

# Report on Cancer Risks Associated with the Ingestion of Asbestos\*

This report is an assessment of all available literature that pertains to the potential risk of cancer associated with ingestion of asbestos. It was compiled by a working group to assist policy makers in the Department of Health and Human Services determine if adequate information was available for a definitive risk assessment on this potential problem and evaluate if the weight of evidence was sufficient to prioritize this issue for new policy recommendations. The work group considered the basis for concern over this problem, the body of toxicology experiments, the individual epidemiologic studies which have attempted to investigate this issue, and the articles that discuss components of risk assessment pertaining to the ingestion of asbestos. In the report, the work group concluded: 1) that no direct, definitive risk assessment can be conducted at this time; 2) that further epidemiologic investigations will be very costly and only possess sufficient statistical power to detect relatively large excesses in cancers related to asbestos ingestion; and 3) that probably the most pertinent toxicologic experiments relate to resolving the differences in how inhaled asbestos, which is eventually swallowed, is biologically processed by humans, compared to how ingested asbestos is processed. The work group believes that the cancer risk associated with asbestos ingestion should not be perceived as one of the most pressing potential public health hazards facing the nation. However, the work group does not believe that information was sufficient to assess the level of cancer risks associated with the ingestion and therefore, this potential hazard should not be discounted, and ingestion exposure to asbestos should be eliminated whenever possible.

## Introduction

It has been well documented that inhalation of asbestos by humans causes asbestosis, lung cancer, and mesothelioma of the pleura and peritoneum. Inhalation of asbestos in the workplace has also been associated with an increase in the incidence of gastrointestinal cancers (1). Recently, there has been concern that ingested asbestos may cause an increase in cancer incidence in exposed populations. Although the potential carcinogenicity of ingested asbestos appeared to be supported by the findings of animal studies beginning in 1967 (2), it was first considered in humans in the 1973 Report of the Advisory Committee on Asbestos Cancers to the Director of the International Agency for Research on Cancer (3). In this report the advisory committee stated that "such evidence as there is does not indicate any risk" and suggested that the "effect of long-term ingestion of fibres of various sizes, shapes and chemical compositions should be studied." In 1974 further impetus was given for such studies when Cook et al. (4) and Nicholson (5) reported mineral fibers in the drinking water supply of Duluth, Minnesota. Since 1974, additional reports have documented the presence of asbestos

in the drinking water of other parts of the United States and Canada (6-9). In some of the reports, asbestos has been measured at concentrations higher than one billion fibers per liter of water, although most reported concentrations have been less than one million fibers per liter of water.

## Perspective on Ambient Asbestos Pollution in Drinking Water

Probable sources of asbestos in drinking water include rain water that has run off asbestos cement shingle roofs into cisterns (10), asbestos cement pipe used for transporting water (11), past indiscriminate dumping of asbestos-containing materials into sources of drinking water (1,2), and the natural leaching process in the ground and surface watershed. The amount of asbestos can vary widely depending on the location and the area's geological composition (9). While asbestos contamination may not be a universal problem in all water supplies, there have been a number of reports of asbestos in the groundwater and the surface waters of several locations (12,13). Although one report indicates that run-off water from asphalt shingles containing asbestos as a binder did not appear to contribute substantially to asbestos fibers found in cistern waters (13), a second report found concentrations as high as 500 million fibers/L in cisterns supplied with run-off water from asbestos cement shingle roofs (10).

There is an estimated 200,000 miles of asbestos cement pipe in the United States (11). A report on water

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transported through asbestos cement pipe (14) described concentrations of asbestos as high as 38 million fibers/L in one Florida town; 47 million fibers/L were found in a Kentucky asbestos cement pipe water system, and a concentration of 480 million fibers/L was found in a portion of a little-used asbestos cement pipe in Massachusetts. The extent of shedding asbestos from asbestos cement pipe is dependent on the characteristics of the pipe (e.g., coated or uncoated), and on the aggressiveness of transported water (11). The ability to shed asbestos is partially dependent on the product of the water's pH, its calcium hardness ( $H$ ), and the total alkalinity ( $A$ ), which is generally expressed by the following equation (7):

$$AI \text{ (aggressiveness index)} = \text{pH} + \log (AH)$$

The EPA considers values of  $AI$  below 10 to be very aggressive (potentially able to shed asbestos), while values above 12 are considered nonaggressive. The lower the aggressiveness of the water, the less shedding of fibers. More than half of the water supplies sampled in the United States were considered to be moderately aggressive, and 16.5% were aggressive (9). Therefore, at least 66.5% of the United States water systems are capable of eroding asbestos cement pipe. The ability of water to leach asbestos from asbestos cement pipe is known to be modified by coatings applied to the inside pipe surface, which inhibit the fibers from leaching into the water supply system.

### Perspective on Possible Asbestos Contamination in Food or in Pharmaceuticals

In 1973, the Center for Science in the Public Interest and the Environmental Defense Fund petitioned the Food and Drug Administration (FDA) to prohibit the use of asbestos filters in food contact applications and in the manufacture of ingested or injected drugs (15). Asbestos has ideal properties for filtration purposes in the preparation of food and pharmaceuticals because the fibers are very fine and have a high tensile strength. The fibers occur as bunches of fibrils that fragment into large numbers of filtering elements and greatly increase the total surface area. The use of asbestos for the final filtration of the product was thought to be necessary to prevent bacterial growth and to remove bacterial toxins (16). In 1973, chrysotile asbestos was used throughout the pharmaceutical industry at various steps in the manufacture of parenteral solutions.

In 1973, the FDA noted that the evidence of increased cancer risk associated with ingestion of asbestos was inconsistent. At that time, the FDA also reported experimental evidence that parenteral administration of asbestos fibers may lead to dissemination of the fibers and to the development of pleural and peritoneal mesotheliomas, as well as to local malignant tumors at the site of injection in animals (15). Based on these findings and on a study by Nicholson et al. (16) that found mea-

surable amounts of asbestos in numerous samples of parenteral solutions, the FDA initiated its own study and found that 11 of 13 samples tested indicated the presence of asbestos. Subsequently, in 1975, the FDA prohibited the use of fiber-releasing (asbestos or other) filters in the manufacture, processing, or packaging of parenteral drugs intended for human use (17). The use of fiber-releasing filters is permitted only when the manufacturer establishes that it is impossible to create the product without such filters. If use of a fiber-releasing filter is necessary, then an additional filter which is not fiber-releasing and has extremely small pore size must be used to reduce the content of particles in the drug product. This exception is now permitted for only a few antibiotic drug substances when prepared chemically for later use in a dosage form product. The final or dosage form product is itself prepared from the antibiotic drug substance without further use of a fiber-releasing filter. Therefore, the patient is protected from any significant number of fibers in the administration of the final drug product. Containers for parenteral drugs, products, or components must be cleansed with water that has been passed through a filter that is not fiber-releasing, as municipal water supplies can be contaminated with asbestos fibers.

