BIOLOGICAL EFFECTS OF ASBESTOS MINERALS

Epidemiological Findings

Numerous epidemiological studies have shown that occupational exposure to asbestos dust can lead to asbestosis (characterized primarily by pulmonary fibrosis); the formation of pleural plaques; a greatly increased risk of bronchogenic carcinoma; pleural mesothelioma; and peritoneal mesothelioma (Selikoff *et al.*, 1973; Newhouse, *et al.*, 1972; Elmes and Simpson, 1971; Selikoff and Churg, 1965; Bogovski *et al.*, 1973; and Lee, 1974). There is also evidence that the elevated risk of bronchogenic carcinoma as a result of occupational exposure to asbestos dust is largely (though perhaps not entirely) confined to cigarette smokers (Hammond *et al.*, 1975). Different types of asbestos may vary in their potency in relation to the effects mentioned above; but this has been difficult to evaluate owing to lack of precise information on degree of exposure, and various other problems.

Although there is little evidence concerning the possible effects of nonoccupational exposure, some cases of mesothelioma have been found among persons working in or living near shipyards and the wives of asbestos workers who handled the dusty clothes of their husbands (Newhouse and Thompson, 1965; Wagner *et al.*, 1960; Anderson *et al.*, 1976).

There has been much discussion of the possibility that the effects of inhaling asbestos mineral dust vary greatly with the length of the particles. However, no epidemiological evidence is available on this matter. The dust to which industrial workers are exposed typically consists of fibers varying in length from very long to extremely short. Fibers sufficiently large to be seen under a light microscope are invariably accompanied by large numbers of far smaller fibers.

It should be noted that all of the epidemiological evidence noted above has come from studies of people who have been exposed to dust from types of asbestos minerals that have been used commercially. There is no direct epidemiological evidence on the effects of various other types of fibrous minerals, some of which may perhaps find their way into drinking water.

The fact that exposure to air heavily polluted with asbestos mineral fibers often leads to the diseases mentioned above does not necessarily indicate that drinking water contaminated with an equally large number of such fibers may lead to the same diseases or perhaps some other diseases. (Site of cancer can vary depending upon the way in which individuals are subjected to a carcinogenic agent, for example: skin

TABLE IV-6 Observed
Cancer of Several Sites amc
Exposed to Asbestos Dus
Seidman, and Churg.

Site of Cancer	Grc Insu (Un Obs Dea
Buccal and pharnyx	15
Esophagus	14
TOTAL	29
Stomach	18
Colon-Rectum	47
TOTAL	94

exposure, inhalation, or inges
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It is important to note tha
numbers of asbestos minerals
the fibers that are inhaled are
trachea, enter the mouth, a
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cavity, esophagus, stomach, ar
to inquire whether death rate
higher among asbestos worker
and calendar-years of exposure
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asbestos fibers by way of i
esophagus, stomach, colon, an
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Group #1. The entire memb
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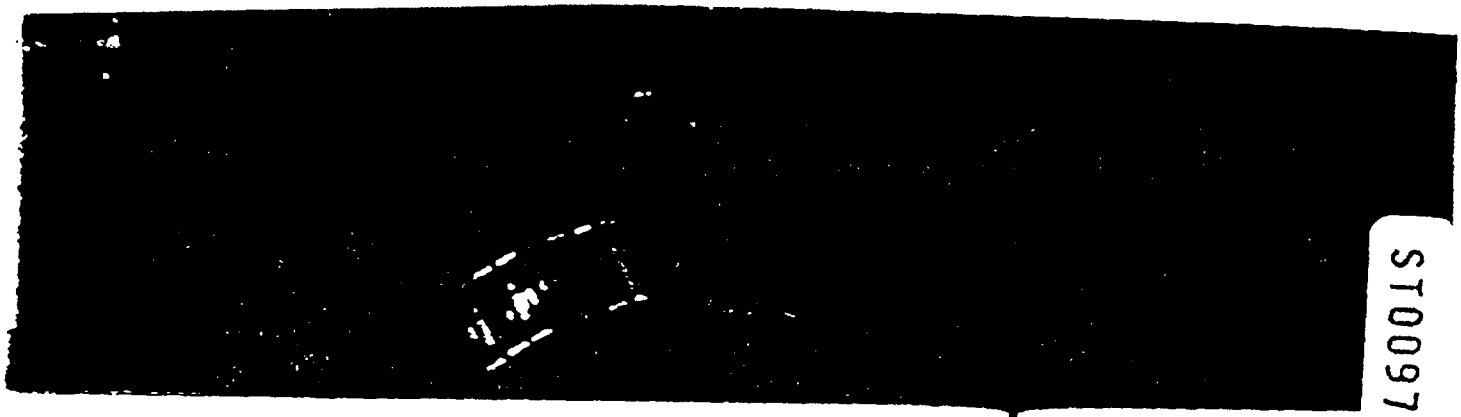
TABLE IV-6 Observed vs. Expected Number of Deaths from Cancer of Several Sites among Two Groups of Workers Occupationally Exposed to Asbestos Dust. Data Provided by Selikoff, Hammond, Seidman, and Churg.

	Group #1. Asbestos Insulation Workers (United States and Canada)			Group #2. "Amosite" Asbestos Factory Workers (New Jersey)		
Site of Cancer	Obs. Deaths	Exp. Deaths	Ratio	Obs. Deaths	Exp. Deaths	Ratio
Buccal and pharnyx	15	7.87	1.91	6	2.04	2.94
Esophagus	14	5.38	2.60	0	1.36	—
TOTAL	29	13.25	2.19	6	3.40	1.76
Stomach	18	11.23	1.60	10	4.89	2.04
Colon-Rectum	47	28.64	1.64	16	7.65	2.09
TOTAL	94	53.12	1.77	32	15.94	2.01

exposure, inhalation, or ingestion.) However, the hypothesis is tenable to the degree that it cannot be ruled out of consideration without evidence to the contrary.

It is important to note that workers exposed to air containing large numbers of asbestos minerals fibers inevitably ingest such fibers. Many of the fibers that are inhaled are later propelled upward from the lungs and trachea, enter the mouth, and are then swallowed. Thus, fibers are brought into direct surface contact with the epithelial lining of the buccal cavity, esophagus, stomach, and intestines. For this reason, it is pertinent to inquire whether death rates from cancer arising in these tissues are higher among asbestos workers than in the general population, age, sex, and calendar-years of exposure being taken into consideration. This has been investigated by Selikoff, Hammond, Seidman, Churg, and their associates. The data shown in Table IV-6 were provided by these investigators. It shows, for each of two groups of workers, the observed and expected number of deaths from cancer of sites directly exposed to asbestos fibers by way of ingestion: buccal cavity and pharynx, esophagus, stomach, colon, and rectum. The two groups are described below.

Group #1. The entire membership of the insulation workers union in the United States and Canada was registered as of January 1, 1967 (17,800 men). Many characteristics of the men were recorded, including date of



birth and onset of work with asbestos. These subjects have been traced through December 31, 1974.

Group #2. This group consisted of the entire workforce (1941–45) of a factory in an eastern U.S. city that manufactured "amosite" asbestos insulation materials (including insulating block and pipe covering and asbestos mattresses), for use by insulation workers in the construction industry, especially in ship construction and repair. The plant opened its doors in June 1941 and remained in business until November 1954. Very few of these production workers studied had had prior occupational exposure to asbestos. Between 1941 and the end of 1945, a total of 933 men were hired; of these, some worked for as little as one day, while others worked until 1954, when the plant closed. Of the 933 men, 881 (94.4%) were traced through December 31, 1973, and the remaining 52 were traced for a part of the period but later lost to follow-up.

For both groups, "observed," as shown in Table IV-6, means the number of men who were found to have died of the indicated cause during the period of observation. "Expected" numbers of deaths are based upon age-specific death rates for white males in the United States during each year of observation.

Group #1 was by far the larger of the two groups, and in consequence the figures are more stable statistically. In this group, the observed number of deaths was substantially higher than the expected number for cancer of each of the four sites. The findings were similar for Group #2, except in respect to cancer of the esophagus (zero observed versus 1.36 expected deaths).

In each of the two groups, the excess of observed over expected number of deaths (for all four sites of cancer combined) was highly significant statistically. It may be argued whether U.S. white males are an appropriate control group in relation to Group #2 (New Jersey "amosite" workers). Therefore, the expected numbers for Group #2 were recomputed based upon New Jersey mortality data. These expected numbers were a little higher than those shown in Table IV-6.

Similar findings in respect to gastrointestinal cancer have been reported by Mancuso (1965) and by Elmes and Simpson (1971). This, taken together with the data presented in Table IV-6, strongly suggests that ingestion of asbestos mineral fibers can result in an increased risk of cancer of several sites. If so, the degree of risk is probably highly dependent upon the number of fibers ingested and the duration of exposure. It may also depend upon the type and size of the fibers, as well as upon other agents to which the individuals have been exposed. For example, both smoking and alcohol increase the risk of cancer of the buccal cavity; and it is possible that exposure of the buccal mucosa to

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Experimental Studies

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asbestos mineral fibers simply increases the risk of cancer occurring among persons also exposed to one or both of these other two factors.

