DRAFT

For Review Only

Public Health Goal for

ASBESTOS

In Drinking Water

NOT A REGULATORY STANDARD

Prepared by

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PREFACE

Drinking Water Public Health Goals

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This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365), amended 1999, requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and publish PHGs for contaminants in drinking water based exclusively on public health considerations. Section 116365 specifies that the PHG is to be based exclusively on public health considerations without regard to cost impacts. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based upon currently available data and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.

9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.

10. PHGs published by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs published by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA Web site at www.oehha.ca.gov.

TABLE OF CONTENTS

LIST OF CONTRIBUTORS ..... **II**

PREFACE ..... **III**

TABLE OF CONTENTS ..... **V**

PUBLIC HEALTH GOAL FOR ASBESTOS IN DRINKING WATER **1**

SUMMARY **1**

INTRODUCTION **2**

CHEMICAL PROFILE **4**

Chemical Identity and Properties 5

Fiber Characterization 6

Production, Import and Export 7

Production 7

Import and Export 8

Uses and Disposal 8

Uses 8

Disposal 9

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE **12**

Air 12

Soil 13

Water 13

Food and Other Sources 16

METABOLISM AND PHARMACOKINETICS **16**

Absorption 17

Study Limitations 18

Distribution 18

Metabolism 21

Excretion 21

TOXICOLOGY **21**

Toxicological Effects in Animals 22

Acute, Subacute, and Chronic Noncancer Effects 22

Immunological and Lymphoreticular Effects 25

Neurological Effects 26

Reproductive Effects 27

Developmental Effects 27

Genotoxicity 27

Cancer 32

Toxicological Effects in Humans: Oral Exposure 38

Acute, Subacute, and Chronic Noncancer Effects 38

Cancer 38

Toxicological Effects in Humans: Inhalation and Other Exposures 41

Acute, Subacute, and Chronic Noncancer Effects 41

Immunological and Lymphoreticular Effects 42

Genotoxicity 43

Cancer 44

DOSE-RESPONSE ASSESSMENT **46**

Noncarcinogenic Effects 46

Carcinogenic Effects 47

CALCULATION OF PHG **49**

Noncarcinogenic Effects 49

Carcinogenic Effects 50

Risk Estimate Based on Human Inhalation Data 50

Risk Estimate Based on Animal Data 51

RISK CHARACTERIZATION **52**

REGULATORY STANDARDS **54**

Maximum Contaminant Level (MCL) and Drinking Water Standards 54

Other Regulatory Standards 54

REFERENCES **56**

PUBLIC HEALTH GOAL FOR ASBESTOS IN DRINKING WATER

SUMMARY

A public health goal (PHG) of 7 million fibers per liter (MFL) or 7×10^6 fibers/L is proposed for asbestos in drinking water. The proposed PHG follows the approach of the United States Environmental Protection Agency (U.S. EPA), which was based on tumorigenic effects observed in experimental animals. An increased incidence of benign adenomatous polyps of the large intestine was observed in male Fischer 344/N rats exposed to chrysotile asbestos fibers, 65 percent of which were greater than 10 micrometer (μm) in length, in a lifetime diet study performed by the National Toxicology Program (NTP, 1985). This is supported by epidemiological data on risk of gastrointestinal tumors after inhalation exposures, as evaluated by the National Academy of Sciences (NAS, 1983). The potential for tumorigenic effects is also supported by findings of genotoxicity in bacterial and mammalian systems both *in vitro* and *in vivo* (IARC, 1996; NTP, 2000).

The voluminous body of evidence that exposure to asbestos through inhalation increases the risk of lung cancer and mesothelioma in humans and animals (ATSDR, 1995; Cantor, 1997; IARC, 1996; IPCS, 1998; Kang *et al*., 1997; U.S. EPA, 2000) substantiates the overall assessment of human carcinogenicity of asbestos. The Office of Environmental Health Hazard Assessment (OEHHA) concurs with the U.S. EPA and the NAS that all the data mentioned above contribute to the overall weight of evidence for asbestos carcinogenicity.

