years before observation.

E. Observed dose-response relationships

1. Lung cancer

Nicholson (1981) reviewed nine studies of the mortality of asbestos workers and derived 11 estimates of the relationship between excess lung cancer incidence and cumulative exposure to asbestos. These estimates are retabulated in Table 4, with background information on each study and a summary of the basis for Nicholson's estimates of dose-response coefficients in each case. Table 5 includes notes and comments by us on the reliability of these estimates.

The measure of response per unit of exposure used in Table 4 is the percentage increase in relative risk for lung cancer per unit of cumulative exposure. Use of this index is predicated on two assumptions:

(i) for a given level of exposure, after an appropriate latent period the relative risk for lung cancer is independent of the elapsed time between exposure and observation;

(ii) the relative risk for lung cancer increases linearly with cumulative dose.

Both these assumptions have substantial empirical basis (see Peto 1979 and Nicholson 1981 for discussion). Table 6 tabulates data on deaths from lung cancer among 17,800 insulation workers in the United States and Canada (Selikoff et al. 1979).

TABLE 4

ESTIMATED INCREASES IN LUNG CANCER RISK PER UNIT OF EXPOSURE TO ASBESTOS (recalculated from Table 4 in Nicholson 1981)

Study Group	Type of Asbestos	Duration of study from onset of exposure; duration of exposure	Estimate of asbestos concentration and basis	Observed range of relative risks	% increase in lung cancer risk per unit dose, (% per f-yr/ml)	Reference
1. Insulation manufacturing, Paterson, NJ	Amosite	35 yr; very short exposures, mostly 1 mo-2 yr	35 f/ml, measured by USPHS in similar facilities	2.45-6.50	9.1%, based on regression of relative risk on dose	Seidman et al, 1979 (see Nicholson 1981, pp. 13-16, 24, Fig. 4, Table 3)
2. Asbestos products manufacturing, London, U.K.	Crocidolite, later chrysotile and amosite	M, 11-42 yr; F, 33-40 yr; duration of exposure not stated	5-20 f/ml, basis not stated but "recently reviewed"	1.27-21.3	M, 1.3%; F, 0.4%, based on regression of relative risk on estimated dose	Newhouse and Berry, 1979 see Nicholson 1981, pp. 34-35, Figure 9)
3. Asbestos manufacturing, several U.S. plants	Amosite, chrysotile, some crocidolite	9-51+ yr; 3-51 yr exposure	Dust measurements for job categories; assumed conversion factor 1 mppcf = 3 f/ml	1.98-7.78	0.3%, based on regression of relative risk on estimated dose	Henderson and Enterline, 1979 (see Nicholson 1981, pp. 19-20, 27-28, Figure 7)
4. Asbestos products manufacturing Manville, NJ	Chrysotile, some amosite and crocidolite	38+ yr; 20-38+ yr exposure	10-80 f/ml, based on company estimates for highest category and "reasonable" assumptions for others	3.96 (lowest category)	1.1%, based on data for lowest category because of saturation effects	Nicholson et al 1981 (see Nicholson 1981, pp. 16-17, 28-29, Table 6)
5. Textile production, U.S.	Chrysotile	10-36+ yr; exposure for more than 6 months	5-80 f/ml, based on dust counts throughout exposure period, with paired and concurrent filter measurements	2.23-15.5	5.3%, based on regression of relative risk on dose	Dement et al 1980 (see Nicholson 1981, pp. 18-19, 33-34, Table 7 Figure 6

TABLE 4, Continued

Study Group	Type of Asbestos	Duration of study from onset of exposure; duration of exposure	Estimate of asbestos concentration and basis	Observed range of relative risks	% increase in lung cancer risk per unit dose, (% per f-yr/ml)	Reference
6. Textile production, Rochdale, U.K.	Chrysotile	10-45 yr; exposure for more than 10 yr	1.1-32 f/ml, based on several techniques and repeatedly revised	1.50-2.50	0.07% (workers employed before 1951); 0.8% (workers employed since 1950), based on group averages	Peto 1980 and others (see Nicholson 1981, pp. 32-33 Tables 10-11)
7. Insulation application, U.S. and Canada	Chrysolite and amosite	10-50+ yr, median 24 yr; duration of exposure variable	15 f/ml, based on 1968-71 measurements in similar applications	4.60	1.7%, based on assumption of 15 yr average exposure	Selikoff et al 1979 (see Nicholson 1981, pp. 25-27)
8. Mining and milling, Québec, Canada	Chrysotile	10-64 yr; "wide range" in duration of employment	25-83 mppcf, based on extensive dust measurements, converted to f/ml using factor of 1 mppcf = 3 f/ml	1.0-2.9	0.06%, based on regression of relative risk on dose	McDonald and Liddell 1979 (see Nicholson 1981, pp. 21, 29-30, Figure 8)
9. Mining and milling, Québec Canada	Chrysotile	36-56+ yr; 20+ yr	45 f/ml, estimated from 1974 measurements and increased to reflect earlier conditions	2.52	0.15% based on group average exposure, assumed continued for 20 yrs	Nicholson et al. 1979 (see Nicholson, 1981, pp. 30-31)

TABLE 5

NOTES ON STUDIES SUMMARIZED IN TABLE IV-4
AND ON NICHOLSON'S DOSE-RESPONSE ESTIMATES

Study No. and Reference	Notes and Comments
1. Seidman et al. 1979	This is the most useful set of data because the workers were exposed to asbestos for only a short period, so that the dose data are not confused by late exposures. However, the dose-response relationship is not a very close fit to a linear relationship (Nicholson's Figure 4). The point for the highest exposure group (ca. 140 f-yr/ml) falls below the linear regression line, probably due to dose saturation (Nicholson, p. 15). The points for the three lowest exposure groups (less than 7 f-yr/ml) fall above the regression line. If the calculations were based only on these three points, the estimate of % increase in lung cancer risk per unit dose would be 37% per f-yr/ml. However, it is possible that the asbestos workers smoked more than the general population of New Jersey with which they were compared. This would explain the elevated rates of lung cancer in workers exposed for only a short period. If the regression line is not constrained to pass through a relative risk of 1 at zero exposure, the estimate of % increase in lung cancer risk per unit dose would be about 2.4% per f-yr/ml.

TABLE 5, Continued

Study No. and Reference	Notes and Comments
2. Newhouse and Berry 1979	These estimates are "necessarily uncertain because of the limited information on both exposure and length of employment" (Nicholson 1981). Nicholson assumed an average of 10 years for those employed more than 2 years. This may be too high. The estimates of cumulative exposure for males are probably too high because some were followed for only 11 years after onset of exposure.
3. Henderson and Enterline 1979	This study was limited to men who had retired at age 65 and hence is likely seriously to underestimate the effects of asbestos exposure. Although Nicholson (1981, p. 28) incorporated a small correction for mortality prior to age 65, he also showed that Henderson and Enterline's study failed to detect a large incidence of mesotheliomas at the same plant. The effective average dose would also have been overestimated because of the inclusion of workers who had started work as little as 6 years prior to the end of follow-up.
4. Nicholson et al. 1981	The estimate of fiber concentration for the low-exposure group (10 f/ml) is tenuous, although the average exposure estimate for the entire factory is close to that of Henderson and Enterline (1979). Even if the concentration is correct, the estimate of cumulative dose (apparently 270 f-yr/ml, or 10 f/ml for 27 years) is probably much too high, both because such a dose would include exposures within 10 years of the end of the study, and because it would be expected to lead to dose saturation effects.

TABLE 5, Continued

Study No. and Reference	Notes and Comments
5. Dement et al. 1981	This study appears to be based on good exposure data, involving calibrated measurements throughout the exposure period. However, the number of lung cancers recorded was small (26 versus 6.5 expected). The exposure estimates included some within 10 years of the end of the study and hence are likely to have overestimated effective dose levels.
6. Peto 1980	This study is difficult to interpret because of the major revisions in the exposure data, the small size of the cohorts, and the unexplained difference in mortality patterns between the workers employed before and after 1951. The early cohort is anomalous because of the low rate of lung cancer (relative risk 1.5) despite a high frequency of asbestosis. Most of the workers in the later group were followed for less than 20 years after first employment, so the effective dose is likely to have been greatly overestimated. When the cohorts were considered by period since first exposure, the relative risks ranged from 0.45-5.34 with the 0.45 risk in the subgroup employed before 1951 with 35+ years since first exposure; and the 5.34 risk in the subgroup employed after 1950 with 20 years since first exposure.

