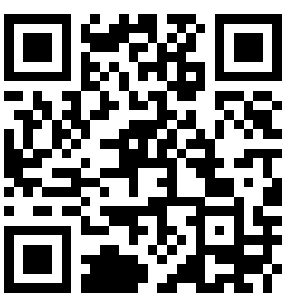
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# TOXICOLOGICAL PROFILE FOR ASBESTOS

Prepared by:

Life Systems, Inc.
Under Subcontract to:

Clement Associates, Inc.
Under Contract No. 205-88-0608

Prepared for:

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

In collaboration with:

U.S. Environmental Protection Agency

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The ATSDR Toxicological Profile for Asbestos is intended to characterize succinctly the toxicological and health effects information for the substance. It identifies and reviews the key literature that describes the substances's toxicological properties. Other literature is presented but described in less detail. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced. The profile begins with a public health statement, which describes in nontechnical language the substance's relevant toxicological properties. Following the statement is material that presents levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine the substance's health effects is described. Research gaps in nontoxic and health effects information are described. Research gaps that are of significance to the protection of public health will be identified in a separate effort. The focus of the document is on health and toxicological information.

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## FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987, on October 20, 1988, on October 26, 1989, and on October 17, 1990.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects,

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects, and

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by CERCLA, as amended.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

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*Foreword*

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning significant health effects associated with exposure to the substance. The adequacy of information to determine a substance's health effects is described. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

William L. Roper, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

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# 1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about asbestos and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). Asbestos has been found at 28 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for asbestos. As EPA evaluates more sites, the number of sites at which asbestos is found may change. The information is important for you to know because asbestos may cause harmful health effects and because these sites are potential or actual sources of human exposure to asbestos.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous substance such as asbestos, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

## 1.1 WHAT IS ASBESTOS?

Asbestos is the name applied to a group of six different minerals (amosite, chrysotile, tremolite, actinolite, anthophyllite, and crocidolite) that occur naturally in the environment. The most common mineral type is white (chrysotile), but others may be blue (crocidolite), gray (anthophyllite), or brown (amosite). These minerals are made up of long, thin fibers that appear somewhat similar to fiber glass. Asbestos fibers are very strong and are resistant to heat and chemicals. Because of these properties, asbestos fibers have been used in a wide range of products, mostly in building materials, friction products, and heat-resistant fabrics. Because the fibers are so resistant to chemicals, they are also very stable in the environment; they do not evaporate into air or dissolve in water, and they are not broken down over time.

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Further information on the properties, uses, and behavior of asbestos in the environment may be found in Chapters 3, 4, and 5.

## 1.2 HOW MIGHT I BE EXPOSED TO ASBESTOS?

You are most likely to be exposed to asbestos by breathing in tiny asbestos fibers suspended in air. These fibers can come from natural outcroppings of asbestos, but many come from the degradation or breakdown of man-made products such as insulation, ceiling and floor tiles, roof shingles, cement, automotive brakes and clutches, and many others. Low levels of asbestos can be detected in almost any air sample. For example, in rural areas, there are usually an average of around 0.03 to 3 fibers present in a cubic meter (f/$m^3$) of outdoor air[a]. (A cubic meter is about the amount of air you breathe in 1 hour). Higher levels are usually found in cities, where there may be 3 to 300 f/$m^3$. Close to an asbestos mine or factory, levels could reach 2,000 f/$m^3$ or higher. Levels could also be above average near a building that is being torn down or renovated, or near a waste site where asbestos is not properly covered up or stored to protect it from wind erosion.

In indoor air, the concentration of asbestos depends on whether asbestos was used for insulation, ceiling or floor tiles, or other purposes, and whether these asbestos-containing materials are in good condition or are deteriorated and easily crumbled. Concentrations measured in homes, schools, and other buildings that contain asbestos range from 30 to 6,000 f/$m^3$. People who work with asbestos (e.g., miners, insulation workers, automobile brake mechanics) are likely to be exposed to much higher levels of asbestos particles in air.

You can also be exposed to asbestos by drinking fibers present in water. Even though asbestos does not dissolve in water, fibers can enter water by being eroded from natural deposits or piles of waste asbestos, or from cement pipes used to carry drinking water. Most drinking water supplies in the United States have concentrations less than 1 million fibers per liter (MFL)[a]. (A liter is about the same as a quart). However, in some locations, there may be 10 to 100 MFL or even higher.

---

[a]The number of fibers depends on how they are measured. Values in air are reported as phase contrast fibers per cubic meter. This is the same measure as used to describe health effects in Section 1.5. The values in water are reported as transmission electron microscope fibers. This method is more sensitive than phase contrast microscopy, so values in air and water are not comparable.

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Further information on how you could be exposed to asbestos is presented in Chapters 2 and 5.

## 1.3 HOW CAN ASBESTOS ENTER AND LEAVE MY BODY?

If you breathe asbestos fibers into your lungs, some of the fibers will be deposited in the air passages and on the cells that make up your lungs. However, very few of these fibers move through your lungs into your body. Instead, most fibers are removed from your lungs by being carried away in a layer of mucus to the throat, where they are swallowed into the stomach. This usually takes place within a few hours, but fibers that are deposited in the deepest parts of the lung are removed more slowly, and some can remain in place for many years and may never be removed.

If you swallow asbestos fibers (either those present in water or those that are moved to your throat from your lungs), nearly all the fibers pass along your intestines within a few days and are excreted in the feces. A small number of fibers become stuck in the cells that line your stomach or intestines, and a few penetrate all the way through and get into the blood. Some of these become trapped in other tissues, and some are removed in the urine.

Further information on what happens to asbestos fibers in the lung and the stomach may be found in Chapter 2.

## 1.4 HOW CAN ASBESTOS AFFECT MY HEALTH?

Information on the health effects of asbestos in humans comes mostly from studies of people who were exposed in the past to high levels of asbestos in the workplace. These asbestos workers were found to have increased chances of getting two types of cancer: cancer of the lung tissue itself, and mesothelioma, a cancer of the thin membrane that surrounds the lung and other internal organs. Both lung cancer and mesothelioma are usually fatal. These diseases do not appear immediately, but develop only after a number of years. There is also some evidence from studies of workers that breathing asbestos can increase the chances of getting cancer in other locations (e.g., stomach, intestines, esophagus, pancreas, kidneys), but this is less certain. Members of the public who are exposed to lower levels of asbestos may also have increased chances of getting cancer, but the risks are usually small and are difficult to measure directly.

Besides causing cancer, breathing asbestos can also cause a slow accumulation of scar-like tissue in the lungs and in the membrane which surrounds the lungs. This scar-like tissue does not expand and contract like normal lung tissue, and so breathing becomes difficult. Blood flow to the lung may also be decreased, and this causes the heart to enlarge. When the injury is mostly in the lung itself, the disease is called asbestosis. This is a serious disease, and can eventually lead to

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disability or death in people exposed to high levels of asbestos. However, asbestosis is not usually of concern to people exposed to low levels of asbestos. Similar injury to the membrane surrounding the lung is quite common in people exposed to asbestos, but effects on breathing are usually not serious.

The health effects from swallowing asbestos are unclear. Some groups of people who have been exposed to asbestos fibers in their drinking water have higher-than-average death rates from cancer of the esophagus, stomach, and intestines. However, it is very difficult to tell whether this is caused by asbestos or by something else. Animals that were given very high doses of asbestos in food did not get any more fatal cancers than usual, although some extra nonfatal tumors did occur in the intestines of rats in one study.

Further information on how asbestos can affect your health is given in Chapter 2.

## 1.5 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

The levels of asbestos in air that lead to lung disease depend on a large number of factors. The most important of these are 1) how long you were exposed, 2) how long it has been since your exposure started, and 3) whether you smoked cigarettes. Also, there is a scientific debate concerning the differences in the amount of disease caused by different fiber types and sizes. Some of these differences may be due to the physical and chemical properties of the different fiber types. There are several studies which suggest that amphiboles (tremolite, amosite, and especially crocidolite) may be more potent than chrysotile. However, most data indicate that fiber size is the most important factor for cancer causing potential. Most studies indicate that long fibers (where "long" means greater than about 1/5,000th of an inch) are more likely to cause injury than short fibers (where "short" means less than about 1/10,000th of an inch). Tables 1-1 and 1-2 show the levels of asbestos that have been found to cause noncancer lung injury in humans and animals, respectively. It is important to stress that the values shown in these tables are the lowest exposures known to have caused noncancer effects, and that not all people exposed to the doses in Table 1-1 would develop the effects.

As noted above, eating or drinking asbestos fibers may increase risk of cancer, but this is not certain. Eating or drinking asbestos fibers is not thought to cause any harmful noncancer effects. This is summarized in Tables 1-3 and 1-4.

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**TABLE 1-1. Human Health Effects from Breathing Asbestos***

| Short-term Exposure (less than or equal to 14 days) | | |
|---|---|---|
| Levels in Air | Length of Exposure | Description of Effects |
| | | The health effects resulting from short-term exposure of humans to air containing specific levels of asbestos are not known. |
| **Long-term Exposure (greater than 14 days)** | | |
| Levels in Air ($f/m^3$) | Length of Exposure | Description of Effects** |
| 1,000,000 | 20 years | Lung injury in some people. |
| 3,400,000 | 20 years | Death from asbestosis in some people. |

*See Section 1.2 for a discussion of exposures encountered in daily life.
**These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

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TABLE 1-2. Animal Health Effects from Breathing Asbestos

| Short-term Exposure (less than or equal to 14 days) | | |
|---|---|---|
| Levels in Air | Length of Exposure | Description of Effects |
| | | The health effects resulting from short-term exposure of animals to air containing specific levels of asbestos are not known. |
| **Long-term Exposure (greater than 14 days)** | | |
| Levels in Air ($f/m^3$) | Length of Exposure | Description of Effects* |
| 54,000,000 | 2 years | Mild lung injury in rats. |
| 1,100,000,000 | 2 years | More severe lung injury in rats. |

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

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**TABLE 1-3. Human Health Effects from Eating or Drinking Asbestos**

| Short-term Exposure (less than or equal to 14 days) | | |
|---|---|---|
| Levels in Food | Length of Exposure | Description of Effects |
| | | The health effects resulting from short-term exposure of humans to food containing specific levels of asbestos are not known. |
| Levels in Water | | The health effects resulting from short-term exposure of humans to water containing specific levels of asbestos are not known. |
| **Long-term Exposure (greater than 14 days)** | | |
| Levels in Food | Length of Exposure | Description of Effects |
| | | The health effects resulting from long-term exposure of humans to food containing specific levels of asbestos are not known. |
| Levels in Water | | The health effects resulting from long-term exposure of humans to water containing specific levels of asbestos are not known. |

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TABLE 1-4. Animal Health Effects from Eating or Drinking Asbestos

| Short-term Exposure (less than or equal to 14 days) | | |
|---|---|---|
| Levels in Food | Length of Exposure | Description of Effects |
| | | The health effects resulting from short-term exposure of animals to food containing specific levels of asbestos are not known. |
| Levels in Water | | The health effects resulting from short-term exposure of animals to water containing specific levels of asbestos are not known. |
| **Long-term Exposure (greater than 14 days)** | | |
| Levels in Food | Length of Exposure | Description of Effects |
| | | The health effects resulting from long-term exposure of animals to food containing specific levels of asbestos are not known. |
| Levels in Water | | The health effects resulting from long-term exposure of animals to water containing specific levels of asbestos are not known. |

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## 1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ASBESTOS?

The most common test used to determine if you have been exposed to asbestos is a chest x-ray. The x-ray cannot detect the asbestos fibers themselves, but can detect early signs of lung disease caused by asbestos. While other things besides asbestos can sometimes produce similar changes in the lungs, this test is usually reliable for detecting asbestos-related effects.

It is also possible to test for the presence of asbestos fibers in urine, feces, mucus, or material rinsed out of the lung by a doctor. Low levels of asbestos fibers are found in these materials for nearly all people. Higher-than-average levels can show that you have been exposed to asbestos, but it is not yet possible to use the results to estimate how much asbestos you have been exposed to, or to predict whether you are likely to suffer any health effects.

Further information about how asbestos can be measured in people and in the environment is presented in Chapter 6.

## 1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

Despite the ongoing debate concerning health effects resulting from the different asbestos fiber types, ATSDR considers the different mineral forms of asbestos to be known human cancer causing substances with a prolonged latency period of between 10 and 30 years between exposure and the onset of disease. The federal government has taken a number of steps to protect citizens from exposure to asbestos. First, the U.S. Environmental Protection Agency (EPA) has established a very broad ban on the manufacture, processing, importation, and distribution of materials or products that contain asbestos. These regulations were initiated in 1990, and will be in full force by 1997. This ban will result in elimination of asbestos in insulation, brakes, floor and ceiling tiles, cement, paper, and nearly all other asbestos-containing materials. Second, EPA has established regulations that require school systems to investigate whether asbestos exposure is a problem inside their school buildings, and if so, to reduce or eliminate the exposure, either by removing the asbestos or by covering it up so it cannot get into air. In addition, EPA provides guidance and support for reducing asbestos exposure in other public buildings. Third, EPA regulates the release of asbestos from factories and during building demolition or renovation to prevent asbestos from getting into the environment. The EPA also regulates the disposal of waste asbestos materials or products, requiring these to be placed only in approved locations. Fourth, EPA has proposed a limit of 7 million fibers per liter on the concentration of long fibers that may be present in drinking water. Fifth, the Food and Drug Administration regulates the use of asbestos in the preparation of drugs, and restricts the use of asbestos in food-packaging materials.

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Finally, the Occupational Safety and Health Administration has established a limit of 200,000 fibers/$m^3$ on the average daily concentration of asbestos allowed in air in the workplace.

Further information about regulations and guidelines to protect people from asbestos is presented in Chapter 7.

## 1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your State Health or Environmental Department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also give you information on the location of the nearest occupational and environmental health clinics. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

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# 2. HEALTH EFFECTS

## 2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to asbestos. Its purpose is to present levels of significant exposure for asbestos based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of asbestos and (2) a depiction of significant exposure levels associated with various adverse health effects.

It is important to recognize that asbestos is not a single chemical, but is the generic name for a family of six related polysilicate fibrous minerals. These minerals differ from each other in physical and chemical properties, and each mineral can exist in a wide range of fiber sizes. These differences between fiber type and size are believed to be important determinants of the health risks posed by asbestos.

## 2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the data in this section are organized first by route of exposure -- inhalation, oral, and dermal -- and then by health effect -- death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods -- acute, intermediate, and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown on the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure

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associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) are of interest to health professionals and citizens alike.

For certain chemicals, levels of exposure associated with carcinogenic effects may be indicated in the figures. These levels reflect the actual doses associated with the tumor incidences reported in the studies cited. Because cancer effects could occur at lower exposure levels, the figures also show estimated excess risks, ranging from a risk of one in 10,000 to one in 10,000,000 ($10^{-4}$ to $10^{-7}$), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1989d), uncertainties are associated with the techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of these procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

### 2.2.1 Inhalation Exposure

**Units of Exposure.** Consideration and comparison of quantitative data on asbestos inhalation studies are complicated by the fact that a number of different methods have been used to measure asbestos levels in air. Currently, the standard method for measuring asbestos concentrations in workplace air employs phase contrast microscopy (PCM). A particle visible under PCM is counted as a fiber if it is 5 μm or more long and has a length/thickness ratio of 3:1 or more. However, the method cannot detect fibers thinner than about 0.3 μm, and cannot distinguish between asbestos fibers and other fibers. Nevertheless, because currently available risk factors for asbestos are expressed in terms of PCM fibers, all air concentration data in this section are expressed in terms of PCM fibers/mL (f/mL) unless otherwise noted.

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Human exposures to airborne fibers are then expressed in terms of cumulative dose (PCM fibers/mL multiplied by years of exposure, or PCM f-yr/mL), and animal exposures to airborne fibers are presented in terms of level of exposure (PCM f/mL) and duration.

When data on airborne levels are available only in terms of mass/volume (e.g., $mg/m^3$), it is difficult to convert this to units of PCM fibers/mL, because the ratio between mass and fiber number depends on fiber type and size distribution, and the measuring technique employed. For the purposes of making rough calculations when a more accurate conversion factor is not available, it is assumed that a concentration of 1 $mg/m^3$ in air is equal to 33 PCM f/mL (EPA 1986a).

Older occupational studies measured dust exposure in units of million particles per cubic foot (mppcf). This method did not distinguish fibrous from nonfibrous particles, and used relatively low magnification so only the largest fibers were detectable. When a more accurate value is not available, it is assumed that a concentration of 1 mppcf is equal to 3 PCM f/mL (BOHS 1968).

**Overview of Health Effects.** Studies in humans and animals indicate that inhalation of asbestos fibers may lead to fibrotic lung disease (asbestosis), cancer of the lung, the pleura, and the peritoneum, and may also increase risk of some extrathoracic cancers. Significant effects on other tissues have not been detected. Studies supporting these conclusions are summarized in Tables 2-1 and 2-2 and Figures 2-1 and 2-2, and the data are discussed below.

### 2.2.1.1 Death

No studies were located in which inhalation exposure to asbestos led to acute or short-term lethality in humans or animals. Inhalation exposure to asbestos can lead to delayed lethality from asbestosis or cancer, as discussed below.

### 2.2.1.2 Systemic Effects

Many studies have been performed on the health effects of inhalation exposure to asbestos, both in humans and animals. These studies have not identified any hematological, musculoskeletal, hepatic, renal, dermal or ocular effects, although such effects are usually not investigated in detail. It is generally considered that these tissues are not affected because only a tiny fraction of inhaled fibers penetrate into the blood and reach other tissues (see Section 2.3.2. below).

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**TABLE 2-1. Levels of Significant Exposure to Asbestos - Inhalation (Humans)**

| Figure Key | Species | Exposure Frequency/ Duration | Effect | NOAEL (f-yr/mL) | LOAEL (Effect) Less Serious (f-yr/mL) | LOAEL (Effect) Serious (f-yr/mL) | Reference | Type of Asbestos |
|---|---|---|---|---|---|---|---|---|
| CHRONIC EXPOSURE | | | | | | | | |
| Death | | | | | | | | |
| 1 | Human | 3.8 yr (aver. occup) | | | | 105 (pneumoconiosis) | Hughes et al. 1987 | CH,CR, AM |
| 2 | Human | 10-30 yr (occup) | | | | 68[a] (asbestosis) | Dement et al. 1983 | CH |
| 3 | Human | 1-20 yr (occup) | | | | 90 (asbestosis) | McDonald et al. 1983 | CH |
| 4 | Human | >5 yr (occup) | | | | 115 (asbestosis) | Peto et al. 1985 | CH,CR |
| 5 | Human | 20+ yrs (occup) | | | | 300 (asbestosis) | Nicholson et al. 1979 | CH |
| 6 | Human | 1-20 yr (occup) | | | | 90 (pneumoconiosis) | McDonald et al. 1980 | CH |
| 7 | Human | >9 yr (occup) | | | | 100 (asbestosis) | Finkelstein 1983 | CH,CR |
| 8 | Human | 3-51 yr (occup) | | | | 300 (asbestosis) | Henderson and Enterline 1979 | CH,CR, AM |
| Systemic | | | | | | | | |
| 9 | Human | >10 yr (occup) | Resp | 20 | 43 (crepitations) | 72 (asbestosis) | Berry et al. 1979 | CH,CR |
| 10 | Human | 15 yr (aver. occup.) | Resp | | | 20[b] (fibrosis) | Wollmer et al. 1987 | CH |
| 11 | Human | 1-20 yr (occup) | Resp | | | 50 (abnormal X-ray) | Irwig et al. 1979 | CR,AM |

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TABLE 2-1 (Continued)

| Figure Key | Species | Exposure Frequency/ Duration | Effect | NOAEL (f-yr/mL) | LOAEL (Effect) Less Serious (f-yr/mL) | LOAEL (Effect) Serious (f-yr/mL) | Reference | Type of Asbestos |
|---|---|---|---|---|---|---|---|---|
| CHRONIC EXPOSURE (Continued) | | | | | | | | |
| Systemic (Continued) | | | | | | | | |
| 12 | Human | 15 yr (occup) | Resp | | | 75 (decr. resp. function) | Enarson et al. 1988 | CH |
| 13 | Human | 10+ yrs (occup) | Resp | | | 25 (asbestosis) | Roach et al. 1983 | CH |
| 14 | Human | 0.1-39 yr (occup) | Resp | | | 17 (fibrosis) | Green et al. 1986 | CH,CR |
| Cancer | | | | | | | | |
| 15 | Human | <2 - >10 yr | | | | 450 CEL (lung cancer, mesothelioma) | Weill et al. 1979 | CH,CR, AM |
| 16 | Human | >2 yr (occup) | | | | 10 CEL (lung cancer, GI cancer, meso-thelioma) | Newhouse and Berry 1979 | CR,CH, AM |
| 17 | Human | 20+ yrs (occup) | | | | 300 CEL (lung cancer, mesothelioma) | Nicholson et al. 1979 | CH |
| 18 | Human | 1-20 yr (occup) | | | | 400 CEL (lung cancer, mesothelioma) | Amandus and Wheeler 1987 | TR,AC |
| 19 | Human | 1-20 yr (occup) | | | | 90 CEL (lung cancer) | McDonald et al. 1983 | CH |
| 20 | Human | 3.8 yr (aver. occup) | | | | 50 CEL (lung cancer, mesothelioma) | Hughes et al. 1987 | CH,CR, AM |
| 21 | Human | >5 yr (occup) | | | | 72 CEL (lung cancer, mesothelioma) | Peto et al. 1985 | CH,CR |
| 22 | Human | ND (occup) | | | | 180 CEL (lung cancer, GI cancer, meso-thelioma) | Enterline et al. 1987 | CH,CR, AM |



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TABLE 2-1 (Continued)

| Figure Key | Species | Exposure Frequency/ Duration | Effect | NOAEL (f-yr/mL) | LOAEL (Effect) Less Serious (f-yr/mL) | LOAEL (Effect) Serious (f-yr/mL) | Reference | Type of Asbestos |
|---|---|---|---|---|---|---|---|---|
| CHRONIC EXPOSURE (Continued) | | | | | | | | |
| Cancer (Continued) | | | | | | | | |
| 23 | Human | >9 yr (occup) | | | | 44 CEL (lung cancer, mesothelioma) | Finkelstein 1983 | CH,CR |
| 24 | Human | 1-20 yr (occup) | | | | 180 CEL (lung cancer) | McDonald et al. 1984 | CH |
| 25 | Human | 10-30 yr (occup) | | | | 14 CEL (lung cancer) | Dement et al. 1983 | CH |
| 26 | Human | 3-51 yr (occup) | | | | 180 CEL (lung cancer, mesothelioma) | Henderson and Enterline 1979 | CH,CR, AM |
| 27 | Human | 1-20 yr (occup) | | | | 45 CEL (lung cancer) | McDonald et al. 1982 | CH,AM, CR |

[a]This value converted to a corresponding exposure of 3,400,000 f/m$^3$ for 20 years for presentation in Table 1-1.
[b]This value converted to a corresponding exposure of 1,000,000 f/m$^3$ for 20 years for presentation in Table 1-1.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; f-yr/mL = fiber-years per milliliter; yr = year; CH = chrysotile; CR = crocidolite; aver. = average; AM = amosite; occup = occupational; Resp = respiratory; decr. = decreased; CEL = cancer effect level; GI = gastrointestinal; TR = tremolite; AC = actinolite; ND = no data.