For the calculation of the proposed PHG, oral cancer potency estimates developed by the U.S. EPA (1985b) were used. It is plausible that the true value of the human oral cancer potency for asbestos in drinking water has a lower bound of zero based on statistical and biological uncertainties. Part of this uncertainty is due to limited suggestive evidence to support a genotoxic mechanism. However, due to the absence of specific scientific information explaining why the animal tumors are irrelevant to humans at environmental exposure levels, a standard health-protective approach was taken to estimate cancer risk. The cancer potency estimate derived from the cancer slope factor (CSF) of the male rat intestinal polyps was 1.4×10^{-13} $(\text{fibers/L})^{-1}$. The proposed PHG was calculated assuming a *de minimis* theoretical excess individual cancer risk level of 10^{-6} (one in a million) from exposure to asbestos. Based on these considerations, OEHHA proposes a PHG for asbestos in drinking water of 7 MFL, which is the same value as the Maximum Contaminant Level (MCL) established by the U.S. EPA (1991a). The proposed PHG is considered to provide an adequate margin of safety for all the noncarcinogenic effects of asbestos, including potential genotoxicity and adverse effects on the gastrointestinal system, immune system, kidney, and body weight.

INTRODUCTION

This document examines available data and evidence on the toxicity of asbestos for establishing a proposed public health goal (PHG) for asbestos in drinking water. The U.S. EPA, in its drinking water criteria documents (U.S. EPA, 1985a; 1985c) and an evaluation of the available literature for the 1993 updates of the Integrated Risk Information System (IRIS) database (U.S. EPA, 2000), concluded that inhalation of asbestos increases the risk of lung cancer and mesothelioma in humans and animals. Human data on asbestos ingestion exposure was considered to be suggestive of carcinogenicity. Data from the National Toxicology Program (NTP) animal studies on ingestion exposure provided "some evidence" of carcinogenicity for intermediate-range [65 percent greater than 10 micrometers (μm) and less than 14 percent greater than 100 μm] chrysotile fibers, but not for short-range (98 percent smaller than 10 μm) chrysotile fibers (NTP, 1985; 1990a). The National Academy of Sciences (NAS, 1983) and the Agency for Toxic Substances and Disease Registry (ATSDR, 1995) also made similar conclusions based on tumorigenic effects observed in experimental animals in the NTP studies (1985).

Asbestos is a generic term used to describe a group of six different types of naturally occurring hydrated silicate minerals that crystallize in fibrous habit: amosite, chrysotile, crocidolite, and the fibrous varieties of tremolite, actinolite, and anthophyllite. The three most common types are chrysotile, amosite, and crocidolite. Asbestos is composed of silicon, oxygen, hydrogen, and various positively charged metal ions. The basic unit of asbestos minerals is the silicate group (SiO_4). The U.S. EPA (1985c) and other regulatory agencies have considered that fibers with an aspect ratio (ratio of length to width) greater than three to one should be regulated, although this definition has been criticized (Skinner *et al*., 1988). Asbestos fibers are resistant to heat and most chemicals. These properties make asbestos useful for insulation, friction products, and a variety of other products. Asbestos may have been so widely used because few other available substances combine the same qualities. However, asbestos mining and use has been greatly decreased in the U.S. due to the potential health hazards of this mineral.

Contamination of municipal drinking water occurs in three ways: through industrial contamination of source water, natural contamination of source water, and the use of asbestos-cement distribution pipes. Industrial contamination occurred in Duluth, Minnesota when taconite mine tailings were dumped into the source water, exposing a city of 100,000 population for over 25 years. Natural contamination occurs in the San Francisco Bay area and in parts of Washington State where source waters flow through serpentine rock formations. Asbestos-cement distribution pipe contamination has been studied in Florida and New York.

Inhalation of asbestos fibers has been clearly associated with lung cancer and mesothelioma. This finding led to the U.S. EPA's intention to ban new uses of asbestos in the U.S. by 1997; however, a federal court overturned the regulation (U.S. EPA, 1989) in October 1991. It is still legal to manufacture, process, and import most asbestos products. Fibers are defined as having an aspect ratio of three to one or greater (U.S. EPA, 1985c). Longer fibers are considered to have greater toxicity (Winner and

Cossette, 1979). The U.S. EPA (2000) lists asbestos as a Group A human carcinogen through the inhalation exposure route on its IRIS database. The International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) lists asbestos as a Group 1 human carcinogen through inhalation (IARC, 1973, 1977, 1987).