Food and beverages can become contaminated with asbestos fibers through the use of asbestos materials in processing and from the normal use of asbestos-containing construction materials. Since the mid 1970s, most, if not all, of the filters used in food and beverage production in the United States are nonasbestos. However, some use of asbestos filters continues in the production of imported beverages. In 1971, Cunningham and Pontefract (18) investigated the level of asbestos fiber contamination in various beverages (the range observed was  $1.1\text{--}172.7 \times 10^6$  fibers/L). They discovered that 12 brands of Canadian beer, wine, sherry, and port; six brands of American beer; six brands of European wine, vermouth, and sherry; and two brands of South African sherry all contained asbestos fibers. The fibers in the Canadian beer and sherry were identified as chrysotile asbestos.

According to the 1979 asbestos report of the Scientific Committee for Food of the Commission of the European Communities, asbestos is widely used in the food and beverage industries of Europe. This report indicated that the use of chrysotile asbestos filters was "unsurpassed" for the manufacture of products such as beer, wine, and soft drinks, since they cannot be heated for sterilization (19). This statement is based on the fact that although some fiber contamination may persist, such filters reduce bacterial, asbestos fiber, and other types of contamination (19). Consequently, asbestos fibers may be present in some imported beverages because of the use of asbestos filters in processing or because of the use of asbestos-contaminated water supplies during production.

On March 14, 1975, the Commissioner of the FDA stated that additional studies showed no evidence indicating that the ingestion of asbestos resulted in in-

creased risk of cancer (17). Pending completion of further studies, the FDA determined that no prohibition on the use of asbestos filters in the processing of food, beverages, and nonparenteral drugs was needed. Manufacturers of these products were requested to investigate possible methods of eliminating the use of asbestos filters and to take all precautions during processing to assure that the amount of asbestos fibers in any food is reduced to the minimum feasible level.

## Recommended Sampling Method for Detecting Asbestos Fibers in Water

The best available technology for determining asbestos content in water is described in a 1983 EPA project report (20). The water sample to be analyzed is initially treated with ozone and ultraviolet light to oxidize suspended organic material. A capillary pore polycarbonate filter (0.1  $\mu\text{m}$  pore size) is then used to filter the water sample. The filter is prepared by carbon extraction replication and then examined with a transmission electron microscope (TEM). Selected area electron diffraction (SAED) and energy dispersive X-ray analysis (EDXA) are used to classify fibers. Chrysotile can be identified by characteristic features measured on a calibrated SAED pattern. Identification of amphibole asbestos fibers is based on a quantitative evaluation of the chemical composition and on a quantitative evaluation of at least one calibrated zone axis SAED pattern. Mineral identification and fiber count results are accomplished by use of computer programs, an integral part of the analytical method, and reported in the standard format. To minimize unnecessary expenditures by applying the above method, a more inexpensive rapid method has been developed to evaluate the need for the more detailed analysis of water samples suspected of containing asbestos fibers. This method is not yet in common use. For more details about the full method and the rapid method, the reader is referred to the EPA report.

## Toxicology

To date, 11 toxicologic studies on asbestos ingestion have been conducted (21–31). Eight of these studies have been reviewed by Condie (32), who concluded that the studies do not provide substantive support for an association between ingestion of asbestos fibers and the induction of cancer. However, Condie found these studies to have many deficiencies in their design and/or conduct. Most were not lifetime studies and used an insufficient number of test animals and controls. Also, the time from first exposure to asbestos to the sacrifice of the animals was often too brief in view of the long latency period known for asbestos-related cancers.

Two recent reports from the National Toxicology Program (NTP) have shown no carcinogenic response after lifetime exposure of Syrian golden hamsters to 1% amosite or chrysotile asbestos in the diet and in F344 rats which were fed 1% amosite or tremolite in their diet during a lifetime study (29,30). All of these studies used

animals reared from dams exposed to the asbestos fibers. Also, the number of animals exposed varied from 125 to 254 hamsters and 250 rats; this is three to five times the number of animals normally used in a standard NTP carcinogen bioassay. Given the number of animals used in these asbestos bioassays and the lifetime exposure used, these lifetime protocols are more sensitive than the normal NTP bioassay.

A third NTP study used F344 rats and a similar protocol (31). This evaluation has shown a marginally significant increase in the number of adenomatous polyps in male rats after lifetime exposure to 1% chrysotile asbestos of intermediate length range (65% of fibers were  $> 10 \mu\text{m}$ ) in the diet. Earlier reports by Donham et al. (25) demonstrated an excess of colon lesions during a lifetime study of Fischer 344 rats fed a diet which was 10% chrysotile asbestos. This excess was not statistically significant compared to control rats, although the authors thought the weight of evidence indicated ingested asbestos was not inert in the colon.

The evidence for the carcinogenicity of inhaled asbestos fibers in man and animals is overwhelming. The data are not as convincing for the carcinogenicity of ingested asbestos. The results of two sensitive bioassays of amosite asbestos (median fiber length of 4.37  $\mu\text{m}$ ) and of chrysotile asbestos (predominantly  $< 10 \mu\text{m}$  in fiber length) did not show carcinogenic potential in hamsters or rats fed a lifetime diet which was 1% asbestos (29,30). However, there was some evidence of weak tumorigenicity of chrysotile asbestos fibers, most of which are greater than 10  $\mu\text{m}$  in length, when fed to male rats at a level of 1% in the diet for their lifetime (31). No other animal studies demonstrate an association between the ingestion of asbestos and carcinogenicity or tumorigenicity.