As described elsewhere in this report, mineral fibers—varying in concentration from trace amounts to hundreds of thousands per liter, or more—are present in drinking water in various locations in the United States. The situation in Duluth, Minn. (as described elsewhere), is of special interest from an epidemiological point of view.

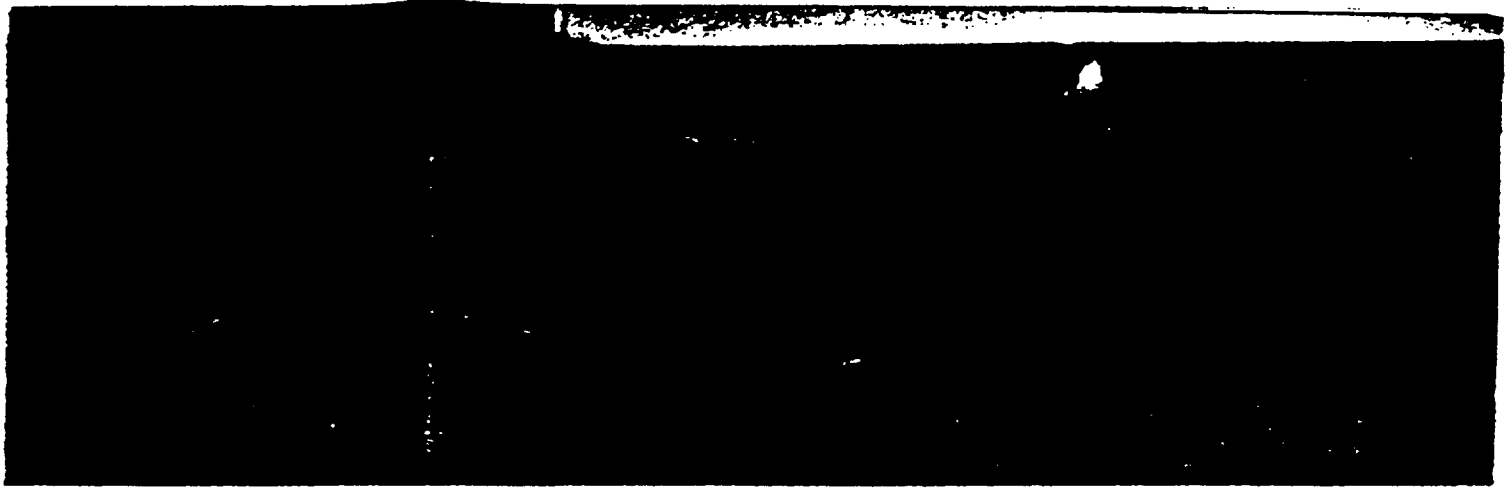
Studies of time trends in cancer death rates and incidence rates in Duluth (as compared with other cities) do not show any increases that could reasonably be attributed to the mineral fiber pollution of the drinking water of that city (Mason *et al.*, 1974; Levy, *et al.*, 1976).

Among persons occupationally exposed to asbestos dust, the increases in death rates from cancer of the stomach, colon, and rectum do not reach measurable proportions until many years after onset of exposure. The lapse of time since Duluth water was first heavily polluted with mineral fibers is not yet sufficient to have produced a significant increase in death rates from these cancers, even if it be assumed that the risk for residents of Duluth is as great as the risk for workers occupationally exposed to asbestos dust. If the risk is not so great—but still of important proportions—it will probably become apparent within another 5, 10, or 15 yr from now. An even lower risk might not become apparent for a much longer period of time—and then it would be difficult if not impossible to pinpoint the cause.

Experimental Studies

As discussed above, epidemiological studies of the population exposed have failed to detect any increase in gastrointestinal cancer that might be ascribed to the asbestos mineral fibers contained in some drinking water. But, since these results do not indicate conclusively that ingestion of water containing such fibers is without risk, and because these substances are widely distributed, it is important also to consider experimental evidence.

An Advisory Committee on Asbestos Cancers to the Director of the International Agency for Research on Cancer, meeting in 1972, considered whether there was evidence of an increased risk of cancer resulting from asbestos minerals present in water, beverages, food, or in the fluids used for the administration of drugs. They concluded that "such evidence as there is does not indicate any risk" (IARC, 1973). The group recommended that the effect of long-term ingestion of fibers of various sizes, shapes, and chemical compositions should be studied. The advisory committee's conclusion can hardly be taken as a categorical denial of



risk, but rather reflected the inconclusive character of the evidence then available.

Published results attest to the difficulties experienced by many investigators in studying, by means of experiments with animals, the biological effects and behavior of inorganic fibrous materials in general, and asbestos mineral fibers in particular. Several different approaches have been taken to the design of such experiments, including administration of different types and preparations of asbestos minerals and glass fibers to several species of experimental animals, by ingestion (feeding), inhalation, surgical implantation and injection. Experiments have also been conducted to test the response to fibers of cell cultures *in vitro*. The results of some representative experiments of these kinds are reviewed below.

Westlake *et al.* (1965, 1974) fed chrysotile to rats and noted the presence of fibers of the material in many sites in the colonic epithelium and lamina propria; and Webster (1974), after feeding crocidolite to baboons, showed that small numbers of fibers appeared in the ashed tissue of the gut wall. Gross *et al.* (1974) reported no such penetration. Bolton and Davis (1976), reporting on the short-term effects of chronic ingestion of asbestos minerals by rats, found no sign of cell penetration by fibers or damage to the gut mucosa. They concluded that penetration of the gastrointestinal wall, if it occurred, must have been on a very small scale.

Pontefract and Cunningham (1973) reported that chrysotile, administered to rats intragastrically by direct injection, was later found to be distributed to other organs, and suggested that the material penetrated the digestive tract. Gross (1974) questioned this interpretation of the study on the grounds that the method of administration was likely to have produced contamination of other organs by leakage. Cunningham and Pontefract (1974) reported the appearance of asbestos mineral fibers in fetal organs after injection of asbestos into the femoral veins of pregnant Wistar rats. While none of these papers demonstrated transport of fibers across tissue boundaries, some included the suggestion that the reported deposition of the material in other organs implied that transport had occurred. Reports such as these have, without resolving the matter, lent interest to the question whether or not human ingestion of asbestos may be accompanied by similar effects.

Experimental investigations with animals of the toxic effects of asbestos mineral fibers have not yet led to the development of an experimental model system that reproduces the putative effects of ingestion of such fibers by man. Nevertheless, various animal studies on

the toxicity of asbestos have beer
experiments are now in progress.

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negatives remains.

More recently, Gibel *et al.* (197
(20 mg/day) to 50 Wistar rats.
(chrysotile, 53%), sulfated cell
authors reported 12 malignant t
material, 2 malignant tumors in
of rats that were fed the same ar
malignant tumors appearing in
comprised 1 lung carcinoma,
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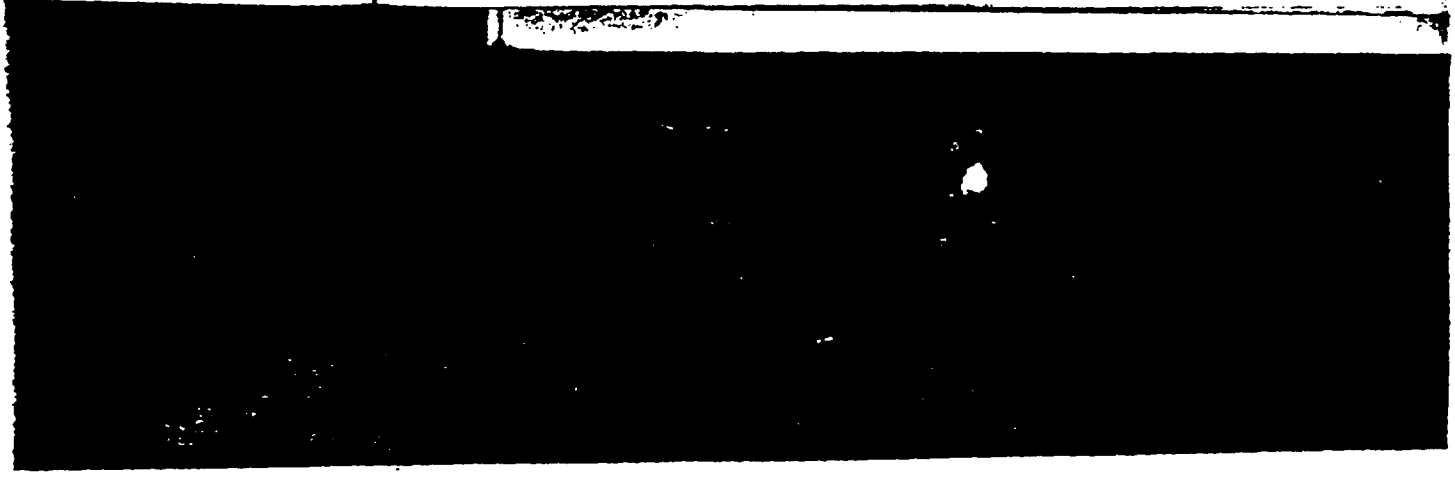
the toxicity of asbestos have been reported, and some large-scale feeding experiments are now in progress.