Recent comprehensive reviews have described in detail the histopathological and clinical features of asbestos related diseases (Kamp and Weitzman, 1999). Asbestos is an established genotoxic and carcinogenic agent that can induce DNA damage, gene mutation, gene transcription, and protein expression in modulating cell proliferation, apoptosis, inflammation, and cell death (IARC, 1996; McDonald, 1998). Evidence implicating various pathways of asbestos-induced diseases includes: 1) the chemical and structural properties of the fibers, 2) the lung fiber burden, 3) fiber uptake by pulmonary epithelial cells, 4) iron-catalyzed free radicals, 5) DNA damage, 6) alterations in cytokines, growth factors, and other inflammatory cell products, and 7) interactions with cigarette smoke and other carcinogens in the environment (Kamp and Weitzman, 1999).

The toxicity of ingested asbestos fibers is less certain. Many animal studies have been inconclusive or negative for ingested asbestos. The NTP (1985) animal studies showed increased benign adenomatous polyps of the large intestine after oral exposure to intermediate-range chrysotile fibers, 65 percent of which were greater than 10 μm in length. A parallel NTP (1985; 1990a) study of short-range fibers, 98 percent of which were shorter than 10 μm in length, did not produce a response in male or female rats. The results for intermediate-range fibers were not statistically significant compared with the concurrent controls. However, the incidence of the neoplasms was highly significant when compared with the incidence of combined benign and malignant epithelial neoplasms of the large intestine of the pooled control groups of all the NTP oral asbestos lifetime studies. The NTP has interpreted the animal studies as providing "some evidence" of carcinogenicity for intermediate-range fibers.

Human studies of ingested asbestos have yielded conflicting results. Some ecological mortality follow-up studies have yielded evidence of carcinogenicity at intermediate stages in the follow-up; none, however, have shown statistically significant evidence of carcinogenicity at the conclusion of the follow-up period. Reviews evaluating the human ingestion epidemiology studies have concluded that it would be impossible for any of the ecological studies to have sufficient power or control over extraneous factors to establish convincing evidence of carcinogenic effect from asbestos consumption through water supply contamination. Therefore, the human evidence of toxicity from ingested asbestos does not appear to be useful in establishing drinking water standards or public health-protective concentrations of asbestos fibers in drinking water.

Given a lack of usable human data on the risk of asbestos ingestion, risk evaluators have turned to two other sources of information: human occupational inhalation studies focusing on gastrointestinal tract cancer, and animal studies of ingested asbestos. Each approach requires extrapolation, either across exposure modality or across species. The use of the occupational inhalation studies assumes that a certain percentage of inhaled particles is cleared from the lungs and swallowed and that gastrointestinal tract cancer is the appropriate endpoint.

The NAS (1977, 1983) evaluated five occupational inhalation studies under the assumption that 30 percent of inhaled particles are cleared and swallowed. Further adjustments were made to transform occupational workday exposures to the exposures anticipated from consumption of contaminated drinking water. Based upon the inhalation studies and the assumptions made to allow transformation to approximate ingestion exposures, the NAS established a 10^{-6} risk level as 0.01 MFL or 1×10^{4} fibers/L for excess cancer risk. However, the NAS (1984) concluded "the association of asbestos with an increased risk of malignancies other than lung cancer and mesothelioma has not been confirmed in animal studies and has not been observed consistently in human studies."

The U.S. EPA (1991a) Science Advisory Board stated that "given the positive signal seen in some epidemiologic studies, plus well-documented evidence for the association between asbestos fiber inhalation and lung cancer, it is hard for the Committee to feel comfortable in dismissing the possibility of an increased risk of gastrointestinal cancer in humans exposed to asbestos fibers from drinking water." The U.S. EPA (1991a) has treated asbestos as a Category II contaminant and established a primary drinking water standard Maximum Contaminant Level (MCL) of 7 MFL for asbestos fibers exceeding 10 μm, as identified by X-ray diffraction and quantified by transmission electron microscopy (TEM) (U.S. EPA, 1985b). The non-enforceable MCL Goal (MCLG) based mainly on evaluation of health effects is also set at 7 MFL by the U.S. EPA (1991a). The ATSDR (1995) used animal toxicology data to establish a 10^{-6} risk level as 7.1 MFL for excess cancer risk.

OEHHA was unable to establish an audit trail on the figures used by NAS (1977, 1983, 1984) in their calculation of 0.01 MFL as the 10^{-6} excess cancer risk level, and considers the quantitative evaluation of cancer risk from the human data used by NAS to be problematic. OEHHA supports the U.S. EPA's approach as more appropriate for deriving a PHG for ingested asbestos in municipal drinking water. The U.S. EPA (1991a) and approximately nine states have set either 7 or 7.1 MFL as a drinking water standard (ATSDR, 1995). According to statute (HSC 116365), OEHHA "may review, and adopt by reference, any information prepared by, or on behalf of, the United States Environmental Protection Agency for the purpose of adopting a national primary drinking water standard or maximum contaminant level goal when it establishes a California maximum contaminant level or publishes a public health goal."