A salient issue in the consideration of the carcinogenicity of ingested asbestos is the ability of asbestos fibers to penetrate the gut tissue for translocation to other sites of action. Cook has recently reviewed the available information from 19 independent investigations on the ability of asbestos fibers to penetrate such tissue (33). He indicates that many of the articles do not provide complete information "... for defining analytic sensitivity, significance of sample contamination, fiber recovery efficiency of the sample preparation procedures, etc." Cook indicates that the absence of a clear limit of detection and the absence of analysis on blank tissue control samples make many of the studies difficult to evaluate and the question of the penetrating ability of asbestos fibers problematic. He does offer the following observations which tend to support the belief that asbestos fibers do penetrate gut tissue:

1. Studies reporting the presence of fiber in body tissues and fluids tend to report the lowest levels of detection and lowest likelihood of fiber contamination, and therefore, these studies are less likely to be false positive observations.
2. Since sample contamination would be of chrysotile asbestos fiber type, available studies which dem-

onstrate the presence in body tissues and fluids of nonchrysotile asbestos-type fibers provide strong evidence of gut penetration of ingested nonchrysotile asbestos.

3. More specifically, ingestion studies of cummingtonite-grunerite and actinolite show the unique range of elemental composition in body tissues and fluids to be the same as the ingested material, and therefore, provide strong evidence for penetration.

Cook also addresses the more critical and less assessable point of what fraction of ingested asbestos may penetrate. The intestinal wall appears to serve as an effective barrier against entry of ingested asbestos fibers into the lymphatic and systemic circulation. Evidence for this is that only  $10^{-8}$  to  $10^{-7}$  of ingested particles are found in lymph and urine samples. Although the intestinal wall may prevent dissemination of those particles, there is evidence that small particles may penetrate the intestinal epithelium and remain sequestered in Peyer's patches and submucosal macrophages. The risk this may pose for local carcinogenesis within the gastrointestinal tract cannot be discounted.

The physical dimensions of asbestos and other fibers are critical factors in determining their potency as carcinogens. After testing several types and sizes of asbestos and other fibers in 72 animal experiments, Stanton et al. (34) concluded that fibers  $\geq 8 \mu\text{m}$  in length and  $\leq 0.25 \mu\text{m}$  in diameter were the most carcinogenic, whereas those fibers that were  $\leq 4 \mu\text{m}$  in length or  $> 1.5 \mu\text{m}$  in diameter were not carcinogenic. In these studies the fibers were injected intrapleurally. In a series of animal inhalation experiments with chrysotile, crocidolite, and amosite, Davis et al. (35) reported that pulmonary fibrosis and lung tumor incidences correlated best with the numbers of airborne fibers  $> 20 \mu\text{m}$  in length. The facts that fibers  $> 5 \mu\text{m}$  in length are cleared from lungs much more slowly than fibers  $< 5 \mu\text{m}$  in length (36) and that longer fibers are much more cytotoxic than shorter fibers (37) support the importance of intermediate length to long fibers in fiber carcinogenesis.

Millette et al. (38) found that the average length of chrysotile fibers found in the water of an asbestos cement pipe distribution system was  $4 \mu\text{m}$ , while the average fiber length of chrysotile fibers in water from other systems was  $1 \mu\text{m}$ . In water from the California Bay area, 2.3% of the fibers were  $> 5 \mu\text{m}$  in length, and in the Washington Puget Sound area, only 0.2% of the fibers were  $> 5 \mu\text{m}$  in length (7). The size of the fibers needs to be considered in evaluating the potential hazards of asbestos in drinking water.

## Epidemiology

A number of epidemiologic evaluations conducted in seven areas of the United States and Canada examined the association between drinking water supplies containing asbestos and cancer mortality (8,39-49,50-54).

Increases were observed in leukemia and in the following site-specific neoplasms: esophagus, stomach, small intestine, colon, rectum, gallbladder, pancreas, peritoneum, lungs, pleura, prostate, kidneys, brain, and thyroid. All but one of the studies fall into the category of epidemiologic research referred to as being ecological in nature. Ecological studies can determine whether the incidence of an adverse outcome observed in a particular area is associated with the average level of exposure to a suspected agent in that area. This approach cannot relate the occurrence of an adverse outcome to the exposure of an individual, so it provides no direct evidence about causality. The reports are discussed below by the geographic area in which they were conducted.

## Duluth, Minnesota

The fiber type of concern in the Duluth drinking water was amphibole, and the concentration of fibers found in the drinking water was in the range of 1 to 65 million fibers/L (39). The population exposed was 100,000, with maximum duration of exposure being 15 to 20 years.

The first study, conducted in 1974 by Mason et al. (40), examined death certificates for all persons who had died of cancer in the United States in the years 1950 through 1969. The data were obtained from the National Center for Health Statistics and were tabulated by the authors to show the number of deaths ascribed to cancer among whites of both sexes for 5-year intervals. Also, the age-adjusted cancer death rates for Duluth were tabulated for comparison with data for the state of Minnesota and Hennepin County, which includes Minneapolis. The deaths were coded by the seventh revision of the International Classification of Diseases, and the age-adjusted death rates were examined for each cancer site. The authors reported that risk ratios in the Duluth group differed significantly ( $p < 0.01$ ) from those of the comparison groups. Mason et al. commented that if the asbestos fibers had induced cancer at a particular site, it would be expected that the mortality rates for that site would have increased in both males and females over time, especially in the most recent 5-year period studied; however, this occurred for only one site, cancer of the rectum. Because other studies of asbestos inhalation revealed excesses of cancer of the upper gastrointestinal tract and not just of the rectum, the authors concluded that their finding was a result of chance. Problems associated with this study include (1) a latency period too short for the induction of cancer that would be expected from exposure to asbestos, (2) the lack of controlling for confounding factors such as occupation, ethnicity, migration, and personal habits, and (3) the absence of data on dose-response along with the absence of data on historical asbestos exposure.

The second Duluth study was done by Levy et al. in 1976 (41). In this study, the authors examined the gastrointestinal cancer incidence rates of Duluth residents from 1969 through 1971 and compared them to the rates of residents of Minneapolis and St. Paul. Incidence rates were also examined for residents of Duluth during 1972.

The authors adjusted the data for both age and sex and found no increase in total gastrointestinal cancers among Duluth residents from 1969 through 1972, although increases were observed for specific gastrointestinal sites (stomach, small intestine, and "peritoneum, retroperitoneum, and abdomen not otherwise specified"). This study, however, suffered from an insufficient latency period for the manifestation of cancers resulting from exposure to asbestos. This study also did not control for race, occupation, ethnicity, migration, or personal habits. In addition, data on dose-response and historical asbestos exposure were missing.