In the experimental studies by Wagner *et al.* (1974), using the UICC reference samples, no association was found between exposure to asbestos by inhalation and excess gastrointestinal cancers. Thus, this animal study did not duplicate the positive epidemiological findings previously discussed. The possible effects of ingested asbestos also were studied experimentally. Several animal feeding studies with asbestos are reported to have shown no increase in cancer with this route of exposure (Bonser and Clayson, 1967; Smith, 1973; and Gross *et al.*, 1974). The asbestos minerals tested included crocidolite, chrysotile, and "amosite." However, none of these studies would be considered adequate under modern constructs of chronic toxicity testing (National Academy of Sciences, 1975; Sontag *et al.*, 1976), and so the possibility of false negatives remains.

More recently, Gibel *et al.* (1976) fed filter material containing asbestos (20 mg/day) to 50 Wistar rats. This material was composed of asbestos (chrysotile, 53%), sulfated cellulose and a condensation resin. The authors reported 12 malignant tumors in the group that was fed the filter material, 2 malignant tumors in a control group, and 3 in a similar group of rats that were fed the same amount of a standard grade of talc. The 12 malignant tumors appearing in the group receiving the filter material comprised 1 lung carcinoma, 3 reticular cell sarcomas, 4 kidney carcinomas, and 4 liver carcinomas. In the control animals and the talc-fed animals the malignant tumors were all liver carcinomas. The average survival times were 441 days in the filter-fed group, 702 days in the controls and 649 days in the talc-fed group. The presence of other substances besides asbestos in the filter material and the manner of reporting the malignant tumor counts suggests that further studies are needed, with asbestos alone, before firm conclusions can be drawn from the results of this study.

A fundamental difficulty associated with these studies is that they seek to duplicate an effect in man by means of animal models that have neither been validated for the route of administration nor for the materials of interest. Negative results may be interpreted as indicating either the absence of the effect under investigation or, simply, as further proof that the model was not valid to start with. At present, the existing animal data base leaves the matter unresolved.

Results obtained from some experiments with animals by direct application of fibrous materials, and with *in vitro* systems, have been adduced to support the view that ingestion of drinking water containing mineral fibers should not be expected to lead to any observed increase in



gastrointestinal cancer in the general population. These experiments are interpreted to show the dependence of biological effect on the size of fibers. In this approach, large quantities of mineral fibers, of various size distributions, are injected into the pleural or peritoneal cavity. Stanton *et al.* (1969) wrapped a plaque of fibrous material around the lung in their animal model studies. This discussion will be limited to the results reported with respect to a carcinogenic response.

The results obtained from these experiments, in which the material under investigation is deposited or applied directly, are limited by the statistics of their individual designs, methods of fiber preparation, and determination of fiber size distribution. They may be summarized as follows:

1. Tumor induction is related to fiber size, shape and durability, and not to the source of the fiber or its chemical composition (Stanton and Wrench, 1972; Stanton, 1973; Stanton *et al.*, 1977; Pott and Fredricks, 1972; Pott *et al.*, 1976).
2. In cell cultures, particles less than 20 μm in length do not induce growth of fibroblasts (Maroudas *et al.*, 1973).
3. Chrysotile containing particles less than 5 μm in length did not elicit a carcinogenic response (Smith, 1974; Smith *et al.*, 1972).
4. Defining a "significant" asbestos fiber as one less than 0.5 μm in diameter and greater than 10 μm in length, there was good agreement between the number of these "significant" fibers in an asbestos sample and its degree of carcinogenicity (Wagner *et al.*, 1973).
5. Man-made mineral fibers less than 1.5 μm in diameter and greater than 8 μm in length have the highest probability of inducing a biological response. The response appears to increase with increasing fiber length at fiber diameters less than 1.5 μm (Stanton *et al.*, 1977).

In contrast to the results summarized above, two other investigations appear to show a different dependence of biological effect on fiber length. In one of these, Pott *et al.* (1972) injected 100 mg of two different preparations of chrysotile intraperitoneally, one sample contained 95% of particles less than 5 μm in length and the other (a milled sample) contained 99% less than 3 μm in length. Both groups gave approximately the same tumor incidence, although the latency period was greater in the latter group. The data subsequently were reported in greater detail by Pott *et al.* (1974). In this, for the unmilled chrysotile, 78.7% of the fibers were less than 2 μm in length and 93.9% were less than 5μm in length; while for the milled sample, 97.4% were less than 2 μm in length and 99.8% were less than 5 μm in le
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fibers were carcinogenic, thou
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Another possible exception
(1976) describing experiments
different preparations of glass
experimental animals. The cha
the results are summarized belo

Characteristics of Glass Fibers

Diameter <0.5μm	
Diameter <1μm	
Median diameter (μm)	
Length >20μm	
Length >50μm	
Median length (μm)	
Results	
No. with mesothelioma	
Absence of hyperplasia in mesothelial cells	

The same weight (20 mg)
there were about 1,000 times
coarser glass (Wagner *et al.*, 19
finer sample contained more "a

On the basis of the animal
infer that, in these experiment
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...two other investigations ...al effect on fiber length. ...0 mg of two different ...ample contained 95% of ...ther (a milled sample) ...ups gave approximately ...eriod was greater in the ...ed in greater detail by ...tile, 78.7% of the fibers ...ss than 5μm in length; ...n 2 μm in length and

99.8% were less than 5 μm in length. After administration of the unmilled chrysotile sample, the elapsed time to appearance of first tumor was 270 days with a tumor incidence of 37.5%, while for the milled chrysotile sample the time to appearance of first tumor was 400 days, with a tumor incidence of 30%. This study would indicate that both short and long fibers were carcinogenic, though the milled sample seems to have been somewhat less active than the unmilled one. But in the absence of information about the distribution of fiber diameters and the number per unit weight it is impossible to assign activity to a particular size class with certainty.

Another possible exception is contained in a paper by Wagner *et al.* (1976) describing experiments with glass fibers. In these experiments two different preparations of glass fibers were injected intrapleurally into experimental animals. The characteristics of the fiber preparations and the results are summarized below.

Characteristics of Glass Fibers

	Finer	Coarser
Diameter <0.5μm	99%	—
Diameter <1μm	—	17%
Median diameter (μm)	0.12	1.8
Length >20μm	2%	—
Length >50μm	—	10%
Median length (μm)	1.7	22
Results		
No. with mesothelioma	4/32	0/32
Absence of hyperplasia in mesothelial cells	1/32	12/32

The same weight (20 mg) of each material was used per animal, and there were about 1,000 times more fibers in the finer glass than in the coarser glass (Wagner *et al.*, 1976). The results indicate, therefore, that the finer sample contained more "active" fibers than did the coarser.

On the basis of the animal experiments noted above, it is possible to infer that, in these experimental systems, short fibers may be biologically unreactive, or less reactive, than longer ones. Since the majority of the fibers that are found in water are short (<5 μm), these may be similarly unreactive, and this may account for failure to detect any increased incidence of various gastrointestinal cancers related to ingestion of mineral fibers in water.

Another hypothesis can be offered for the inability to detect, in the general population, any increase in gastrointestinal cancers attributable to ingestion of asbestos mineral fibers in water. Assuming that the heavily exposed asbestos workers (who showed an excess gastrointestinal cancer rate) swallowed a large fraction of the fibers, of all sizes, that they inhaled, the dose so acquired would have been several orders of magnitude greater than that ingested in drinking water by members of the general population. It would therefore be expected that any excess gastrointestinal cancer due to fibers in water would be much smaller in the general population than that found in asbestos workers, and if sufficiently low might be very difficult to detect against the usual background incidence of cancers of the colon, sigmoid, and rectum, and less so for cancers of the esophagus and stomach.

The results of experiments on the chronic toxicity of asbestos mineral fibers fall very far short of rigorously clarifying the risk to health that may be associated with potable water—either qualitatively or quantitatively. Although no harmful effects of fibrous contamination of drinking water on the present state of public health have been demonstrated, it is possible, as noted in the discussion of the epidemiology, that they may be observed in the future.

The development of gastrointestinal cancers among the heavily exposed asbestos workers has been slow (20 to 30 yr or more), and the possibility of long-delayed effects of mineral fiber ingestion through water cannot be ignored. Research on the unresolved problems of the chronic effects of ingesting asbestos mineral fibers therefore merits strong support.