In this document, we evaluate the available data on asbestos toxicity, with a primary focus on the oral exposure literature that is deemed most appropriate to establish a PHG for drinking water. The studies that can be used to identify public health-protective levels are reviewed and evaluated; many studies on other aspects of asbestos toxicity not directly applicable are not cited. Portions of this document are abstracted from "Toxicological Profile for Asbestos Update" (ATSDR, 1995) as well as "Drinking Water and Health, Volume 5" (NAS, 1983).

CHEMICAL PROFILE

Asbestos is the general name applied to a group of six different fibrous minerals that occur naturally in the environment, including the three most common types: chrysotile, amosite, and crocidolite; and the fibrous varieties of tremolite, actinolite, and

anthophyllite. Nonasbestos, nonfibrous forms of tremolite, actinolite, and anthophyllite with similar physical and chemical properties as asbestos are also found naturally. Asbestos can be found naturally in both soil and rocks in some areas. The most common asbestos mineral type is white chrysotile; other types include blue crocidolite, gray anthophyllite, and brown amosite. Other natural mineral fibers that may be considered potentially hazardous because of their physical and chemical properties similar to asbestos are erionite, wollastonite, attapulgite and sepiolite.

The asbestos minerals are made up of fibers that vary in length and may be straight or curled. Asbestos fibers do not have any detectable odor or taste. Asbestos fibers are resistant to heat and most chemicals. The major properties of concern for commercial uses are length, granular content, degree of openness or effective surface area, surface charge, drainage or filtration rate, color, absorption, electrical resistivity, bulk density, and tensile strength. Because of these properties, asbestos fibers have been mined for use in a wide variety of man-made products, mostly in building materials, friction products such as brake shoes, and heat-resistant fabrics. Asbestos content of products is not necessarily an indication of its relative health risk, for in many products fibers are tightly bound to the matrix or encapsulated. Potential health risks arise when asbestos fibers are set free, for example during drilling or sawing of asbestos cement sheets (HSDB, 2000), or when asbestos-reinforced concrete pipe releases fibers into the water.

Chemical Identity and Properties

Asbestos is a generic term for a class of six naturally-occurring hydrated fibrous minerals with a basic unit of the silicate SiO_4 group. This group can form a variety of polymeric structures through formation of Si-O-Si bonds. Asbestos fibers are generally white, gray, green, or brown fibers. They have exceptional tensile strength, and are moldable with varying textures and degrees of flexibility (ATSDR, 1995). Table 1 lists common synonyms and other pertinent identification information for generic asbestos and the six individual asbestos minerals (ATSDR, 1995).

Asbestos is divided into two groups, namely, serpentine and amphibole. Serpentine asbestos is the mineral chrysotile, also called white asbestos. Serpentine is the most common form of asbestos. Chrysotile is a magnesium silicate with strong, flexible fibers. It is possible to spin the longer serpentine fibers. For the serpentine class, the polymeric form is an extended sheet. This extended sheet tends to wrap around itself, forming a tubular fiber structure. These serpentine fibers are usually curved in contrast to the straight morphology of the amphiboles.

Amphibole asbestos includes various silicates of magnesium, iron, calcium, and sodium. Subdivisions of amphibole asbestos include five species identified as actinolite, amosite, anthophyllite, crocidolite, and tremolite. Crocidolite is also called blue asbestos, while amosite is also called brown asbestos. For the amphibole class of asbestos, the polymeric structure consists of a linear double chain. These chains crystallize into long, thin, straight fibers, which are the characteristic structure of this type of asbestos.

Table 2 summarizes the physical and chemical properties of the six asbestos minerals (ATSDR, 1995). Asbestos fibers are basically inert chemically, or nearly so. They are

noncombustible and conduct heat poorly. They are odorless, and do not evaporate, dissolve, burn, rot, or undergo significant reactions with most chemicals. It is these properties that have made asbestos so useful, with modern industrial use dating from about 1880 when the Quebec chrysotile fields began to be exploited (IARC, 1977). Asbestos fibers are resistant to acids, bases, and high temperature; only chrysotile is not stable in acids and hydroxides (HSDB, 2000). In tissues, chrysotile fibers are more soluble than amphiboles, which tend to remain intact (ATSDR, 1995). However, case studies of chrysotile asbestos and related lung cancer cases show fibers 40 years after exposure. Asbestos is nonbiodegradable and environmentally cumulative (HSDB, 2000).