The third Duluth study was done by Sigurdson and reported in 1981 and 1983 (42,43). In this study, Sigurdson used data from the Third National Cancer Survey (TNCS) and from the Surveillance and Epidemiology End Results (SEER) Program. Duluth 1969 through 1971 cancer rates were compared with TNCS rates for the cities of Minneapolis and St. Paul during 1969 through 1971; then Duluth rates during 1974 through 1976 were compared with Duluth rates during 1969 through 1971. Finally, Duluth rates during 1979 through 1980 were compared with Duluth rates during 1969 through 1971 and with the SEER data collected in Iowa. Statistically significant excesses of cancer were observed for several primary sites among Duluth residents. However, lung cancer in Duluth females was the only primary site considered of biological significance. There was no statistically significant excess of mesothelioma, with only a single case reported among females in Duluth in the period 1974 through 1976 and no cases reported in the period 1969 through 1971. This study was controlled for sex only, leaving other factors such as race, occupation, ethnicity, migration, and personal habits uncontrolled. Also, no data on dose-response or previous history of exposure to asbestos were noted by the author.

## Connecticut

The type of asbestos of concern in Connecticut was chrysotile, and the concentrations reported in the drinking water ranged from below the level of detection to 700,000 fibers/L. The population exposed was 576,800, and the maximum duration of exposure was 23 to 44 years (39).

The first Connecticut study was conducted by Harrington et al. and reported in 1978 (44). This study was designed to observe the effects of the use of asbestos cement pipe for the public water supply on the incidence of stomach, colon, and rectal cancer in Connecticut from 1935 through 1973. Tumor incidence by township was obtained from the state's tumor registry. Data were collected from all towns to determine the use of asbestos cement pipe, the dates of pipe installation, the length of time that this type of pipe was used compared with other types, and the population observed. The authors found no association between cancer incidence and the use of asbestos cement pipe. In this study, there was sufficient latency time to observe the effects of exposure

to asbestos and the development of cancer. The only two factors controlled for were sex and population density; race, occupation, ethnicity, migration, and personal habits were not controlled. Data on dose-response and previous exposure to asbestos were missing.

The second Connecticut study by Meigs et al., reported in 1980 (8), looked at the associations between the use of asbestos cement pipes for public water distribution and the incidence of cancer for 169 Connecticut townships. The number of newly diagnosed cases of malignant neoplasms for primary sites by sex, age, and year of diagnosis was recorded for each township between 1955 and 1974. Measurements of asbestos fibers per liter at the water source and in water that had passed through the asbestos cement pipe were made. Variables such as length of time that the asbestos cement pipe was used and the degree of eroding of the pipes were examined. Town density was also measured, along with socioeconomic status. The analytical methods in this study were more refined and powerful than those in the previous study (8), and the environmental information was more detailed. The analysis gave no consistent indication that use of asbestos cement pipe for the public water supply was followed by an increase in the incidence of all cancer or of site-specific cancers. The average possible duration of exposure was about 20 years, with a range of 5 to 30 years, which may be insufficient latency for the manifestation of an asbestos-related cancer risk. The potential exposure to asbestos fibers being considered in this study was probably quite low.

## Quebec

The principal type of asbestos fiber here was chrysotile, and the concentrations found in the drinking water ranged from 1.1 million to 1.3 billion fibers/L of water. The population exposed was 420,000, and the maximum duration of exposure was greater than 50 years (39).

The first Quebec study was conducted in 1977 by Wiggle (45), who evaluated the cancer mortality in 22 communities of the province of Quebec and grouped the communities by degree of exposure to asbestos in the drinking water supplies ranging from high to low exposures. The expected numbers of cancer deaths were calculated by applying the Quebec age-specific (5-year groups), sex-specific, site-specific, and period-specific (1965-1967, 1970-1972) mortality rates to the 1966 or 1971 census population delineated by age and sex for each community. Excesses of cancer were identified for the stomach and lung in men and for the pancreas in women for the two communities identified with high exposure to asbestos. The authors, however, caution that the high excesses of stomach and lung cancers among the men may be due to occupational exposures to asbestos. Because there was no excess of cancer of the pancreas in men, the authors conclude that the association between pancreatic cancer and exposure to asbestos in the drinking water was not supported. Likewise, the association of an excess of cancer of the stom-

ach was not supported because it was not in excess among women. This study does have sufficient latency to show cancers due to exposure to asbestos and was the first study thus far to develop some sort of dose-response estimation or to examine the duration and intensity of exposure; however, like most of the previously discussed studies, sex was the only variable controlled for in analyses.

Toft et al. reported in 1981 that they had examined samples of raw and treated tap water from 71 locations across Canada and analyzed them for asbestos using the transmission electron microscope (9). They found that filtration systems can efficiently remove asbestos fibers from the drinking water. In their analysis, mortality patterns between these communities were ranked by degree of exposure. The study failed to show any association between exposure to asbestos in the drinking water and excess cancer mortality. The excesses for age-standardized mortality rates for lung cancer and the nonneoplastic respiratory diseases that were noted among males in the Thetford Mines were probably due to occupational exposure to asbestos. This study had a sufficient latency period in which to observe cancers associated with exposure to asbestos and did attempt to evaluate whether a dose-response relationship existed.

## Bay Area, California

The fiber type of concern was chrysotile, and the concentrations found in drinking water ranged from 25,000 to  $36 \times 10^6$  fibers/L. The population exposed was  $3 \times 10^6$ , and the maximum duration of exposure was greater than 40 years (39).

In 1980, Kanarek et al. (46) reported on the age-adjusted, sex- and race-specific 1969 through 1971 cancer incidence ratios for the 722 census tracts of the San Francisco-Oakland Standard Metropolitan Statistical Area. The authors compared these ratios with measured asbestos counts in the drinking waters of the census tracts. Using the *t*-statistical test for multiple regression coefficients and the *t*-statistical test for correlation coefficients, the authors found a significant relationship between asbestos content in the census tracts' drinking water and lung cancer in white males, gall bladder and pancreas cancer in white females, and peritoneal cancers in both sexes ( $p < 0.01$ ). Excesses in cancers of the esophagus, pleura, and kidney in females and excesses of stomach cancers in both sexes ( $p < 0.05$ ) were also observed. The associations appeared to be independent of income, education, occupations involving exposure to asbestos, marital status, country of origin, and mobility. Although inferences from this study were limited because of its ecological nature, when compared with the other studies, this analysis was the most sophisticated in that it controlled for race, sex, occupation, socioeconomic status, ethnicity, and migration.