TABLE 5, Continued

Study No. and Reference	Notes and Comments
7. Selikoff et al. 1979	This estimate appears low for at least three reasons. (1) Actual measurements of asbestos concentration were in the range 3-9 f/ml; Nicholson's estimate of 15 f/ml is based on assumptions of greater exposure in the past. (2) Nicholson assumed exposure for 15 years, which is probably too long for contribution to effective dose. (3) At such doses, dose saturation effects would be expected.
8. McDonald and Liddell 1979	This estimate may be low because some workers may have been employed for as little as 10 years at the end of the study. Nevertheless, a good linear dose response relationship was obtained (Nicholson 1981, Table 8). This study also yielded anomalously low figures for incidence of mesothelioma and asbestosis, considering the very high dust levels.
9. Nicholson et al. 1979	The estimate of fiber concentration is tenuous, and the assumed period of 20 years exposure is probably much too long to contribute to effective dose. Although the estimate of risk per unit dose is 2-3 times higher than that of McDonald and Liddell (1979) it is still an order of magnitude lower than that in most other studies. This may reflect lower risks from mining asbestos than for the other processes that have been studied.

Although the number of lung cancers per 1,000 person-years increased rapidly with elapsed time since start of employment, the relative risk did not vary markedly, at least after the 25th year. Table 7, based on data from Seidman et al. (1979), similarly shows that relative risks were more or less constant in each exposure category after about the 20th year from onset of exposure. Figures 1-5 illustrate the dose-response relationships compiled by Nicholson (1981) from data available from five independent studies. In at least four cases, the data can be fitted closely by a linear dose-response relationship. In the fifth case (the study of Seidman et al. 1979, illustrated in Figure 1), the curve rises rapidly at low doses and flattens off at the highest exposure level (interpreted by Seidman et al. as a dose "saturation" effect); the three points for the lowest exposures fall significantly above a fitted straight line. This may indicate that this curve is not linear, and that incremental risks per unit of exposure were higher at low doses (see discussion in Table 5, note 1).

With these limited exceptions, epidemiologic data support the assumptions that relative risk is independence of elapsed time and is linearly dependent on cumulative exposure. Hence the slope of the linear relationship (incremental increase in relative risk per unit of cumulated dose) is a stable measure of the incremental risks of asbestos exposure, and may be used to characterize the results of each study.

TABLE 6

DEATHS AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE U.S. AND CANADA, 1967-1976, ANALYZED BY DURATION SINCE ONSET OF EMPLOYMENT (Retabulated from Table 17 in Selikoff et al. 1979)

Duration from onset (yr)	No. of men	Lung Cancers			Mesotheliomas		
		No. Observed	No./1000 person-years	Relative risk*	No. Observed	No./1000 person-years	Mesotheliomas/ lung cancers
<10	8,190	0	0	0	0	0	0
10 - 14	9,063	7	0.24	2.55	0	0	0
15 - 19	9,948	29	0.85	1.40	5	0.15	0.17
20 - 24	8,887	59	1.89	3.48	9	0.29	0.15
25 - 29	6,596	105	5.08	5.00	32	1.55	0.30
30 - 34	3,547	112	9.66	6.08	32	2.76	0.29
35 - 39	2,020	65	12.03	5.68	34	6.29	0.52
40 - 44	1,108	40	12.66	4.93	20	6.33	0.50
>45	1,448	69	13.01	3.89	43	8.11	0.62

*Number observed divided by number expected in white males of same age distribution, based on age-specific U.S. death rates.

TABLE 7

RELATIVE RISKS FOR LUNG CANCER BASED ON CUMULATIVE PROBABILITIES OF DEATH AT DIFFERENT ELAPSED TIMES FROM ONSET OF WORK IN AN AMOSITE ASBESTOS FACTORY. (RETABULATED FROM DATA IN TABLE 6B IN SEIDMAN ET AL. 1979)

Length of time worked	Elapsed time (years) since onset of work			
	5 - 20	5 - 25	5 - 30	5 -35
<1 month	0	0.74	0.77	1.24
1 month	2.05	1.60	1.43	1.47
2 months	1.42	1.72	1.82	1.58
3-5 months	1.27	1.76	1.69	1.76
6-11 months	1.78	1.84	2.00	2.01
1-2 years	1.67	2.14	2.89	3.20
2+ years	3.11	2.63	2.78	2.79

FIGURE 1

RELATIVE RISK OF DEATH FROM LUNG CANCER AMONG AMOSITE INSULATION PRODUCTION WORKERS ACCORDING TO THE ESTIMATED EXPOSURE TO ASBESTOS IN FIBER-YEARS/Ml (redrawn from Figure 4 in Nicholson 1981; data from Seidman et al. 1979)

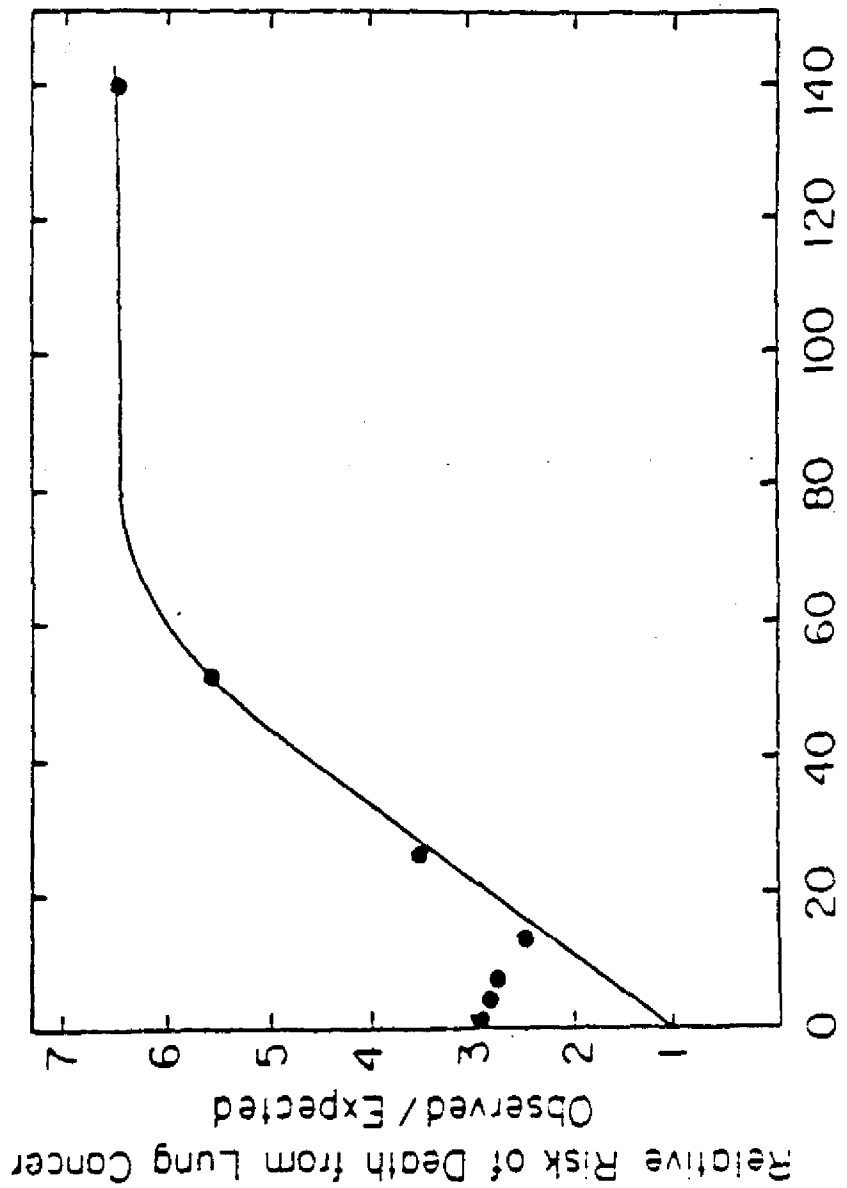

FIGURE 2

RELATIVE RISK OF DEATH FROM LUNG CANCER AMONG WORKERS IN A U.S. TEXTILE MILL, ACCORDING TO THE ESTIMATED EXPOSURE TO ASBESTOS IN FIBER-YEARS/Ml (redrawn from Figure 6 in Nicholson 1981; data from Dement et al. 1980)