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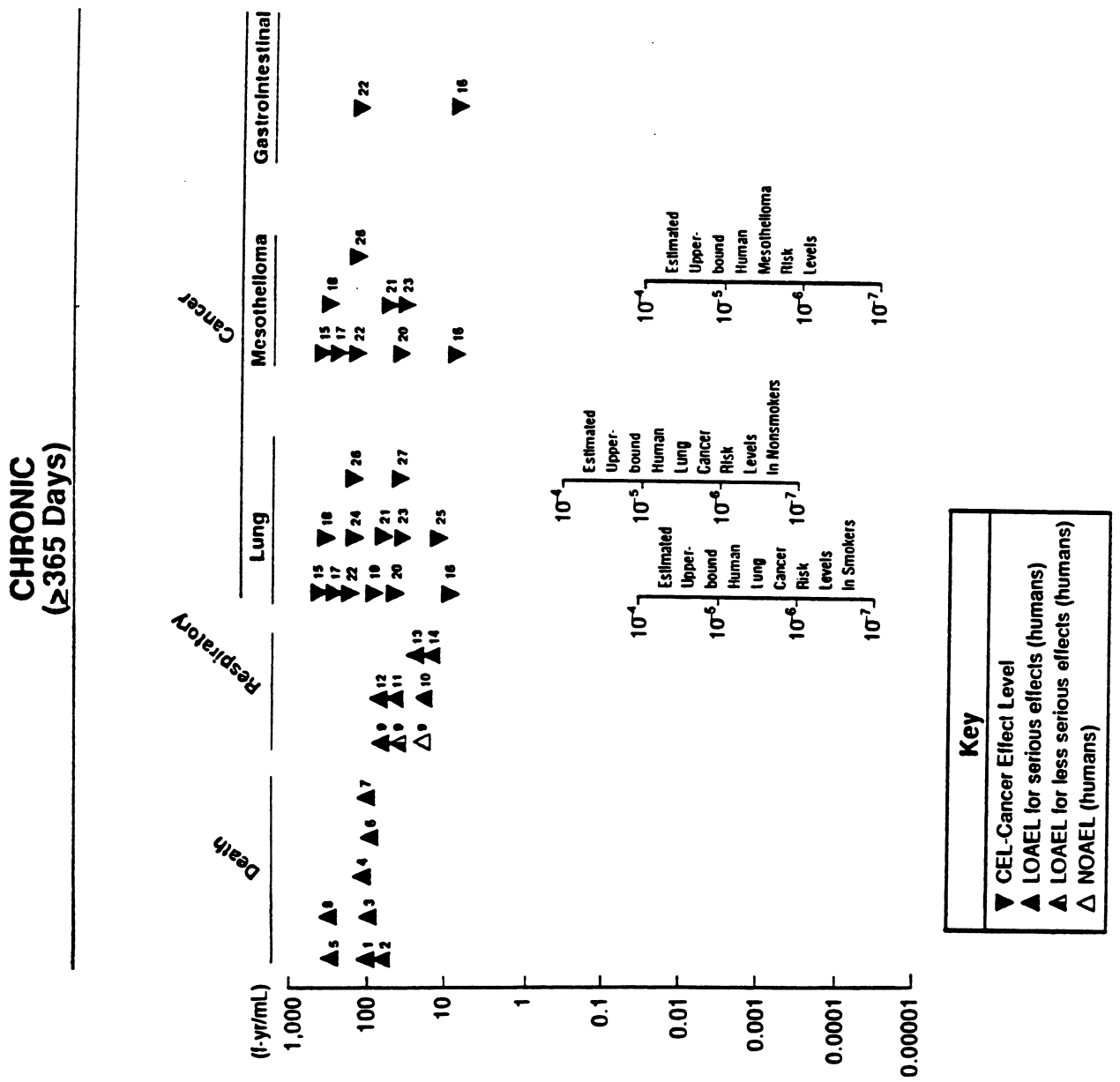



**FIGURE 2-1. Levels of Significant Exposure to Asbestos – Inhalation (Humans)**

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**TABLE 2-2. Levels of Significant Exposure to Asbestos - Inhalation (Animals)**

| Figure Key | Species | Exposure Frequency/ Duration | Effect | NOAEL (PCM f/mL) | LOAEL (Effect) Less Serious (PCM f/mL) | LOAEL (Effect) Serious (PCM f/mL) | Reference | Type of Asbestos |
|---|---|---|---|---|---|---|---|---|
| CHRONIC EXPOSURE | | | | | | | | |
| Systemic | | | | | | | | |
| 1 | Rat | 2 yr 4d/wk 4hr/d | Resp | | | 54[a] (mild fibrosis) | Reeves at al. 1974 | CH |
| 2 | Rat | 2 yr 4d/wk 4hr/d | Resp | | | 1105[b] (marked fibrosis) | Reeves at al. 1974 | CR |
| 3 | Rat | 12 mo 5d/wk 7hr/d | Resp | | | 1600 (fibrosis) | Davis et al. 1985 | TR |
| 4 | Rat | 12 mo | Resp | | | 330[c] (fibrosis) | Davis et al. 1980b | AM,CH |
| 5 | Rat | 12 mo 5d/wk 7.5hr/d | Resp | | | 430 (fibrosis) | Wagner et al. 1980a | CH |
| 6 | Rat | 1 yr 1-5d/wk 7hr/d | Resp | | | 70[c] (fibrosis) | Davis et al. 1980a | CH |
| 7 | Rat | 1 yr 1-5d/wk 7hr/d | Resp | | | 330[c] (fibrosis) | Davis et al. 1980a | AM |
| 8 | Rat | 12 mo 5d/wk 7hr/d | Resp | | | 2060 (fibrosis) | Davis et al. 1986a | AM-L |
| 9 | Rat | 2 yr 4d/wk 4hr/d | Resp | | | 860 (fibrosis) | Reeves at al. 1974 | AM |
| 10 | Rat | 24 mo 5d/wk 7hr/d | Resp | | | 350[c] (fibrosis) | Wagner et al. 1974 | AM,AN, CR,CH |



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TABLE 2-2 (Continued)

| Figure Key | Species | Exposure Frequency/ Duration | Effect | NOAEL (PCM f/mL) | LOAEL (Effect) Less Serious (PCM f/mL) | LOAEL (Effect) Serious (PCM f/mL) | Reference | Type of Asbestos |
|---|---|---|---|---|---|---|---|---|
| CHRONIC EXPOSURE (Continued) | | | | | | | | |
| Cancer | | | | | | | | |
| 11 | Rat | 12 mo | | | | 330[c] CEL (lung cancer) | Davis et al. 1980b | AM,CH |
| 12 | Rat | 1 yr 1-5d/wk 7hr/d | | | | 330[c] CEL (lung cancer) | Davis et al. 1980a | AM |
| 13 | Rat | 1 yr 1-5d/wk 7hr/d | | | | 70[c] CEL (lung cancer) | Davis et al. 1980a | CH |
| 14 | Rat | 12 mo 5d/wk 7.5hr/d | | | | 430 CEL (lung cancer, mesothelioma) | Wagner et al. 1980a | CH |
| 15 | Rat | 24 mo 5d/wk 7hr/d | | | | 350[c] CEL (lung tumors, mesothelioma) | Wagner et al. 1974 | AM,AN, CR,CH |
| 16 | Rat | 1 yr 5d/wk | | | | 1170 CEL (lung cancer mesothelioma) | Davis and Jones 1988 | CH-S |

[a]This value (expressed as 54,000,000 f/m$^3$) presented in Table 1-2.
[b]This value (expressed as 1,100,000,000 f/m$^3$) presented in Table 1-2.
[c]This value calculated from exposure level given in units of mg/m$^3$, using a conversion factor of 1 mg/m$^3$ = 33 PCM f/mL (EPA 1986a).

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PCM f/mL = phase contrast microscopy fibers per milliliter; yr = year; Resp = Respiratory; CH = chrysotile; d = day; wk = week; hr = hour; CR = crocidolite; mo = month; TR = tremolite; AM = amosite; L = long; AN = anthophyllite; CEL = cancer effect level; S = short.



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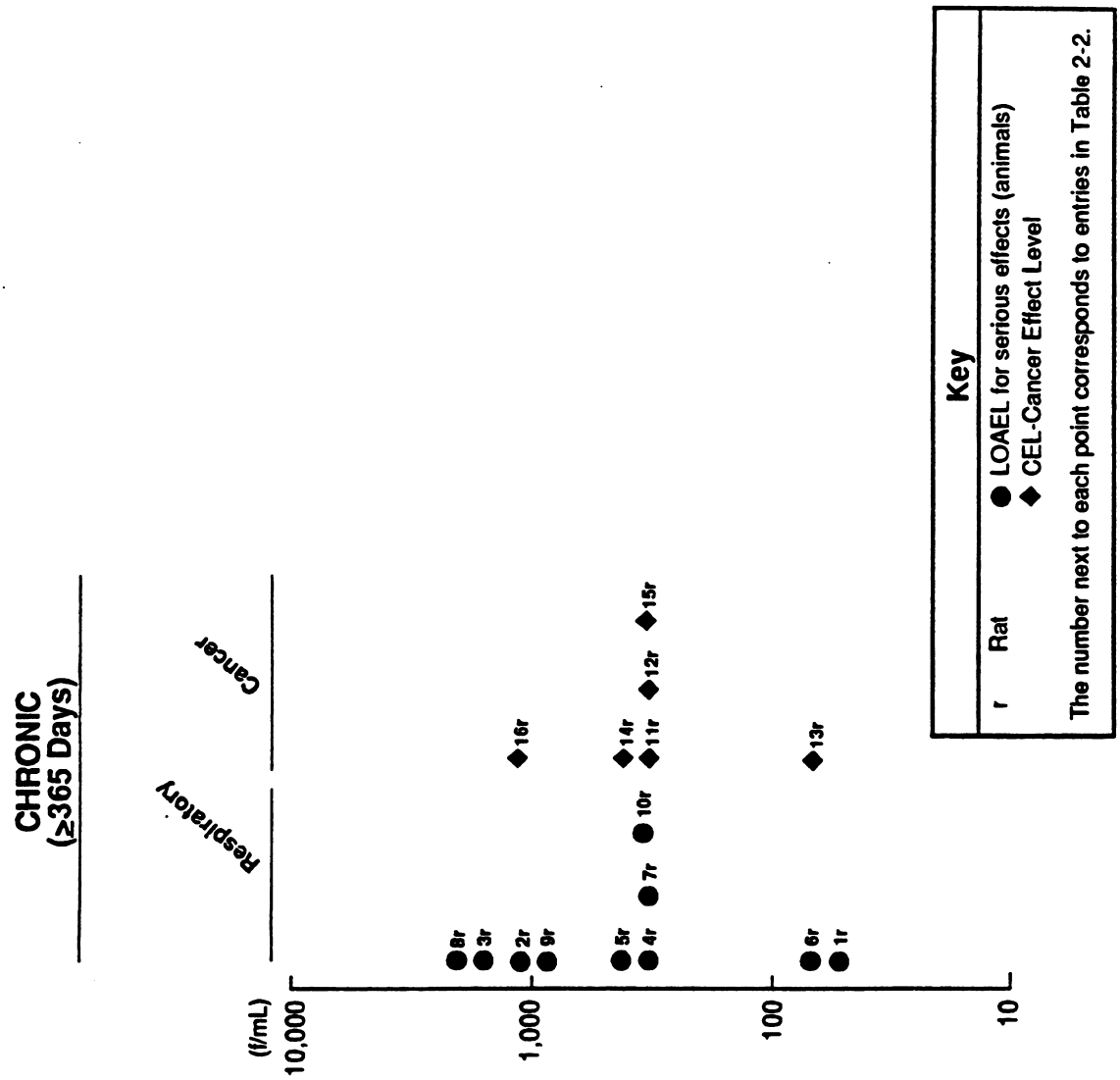



**FIGURE 2-2. Levels of Significant Exposure to Asbestos – Inhalation (Animals)**

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**Respiratory Effects.** Numerous studies in humans have established that inhalation exposure to asbestos fibers can lead to a characteristic pneumoconiosis termed asbestosis. The main clinical symptom of this disease is shortness of breath, often accompanied by rales or cough (Churg 1986; Enarson et al. 1988; Finkelstein 1986). In severe cases, impairment of respiratory function may ultimately result in death, and asbestosis has led to excess mortality in a number of groups of asbestos workers (McDonald et al. 1983; Peto et al. 1985; Selikoff et al. 1979).

Studies in animals indicate that asbestosis stems from the inflammatory response triggered in the lung by the deposition of asbestos fibers (Davis 1970). Fibers deposited in the ciliated portion of the airway are removed by mucociliary transport (see Section 2.3.4) and do not appear to injure the lung. However, fibers deposited in the terminal bronchioles and alveoli are not cleared as rapidly, and these can stimulate an influx of macrophages (Chang et al. 1988) which then release a variety of inflammatory mediators (chemotractants, lysosomal enzymes, activated oxygen species, growth factors, etc.) (Davis 1972; Hansen and Mossman 1987; Kagan 1988; Miller et al. 1978). This is thought to be responsible for the gradual loss of some epithelial cells and the deposition of collagen by fibroblasts (Davis et al. 1986c; Davis and Jones 1988). In animals, histological signs of tissue injury can be detected at the site of deposited fibers within a few days, although in humans, measurable abnormalities of lung function do not usually appear for a number of years (Dement et al. 1983; Hughes et al. 1987; Kagan 1988).

As shown in Table 2-1 and Figure 2-1, cumulative doses of around 15 to 75 f-yr/mL have been found to result in signs of fibrotic lung lesions in humans (Berry et al. 1979; Enarson et al. 1988; Green et al. 1986; Irwig et al. 1979; Wollmer et al. 1987). Death from asbestosis has been reported in humans with cumulative doses of around 70 to 300 f-yr/mL (Dement et al. 1983; Hughes et al. 1987; McDonald et al. 1980, 1983a; Peto et al. 1985). Death from asbestosis might occur at even lower doses (Dement et al. 1983), but there were too few cases to establish this with certainty.

An important aspect of the pathobiology of asbestosis is that because asbestos fibers are so resistant to breakdown, the inflammatory response triggered by the fibers is ongoing, even after exposure has ceased (Finkelstein 1986; Wagner et al. 1974). Consequently, the severity of pathological lesions and clinical symptoms tends to progress with time. For this reason, EPA (1986a) has suggested that a cumulative dose of 10 f-yr/mL might be an appropriate estimate of the threshold for minimal functional impairment in exposed workers. This corresponds to a

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concentration of 0.05 f/mL for an individual exposed continuously for 50 years. As discussed more fully in Chapter 5, exposures of this magnitude are very unlikely to occur outside the workplace, so asbestosis is not likely to occur in members of the general public.

Available evidence indicates that all asbestos fiber types are fibrogenic (Bignon and Jaurand 1983; Davis 1972; EPA 1986a; Lippman 1988). Most studies in humans have involved exposure to chrysotile (Dement et al. 1983; McDonald et al. 1983, 1984; Nicholson et al. 1979), but asbestosis has also been noted in populations exposed mainly to amosite (Seidman et al. 1979), crocidolite (Wignall and Fox 1982), and anthophyllite (Meurman et al. 1974). Fibrosis has been produced in animals by inhalation or intratracheal exposure to chrysotile (Chang et al. 1988; Davis et al. 1980a, 1980b; Wagner et al. 1980a), amosite (Davis et al. 1986a; Reeves et al. 1971, 1974), anthophyllite (Wagner et al. 1974), crocidolite (Reeves et al. 1971, 1974; Wagner et al. 1974), and tremolite (Davis et al. 1985). A number of studies have indicated that long fibers (e.g., 5 $\mu$m or more) have high fibrogenic activity, while short fibers have low fibrogenic potential (Adamson and Bowden 1987a, 1987b; Davis et al. 1986a; Davis and Jones 1988; Platek et al. 1985). This may be related to the inability of macrophages to engulf and remove fibers that are significantly larger than themselves (Bignon and Jaurand 1983).

Inhalation of asbestos fibers can lead not only to injury to the lung parenchyma, but also to a number of changes in the pleura (Churg 1986; Jones et al. 1988b). The most common lesions are pleural plaques. These are generally oval areas of acellular collagen deposits, usually located on the inferior and posterior surfaces of the pleura. Diffuse thickening and fibrosis of the pleura may also occur, as may areas of pleural effusions.

The incidence of pleural abnormalities (usually detected by x-ray examination) is often quite high (20% to 60%) in people employed in asbestos-related occupations (Anton-Culver et al. 1989; Baker et al. 1985; Gibbs 1979; Jarvholm et al. 1986; Ohlson et al. 1985; Viallat and Bouten 1980). Pleural abnormalities are also common in household contacts and family members of asbestos workers (where exposure is presumably due to asbestos carried home on the workclothes) (Anderson et al. 1976, 1979), and in people who live in regions with high asbestos levels in the soil (Churg and DePaoli 1988; Jarvholm et al. 1986). The incidence of pleural abnormalities (specifically, pleural thickening) in members of the general population of the United States was found to be 2.3% in males, and 0.2% in females, most of which is probably due to occupational exposure to asbestos (Rogan et al. 1987).

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The health significance of asbestos-induced pleural abnormalities is not precisely defined, but most researchers consider pleural plaques to be essentially benign (Becklake 1976; Jones et al. 1988b; Ohlson et al. 1984, 1985). However, diffuse pleural thickening can lead to decreased ventilatory capacity, probably because of the restrictive effect of pleural fibrosis (Baker et al. 1985; Britton 1982; Chang 1986; Jarvholm and Larsson 1988; Jones et al. 1988b; McGavin and Sheers 1984). In some cases, the pulmonary impairment from pleural thickening can be very severe, even causing death (Miller et al. 1982).

**Cardiovascular Effects.** No studies were located to suggest that inhalation exposure to asbestos has any direct effect upon the cardiovascular system. However, fibrosis of the lung can lead to increased resistance to blood flow through the pulmonary capillary bed, leading in turn to pulmonary hypertension and compensatory hypertrophy of the right heart (Selikoff and Lee 1978). This condition is known as cor pulmonale. Cor pulmonale may be detected by standard clinical and radiological tests of cardiac function and by changes in the electrocardiogram (Kokkola and Huuskonen 1979), although this is not a very sensitive test (Selikoff and Lee 1978). Cor pulmonale is usually associated with severe cases of asbestosis (Lemen et al. 1980), although pulmonary hypertension may occur in some cases prior to measurable decreases in respiratory function (Tomasini and Chiappino 1981).

**Gastrointestinal Effects.** As discussed in Section 2.3, the majority of asbestos fibers which are deposited in the lung during inhalation exposure are transported by mucociliary action to the pharynx, where they are swallowed. Consequently, the gastrointestinal epithelium is also directly exposed to fibers. While there is some evidence that inhalation exposure to asbestos may increase the risk of gastrointestinal cancer in humans (see Section 2.2.1.8, below), no information was located to indicate that any nonneoplastic effects occur in the gastrointestinal system following inhalation exposure.

### 2.2.1.3 Immunological Effects

A number of studies have investigated the status of the immune system in humans who have been exposed to asbestos. Although there is some variability, most studies indicate that cell-mediated immunity (measured by tests of dermal sensitization *in vivo* and lymphocyte responsiveness and function *in vitro*) is depressed in workers who have radiological evidence of asbestosis (DeShazo et al. 1988; Gaumer et al. 1981; Kagan et al. 1977; Lange et al. 1986). Concentrations of autoantibodies (rheumatoid factor, antinuclear antibodies) also tend to be abnormally high in these workers (Anton-Culver et al. 1988; Pernis et al. 1965; Warwick et al. 1973). In some cases, this can lead to rheumatoid arthritis (Caplan's Syndrome), although this is more common

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in coal miners and workers with other pneumoconioses than in workers with asbestosis (Constantinidis 1977; Greaves 1979). Immunological abnormalities are usually mild or absent in asbestos-exposed workers who have not developed clinical signs of asbestosis (DeShazo et al. 1988; Kagan 1988; Selikoff and Lee 1978; Warwick et al. 1973). Although the biological significance of these immunological changes is difficult to judge, they are of special concern because depressed immune function might be a factor in the etiology of asbestos-induced cancer (Lew et al. 1986).

No studies were located regarding the following effects in humans or animals following inhalation exposure to asbestos.

**2.2.1.4 Neurological Effects**

**2.2.1.5 Developmental Effects**

**2.2.1.6 Reproductive Effects**

**2.2.1.7 Genotoxic Effects**

**2.2.1.8 Cancer**

There is a voluminous body of evidence which establishes that inhalation exposure to asbestos increases the risk of lung cancer and mesothelioma in humans and animals. There is also suggestive evidence that inhalation exposure to asbestos increases risk of cancer at other sites (especially the gastrointestinal tract). Each of these carcinogenic effects are discussed separately below.

Lung Cancer. Evidence for the role of asbestos in human lung cancer is derived primarily from studies of the cause of death of occupationally-exposed workers. For example, Selikoff et al. (1979) studied the causes of death in a very large cohort of insulation workers (17,800 men) in the United States and Canada. Between 1967 and 1976, there were 2,271 deaths in this group, of which 486 were attributable to lung cancer. This is 4.6 times the number of lung cancer deaths that would have been expected in this group based on the lung cancer rates in the average male population of the United States. Similar findings have been reported in a very large number of analogous studies under a wide variety of occupational circumstances. In a recent review, EPA (1986a) noted that statistically significant ($p < 0.05$) increases in lung cancer death rates had been reported in 32 of 41 recent studies.

There is little doubt that all types of asbestos can cause lung cancer. For example, statistically significant increases in lung cancer mortality have been reported in workers exposed primarily to chrysotile

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(Dement et al. 1983; McDonald et al. 1980, 1983; Nicholson et al. 1979), amosite (Seidman et al. 1979), crocidolite (Wignall and Fox 1982), anthophyllite (Meurman et al. 1974), and tremolite (Amandus and Wheeler 1987; Kleinfeld et al. 1974; McDonald et al. 1986). This conclusion is supported by animal experiments in which increased incidence of lung cancer has been observed following chronic inhalation exposure to chrysotile (Gross et al. 1967; Wagner et al. 1974), amosite (Davis et al. 1980a, 1980b, 1986a), crocidolite (Wagner et al. 1974), anthophyllite (Wagner et al. 1974) and tremolite (Davis et al. 1985).

As with most carcinogenic agents, there is a substantial latency period (10 to 30 years in humans) between the onset of exposure to asbestos and the occurrence of lung cancer (Dement et al. 1983; McDonald et al. 1983; Nicholson et al. 1979; Selikoff et al. 1979). After sufficient time (e.g., 20 years), the risk of lung cancer in exposed workers is generally observed to increase in proportion to the cumulative exposure (f-yr/mL). Most researchers have found that the chances that asbestos exposure will lead to lung cancer depends not only on the cumulative dose of asbestos, but also on the underlying risk of lung cancer due to other factors (Enterline et al. 1987; EPA 1986a; McDonald et al. 1982, 1983; Peto et al. 1985). For example, asbestos exposure results in a larger increase in lung cancer risk in smokers than nonsmokers, because smokers have a higher underlying risk of lung cancer than nonsmokers. (See Section 2.7 for additional discussion of the interaction between smoking and asbestos). Figure 2-1 displays the levels of asbestos exposure that are estimated by EPA (1986a) to be associated with excess lifetime lung cancer risks of $10^{-4}$ to $10^{-7}$ for smokers and nonsmokers. Appendix B provides further details on the derivation of these risk estimates. While these values are considered to be the best available for assessing risk from environmental exposures to airborne asbestos, the range of uncertainty is probably a factor of 2.5 to 10 (EPA 1986a).

A number of studies suggest that not all asbestos fibers are equally likely to lead to lung cancer. Some of this variation in potency between fibers may be due to differences between mineral types with respect to surface properties such as surface charge density (Bonneau et al. 1986; Davis et al. 1988), but the bulk of the available data indicate that fiber size is the most important determinant of carcinogenic potential. The strongest evidence for this conclusion comes from studies in animals, where chronic inhalation exposure to dust clouds rich in long fibers (those in excess of 5 $\mu$m) produces a higher incidence of lung cancer than exposure to dust clouds rich in short fibers (mostly less than 5 $\mu$m) (Davis et al. 1986a; Davis and Jones 1988). The reason that longer fibers are more carcinogenic than short is not known, but may be related to the ability of macrophages to engulf short but not long fibers (Bignon and Jaurand 1983; Stanton et al. 1981).

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Some epidemiological studies have detected little or no increase in lung cancer risk until the cumulative dose of asbestos exceeds 25 to 100 f-yr/mL (Berry and Newhouse 1983; Hughes and Weill 1980; McDonald et al. 1980; Weill et al. 1979), and this has led to the proposal that there may be a dose threshold for asbestos-induced lung cancer (Browne 1986a, 1986b). However, a number of other studies indicate that lung cancer risk is linearly related to cumulative dose without any obvious threshold (Dement et al. 1983; Finkelstein 1983; Henderson and Enterline 1979; Hughes et al. 1987; McDonald et al. 1983; Seidman et al. 1979). In general, dose-response data from epidemiological studies lack the statistical power to detect small effects at low doses, so it is not possible to conclude from such data that a hazardous chemical does (or does not) have a threshold dose. Consequently, it seems most appropriate at present to continue to assume that there is no threshold for asbestos-induced lung cancer. Possible areas of additional research on this subject are discussed in Section 2.9.3.