Asbestiform refers to a group of natural fibrous minerals comprised of fibrous clays and other fibrous silicates. Fibrous clays include attapulgite and sepiolite. Attapulgite is also named palygorskite. Other fibrous silicates include wollastonite, nemalite, talc, and zeolites. Nemalite is also named fibrous brucite. Zeolites can be divided into erionite and mordenite. These materials have characteristics and biological activities similar to asbestos (Bignon, 1989).

Fiber Characterization

Fiber characteristics make for differences in toxicity and potency. In general, fibers that are long and thin appear to be more carcinogenic than fibers that are short and thick (Stanton *et al*., 1977). The full characterization of asbestos fiber in a test sample is an essential step in the understanding of the mechanisms of fiber carcinogenesis. The consensus report (IARC, 1996) prepared by the group of invited experts convened at IARC in 1996 provided an in-depth review of the parameters necessary for fiber characterization and the methodology needed to obtain these data.

The only analytical method approved by the U.S. EPA (1991a) to comply with the federal drinking water monitoring requirements beginning December 31, 1995, is the use of transmission electron microscopy (TEM) for quantification, together with X-ray diffraction for identification. The accuracy of this method is sensitive to the quality of the water sample and to the presence of interfering substances. U.S. EPA (1985b, 1991a) has determined that TEM is the best available technique because of its ability to differentiate chrysotile from amphibole asbestos fibers, its effectiveness in distinguishing between asbestos and nonasbestos fibers, and its ability to determine the number of fibers per volume and quantitate both length and width of the fibers. U.S. EPA (1991a) established the MCLG for asbestos based on assessments using data from TEM analyses.

The physico-chemical and structural properties of fibers, such as surface charge, solubility, surface chemistry, surface area, dimensions, aspect ratio, size distribution, exposed surface, chemical composition, etc., are generally considered to be the primary determinants of their biological effects (Bonneau *et al*., 1986; Fubini, 1996). Measurements of dimensions are best accomplished by TEM. The carcinogenic potential of a fiber is associated with the length and aspect ratio of the fiber (U.S. EPA, 1985c). Crystallinity and the type of exposed crystal faces determine reactivity and solubility, and consequently, biopersistence. Micromorphology such as surface irregularities, indenting, steps, kinks, and edges also affect reactivity, durability, and solubility (Kane, 1996).

The chemical composition of a fiber determines its adsorption of exogenous or endogenous materials, its potential for free-radical generation at the solid-liquid interface, its potential for the mobilization of metal ions by endogenous chelators, and its propensity for selective leaching. The free radicals may cause reactive oxygen/nitrogen species formation, DNA damage and lipid peroxidation (Kane, 1996). Asbestos can stimulate cells to generate reactive oxygen species via reactions mediated by iron present on the surface of asbestos. This transition metal catalyzes the reduction of hydrogen peroxide to generate hydroxyl radical, and the hydroxyl radical can damage various cellular components, causing DNA strand breaks, protein modification, and lipid peroxidation (Fubini and Mollo, 1995). Asbestos can trigger a number of molecular and cellular events via reactions mediated by reactive oxygen species, including pro-inflammatory cytokine expression, enhanced toxicity, development of asbestosis, and carcinogenesis (Ding *et al*., 1999; Jaurand, 1997).

Production, Import and Export

Because asbestos fibers may produce adverse health effects in exposed persons, the U.S. EPA (1989) published a final rule of commerce prohibitions in manufacture, importation, processing, and distribution in 1989 (40 CFR Part 763, Subpart I). The rule would have banned by 1997 about 94 percent of the new uses of asbestos in the U. S. based on 1985 estimates. Uses established before July 12, 1989 would still be allowable. However, in 1991, the U.S. Court of Appeals, Fifth Circuit, vacated and remanded the majority of the rule. Currently, the manufacture, importation, processing and distribution of most asbestos-containing products is still legal. Proper destruction and disposal of these asbestos-containing products are required under regulations.