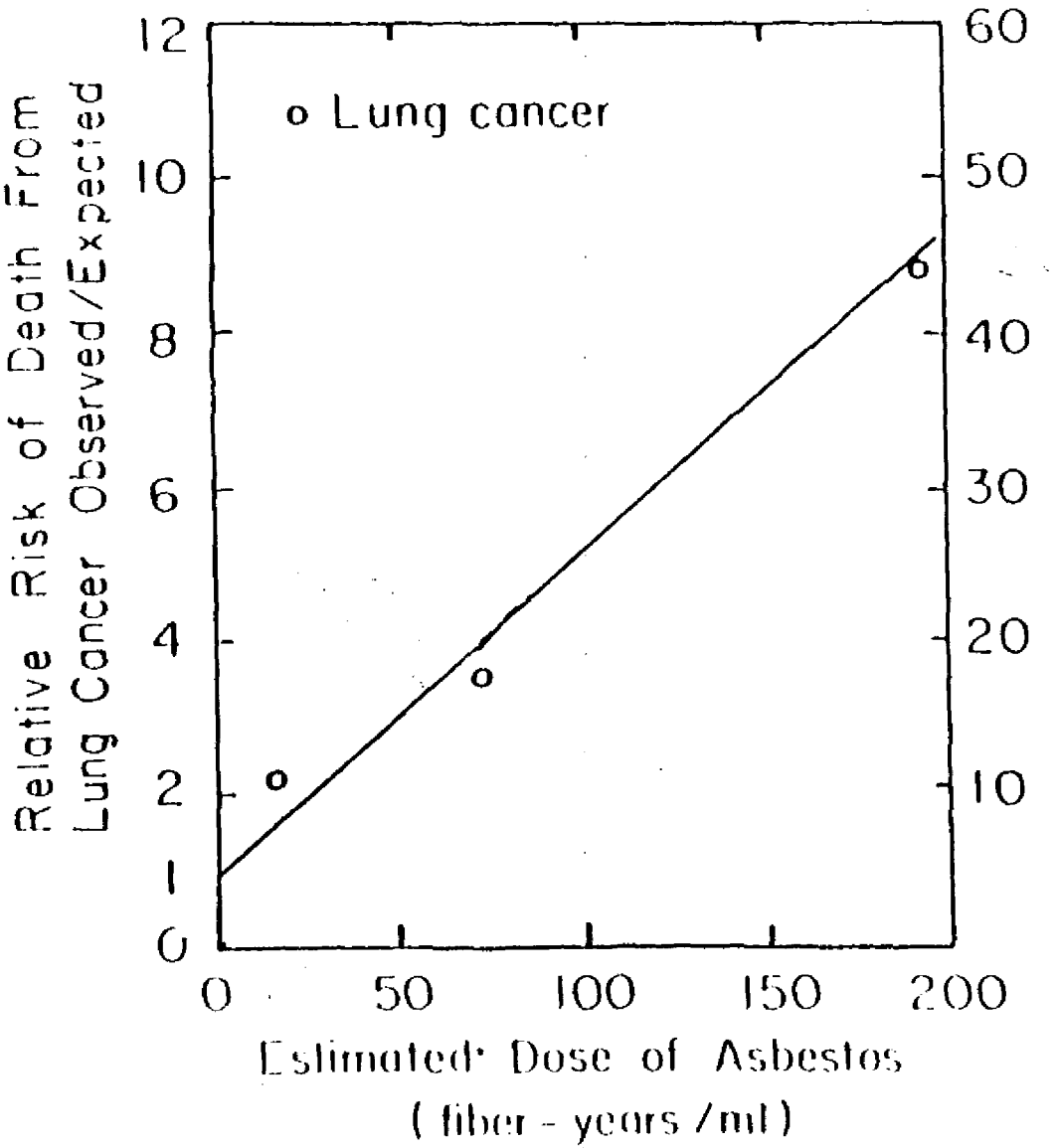

FIGURE 3

RELATIVE RISK OF DEATH FROM LUNG CANCER AMONG WORKERS IN A QUEBEC ASBESTOS MINE AND MILL ACCORDING TO CUMULATIVE DUST EXPOSURE (redrawn from Figure 8 in Nicholson 1981; data from McDonald et al. 1977)

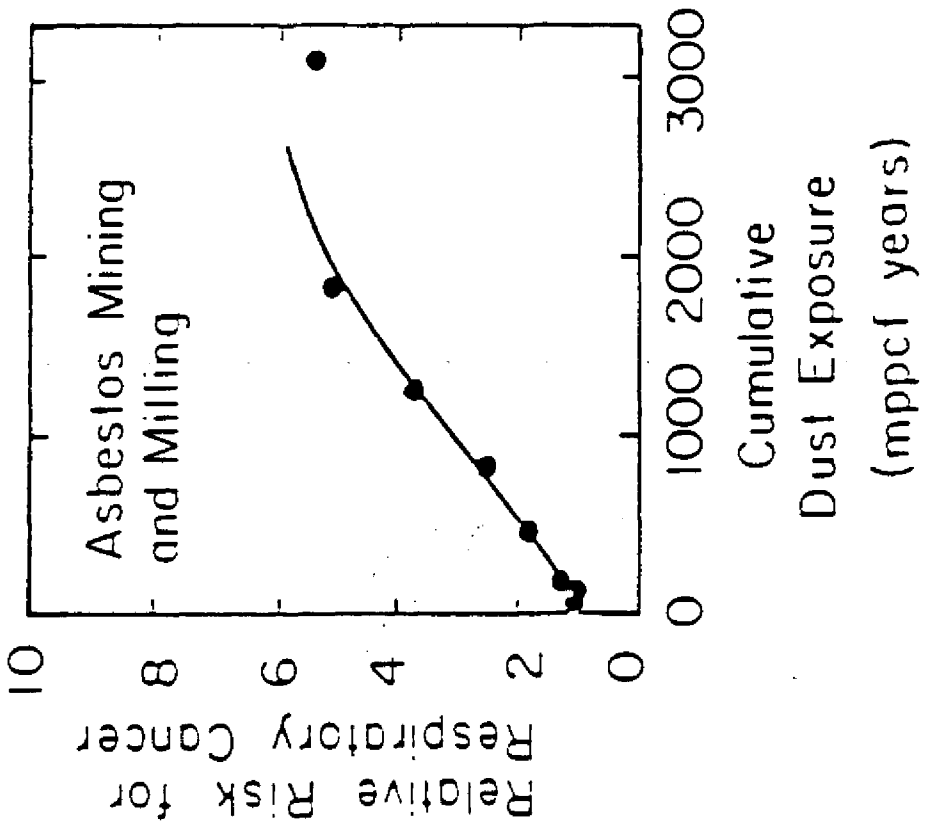

FIGURE 4

RELATIVE RISK OF DEATH FROM LUNG CANCER AMONG RETIREES FROM A U.S. ASBESTOS PRODUCTS FACILITY ACCORDING TO CUMULATIVE DUST EXPOSURE (redrawn from Figure 7 in Nicholson 1981; data from Henderson and Enterling 1979)

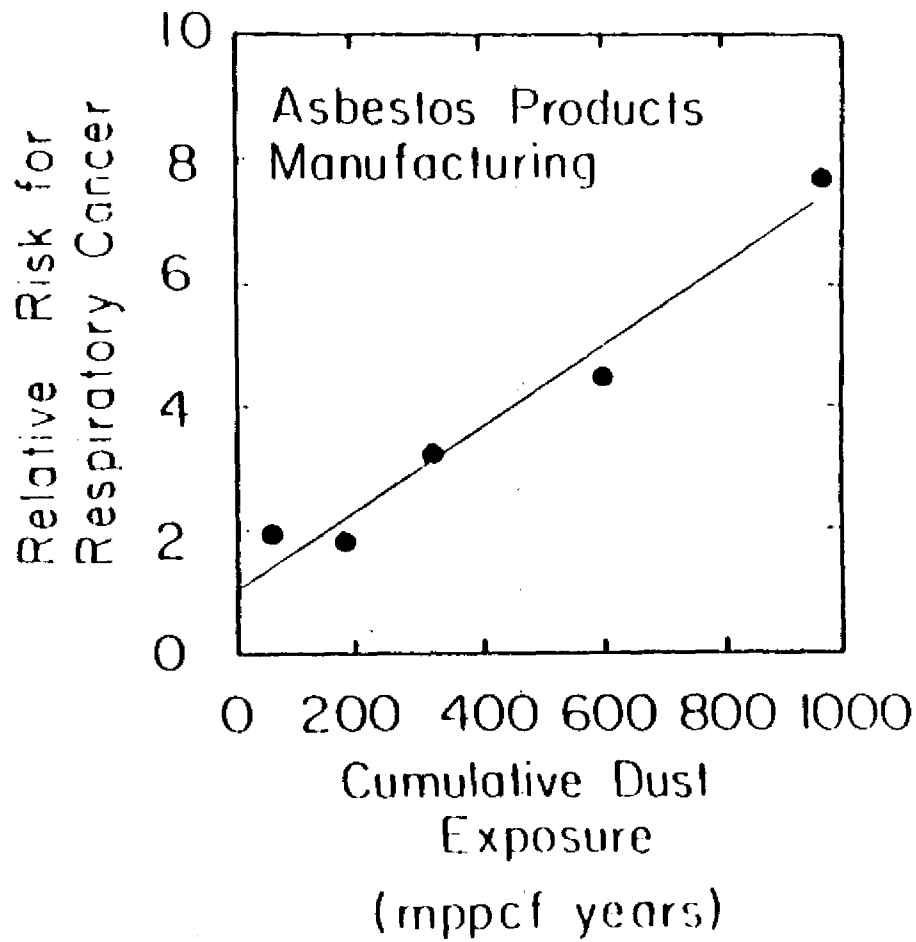

FIGURE 5

RELATIVE RISK OF DEATH FROM LUNG CANCER AMONG WORKERS AT A BRITISH ASBESTOS PRODUCTS FACTORY ACCORDING TO ESTIMATED EXPOSURE TO ASBESTOS IN FIBER-YEARS/Ml (redrawn from Figure 9 in Nicholson 1981; data from Newhouse and Berry 1979)