In a 1981 follow-up study to the Kanarek et al. study, Conforti et al. (47) reported on correlations in which "super tracts" (groupings of census tracts that yield

geographical boundary parity between censuses, in this study between 1970 and 1980) were made with differing asbestos counts in the drinking water and compared for cancer incidence while controlling for potentially confounding factors such as race, sex, occupation, socioeconomic status, ethnicity, and migration. Positive associations were found in both sexes for all cancers and specifically for esophagus cancers, stomach cancers, and cancers of the pancreas. Colon cancer was significantly in excess in males; cancer of the peritoneum was in excess in females. Pleura cancer was also in excess in females, and cancer of the prostate was in excess in males. This study provided further support for the original findings of Kanarek et al. (46).

Tarter et al. (48,49) analyzed the available waterborne asbestos concentration levels and digestive system cancer data from the San Francisco Bay Area to address interrelationships between these variables and population density. They observed that higher waterborne asbestos concentration levels and higher incidence rates of digestive system cancer were reported in the densely populated census tracts of the city of San Francisco compared to the non-San Francisco census tract (49). The authors concluded that the degree of association between waterborne asbestos concentration levels and digestive system cancer rates differed considerably between San Francisco census tracts and non-San Francisco census tracts, suggesting that population density or some other factor associated with living in San Francisco might be an important confounding variable.

The California Department of Health Services (CDHS) has recommended since 1974 that any water supply system which uses asbestos-laden water sources should use filters to minimize asbestos fiber exposure. On the release of the original Kanarek et al. report (46), CDHS reemphasized its recommendation for the filtration of asbestos-laden water sources and further stipulated that the filtration should be optimized (personal communication from David Spath of the Sanitary Engineering Branch, California Department of Health Services on January 2, 1985).

## Utah

In the Utah study, the fiber type of concern was chrysotile; however, there were no data available on the concentrations of fibers found in the drinking water. The population exposed was 24,000, with a maximum duration of exposure between 20 to 30 years (39).

A study reported by Sadler et al. in 1981 (50) was based on the cancer incidence of several Utah communities known to use asbestos cement pipe for their drinking water supply. The study suffered from insufficient latency, so cancer as a result of exposure to asbestos was not reliably observed. The study did control for sex, socioeconomic status, population density, and migration. Only gallbladder cancer in females and kidney cancer and leukemia in males were found to have a positive association with the use of asbestos cement

pipe. The lack of a consistent observation for any one particular cancer site in both sexes weakens the argument linking these cancer excesses with exposures resulting from asbestos cement pipe.

### **Puget Sound, Washington**

The fiber type of concern was chrysotile and was found to range from a concentration of 7,300,000 to 206,500,000 fibers/L in the drinking water. The population exposed was 200,000, and the maximum duration of exposure was greater than 40 years (39).

Studies by Severson (51) and Polissar et al. (52) evaluated the cancer incidence of the Puget Sound area because of the known fact that three of the largest metropolitan areas of western Washington State have been continuously serviced since the early part of the 20th century by water supplies containing a wide range of exposures to asbestos fibers. Severson found no associations with excesses in cancer in the population that could be related to asbestos exposures; in fact, he found a negative association in both sexes for colon cancer.

The Polissar et al. study found an odds ratio for cancer of the small intestine elevated in both sexes, but it was not statistically significant. This was also true for cancer of the thyroid in both sexes and for cancers of the prostate and brain, and leukemia in males. Both studies controlled for sex, socioeconomic status, and migration; the Polissar et al. study also controlled for occupation and population density. Neither of these studies provided evidence of statistically significant excess risks of cancer.

In 1984, Polissar et al. (53) reported the results of a follow-up case-control study in the Everett, Washington, area based on 382 cases, reported between 1977 and 1980, that were diagnosed as having cancer of the buccal cavity, pharynx, respiratory system, bladder, digestive system, or kidney, and 462 controls. Polissar et al. reported significantly increased odds ratios for cancer of the stomach and of the pharynx in males. The same effect was not observed in females, and the authors noted that these significant findings observed in males might be chance occurrences given the number of analyses conducted. Overall, Polissar et al. concluded that they found "no convincing evidence" for an association between site-specific cancer risk and the ingestion of asbestos in water based on the experience of Everett, Washington, residents.

### **Escambia County, Florida**

The type of asbestos of concern in this study was predominantly chrysotile (54); however, some amphiboles were found in the water system. The levels ranged from nondetectable to 32,700,000 fibers/L. The study was categorized as follows: 46,123 individuals were exposed to water with high concentrations of asbestos fibers; 86,897 were exposed to water with low concentrations; and 51,378 were exposed to water with no significant concentration of asbestos fibers. These ex-

posure categorizations were based on the degree to which drinking water was supplied through asbestos cement pipe within the census tract of residence. The maximum duration of exposure ranged from 30 to 40 years.

No statistical associations were observed between cancer deaths and the use of asbestos cement pipe (54). The authors noted that their study did not have the statistical power necessary to detect site-specific cancer excesses for the kidney, bladder, or liver unless the excesses were greater than 300%, and an increase in total gastrointestinal cancer of 70% or greater would be required for detection.

### **Risk Assessment**

Animal studies have not demonstrated a definitive risk of malignant tumors resulting from ingestion of asbestos fibers. A major question which needs to be addressed is how the results which show an increased risk of benign tumors in the gastrointestinal tract of experimental animals should be used in human quantitative risk assessment. This is an issue which has stimulated considerable debate between parties within DHHS interested in risk assessment. The range of various positions include (1) benign and malignant tumors should always be combined and used for quantitative risk assessment of carcinogenesis, (2) benign tumors should not be included with malignant tumors in quantitative risk assessment of carcinogenicity unless substantive information exists which demonstrates that the specific benign tumors are an integral part of the carcinogenicity process, or (3) benign tumors should be included with malignant tumors in quantitative risk assessment of carcinogenicity unless substantive information exists which demonstrates that the specific benign tumors are unrelated to the specific carcinogenic process of interest. These different options would clearly influence the risk estimates developed for asbestos ingestion.