**Mesothelioma.** Mesotheliomas are tumors arising from the thin membranes that line the body cavity and surround internal organs. Mesotheliomas are relatively rare in the general population (approximately 2 per million) (Enterline and Henderson 1987), but are often observed in populations of asbestos workers. For example, in the mortality study of insulation workers by Selikoff et al. (1979), there were 175 deaths attributable to mesotheliomas, 63 arising from the pleural membrane and 112 arising in the peritoneum. Mesotheliomas are often difficult to diagnose, so use of death certificate information may lead to an underestimate (Selikoff et al. 1979) or occasionally an overestimate (Bignon et al. 1979) of the true incidence of this disease.

Cases of death from mesothelioma have been reported in studies of workers exposed to each of the main types of asbestos, including chrysotile (McDonald et al. 1980), amosite (Seidman et al. 1979), crocidolite (Jones et al. 1980a), and tremolite (Kleinfeld et al. 1974). Although these findings indicate that all asbestos types can cause mesothelioma, there are several studies which suggest that amphiboles (tremolite, amosite, and especially crocidolite) may be more potent than chrysotile (Berry and Newhouse 1983; Churg 1986; Churg and Wright 1989; Henderson and Enterline 1979; Hughes et al. 1987; Jones et al. 1980a; Weill et al. 1979). For example, Berry and Newhouse (1983) studied a group of workers in a friction materials plant that used mainly chrysotile, but where crocidolite had also been used on two occasions. In a case-control analysis, it was found the workers dying from mesothelioma (10 cases) were 8-times more likely to have been exposed to crocidolite than workers dying from other causes. In another approach, Churg and Wright (1989) analyzed the chrysotile and amphibole content of lungs from persons dying from mesothelioma, and concluded that amphiboles were two orders of magnitude more potent for inducing

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mesothelioma than chrysotile. This has led to the hypothesis that many cases of mesothelioma in chrysotile-exposed workers are really due to the presence of amphibole contamination (Churg 1988; McDonald et al. 1989). However, it is difficult to draw strong inferences regarding relative potency of different mineral types from lung burden data, because amphiboles are more stable in lung than chrysotile (see Sections 2.3.3.1 and 2.5). Based on an analysis of the ratio of excess deaths from mesothelioma to excess deaths from lung cancer in a number of studies, EPA (1986a) concluded that crocidolite could be two- to four-times more potent for mesothelioma than chrysotile, but that this difference was generally overshadowed by differences in fiber size distribution and differences between cohorts.

Several studies (Newhouse and Berry 1976; Nicholson et al. 1982; Peto et al. 1982) have indicated that risk of mesothelioma from a given level of exposure to asbestos depends primarily upon the time elapsed since exposure (latency), with risk increasing exponentially with time after a lag period of about 10 years. In contrast to the situation for lung cancer, the effect of asbestos on mesothelioma risk does not appear to be increased by smoking (Berry et al. 1985; Hammond et al. 1979; Selikoff et al. 1980). By extrapolating from epidemiological studies in asbestos workers, EPA (1986a) estimated that continuous lifetime exposure to air containing 0.0001 f/mL of asbestos would result in about 2 to 3 cases of mesothelioma per 100,000 persons. The corresponding cumulative lifetime exposures associated with excess risks of $10^{-4}$ to $10^{-7}$ are shown in Figure 2-1. Appendix B provides further details on the derivation of this risk estimate.

**Cancer at Extrathoracic Sites.** Mortality studies of asbestos workers have often revealed small increases in the incidence of death from cancer at one or more extrathoracic sites, mostly in tissues of the gastrointestinal system. For example, Selikoff et al. (1979) observed a total of 99 deaths from cancers of the esophagus, stomach, colon or rectum in a cohort of 17,800 insulation workers, while only 59.4 deaths of this sort were expected. Similarly, McDonald et al. (1983) observed 26 deaths from gastrointestinal cancer in a group of 2,500 asbestos textile workers, where only 17.1 were expected. In this study, there was an approximately linear increase in gastrointestinal cancer death rate as a function of cumulative exposure to asbestos. Similar increases in gastrointestinal cancer rates in asbestos workers have been reported by Enterline et al. (1987), Newhouse and Berry (1979), Seidman et al. (1979, 1986), and others. Some studies have also noted excess deaths from cancers at other sites, such as the kidney (Enterline et al. 1987; Selikoff et al. 1979). In contrast, a number of other

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associations between increased risk of extrathoracic cancers and asbestos exposure (Acheson et al. 1982; Hughes et al. 1987; McDonald et al. 1984; Meurman et al. 1974; Nicholson et al. 1979; Wignall and Fox 1982).

A number of researchers and regulatory groups have reviewed the weight of evidence on the issue of cancer at extrathoracic sites following inhalation exposure to asbestos in the workplace, and have reached differing conclusions. For example, EPA (1986a, 1989c), OSHA (1986), and Frumkin and Berlin (1988) believe that the data constitute strong or substantial evidence that inhalation of asbestos in the workplace does increase risk of extrathoracic cancer. In contrast, others feel the evidence is not adequate to reach a firm conclusion (Dupre et al. 1984; Morgan et al. 1985; NRC 1984; WHO 1986), and some believe that the observed increases in gastrointestinal cancer are probably due to other factors (misdiagnosis, diet, alcohol, etc.) and can not be attributed to asbestos (Doll 1989; Doll and Peto 1985; Edelman 1988a).

As these conflicting analyses illustrate, when epidemiological studies provide limited evidence for a small increase in cancer risk at a site, it is difficult to distinguish between two alternative interpretations: 1) the risk is real, and inconsistencies in the data are due to limitations in the sensitivity and accuracy of epidemiological studies; or 2) the risk is not real, and the apparent effects are attributable to other causes or reasons. In view of the limitations and uncertainties in the data available, it does not appear that a definitive distinction can currently be drawn between these alternatives. However, it seems only prudent to consider increased risk of gastrointestinal cancer an effect of concern.

### 2.2.2 Oral Exposure

**Units of Exposure.** The principal way that humans are exposed to asbestos by the oral route is through ingestion of asbestos-contaminated drinking water (see Chapter 5). As discussed in Section 5.4.2, most asbestos fibers in water are chrysotile, and are less than 5 $\mu$m in length. The concentration of asbestos in water is generally determined by transmission electron microscopy (TEM), and the results are expressed as millions of TEM fibers per liter (MFL). Since it is very difficult to convert from MFL to other units of dose, human exposure to asbestos via drinking water is reported below simply in terms of exposure level (MFL). In contrast, animal studies usually describe oral exposure in terms of mass (mg/day), and often it is not possible to convert

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terms of mass (mg/day), and often it is not possible to convert accurately from this dose to units of exposure equivalent to those used for humans. Consequently, animal doses are reported below in units of mg/kg/day, and information on fiber dimensions is included when available.

**Overview of Oral Health Effects.** Studies in humans and in animals indicate that ingestion of asbestos causes little or no risk of noncarcinogenic injury. However, there is some evidence that chronic oral exposure may lead to increased risk of gastrointestinal cancer. Studies supporting these conclusions are summarized in Table 2-3 and Figure 2-3, and the data are discussed below.

### 2.2.2.1 Death

No cases of acute or short-term lethality due to asbestos ingestion were located for either humans or animals. Feeding studies in rats and hamsters indicate that ingestion of high amounts (1% in the diet, equivalent to doses of 500 to 800 mg/kg/day) of chrysotile, amosite, crocidolite or tremolite does not cause premature lethality, even when exposure occurs for a lifetime (NTP 1982a, 1982b, 1983b, 1985, 1988, 1990).

### 2.2.2.2 Systemic Effects

A number of epidemiological studies have been performed on groups of humans exposed to asbestos in drinking water, but these studies have focused on cancer (see Section 2.2.2.8 below) and have not specifically searched for the occurrence of systemic effects in those populations. Studies in rats and hamsters exposed to high doses (1% in the diet) of chrysotile, amosite, crocidolite, or tremolite have not detected histological or clinical evidence of injury to any systemic tissues (NTP 1982a, 1982b, 1983, 1985, 1988). These findings are consistent with the concept that very few asbestos fibers cross from the gastrointestinal lumen into the blood (see Section 2.3.1), and that the risk of noncarcinogenic injury to tissues such as lung, heart, muscle, liver, kidney, skin or eyes is negligible.

**Gastrointestinal Effects.** Because most ingested asbestos fibers are retained in the gastrointestinal tract (see Section 2.3.1), the tissue most directly exposed to ingested asbestos is the gastrointestinal epithelium. A few studies in rats have described some histological or biochemical alterations in cells of the gastrointestinal tract following chronic exposure to oral doses of 20 to 140 mg/kg/day of chrysotile (Delahunty and Hollander 1987; Jacobs et al. 1978a, 1978b). However, no excess nonneoplastic lesions of the gastrointestinal epithelium have been detected in a number of other animal feeding

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TABLE 2-3. Levels of Significant Exposure to Asbestos - Oral

| Figure Key | Species | Route | Exposure Frequency/ Duration | Effect | NOAEL (mg/kg/day) | LOAEL (Effect) Less Serious (mg/kg/day) | LOAEL (Effect) Serious (mg/kg/day) | Reference | Type of Asbestos |
|---|---|---|---|---|---|---|---|---|---|
| **INTERMEDIATE EXPOSURE** | | | | | | | | | |
| **Developmental** | | | | | | | | | |
| 1 | Rat | (F) | 2-12 wk | | 500 | | | NTP 1982a, 1982b, 1985, 1988 | CH, CR, TR, AM |
| 2 | Mouse | (W) | 15 d Gd1-15 | | 33 | | | Schneider and Maurer 1977 | CH |
| 3 | Hamster | (F) | 3-6 wk | | 830 | | | NTP 1983a, 1983b | CH, AM |
| **Reproductive** | | | | | | | | | |
| 4 | Rat | (F) | 2-12 wk | | 500 | | | NTP 1982a, 1982b, 1985, 1988 | CH, CR, TR, AM |
| 5 | Hamster | (F) | 3-6 wk | | 830 | | | NTP 1983a, 1983b | CH, AM |
| **CHRONIC EXPOSURE** | | | | | | | | | |
| **Death** | | | | | | | | | |
| 6 | Rat | (F) | lifetime | | 500 | | | NTP 1982a, 1982b, 1985, 1988 | CH, CR, TR, AM |
| 7 | Rat | (F) | 25 mo | | 100 | | | Bolton et al. 1982a | AM, CR, CH |
| 8 | Hamster | (F) | lifetime | | 830 | | | NTP 1983a, 1983b | CH, AM |
| **Systemic** | | | | | | | | | |
| 9 | Rat | (F) | 21 mo | Gastro | 2500 | | | Gross et al. 1974 | CH |
| 10 | Rat | (F) | 21 mo | Other | 2500 | | | Gross et al. 1974 | CH |



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TABLE 2-3 (Continued)

| Figure Key | Species | Route | Exposure Frequency/ Duration | Effect | NOAEL (mg/kg/day) | LOAEL (Effect) Less Serious (mg/kg/day) | LOAEL (Effect) Serious (mg/kg/day) | Reference | Type of Asbestos |
|---|---|---|---|---|---|---|---|---|---|
| CHRONIC EXPOSURE (Continued) | | | | | | | | | |
| Systemic (Continued) | | | | | | | | | |
| 11 | Rat | (F) | 15 mo | Gastro | | 140 (incr. DNA synthesis) | | Jacobs et al. 1978a | CH |
| 12 | Rat | (F) | lifetime | Other | 500 | | | NTP 1982a, 1982b, 1985, 1988 | CH, CR, TR, AM |
| 13 | Rat | (W) | 1.5 yr | Gastro | | 20 (altered permeability) | | Delahunty and Hollander 1987 | CH |
| 14 | Rat | (F) | lifetime | Gastro | 500 | | | NTP 1982a, 1982b, 1985, 1988 | CH, CR, TR, AM |
| 15 | Rat | (F) | 25 mo | Gastro | 100 | | | Bolton et al. 1982a | AM, CR, CH |
| 16 | Rat | (F) | 14 mo | Gastro | | 150 (damage to ileum) | | Jacobs et al. 1978a | CH |
| 17 | Hamster | (F) | lifetime | Other | 830 | | | NTP 1983a, 1983b | CH, AM |
| 18 | Hamster | (F) | lifetime | Gastro | 830 | | | NTP 1983a, 1983b | CH, AM |
| Neurological | | | | | | | | | |
| 19 | Rat | (F) | lifetime | | 500 | | | NTP 1982a, 1982b, 1985, 1988 | CH, CR, TR, AM |
| 20 | Hamster | (F) | lifetime | | 830 | | | NTP 1983a, 1983b | CH, AM |
| Cancer | | | | | | | | | |
| 21 | Rat | (F) | lifetime | | | | 500 CEL (intestinal polyps) | NTP 1985 | CH-I |

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; mg/kg/d = milligrams per kilograms per day; (F) = food; wk = week; CH = chrysotile; CR = crocidolite; TR = tremolite; AM = amosite; (W) = water; d = day; Gd = gestation day; mo = month; gastro = gastrointestinal; incr. = increase; DNA = deoxyribonucleic acid; yr = year; I = intermediate.



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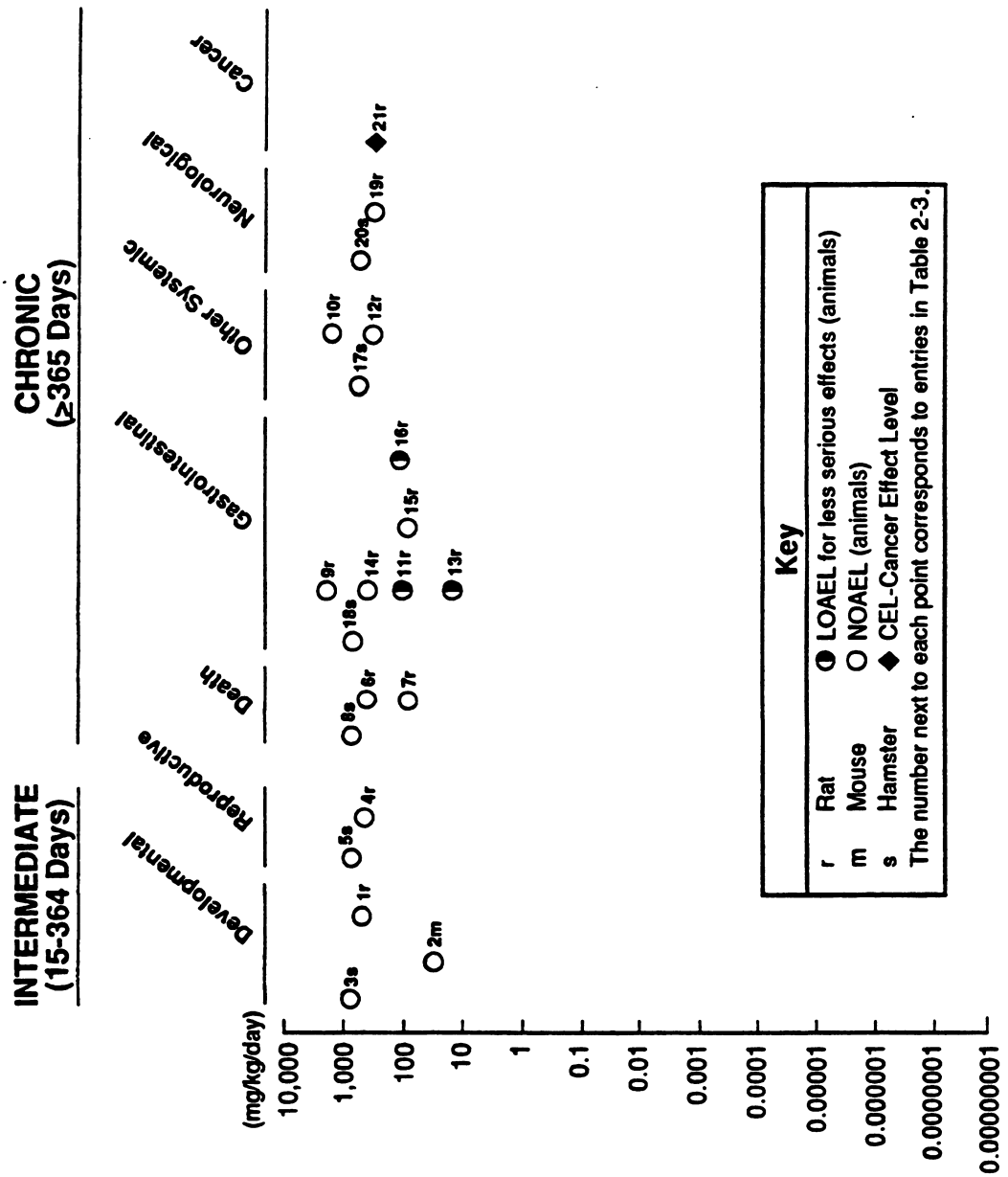



**FIGURE 2-3. Levels of Significant Exposure to Asbestos – Oral**

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studies (Bolton et al. 1982a; Donham et al. 1980; Gross et al. 1974), including an extensive series of lifetime studies in rats and Syrian hamsters in which such effects were carefully investigated (NTP 1982a, 1982b, 1983, 1985, 1988,1990). Thus, the weight of evidence indicates that asbestos ingestion does not cause any significant noncarcinogenic effects in the gastrointestinal system.

#### 2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals following oral exposure to asbestos.

#### 2.2.2.4 Neurological Effects

No studies were located to indicate that ingestion of asbestos leads to neurological effects in humans. No histological or clinical evidence of neurological injury was detected in rats or hamsters chronically exposed to high doses (1% in the diet) of chrysotile, amosite, crocidolite, or tremolite (NTP 1982a, 1982b, 1983, 1985, 1988, 1990).

#### 2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to asbestos. Although detailed studies were not performed, no teratogenic effects were noted in the offspring of rats or hamsters exposed to chrysotile, amosite, crocidolite or tremolite (1% in the diet) during gestation (NTP 1982a, 1982b, 1983, 1985, 1988, 1990). A slight reduction in pup birth weight was noted in some cases (NTP 1982a, 1985), but it seems unlikely that this was the result of any direct effect on the fetus. Schneider and Maurer (1977) found no teratogenic effects in mice given doses up to 33 mg/kg/day of chrysotile during gestation.

#### 2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to asbestos. Although detailed studies were not performed, no effects on fertility were observed in rats or Syrian hamsters exposed to chrysotile, amosite, crocidolite or tremolite (1% in the diet) during breeding, gestation and lactation (NTP 1982a, 1982b, 1983, 1985, 1988, 1990).

#### 2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to asbestos.

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### 2.2.2.8 Cancer

As discussed earlier (Section 2.2.1.8), a number of epidemiological studies of workers exposed to asbestos fibers in workplace air suggest that workers may have increased risk of gastrointestinal cancers. It is usually assumed that any effect of asbestos on the gastrointestinal tract following inhalation exposure is most likely the result of muco-ciliary transport of fibers from the lung to the stomach (see Section 2.3.4). Because of these findings, a number of researchers have investigated the carcinogenic risk (especially the risk of gastro-intestinal cancer) in humans and animals when exposure to asbestos occurs by the oral route.

**Human Studies.** A number of epidemiological studies have been conducted to determine if human cancer incidence is higher than expected in geographical areas where asbestos levels in drinking water are elevated (usually in the range of 1 to 200 MFL) (Conforti et al. 1981; Kanarek et al. 1980; Levy et al. 1976; Polissar et al. 1982, 1984; Sigurdson et al. 1981; Toft et al. 1981; Wigle 1977). Most of these studies have detected statistically significant increases in cancer death or incidence rates at one or more tissue sites (mostly gastrointestinal) in populations exposed to elevated levels of asbestos in their drinking water. However, the magnitudes of the increases in cancer incidence are usually rather small, and there is relatively little consistency in the observed increases, either within studies (i.e., between sexes) or between studies.

The basis of these inconsistent findings is not certain. On one hand, it seems likely that at least some of the apparent associations are random or are due to occupational exposures (Polissar et al. 1982, 1984; Toft et al. 1981; Wigle 1977). On the other hand, failure of some studies to detect effects may be due to lack of statistical power, stemming from limitations regarding study design, exposure level and duration, latency since exposure, population size and mobility, population density, exposure to other risk factors, differences in sensitivity between sexes and groups, differences in asbestos fiber types and size, and numerous other possible confounding factors. Marsh (1983) reviewed the data from 8 independent epidemiological studies and concluded that the number of positive findings for neoplasms of the esophagus, stomach, pancreas and prostate were unlikely to have been caused by chance alone. In a more recent review, Kanarek (1989) also noted that there were relatively consistent findings for increased stomach and pancreatic cancer among the studies. However, none of the studies provides a basis for identification of an oral exposure level that may be definitely stated as having caused increased death from cancer.

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**Animal Data.** Early animal studies on gastrointestinal cancer from ingested asbestos were mostly negative (Cunningham et al. 1977; Gross et al. 1974), although some studies yielded nonstatistically significant increases in tumor frequency (Bolton et al. 1982a; Donham et al. 1980; Ward et al. 1980). Many of these studies were limited by use of experimental groups that were too small, or by exposures that were too brief (Condie 1983). More recently, a series of large scale, lifetime feeding studies have been performed by the National Toxicology Program (NTP). These studies have also yielded mostly negative results, although some suggestive increases in tumor frequencies did occur (Table 2-4). The most convincing finding was for increased incidence of a benign adenomatous polyp of the large intestine in male rats exposed to 1% intermediate range chrysotile (65% of all fibers over 10 μm) in the diet (NTP 1985). These tumors were not observed either in female rats or in Syrian hamsters exposed to the same diet. Overall, the data were interpreted as providing "some evidence" of carcinogenicity for intermediate range chrysotile fibers. No tumorigenicity was noted for short-range chrysotile (NTP 1985).

**Interpretation and Quantification.** Observations in humans and animals regarding risk of gastrointestinal cancer following oral exposure to asbestos are difficult to interpret with certainty. The positive associations which have been detected, both in humans and animals, indicate that it is prudent to consider asbestos a possible human carcinogen by the oral route. However, the frequent negative findings in human studies indicate that whatever risk exists is quite low. This conclusion is similar to that reached by a working group for the U.S. Department of Human Health Services (Lemen et al. 1987).

None of the available epidemiological studies of cancer risk in humans exposed to asbestos in drinking water are suitable for estimating quantitative dose-response relationships. However, both EPA (1980) and NAS (1983) have sought to estimate risk of gastrointestinal cancer following oral exposure by extrapolating dose-response data from occupational studies. As noted before, this approach rests on the assumption that the observed excess gastrointestinal cancer risk in the occupational studies is due to the swallowing of fibers that have been deposited in the lung. These calculations indicate that lifetime ingestion of water containing 1.0 MFL would produce an excess gastrointestinal cancer risk of about $3 \times 10^{-5}$ to $10 \times 10^{-5}$ (EPA 1980; NAS 1983). It should be noted that this approach requires a number of assumptions, and that the risk estimates should be considered to be only approximate. It is also important to note that if these risk estimates are correct, then the expected relative risk of gastrointestinal cancer in populations consuming drinking water at concentrations of 1 to 200 MFL would be quite low, and would likely not be consistently detectable in epidemiological studies (NAS 1983).