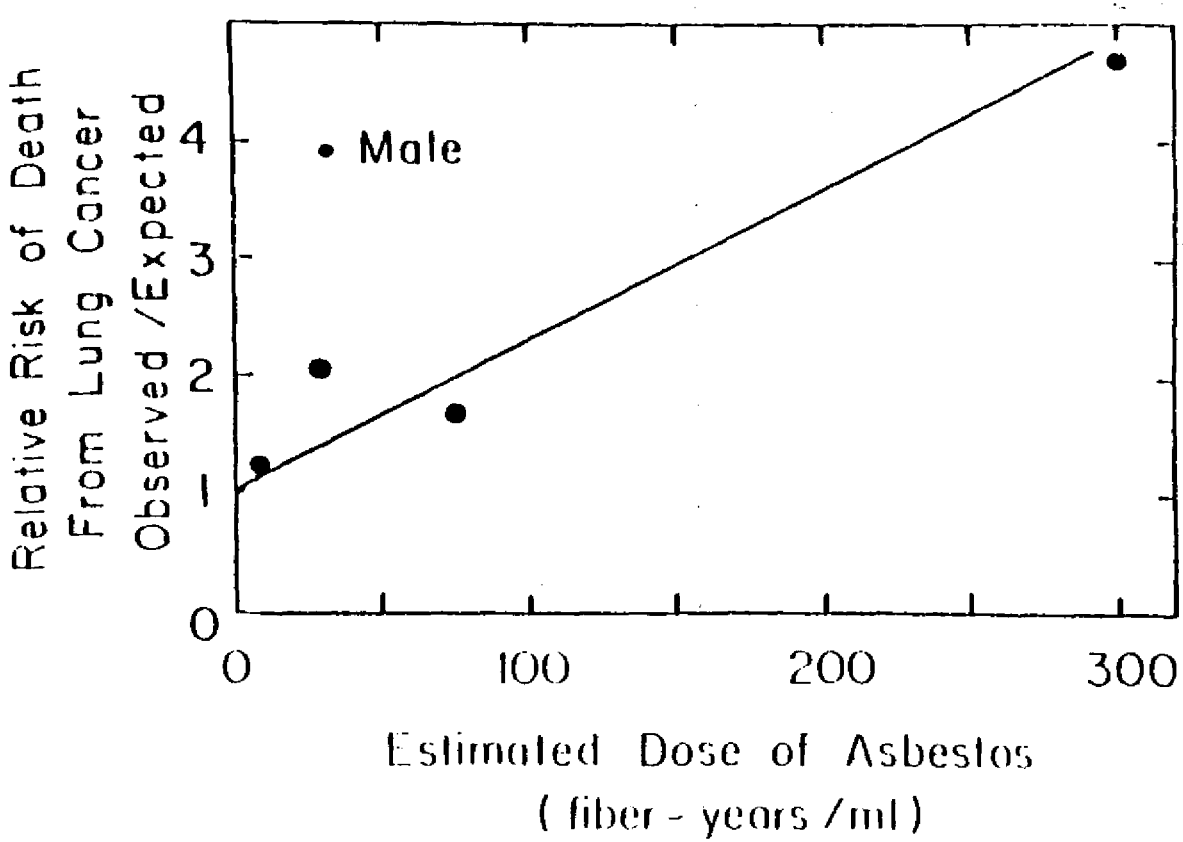

Table 4 shows that estimates of this quantity vary over a 150-fold range, from 0.06 to 9.1% increase in lung cancer risk per fiber-year/ml of exposure. However, 6 of the 11 estimates fall in the more limited range between 1.1 and 9.1% per f-yr/ml. As shown in the notes in Table 5, each of the five lower estimates is anomalous in one way or another:

(i) Study No. 3 (Henderson and Enterline 1979) was based only a study of retirees older than 65, and there is independent evidence that it missed a substantial fraction of asbestos-related deaths.

(ii) In Study No. 6 (Peto 1980, and other reports), there was an unexplained difference between early and late cohorts of workers in the same factory. The early cohort had an anomalously low frequency of other asbestos-related diseases, and the later cohort was not followed for long enough (maximum 25 years after onset of exposure) for adequate measurement of effects.

(iii) Although studies 8 and 9 (McDonald and Liddell 1979, Nicholson et al. 1979) both involved uncertainty in estimating dose, this is unlikely to explain the extremely low estimates of risk per unit dose. Both studies also reported anomalously low frequencies of other asbestos-related deaths. Both studies were of workers exposed during mining and milling operations, raising the possibility that risks are in fact much lower in these operations than in those involving manufacturing and application of asbestos products. A review of the response of these workers to cigarette smoking also showed the possibility of substantial underreporting of lung cancer mortality, or very large competing risks that killed the potential lung cancer cases at earlier ages.

For these reasons, we place primary weight on the dose-response data in the range between 1 and 10 percent increase in lung cancer risk per unit of exposure in fiber-year/ml; although several sets of data yield substantially lower estimates, these estimates are either questionable or of doubtful relevance to general population exposure. Within the range of 1-10% per

f-yr/ml, there appears to be substantial variability from study to study. Some estimates may be too low because of overestimation of effective doses, and the highest estimate is uncertain because of deviations from the linear model (see notes to Table 5).

Data presented by Hammond et al. (1979) show that asbestos and cigarette smoking act synergistically in increasing the risk of lung cancer.[1] Compared to nonsmoking controls, smokers not exposed to asbestos had a relative risk for lung cancer of 10.85; non-smoking asbestos workers had a relative risk of 5.17; and smoking asbestos workers had a relative risk of 50-55. These data can be used to estimate lifetime risks separately for smokers and non-smokers. In the United States population as a whole, the lifetime risks for men of developing lung cancer are about 0.1 for smokers and 0.01 for nonsmokers; for U.S. females, the corresponding lifetime risks are about 0.04 and 0.005, respectively.[2] Hence, the estimated increase of 1-10% in these rates

---

[1] It has been suggested that the major cigarette-smoking effect may be to move forward in time the age at which the lung cancers occur. This suggestion says that followed enough, the nonsmokers would eventually develop as much lung cancer as the smokers.

[2] If the lifetime risk for nonsmokers is r and that for smokers is Sr, and if the proportion of smokers in the population is p, then the average lifetime risk for the population R is

$$R = pr + (1-p)Sr.$$

For U.S. males, R=0.0595, S=10.85, and p is assumed to be 0.5 for the period 1940-1960 (data from Hammond et al. 1979 and Schneiderman et al. 1979). Hence, r is approximately 0.01 and Sr is approximately 0.11. For U.S. females, R=0.01559, S=8, and p is assumed to be 0.3. Hence, r is approximately 0.005 and Sr is approximately 0.04.

per f-yr/ml exposure to asbestos would lead to the following increases in lifetime risk of lung cancer[1]:

male smokers:	0.001 to 0.01
male nonsmokers:	0.0001 to 0.001
female smokers:	0.0004 to 0.004
female nonsmokers:	0.00005 to 0.0005

According to the model used here, these risks would be more or less independent of the age at which the exposure took place, provided that it started at least 10 years before the age (about 55 years) when lung cancer incidence begins to become large (see Peto 1979).

2. Mesotheliomas

There has been little published discussion of dose-response relationships for mesotheliomas, and the following analysis has been developed for this report. Pleural and peritoneal mesotheliomas are considered together in this analysis, since

---

[1]These estimates do not depend on the prevalence of cigarette smoking among asbestos workers, because all the calculations of relative risk underlying the data in Table 4 involved comparisons with lung cancer rates in the general United States population. According to Hammond et al. (1979) about 83% of asbestos insulation workers in the United States and Canada smoke (or formerly smoked) cigarettes. Even in the absence of asbestos exposure, this would increase their relative risk for lung cancer to about 1.6. This may explain the anomalously high relative risk for highly exposed workers in the study by Seidman et al. (1979), which may have led to an erroneously high estimate of the dose-response curve (Note 1 to Table 5). However, this is apparently not a general problem, because relative risks as low as 1.1 and 1.27 have been reported in workers with low exposure in other studies.

their patterns of occurrence are often (although not always) parallel.