Production

The asbestos mineral is mined or quarried with its parent rock. Historical records show that asbestos has been known for more than 2,000 years. Chrysotile, amosite, and crocidolite are the asbestos species of major commercial significance (HSDB, 2000). Chrysotile is the predominant form of asbestos in international commerce and accounts for 99 percent of current world production of 2 million tonnes (Landrigan *et al*., 1999). The production volume of asbestos in the U.S. has decreased substantially from peak production of over 299 million pounds (about 136,000 metric tons) estimated in the late 1960s and early 1970s (SRI, 1982), to 112 million pounds (about 51,000 metric tons) estimated in 1987, 37 million pounds (about 17,000 metric tons) estimated in 1989, to a low of 15,000 metric tons estimated in 1993 (HSDB, 2000; U.S. Bureau of Mines, 1994).

In the U.S., asbestos was commercially mined and milled in California, Arizona, North Carolina, and Vermont, but many of these companies suspended asbestos mining operations in the 1970s (HSDB, 2000). Over 30 million tons of asbestos have been mined, processed, and applied in the U.S. since the early 1900s (Kamp and Weitzman, 1999). In 1985, three U.S. companies produced asbestos fibers including Calaveras Asbestos, Ltd., Calaveras County, California; KCAC, Inc., San Benito County, California; and Vermont Asbestos Group, Orleans County, Vermont. By 1991, only two

firms produced asbestos, one each in California and Vermont (U.S. Bureau of Mines, 1994).

In the U.S., asbestos was primarily 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 was 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 (U.S. EPA, 1988).

Sales of chrysotile asbestos have significantly decreased in Northern America and Western Europe because of widespread recognition of its health hazards. However, asbestos sales remain strong in Japan and across Asia as well as in developing countries worldwide (Landrigan *et al*., 1999).

Import and Export

Most asbestos used in the U.S. is imported. Imports from 1950 to 1974 varied from about 1,287 million pounds to 1,580 million pounds (about 585,000 to 718,000 metric tons) per year. During the late 1970s, imports began decreasing, with a sharp drop after 1980. By 1984, imports were down to 462 million pounds estimated (about 210,000 metric tons), to 81 million pounds (about 35,000 metric tons) estimated by 1991, and to 33,000 metric tons estimated in 1993. Most asbestos, about 98 percent, imported to this country came from Canada, but about one percent was imported from South Africa (ATSDR, 1995).

Exports of asbestos were small until the mid-1960s, when a significant increase in exports occurred. In recent years, export volumes have generally decreased from 132 million pounds (about 60,000 metric tons) estimated in 1987 to 48 million pounds (about 22,000 metric tons) estimated in 1991 (SRI, 1982; U.S. Bureau of Mines, 1992; 1994). Exports then increased to an estimated 32,000 metric tons in 1993, mainly as asbestos-containing finished products.

Uses and Disposal

Uses

It is estimated that asbestos, almost exclusively chrysotile, has been used in over 3,000 different products in the U.S. as well as worldwide. Chrysotile accounts for over 95 percent of world asbestos consumption (Kamp and Weitzman, 1999). The largest use is in asbestos cement for products such as pipes, ducts, and flat and corrugated sheets. Asbestos is widely used in manufactured goods in construction, mostly roofing shingles, ceiling, and floor tiles, and asbestos cement sheets are used in a wide variety of construction applications. Other main uses have been in paper products, friction

products, fire-resistant textiles, packings and gaskets, coatings, and asbestos-reinforced plastics. There have also been numerous other miscellaneous uses. Pipe products are used in water supply, sewage disposal, and irrigation systems (HSDB, 2000).

The U.S. used approximately six percent of the world production of asbestos in 1982. Reported consumption of asbestos in the U.S. was 790 million pounds (about 359,000 metric tons) in 1980, 497 million pounds (about 226,000 metric tons) in 1984, 185 million pounds (about 84,000 metric tons) in 1987, 81 million pounds (about 35,000 metric tons) in 1991, and 33,000 metric tons in 1994 (SRI, 1982; U.S. Bureau of Mines, 1992, 1994). In 1993, 30 percent of the total apparent asbestos consumption was used for friction products such as automobile clutch, brake, and transmission components, with five percent used for asbestos-cement pipe, 50 percent for roofing products, 10 percent for packing and gaskets, and five percent for other uses (U.S. Bureau of Mines, 1994). Approximately 99 percent of asbestos used in the U.S. in 1993 was chrysotile (ATSDR, 1995; U.S. Bureau of Mines, 1994). In Europe, asbestos consumption in 1994 ranged between 0.004 kg per capita in Northern Europe and 2.4 kg in the former Soviet Union (Albin *et al*., 1999).