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**TABLE 2-4. Summary of NTP Asbestos Feeding Studies**

| Asbestos Type | Species | Median Length (μm) | Size Distribution | Carcinogenic Effects | Comments | Conclusion | Reference |
|---|---|---|---|---|---|---|---|
| Amosite | Rat | 4.37 | 74% > 6 μm | Increased C-cell carcinoma (males) | Not considered treatment related | Not carcinogenic | NTP 1982a |
| | | | | Increased leukemia (males) | Questionable biological and statistical significance | | |
| | Syrian hamster | 4.37 | 74% > 6 μm | None | | Did not cause a carcinogenic response | NTP 1983a |
| Crocidolite | Rat | 10 | 73% > 8 μm | None | | Did not cause a carcinogenic response | NTP 1988 |
| Tremolite | Rat | No data | 22% > 5 μm | None | | Did not cause a carcinogenic response | NTP 1982b |
| Chrysotile (short range) | Rat | 0.66 | 30% > 4.5 μm | None | | No evidence of carcinogenicity | NTP 1985 |
| Chrysotile (intermediate range) | Rat | 0.82 | 60% > 5.4 μm | Benign intestinal polyps (males) | Not significant based on concurrent controls; highly significant based on historical controls | Some evidence of carcinogenicity | NTP 1985 |
| | | | | Clitoral gland neoplasm (females) | Not significant compared to historical controls | No evidence of carcinogenicity | |
| Chrysotile (short range) | Syrian hamster | 0.66 | 30% > 4.5 μm | Adrenal cortical adenomas (males) | Not significant compared to historical controls | Not carcinogenic | NTP 1983b |
| Chrysotile (intermediate range) | Syrian hamster | 0.82 | 60% > 5.4 μm | Adrenal cortical adenomas (males and females) | | Not carcinogenic | |

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Another quantitative estimate of gastrointestinal cancer risk has been calculated based on the incidence of intestinal polyps in male rats exposed to 1% chrysotile (65% > 10 μm long) in the diet (EPA 1985a). This calculation indicates the lifetime excess risk from ingesting water containing 1.0 MFL would be about $1.4 \times 10^{-7}$.

Figure 2-4 summarizes the risk estimates of NAS (1983) and EPA (1985a). It should be noted that these estimates differ by several orders of magnitude. There are many possible reasons for this substantial difference, including uncertainty in each model's assumptions or conversion factors, differences in fiber potency (due to differences in type and/or length), and inherent differences between humans and rats. Appendix B provides further details on the derivation of these risk estimates.

### 2.2.3 Dermal Exposure

The only adverse health effect that has been reported following dermal contact with asbestos is the formation of small "warts" or corns. No quantitative dose-response data are available, but in a group of workers installing amosite insulation in ships, nearly 60% of the people had one or more of these lesions, mostly on the hands (Alden and Howell 1944). All of the workers with lesions reported an original pricking sensation and the feeling of a small splinter-like foreign body. This strongly indicates that the lesions are associated with penetration of the skin by a macroscopic spicule, although histological examination of the corns did not reveal the presence of a fiber. The corns develop within about 10 days, and are painful at first. They later become highly cornified, and do not appear to be of pathological concern (Alden and Howell 1944; Dupre et al. 1984; Selikoff and Lee 1978).

No studies were located to indicate that dermal exposure of humans or animals to asbestos leads to any of the following effects.

#### 2.2.3.1 Death

#### 2.2.3.2 Systemic Effects

#### 2.2.3.3 Immunological Effects

#### 2.2.3.4 Neurological Effects

#### 2.2.3.5 Developmental Effects

#### 2.2.3.6 Reproductive Effects

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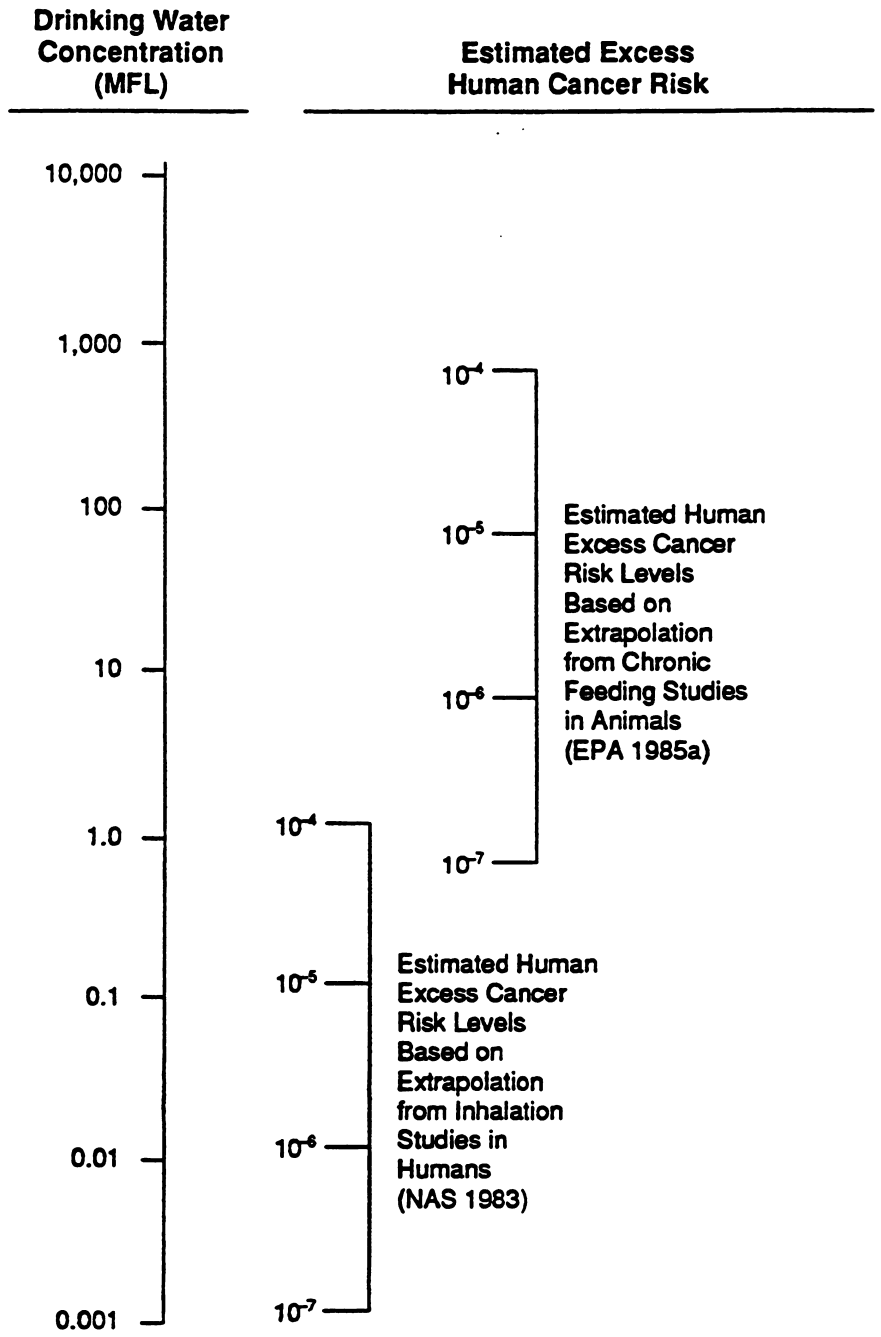



**FIGURE 2-4. Summary of Calculated Gastrointestinal Cancer Risks from Ingestion of Asbestos**

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2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

When asbestos fibers are inhaled, many are deposited on the epithelial surface of the respiratory tree. The number of fibers that are deposited, and the location within the airway where deposition occurs, is a function of the aerodynamic properties of the fibers. For typical fibers of chrysotile, amosite, and crocidolite, about 30% to 40% of all the fibers in inhaled air are retained, with most of these (about 60%) being deposited in the upper airways (nose, throat, trachea) (Evans et al. 1973; Morgan et al. 1975). The fibers in the upper airway consist mainly of relatively thick fibers (greater than about 3 μm), with thinner fibers being carried deeper into the airways (Timbrell 1982). Many of these smaller fibers deposit preferentially at bifurcations in the terminal bronchioles (Brody 1986; Evans et al. 1973), with the number of fibers deposited at each location decreasing in proportion to the preceding airway pathlength and the number of preceding branch points (Pinkerton et al. 1986).

Most fibers deposited in the airways are removed from the lung by mucociliary transport or by macrophages (see Section 2.3.4), but a small fraction remain in the lung for long periods (Jones et al. 1988a). In addition, some fibers appear to pass from the lung to the pleura, although the precise mechanism of transport is not known (Hillerdal 1980; Rudd 1989). The presence of asbestos fibers in the pleura following inhalation exposure has been demonstrated by a number of researchers (Jones et al. 1980b; Sebastien et al. 1980a; Stephens et al. 1987; Viallat et al. 1986). Available data are not sufficient to estimate the fraction of deposited asbestos fibers which penetrate the lung in this way, but it is quite small.

2.3.1.2 Oral Exposure

Most asbestos fibers which are ingested are not absorbed across the gastrointestinal tract (Gross et al. 1974). However, electron micrographic studies indicate that some fibers penetrate into the gastrointestinal epithelium (Storeygard and Brown 1977; Westlake et al. 1965). In addition, some fibers pass through the gastrointestinal wall and reach blood, lymph, urine and other tissues (Carter and Taylor 1980; Cook 1983; Cunningham and Pontefract 1973; Cunningham et al. 1977; Hallenbeck and Patel-Mandlik 1979; Patel-Mandlik and Millette 1983;

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Sebastien et al. 1980b; Weinzweig and Richards 1983). The mechanism by which asbestos fibers pass through the gastrointestinal wall is not known with certainty, but Volkheimer (1974) has noted that a wide variety of μm-sized particles (e.g., starch granules, cellulose particles, pollen) can cross the gut by passing between (not through) the cells of the epithelial layer in a process termed persorption, and it seems likely that this may account for uptake of asbestos fibers as well. Available data are not sufficient to make a precise estimate of the fraction of ingested fibers which pass through the gastrointestinal wall, but there is agreement that it is a very small amount (Cook 1983; Sebastien et al. 1980b; Weinzweig and Richards 1983). Several researchers have found that the average length of fibers in extra-gastrointestinal tissues or fluids is shorter than the average length of the fibers ingested (Cunningham et al. 1977; Patel-Mandlik and Millette 1983; Weinzweig and Richards 1983), suggesting that short fibers pass through the gastrointestinal epithelium more easily than long fibers. However, the opposite finding was reported by Sebastien et al. (1980b).

#### 2.3.1.3 Dermal Exposure

No studies were located regarding asbestos penetration of the skin. It is generally believed that this is not a significant route of asbestos uptake.

### 2.3.2 Distribution

#### 2.3.2.1 Inhalation Exposure

As noted above, only a tiny fraction of inhaled fibers penetrate through the epithelial layer of the lungs. No quantitative studies were located regarding the distribution of these fibers in the rest of the body following inhalation exposure, but some appear to be retained in the pleura, with others passing into the lymph (Hillerdal 1980; Holt 1983; Rudd 1989). Those fibers that enter the lymph are presumably able to reach other tissues of the body. This is supported by the finding of Auerbach et al. (1980) that people with high levels of asbestos fibers in the lung (measured as asbestos bodies) also had asbestos bodies in kidney, heart, liver, spleen, adrenals, pancreas, brain, prostate, and thyroid.

#### 2.3.2.2 Oral Exposure

Asbestos fibers have been detected in blood (Weinzweig and Richards 1983) and lymph (Sebastien et al. 1980b) of rats exposed to oral doses of asbestos, suggesting that fibers penetrating the gut might be carried to tissues throughout the body. In support of this, Pontefract and Cunningham (1973) and Cunningham et al. (1977) reported the presence of asbestos fibers in lung, kidney, liver, brain, heart, and spleen of rats

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that had been exposed to asbestos in the diet. Highest levels of fibers were found in the omentum (a fold of the peritoneum connecting abdominal viscera to the stomach), supporting the idea that the fibers were emanating from the gastrointestinal tract.

### 2.3.2.3 Dermal Exposure

No studies were located regarding distribution of asbestos fibers following dermal exposure. It is generally considered that dermal uptake of asbestos is not significant.

## 2.3.3 Metabolism

### 2.3.3.1 Inhalation Exposure

Asbestos fibers are not metabolized in the normal sense of the word, and amphibole fibers which are retained in the lung do not appear to undergo any significant change (Bellmann et al. 1987; Carter and Taylor 1980; Roggli et al. 1987a). However, chrysotile fibers appear to undergo some type of breakdown or alteration in the lung. This conclusion is based primarily on measurements of asbestos levels in the lung as a function of exposure duration. While amphibole levels tend to rise linearly, chrysotile levels reach a steady-state concentration within several months (Wagner et al. 1974). This data from animal studies is supported by a number of human studies in which the ratio of amphibole to chrysotile concentration in lung tissue was much higher than expected based on the composition of the inhaled fibers (Jones et al. 1980a, 1980b; Pooley 1976; Stephens et al. 1987; Wagner et al. 1982a, 1982b, 1986).

The basis of this apparent loss of chrysotile fibers is not clear, but it may be related to a slow dissolution of the fibers in tissue fluids or in macrophages (Jaurand et al. 1984), or to a separation of the fibers into much finer component fibrils (Bellmann et al. 1987; Cook et al. 1982; Roggli et al. 1987a). In the latter case, the apparent loss of fibers could be an artifact due to the inability of normal methods for fiber isolation and quantification in tissues to detect very fine fibrils.

### 2.3.3.2 Oral Exposure

No studies were located regarding any changes in asbestos fibers in the gastrointestinal tract *per se*. However, chrysotile fibers incubated in simulated gastric juice underwent leaching of magnesium ion from the silica framework, with a resultant change in net fiber charge from positive to negative (Seshan 1983), and chrysotile fibers with altered appearance and x-ray diffraction patterns were detected in the urine of animals (Hallenbeck and Patel-Mandlik 1979; Patel-Mandlik and Millette

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1983). These observations, although limited, suggest that chrysotile fibers undergo some metal ion exchange and alterations in gross structure in biological fluids following oral exposure.

### 2.3.3.3 Dermal Exposure

No studies were located regarding any changes in asbestos fiber composition or structure following dermal exposure.

### 2.3.4 Excretion

### 2.3.4.1 Inhalation Exposure

The principal pathway by which fibers are removed from the lung is mucociliary transport. This is mediated by ciliated epithelial cells which move the layer of mucus coating the epithelial tissue upwards toward the throat, where it is swallowed. Fibers deposited in this mucus layer are carried along and are ultimately excreted in the feces (Cunningham et al. 1976; Evans et al. 1973; Morgan et al. 1978).

Clearance of fibers from the upper airways is generally complete within a few hours (Bolton et al. 1983; Evans et al. 1973). However, clearance from the lower airways is slower, with half-times ranging from 30 to 160 days (Bellmann et al. 1987; Evans et al. 1973; Morgan et al. 1978). This slow clearance is mediated largely by macrophages, which engulf fibers in the bronchioles and alveoli (which are not ciliated), and carry them to the ciliated portion of the airway for transport upward (Holt 1974). Macrophages may also translocate some fibers from the lung to the pleura (Holt 1983). Long fibers (in excess of 5 or 10 $\mu$m) are cleared from the lower airways more slowly than short fibers (Bellmann et al. 1987; Morgan et al. 1978; Roggli et al. 1987a), probably because long fibers cannot be easily engulfed and moved by a single macrophage (Morgan et al. 1978).

As noted earlier, most inhaled fibers are ultimately excreted in the feces, but small numbers of fibers penetrate through the epithelial layers of the lung and/or the gastrointestinal tract, and some of these may be excreted in the urine (Finn and Hallenbeck 1984). In addition, some fibers are not cleared from the lung, leading to a gradual accumulation with time (Jones et al. 1988a; Wagner et al. 1974).

### 2.3.4.2 Oral Exposure

Nearly all asbestos fibers which are ingested are excreted in the feces. This is essentially complete within 48 hours following a single oral dose (Gross et al. 1974). Small numbers of fibers may also be

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excreted in the urine (Boatman et al. 1983; Hallenbeck and Patel-Mandlik 1979), but this accounts for only a very small fraction of the ingested dose (Cook and Olson 1979).

#### 2.3.4.3 Dermal Exposure

No studies were located regarding excretion of asbestos fibers following dermal exposure. It is generally considered that dermal exposure does not result in uptake of asbestos.

## 2.4 RELEVANCE TO PUBLIC HEALTH

Asbestos has been used in a very wide variety of products in modern society, and most people are exposed to low levels in air and/or water. This is of considerable public health concern because of the strong evidence that breathing asbestos increases the risk of respiratory cancer, and the more limited evidence that breathing or drinking asbestos may increase risk of gastrointestinal and other cancers. Other health effects are less likely to be of concern to the general public. These conclusions are discussed more fully below.

**Death.** Exposure to asbestos, either by inhalation or ingestion, has not been observed to result in acute or short-term lethality in humans or animals. However, delayed mortality may occur as the result of asbestosis or cancer.

**Systemic Effects.** The main tissues which are contacted by asbestos fibers following inhalation or oral exposure are the respiratory and gastrointestinal epithelium. Small numbers of fibers may penetrate intact from the lungs or the gastrointestinal tract into the blood or lymph, but this does not appear to result in any systemic injury.

A few studies suggest that fibers in the gastrointestinal tract may cause some histological or biochemical changes (Delahunty and Hollander 1987; Jacobs et al. 1978a), but most studies indicate that there are no significant noncarcinogenic effects (NTP 1982a, 1982b, 1983, 1985, 1988, 1990).

Deposition of asbestos fibers in the lung, however, can lead to substantial fibrotic injury and may even cause death. This disease, termed asbestosis, results from a prolonged inflammatory response stimulated by the presence of the fibers in the lung. Alveolar macrophages, which normally phagocytize foreign bodies deposited in the lungs, seek to engulf the asbestos fibers and remove them. While short fibers may be cleared in this way, long fibers cannot be removed, and this results in an ongoing focal inflammatory response. With time, epithelial cells are lost and are replaced with fibrous tissue,

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resulting in a progressive loss of lung compliance and respiratory function. This can also result in increased resistance to blood flow through the lungs, leading to pulmonary hypertension and compensatory hypertrophy of the right heart (a condition termed cor pulmonale).

The level of asbestos exposure needed to cause asbestosis is not known precisely, but human studies indicate that effects are likely to be minimal or absent following workplace exposures of 10 f-yr/mL or less (Berry et al. 1979; BOHS 1983; EPA 1986a; Wollmer et al. 1987). This corresponds to 50 years of workplace exposure to an average asbestos concentration of 0.2 f/mL. Exposures at 10- to 100-times this level or even higher were at one time common in the workplace, and many asbestos workers have developed asbestosis. However, as discussed in Section 5.4.1, levels of asbestos in ambient air and in the indoor air of homes and schools are usually much lower than this, so asbestosis is unlikely to be of concern for most people (Hallenbeck 1988).

Another tissue that is may be affected in humans exposed to asbestos in air is the pleura. The most common effect is formation of thickened fibrous areas called plaques, but diffuse thickening and fibrosis may also occur, as may areas of pleural effusions. Localized pleural plaques are not thought to be of significant health concern, although diffuse pleural thickening is associated with impairment of respiratory function. This is normally very mild, but may be severe in a few cases (Churg 1986; Jarvholm et al. 1986; Miller et al. 1982).

**Immunological Effects.** Studies of workers suffering from asbestos-related diseases such as asbestosis or mesothelioma indicate that the cellular immune system in such patients is often significantly depressed (DeShazo et al. 1988; Gaumer et al. 1981; Lange et al. 1986; Lew et al. 1986). This is an effect of particular interest and concern, since impaired immune surveillance might be directly contributory to the increased incidence of cancer in asbestos-exposed people. Moreover, variations in the immune system between people might be an important determinant of why some people develop cancer or asbestosis while others, with approximately equal exposures, do not. However, it is very difficult to distinguish whether the alterations in immune function noted in such studies are the cause or the result of asbestos-induced disease. The frequency of impaired cellular immunity in exposed workers without clinically-apparent disease is generally low (DeShazo et al. 1988; Kagan 1988; Selikoff and Lee 1978). This could mean that the immune changes do not occur until the disease develops (i.e., the changes are the result of the disease). Alternatively, it could mean that workers with immune systems that are not impaired by asbestos do not get serious disease, while workers whose immune systems are injured

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by asbestos do tend to develop disease (i.e., effects on the immune system are the cause of the disease). Available data do not allow a firm distinction between these alternatives at present, but the possible immunotoxic effects of asbestos are of clear concern.

**Neurological Effects.** Studies of humans and animals exposed to asbestos either by inhalation or by ingestion have not provided evidence that the nervous system is impaired by asbestos. Detailed studies have not been performed to search for subtle (preclinical) effects that might occur, but it is difficult to envision a mechanism that could lead to serious neurological injury.

**Developmental Effects.** Studies of possible adverse developmental effects from inhalation or oral exposure to asbestos have not been performed in humans. No obvious developmental effects were seen in a series of experiments in rats and Syrian hamsters exposed to high doses of asbestos in the diet during gestation, but such effects were not specifically investigated. Although asbestos fibers have been reported to cross the placenta (Cunningham and Pontefract 1974), the number of fibers that would be expected to reach the fetus via the maternal circulation is so low that developmental toxicity is unlikely to be of significant concern.

**Reproductive Effects.** Studies have not been performed to determine if asbestos exposure can cause adverse reproductive effects in humans, but no injury to reproductive tissues and no impairment of fertility was detected in rats and Syrian hamsters exposed to high concentrations of asbestos in the diet preceding and during gestation (NTP 1982a, 1982b, 1983, 1985, 1988, 1990). As noted earlier, it does not seem likely that a sufficient number of fibers could penetrate from the lungs or the gastrointestinal tract to cause any adverse effects on reproductive tissues.

**Genotoxic Effects.** The genotoxicity of asbestos has been investigated in a number of *in vitro* test systems, as summarized in Table 2-5. Most tests for gene mutations have been negative, both in prokaryotes (Chamberlain and Tarmy 1977) and eukaryotes (Kelsey et al. 1986; Kenne et al. 1986; Reiss et al. 1982). Marginal evidence for weak mutagenicity of chrysotile, crocidolite and amosite in Chinese hamster ovary (CHO) cells was reported by Huang (1979).

A large number of studies indicate that asbestos fibers can cause chromosomal aberrations in Chinese hamster ovary (CHO) and Syrian hamster embryo (SHE) cells. The aberrations include aneuploidy (usually polyploidy), fragmentation, breaks, rearrangements, gaps, dicentrics, inversions, and rings (Kelsey et al. 1986; Lavappa et al. 1975; Oshimura

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**TABLE 2-5. Genotoxicty of Asbestos In Vitro**

| End Point | Species (Test System) | Asbestos Type[a] | Results[b] | Reference |
|---|---|---|---|---|
| Procaryotic organisms: | | | | |
| Gene mutation | Salmonella typhimurium | CR, CH, AM | - | Chamberlain and Tarmy 1977 |
| | Escherichia coli CP2 | AN | - | |
| Mammalian cells: | | | | |
| Gene mutation | Chinese hamster CHO cells | CR | - | Kenne et al. 1986 |
| | Chinese hamster, CCL 39 cells | CR, CH, AM | (+) | Huang 1979 |
| | Rat liver epithelial cells | CR, CH, AM | - | Reiss et al. 1982 |
| | Human TK6 cells | CR | - | Kelsey et al. 1986 |
| Chromosomal aberrations | Chinese hamster CHO-K1 cells | CR, CH, AM, AN | + | Sincock 1977 |
| | Chinese hamster CHO-K1 cells | CR | + | Sincock and Seabright 1975 |
| | Chinese hamster CHO cells | CR | + | Kenne et al. 1986 |
| | Chinese hamster CHO cells | CR | + | Kelsey et al. 1986 |
| | Chinese hamster CHO cells | CH | + | Sincock et al. 1982 |
| | Chinese hamster V79 cells | CR, CH | + | Palekar et al. 1987 |
| | Syrian hamster cells | CH | + | Lavappa et al. 1975 |
| | Syrian hamster cells | CH | + | Oshimura et al. 1986 |
| | Human lymphocytes | CH | + | Valerio et al. 1980 |
| | Human fibroblasts | CH | - | Sincock et al. 1982 |
| | Human lymphoblastoid cells | CH | - | Sincock et al. 1982 |
| Sister chromatid exchange | Chinese hamster CHO cells | CR | - | Kelsey et al. 1986 |
| | Chinese hamster CHO cells | | - | Casey 1983 |
| | Chinese hamster CHO cells | CR, CH, AM | + | Livingston et al. 1980 |
| | Chinese hamster CHO cells | CH | + | Babu et al. 1980 |
| | Chinese hamster V79-4 cells | CR | - | Price-Jones et al. 1980 |
| | Rat mesothelial cells | | - | Kaplan et al. 1980 |
| | Human fibroblasts | | - | Casey 1983 |
| | Human lymphoblastoid cells | | - | Casey 1983 |
| DNA strand breakage | Hamster tracheal epithelial | CR, CH | - | Mossman et al. 1983b |
| | Human bronchial cells | CR, CH, AM | - | Lechner et al. 1983 |
| | Human fibroblasts | | - | Hart et al. 1979 |
| Cell transformation | Syrian hamster embryo cells | CH, CR | + | Hesterberg and Barrett 1984 |
| | Mouse fibroblasts | CR, AM | - | Brown et al. 1983 |
| Cell transfection | Monkey COS-7 cells | CH | + | Appel et al. 1988 |
| | Chimp, human, monkey, mouse | AM, AN, CH, CR | + | Dubes and Mack 1988 |

[a]CR = Crocidolite; CH = Chrysotile; AM = Amosite; AN = Anthophyllite
[b]- = negative result; (+) = weakly positive; + = positive

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by chrysotile in one study using human cells (Valerio et al. 1980), but not in another (Sincock et al. 1982). The mechanism by which these clastogenic effects occur is not clear, but could be related to physical interference by the asbestos fiber in the mitotic process (Palekar et al. 1987).