Since mesotheliomas are rare in the general population unexposed to asbestos, figures for relative risk cannot be calculated. In groups of workers exposed to asbestos, the incidence rate of mesotheliomas increases rapidly with age and duration of exposure, at least until the age where other causes of death become important (Table 6, Newhouse and Berry 1976). Where comparisons are possible, the incidence rate of mesotheliomas increases more rapidly with time than that of lung cancers (Table 6). Hence, the ratio of mesotheliomas to lung cancers increases with time, approaching one in some exposed groups towards the end of life.

Because the frequency of mesotheliomas varies so strongly with time, it is often difficult to obtain comparable measures of response from different studies. In most cases reviewed below, data are available on the number of mesothelioma deaths in the study groups 35-40 years after the onset of exposure. However, these measures are not always strictly comparable: they may significantly underestimate effects in groups within which exposure was started at different times.

Tables 8 and 9 summarize data from two studies in which the frequency of mesotheliomas was recorded in several groups of workers with different degrees of exposure. Despite the limited number of mesotheliomas and the uncertainty in exposure

TABLE 8

DOSE-RESPONSE RELATIONSHIP FOR PLEURAL AND PERITONEAL MESOTHELIOMAS IN AMOSITE INSULATION WORKERS, FOLLOWED FOR 35 YEARS AFTER A LIMITED PERIOD OF EXPOSURE.

	Length of time worked				
	<3 mo	3-5 mo	6-11 mo	1-2 yr	2+ yr
Cumulative dose (f-yr/ml)	5	12	26	52	140
No. of workers	223	149	125	125	188
No. of deaths from mesothelioma between 5 and 35 yrs after onset	0	0	3	4	7
% of workers with mesothelioma	0	0	2.4	3.2	3.7
% occurrence per f-yr/ml	0	0	0.09	0.06	0.03

(Compiled from data of Seidman et al. 1979, using estimates of fiber concentration from Nicholson 1981.)

TABLE 9

DOSE-RESPONSE RELATIONSHIP FOR PLEURAL AND PERITONEAL MESOTHELIOMAS IN ASBESTOS PRODUCTS MANUFACTURING WORKERS, FOLLOWED FOR UP TO 42 YEARS AFTER VARIABLE PERIODS OF EXPOSURE.

Concentration of dust in workplaces:	Low/moderate		High	
Period of work:	<2 yr	>2 yr	<2 yr	>2 yr
Nicholson's estimate of cumulative exposure (f-yr/ml):	7.5	75	30	300
Males (11-42 yr followup from onset of work)				
Concentration of dust in workplaces:	Low/moderate		High	
No. of men	884	554	937	512
No. of deaths from mesothelioma	4	7	16	19
% dying with mesothelioma	0.45	1.26	1.7	3.7
% occurrence per f-yr/ml	0.06	0.017	0.06	0.013
Females (33-40 yr followup from onset of work)				
Concentration of dust in workplaces:	Low/moderate		High	
No. of women	98		396	199
No. of deaths from mesothelioma	1		13	7
% dying with mesothelioma	1.0		3.3	3.5
% occurrence per f-yr/ml	ca. 0.03		0.11	0.012

(Compiled from data of Newhouse and Berry 1979, using estimates of cumulative exposure from Nicholson 1981.)

levels (see note 2 to Table 5), all the estimates of response per unit dose were of the same order of magnitude, between 0.012 and 0.11% per f-yr/ml. Although this is not strong statistical evidence for the hypothesis of linearity of dose-response relationships, the data are consistent with this hypothesis. In the remainder of the analysis, the assumption of linearity will be made, and the measure of response per unit dose that is presented will be the percentage of occurrence of mesotheliomas (through about 35 years after onset of work) per unit of exposure (f-yr/ml), with the recognition that duration of followup is of considerable importance.

Table 10 summarizes data from seven studies which permit such estimates. As in the case of lung cancer, the two studies of mining and milling operations yielded much smaller estimates than all the others. In the case of mesotheliomas, the discrepancy is so large (by two orders of magnitude) that it is difficult to explain it away as due to methodological problems: it suggests that asbestos from these operations may be much less hazardous than that from manufacturing operations and application. Despite the considerable uncertainties in the calculations, all the other estimates fall within a reasonably limited range, 0.005-0.06% occurrence per f-yr/ml. Because the lowest of the figures is based on a very small sample (and derives from a study which yielded an anomalously low risk for other cancers also), we suggest that the range most relevant for predicting risks in other situations is 0.01-0.06% occurrence per

TABLE 10

ESTIMATED INCREASES IN RISK OF PLEURAL AND PERITONEAL MESOTHELIOMAS PER UNIT OF EXPOSURE TO ASBESTOS (compiled in parallel to Table 4, using data from cited references and estimates of exposure by Nicholson 1981).

	Study Group	Type of Asbestos	Duration of Study from Onset of Exposure	Subgroup Categorized by Exposure	Cumulative Frequency of Mesothelioma (%)	Estimated Cumulative Exposure (f-yr/ml)	Response per Unit Dose (% per f-yr/ml)	Mesothelioma as % of Lung Cancers
1.	Insulation manufacturing (Seidman et al 1979)	Amosite	35 yr (short exposures)	<9 month	0.4% (2/481)	11	0.04	6% (2/36)
				>9 month	3.5% (12/339)	70	0.05	21% (12/57)
2.	Asbestos products manufacturing (Newhouse and Berry 1979)	Crocidolite, later chrysotile and amosite	M, 11-42 yr	Low	0.8% (11/1438)	30	0.03	38% (11/29)
				High	2.4%	120	0.02	47% (35/74)
			F, 33-40 yr	Low	1% (1/98)	30	0.03	50% (1/2)
				High	3.4% (20595)	120	0.03	80% (20/25)
4.	Asbestos products manufacturing (Nicholson et al 1981)	Chrysotile, some crocidotile and amosite	37+ yr	Low	4.1% (12/293)	100	0.04	71% (12/17)
				Medium	4.1% (10/244)	200	0.02	83% (10/12)
				High[a]	5% (4/81)	400	0.03	100% (4/4)
6.	Textile production (Peto 1980 and others)	Chrysolite	10-35+ yr	Pre-1951 only	1.65% (7/424)	230	0.007	25% (7/28)
7.	Insulation application (Selikoff et al. 1979)	Chrysotile and amosite	10-50+ yr, median 24 yr	--	1.4% (170/12051)	225	0.006	38% (170/450)
8.	Mining and milling (McDonald and Liddell 1979)	Chrysotile	10-64 yr	--	0.09% (10/10939)	900	0.0001	4% (10/250)
9.	Mining and milling (Nicholson et al 1979)	Chrysotile	36-56+ yr	--	0.2% (1/544)	900	0.0002	4% (1/28)

[a]Data for the highest exposure group are omitted because of the high death rate from competing causes (41% of deaths due to asbestosis).

f-yr/ml. This represents the cumulative risk to about 35 years after onset of exposure. The data in Table 6 suggest that risks continue to rise rapidly after 35 years; for the workers whose experience was summarized in Table 6, more than 80% of the lifetime risk occurred after the 35th year.

The last column of Table 10 gives the ratio between the number of mesotheliomas and the number of lung cancers in each study. This ratio has varied widely, from 4% to 100% in different groups of workers. The data in Table 10 suggest that this ratio may increase with increasing exposure, suggesting that the dose-response relationship for one or the other type of cancer may deviate from linearity. It is not clear whether the dose-response function for mesotheliomas tends to curve upwards, or that for lung cancers tends to curve downwards, but the data in Figure 1 suggest that the latter may occur.

3. Conclusions

(i) Data for both lung cancers and mesotheliomas are generally consistent with linear dose-response relationships. Several sets of data for lung cancers agree closely with linear relationships.

(ii) After exposure to asbestos, incidence rates for lung cancer increase with time in a manner generally parallel to that of rates in unexposed controls, so that relative risks are more or less constant.

(iii) Incidence rates for mesothelioma increase with time more rapidly than those for lung cancer, and may equal them 45 or more years after the start of exposure.

(iv) For lung cancer, excess risks per unit of exposure vary widely, but estimates are clustered between 1 and 10 percent increase in cancer risk per f-yr/ml. Lower figures derived from some studies may be explained by difficulties in estimating exposure or by variations in exposure situations. Some variability in apparent

dose-response relationships may be due to the confounding effect of cigarette smoking.

(v) For mesotheliomas, most estimates range between 0.01 and 0.06 percent (cumulative risk after 35 years' exposure) per f-yr/ml. Two estimates for mining and milling operations are lower than this by two orders of magnitude. Depending on the age at first exposure, lifetime risks may be five or more times higher than this.

(vi) Except for the apparently much lower risks resulting from exposure to asbestos (chrysotile) from mining and milling operations, there is no clear evidence that risks depend strongly on the type or formulation of asbestos.