It is our opinion that the benign epithelial neoplasms of the intestinal tract found in the most recent NTP study (31) should not be ignored in the qualitative and quantitative risk estimation of ingested asbestos. However, it would be a mistake to attach the same importance to these benign neoplasms as to a malignant lethal carcinoma in estimating risk. In addition, it may be a mistake to use the intermediate range fiber length (fibers which are predominantly  $> 10 \mu\text{m}$ ) chrysotile results for risk estimation universally for all types of ingested asbestos.

All but one epidemiologic investigation of the possible cancer risks associated with the ingestion of asbestos fiber have been ecological in nature. These ecological studies have attempted to relate area average ambient asbestos pollution levels found in drinking water to area average cancer mortality rates but not the exposure of specific individuals to their cancer risks. Only one of these ecological studies, the one reported by Kanarek et al. (46) on cancer mortality of the California Bay

Area, has demonstrated an association between area cancer rates and area ambient asbestos pollution of drinking water sources. The sole nonecological investigation, a case-control study reported by Polissar et al. (53), did not demonstrate any definitive excess of cancer mortality associated with asbestos pollution of the drinking water. Since none of the epidemiology studies provide useful information concerning a dose-response relationship, they do not form an adequate basis to perform a quantitative risk assessment.

Most of the concern about the possible risks of asbestos-related cancer resulting from the ingestion of asbestos fibers results from extrapolations of results observed in occupational epidemiologic studies. The risk observed in occupational epidemiologic studies may not be completely comparable to the health risks associated solely with the ingestion of ambient asbestos pollution because of differences in a number of factors, such as the main route of exposure, the type of asbestos, the physical status of the asbestos, and the nature of physiologic response to the fiber's presence in various tissues, etc. Most of the inhaled asbestos is evidently cleared from the lung and then swallowed and can present an exposure to the gastrointestinal tract. The results of occupational epidemiologic studies may provide an analogy for qualitative (and to some extent, for quantitative) assessment of the risk which may be associated with ingestion of asbestos. It is not clear if the observed increases in gastrointestinal cancer found among occupationally exposed workers are due to the swallowing of fibers previously inhaled and then expelled from the lung (55,56).

A number of reviews of occupational epidemiologic data which reflect on the potential risk of asbestos ingestion were available to the committee. In the 1977 and 1983 reports *Drinking Water and Health*, the Safe Drinking Water Committee of the National Research Council noted that increased cancer risks of various sites within the gastrointestinal tract have been reported in a number of occupational studies (57,58). The reports discuss the common fate of most inhaled and ingested asbestos, indicating that an increased risk of cancer from ingestion of ambient asbestos pollution in drinking water is plausible. The first of these reports made no attempt to quantify this risk but noted that it would be highly dependent on the number of fibers ingested, as well as on the duration of exposure (57). In the second report, the range of estimated excess of gastrointestinal cancer risk is 0.039 to 0.22, with the best estimate of 0.05 excess gastrointestinal cancers per individual for every  $10^{12}$  fibers swallowed, as detected with the transmission electron microscope, based on extrapolation from available occupational data (58).

In 1980, EPA developed a cancer risk estimate for the ingestion of asbestos based on extrapolation from occupational epidemiologic studies (11). The EPA is in the process of developing a new document, *Drinking Water Criteria Document for Asbestos*, which may modify the 1980 position (59). Occupational data from five studies were used and account was taken of the fact

that occupational exposures are less than lifetime (60-64).

Toft et al. of the Canadian Department of National Health and Welfare (65) used the EPA cancer risk estimate to generate the expected number of excess gastrointestinal cancers and peritoneal mesotheliomas in specific Canadian urban localities for individuals aged 35 or more and compared these values to observed numbers of excess deaths (excess deaths were based relative to expected deaths derived from matched urban localities). The details of how Toft et al. computed these expected deaths and observed excess deaths were not given. For example, it was not indicated whether excess number of deaths took into account the actual level of ambient asbestos pollution in the drinking water, whether the history of ambient asbestos pollution in the water supplies of these urban localities had been reviewed, whether the resident patterns and average residence time in the communities had been considered, or whether the matching criterion used to generate the expected number of deaths selected appropriate urban localities. Toft et al. reported that some of the expected and observed excess deaths were in close agreement and some were quite discrepant, observing that the use of the EPA criterion yielded predicted excess numbers of gastrointestinal cancers that deviated in both directions from the observed number of excess cancer deaths. They concluded that the available data were insufficient to permit meaningful estimations of cancer risk associated with the ingestion of asbestos fibers found in drinking water. Furthermore, they recommended conducting case-control or cohort epidemiologic studies in areas with large populations and substantial ambient asbestos pollution in drinking water supplies if the existence of such cancer risks are going to be credibly tested.

Several comprehensive reviews of the epidemiologic literature dealing specifically with the risk of asbestos fiber ingestion have considered issues important for conducting risk assessment activities (39,66,67). These articles have discussed many of the same issues mentioned earlier, such as the weakness of available environmental epidemiologic studies due to their ecological nature, the inadequacy of most of the study population sizes to detect the expected modest to small increases in asbestos-related cancer, the imprecision in exposure assessment, and the lack of adjustment for potential confounding factors. All three articles indicate that more powerful epidemiologic studies using case-control or cohort study designs of an extremely large general population from an area which has used a water supply system contaminated with relatively high concentrations of asbestos fibers are needed to address further the question of cancer risks associated with the ingestion of asbestos. Each of these comprehensive reviews has made unique assertions which are valuable to consider.