ORGANIC PARTICULATES IN WATER

The organic particulate matter found in natural water systems may be classified as follows:

1. Organic matter associated with soil particles.
2. Organic particles from effluent of sewage treatment facilities and industrial waste disposal facilities.
3. Plant and animal debris.
4. Microorganisms.
5. Organic colloids.

Microorganisms are discussed in Chapter III; the other categories are discussed below.

Organic Matter Associated w

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In order to understand the
systems, it is necessary to
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in strong base but insoluble
acid and base; and humin is

Humic acids contain p

tors that may account for the observed differences in clinical studies as well as the effects of diet, race, and climate.

Research should also be designed to evaluate the possible essentiality of arsenic for humans—a requirement that has been demonstrated in four mammalian species. In the absence of new data, the conclusion reached in the third volume of *Drinking Water and Health* remains valid, i.e., "If 0.05 mg/kg of dietary [total] arsenic is also a nutritionally desirable level for people, then the adequate human diet should provide a daily intake of approximately 25 to 50 μg. The current American diet does not meet this presumed requirement" (National Research Council, 1980). The unresolved status of this issue is further reason for maintaining the current MCL for arsenic.

ASBESTOS

Asbestos fibers in drinking water and their putative health effects were reviewed in the first volume of *Drinking Water and Health* (National Research Council, 1977, pp. 144-168). At that time, there were only limited data from which to evaluate the potential adverse health effects of orally ingested asbestos. A number of research recommendations suggested in that volume have been, to some extent, fulfilled. Advances have been made in the detection, identification, and quantification of asbestos fibers in drinking water. Several chronic feeding studies completed since that time have failed to show an effect between the ingestion of various fiber types and the development of cancer at any site.

There have also been a number of epidemiological studies in which the exposure to asbestos in drinking water and the incidence of cancer at selected sites have been investigated. This review is limited to a discussion and evaluation of those studies and the development of a model to predict the risks, if any, from such exposure.

BACKGROUND

A marked increase in the incidence rates of lung cancer and both pleural and peritoneal mesothelioma has been observed in workers exposed to asbestos through inhalation (International Agency for Research on Cancer, 1977). An excess of gastrointestinal tract cancers has also been found in these occupationally exposed groups.

The general population may be exposed to asbestos fibers in "air, beverages, drinking water, food and pharmaceutical and dental preparations and by consumer use of asbestos containing products" (International

Agency for Research on Cancer, 1977). The possible effects of such exposure from drinking water became a matter of some public concern when the Duluth, Minnesota, water supply obtained from Lake Superior was found to be heavily contaminated with asbestos fibers.

The potential hazard from asbestos in drinking water was considered by the American Water Works Association Research Foundation (1974). However, the report of this group refers only to asbestos fibers released into the water from asbestos-cement pipe. It concluded, "Calculations comparing the probable ingestion exposure in occupational groups to that likely to occur as a result of ingestion of potable water from asbestos-cement pipe systems suggest that the probability of risk to health from the use of such systems is small approaching zero." This conclusion has been questioned (McCabe and Millette, 1979; U.S. Environmental Protection Agency, 1979).

EXPOSURE TO ASBESTOS FROM DRINKING WATER

The results of an extensive EPA survey of asbestos concentrations in drinking water have recently been published by Millette *et al.* (1979). A summary of the data is given in Table III-1. More than 20% of the cities surveyed had water containing more than 1 million fibers per liter, as measured by transmission electron microscopy (TEM), and almost 11% of them had water containing more than 10 million fibers per liter. (This EPA survey was not a representative sampling of U.S. water supplies: therefore, caution should be exercised when drawing conclusions from the table.) The asbestos in these supplies was derived from a variety of sources: min-

TABLE III-1 Asbestos Concentrations in Drinking Water from 365 Cities in 43 States, Puerto Rico, and the District of Columbia, as Measured by Transmission Electron Microscopy[a]

Asbestos Concentration, 10^6 fibers/liter	Number of Cities	Percentage of Samples
Below detectable limits	110	30.1
Not statistically significant	90	24.7
Less than 1	90	24.7
From 1 to 10	34	9.3
Greater than 10	41	11.2
TOTAL	365	100.0

[a]Data from Millette *et al.*, 1979.

ing process discharge into Lake Superior, natural erosion of serpentine rock in the Bay Area of California and in Seattle, asbestos-cement roofs, and asbestos-cement pipe. Some of the water supplies surveyed are now being filtered to reduce the asbestos fiber levels.

Asbestos concentrations in water have also been reported as mass per liter, but this measurement is not considered useful in the evaluation of possible carcinogenic effects (see Harington, 1981). Experiments in which gelatin pellets of asbestos were implanted into the pleura of rats indicate that the physical dimensions of the fibers, but not their type, are important and that the long, thin fibers are the most effective inducers of mesotheliomas (Stanton *et al.*, 1981). The relevance of this work to the carcinogenicity of asbestos in humans has been reviewed by Selikoff and Lee (1978) and more recently in great detail by Harington (1981). Harington concluded that the "Stanton hypothesis," emphasizing the fiber dimensions as important determinants of carcinogenicity, appeared to hold true for the very limited, relevant data on humans. However, the critical fiber dimensions in humans, at least for mesothelioma, are probably much smaller than those suggested in the rat experiments, the most carcinogenic fibers apparently being those with diameters less than 0.05 μm and lengths greater than 3 μm (Harington, 1981).

The size distribution of asbestos fibers in water varies by source (Millette *et al.*, 1980). The smallest fibers are found in water contaminated by the natural erosion of serpentine rock. These fibers have an average width of approximately 0.04 μm and an average length of 1 μm, compared to an average width of 0.1 μm and an average length of 1 μm for fibers from the Whitekloff asbestos mine, which was associated with a high incidence of mesothelioma (Harington, 1981). Thus, the average aspect ratio (length: width) for the waterborne fibers from natural sources is approximately 3 times greater than that for the airborne fibers found in the Whitekloff mine. Approximately 10% of the waterborne fibers are longer than 3 μm. Water contaminated by asbestos from asbestos-cement pipe contained fibers with an average diameter of 0.044 μm and an average length of 4.3 μm, which gives an average aspect ratio of 121 (Millette *et al.*, 1980). Approximately 30% of these fibers were longer than 3 μm. The committee concluded that there appears to be no reason to consider fibers from either source as free from risk in comparison to fibers found in occupational settings.

Harington (1981) very tentatively concluded that fiber dimensions "may in time be applicable to regulatory practice," essentially agreeing with Selikoff and Lee (1978) that "there seems to be little basis . . . at present . . . for seeking to base selective control measures on such hypotheses," i.e., fiber dimensions. The committee concurs with these authors.

ESTIMATING THE CANCER RISK FROM SWALLOWED ASBESTOS FOLLOWING OCCUPATIONAL EXPOSURE

There have been a number of epidemiological studies of gastrointestinal (GI) cancer (in this report this term refers only to cancer of the esophagus, stomach, small intestine, colon, and rectum) associated with occupational exposure to asbestos. The reported relative risks (RR's) of observed to expected cases in these studies are not very large (between 1.5 and 3), and a number of other studies have failed to detect any risk of GI cancer (Advisory Committee on Asbestos, 1979). Thus, one must consider the possibility that the studies with positive results might have been affected by unrecorded biases. However, careful review of these studies by many authors and by a Working Group of the International Agency for Research on Cancer concluded that the association was one of cause and effect (Advisory Committee on Asbestos, 1979; International Agency for Research on Cancer, 1977; Miller, 1978). The committee concurs with these reviews.

Assuming that the exposed and unexposed workers have the same general risk factors for GI cancers and that their observed GI cancer rates are r_e and r_u, respectively, then the GI cancer burden from the exposure can be expressed either as a ratio of rates, or relative risk, i.e., $RR = r_e/r_u$, or a difference of rates, i.e., $DR = r_e - r_u$. For general risk assessment purposes, these can be expressed on a per unit exposure basis by dividing RR or DR by the exposure dose.

Both RR and DR are valid measures of the risk to the occupational group, but they implicitly make very different assumptions about the risks to individuals with different risk factors. The relative risk (or multiplicative) index (RR) implicitly assumes that the risk of GI cancer is increased in proportion to the individual's underlying risk. The difference of risk (or additive) index (DR) implicitly assumes that the amount of increased risk of GI cancer is independent of the individual's underlying GI cancer risk.