(vii) Lifetime risks for workers exposed to 1 f-yr/ml are expected in most cases to lie within the following ranges:

Lung cancer (male nonsmokers): $1 - 10 \times 10^{-4}$

Lung cancer (male smokers): $10 - 100 \times 10^{-4}$

Lung cancer (female nonsmokers): $0.4 - 4 \times 10^{-4}$

Lung cancer (female smokers): $3 - 30 \times 10^{-4}$

Mesotheliomas (first exposure at age 35): $1 - 6 \times 10^{-4}$

Mesotheliomas (first exposure all age 20): $4 - 20 \times 10^{-4}$

(viii) Although the above are the most appropriate ranges to use as the basis for estimation of environmental risks, it is recognized that several studies suggest that risks may be substantially lower in appropriate circumstances.

V. EXTRAPOLATION TO LOW EXPOSURE LEVELS

The problems involved in estimating risks to the general population exposed to low ambient levels of asbestos were discussed in the introduction to Section IV. Direct measurement of low-level effects in the general population is generally impracticable, and has not been attempted, so that it is necessary to estimate low-level risks from data on workers exposed to much higher levels. Such extrapolation involves at least three separate steps:

(i) extrapolation from high to low exposure levels;

(ii) extrapolation from exposures during a working lifetime to exposures throughout life;

(iii) extrapolation from the active, primarily male, working population to the general population.

A. Empirical and theoretical bases for low-dose extrapolation models

The principal question at issue is whether a linear, non-threshold dose-reponse relationship can be assumed to be valid at low exposure levels. Several empirical and theoretical considerations bear on this question.

(i) As discussed in Section IV, at least five sets of empirical data indicate that dose-response relationships for lung cancer and mesothelioma in exposed workers are consistent with linear dose-response relationships over a wide range of cumulative doses, from 900 f-yr/ml down at least to 1.5 f-yr/ml.

(ii) Tarter (1981) has recently analyzed data on gastrointestinal and other cancers in the San Francisco Bay area of California in relation to asbestos fiber concentration in drinking water. Using sophisticated statistical procedures in the field of pattern recognition, Tarter found a relationship between cancer incidence and exposure that appeared to be linear down into the lowest range of exposures (less than 30 fibers/ml). Although the procedures used were not fully specified in the published paper, Tarter reported extensive testing of alternative treatments of the data and found that all treatments yielded linear nonthreshold relationships. Although this study deals with cancer at different sites, it demonstrates that asbestos can induce cancer at low (environmental) levels of expousre.

(iii) It is now widely accepted that the development of cancer is a multistage process, and multistage models are generally preferred in low-dose extrapolation, unless there is compelling reason to use another model in any specific case (Armitage and Doll 1961, Crump et al. 1976, NAS 1977, 1980). Extensive discussion of the multistage and other models has been published by the Safe Drinking Water Committee of the U.S. National Academy of Sciences in two recent volumes of Drinking Water and Health (NAS 1977, 1980). The multistage model is preferred for five main reasons: (i) its generality; (ii) its consistency with a wide variety of plausible biological mechanisms; (iii) extensive empirical evidence for multistage mechanisms in carcinogenesis; (iv) the generally good fit between the multistage model

and empirical data; and (v) its conservatism. At low doses, the multistage model generally predicts a linear relationship between cancer risk and dose. Such a relationship is more generally required by any biological model in which the effect of an agent is to add to a biological effect that is already taking place (Crump et al. 1978). It is important to note that the multistage model predicts linear, nonthreshold dose-response relationships for agents that act at any stage in the development of cancer.

(iv) It is now widely accepted that in many or all cases, the first stage ("initiation") in the development of cancer involves an irreversible change in the genetic information in a cell. This change often involves change in a single base in DNA, so in theory it can be effected by one or a very small number of molecules. Thus, at least for "genotoxic" carcinogens ("initiators"), there are theoretical reasons for expecting a nonthreshold relationship.

As yet little is known precisely about the mechanism of action of asbestos. Although there is no evidence that asbestos interacts directly with DNA, it may carry genotoxins or facilitate their entry into cells. At least for mesothelioma, there is evidence from the form of response-time relationships that asbestos acts an early stage (Day and Brown 1980).

(v) It is often stated that thresholds are to be expected for agents that act at later stages (including "promoters"). However, there is little or no empirical evidence for this

assumption, and the theoretical arguments for it are limited. The most plausible mechanisms by which threshold-type dose-response relationships could arise are the following: (a) cellular thresholds for physiological changes (Dimman 1972); (b) metabolic overloading (Gehring and Blau 1977); (c) overload of repair mechanisms (Cornfield 1977, 1980). Apart from theoretical and practical objections to nonthreshold models based on these mechanisms (NAS 1977, 1980), none of them could be applied to asbestos. Unlike chemical carcinogens, for which reduction of the dose administered to the animal leads to proportional reduction in cellular doses, asbestos is a discrete material in which the fiber is large compared with the cell. Hence, reduction in intake by the organism is expected to lead to reduction in the number of cells in contact with asbestos, but not to a reduction in the dose to any target cell. For this reason, a linear nonthreshold dose-response relationship is likely for asbestos, regardless of the mechanisms of its action at the cellular level.

For these reasons, we assume generally that risks to the general population at low exposure levels can be estimated by simple linear extrapolation from the dose-reponse data observed in workers.

B. Extrapolation to Lifetime Exposures

The dependence of risks on age and duration of exposure has already been discussed in Section IV-B. For the reasons discussed therein, we assume that:

(i) for mesotheliomas, the risk per unit dose to a person exposed for a full lifetime (0-73 years) is approximately eight times that observed in workers exposed for half a lifetime (e.g., 20-56 years) (see Table 3 for illustration);

(ii) for lung cancers, the increased risk per unit dose to a person exposed for a full lifetime is approximately equal to that observed in workers exposed for shorter periods (see Table 2 for illustration).

For the reasons stated in Section IV.D, we assume that the effective exposure period for the general population is the first 20 years of life for the induction of mesotheliomas, but the first 36 years of life for the induction of lung cancer.

C. Extrapolation to the General Population

There is no empirical basis for the extrapolation of dose-response data from worker populations to the more heterogeneous general population. The limited data on occupationally exposed women show no clear differences in sensitivity from men with comparable exposure (Tables 5 and 10). The existence of a "healthy worker effect" in some studies (e.g., Selikoff et al. 1979) suggests that the general population may be somewhat more susceptible to lung cancer, inter alia, than asbestos workers, but the difference is small compared to other uncertainties. There is no information on the susceptibility of children, except that they are known to respire a greater volume of air per unit body weight than adults. In the absence of definitive reason to the contrary, we will assume that the general population

is as sensitive as the workers. We will assume that cigarette smoke acts at a late stage in the development of lung cancer (Day and Brown, 1980), so that data on smoking asbestos workers can be applied to persons who are exposed to asbestos from birth and who start smoking in adolescence.

D. Estimates of "Virtually Safe" Exposure Levels

The data and assumptions discussed above can now be used to derive estimates of risks likely to be experienced by individuals in the general population who are hypothetically exposed to a constant airborne concentration of asbestos throughout life, from birth onwards. These estimates of risks are tabulated in Table 11, in which separate estimates are presented for lung cancers and for mesotheliomas. The estimates for lung cancer are further subdivided according to sex and smoking habits, to utilize the separate estimates dervived in Section IV.E.

The third column in Table 11 tabulates estimates of lifetime risks for individuals exposed to a cumulative dose of 1 f-yr/ml of asbestos, starting at birth. For lung cancer, these are the same as the estimates for exposed workers derived in Section IV.E. For mesotheliomas, we assume that lifetime risks would be about 8 times higher than the risks observed in workers followed for half a lifetime after first exposure. Since the estimates are derived from studies of occupationally-exposed workers, they are appropriate for exposure to a concentration of 1 f/ml for one working year (i.e., about 40 hr/wk x 50 wk/yr).

The last three columns in Table 11 tabulate estimates of "virtually safe" exposure levels, i.e., the average concentration levels which would be expected to correspond to an excess lifetime risk of 10^{-6} (1 in a million). These estimates are derived by dividing the cumulative dose of 1 f-yr/ml by the effective exposure period (36 yr for lung cancers, 20 yr for mesotheliomas, as discussed above), and adjusting for expected differences in the duration of exposure each week. The fourth column presents estimates appropriate for outdoor, nonoccupational exposure; the fifth column presents estimates appropriate for indoor exposure, including that in the home; the sixth column represents estimates appropriate for both indoor and outdoor exposure. Data on the average amount of time spent indoors and outdoors by persons in the FRG have been tabulated in a review by Szalai (1973). However, this review did not include specific data for children and adolescents, the age-groups whose exposure contributes most to lifetime risk. In the absence of precise data, we have assumed a figure of 20 hours per week for the average period spent outdoors by persons under the age of 20.