Marsh (39) conducted a probability analysis on selected epidemiologic reports in the five study areas to assess the consistency of the observed findings and probability of observing such findings. He concluded

that the number of observations of cancer excesses of the esophagus, stomach, pancreas, and prostate were greater than what would be expected by chance ( $p < 0.05$ ); however, the degree of concordance between males and females was moderate to low. Erdreich (66) evaluated the ability of various studies to detect a cancer risk as low as that predicted by EPA (9) in the 1980 *Ambient Water Quality Criteria for Asbestos*. She demonstrated that based on sensitivity calculations developed for cohort studies (using statistical criteria of 80% power [ $1 - B$ ] and a level of significance,  $p$ , of 0.05), the California Bay Area study was capable of detecting a gastrointestinal cancer relative risk of 1.1, and the Puget Sound study was capable of detecting a gastrointestinal cancer relative risk of 1.5. The estimated gastrointestinal cancer relative risks arising from the EPA predicted value would be 1.01 for the California Bay Area and 1.1 for Puget Sound. Therefore, she asserted that it is doubtful that any of the available studies could detect the risk predicted by the 1980 EPA *Ambient Water Quality Criteria for Asbestos*, with the two aforementioned studies being the best candidates.

Tollefson (67) gave a very concise discussion of the potential pitfalls of applying risk estimates derived from occupational studies of inhaled asbestos to the question of risk associated with ingested asbestos because of the potential differences in toxic and physiologic responses. She discussed the need for additional epidemiologic studies. Also, she made the point that a very large, expensive epidemiologic study of this issue could be futile and not demonstrate an increased risk of gastrointestinal cancer which truly existed if that increase in risk was quite small.

Perhaps one of the most thorough reviews of asbestos-related cancer risks and attempts at risk assessment has been completed by Dr. William Nicholson of Mt. Sinai Medical Center for the U.S. EPA (68). In this document, Nicholson discusses the evidence for a gastrointestinal cancer risk from exposure to asbestos based on occupational studies. He points out that it is always much lower than the respiratory cancer risk but is consistently elevated whenever there is a significant increase in respiratory cancer risks. The excess of gastrointestinal tract cancer rates averages 10 to 15% of the excess of respiratory cancer in recent studies; the consistency of this observation adds additional credence to the existence of a gastrointestinal cancer risk associated with asbestos exposure via inhalation. However, the increased gastrointestinal cancer risks are frequently below the level of statistical detectability.

In a separate article, Nicholson (69) reflected on the uncertainties of assessing the human cancer risk associated with the ingestion of asbestos. He considers a hypothetical study population of 1 million people living in a city with a water source which is contaminated with asbestos at the level of 100 million fibers/L (Nicholson indicates this is an overestimate of exposure). He assumed that the average residence time was 14 years, with residence time following an exponential distribution and that 7 years were required for the manifesta-

tion of an increase in the asbestos-related malignancy risk. Average lifetime risk was calculated by considering the proportion of the hypothetical study population that would fall into specific categories of residence time and by considering the EPA Ambient Water Quality Criteria predictions of excess cancer risk for specific asbestos exposure. This average lifetime risk would be  $3.3 \times 10^{-3}$  excess deaths per person under the assumed study conditions. Following this hypothetical study scenario, Nicholson stated that either the level of fiber exposure would have to be increased by a factor of 7.5, or the study population would have to be increased by a factor of 50 to detect a statistically significant excess in gastrointestinal cancer at the rate predicted by the 1980 EPA excess risk estimate because of the standard deviation which would be associated with the expected number of excess cancer deaths. This would necessitate a greater exposure and/or a larger population than any of those studied to date.

## Summary

The collective conclusions of available reviews and our panel indicate that the information is inadequate for a credible risk assessment of cancer risks associated with the ingestion of asbestos based on information developed from studies of asbestos ingestion. Existing cancer risk assessments have had to rely on the extrapolation of risk estimates based on occupational asbestos inhalation studies. Epidemiologic studies have not definitively established the existence of an association between asbestos ingestion and gastrointestinal cancer or other cancers. While one study does provide support for such a hypothesized association, the research designs used in the negative studies, as previously discussed, limit our ability to definitely state that there is no increased cancer risk from ingested asbestos. Instead, the weight of epidemiologic data and analysis leads us to the following conclusions: (1) if such an association exists, then it is probably weak relative to background cancer rates; and (2) epidemiologic research methodology is limited in its ability to detect small increases in risk. If additional epidemiologic research is undertaken, then it should be recognized that studies will require a substantial amount of time for completion, will be very expensive, and will provide only limited information about small increases in risk, possibly providing an upper limit estimate of risk.

Probably the two most critical factors of the available epidemiologic studies are the fact that all but one of the studies are ecological or geographical correlation studies and/or that the studies are of insufficient size to detect the modest increases in cancer risk which would conceivably be associated with low level exposure to asbestos via ingestion when exposure effects are small. As discussed previously, ecological studies have major drawbacks which introduce the potential for bias and confounding in effect estimates. This creates serious limitations and does not permit a definitive conclusion to be made from the available studies as to the possible

adverse health effects of ingested asbestos. Misclassification of asbestos exposures is another limitation of ecological studies. This misclassification can result from several factors: (1) the basic ecological design which assigns a specific exposure level to an entire geographic area, (2) assumptions regarding the extent of asbestos contamination from asbestos cement pipes, (3) the lack of reliable historical asbestos exposure data, and (4) the mobility of the study populations. A large variability in findings is seen in these studies, as well as considerable discrepancy in the results for males and females. These inconsistencies suggest that factors other than asbestos exposure may have influenced the results. Other factors, such as the characteristics of asbestos cement pipe used, the concentration of other possible carcinogenic contaminants of water, and the physical properties of asbestos fibers (e.g., whether asbestos is present as a cluster of fibers or as individual fibers and which fiber types and fiber lengths are found), were likely to have varied in the areas studied.

The use of available toxicology results also is limited currently for risk assessment purposes. The results would be subject to the traditional risk assessment uncertainties resulting from extrapolations between species, extrapolation from bioassay high doses to ambient human doses, and extrapolations from the controlled laboratory environments to the complex milieu of the human living environment. Additionally, the unanswered questions which have been enumerated in other parts of this report require consideration before toxicology data can most effectively be used to quantitatively assess human cancer risks from ingestion of asbestos. These questions would include: (1) How does the ultimate action of inhaled asbestos which enters the gastrointestinal tract differ from that of asbestos ingested directly? (2) What are the critical fiber characteristics (size and/or type) which determine carcinogenicity? (3) What proportion of ingested asbestos fibers penetrate or are deposited in the gastrointestinal tract? (4) How should we use benign tumors in carcinogenesis risk assessment?