None of the occupational studies of exposure to asbestos and GI cancer provided data that would enable the committee to distinguish between these possible models (i.e., the multiplicative or additive models, or something intermediate). In fact, because of the limited data and lack of any known strong risk factors for GI cancer, except for increasing age, it is difficult to know how the studies could shed light on this issue. However, selection of a model is of critical importance in risk assessment and cannot be avoided. In the absence of evidence to the contrary, this committee has usually selected the additive model. For asbestos, however, some information suggests that the multiplicative model is to be preferred. The data relating lung cancer risk to joint exposures to asbestos and cigarettes are inadequately described by the additive model, whereas the multiplicative

model is generally regarded as providing a reasonable description of the data (see Saracci, 1977). The results of Seidman *et al.* (1979), who studied lung cancer in persons exposed for a limited time in an amosite asbestos factory in New Jersey, indicate that the excess lung cancer increased with age at exposure. Therefore, the additive model is clearly inadequate, but the data are again reasonably compatible with a multiplicative model. Unfortunately, the observations by Seidman *et al.* (1979) may have been severely confounded by possible age-related differences in cigarette-smoking habits, but a very similar pattern of risk was also observed for other "asbestos disease," i.e., asbestosis and other noninfectious pulmonary diseases, mesotheliomas, and cancers of the esophagus, stomach, colorectum, larynx, buccal cavity, pharynx, and kidney. The relative risks associated with exposure to asbestos are similar for all subsites in the GI tract (Miller, 1978; National Research Council, 1977). Although the above information may not constitute proof for the correctness of the multiplicative model, there is clearly no basis for favoring an alternative model for risk assessment.

Studies of Asbestos Workers

Table III-2 shows the results of five cohort studies of GI cancers in asbestos workers. The reports of Newhouse and Berry (1979) and Henderson and Enterline (1979) only give data for GI and certain other sites combined (see footnote to Table III-2). The committee adjusted the RR's to refer only to GI cancer by assuming that all excess deaths occurred in this grouping.

To make the observed RR's of use in estimating the possible consequences of ingesting asbestos fibers in drinking water, it is essential to have some measure of the amount of asbestos swallowed by these workers. Such estimates can only be approximate because so few measurements of airborne asbestos have been made in the workplace (and then, often years after actual exposure) and because those measurements then had to be applied to broad categories of employees (Peto, 1979). Table III-3 shows the estimates derived either from the published studies or from personal communication with the authors.

CONVERTING RISK TO ASBESTOS WORKERS TO RISK FROM SWALLOWED ASBESTOS

In converting the observed risk of GI cancers in asbestos workers to risk of GI cancer from ingested asbestos fibers, a number of steps should be clearly distinguished.

TABLE III-2 Results of Five Cohort Studies of Gastrointestinal Tract Cancer in Asbestos Workers

Exposed Group	Cancer Site Codes[a]	Deaths				Reference
		Observed (O)	Expected (E)	Ratio, O/E	RR[b]	
U.S. and Canadian insulation workers	150-154	94	59.4	1.58	1.58	Selikoff *et al.*, 1979
N.Y. and N.J. insulation workers	150-154	43	15.1	2.85	2.85	Selikoff *et al.*, 1979
U.S. factory workers	150-154	32	21.5	1.49	1.49	Seidman *et al.*, 1979; U.S. EPA, 1979
London factory workers	150-158[c]	40	34.0	1.18	1.32	Newhouse and Berry, 1979
U.S. factory workers	150-159	55	39.9	1.38	1.55	Henderson and Enterline, 1979

[a]150 = esophagus
151 = stomach
152 = small intestine
153 = large intestine
154 = rectum
155 = liver
156 = gallbladder
157 = pancreas
158 = retroperitoneum and peritoneum
159 = gastrointestinal tract, not otherwise specified
[b]Standardized mortality ratio = 100 × RR (relative risk for cancer site codes 150-154 [see text])
[c]Excluding mesotheliomas.

Step 1: Measurement of Dose and Adoption of Risk Model

Since the committee is interested in effects at low doses, a model relating relative risk to dose must be used. The standard linear dose-effect model may be written:

$$RR = 1 + a \times \text{dose}. \quad (1)$$

where a is a constant to be estimated. For asbestos workers, dose is a function of both intensity and duration of exposure. Intensity of exposure is measured in terms of the number of fibers that can be seen with the light microscope (LM) per milliliter of air. Dose is the simple product of inten-

TABLE III-3 Average Asbestos Exposure Estimated for the Workers in Studies Shown in Table III-2 and Calculation of Increment in Relative Risk Based on Doses Measured with the Light Microscope

	Exposure				
RR	Intensity (LM fibers/ml air)	Duration (years)	Cumulative Dose (LM fibers/ml air)(years)	Relative Risk per Unit Cumulative Dose[a]	Reference
1.58	15	34	510	0.00114	Selikoff *et al.*, 1979
2.85	15	40	600	0.00308	Selikoff *et al.*, 1979
1.4	40	1.9	76	0.00645	Seidman *et al.*, 1979; U.S. EPA, 1979
1.32	10-30	—	170[b]	0.00188	Newhouse and Berry, 1979
1.55	—	—	498[c]	0.00110	Henderson and Enterline, 1979

[a]Increase in RR for each year of exposure to one fiber identified by the light microscope (parameter *a* in equations 1 and 2).

[b]Calculated from Newhouse and Berry (1979) using the method from U.S. Environmental Protection Agency, 1979.

[c]Calculated from Table 2 of Henderson and Enterline (1979), assuming 1 mppcf (million particles per cubic foot) = 2 fibers/ml.

sity of exposure and duration of such exposure, usually measured in years (Y), and expressed as numbers of LM fibers/ml air times Y. It is not self-evident that equal doses measured in this way must have equal effects (e.g., cigarette smoking measured as pack-years does not have a fixed effect on lung cancer incidence but is greater at a low intensity for a long time); however, authors of all studies on asbestos-induced cancer concur that measurement of dose on this scale fits the data reasonably well and no alternative model has been seriously proposed. In particular, there is evidence that even the briefest exposures (less than 6 months) have very long-term effects on lung cancer rates with no diminution of the associated RR with the passage of time (up to 35 years) after exposure (Seidman *et al.*, 1979). A linear dose-effect relationship for lung cancer and exposure to asbestos is most clearly shown by results reported by Henderson and Enterline (1979). For GI cancers, too few data have been published to establish or refute linearity, even at high doses. Peto (1979) has discussed these issues at some length.

Assuming the dose-effect model given by equation (1), one may estimate the value of parameter a as follows:

$$a = (RR - 1)/\text{dose}. \quad (2)$$

The calculated values of a from the different studies are given in the Table III-3.

In the dose-effect model given by equations (1) and (2), dose is used to mean the cumulative dose calculated up to the age at which the cancer is diagnosed. This may be considered as the correct dose for a no-latent-period model, and as having general applicability if the dose was received over a brief period some time before the associated cancer was recorded. This would result in an overestimation of the dose to workers still occupationally exposed to asbestos when their cancer rates were being observed. This overestimation will generally be small, and as long as we adopt the same convention when calculating the risk from asbestos in the water supply, the error will have a very small effect on the computation of risk.

Step 2: Conversion of Dose of Asbestos Inhaled to Dose of Asbestos Swallowed

Since the excess GI cancers in the workers are assumed to be caused by the asbestos fibers that these workers swallowed rather than simply inhaled, the dose calculated in Step 1 must be converted to fibers swallowed. The committee estimated that

breathing 1 LM fiber/ml for 1 year
$= 588 \times 10^6$ LM fibers swallowed. (3)

where 588×10^6 is the product of 10^6 (ml in m^3), times 8 (m^3 of air breathed per day at work), times 5 (days worked per week), times 49 (number of weeks worked per year), times 0.3 (proportion of inhaled fibers that are subsequently swallowed). Only this last factor of 0.3 needs discussion.

Studies of short-term (30-minute) inhalation exposures of rats to Union Internationale Contre le Cancer (UICC) standard reference samples of asbestos indicated that an average of 40% of the various types and sizes of inhaled material is deposited somewhere in the respiratory tract (Morgan *et al.*, 1975). Although there is a lack of relevant data on the deposition of asbestos fibers in humans, Dement (1979) used a mathematical model of fiber behavior to calculate that roughly 28% of inhaled chrysotile fibers is deposited in humans and that approximately twice as much amosite is de-

posited. Morgan *et al.* (1975) did not find such a large difference in their study on rats, although they did find that the deposition of one form of chrysotile was 25% less than that of amosite. Evans and his colleagues (1973) reported that approximately 65% of the material deposited in rats is cleared through the GI tract within a month. Their results suggest that this clearance process continues until almost all the deposited material is cleared. Relevant data on clearance in humans are again lacking, but the work of Cohen *et al.* (1979) on the clearance of ferrosoferric oxide (Fe_3O_4) dust from experimentally exposed men suggests that lung clearance in humans is similar to that in rats and that most of the deposited dust will be cleared in humans. For rats, then, approximately 40% of inhaled asbestos will enter the GI tract and a somewhat lower figure of 30% appears to be a reasonable estimate for humans. Note: no allowance has been made for the possibility that asbestos is ingested directly. Neglect of this could result in an overestimation of the effect of a unit dose of swallowed asbestos.