Results of tests for other genotoxic effects (increased sister chromatid exchange, DNA strand breaks, cell transformations) have been largely negative (Brown et al. 1983; Casey 1983; Hart et al. 1979; Kelsey et al. 1986; Lechner et al. 1983; Mossman et al. 1983b; Price-Jones et al. 1980), although positive results have been noted in a few cases (Babu et al. 1980; Hesterberg and Barrett 1984; Livingston et al. 1980). Of special interest, the cell transformation reported by Hesterberg and Barrett (1984) was abolished when the fibers were milled to a short length. Asbestos fibers have also been found to mediate cell transfection (uptake of extracellular nucleic acids) in a variety of cultured mammalian cell systems (Appel et al. 1988; Dukes and Mack 1988).

These observations, especially the consistant findings of cytogenotoxicity, are fully consistent with the observed carcinogenic potential of long asbestos fibers, and support possible mechanisms by which asbestos might be acting.

Cancer. There is no doubt that inhalation of asbestos can lead to increased risk of lung cancer and mesothelioma. This has been conclusively demonstrated in numerous studies of occupationally exposed workers, and has been confirmed in a number of animal experiments. For lung cancer, the magnitude of the risk appears to be a complex function of a number of parameters, most important of which are: 1) the level and the duration of exposure; 2) the time since exposure occurred; 3) the age at which exposure occurred; 4) the tobacco-smoking history of the exposed person; and 5) the type and size distribution of the asbestos fibers.

The last parameter is of special practical importance, since the variability in potency between fibers means that cancer risk from asbestos exposure may vary widely from location to location. Some of this variation may be attributable to differences between the mineral types, but fiber size (length and thickness) appear to be of prime importance. There is strong evidence from inhalation studies (Davis et al. 1980; Davis and Jones 1988), intrathoracic and intraperitoneal dosing studies (Bolton et al. 1982b; Davis et al. 1985, 1986; Davis and Jones 1988; Jaurand et al. 1987; Stanton et al. 1981; Wagner et al. 1973, 1980a), and <u>in vitro</u> studies (Hesterberg and Barrett 1984), that long fibers are more carcinogenic than short fibers. However, this should not be construed to mean that shorter fibers are totally without

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carcinogenic potency. As discussed by Lippmann (1988), the relation between fiber size and carcinogenicity may vary between lung cancer and mesothelioma, but this is not yet clear.

Because of the large number of variables, it is difficult to make reliable predictions of the magnitude of the cancer risk that may result from exposures of the general population to asbestos levels that are likely to be encountered outside the workplace. Although there is considerable uncertainty in the estimates, EPA (1986a) calculated that lifetime exposure to asbestos dust containing 0.0001 fiber greater than 5 μm in length per mL of air could result in about 2 to 4 excess cancer deaths (lung cancer plus mesothelioma) per 100,000 people.

While lung cancer and mesothelioma are generally associated with chronic exposure to asbestos, there are several studies which indicate that short-term exposures are also of concern. For example, Seidman et al. (1979, 1986) and Jones et al. (1980a) noted workers exposed to asbestos for only 1 to 12 months had an increased risk of developing lung cancer a number of years later. In animals, Wagner et al. (1974) noted that mesotheliomas developed in two rats exposed to amosite or crocidolite for only one day. These data are not extensive enough to define the dose- or time-dependency of health risks from short-term exposure to asbestos, but the data do indicate that short-term exposures should not be disregarded.

Asbestos exposure is also suspected of increasing the risk of cancer in the gastrointestinal tract and at other extrathoracic sites. However, this is a controversial subject. Data supporting this view have been derived mainly from three types of study. First, workers exposed to asbestos by inhalation are frequently noted to have small excesses in death rates from gastrointestinal cancer. This is presumed to be due to the transfer of inhaled fibers from the lung to the gastrointestinal tract. Second, some studies suggest that populations with high levels of asbestos fibers in drinking water may have increased risk of gastrointestinal cancers. Third, one lifetime feeding study in rats indicated that intermediate length chrysotile can increase the frequency of intestinal tumors in rats.

However, none of these lines of evidence are entirely convincing. The excess gastrointestinal mortality noted in workers and in populations exposed through drinking water are usually quite small (from an epidemiological point of view), and it is very difficult to determine whether the excesses are due to asbestos or to other factors (exposure to other chemicals, misdiagnosis, dietary factors, alcohol intake, etc). With regard to the one positive tumorigenicity finding in animals, this must be balanced against the fact that the tumors were both infrequent and benign, and that no significant excess of gastrointestinal tumors was noted in a number of other animal studies.

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It is not possible at present to draw definitive conclusions from the available data regarding the magnitude of the risk of gastrointestinal cancer from inhalation or ingestion of asbestos. However, there are certainly adequate data to conclude that this is an effect of concern that should not be discounted.

## 2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc and selenium). Biomarkers of exposure to asbestos are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by asbestos are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic. It can be an intrinsic genetic or

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other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

### 2.5.1 Biomarkers Used to Identify or Quantify Exposure to Asbestos

At present, there are no routine methods used to identify or quantify exposure to asbestos in living person except for measuring asbestos fiber concentrations in air or water. Chest x-rays are useful in identifying early signs of asbestos-related lung effects following inhalation exposure, but asbestos fibers are far too small to be seen by this approach. Another approach is to collect a sample of cells from the lung by bronchoalveolar lavage, and to examine the cells (mainly macrophages) for the presence of asbestos fibers or asbestos bodies (Barbers and Abraham 1989; De Vuyst et al. 1982; Johnson et al. 1986). This method is relatively noninvasive, and offers a convenient means for confirming that asbestos exposure has occurred. However, it is not possible to use the data to quantify exposure or predict any likely health effects.

Asbestos fibers can also be measured in urine (see Section 6.1), and limited data indicate that above average exposures in the workplace (Finn and Hallenbeck 1984) and through drinking water (Cook and Olson 1979) can be detected by this means. However, only a tiny fraction of inhaled or ingested fibers are excreted in the urine, and the quantitative relationship between exposure and urinary fiber concentration appears quite variable. Moreover, urinary levels presumably are mainly a reflection only of recent exposures. Thus, urinary analysis for fibers has not been established or validated as a reliable means of biomonitoring for chronic asbestos exposure.

Most studies rely on analysis of tissue samples taken at autopsy to quantify asbestos exposure. These studies indicate, as might be anticipated, that lung burdens of asbestos are generally higher in persons with asbestos-related disease than in persons without disease. In the case of asbestosis (where the severity of functional, radiological and histological effects can be scored on a scale of 0 to 10), there is a generally linear relation between lung burden and severity score (Lippman 1988). However, the quantitative relationship between lung burden and disease is difficult to define, due to differences between studies in level and duration of exposure, type of asbestos, and latency since exposure. This variability is compounded by differences between laboratories in the methods used to measure tissue burdens (Gylseth et al. 1985). For example, Wagner et al. (1986) found that asbestosis was not clinically significant in naval dockyard workers at lung burdens up to around 25 x $10^6$ fibers per gram dry lung tissue (f/g) (measured by electron microscopy), but that severe lung disease

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was common in workers with levels of 50 x $10^6$ to 350 x $10^6$ f/g. In contrast, Gylseth and Skaug (1986) found that within the lung of a single person, fibrosis was minimal in regions where fiber burdens ranged from 100 to 200 x $10^6$ f/g dry lung tissue.

The high fiber content in lung of workers with asbestosis is usually due almost entirely to an increase in amphibole content (crocidolite and amosite), while chrysotile levels are often not much different from persons without apparent disease (Wagner et al. 1982b). This observation is sometimes taken to indicate that it is the amphiboles which are the principal cause of the asbestosis. For example, Churg and Wright (1989) compared the lung burden of asbestos in people with asbestosis who had either been exposed in the chrysotile industry (low amphibole exposure) or in the shipyard and insulation industry (higher amphibole exposure). The mean tissue burden was 330 f/g in asbestosis cases who had been exposed to chrysotile, but was only 30 f/g in asbestosis cases from the shipyard and insulation industries. While this suggests that amphiboles may be more potent than chrysotile in inducing asbestosis, interpretation of this data is complicated by the preferential breakdown or dissolution of chrysotile fibers in the lung, with little or no loss of amphibole fibers (see Section 2.3.3). Consequently, the relationship between asbestosis and lung burden is difficult to establish.

Similar dose-response data correlating asbestos lung burden and disease are not available for respiratory tumors, but several studies confirm that lung burdens of asbestos are higher in cancer cases than controls. For example, Whitwell et al. (1977) compared the distribution of fiber levels (measured by phase contrast microscopy) in a group of mesothelioma patients, and found that levels ranged from around 0.02 x $10^6$ to 20 x $10^6$ f/g of dried lung tissue, in comparison to controls where levels ranged from 0.005 x $10^6$ to 0.05 x $10^6$ f/g. Similar results were reported by Berry and Newhouse (1983), where the asbestos tissue burden ranged from around 5 x $10^6$ to 60 x $10^6$ f/g in mesothelioma cases, but rarely exceeded 1 x $10^6$ f/g in controls. As noted above, the higher tissue levels are due mostly to amphiboles rather than chrysotile (Jones et al. 1980b), but this does not necessarily imply that the amphiboles are the chief cause of the disease. Interpretation of these data is also complicated by the fact the fiber retention in lung parenchyma does not correlate well with pleural retention, with differences in both fiber level and type (Sebastien et al. 1980a).

### 2.5.2 Biomarkers Used to Characterize Effects Caused by Asbestos

The most common means of characterizing the effects of inhalation exposure to asbestos in living persons is the chest x-ray (e.g., Anton-Culver et al. 1989; Jones et al. 1988b). This method is capable of detecting both pleural and parenchymal abnormalities, but sensitivity

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and specificity are limited (Gefter and Conant 1988). In particular, x-ray changes are rarely detectable until after some degree of physiological impairment has occurred (Aberle et al. 1988a). Computerized tomography (CT) and high-resolution computed tomography (HRCT) may be superior to conventional radiological examination in some cases (Aberle et al. 1988a, 1988b; Gamsu et al. 1989; Sluis-Cremer et al. 1984).

Another approach often used for evaluating the effects of asbestos inhalation is quantitative analysis of lung function (e.g., Ernst et al. 1989; Finkelstein 1986). The specific end points of greatest value are $FEV_1$ (forced expiratory volume in one second) and FVC (forced vital capacity), since these are most affected by fibrotic changes in the lung. Most studies find that respiratory changes parallel radiological changes (e.g., Britton 1982; Cordier et al. 1987), although several studies report measurable respiratory decrements in the absence of radiological changes (Weill et al. 1975; Ohlson et al. 1984).

It is important to stress that neither radiological nor respiratory tests are specific for asbestos-induced lung injury. Consequently, other causes of lung injury (e.g., smoking, occupational exposures to other chemicals, lung infections) must also be considered when such changes are detected in an individual.

## 2.6 INTERACTIONS WITH OTHER CHEMICALS

In epidemiological studies, an interaction between two risk factors is generally defined as a greater-than-additive risk when both risk factors are present (Steenland and Thun 1986). With respect to lung cancer, several studies indicate that the interaction between asbestos and smoking is greater than additive (DHHS 1985; Selikoff et al. 1968). The most dramatic data are those of Hammond et al. (1979), who found an age-standardized mortality ratio of 5.17 for nonsmoking asbestos workers, 10.85 for smokers not exposed to asbestos, and 53.2 for asbestos-exposed smokers. The risk from combined exposure clearly exceeds the predicted risk based on additivity (15.0), and the data suggest a multiplicative interaction. Other studies have found that smoking increases the risk of lung cancer from asbestos exposure more than predicted by additivity, but often less than predicted by a multiplicative model (Berry et al. 1985; McDonald et al. 1980; Saracci 1987; Selikoff et al. 1980; Thomas and Whittemore 1988).

The mechanism by which smoking and asbestos interact to increase risk of lung cancer is not known, but several hypotheses (which are not mutually exclusive) have been suggested. One possible mechanism is a smoking-induced decrease in clearance of fibers from the lung, perhaps by interference with ciliary action or macrophage activity (Plowman 1982), leading in turn to increased penetration of the respiratory

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epithelium by fibers (Hobson et al. 1988; McFadden et al. 1986). Another proposal is that asbestos fibers (either in air or in the lung) may adsorb carcinogenic substances present in smoke, thereby increasing levels of these substances in the lung (Menard et al. 1986; Mossman et al. 1983a). Finally, on the assumption that cancer is a multistep process, asbestos and smoking could interact by affecting different steps in the process. An interaction of this sort between dimethylbenzanthracene and asbestos has been demonstrated in a two-stage carcinogenicity assay in vitro (Topping and Nettesheim 1980), with asbestos displaying effects characteristic of a promoter.

There is also good evidence that smoking increases the risk of asbestosis. For example, Hammond et al. (1979) found the death rate from asbestosis was 2.8 times higher in asbestos-exposed smokers than in asbestos-exposed nonsmokers, and a similar effect was noted by Selikoff et al. (1980). Evidence of increased frequency of clinical signs of asbestosis (rales, dyspnea, crepitations) in smoking versus nonsmoking workers was reported by Berry et al. (1979) and Lerman et al. (1986), and Blanc et al. (1988) reported a synergistic effect of smoking on the occurrence of parenchymal opacities in the lungs of asbestos workers. On the other hand, several researchers have reported that the effects of asbestos and smoking on these signs are additive rather than synergistic (Begin et al. 1987b; Hnizdo and Sluis-Cremer 1988; Weiss 1984).

In contrast to the interactive effect of smoking on lung cancer and fibrosis, smoking does not appear to increase the risk of mesothelioma (Berry et al. 1985; Hammond et al. 1979; Selikoff et al. 1980).

Data are not available on interactive effects between asbestos and other substances following oral exposure of humans. In animals, chronic oral exposure to asbestos caused no convincing increase in tumors in animals that had been treated with a known intestinal carcinogen (dimethylhydrazine) compared to the incidence in animals treated with dimethylhydrazine alone (NTP 1982a, 1983, 1985). However, these studies were judged to be inconclusive, since the doses of dimethylhydrazine employed gave either too few or too many gastrointestinal tumors to allow easy detection of an effect by asbestos (NTP 1982a, 1983).

## 2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Studies of workers who are exposed to asbestos in workplace air indicate that not all people who are exposed to equal doses of asbestos are equally affected. As discussed above (Section 2.7), it is likely that one main source of this variability in susceptibility between people is smoking history or the degree of exposure to other risk factors with which asbestos interacts. Another important factor is age, with people who are exposed in their youth being more likely to develop asbestos-related disease than people exposed later in life. This is

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probably not because young people are inherently more susceptible to asbestos than older people, but because of the long latency period (10 to 40 years) typically associated with asbestosis and cancer.

## 2.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of asbestos is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of asbestos.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

### 2.8.1 Existing Information on the Health Effects of Asbestos

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to asbestos are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of asbestos. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

There have been a very large number of studies, both in animals and humans, focusing on the major health effects associated with inhalation exposure (asbestosis, lung cancer and mesothelioma) and oral exposure (gastrointestinal cancer). There have also been a number of studies on immune system changes in humans exposed by inhalation, but this has not been investigated in people exposed orally. There are few formal studies focusing on other possible effects of asbestos. However, because so few fibers are able to penetrate from the lungs or the gastrointestinal tract into the body, there is little reason to believe that other effects are of major concern.

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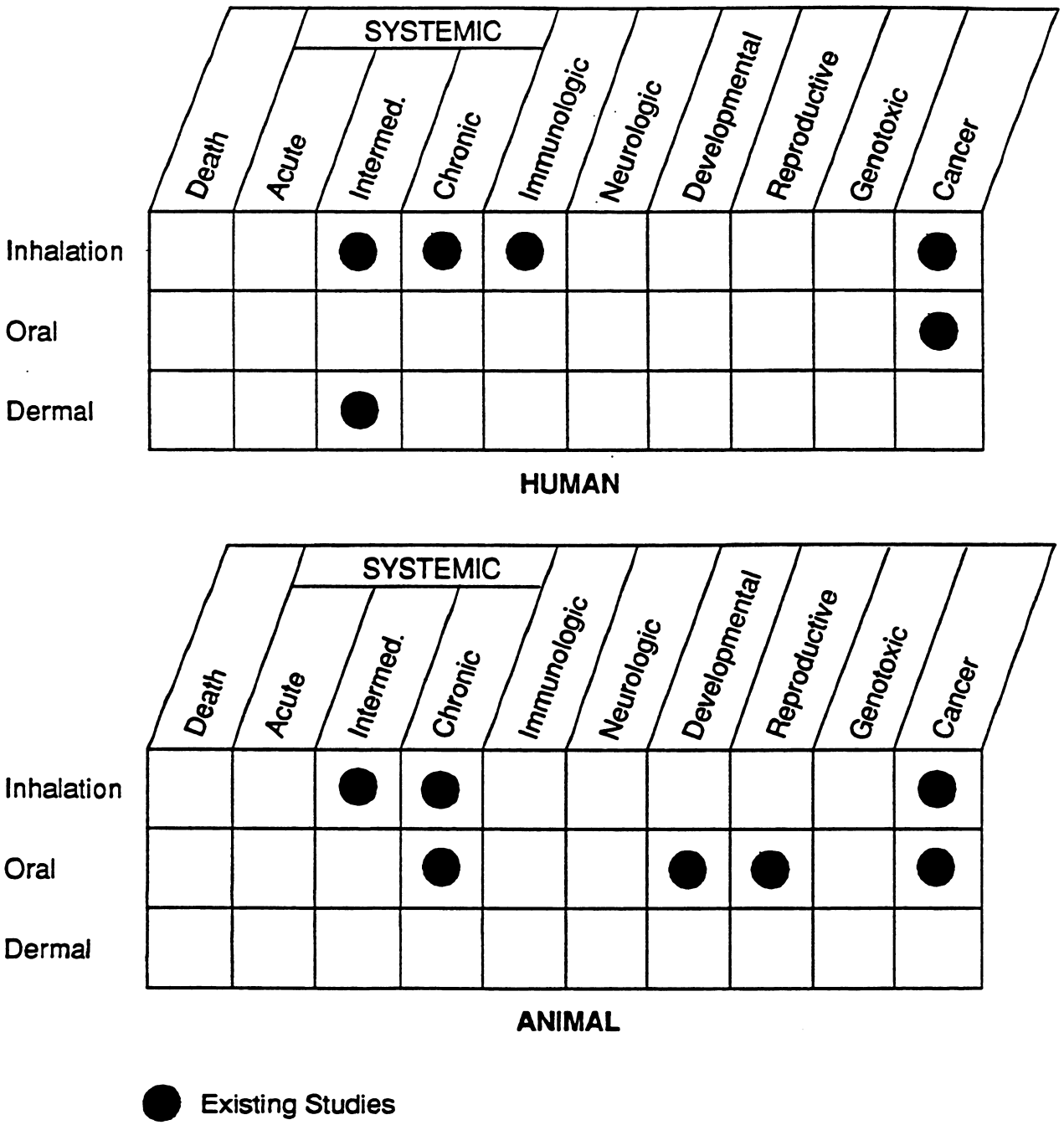



**FIGURE 2-5. Existing Information on Health Effects of Asbestos**

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### 2.8.2 Identification of Data Needs

**Acute-Duration Exposure.** Very few inhalation or oral studies have sought to determine the effects of single exposures to asbestos. There are no data on noncancer effects following acute exposures, and no acute-duration MRLs have been derived. This is probably not a critical data gap, since risk of health effects from asbestos is usually associated with chronic exposure. However, there is one study (Wagner et al. 1974) which suggests that a single inhalation exposure in animals might cause cancer. This is an important point, since many people might have one or two significant exposures to asbestos during their life. Additional studies on the long-term effects of acute inhalation exposure would be valuable to determine if this is of concern, and if it is, to define the dose-response relationship for cancer, fibrosis, and other biologic outcomes.

**Intermediate-Duration Exposure.** Several studies (Jones et al. 1980a; Seidman et al. 1979, 1986) in humans suggest that workers exposed to asbestos for periods of 1 to 12 months may subsequently develop asbestos-associated lung disease. However, these studies do not provide sufficient dose-response data to derive a reliable intermediate-duration inhalation MRL. Further inhalation studies in animals to investigate the fibrogenic and carcinogenic risks from short-term exposures would be helpful in assessing the risks in humans who may only be exposed for a limited period. Several intermediate-duration oral studies in animals have been performed, and these have not revealed any evidence of noncancer effects. In the absence of data to suggest that a significant noncancer risk exists following oral exposure, it does not seem that additional studies of this sort are critical.

**Chronic-Duration Exposure and Cancer.** There are numerous studies in animals and humans which describe the effects of chronic inhalation exposure on the lung and pleura. These studies provide an estimate of the cumulative dose that leads to asbestosis, but there is sufficient uncertainty in the NOAEL and in the dose-time dependence that a chronic inhalation MRL has not been derived. Further studies on the occurrence of noncancer effects (radiological changes, altered respiratory function) in exposed humans would be valuable in clarifying these dose and time relationships, even though the risk of cancer will typically be of chief concern following chronic inhalation exposure.

The carcinogenic effects of chronic inhalation exposure to asbestos have been amply demonstrated, both in humans and animals. However, a number of important issues remain to be resolved. In particular, it would be useful to know if there are maximum and/or minimum lengths and diameters beyond which fibers lack carcinogenic effects, or whether there are continuous gradients of carcinogenicity as a function of fiber

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length and diameter. In this regard, additional research on the mechanism of carcinogenicity is more likely to be useful than additional epidemiological or animal studies, since it is very difficult to prove the presence or absence of a low-dose cancer threshold by direct observation. This would include studies on the molecular and cellular mechanisms by which asbestos causes lung cancer and mesothelioma. With regard to lung cancer, asbestos appears to act mainly as a promoter, suggesting that there might be a threshold with respect to dose. If true, this would be of considerable importance, since most environmental exposures are at very low doses. The results of studies focusing on whether or not there are length, diameter, or dose thresholds could lead to important refinements in risk assessment models, which currently assume that risk is linearly related to the number of fibers greater than 5 $\mu$m in length.

Along these same lines, further work would be helpful in defining other fiber characteristics that are important determinants of carcinogenicity. It is suspected, for example, that crocidolite and other amphiboles are more likely to cause mesothelioma than chrysotile, but it is not certain if this is attributable to differences in fiber length alone or to differences in chemical properties (e.g., fiber morphometry, stability in biological fluids and tissues). Consequently, comparative studies of the relative carcinogenicity of different mineral preparations, carefully matched with regard to fiber size distribution, would be valuable.

Another important area where further research would be valuable is the synergistic interaction between asbestos and other risk factors for lung cancer, especially smoking. Particularly helpful would be further studies on the mechanism of such interactions, since this could help improve current means of predicting the consequences of exposures to substances such as cigarette smoke.