The Consumer Product Safety Commission (CPSC) banned general use garments containing asbestos in 1978. However, the use of asbestos in special garments such as fire fighting suits is permitted if they are constructed so that asbestos fibers will not become airborne under normal conditions of use (HSDB, 2000). At present, only asbestos-containing products that were not being manufactured, imported, or processed on July 12, 1989 are subject to the prohibition requirements of the U.S. EPA (1992a) regulation.

The largest use of asbestos is in asbestos cement for products such as pipes, ducts, and flat and corrugated sheets. Pipe products are used in water supply, sewage disposal, and irrigation systems. Asbestos cement sheets are used in a wide variety of construction applications. Other uses of asbestos include fire resistant textiles, friction materials such as brake linings, underlayment and roofing papers, and floor tiles (HSDB, 2000). Substitutes for asbestos are constantly being developed (U.S. EPA, 1989). Nonasbestos friction materials are currently being used in disk brake pads, and substitutes are being developed for drum brake linings. Primary substitutes include semi-metallic materials for disc brakes and nonasbestos organics (e.g., fiberglass, para-aramid, mineral fibers, steel wool and fibers, and resins) for brake drums. Since it is not possible to use asbestos safely, safer substitutes should be considered for all uses (Landrigan *et al*., 1999).

Disposal

Currently, asbestos-containing wastes may only be deposited in landfills that are approved and regulated by the federal government. Regulations include wetting or using dust suppression agents, covering with at least 15 centimeters (about six inches) of nonasbestos-containing material, and deterring public access with a fence or natural barrier (U.S. EPA, 1990). 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.

Table 1. Chemical Identity of Asbestos

Characteristic	Asbestos	Chrysotile	Actinolite	Amosite	Anthophyllite	Crocidolite	Tremolite
Synonyms	No data	Serpentine asbestos, white asbestos	No data	Mysorite, brown asbestos, fibrous cummingtonite/ grunerite	Ferroanthophylliteaz bolen asbestos	Blue asbestos	Silicic acid, calcium magnesium salt (8:4)
Trade name	No data	Avibest; Cassiar AK, Calidria RG 144, Calidria RG 600	No data	No data	No data	No data	No data
Chemical formula	No data	$Mg_3Si_2O_5(OH)_4$	$[Ca_2(Mg,Fe)_5 Si_8O_{22}(OH)_2]_n$	$[(Mg,Fe)_7Si_8 O_{22}(OH)_2]_n$	$[(Mg,Fe)_7Si_8 O_{22}(OH)_2]_n$	$[NaFe_3^{2+}Fe_2^{3+} Si_8O_{22}(OH)_2]_n$	$[Ca_2Mg_5Si_8O_{22} (OH)_2]_n$
Chemical structure	N/A	Extended sheet	Double chain	Double chain	Double chain	Double chain	Double chain
Identification numbers:							
CAS registry	1332-21-4	12001-29-5	13768-00-8	12172-73-5	17068-78-9	12001-28-4	14567-73-8
NIOSH RTECS	CI6475000	GC2625000	AUO550000	BT6825000	CA8400000	GP8225000	XX2095000
DOT/UN/NA/ IMCO shipping	IMCO 9.0 UN2212	IMCO 9.3 UN2590	No data	No data UN2212	No data	No data UN2212	No data
HSDB	511	2966	No data	2957	No data	No data	4212
NCI	CO8991	C61223a	No data	No data	No data	CO9007	CO8991

Abstracted from ATSDR (1995), Table 3-1; sources: HSDB (2000); IARC (1977); U.S. EPA (1985b).
CAS = Chemical Abstract Service; 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; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances.