Step 3: Conversion of Number of Fibers Seen by Light Microscope to Number of Fibers Seen by Transmission Electron Microscope

Asbestos contamination of drinking water is measured in terms of number of fibers seen with the transmission electron microscope (TEM). To convert from light microscope (LM) measurements to TEM measurements, the committee has used the following equation:

$$1 \text{ LM fiber} = 50 \text{ TEM fibers.} \tag{4}$$

This equation is based on the report of Lynch *et al.* (1970), who found that a conversion factor of 50 is roughly appropriate for asbestos exposure from textile manufacturing, friction work (i.e., mixing, grinding, cutting, and drilling), and pipe manufacturing. Conversion factors larger than this have been reported in the literature, e.g., McCabe and Millette (1979) used 100 and the U.S. Environmental Protection Agency (1979) used 200 in the criteria document, but these estimates do not appear to be based on the industrial exposure data considered in this chapter.

The relative risk equation (1), which applies to measurements made by the LM, may thus be expressed as follows for doses swallowed, as measured by the TEM:

$$\begin{aligned} RR &= 1 + [a/(588 \times 10^6 \times 50)] \times \text{dose (in TEM fibers swallowed)} \\ &= 1 + (a/0.0294) \times \text{dose (in TEM fibers swallowed}/10^{12}) \\ &= 1 + b \times \text{dose (in TEM fibers swallowed}/10^{12}). \end{aligned} \tag{5}$$

Estimated values of b derived from the studies listed in Table III-3 are given in Table III-4. These values vary from 0.039 to 0.22; a "best" value (obtained by weighting the individual estimates of b inversely proportional to their estimated variance) is approximately 0.05.

Thus, the RR for GI cancer for a person who has swallowed $h \times 10^{12}$ TEM fibers can be estimated as follows:

$$RR = 1 + 0.05 \times h. \tag{6}$$

PREDICTING THE RESULTS OF EPIDEMIOLOGICAL STUDIES OF GI CANCER RISK FROM ASBESTOS-CONTAMINATED DRINKING WATER

Equation (6) makes direct estimates of relative risks observable in epidemiological studies correlating exposure to asbestos in drinking water and GI cancer mortality rates. It is also reasonable to assume that the relative risks derived from this equation will be approximately correct if applied to studies of cancer incidence.

A man who has been drinking water containing $d \times 10^6$ TEM fibers/liter for n years has consumed $h \times 10^{12}$ TEM fibers, where

$$h = n \times 365.25 \times 2 \times d \times 10^{-6}.$$

His relative risk of GI cancer in this nth year of exposure is:

$$RR = 1 + 0.05 \times h \tag{6}$$
$$= 1 + 3.6525 \times 10^{-5} \times n \times d. \tag{7}$$

For example, if $n = 20$ years and $d = 15 \times 10^6$ TEM fibers/liter, then the associated relative risk is:

$$RR = 1 + 3.6525 \times 10^{-5} \times 20 \times 15$$
$$= 1.011.$$

Equation (7) is directly applicable to epidemiological studies in which contamination of drinking water took place for only a limited time, e.g., in Duluth. To make equation (7) applicable to epidemiological studies in areas where the contamination has been present for a very long time, the different durations of exposure of different age segments of the population first need to be evaluated. The associated relative risks must then be calculated from equation (7), and then some "average" determined. The exact

TABLE III-4 Estimates of Increment in Relative Risk of Gastrointestinal Cancers per Unit Exposure

a, Increment per LM Fibers/ml Air Times Years	*b*, Increment per 10^{12} TEM Fibers Swallowed	Reference
0.00114	0.0388	Selikoff *et al.*, 1979
0.00308	0.1048	Selikoff *et al.*, 1979
0.00645	0.2194	Seidman *et al.*, 1979; U.S. Environmental Protection Agency, 1979
0.00188	0.0640	Newhouse and Berry, 1979
0.00110	0.0374	Henderson and Enterline, 1979

form of this average would depend on the type of statistic used to describe the overall relative risk of GI cancer in the exposed community.

CONVERTING RR'S TO LIFETIME GI CANCER RISKS

As discussed above, expressing the risk from any agent in terms of relative risks implies that the effect of the agent is to multiply whatever "normal" or background cancer rate exists. Table III-5 shows the results of calculations based on equation (6), indicating the consequences for U.S. white males who drink 2 liters of water containing $d \times 10^6$ TEM fibers/liter daily throughout life. To understand this table, consider a man aged 57.5 years. He has consumed water containing $57.5 \times 365.25 \times 2 \times d \times 10^6$ TEM fibers, or 42.0×10^9 TEM fibers up to this point in his life, and his relative risk of GI cancer is currently:

$$\begin{aligned} RR &= 1 + 0.05 \times 0.0420 \times d \\ &= 1 + 0.0021 \times d. \end{aligned}$$

The additional RR is thus $0.0021d$, and the additional probability of GI cancer occurrence in this, his 58th year is:

$$0.0021d \times 131.1/10^5 = 0.2754d/10^5,$$

where $131.1/10^5$ is the 1970 GI cancer incidence rate in the United States for white males in the 55- to 59-year age group (Cutler and Young, 1975). Summing these additional probabilities of GI cancer deaths up to age 70 gives us a lifetime risk of $9.1060d/10^5$.

TABLE III-5 Gastrointestinal Cancer Incidence in White Males[a] and Calculation of Additional Risk from Swallowing $2 \times d \times 10^6$ TEM Fibers Daily Throughout Life. Additional Relative Risk Per 10^{12} TEM Fibers Swallowed Assumed to be 0.05.

Age Group, years	Incidence Rate per 100,000/year[b]	Asbestos Swallowed, 10^9 TEM Fibers	Additional Relative Risk	Additional Incidence Rate
10-14	0.1	9.13*d*	0.00046*d*	0.0000*d*
15-19	0.9	12.78*d*	0.00064*d*	0.0006*d*
20-24	1.2	16.44*d*	0.00082*d*	0.0009*d*
25-29	2.5	20.09*d*	0.00100*d*	0.0025*d*
30-34	5.0	23.74*d*	0.00118*d*	0.0058*d*
35-39	8.5	27.39*d*	0.00136*d*	0.0116*d*
40-44	20.2	31.05*d*	0.00156*d*	0.031?*d*
45-49	43.1	34.70*d*	0.00174*d*	0.07?8*d*
50-54	79.1	38.35*d*	0.00192*d*	0.151?*d*
55-59	131.1	42.00*d*	0.00210*d*	0.2754*d*
60-64	209.1	45.66*d*	0.00228*d*	0.4774*d*
65-69	320.1	49.31*d*	0.00246*d*	0.7892*d*
TOTAL	4,104.5			9.1060*d*

[a] Codes 150-154, as defined in Table III-2.
[b] Cutler and Young, 1975.

Expressing this in the more usual terms, the committee estimates that drinking water containing $(1/9.1060) \times 10^6 = 0.11 \times 10^6$ TEM fibers/liter may lead to one GI cancer case per 10^5 persons exposed over a 70-year lifespan. The equivalent figure for U.S. white women is 0.17×10^6 TEM fibers/liter.

EPIDEMIOLOGICAL STUDIES OF CANCER RISK FROM ASBESTOS-CONTAMINATED DRINKING WATER

Some epidemiological studies of communities with asbestos-contaminated drinking water are reviewed in this section. Their findings are compared to the predictions made from equations (6) and (7).

Duluth

Electron microscope studies revealed that during 1973 the Duluth, Minnesota, water supply contained from 1×10^6 to 30×10^6 TEM fibers/liter, depending on weather conditions on Lake Superior (Cook *et al.*, 1974). From details of x-ray diffraction studies reported in the paper by Cook and his colleagues, one may estimate the mean number of asbestos fibers in the

drinking water over the year to be approximately 8×10^6 TEM fibers/liter. The contamination of Lake Superior and, hence, of the Duluth water supply was due to the dumping of industrial waste, a practice that had begun in 1955 (Masson *et al.*, 1974).

Masson and his colleagues (1974) studied the cancer death rates in Duluth over four 5-year periods (1950-1954, 1955-1959, 1960-1964, and 1965-1969) by specific site of cancer and for males and females separately. They compared these rates to those of the entire state of Minnesota and to those of Hennepin County alone, which includes Minneapolis. They summarized their results as follows: "If the asbestos fibers had induced cancer at a particular [body] site [in Duluth], one would expect the mortality rates for that site to have increased in males and females [compared to the comparison groups], especially in the most recent five-year period (1965 to 1969).... The only site that fell into this category was cancer of the rectum." In commenting on this result, they concluded that this effect "was observed by chance."

Levy and his colleagues (1976) compared GI cancer incidence rates in Duluth for the 3-year period 1969 to 1971 to such rates in the cities of Minneapolis and St. Paul, but could not study changes that occurred since the asbestos dumping began. They concluded, "Although some differences in GI cancer incidence occurred among the three cities in 1969-1971, there was no consistent pattern of statistically significant differences observed." This study adds very little to the finding of Masson *et al.* (1974).