In view of the uncertainty regarding the risk of gastrointestinal cancer following direct or indirect ingestion of asbestos, further research in this area would be of great value. Although an extensive series of lifetime feeding studies have already been performed by NTP, only two of these studies (NTP 1983, 1985) focused on the issue of fiber length in oral carcinogenicity. Further studies to investigate the role of fiber length in gastrointestinal cancer would be valuable, with special emphasis on whether there is a minimum length below which carcinogenic risk is minimal. This would have considerable practical consequence in evaluating the potential risk to human health associated with ingestion of asbestos in drinking water. Additional epidemiological studies could also be helpful, especially if they were carefully designed to address the uncertainties and limitations in the evidence currently available.

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**Genotoxicity.** The genotoxic effects of asbestos have not been studied *in vivo* in humans or animals. Available *in vitro* studies in eukaryotic cells indicate that asbestos is probably not mutagenic, but that it is clastogenic, causing a variety of chromosomal aberrations. This is an observation of importance, since genotoxic effects of this sort might be involved in the carcinogenic effects of asbestos. Further studies to determine the mechanism of clastogenicity, the dependency of clastogenicity on fiber size and type, and the relative genotoxic sensitivity of different respiratory and gastrointestinal epithelial cells would be valuable.

**Reproductive Toxicity.** There are no studies in humans on potential reproductive effects of asbestos exposure. There is limited evidence from studies in animals that chronic ingestion of asbestos does not injure reproductive tissues, and that exposure during gestation does not reduce fertility. This indicates that reproductive effects are probably not of concern, and indeed there is little mechanistic basis for thinking this could occur. For these reasons, further studies on this endpoint do not appear critical.

**Developmental Toxicity.** There are no studies in humans on potential developmental effects of asbestos exposure. Limited studies in animals have not detected any teratogenic effect in offspring of dams exposed to asbestos by the oral route, although decreased body weight at birth and later in life were noted in some cases (NTP 1982a, 1985). It seems likely that these effects were either random or were secondary to reduced food intake by the dams, but additional studies to confirm that this is not an effect of concern would be helpful.

**Immunotoxicity.** There are numerous studies of the immune system in workers who have been exposed to asbestos in workplace air. These studies indicate that the immune system is often significantly depressed in individuals who have developed clinical signs of injury, such as asbestosis or cancer. However, the cause-effect relationship between the immunological changes and the asbestos-related diseases is not certain. Also, it is not known if similar effects occur following oral exposure, or if the effects are inhalation specific. Prospective studies on this subject would be very useful, both in discerning the importance of immune system injury in the etiology of asbestos-induced disease, and also to determine if immune function can be used as a possible early test of individual sensitivity to asbestos.

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**Neurotoxicity.** There are no reliable indications in studies of humans or animals that exposure to asbestos leads to neurotoxicity. Even though tests have not been performed to search for possible subtle effects, there is little reason to suspect that this is an effect of concern, and detailed studies on this effect do not appear to be essential.

**Epidemiological and Human Dosimetry Studies.** There have been a very large number of epidemiological studies performed on workers exposed to relatively high concentrations of asbestos in air. Of value would be further epidemiological studies on populations with lower exposure levels, such as family members of asbestos workers, workers in buildings with asbestos-containing materials, or sailors exposed aboard ships. Endpoints of concern would include not only cancers, but also pleural changes and respiratory function. Such studies may help estimate the magnitude of the health risks posed by current levels of asbestos inside buildings, in the ambient environment, and near waste sites.

Of special value in any ongoing or future epidemiological study, either in the workplace or in the ambient environment, is good dosimetry data, including data on the level, length and duration of exposure, and the type and size of the fibers involved. When accurate dosimetry data are not available (as is often the case), an indirect approach that can be useful is analysis of asbestos types and levels in tissue samples taken at autopsy. The main limitation of this approach is that chrysotile fibers tend to undergo breakdown or dissolution in tissues, while amphiboles tend to remain intact. Consequently, the relationship between tissue burden and exposure is not straightforward. Further investigations to clarify the dependency of asbestos levels in tissue on the type and level of asbestos exposure would be very helpful in improving the ability to predict human cancer risk from exposure to asbestos.

**Biomarkers of Exposure and Effect.** The most relevant parameter for quantifying exposure to asbestos is the body burden of retained fibers. However, there are no methods currently available for measuring tissue levels of fibers in living persons other than by biopsy. Alveolar lavage is useful for detecting the presence of asbestos fibers in respiratory macrophages, but this has not been developed as a quantitative indicator of exposure. Fibers can also be detected in urine and feces, but these methods would likely reflect only recent exposures (within the last several days) and not the cumulative tissue burden. Efforts to develop a noninvasive method for measuring fiber levels in tissues (especially in the lung) would be particularly valuable in assessing human exposures to asbestos.

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No specific and sensitive biomarkers of asbestos-induced disease are known. Chest x-rays can detect both the noncarcinogenic and carcinogenic lesions produced by asbestos in the lung and pleura, but usually not until after significant injury has occurred. Similarly, spirometric tests of lung function can detect early stages of asbestos-induced disease, but only after functional decrements. Further studies would be valuable to determine if changes such as depressed immune system function or altered levels of other biochemical parameters can be used as an indicator of risk of asbestos-induced cancer or fibrosis. Also, further efforts would be valuable to improve diagnostic methods for detecting early asbestos-related effects, such as high-resolution computed tomography to detect pleural thickening or pleural plaques (Aberle et al. 1988a, 1988b).

**Absorption, Distribution, Metabolism, Excretion.** Because asbestos consists of insoluble fibers, it does not undergo absorption, distribution, metabolism or excretion in a fashion similar to most other chemicals. With respect to inhalation exposure, the toxicokinetic parameters of greatest relevance are the extent and location of fiber deposition in the airway, the rate of fiber removal from the airway by mucociliary transport, and translocation of fibers within and across the lung. A number of studies are available on the deposition and clearance of asbestos fibers from the lungs, both in humans and animals, and these processes are fairly well understood. However, additional research would be valuable to clarify the biological and mineralogical parameters which influence fiber penetration through the lungs into the pleural membrane, since this is a likely determinant of mesothelioma risk. Similar studies on the penetration of the gastrointestinal tract by fibers would also be helpful, since this might be key in extrathoracic cancer risks following oral intake. Additional studies on the long-term stability of fibers in the lung would be helpful in understanding why amphibole fibers appear to be more durable than chrysotile.

**Comparative Toxicokinetics.** Studies in humans and animals indicate the lung is the principal target organ following inhalation exposure. Comparative studies between humans and animals with respect to the details of where fibers are deposited, how that pattern depends on fiber dimension, and the rate of clearance from various locations in the respiratory tree, would be valuable in extrapolating animal deposition and clearance data to humans, and in identifying the best animal model for studying human health effects.

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### 2.8.3 On-going Studies

Asbestos toxicity continues to be a matter of great concern, and a large number of studies are being performed to provide additional data on the health effects of this fiber class. Studies sponsored by the National Institutes of Health that are being carried out in animals or in vitro are summarized in Table 2-6, and some on-going epidemiological studies in the United States and other countries around the world are summarized in Table 2-7.

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TABLE 2-6. Summary of On-going Studies on Asbestos Toxicity

| Principal Investigator | Affiliation | Research Description |
|---|---|---|
| A. A. Roman-Franco | University of Puerto Rico, Rio Piedras | Mechanism of action of carcinogenic fibers |
| J. M. Wallace | University of California, Los Angeles | Study of bronchoalveolar lavage fluid from asbestos-exposed patients with lung disease |
| E. C. Lawrence | Baylor College of Medicine, Houston | Asbestos effects on human alveolar macrophage functions |
| B. E. Bozelka | Tulane University, New Orleans | Intrapulmonary cellular mechanism in asbestos-induced fibrotic lung disease |
| B. T. Mossman | University of Vermont, Burlington | Prevention of asbestos-associated pulmonary fibrosis in rats |
| J. E. Craighead | University of Vermont, Burlington | Mechanism of transformation of rat mesothelial cells |
| J. C. Barrett | NIEHS, Research Triangle Park, NC | Studies of mechanism of transformation and chromosomal mutations in Syrian hamster embryo cells |
| K. E. Pinkerton | University of California, Davis | Lung epithelium and interstitial asbestos accumulation |

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TABLE 2-6 (Continued)

| Principal Investigator | Affiliation | Research Description |
|---|---|---|
| M. Lippman | New York University, New York | Effects of fiber length on asbestos carcinogenicity in rats |
| C. M. Smith | University of California, San Diego | Nature and sequences of immunologic, cellular and histologic events in lungs of rats exposed to asbestos via inhalation |
| A. B. Kane | Brown University, Providence | Biochemical and structural changes in P388D1 cells injured by asbestos, and in co-cultures of mouse mesothelial cells and peritonealmacrophages exposed to asbestos |
| B. I. Gerwin | National Cancer Institute, Bethesda, MD | Molecular analysis of gene regulation and proliferative control in human bronchial epithelial cells exposed to asbestos |
| J. W. McLarty | University of Texas, Tyler | Role of beta-carotene as lung cancer preventive agent using men occupationally exposed to asbestos |
| J. G. Rheinwald | Dana-Farber Cancer Institute, Boston | Mechanism of malignant transformation of mesothelial cells from humans, rats and mice |

Source: Adapted from CRISP database (1988)

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TABLE 2-7. Summary of On-going Epidemiological Studies on Asbestos

| Principal Investigator | Affiliation | Research Description |
|---|---|---|
| N. L. Sprince | Massachusetts General Hospital, Boston | Prospective study of asbestos workers to relate abnormalities of the cellular immune system to extent of asbestos exposure and presence of asbestos related disease |
| E. A. Eisen | Harvard School of Public Health, Boston | Evaluation of pleural plaques as marker for risk of asbestos related cancer |
| A. I. Neugut | Columbia University, New York | Asbestos as one risk factor to be evaluated in colorectal polyps |
| L. Glickman | Mount Sinai School of Medicine, New York | Prospective study on association of psychosocial stress in asbestos-related cancer morality |
| R. Spirtas | National Cancer Institute, Bethesda, MD | Role of asbestos in etiology of mesothelioma in a case-control study |

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TABLE 2-7 (Continued)

| Principal Investigator | Affiliation | Research Description |
|---|---|---|
| J. C. Wagner | MRC External Staff Team, Llandough Hospital, Penarth, United Kingdom | In post mortem lung samples, compare types and quantities of asbestos fibers with histological findings. Investigations include United Kingdom, United States, Canada, Turkey, Cyprus |
| R. D. Jones | Epidemiology and Medical Statistics Unit, Liverpool, United Kingdom | Mortality in male asbestos workers in England and Wales, 1971-1981 |
| J. H. M. Langlands | Belfast City Hospital, Belfast, United Kingdom | Relation between changing work conditions in asbestos-related occupations in Northern Ireland and incidence of asbestos-related cancers |
| G. N. Hillderdal | University Hospital Uppsala, Sweden | Swedish mesothelioma study, cases to be reviewed and reported |
| D. Surcel | Institute of Hygiene and Public Health, Cluj-Napoca, Romania | Correlation of cytological findings in asbestos workers to duration of exposure, respiratory symptoms, particle size and asbestos fiber type |

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TABLE 2-7 (Continued)

| Principal Investigator | Affiliation | Research Description |
|---|---|---|
| K. Morinega | Center of Adult Diseases, Osaka, Japan | Evaluation of tissues from malignant mesotheliomas; relation of fiber type to lesion |
| B. Terracini | Complesso Universita, Torino, Italy | Cancer mortality among amosite exposed workers |
| C. Bianchi | Hospital of Monfalcone, Monfalcone, Italy | Incidence of asbestos exposure in shipyards workers and relationship to smoking and alcohol use |
| M. Botta | Ospedale Santo Spirito, Casale Monferrato, Italy | Cohort study of workers in asbestos cement production |
| H. J. Woitowitz | Justus-Liebig University, Geissen, West Germany | Prospective follow-up study of workers occupationally exposed to asbestos |
| H. Otto | Pathologisches Institut der Stadtischen Kliniken, West Germany | Central registry of all cases of mesothelioma, occupational and nonoccupational |

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TABLE 2-7 (Continued)

| Principal Investigator | Affiliation | Research Description |
|---|---|---|
| A. F. Hirsch | Hospital St. Louis, Paris, France | Evaluation of chromosomes of blood lymphocytes of workers exposed to combination of ionizing radiation, tobacco smoke and/or asbestos |
| J. Bignon | Centre Hospitalier Intercommunal Cedex, France | French Mesothelioma Register |
| S. G. Hernberg | Institute of Occupational Health, Helsinki, Finland | Association of mesothelioma and occupational exposure to asbestos and other causes |
| S. Gonzales | Catholic University of Chile, Santiago, Chile | Prospective study of insulation workers in Chile to detect pre-cancerous and cancerous lesions in workers with 10 or more years of exposure |
| D. A. Ferguson | University of Sydney, Sydney, Australia | Mesothelioma surveillance program for Australia, continuing collection of data (initiated 1980) |

Source: Adapted from Parkin et al. (1987)

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# 3. CHEMICAL AND PHYSICAL INFORMATION

## 3.1 CHEMICAL IDENTITY

Asbestos is a generic term for a group of six naturally occurring fibrous minerals. The basic unit of asbestos-class minerals is the silicate ($SiO_4$) group. This group can form a variety of polymeric structures through formation of Si-O-Si bonds. For the amphibole class of asbestos (amosite, crocidolite, tremolite, anthophyllite, actinolite), the polymeric structure consists of a linear double chain, as shown in Figure 3-1 (top). These chains crystalize into long, thin, straight fibers, which are the characteristic structure of this type of asbestos. For the serpentine class (chrysotile), the polymeric form is an extended sheet (Figure 3-1, bottom). This extended sheet tends to wrap around itself forming a tubular fiber structure. These fibers are usually curved ("serpentine"), in contrast to the straight morphometry of the amphiboles. Table 3-1 lists common synonyms and other pertinent identification information for asbestos (generic) and the six individual asbestos minerals.

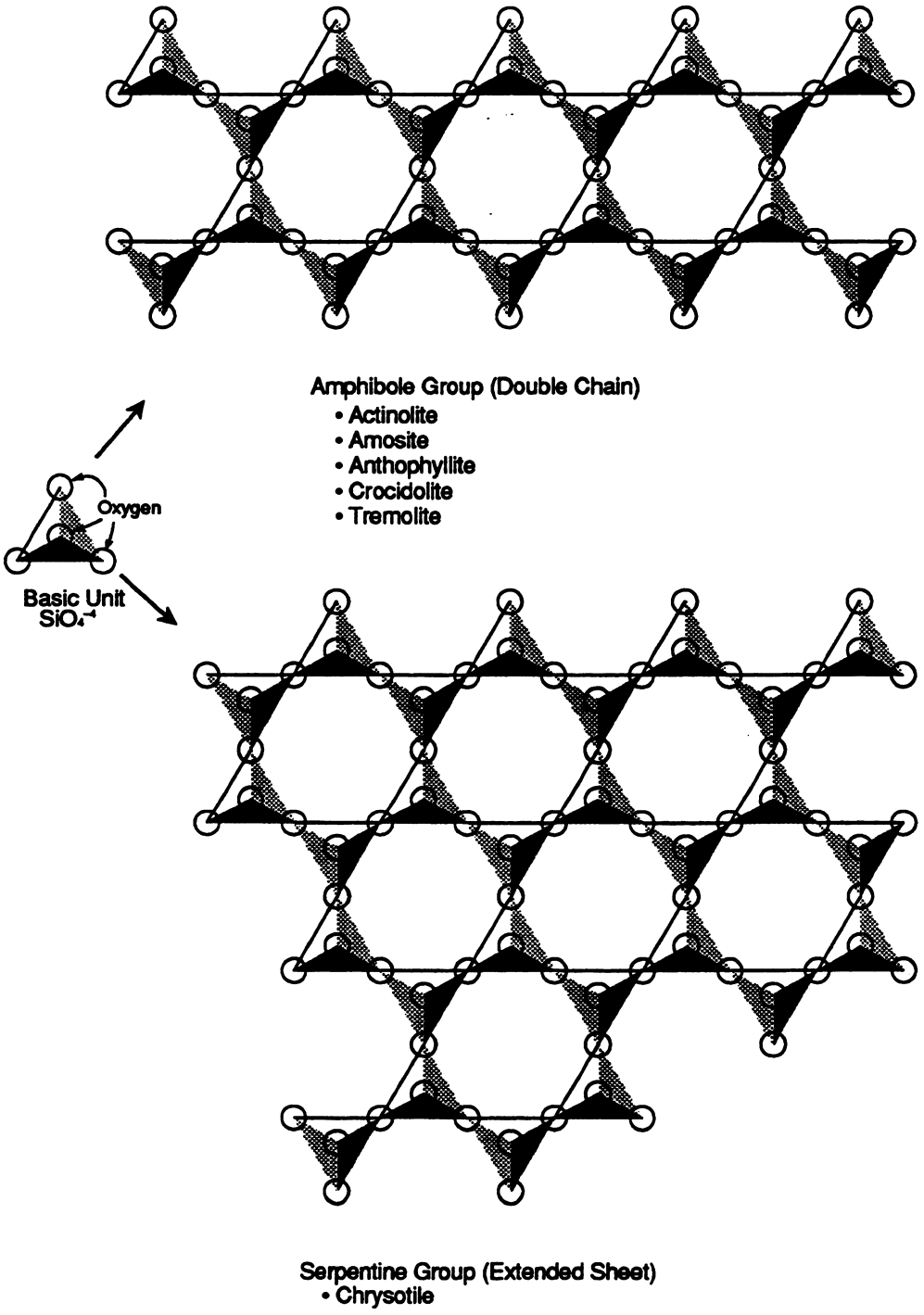
## 3.2 PHYSICAL AND CHEMICAL PROPERTIES

Asbestos fibers are basically chemically inert, or nearly so. They do not evaporate, dissolve, burn or undergo significant reactions with other chemicals. Indeed, it is this property that has made asbestos so useful. Table 3-2 summarizes some of the physical and chemical properties of the six asbestos minerals.

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Adapted from Hurlbut and Klein 1977

**FIGURE 3-1. Basic Polysilicate Structures of Asbestos**

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**TABLE 3-1. Chemical Identity of Asbestos**

| Parameter | Mineral Type | | | | | | |
|---|---|---|---|---|---|---|---|
| Chemical Name | Asbestos | Amosite | Chrysotile | Tremolite | Actinolite | Anthophyllite | Crocidolite |
| Synonyms | No data | Mysorite, brown asbestos, fibrous cummingtonite/ grunerite | Serpentine asbestos; white asbestos | Silicic acid, calcium magnesium | No data<br>salt (8:4) | Ferroantho-phyllite; azbolen asbestos | Blue asbestos |
| Trade name | No data | No data | Avibest; cassiar AK; Calidria RG 144; Calidria RG 600 | No data | No data | No data | No data |
| Chemical formula | No data | $[(Mg,Fe)_7Si_8O_{22}(OH)_2]_n$ | $Mg_3Si_2O_5(OH)_4$ | $[Ca_2Mg_5Si_8O_{22}(OH)_2]_n$ | $[Ca_2(Mg,Fe)_5Si_8O_{22}(OH)_2]_n$ | $[(Mg,Fe)_7Si_8O_{22}(OH)_2]_n$ | $[NaFe_3^{2+}Fe_2^{3+}Si_8O_{22}(OH)_2]_n$ |
| Chemical structure | See Figure 3-1 | | | | | | |
| Identification numbers: | | | | | | | |
| CAS Registry | 1332-21-4 | 12172-73-5 | 12001-29-5 | 14567-73-8 | 13768-00-8 | 17068-78-9 | 12001-28-4 |
| NIOSH RTECS | CI6475000 | BT6825000 | GC2625000 | XX2095000 | AU0550000 | CA8400000 | GP8225000 |
| EPA Hazardous Waste | No data | No data | No data | No data | No data | No data | No data |
| OHM/TADS | 7217043 | No data | No data | No data | No data | No data | No data |
| DOT/UN/NA/ IMCO Shipping | IMCO 9.0<br>UN2212<br>UN2590 | No data | No data | No data | No data | No data | No data |
| HSDB | 511 | 2957 | 2966 | 4212 | No data | No data | No data |
| NCI | CO8991 | No data | C61223A | CO8991 | No data | No data | CO9007 |

CAS = Chemical Abstracts Service; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute.

Sources: EPA 1985b; HSDB 1988, 1989; IARC 1977

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# 4. PRODUCTION, IMPORT, USE, AND DISPOSAL

## 4.1 PRODUCTION

In the United States, asbestos is mainly mined in open pits. Ore is blasted or drilled from the pit, crushed, dried and stored until milling. The milling process removes asbestos fibers from the ore by a series of crushing, fiberizing, screening, aspirating and grading operations.

More recently, an alternative method of mining has been developed in order to reduce air emissions of fibers. This method uses bulldozers and scrapers (rather than blasting) to remove the ore from the pit. The ore is watered down to prevent air dispersion of the fibers, and is crushed, sized and screened in a wet condition. After being dewatered, the fibers are pelletized, dried and prepared for shipment either as pellets or further processed to yield open fibers (ICF 1988).

In 1985, three United States companies produced asbestos fibers: Calaveras Asbestos, Ltd., Calaveras County, California; KCAC, Inc., San Benito County, California; and Vermont Asbestos Group, Orleans County, Vermont. In the past, asbestos was also produced at other companies in California, Arizona, and North Carolina, but these companies suspended asbestos mining operations in the 1970's.

The production volume of asbestos in the United States has decreased substantially from peak production of over 136,000 kkg (1 kkg is equal to 1 metric ton, or 2,200 pounds) in the late 1960's and early 1970's (SRI 1982) to 52,000 kkg in 1987 (U.S. Bureau of Mines 1988). Production volume will probably continue to decrease because many uses of asbestos have now been banned and others will be phased out over the next seven years (EPA 1989c).

## 4.2 IMPORT

Most asbestos used in the United States is imported. Imports from 1950 to 1974 varied from about 585,000 kkg to 718,000 kkg per year. During the late 1970's, imports began decreasing, with a sharp drop after 1980. By 1984, imports were down to 210,000 kkg and to 98,000 kkg by 1987. Most asbestos imported to this country comes from Canada, but small amounts also are imported from South Africa.

Exports of asbestos were small until the mid-1960's, when a significant increase in exports occurred. In recent years, export volumes have generally fluctuated between 40,000 and 65,000 kkg/yr (SRI 1982; U.S. Bureau of Mines 1988).

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# 4. PRODUCTION, IMPORT, USE, AND DISPOSAL

## 4.3 USE

It is estimated that asbestos (mainly chrysotile) has been used in over 3,000 different products in the United States. The main uses are in paper products, asbestos cement products, friction products, textiles, packings and gaskets, coatings, and asbestos-reinforced plastics, and there are numerous other miscellaneous uses. Reported consumption of asbestos in the United States was 359,000 kkg in 1980, 226,000 kkg in 1984 and an estimated 107,000 kkg in 1987 (SRI 1982; U.S. Bureau of Mines 1988). In 1987, 22% of the total asbestos consumption was used for friction products (automobile clutch, brake and transmission components), with 17% used for asbestos cement pipe, 17% for roofing products 15% for coatings and sealants, 11% for paper products, and 18% for other uses (U.S. Bureau of Mines 1988).

As noted above, as a consequence of recent regulations (EPA 1989c), most uses of asbestos will be reduced or eliminated within seven years.

## 4.4 DISPOSAL

Currently, asbestos-containing wastes may only be deposited in landfills that are approved and regulated by the federal government. These regulations are intended to ensure that asbestos at these sites is not dispersed into the environment. No data were located on amounts of asbestos in such sites. Proposed new recordkeeping and reporting requirements will help ensure that disposers provide this type of data in the future (EPA 1989a).

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# 5. POTENTIAL FOR HUMAN EXPOSURE

## 5.1 OVERVIEW

Although asbestos is neither volatile nor soluble, small fibers may occur in suspension in both air and water. These fibers are very stable and do not undergo significant degradation in the environment. Large fibers are removed from air and water by gravitational settling at a rate dependent upon their size, but small fibers may remain suspended for long periods of time.