In inhalation studies, the retention of asbestos in the lung may account for the excess cancer at various sites. These retained fibers may migrate to other organs or react with tissues in the lung. On the other hand, the rapid clearance of ingested materials from the gastrointestinal tract may well play a role in the reduced association of excessive cancer of the gastrointestinal tract with ingestion of asbestos fibers. By limiting the mucosal contact time of asbestos fibers, gastrointestinal motility may reduce the asbestos fiber's ability to penetrate the gut and to migrate to other organs.

An issue that does not appear to have been adequately addressed in the scientific literature is the possible cocarcinogenic or the synergistic effects of asbestos on body organs other than the respiratory tract which might occur when asbestos exposure occurs in combination with other environmental factors. The synergism between asbestos and cigarette smoke in the production of lung cancer is well established. These issues deserve

attention in future research to determine whether the swallowing of inhaled asbestos and the direct ingestion of asbestos increases the risk of gastrointestinal cancer of specific subgroups in a population.

## Recommendations

Our working group believes the following options and issues need to be considered as a course of action is developed to resolve the questions about whether asbestos ingestion poses a cancer risk.

### Points About Epidemiologic Research

1. Statistical power considerations indicate that epidemiologic research can provide very limited insight if increases in cancer risks are small.
2. Exposure assessment data about current and historical exposure to asbestos are insufficient, and any further epidemiologic research should have adequate resources allocated to assure that exposure assignment (level of exposure) of study members is sufficient and that the asbestos fibers are adequately characterized (fiber types and size range).
3. Future epidemiologic studies should address the possible association directly (i.e., they should not be ecological in nature). The most appropriate study designs for quantitative risk assessment would be case-control and cohort studies. While additional adequate retrospective studies would provide useful insight, prospective studies would provide the best opportunities to collect the highest quality of data (such as direct questionnaire responses, verifiable disease information, and correct exposure assessment). The questions of feasibility and resource allocation are critical issues which need to be considered prior to commitment to conduct further epidemiologic studies.
4. Epidemiologic studies will require a substantial amount of time for completion and consume considerable amounts of research resources. Retrospective studies would require several years (2-4) for completion, a major portion of a principal investigator's time with sufficient clerical staff support, and likely more than \$100,000 per year for the duration of the study (this could well be an underestimate). Prospective studies would consume much more time and research resources, probably requiring decades for completion, a substantial effort of principal investigators with a larger staff for interviewing, as well as clerical support and financial allocations of several million dollars or more.
5. Assuming that the risks are small (probably less than 10% above background, as indicated by available studies), such efforts can provide, at best, only an upper range on possible asbestos ingestion-related cancer risk and will not provide a definitive

answer about whether the ingestion of asbestos does elevate cancer risks.

6. Since one positive animal experiment demonstrated an excess in gastrointestinal benign tumors, determining whether such benign tumors, in addition to malignancies, could be assessed in the San Francisco Bay Area Register and the Seattle Tumor Register (Puget Sound) data may be useful when considering further possibilities for epidemiologic research.

### Points About Toxicologic Research

1. Research findings from one bioassay document that the ingestion of chrysotile asbestos fibers of intermediate length over the lifetime of male rats results in a weak tumorigenic response. Various working group participants debated the merit of conducting additional animal bioassays. As with the epidemiologic research, additional bioassays are feasible; however, it remains to be determined whether such studies would be cost effective in generating data of more value for the assessment of the human health hazard from the ingestion of asbestos fibers.
2. The assessment of risk to man posed by the ingestion of asbestos fibers requires more adequate studies on the size distribution and physicochemical properties of asbestos fiber types found in water, food, and drugs.
3. Since a number of studies have shown that asbestos fibers of appropriate size inhibit DNA repair, produce SCEs, and are cytotoxic in *in vitro* tests, short-term *in vivo* studies of the cocarcinogenic effects of asbestos may be of value.

### Conclusions

We conclude that sufficient direct evidence is not available for a credible quantitative cancer risk assessment of asbestos ingestion at this time. Furthermore, we question whether conducting additional epidemiologic or animal bioassay studies is a wise expenditure of resources and whether they could be expected to provide definitive information. As pointed out earlier, excesses of gastrointestinal cancer have been consistently observed in a number of occupational populations exposed to asbestos via inhalation. Unresolved at this point is how to equate excess cancer risks associated with asbestos inhalation to risk of cancer resulting from the ingestion of asbestos. If more research is to be funded on this issue, we recommend toxicologic studies that are aimed at addressing the role of asbestos fiber size in carcinogenesis, the physicochemical nature and fate of inhaled versus ingested asbestos fibers, the mechanism of fiber carcinogenesis, and the potential interaction of asbestos and other environmental factors to produce a carcinogenic effect. These types of toxicologic research could assist in determining the validity of extrapolating and the extent to which one can ex-

trapolate the risk estimates developed from inhalation studies for the purposes of assessing the risk from ingesting asbestos. Also, environmental surveys which characterize the distribution of waterborne asbestos and its associated size characteristics would be useful for future assessments. Given the available data, we do not believe that from a qualitative cancer risk assessment perspective the cancer risks associated with the ingestion of asbestos are among the most pressing environmental health hazards in the United States. Nonetheless, this should not be taken to mean that the potential hazard associated with ingested asbestos is an unimportant issue which does not warrant further research. Even if the increased rate of cancer is less than 10% of the background rate and cannot be demonstrated by available research tools, the ingestion of water, food, or drugs laden with asbestos by millions of people over their lifetimes could result in a substantial number of cancers.

Several of the members of this working group believe it is prudent, preventive public health policy to recommend eliminating possible sources of ingestion exposure to asbestos whenever and to whatever extent possible. This should not be interpreted as a recommendation of the Department of Health and Human Services or its member agencies. Some of the approaches which could be pursued include the following: eliminating asbestos cement pipe in water supply systems; eliminating the use of asbestos filters in the processing of beverages, foods, and medications; and reducing the levels of asbestos fibers in drinking water supplies. It should be noted that on January 29, 1986, EPA proposed prohibiting the manufacture of asbestos cement pipe (70); therefore, future abatement efforts of this potential exposure source may only involve replacement of existing pipe.

This is a DHHS working group report; however, input from the identified individuals of agencies outside DHHS was sought and received. While EPA and WHO staff participated in developing this document, it does not reflect EPA or WHO policy. Both of these agencies are in the process of reviewing their own position on this topic and are developing a new document.

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