It it is assumed that Duluth drinking water contained some 8×10^6 TEM fibers/liter (the observed average value in 1973) ever since contamination began in 1955, equation (7) predicts the following relative risk for GI cancer in 1970—the mid-year in the study by Levy *et al.* (1976):

$$\begin{aligned} RR &= 1 + 3.6525 \times 10^{-5} \times 8 \times 15 \\ &= 1.004. \end{aligned}$$

This relative risk is an overestimate of the true relative risk predicted by equation (7) since it assumes that the level of asbestos contamination reached the 1973 level immediately after dumping began, which is not likely. Predicted relative risks for the findings of Masson *et al.* (1974) will be smaller than this since the exposure periods were shorter. Relative risks of this order of magnitude are far too small for any epidemiological study to detect, let alone differentiate from possible confounding variables.

Connecticut

Harrington and his colleagues (1978) investigated the use of asbestos-cement pipe and the incidence of GI cancers in Connecticut for the period

1935 to 1973. The authors summarized their study as follows: "The age adjusted sex specific incidence data for stomach, colon, and rectal cancer for Connecticut townships for the period 1935 to 1973 were used to investigate whether asbestos cement pipe usage for domestic drinking water is associated with gastrointestinal cancer. The townships were grouped according to the Assessment of Exposure (AOE) and Risk Factor (RF) for asbestos. These are composite indices of asbestos exposure including factors relating to the age of the pipe, the ability of water to leach asbestos from the pipe, and the length of pipes used by the population. No association was noted between these asbestos risk scores and gastrointestinal tumor incidence."

This study is fundamentally flawed by the lack of data on actual levels of exposure to asbestos. We know only that measurements of asbestos fiber levels in the drinking water of the exposed populations "ranged from below detectable limits (10,000 fibers per liter) to 700,000 fibers per liter," and that asbestos-cement pipe was introduced "around 1950." Equation (7) would predict as an outside maximum possible observable relative risk:

$$\begin{aligned} RR &= 1 + 3.6525 \times 10^{-5} \times 24 \times 0.7 \\ &= 1.0006. \end{aligned}$$

where 24 (the period from 1950 to 1973) is the maximum duration of exposure and 0.7×10^6 TEM fibers/liter is the maximum observed asbestos contamination of the water supplies. As for Duluth, such relative risks are far too small to be sensibly detected by any epidemiological study.

San Francisco Bay Area

Drinking water in certain parts of the San Francisco Bay Area is contaminated with asbestos from naturally occurring serpentine rock. Concentrations as high as 180×10^6 TEM fibers/liter have been recorded by Kanarek *et al.* (1980). These investigators compared the observed to expected ratios of cancer incidence for 1969 to 1971 for the 722 census tracts of the San Francisco-Oakland Standard Metropolitan Statistical Area with the measured asbestos counts in tract drinking water. Their results for all GI tract tumors combined are given in Table III-6. The statistical significance of the observed ratios apparently disappeared when adjustment was made for individual tract values of "median family income, median school years completed, marital status, asbestos industry workers, [and] country of origin." The adjusted ratios are not given in the paper.

Based on the extreme assumption that the mean duration of relevant water exposure of cancer cases is 60 years, equation (7) predicts ratios of 1.00, 1.00, 1.02, and 1.06 at the four levels of asbestos contamination

TABLE III-6 Ratio[a] of Observed to Expected Gastrointestinal Cancer[b] Incidence for White Males and Females for Census Tract Groupings by Chrysotile Asbestos Fiber Counts in San Francisco Bay Area, from 1969 to 1971[c]

	Asbestos TEM Fibers/liter × 10^6			
Sex	−0.15	−0.6	−8	−26
Male	1.00	1.01	1.11	1.28
Female	1.00	1.02	1.11	1.19

[a]Adjusted to 1.00 for lowest asbestos exposure tracts.
[b]Codes 150-154, as defined in Table 3-2.
[c]From Kanarek *et al.*, 1980.

shown in the table. The observed ratios are some 4-fold higher than these predicted values, but, as noted above, the statistical significance of the observed values disappeared after adjustments were made for various risk-modifying factors, and the adjusted ratios may be reasonably close to these predicted values. However, the predicted values themselves are likely to be too high, in that the 60-year mean exposure assumption is equivalent to the unlikely assumption that the population in the older, high-cancer-incidence age range had lived in their 1970 census tracts most of their lives. As pointed out by Kanarek and his colleagues, roughly one-half of the individual census tracts lost more than one-half of their residents between 1965 and 1970.

Lung cancer in males was found to be strongly related to asbestos in the water supply, even after adjustment for the risk-modifying factors mentioned above (Kanarek *et al.*, 1980). The authors attributed this to "the carcinogenic potential of ingested asbestos fibers which migrate to the lungs...." It is, however, at least as likely that this observed lung cancer effect merely demonstrates that the adjustments for other risk-modifying factors are not adequate. This possibility is strengthened by their observation that cancer of the endometrium has a negative association with the asbestos content of the water supply.

In summary, this study of cancer incidence in the San Francisco Bay Area has produced results that are not incompatible with predictions made from equation (7).

Puget Sound Area

Drinking water in certain parts of the Puget Sound area of western Washington State is also naturally contaminated with chrysotile asbestos (Polissar *et al.*, 1982). The Sultan River source is especially affected; average

asbestos concentrations of 206 × 10^6 TEM fibers/liter were found in grab samples of tap water obtained from this source.

Polissar and his colleagues compared the cancer incidence data for 1974 to 1977 and the cancer mortality data for 1955 to 1975 from the census tracts with a Sultan River water source to such data from census tracts in the Puget Sound area with average asbestos concentrations in tap water of 7 × 10^6 TEM fibers/liter. Table III-7 shows their results for GI cancers. No effect of asbestos concentration is evident. However, a proportional incidence analysis of GI cancer in which long-term (>30 years) residents were compared with short-term (<30 years) residents of Everett—the main city served by Sultan River water—did show proportional incidence ratios of 1.49 and 1.39 for males and females, respectively.

It is evident from the "Average Annual Population at Risk" rows in Tables 3 and 4 in Polissar *et al.* (1982) that there was tremendous population growth in the census tracts served by the Sultan River between 1955 and 1977. The average annual total population from 1955 to 1975 was 45,272, and from 1974 to 1977 it was 156,099, i.e., the 1975 population appears to have been roughly 3.5 times the size of the 1965 population. In these Sultan River water tracts, the average duration of residence for persons in the cancer age range may therefore be as short as 5 years. Using this figure, equation (7) predicts a relative risk of 1.04.

If we assume that the cases with long-term (more than 30 years) residence in Everett had been there for 60 years and that cases with short-term residence had been there for 5 years, then equation (7) predicts a relative risk of 1.41, which is in close agreement with the observed proportional incidence ratios.

TABLE III-7 Odds Ratios for Gastrointestinal Cancer Incidence (1974-1977) and Mortality (1955-1975) for Males and Females in Census Tracts with a Sultan River Water Source[a]

Sex	Type of Data	Odds Ratio[b]
Male	Incidence	1.10
	Mortality	0.79
Female	Incidence	0.97
	Mortality	0.86

[a]From Polissar *et al.*, 1982.

[b]Calculated from Tables 3, 4, and 7 in Polissar *et al.*, 1982: odds ratio for census tracts with a Sultan River water source versus census tracts in the Seattle-Everett-Tacoma metropolitan areas, which have the Cedar River, Tolt River, Green River, or Lakewood Wells as their water sources.

Within the inherent limitations of the study design, therefore, the results of this study are compatible with the predictions of equation (7).

EPA CRITERIA DOCUMENT METHODOLOGY

In the Ambient Water Quality Criteria Document, the U.S. Environmental Protection Agency (1979) considers much the same data discussed in this chapter, but uses a very different method of calculating the "additional lifetime cancer risk of 1 in 100,000." The agency's method of calculation can be analyzed by dividing it into a number of distinct steps:

Step 1: Conversion of LM Fibers/ml Air to TEM Fibers Swallowed

(This is the equivalent of Steps 3 and 4 in the committee's method.) A man breathing 1 LM fibers/ml air at work is considered by the EPA to swallow an average of

$$200 \times 8 \times 10^6 \times 5/7 = 1{,}142.9 \times 10^6 \text{ TEM fibers/day,}$$

where 1 LM fiber = 200 TEM fibers, 8 = m^3 of air breathed per day at work, 10^6 = ml in m^3, and 5/7 = proportion of working days in a week. (The committee used a conversion factor of 50 for LM to TEM, a factor of 49/52 to represent working weeks in a year, and 0.3 as the proportion of inhaled asbestos fibers that are subsequently swallowed. As a result, the risks calculated by the committee are only 7.07% of those calculated by the EPA.)