Fibers in air may arise from natural sources (weathering of asbestos-containing ores), but many come from wear or breakdown of asbestos (mainly chrysotile) -containing materials such as insulation or automobile brakes. The concentrations of fibers in outdoor air are highly variable, ranging from below 0.1 ng/$m^3$ (3 x $10^{-6}$ PCM f/mL) in rural areas to over 100 ng/$m^3$ (3 x $10^{-3}$ PCM f/mL) near specific industrial sources such as an asbestos mine. The concentration of fibers in indoor air is also highly variable, depending on the amount and condition of asbestos-containing materials in the building. Typical concentrations range from 1 to 200 ng/$m^3$ (3 x $10^{-5}$ to 6 x $10^{-3}$ PCM f/mL). For a human exposed for a lifetime (70 years), this range of exposures corresponds to cumulative doses of around 0.0002 to 0.4 PCM f-yr/mL.

Fibers in water arise mainly by erosion from natural deposits of asbestos, or by corrosion of fibers from pipes made with asbestos-containing cement. Concentrations in most water supplies are less than 1 million fibers per liter (MFL), but may exceed 100 MFL in some cases. For a human consuming 2 L/day, this would yield a dose of about 2 to 200 million fibers per day. This is about the same dose as would be transferred to the stomach from the lungs of a person breathing air containing 0.0007 to 0.7 PCM fibers per milliliter (f/mL).

Another location where people may be exposed to asbestos is near chemical waste sites where asbestos is not properly stored. At this time, asbestos has been detected at 28 of 1,177 NPL hazardous waste sites in the United States (VIEW Database 1989). The frequency of the sites within the United States can be seen in Figure 5-1.

## 5.2 RELEASES TO THE ENVIRONMENT

### 5.2.1 Air

Although asbestos is not volatile, small fibers and clumps of fibers may be released to air as a dust-like suspension. One source is the erosion of natural deposits of asbestos-bearing rocks. While this

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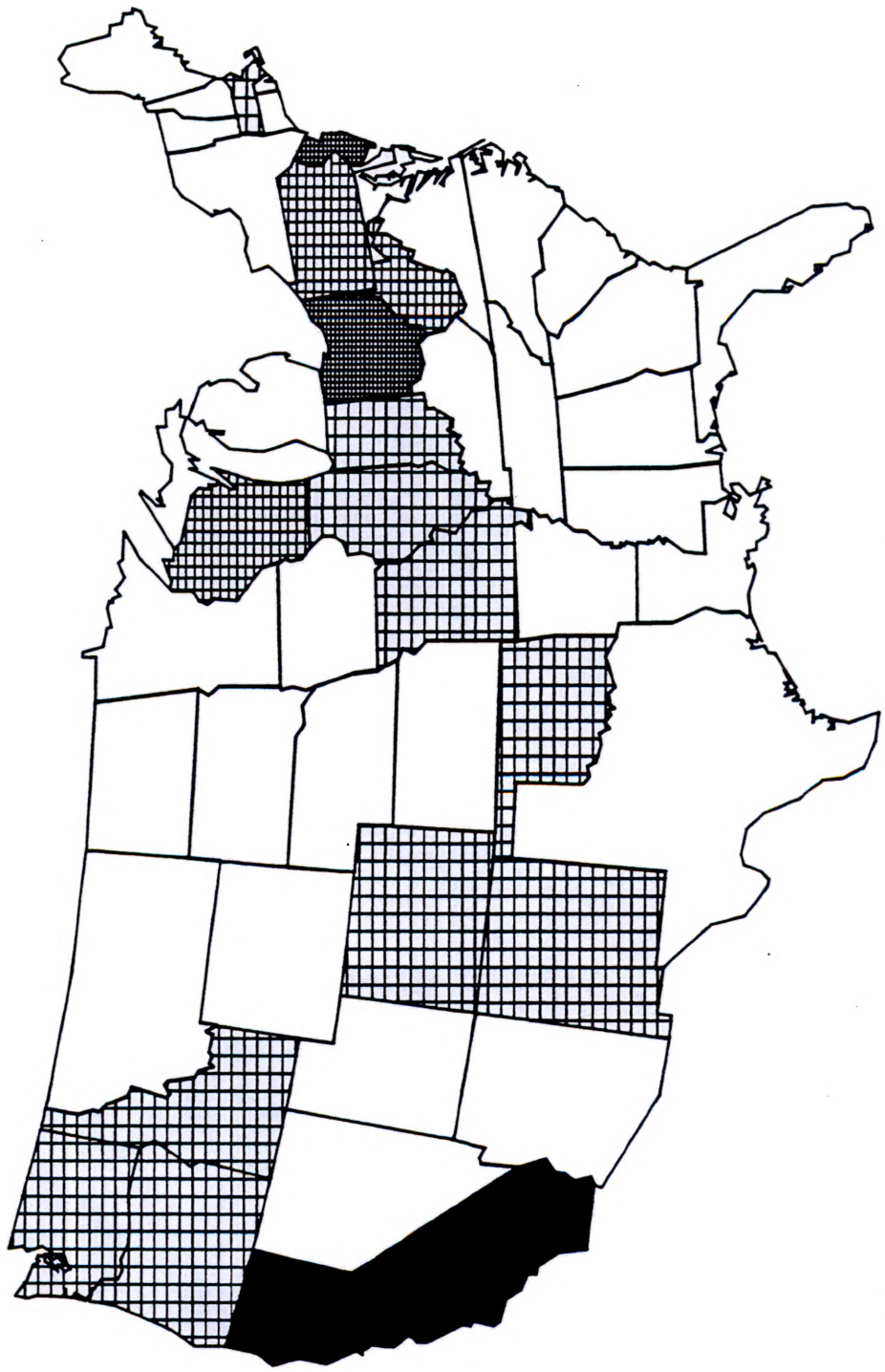



FIGURE 5-1. Frequency of Sites with Asbestos Contamination



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is known to be of concern in Turkey (Baris et al. 1987; Sebastien et al. 1984) and Cyprus (McConnochie et al. 1987), no quantitative data were located on the amounts of asbestos released to the air from natural sources in the United States.

Table 5-1 summarizes the estimated release of asbestos to air from a variety of asbestos-related industries in the United States (ICF 1988). These values were calculated from measurements of typical asbestos levels in air at each type of operation.

Another source of asbestos release is from clutches and brakes on cars and trucks. This has been estimated to result in emissions of 5 to 10 kkg/yr (Versar 1987). Release of asbestos from insulation or other building materials is discussed in Section 5.4.1, below.

### 5.2.2 Water

Asbestos is released to water from a number of sources, including erosion of natural deposits and waste piles, corrosion from asbestos-cement pipes, and disintegration of asbestos roofing materials with subsequent transport via rainwater into cisterns, sewers, etc. (Millette et al. 1980). Wastewater from asbestos-related industries may also carry significant burdens of asbestos fibers (Stewart et al. 1976). The total amount of asbestos released to water has been estimated to be 50 to 100 kkg/yr (NRC 1984).

### 5.2.3 Soil

Soil may be contaminated with asbestos by the weathering of natural asbestos deposits, or by land-based disposal of waste asbestos materials. While disposal of waste asbestos to landfills was a common practice in the past, current regulations restrict this practice (see Chapters 4 and 7). No data were located regarding the amount of asbestos currently released to soil.

## 5.3 ENVIRONMENTAL FATE

### 5.3.1 Transport and Partitioning

Asbestos fibers are nonvolatile and insoluble, so their natural tendency is to fall out of air and water and be deposited in soil or sediment (Callahan et al. 1979; Fuller 1977). However, some fibers are sufficiently small that they can remain in suspension in both air and water and be transported long distances. For example, fibers with aerodynamic diameters of 0.1 to 1 $\mu$m can be carried thousands of kilometers in air (Janenicke 1980), and transport of fibers over

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## 5. POTENTIAL FOR HUMAN EXPOSURE

**TABLE 5-1. Summary of Asbestos Release from Industrial Sources in the United States**

| Source | Air Releases (kg/yr) |
|---|---|
| Mining | 11 |
| Milling | 4,495 |
| Primary Product Manufacture | 5,676 |
| Secondary Product Manufacture | 1442 |
| Brake repair | 17 |
| Construction | 318 |
| Miscellaneous | 9 |

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75 miles has been reported in the water of Lake Superior (Callahan et al. 1979). Adsorptive interactions between the fibers and natural organic contaminants may favor coagulation and precipitation of the fibers (Bales 1985; Callahan et al. 1979).

### 5.3.2 Transformation and Degradation

#### 5.3.2.1 Air

Asbestos fibers in air are not considered to undergo any significant transformation or degradation (Callahan et al. 1979).

#### 5.3.2.2 Water

Asbestos fibers in water may undergo dissolution of some of the metal ion and hydroxyl ion content, but the basic silicate structure of the fiber remains intact (Choi and Smith 1972; Morgan and Holmes 1986).

#### 5.3.2.3 Soil

Asbestos fibers in soil are not known to undergo significant transformation or degradation.

## 5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

### 5.4.1 Air

The concentration of asbestos fibers in both outside and inside air is of considerable health concern, and numerous measurements have been performed. These studies have reported their results in a variety of units, including ng/$m^3$, TEM f/mL (fibers measured by transmission electron microscopy), and PCM f/mL (fibers measured by phase contrast microscopy). The conversion factors between these units are highly variable, depending on the size and length distribution of the fibers, and no single set of factors will be accurate for all samples. With this limitation in mind, the NRC (1984) suggested that crude approximations could be achieved by assuming that one phase contrast fiber per mL is about equal to 60 transmission electron microscope fibers per mL, and that both are about equal to 30 $\mu g/m^3$. Since the health effects data regarding inhalation exposure to asbestos is usually expressed in terms of phase contrast fibers per mL, ambient air data reported in units of ng/$m^3$ or TEM f/mL are converted to units of PCM fibers/mL using the factors suggested by NRC (1984).

Ambient air, remote from any special sources, is generally found to contain 0.001 to 0.1 ng/$m^3$ of asbestos (3 x $10^{-8}$ to 3 x $10^{-6}$ PCM f/mL) (NRC 1984). In urban areas, most ambient air concentrations range from 0.1 to 10 ng/$m^3$ (3 x $10^{-6}$ to 3 x $10^{-4}$ PCM f/mL), but may range up to

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100 ng/$m^3$ (3 x $10^{-3}$ PCM f/mL) (IARC 1977; Nicholson and Pundsack 1973, 1987; Selikoff et al. 1972). The median concentration in United States cities has been estimated to be 2.3 ng/$m^3$ (7 x $10^{-5}$ PCM f/mL) (NRC 1984). Near industrial operations involving asbestos, levels may be as high as 50 to 5,000 ng/$m^3$ (1.5 x $10^{-3}$ to 1.5 x $10^{-1}$ PCM f/mL) (IARC 1977).

Indoor air is of special concern, because it may become contaminated due to release of asbestos from a variety of building materials such as insulation, ceiling tiles, and floor tiles (Strenio et al. 1984). Measured indoor air values range widely, depending on the amount, type, and condition (friability) of asbestos-containing materials used in the building. In a review of indoor air monitoring data from a variety of locations, Nicholson (1987) reported that arithmetic mean concentrations ranged from 1 to 200 ng/$m^3$ (3 x $10^{-5}$ to 6 x $10^{-3}$ PCM f/mL). In a recent survey performed by EPA (1988c), levels of asbestos in 94 public buildings that contained asbestos ranged from 0 to 0.2 TEM f/mL (0 to 3 x $10^{-3}$ PCM f/mL), with an arithmetic mean concentration of 0.006 TEM f/mL ($10^{-4}$ PCM f/mL). Asbestos concentrations in 41 schools that contained asbestos ranged from 0 to 0.1 TEM f/mL (0 to 2 x $10^{-3}$ PCM f/mL), with an arithmetic mean of 0.03 TEM f/mL (5 x $10^{-4}$ PCM f/mL) (EPA 1988c). In general, direct comparison of levels inside and outside buildings that contain asbestos indicate that typical (nondisturbed) indoor levels are usually about 2- to 3-times higher than outside (Chesson et al. 1990).

### 5.4.2 Water

The concentration of asbestos fibers in water (expressed as million TEM fibers per liter, MFL) ranges widely. Concentrations in most areas are less than 1 MFL (Millette et al. 1979), but values of 1 to 100 MFL and occasionally higher have been detected in areas contaminated by erosion from natural asbestos deposits (Kanarek et al. 1980; Stewart et al. 1976) or from mining operations (Sigurdson et al. 1981).

Release of asbestos from asbestos-cement pipes used in drinking water distribution systems may also be significant in some cases. The amount of asbestos contributed from asbestos-cement pipe is negligible in some locations (Hallenbeck et al. 1978), but may result in concentrations of 1 to 10 MFL at other locations (Kanarek et al. 1981; Craun et al. 1977). The variability in the amount of fibers coming from asbestos-cement pipe appears to depend on a number of parameters, but is mostly related to characteristics of the water such as pH and hardness, which influence the rate at which the water can corrode the pipe (NAS 1982). The large majority of all fibers found in water are chrysotile, and are less than 5 μm in length (Hallenbeck et al. 1978; Millette et al. 1980; Pitt 1988).

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### 5.4.3 Soil

No studies were located regarding the concentration of asbestos fibers that occur in soil. Asbestos was found in about 80% of a number of samples of street dirt, at concentrations ranging from 100 million to 1 billion f/g (Pitt 1988). These were primarily chrysotile fibers and most were less than 2 μm in length. It is likely that the main source of these fibers was from automobile brakes.

### 5.4.4 Other Media

In the past, filters made from asbestos were employed in the preparation of wines, beers and other items consumed by humans, and asbestos concentrations in these materials ranged from 1 to 10 MFL (Cunningham and Pontefract 1973). The use of asbestos filters in food or pharmaceutical preparation has been discontinued in the United States, and intake of asbestos through foods or drugs is now unlikely.

## 5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

As noted above, the concentrations of asbestos found in indoor air, outdoor air and drinking water vary widely, and it is not possible to calculate human exposure levels accurately except on a site-by-site basis. With this limitation in mind, Table 5-2 presents some rough estimates of exposure levels for a general population living in an urban or suburban area, and for asbestos workers. The exposure levels used for the general public are intended to represent the central portion of the typical range of exposures; thus, some persons could be exposed to higher levels, while others could be exposed to less. The workplace air concentration used to estimate worker exposure (0.1 f/mL) is 50% of the current workplace exposure limit. Actual workplace exposures could be higher or lower. Dose of fibers transferred to the gastrointestinal tract following inhalation exposure were calculated using the same assumptions as employed in similar calculations by NAS (1983).

## 5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The populations most likely to have high exposure to asbestos are workers who come into contact with asbestos while on the job. This includes persons involved in the mining and manufacture of asbestos products, and also people who install, service, or use these products. Although recent regulations have resulted in a marked decrease in airborne exposure levels in the workplace, the currently acceptable upper limit in workplace air (0.2 f/mL) is still considerably higher than levels found outside the workplace (usually less than 0.001 f/mL). In the past, workers may have carried asbestos home on their clothing or in their hair, resulting in exposure of family members (Anderson et al. 1979). However, this is not likely to be of concern at the present.

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**TABLE 5-2. Summary of Typical General Population and Occupational Exposures**

| Exposed Population | Exposure Medium | Typical Concentration | Assumed Exposure | Dose | |
|---|---|---|---|---|---|
| | | | | Lungs[a] | GI Tract[b] |
| General population | Ambient (outdoor) air | 1 ng/m$^3$[c] (3.3 x 10$^{-5}$ PCM f/mL) | 20 m$^3$/d, 70 yrs (10% of time outdoors)[d] | 0.0002 f-yr/mL | 0.001 MF/day[e] |
| | Indoor air | 10$^{-4}$ PCM f/mL[f] | 20 m$^3$/day, 70 yrs (90% of time indoors)[d] | 0.006 f-yr/mL | 0.027 MF/day |
| | Drinking water | 1.0 MFL[g] | 2 L/d | - | 2 MF/day |
| Asbestos worker | Workplace air | 0.1 PCM f/mL[h] | 40 yrs, 8 m$^3$/day, 5 days/week, 49 weeks/yr[i] | 1.1 f-yr/mL[j] | 8.1 MF/day[e,k] |

[a]Dose to lungs expressed as phase contrast microscopy (PCM) fibers.

[b]Dose to GI tract expressed as transmission electron microscopy (TEM) fibers (1 PCM fiber assumed to equal 50 TEM fibers) (NAS 1983).

[c]NRC (1984)

[d]Approximate value, based on EPA 1989e.

[e]Assumes 30% of inhaled fibers are transferred to stomach (NAS 1983).

[f]Applies only to buildings containing asbestos building materials.

[g]Millette et al. (1979). Concentration expressed as TEM fibers.

[h]This value is arbitrarily assumed to be one-half of the occupational exposure limit of 0.2 PCM f/mL (OSHA 1986).

[i]NAS (1983).

[j]Expressed in terms of average continuous exposure (20 m$^3$/day, 365 days/yr), rather than in terms of years of occupational exposure (8 m$^3$/day, 5 days/wk, 49 weeks/yr).

[k]Daily dose (12 million fibers/day) adjusted to account for exposure 5 days/week, 49 weeks/yr (NAS 1983).

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# 5. POTENTIAL FOR HUMAN EXPOSURE

People who live near an asbestos-related industry or near an asbestos-containing waste site may encounter higher-than-average levels of asbestos in air. People may also receive higher-than-average exposure from a variety of asbestos-containing products, and from living or working in a building with deteriorating asbestos insulation. Working in a building with asbestos-containing material that is in good condition has not been shown to result in significantly elevated levels of asbestos in air.

Some people may also be exposed to elevated levels of asbestos in drinking water, particularly where there are widespread natural deposits of asbestos (e.g., San Francisco Bay area), disposal of asbestos-containing ore tailings (e.g., Duluth, Minnesota), or the use of asbestos-containing cement pipes in drinking water distribution systems (Craun et al. 1977; Kanarek et al. 1981).

## 5.7 ADEQUACY OF THE DATA BASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of asbestos is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of asbestos.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

### 5.7.1 Identification of Data Needs

**Physical and Chemical Properties.** The physical and chemical properties of asbestos are well characterized (see Chapter 3), and there does not appear to be a need for further research in this area.

**Production, Use, Release, and Disposal.** Asbestos is widely used by humans in a variety of products, and exposures are likely from a number of sources (especially insulation). Extensive data are available on current production, import, and use of asbestos. It is likely that production and use will tend to decrease in the future as new regulations come into effect that ban asbestos in most products and applications. Releases to the environment may occur either to air or to

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soil and water, with releases to air being of greatest health concern. Waste asbestos is regulated as a hazardous substance, so disposal is permitted only in authorized waste sites. However, data are lacking on the amount of asbestos disposal in waste sites, and on the location and status of these sites.

According to the Emergency Planning and Community Right to Know Act of 1986 (EPCRTKA), (§313), (Pub. L. 99-499, Title III, §313), industries are required to submit release information to the EPA. The Toxic Release Inventory (TRI), which contains release information for 1987 and 1988, became available in May of 1989. This database will be updated yearly and should provide a more reliable estimate of industrial production and emission.

**Environmental Fate.** Asbestos fibers are fundamentally rather inert, and are not considered to undergo transport or degradative processes analogous to organic pollutants. Additional studies on the behavior of fibers in water (processes such as change in metal ion and hydroxyl ion composition, adsorption to of organic materials, flocculation and precipitation, etc.) would be helpful in evaluating water-based transport of fibers, as well as in improving methods for removal of fibers from water. Transport of fibers in air is governed by processes and forces which apply to all particulate matter, and these processes are reasonably well-understood.

**Bioavailability from Environmental Media.** Asbestos fibers are insoluble and are not absorbed in the usual sense following inhalation, oral, or dermal exposure. Most exposures occur either to fibers in air or water, so the effect of matrices such as soil or food are largely unknown. It is possible that adsorption of fibers onto other dust particles could influence the location of deposition in the lung, and might even influence the cellular response to the fibers. Research to determine if this occurs and is of biological significance would be helpful.

**Food Chain Bioaccumulation.** No data were located on asbestos levels in the tissues of edible organisms. However, it is not expected that either aquatic or terrestrial organisms will accumulate a significant number of fibers in their flesh. Consequently, food chain bioaccumulation or biomagnification does not appear to be of concern.

**Exposure Levels in Environmental Media.** There have been extensive surveys of asbestos levels in water and air (both outside air and inside air). These studies have revealed that wide ranges of asbestos levels may be encountered, indicating that human exposures can only be estimated on a site-specific basis. However, further studies on the sources of the fibers and key determinants of exposure level would be

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valuable. It is especially important that further studies of asbestos levels in environmental media investigate and report on the size distribution of the fibers, because this is important in evaluating the resultant risk. Few data exist on asbestos levels in soil, especially near waste sites, and more thorough and recent data on this would be helpful in assessing human intake of asbestos near such sites.

**Exposure Levels in Humans.** Asbestos fibers have been detected in many tissues (especially lung and pleura) of exposed people, and low levels can also be detected in urine. However, most data are based on occupationally exposed populations, and human exposure levels near waste sites are not known. Studies of asbestos levels in urine or in autopsy samples from residents near waste sites known to contain asbestos would be helpful in estimating the magnitude of exposure that can result from waste sites.

**Exposure Registries.** No exposure registries for persons environmentally exposed to asbestos were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

Many industries and researchers interested in studying the health effects of asbestos in exposed workers maintain registries of individuals who were exposed to asbestos on the job.

### 5.7.2 On-going Studies

No information was located regarding on-going studies on the stability and migration of asbestos in the environment. The EPA and many state and local agencies are continuing to make measurements of asbestos levels in air and in water in order to identify locations where significant health concerns may be warranted.

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## 6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring asbestos in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify asbestos. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect asbestos in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by a trade association such as the American Society for Testing and Materials (ASTM). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

As discussed in Chapter 3, asbestos is not a single chemical entity, but is the name for a group of six hydrated fibrous polysilicates. Because the toxicity of asbestos appears to be related primarily to fiber number and size, modern analytical methods focus on providing information on these parameters as well as on total amount and mineral type. At present, the number and size distribution of fibers in a sample can only be determined by direct microscopic examination. This may be performed using either light or electron microscopy, as discussed below.

**Light Microscopic Method.** The standard method for measuring asbestos fibers in the workplace is phase contrast optical microscopy (PCM) (NIOSH 1976). Fibers are collected on a filter which is then transferred to a microscope slide where it is dissolved or treated to make it transparent. The residual material is viewed at 400 to 500x under phase contrast, and a fiber is defined as any object whose length is greater than 5 $\mu$m and whose length-to-diameter ratio is 3:1 or greater. Although this method is relatively fast and inexpensive, it cannot distinguish between asbestos and nonasbestos fibers, and it cannot detect fibers shorter than 5 $\mu$m or thinner than 0.25 $\mu$m. Consequently, this method is most useful for analysis of samples that are composed mainly of asbestos, and where a significant fraction of the fibers are large enough to be counted. Recent improvements in filter preparation procedures now allow for viewing at higher magnification (1250x), resulting in a several-fold improvement in sensitivity (Pang et al. 1989). Polarized light microscopy is frequently used for determining the asbestos content of bulk samples of insulation or other building materials (EPA 1988d), however this approach is not used for measuring asbestos in environmental media.

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# 6. ANALYTICAL METHODS

**Electron Microscopic Methods.** Examination of a fiber sample by either scanning electron microscopy (SEM) or transmission electron microscopy (TEM) allows the detection of much smaller fibers than light microscopy, and so more thorough data can be collected on fiber length and diameter distribution. Of these two methods, TEM has greater sensitivity for small fibers, and is the most common method for measuring asbestos in ambient air or inside schools or other buildings. In addition, most modern transmission electron microscopes are equipped with instrumentation that allows examination of individual fibers by electron diffraction or energy dispersive x-ray analysis. This permits determination of the crystalline and elemental composition of the fiber. Thus, reliable distinctions can be made not only between asbestos and nonasbestos fibers, but also between different asbestos mineral classes. Although TEM clearly provides the most information about a fiber sample, TEM methods are relatively slow and costly compared to PCM methods.

Application of either PCM or TEM methods to the determination of asbestos fibers in biological or environmental media requires that the fibers be separated from interfering material and collected on appropriate supports. Methods for preparing biological and environmental samples for microscopy are described below.