All estimates of "virtually safe" exposure concentrations in Table 11 are given in units of fibers/ml. For comparison with reported concentrations of asbestos in ambient air, which are usually reported in units of ng/ml ambient air, it would be desirable to express them in these units. Appendix A summarizes a number of estimates of the conversion factors between

TABLE 11

RISK ASSESSMENTS FOR THE GENERAL POPULATION EXPOSED THROUGHOUT LIFE TO CONSTANT LOW CONCENTRATIONS OF ASBESTOS

Type of cancer	Sex and smoking habits	Estimated lifetime risk from exposure to 1 f-yr/ml, starting at birth	Estimated fiber concentration (f/ml) for 10^{-6} lifetime risk[2] based on weekly exposure for		
			20 hr[3]	148 hr[4]	168 hr
Lung	Male smokers	$10\text{-}100 \times 10^{-4}$	$6\text{-}60 \times 10^{-6}$	$0.8\text{-}8 \times 10^{-6}$	$0.7\text{-}7 \times 10^{-6}$
Lung	Male nonsmokers	$1\text{-}10 \times 10^{-4}$	$60\text{-}600 \times 10^{-6}$	$8\text{-}80 \times 10^{-6}$	$7\text{-}70 \times 10^{-6}$
Lung	Female smokers	$3\text{-}30 \times 10^{-4}$	$20\text{-}200 \times 10^{-6}$	$2.5\text{-}25 \times 10^{-6}$	$2\text{-}20 \times 10^{-6}$
Lung	Female nonsmokers	$0.4\text{-}40 \times 10^{-4}$	$150\text{-}1500 \times 10^{-6}$	$20\text{-}200 \times 10^{-6}$	$20\text{-}200 \times 10^{-6}$
Meso-theliomas[5]	All	$8\text{-}50 \times 10^{-4}$	$10\text{-}60 \times 10^{-6}$	$1.4\text{-}9 \times 10^{-6}$	$1.3\text{-}8 \times 10^{-6}$

[1]Lifetime risk for lung cancer assumed to be independent of age at first exposure; lifetime risk for mesotheliomas assumed to be 8 times that observed in workers followed for half a lifetime after first exposure (see text)

[2]Effective exposure period assumed to be 20 yrs. for mesotheliomas, 36 years for lung cancer (see text)

[3]Average period for which children and adolescents remain outdoors per week (see text)

[4]Average period for which children and adolescents remain indoors per week (see text)

[5]Pleural and peritoneal mesotheliomas combined

fibers/ml and ng/ml, based on simultaneous measurements by two or more techniques. Although most of these estimates indicate that 1 ng of asbestos corresponds to between 5 and 50 fibers greater than 5 μm in length, some measurements indicate conversion factors as low as 0 or as high as 6,570 fibers/ng. Until the reasons for this variability are better understood, we recommend that both risk assessments and ambient environmental criteria should be presented in units of fibers/ml.

The estimates presented in Table 11 have three unexpected features:

1. For all subgroups except male smokers, estimates of lifetime risk for mesotheliomas are higher than those for lung cancers. This contrasts with the observations in exposed workers, in which lung cancers almost always have been more frequent (Table 10). The difference originates from our assumption that the lifetime risk for mesotheliomas (but not for lung cancers) depends strongly on the age at first exposure. Although there is substantial empirical evidence for a difference in the temporal dependence of risk, as discussed above, our assumption may exaggerate the difference, and hence understate the relative lifetime risk for lung cancer.

2. According to the mathematical models used in this report, the most significant exposures to asbestos are those that occur in the first 20 years of life, but most of the effects are expected to be manifested after age 55.

3. The figures in Table 11 predict extremely high risks per unit of exposure. The "virtually safe" exposure levels are of the order of 10^{-5} to 10^{-4} fibers/ml for outdoor exposure, and 10^{-6} to 10^{-5} fibers/ml for indoor exposure. These levels are much lower than the lowest level at which asbestos can be detected and measured, which is about 10^{-3} f/ml (NIOSH 1976). Thus, even if ambient asbestos concentrations could be maintained below this nominal detection limit, this would not suffice to ensure that lifetime risks to the general population were even as low as 10^{-5} to 10^{-4}.

E. Uncertainties in the Estimates

Although unusually extensive data are available on human responses to asbestos, it will be apparent from the analysis of data and discussion in this report that the estimates presented in Table 11 are subject to a number of uncertainties. These uncertainties arise from a number of sources: (1) difficulties in deriving dose-response data from the occupational studies; (2) discrepancies and variability within and between the occupational studies; (3) variability in the physical and biological properties of asbestos; and (4) uncertainties in extrapolating the occupational data to low exposure concentrations and to the general population. These points are discussed summarily below.

1. Difficulties in interpreting the occupational studies have been discussed fully in Section IV. Problems in measuring response include under-reporting of effects (especially of

mesotheliomas), too short followup in some studies, and competing mortality in others. Problems in relating response to dose include the pooling of groups with different exposures or different periods of followup, dose saturation effects, and overestimation of the effective exposure period. All these methodological deficiencies are discussed by Nicholson (1981) and in Table 5. In most cases their effect is expected to be to lead to underestimates of response, overestimates of effective dose, or both. This may be the reason for some of the low estimates of response per unit dose in Table 4 (see discussion in Table 5). However, we agree with Nicholson (1981) that the results of the five studies on which primary weight is placed in this report are comparatively free from these problems.

A more serious problem is the difficulty in deriving estimates of exposure for the critical periods in the past, before modern methods of measurement were developed. In this report we have relied primarily on the ingenious reconstructions of past data by Nicholson (1981). However, we recognize that in most cases Nicholson's estimates of cumulative exposure are subject to errors by factors of up to 3 or more.

2. Discrepancies and variability within and between the various studies are illustrated in Tables 4 and 10 and discussed in Table 5. For the five studies judged to provide the best data, estimates of response per unit dose all fall within a range of one order of magnitude. However, several other studies

provide substantially lower estimates, and these differences can be explained only partially by methodological deficiencies.

3. The data in Tables 4 and 11 provide no clear evidence for differences between the dose-response relationships for the three major types of asbestos that have been studied (chrysotile, amosite, and crocodilite). However, these materials differ and vary considerably in physical and chemical properties. Measurements of fiber concentrations are unlikely to provide an exact measure of biological activity, and some variation in dose-response coefficients is likely to arise from this source alone. Striking examples of this are the very low biological activity of asbestos at early stages in processing. In this report we have assumed that data for later stages in processing are generally more relevant to estimation of risks from environmental asbestos contamination. (However, this assumption will probably not apply to unprocessed forms of asbestos, such as that arising from uses of serpentine for road surfacing.)

4. Extrapolation of risks from occupational studies to predict general population risks requires a number of assumptions about the form of the relationships between response, dose, and time. (See discussion in Sections IV and V.A.) The most important assumption is that the relationship between dose and response is linear and nonthreshold, so that the observed risks of between 10^{-1} and 10^{-3} in exposed workers can be extrapolated to predict risks in the general population at exposure

levels 2-4 orders of magnitude lower. Although there are considerable theoretical and empirical reasons for assuming a linear, nonthreshold relationship (see Section V.A), it has to be recognized that the use of this assumption may lead to substantial overestimation of risks at low exposure levels. Other uncertainties are raised by limited knowledge of the relationships between risk, age, and duration of exposure. In this respect, the data for mesotheliomas are more consistent and more compatible with a reasonable theoretical model than those for lung cancer. Risk estimates for the latter may be substantially underestimated if age at first exposure is in fact important.

To summarize the likely magnitude of these uncertainties, we make the following points:

1. The estimates of general population risk tabulated in Table 11 are expected to be reliable, at best, to order of magnitude only. For this reason, a 10-fold range of values is given for each category of risks.

2. The 10-fold range of risk estimates presented in Table 11 reflects the variability in dose-response estimates derived from the occupational studies. It probably reflects variability in the properties of asbestos, errors in measuring both dose and response in the occupational studies, and uncertainties in relating response to dose.

3. Uncertainties in extrapolating to low doses and to full-lifetime exposures are not reflected in the range of estimates given in Table 11. If the assumption of linear, nonthreshold

dose-response relationships is incorrect, all the estimates in Table 11 would be too high.

4. Dose-response data on mesotheliomas are generally more consistent and can be extrapolated with greater confidence than those for lung cancers. The risk estimates for lung cancers in Table 11 are more uncertain and may be generally too low.