Step 2: Conversion of LM Fibers/ml Air to TEM Fibers/Liter in Drinking Water for a 70-Year Exposure

1 LM fiber/ml air at work for 1 year

= $1{,}142.9 \times 10^6$ TEM fibers swallowed daily for 1 year
= $(1{,}142.9 \times 10^6)/2$ TEM fibers/liter drinking water for 1 year
= 571.4×10^6 TEM fibers/liter for 1 year
= $(571.4 \times 10^6)/70$ TEM fibers/liter for a lifetime of 70 years
= 8.163×10^6 TEM fibers/liter lifetime exposure.

(The committee's method agrees with the principles of this calculation.) For example, the 510 LM fibers/ml air-year result of Selikoff and his colleagues (1979) given in the first row of their Table 3 becomes the equivalent

of $510 \times 8.163 \times 10^6 = 4{,}163.6 \times 10^6$ TEM fibers/liter in drinking water for 70 years.

Step 3: Conversion of TEM Fibers/Liter for 70 years to Additional Lifetime Cancer Risk per 100,000

The EPA assumes that the number of TEM fibers/liter over 70 years calculated in Steps 1 and 2 will have the same effect as the original occupational exposure on GI cancer and peritoneal mesothelioma. In the criteria document, this effect (X) is considered to be:

X = (number of excess deaths from GI cancer or peritoneal mesothelioma)/(total expected number of deaths from all causes),

where the expected numbers are calculated in the absence of asbestos exposure. The EPA then equates X with an additional lifetime cancer risk of X. The required TEM fibers/liter for an additional lifetime cancer risk of 1 in 100,000 is then obtained by simple proportion, i.e.:

X/(calculated TEM fibers/liter over 70 years)
$= (1 \times 10^{-5})$/(required TEM fibers/liter over 70 years).

Thus,

required TEM fibers/liter
= (calculated TEM fibers/liter over 70 years)/$(10^5 \times X)$.

For example, the 510 LM fibers/ml air-year result of Selikoff *et al.* (1979) given in the first row of their Table 3 was associated with 148.9 excess deaths from GI cancer (39.9) or peritoneal mesothelioma (109). As given in Table 30 of the criteria document, the total number of expected deaths from all causes was 1,660.96,

$$X = 148.9/1{,}660.96$$
$$= 0.0896$$

and

required TEM fibers/liter over 70 years
$= (4{,}163.6 \times 10^6)/(10^5 \times 0.0896)$
$= 0.536 \times 10^6$ TEM fibers/liter.

(Note: if the conversion factors in Step 1 were replaced by the committee's estimates, then the last figure would need to be multiplied by 7.07%, giving required water quality of $0.536 \times 10^6 \times 7.07\% = 0.038 \times 10^6$ TEM fibers/liter.)

The critical assumption in Step 3 is equating excess deaths as a proportion of all deaths with additional lifetime cancer risk. This assumption is demonstrably false. Suppose that all causes of death except GI cancer and peritoneal mesothelioma were somehow eliminated from the population. By definition, this should make no difference to the calculation of lifetime risk from GI cancer or peritoneal mesothelioma from asbestos exposure, since these sites were not altered. But X will be drastically changed. In the study by Selikoff *et al.* (1979), the total expected number of deaths from all causes is reduced from 1,660.96 to 59.1, so that X changes from 0.0896 to 2.519, or a 28.1-fold increase. The required TEM fibers/liter is reduced from 0.536×10^6 to 0.019×10^6.

ANIMAL EXPERIMENTS

When there are few or no epidemiological data on which to base estimates of a compound's carcinogenicity in humans, one recourse is the use of data from experiments in animals. Although this is not the case for asbestos, confirmatory evidence that ingested asbestos is a GI tract carcinogen in animals would add some weight to the epidemiological data.

Asbestos has been shown to cause mesotheliomas in rats and hamsters when implanted into the pleural cavity and when inhaled (Port, 1980; Wagner *et al.*, 1980), but results of long-term asbestos ingestion studies in rats and hamsters have not produced any convincing evidence of an increase in GI tract tumors in either species. Table III-8 gives details of four feeding studies with substantial numbers of animals that provided little, if any, evidence of an effect on GI tract tumors.

Equation (6) suggests that the relative risk of GI cancers from asbestos exposure of humans may be written as:

$$RR = 1 + 0.05 \times h,$$

where $h \times 10^{12}$ is the number of TEM fibers swallowed. If we assume that the daily dose to an animal over a lifetime had an effect equivalent to that in humans exposed for 70 years, then the "Maximum Daily Dose" column of Table III-8 may be multiplied by $1.28 \times 10^{-9} = 0.05 \times 70 \times 365.25 \times 10^{-12}$ to give the expected excess relative risk (RR − 1) as shown in the table. On this basis only the experiments with chrysotile should have definitely produced a positive result, i.e., an increase in GI tumors.

TABLE III-8 Recent Long-Term Asbestos-Feeding Experiments

Animal	Route	Maximum Daily Dose, TEM fibers	Equivalent Daily Dose for Humans, TEM fibers[a]	Expected Excess Relative Risk (1)[b]	Expected Excess Relative Risk (2)[c]	Reference
Syrian golden hamsters	Drinking water	175×10^6 amosite	82×10^9	0.22	105	Smith *et al.*, 1980
Fischer 344 rats	Diet	258×10^9 chrysotile	$.36 \times 10^{12}$	330	46,080	Dunham *et al.*, 1980
Syrian golden hamsters	Diet	699×10^9 chrysotile	445×10^{12}	895	569,600	National Toxicology Program, 1981a
Syrian golden hamsters	Diet	398×10^6 amosite	253×10^9	0.51	324	National Toxicology Program, 1981b

[a] Calculated to give equal daily per kg bw doses.
[b] Based on daily dose equivalence between animals and humans.
[c] Based on daily dose per kg bw equivalence between animals and humans

The usual method of converting experimental results in animals to humans is based on mass of the test compound per kilogram of body weight or per square meter of body surface area. If we use the body weight correction, then the equivalent asbestos doses to humans are, of course, greatly increased (see column "Equivalent Daily Dose for Humans"), and the expected excess relative risks are more than 100 for all the experiments.

The reasons for the negative results in animals are unknown. It may be that the methods used to extrapolate data from humans to animals are totally wrong for physical carcinogens such as asbestos.

SUMMARY AND CONCLUSIONS

An excess of GI tract cancers has been observed in some, but not all, occupational groups exposed to asbestos. The reasons for the inconsistent results have not been established, but careful reviews of all the studies indicate that the results of the positive studies are real and that the demonstrated association of asbestos exposure and GI tract cancer is most likely one of cause and effect.

For asbestos this committee considers a multiplicative model for carcinogenic risk assessment to be the most defensible. This model assumes that the risk of GI tract cancer in persons exposed to asbestos at some given level will be some fixed multiple of their normal or background GI tract cancer rate. Many data on the relationship between asbestos exposure and cancer suggest that this multiplying factor, or relative risk (RR), may be accurately represented as a linear function of asbestos dose where asbestos dose is measured in terms of cumulative fiber exposure.

Data from a number of occupational studies suggest that the RR for GI tract cancer is $1 + 0.05 \times \text{dose} \times 10^{-12}$, where dose is the number of fibers swallowed, as counted by TEM. Using this equation, and assuming a daily consumption of 2 liters of water, the committee calculated that drinking water containing 0.11×10^6 TEM fibers/liter may lead to one additional GI tract cancer per 100,000 men exposed over a lifetime of 70 years. For women, drinking water containing 0.17×10^6 TEM fibers/liter may lead to one additional GI tract cancer per 100,000 exposed over a lifetime of 70 years.

Peritoneal mesotheliomas are associated with occupational exposure to asbestos, and indeed asbestos may be virtually the sole cause of this tumor. If peritoneal mesotheliomas are caused by asbestos fibers migrating from the gastrointestinal tract, which must be considered a definite possibility, then risk of such tumors needs to be included in evaluating the total cancer risk from swallowed asbestos. In the five studies shown in Table III-2, approximately 165 peritoneal mesotheliomas were observed; this compares to

the excess of approximately 94 other cancers shown in the table. If these tumors are simply included in the "Observed" column of Table III-2 and the calculations redone, then the risk estimates will be approximately 2.75 times as great. A multiplicative model for risk estimation is, however, not applicable in the absence of an underlying risk, so that for peritoneal mesotheliomas an additive model is required. The data from the studies of asbestos workers does not allow one to construct such a model. For the present, therefore, the estimates of risk given above should simply be considered as possible underestimates of the true risk.

The designs of the epidemiological studies of cancer rates in populations exposed to asbestos in drinking water all have major deficiencies, but the above estimates of risk are quite compatible with the results of these studies. Adequate animal feeding studies conducted to date have failed to confirm a cancer risk from ingested asbestos. Further work aimed at understanding the inconsistent results of GI cancer excess in occupationally exposed groups is clearly warranted.

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