## 6.1 BIOLOGICAL MATERIALS

Asbestos fibers are particularly resistant to chemical and thermal degradation, and this property is used to advantage in the analysis of biological materials for asbestos. In most cases, the bulk of the biological material is solubilized by digesting the tissue in strong base (e.g., KOH) or a powerful oxidant (e.g., hypochlorite). The insoluble residue (including the asbestos fibers) is collected by ultracentrifugation or filtration, and may be further cleared of biological material by ashing. In some cases, biological material may be removed by ashing without prior digestion. Residual material is then dispersed and transferred to a suitable support for microscopy. Table 6-1 summarizes several representative studies where these approaches have been applied to a variety of biological materials.

## 6.2 ENVIRONMENTAL SAMPLES

For the analysis of asbestos fibers in air, the sample is drawn through a filter by a vacuum pump (usually at a flow rate of around 1 to 2 liters per minute), and the fibers retained on the filters are examined microscopically. The sensitivity of the methods depends on the volume of air drawn through the filter, and the microscopic method employed. In the workplace, where PCM is the standard method, the theoretical detection limit for a short-term sample (15 min) is around 0.04 PCM f/mL, but may be reduced to 0.001 f/mL using on 8-hour sample

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**TABLE 6-1. Analytical Methods for Determining Asbestos in Biological Materials**

| Sample Matrix | Sample Preparation | Analytical Method | Approximate Detection Limit | Accuracy (% Recovery) | Reference |
|---|---|---|---|---|---|
| Urine | Mix with $H_2O_2$; digest for 20 hr; collect residue on filter | TEM | 0.1 - 0.3 x $10^{-6}$ f/L | No data | Boatman et al. 1983 |
| Urine | Filter through polycarbonate filter; ash filter; wash, collect residue on second filter | TEM | 5 x $10^3$ f/mL | No data | Finn and Hallenbeck 1984 |
| Feces | Dry, ash, dissolve residue in HCl; filter; ash filter, transfer residue to grid | TEM | 0.15 x $10^6$ f/g | 85.5 | Cunningham et al. 1976 |
| Lung tissue | Dry to constant weight; digest with NaOH (90°C); ash residue; collect on Nucleopore filter | TEM | 0.1 x $10^6$ f/g | No data | Wagner et al. 1982a |
| Lung tissue | Digest wet tissue in KOH; wash residue with water, transfer residue to slide | PCM | 5,000 f/g | No data | Whitwell et al. 1977 |
| Tissue sections | Ash on slide; transfer residue to carbon support | TEM | No data | No data | Pooley 1976 |
| Tissue specimens | Predigest in 10% KOH; collect residue by ultra-centrifugation; ash residue, transfer to carbon grids | TEM | 0.2 x $10^5$ f/g | 13-70% | Carter and Taylor 1980 |

TEM = transmission electron microscopy; PCM = phase contrast microscopy.

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(NIOSH 1976). In practice, such low detection limits are not readily achievable, and measured values below 0.1 PCM f/mL should not usually be considered reliable (ASTM 1988). Sensitivity of TEM methods for ambient or indoor air are usually around 0.1 to 1 ng/m$^3$.

A similar approach is used for measuring asbestos in water. A known volume (generally at least one liter) is drawn through a filter, and the filter is then prepared for examination, usually by TEM. Under favorable conditions, concentrations as low as 0.01 MFL can be detected (Anderson and Long 1980). Table 6-2 summarizes several representative methods for the analysis of asbestos in air and water.

## 6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of asbestos is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of asbestos.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

### 6.3.1 Identification of Data Needs

**Methods for Determining Biomarkers of Exposure and Effect.** Reliable methods exist for measuring asbestos fibers in biological tissues and fluids. These methods (based on microscopic examination of fibers remaining after ashing and digestion) are sufficiently sensitive to quantify fiber burden in samples from both control (background) and exposed populations. However, there is considerable variability in the details of sample preparation and this makes inter-study comparisons difficult. For this reason, it would be helpful to develop a standardized method or group of methods for analysis of asbestos in biological materials, similar to the standardized methods for asbestos in air and water. A major limitation to current methods is that lung burdens can only be measured in excised tissue samples. Consequently, it is not possible to measure lung burdens in living persons except by biopsy. Development of some noninvasive method that would permit estimation of asbestos content in vivo would be especially valuable.

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TABLE 6-2. Analytical Methods for Determining Asbestos in Environmental Samples

| Sample Matrix | Sample Preparation | Analytical Method | Sample Detection Limit | Accuracy (% Recovery) | Reference |
|---|---|---|---|---|---|
| Air | Pump air through filter membrane, convert to optically transparent gel | PCM | <0.5 f/mL | ±35% | ASTM 1988 |
| Air | Filtration | PCM | No data | No data | NIOSH 1987a |
| Air | Filtration, mount on carbon film | TEM | <0.04 f/mL | No data | NIOSH 1987b |
| Water | Filter, mount on carbon film | TEM at 20,000X | 0.01 MFL | 100±35 | Anderson and Long 1980 |
| Water | Extract into isooctane from water containing anionic surfactant | Microscope or color spot test | 0.1 MFL | No data | Melton et al. 1978 |
| Water | Filter, mount on carbon film | TEM | No data | No data | WHO 1986 |

PCM = phase contrast microscopy; TEM = transmission electron microscopy.

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**Methods for Biomarkers of Exposure.** There are no chemical analytical methods recognized for measuring asbestos-induced health effects in humans. Clinical methods (x-ray, spirometry) for evaluating effects are discussed in Section 2.5. Development of sensitive and specific chemical or biochemical tests for asbestos-induced effects would be very valuable, especially if preclinical changes could be detected.

**Methods for Determining Parent Compounds and Degradation Products in Environmental Media.** Standardized methods have been established for measurement of asbestos in air and water, since these are the media most likely to lead to human exposure. These methods are sufficiently sensitive to quantify asbestos both at background levels and at levels of health concern. However, the electron microscopic techniques which give the greatest amount of useful data are also the slowest and most costly. Further efforts to reduce the time and cost per analysis would be helpful.

### 6.3.2 On-going Studies

Given the need and financial incentives for improved, faster asbestos analysis, studies are ongoing to improve these areas. Intense activity is underway in the areas of automation and computerization, especially with transmission electron microscopy and analytical electron microscopy.

A major area of concern is the possibility that asbestos fibers carry carcinogens in smoke such as benzidine, N,N-dimethylanaline, and benzo(a)pyrene to cells. Investigations are being carried out to detect such chemical impurities on asbestos fiber surfaces by a technique known as laser microprobe mass analysis (Warner 1988).

Reliability of asbestos analysis should be improved by new regulations requiring accreditation of asbestos-testing laboratories. The National Institute of Science and Technology (formerly the National Bureau of Standards) is conducting programs for accreditation of polarized light microscopy and transmission electron microscopy laboratories.

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# 7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, numerous regulations and advisories have been established for asbestos by various international, national and state agencies. Major regulations and advisories pertaining to asbestos are summarized in Table 7-1.

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# 7. REGULATIONS AND ADVISORIES

**TABLE 7-1. Regulations and Guidelines Applicable to Asbestos**

| Agency | Description | Value | Reference |
|---|---|---|---|
| | **International** | | |
| IARC | Carcinogenic classification | Group 1[a] | IARC 1982 |
| | **National** | | |
| Regulations: | | | |
| a. Air: | | | |
| EPA OAQPS | Hazardous Air Pollutant NESHAP (emissions disposal record-keeping, reporting) | NA | 40 CFR 61 |
| | Proposed revision | | EPA 1989a |
| OSHA | PEL TWA | 0.2 fiber/cc | OSHA 1986, 1988 (29 CFR 1910.1001, 1926.58) |
| | Action level | 0.1 fiber/cc | |
| | Excursion limit (30 minute) | 1 fiber/cc | |
| b. Water: | | | |
| EPA ODW | MCL (Proposed) | $7x10^6$ fibers/L | EPA 1989b |
| EPA OWRS | General permits under NPDES | NA | 40 CFR 122, Appendix D, Table II |
| | General pretreatment regulations for existing and new sources of pollution | NA | 40 CFR 403 |
| c. Nonspecific media: | | | |
| EPA OERR | Reportable quantity | 1 lb | EPA 1985b (40 CFR 302.4) |
| | Reportable quantity (proposed) | 1 lb | EPA 1987a |
| EPA OTS | Prohibition of manufacture and use of certain products and phase out of use in all other products | NA | EPA 1989c (40 CFR 763) |
| | Asbestos Abatement Projects | NA | EPA 1986d |
| | Worker protection rule | | (40 CFR 763 Subpart G) |
| | Asbestos containing materials in schools rule | | EPA 1987b (40 CFR 763) |
| | Health and Safety Reporting Rule | NA | EPA 1988a (40 CFR 716.120) |
| | Toxic Chemical Release Reporting | NA | EPA 1988b (40 CFR 372) |
| FDA | Component of food packaging material | NA | 21 CFR 175 |
| Guidelines: | | | |
| a. Air: | | | |
| ACGIH | TLV TWA[b] | | ACGIH 1986 |
| | Amosite | 0.5 fibers/cc | |
| | Chrysotile | 2 fibers/cc | |
| | Crocidolite | 0.2 fibers/cc | |
| | Other forms | 2 fibers/cc | |

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# 7. REGULATIONS AND ADVISORIES

**TABLE 7-1 (Continued)**

| Agency | Description | Value | Reference |
|---|---|---|---|
| NIOSH | Recommended exposure limit, TWA[b] | 0.1 fiber/cc | NIOSH 1988c |
| b. Water: | | | |
| EPA ODW | MCLG (proposed) | 7 x $10^6$ fibers/L | EPA 1989b |
| EPA OWRS | Ambient water quality criteria Ingesting water and organisms | 3 x $10^{-4}$ fibers/L | EPA 1980 |
| c. Other: | | | |
| EPA | Carcinogenic classification | Group A[c] | IRIS 1988 |
| | Cancer slope factor (inhalation) | 0.23 $(fibers/mL)^{-1}$ | |
| | **State** | | |
| Regulations: | | | |
| a. Air: | Acceptable ambient air concentration | | NATICH 1988 |
| Connecticut | | 0.001 $\mu g/m^3$ (8 hr) | |
| Nevada | | 0.00 | |
| Nevada-Las Vegas | | 1000 fibers/$m^3$ (24 hr) | |
| New York | | 5.0 $\mu g/m^3$ (1 yr) | |
| North Carolina | | 0.0 $\mu g/m^3$ (24 hr) | |
| North Dakota | | 0.0 | |
| Pennsylvania - Philadelphia | | 0.005 $\mu g/m^3$ (1 yr) | |
| South Carolina | | 0.0 $\mu g/m^3$ (24 hr) | |
| Virginia | | 2.0 $\mu g/m^3$ (24 hr) | |
| Massachusetts | | 0.0001 fibers/$cm^3$ (annual)<br>0.0002 fibers/$cm^3$ (24 hr) | MDEQE 1989 |
| b. Water: | Drinking water | | FSTRAC 1988 |
| Kansas | | 7.1 x $10^6$fibers/L | |
| Minnesota | | 7.1 x $10^6$fibers/L | |

[a]Group 1: Sufficient evidence for carcinogenicity in animals and humans.
[b]Fibers greater than 5 µm in length.
[c]Group A: Human carcinogen.

IARC = International Agency for Research on Cancer; EPA = Environmental Protection Agency; OAQPS = Office of Air Quality, Planning and Standards; NESHAP = National Emission Standards for Hazardous Air Pollutants; NA = not applicable; OSHA = Occupational Safety and Health Administration; PEL = Permissible Exposure Limit; TWA = Time-Weighted Average; ODW = Office of Drinking Water; MCL = Maximum Contaminant Level; OWRS = Office of Water Regulations and Standards; NPDES = National Pollutant Discharge Elimination System; OERR = Office of Emergency and Remedial Response; OTS = Office of Toxic Substances; FDA = Food and Drug Administration; ACGIH = American Conference of Governmental Industrial Hygienists; TLV = Threshold Limit Value; NIOSH = National Institute for Occupational Safety and Health; MCLG = Maximum Contaminant Level Goal.

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# 9. GLOSSARY

**Actinolite** -- A type of asbestos in the amphibole group; it is not used commercially, but is a common impurity in chrysotile asbestos.

**Acute Exposure** -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

**Adsorption Coefficient ($K_{oc}$)** -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

**Adsorption Ratio ($K_d$)** -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

**Amosite** -- A type of asbestos in the amphibole group; it is also known as brown asbestos.

**Amphibole** -- The group name for a family of naturally occurring minerals, characterized by a double chain of silicate ions. This group includes the amosite, actinolite, crocidolite, and tremolite forms of asbestos.

**Bioconcentration Factor (BCF)** -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same time period.

**Cancer Effect Level (CEL)** -- The lowest dose of chemical in a study or group of studies which produces significant increases in incidence of cancer (or tumors) between the exposed population and its appropriate control.

**Carcinogen** -- A chemical capable of inducing cancer.

**Ceiling value (CL)** -- A concentration of a substance that should not be exceeded, even instantaneously.

**Chronic Exposure** -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

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# 9. GLOSSARY

**Chrysotile** -- The most common type of asbestos, also referred to as white asbestos.

**Crocidolite** -- A type of asbestos in the amphibole group; it is also known as blue asbestos.

**Developmental Toxicity** -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

**Embryotoxicity and Fetotoxicity** -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

**EPA Health Advisory** -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

**Immediately Dangerous to Life or Health (IDLH)** -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

**Intermediate Exposure** -- Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

**Immunologic Toxicity** -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

**In Vitro** -- Isolated from the living organism and artificially maintained, as in a test tube.

**In Vivo** -- Occurring within the living organism.

**Lethal Concentration($_{LO}$) ($LC_{LO}$)** -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

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**Lethal Concentration($_{50}$) ($LC_{50}$)** -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

**Lethal Dose($_{LO}$) ($LD_{LO}$)** -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

**Lethal Dose($_{50}$) ($LD_{50}$)** -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time($_{50}$) ($LT_{50}$)** -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

**Lowest-Observed-Adverse-Effect Level (LOAEL)** -- The lowest dose of chemical in a study or group of studies which produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

**Malformations** -- Permanent structural changes that may adversely affect survival, development, or function.

**Minimal Risk Level (MRL)** -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

**Mutagen** -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

**Neurotoxicity** -- The occurrence of adverse effects on the nervous system following exposure to a chemical.

**No-Observed-Adverse-Effect Level (NOAEL)** -- That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

**Octanol-Water Partition Coefficient ($K_{ow}$)** -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

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**Permissible Exposure Limit (PEL)** -- An allowable exposure level in workplace air averaged over an 8-hour shift.

**$q_1^*$** -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The $q_1^*$ can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu g/L$ for water, mg/kg/day for food, and $\mu g/m^3$ for air).

**Reference Dose (RfD)** -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

**Reportable Quantity (RQ)** -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

**Reproductive Toxicity** -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

**Short-Term Exposure Limit (STEL)** -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

**Target Organ Toxicity** -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

**Teratogen** -- A chemical that causes structural defects that affect the development of an organism.

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# 9. GLOSSARY

**Threshold Limit Value (TLV)** -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

**Time-weighted Average (TWA)** -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

**Toxic Dose ($TD_{50}$)** -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

**Tremolite** -- A type of asbestos in the amphibole group; it is not used commercially in the United States, but is a common impurity in chrysotile asbestos.

**Uncertainty Factor (UF)** -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of humans, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

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# APPENDIX A

## PEER REVIEW

A peer review panel was assembled for asbestos. The panel consisted of the following members: Dr. Lincoln Polissar, Associate Professor, Department of Biostatistics, University of Washington, Seattle, WA; Dr. Marty Kanarek Associate Professor, Department of Preventative Medicine, University of Wisconsin, Madison, Wisconsin; Dr. Andrew L. Reeves, Professor, Department of Occupational and Environmental Health, Wayne State University, Detroit, Michigan; Dr. Irving Selikoff, Professor Emeritus, Mount Sinai School of Medicine, New York, New York; Dr. Brooke Mossman, Associate Professor, Department of Pathology, College of Medicine, University of Vermont; Dr. Neil Johnson, Experimental Pathologist, Inhalation Toxicology Research Institute, Kirkland Air Force Base, Albuquerque, New Mexico. These experts collectively have knowledge of asbestos's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation and Liability Act, as amended.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.

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# APPENDIX B

## RISK ASSESSMENT SUMMARY

### 1.0 LUNG CANCER

Most studies of the risk of asbestos-related lung cancer in occupationally exposed workers indicate that the dose-response relationship is best described by a relative risk model, given by the equation:

$$\text{Relative Risk} = 1.00 + K_L \cdot (\text{cumulative dose}).$$

Using this equation, EPA (1986a) calculated the value of $K_L$ (the fractional increase in relative risk of lung cancer per f-yr/mL) for a number of epidemiological studies in which quantitative exposure-risk data were available. The resulting values varied widely, ranging from 0.0006 $(\text{f-yr/mL})^{-1}$ (McDonald et al. 1980) to 0.067 $(\text{f-yr/mL})^{-1}$ (Finkelstein 1983). The geometric mean of all the studies was 0.065 $(\text{f-yr/mL})^{-1}$. When studies involving mining and milling were excluded (these were judged to be less typical of the risks likely to be encountered in the environment), the resulting value was 0.010 $(\text{f-yr/mL})^{-1}$. It is important to stress that this relates to fibers measured by phase contrast microscopy, and not to the total number of fibers measured by transmission electron microscopy.

Since this is a relative risk model, the absolute risk of lung cancer due to asbestos exposure depends not only on cumulative asbestos dose, but also on the underlying risk of lung cancer due to other causes:

$$\text{Absolute Risk} = \text{Relative Risk} \times \text{Underlying Risk}$$

Based on national average lung cancer risk data for male and female smokers and nonsmokers, EPA (1986a) calculated that lifetime exposure to 0.0001 f/mL corresponded to the excess lung cancer risks tabulated in Table B-1.

For the purposes of preparing a simplified graphical display of cancer risk levels for presentation in Figure 2-1, risks from males and females were averaged, both for smokers and nonsmokers, and the cumulative doses corresponding to a lifetime lung cancer risk of $1 \times 10^{-4}$ were calculated as shown in Table B-1.

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# APPENDIX

TABLE B-1 Risk Assessment for Asbestos-Associated Lung Cancer

| Parameter | Smokers | | | Nonsmokers | | |
|---|---|---|---|---|---|---|
| | Male[a] | Female[a] | Average[b] | Male[a] | Female[a] | Average[b] |
| Lung cancer risk from lifetime exposure to 0.0001 f/mL | 2.4E-5 | 1.5E-5 | 2.0E-5 | 0.2E-5 | 0.2E-5 | 0.2E-5 |
| Concentration (f/mL) corresponding to lifetime excess risk level of $10^{-4}$ | | | 5.0E-4 | | | 5.0E-3 |
| Cumulative dose (f·yr/mL) for a 70-yr exposure corresponding to $10^{-4}$ risk level | | | 3.5E-2 | | | 3.5E-1 |

[a]Source: EPA(1986a)
[b]Average of males and females

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# APPENDIX

## 2.0 MESOTHELIOMA

Several studies (e.g., Newhouse and Berry 1976; Nicholson et al. 1982; Peto et al. 1982) indicate that the risk of mesothelioma from a given level of exposure to asbestos depends primarily upon the time elasped since exposure (latency), with risk increasing exponentially with time after a lag period of about 10 years. Based on this, EPA (1986a) fit exposure-incidence data from four studies (Finkelstein 1983; Peto 1980; Peto et al. 1982; Seidman 1984) to the following equation:

$$\text{Incidence} = K_M \cdot f \cdot [(T-10)^3-(T-10-d)^3]$$

where:

$K_M$ = empirical constant
f = intensity of exposure (f/mL)
T = latency (years since first exposure)
d = duration of exposure (years)

The resulting values of $K_M$ ranged from $1 \times 10^{-8}$ to $3 \times 10^{-8}$ for three of the studies, with one study (Finkelstein 1983) giving a higher value ($12 \times 10^{-8}$). Based on an analysis of the relative risk of mesothelioma compared to lung cancer in other studies, a value of $1 \times 10^{-8}$ was identified as the most reasonable estimate for $K_M$ (EPA 1986a). Although this value has considerable uncertainty (about a factor of 10), it can be used to make rough predictions of mesothelioma incidence at low exposure levels, similar to those likely to be encountered in the environment. Assuming lifetime continuous exposure to air containing 0.0001 f/mL, the expected incidence is 2 to 3 mesothelioma deaths per 100,000 persons (EPA 1986a), as shown in Table B-2.

For the purposes of preparing a simple graphical presentation of these risk estimates for inclusion in Figure 2-1, the data from all four groups were combined (since there is little difference between males and females or between smokers and nonsmokers), to yield an average $10^{-4}$ risk level of $3.1 \times 10^{-2}$ f-yr/mL.

## 3.0 COMBINED RISK OF LUNG CANCER AND MESOTHELIOMA

The combined risk of lung cancer and mesothelioma has been estimated by EPA (IRIS 1988), based on the risk calculations presented in EPA (1986a). The average unit risk value was calculated as a composite value for males and females. The epidemiological data show that cigarette smoking and asbestos exposure interact synergistically for production of lung cancer and do not interact with regard to mesothelioma. The unit risk value is based on risks calculated using United States general population cancer rates and mortality patterns without consideration of smoking habits. The risks associated with

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APPENDIX

TABLE B-2 Risk Assessment for Asbestos-Related Mesothelioma

| | Smokers[a] | | Nonsmokers[a] | | |
|---|---|---|---|---|---|
| | Male | Female | Male | Female | Average[b] |
| Lung cancer risk from lifetime exposure to 0.0001 f/mL | 1.8E-5 | 2.5E-5 | 2.2E-5 | 2.7E-5 | 2.2E-5 |
| Concentration (f/mL) corresponding to lifetime excess risk level of $10^{-4}$ | | | | | 4.5E-4 |
| Cumulative dose (f·yr/mL) for a 70-yr exposure corresponding to $10^{-4}$ risk level | | | | | 3.1E-2 |

[a]Source: EPA (1986a)
[b]Average of all four groups.

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APPENDIX

occupational exposure were adjusted to continuous exposure by applying a factor of 140/50, based on the assumption of 20 $m^3$/day (140 $m^3$/week) for total ventilation and 10 $m^3$/8-hour workday (40 $m^3$/week) in the occupational setting. The results of these calculations indicate that a concentration of 4E-4 f/mL corresponds to a lifetime excess risk level of $10^{-4}$. This combined risk estimate was not presented in Figure 2-1, since both the text and the Figure deal with lung cancer and mesothelioma separately.

## 4.0 GASTROINTESTINAL CANCER

### 4.1 Risk Estimate Based on Animal Data

In a lifetime feeding study in rats, exposure to intermediate length chrysotile fibers lead to an increased incidence of intestinal polyps (NTP 1985). Based on these data, EPA (1985b) calculated that the $10^{-4}$ risk level corresponded to an asbestos concentration of 7.1 x $10^8$ f/L in drinking water.

In order to present this risk estimate in Figure 2-2, the concentration of 7.1 x $10^8$ f/L was converted to a dose of 2.0 x $10^7$ f/kg/day (assuming ingestion of 2 L/day by a 70-kg adult), and this was converted to a dose of 0.16 mg/kg/day by dividing by 0.129 x $10^9$ f/mg (reported in NTP 1985).

### 4.2 Risk Estimate Based on Human Inhalation Data

Since there are no human studies in which ingestion of a known amount of asbestos can be associated with a clear increase in gastrointestinal cancer risk, NAS (1983) extrapolated data on gastrointestinal risk from epidemiological studies of workers exposed to asbestos by inhalation. These calculations indicated that lifetime ingestion of 1.1 x $10^6$ TEM fibers/liter of water corresponded to an excess gastrointestinal cancer risk of $10^{-4}$ (NAS 1983).

In order to present this risk estimate in Figure 2-2, the concentration of 1.1 x $10^6$ f/L was converted to a dose of 3.1 x $10^4$ f/kg/day (assuming ingestion of 2 L/day by a 70-kg adult), and this was converted to a dose of 1.6 x $10^{-5}$ mg/kg/day by multiplying by a factor of 5.0 x $10^{-10}$ mg/TEM fiber (NRC 1984).

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