VI. GASTROINTESTINAL AND OTHER CANCERS

Several studies of occupationally exposed workers have shown significant excesses of cancers at sites other than the lung, pleura, and peritoneum (Selikoff et al. 1979, Nicholson et al. 1979, Henderson and Enterline 1979). The principal sites involved are the larynx and the gastrointestinal tract (esophagus, stomach, colon, and rectum); reported excesses of incidence of pancreatic cancer are probably due to misdiagnosis of peritoneal mesotheliomas. Cancers of the gastrointestinal tract probably result after inhaled asbestos is trapped in mucus in the respiratory tract and subsequently swallowed. Recent studies have also shown an association between asbestos concentrations in drinking water and excess cancers of the gastrointestinal tract in the general population (Kanarek 1980, Tarter 1981).

Several studies have indicated that cancers of the lung, pleura, and peritoneum comprise about 80 percent of the total number of excess cancers in workers exposed to asbestos (Selikoff et al. 1979, Newhouse and Berry 1979, Henderson and Enterline 1979, Nicholson 1981). Accordingly, the risk estimates presented in this paper would underestimate total cancer risks to workers by about 25 percent. We have not attempted to analyze the time-dependence and age-dependence of the gastrointestinal and other cancers, but we estimate that they could probably add about 20-30 percent to the risks tabulated in Table 11. This estimate is limited to cancers resulting from inhalation of asbestos

from ambient air; ingestion of asbestos (in water or food) would further increase the risks of gastrointestinal cancer.

REFERENCES

ADVISORY COMMITTEE ON ASBESTOS. 1979. Vol. 1: Final report on the Advisory Committee and Vol. 2: Papers prepared for the Advisory Committee. Health and Safety Commission. Her Majestry's Stationary Office, London

ARMITAGE, P., and DOLL, R. 1961. Stochastic models for carcinogenesis. In Proceedings of the Fourth Berkeley Symposium on Mathematical Statistics and Probability. Vol. 4. University of California Press. Pp. 19-38

AYER, H.E., ET AL. 1965. A comparison of impinger and membrane filter techniques for evaluating air samples in asbestos plants. Ann. N.Y. Acad. Sci. 132:274-287

CORNFIELD, J. 1977. Carcinogenic risk assessment. Science 198:693-699

CRUMP, K.S., HOEL, D.G., and GUESS, H.A. 1976. Fundamental carcinogenic processes and their implication for low-dose risk assessment. Cancer Res. 36:2973-2979

DAY, N.E., and BROWN, C.C. 1980. Multistage models and primary prevention of cancer. JNCI 64:977-989

DINMAN, B.D. 1972. "Non-concept" of "no-threshold" chemicals in the environment. Science 175:495-497

ERBEN, R. 1979. Proportion of current smokers (cigarettes) in Proceedings of the 4th World Conference on Smoking and Health, Stockholm, Almquist and Wiksell. Pp. 67-68 (see also: L.M. Ranstromm, ed. 1980. The Smoking Epidemic: A matter of world-wide concern. Almquist and Wiksell International, Stockholm)

GEHRING, P.J., and BLAU, G.E. 1977. Mechanisms of carcinogenesis: Dose response. J. Environ. Pathol. Toxicol. 1:163-179

GIBBS, G.W., and LACHANCE, M. 1974. Dust fiber relationships in the Quebec chrysotile industry. Arch. Environ. Health 28:69-71

HAMMOND, E.C., SELIKOFF, I.J., and SEIDMAN, H. 1979. Asbestos exposure, cigarette smoking, and death rates. Ann. N.Y. Acad. Sci. 330:473-490

HENDERSON, V.I., and ENTERLINE, P.E. 1979. Asbestos exposure: Factors associated with excess cancer and respiratory disease mortality. Ann. N.Y. Acad. Sci. 330:117-126

CCC85

HOLMES, S. 1965. Developments in dust sampling and counting techniques in the asbestos industry. Ann. N.Y. Acad. Sci. 132:288-297

KANAREK, M.S., CONFORTI, P.M., JACKSON, L.A., COOPER, R.C., and MURCHIO, J.C. 1980. Asbestos in drinking water and cancer incidence in the San Francisco Bay area. Am. J. Epidemiol. 54-72

LANGER, A.M., ROHL, A.N., WOLFF, M.S., and SELIKOFF, I.J. 1979. Asbestos, Fibrous Minerals and Acicular Cleavage Fragments: Nomenclature and Biological Properties. In Dusts and Diseases, edited by Lemen, R., and Dement, J.M. Pathotox Publishers, Inc. Illinois, pp. 1-22

LANGER, A.M. 1974. Approaches and Constraints to Identification and Quantitation of Asbestos Fibers. Environ. Health Perspect. 9:133-136

LANGER, A.M., MACKLER, A.D., and POOLEY, F.D. 1974. Electron Microspical Investigation of Asbestos Fibers. Environ. Health Perspect. 9:63-80

MCDONALD, J.C., and LIDDELL, F.D.K. 1979. Mortality in Canadian miners and millers exposed to chrysotile. Ann. N.Y. Acad. Sci. 330:1-9

NATIONAL ACADEMY OF SCIENCES (NAS). 1977. Drinking Water and Health. Vol. 1. Safe Drinking Water Committee, National Academy of Sciences, Washington, D.C.

NATIONAL ACADEMY OF SCIENCES (NAS). 1980. Drinking Water and Health. Vol. 3. Safe Drinking Water Committee, National Academy of Sciences, Washington, D.C.

NATIONAL CANCER INSTITUTE, 1978. Asbestos: An Information Resource. DHEW Publication (NIH) 78-1681, May, 1978

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH). 1972. Criteria for a Recommended Standard. Occupational Exposure to Asbestos. U.S. Dept of HEW, Public Health Service. Health Services and Mental Health Administration, NIOSH.

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH). 1976. Revised Recommended Asbestos Standard. U.S. Dept. of Health, Education, and Welfare. Public Health Service, Center for Disease Control, NIOSH.

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH). 1979. USPHS/NIOSH Membrane Filter Method for Evaluating Airborne Asbestos Fibers. DHEW Publication 79-127, U.S. Government Printing Office, Washington, D.C.

NEWHOUSE, M.L., and BERRY, G. 1976. Predictions of mortality from mesothelial tumors in an asbestos factory. Brit. J. Indus. Med. 33:147-151

NEWHOUSE, M.L., and BERRY, G. 1979. Patterns of disease among long-term asbestos workers in the United Kingdom. Ann. N.Y. Acad. Sci. 330:53-60

NICHOLSON, W.J., et al. 1972. Proc. Int. Symposium on Safety and Health in Shipbuilding and Shiprepairing, Helsinki. Occup. Safety and Health Series 27:27. International Labor Organization. Geneva, Switzerland.

NICHOLSON, W.J. 1976. Asbestos: The TLV approach. Ann. N.Y. Acad. Sci. 271:152-169

NICHOLSON, W.J., SELIKOFF, I.J., SEIDMAN, H., LILIS, R., and FORMBY, P. 1979. Long-term mortality experience of chrysotile miners and millers in Thetford Mines, Quebec. Ann. N.Y. Acad. Sci. 330:11-21

NICHOLSON, W.J. 1981. Dose-Response Relationships for Asbestos and Inorganic Fibers. Environmental Sciences Laboratory. Mount Sinai School of Medicine. New York, New York

PERCY, C., STANEK, E., and GLOECKLER, L. 1981. Accuracy of cancer death certificates and its effect on cancer mortality statistics. Am. J. Public Health 71:242-250

PETO, J. 1979. Dose-response relationships for asbestos-related disease: Implications for hygiene standards. Part II. Mortality. N.Y. Academy of Sciences 330:195-203

PETO, J. 1980. Lung cancer mortality in relation to measured dust levels in an asbestos textile factory.

POTT, F. 1978. Some aspects on the dosimetry of the carcinogenic potency of asbestos and other fibrous dusts. Staub Reinhalt. Luft. 38:486-490 (as cited in Langer et al. 1979)

SEIDMAN, H., SELIKOFF, I.J., and HAMMOND, E.C. 1979. Short-term asbestos work exposure and long-term observation. Ann. N.Y. Acad. Sci. 330:61-90

SELIKOFF, I.J., HAMMOND, E.C., and SEIDMAN, H. 1979. Mortality experience of insulation workers in the United States and Canada. Ann. N.Y. Acad. Sci. 330:91-116

SZALAI, A., ed. 1973. The use of time: daily activities of urban and suburban populations in 12 countries. The Hague, Mouton.

TARTER, M.E. 1981. Pattern Recognition in the Context of an Asbestos Cancer Threshold Study. Preprint: Proceedings of the Thirteenth Annual Symposium on the Interface: Computer Science and Statistics. To be published by Springer-Verlag

TOBACCO INTERNATIONAL, September 19, 1980

WINER, A.A., and COSSETTE, M. 1979. The effect of aspect ratio on fiber counts: A preliminary study. Ann. N.Y. Acad. Sci. 330:661-672

CUCPR