Table 2. Physical and Chemical Properties of Asbestos Materials

Property	Chrysotile	Actinolite	Amosite	Anthophyllite	Crocidolite	Tremolite
Molecular weight[a]	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Color	White, gray, green, yellowish	No data	Brown, gray, greenish	Gray, white, brown-gray, green	Lavender, blue, green	White to light green
Physical state	Solid	Solid	Solid	Solid	Solid	Solid
Melting point/decomposition temperature	800-850°C	No data	600-900°C	950°C	800°C	1,040°C
Specific gravity	2.55	No data	3.43	2.85-3.1	3.37	No data
Solubility: Water Organic solvents Acids[b] Bases[b]	 Insoluble Insoluble 56.00 1.03	 Insoluble Insoluble No data No data	 Insoluble Insoluble 12.00 6.82	 Insoluble Insoluble 2.13 1.77	 Insoluble Insoluble 3.14 1.20	 Insoluble Insoluble No data No data
Isoelectric point	11.8	No data	5.2-6.0	No data	No data	No data
Electrical charge at neutral pH	Positive	No data	Negative	Negative	Negative	No data
Length distribution in UICC reference samples % > 1 μm % > 5 μm % > 10 μm	36-44 3-6 1-3	No data No data No data	46 6 1	46 5 1	36 3 0.7	No data No data No data
Flammability limits	Nonflammable	Nonflammable	Nonflammable	Nonflammable	Nonflammable	Nonflammable

Abstracted from ATSDR (1995), Table 3-2; sources: HSDB (2000); IARC (1977); NAS (1977); SRI (1982); U.S. EPA (1980, 1985b).
[a]All forms of asbestos are indefinite polymers.
[b]Percent loss in weight due to loss of counter-ions; silicate structure remains intact.

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Asbestos is widely distributed in the earth's crust. Chrysotile, which accounts for more than 95 percent of the world asbestos trade, is exploited in more than 40 countries, mostly in Brazil, Canada, China, Kazakhstan, the Russian Federation, South Africa, and Zimbabwe. Asbestos deposits are located in many parts of California and are commonly associated with serpentine, although other types of asbestos are also found in California. Serpentine rock, which often contains chrysotile asbestos, is abundant in the Sierra foothills, the Klamath Mountains, and the Coast Ranges, and is the California state rock. Asbestos is ubiquitous in the environment because of its extensive industrial use and the dissemination of fibers from natural sources.

Asbestos minerals occur naturally as fiber bundles that may be several centimeters long. However, when manipulated, they break down into smaller fibers that may have dimensions in the submicron range. It is these small fibers that can pose health risks. Occupational exposure appears to be the major cause for diseases in humans related to asbestos exposure. Population surveys indicate that male workers in construction or in shipyards have had the highest potential for asbestos exposure (Albin *et al*., 1999). People have also been exposed to asbestos by living with asbestos workers or living in the vicinity of asbestos mines and factories. Indoor air in buildings with asbestos-containing materials can be a major source for nonoccupational asbestos exposure (HEI, 1991).

Asbestos fibers are not able to move through soil and are not broken down to other compounds in the environment. Therefore, they can remain in the environment for decades or longer (ATSDR, 1995). Asbestos fibers may bioaccumulate in animals and humans. The general population may be exposed to asbestos fibers in outdoor and indoor air, beverages, drinking water, food, pharmaceutical and dental preparations, and by consumer use of asbestos-containing products (IARC, 1977).

Air

Although asbestos is not volatile, small fibers and clumps of fibers may be released to air as a dust-like suspension. Chrysotile appears to be the predominant fiber found in the outdoor air. IPCS (1986; 1998) reported asbestos concentrations of fibers longer than 5 µm measured at various locations in Austria, Canada, Germany, South Africa, and the U.S. ranging from less than 1×10^{-4} to about 1×10^{-2} fibers/mL, mainly analyzed by TEM. Analyzed by light microscopy (LM) and expressed as phase-contrast optical microscopy (PCOM) equivalent fibers longer than five µm, asbestos concentrations in outdoor air are generally less than 5×10^{-4} fibers/mL in remote areas in the U.S., and up to 2×10^{-3} fibers/mL in urban areas (IPCS, 1998). Measurements reported by the California Air Resources Board (1986) ranged from 8 to 500 fibers/m^3, with the higher concentrations associated with proximity to production and use facilities.

U.S. EPA (1991b) requires the establishment of an administrative record of asbestos in buildings, especially in school buildings where children may be exposed to airborne asbestos through indoor air inhalation. IARC (1976) summarized indoor air measured in

1972 in U.S. school buildings with sprayed-on asbestos, showing as high as 3.8 fibers/mL. Indoor air concentrations measured in various buildings in the U.S., Canada, and Germany ranged from below the detection limit of the analytical method to 1×10^{-2} fibers/mL (IPCS, 1986; 1998).

One source of asbestos in the environment is the erosion of natural deposits of asbestos-bearing rocks. Asbestos can also be released into the environment by human activities. It is estimated that emissions from asbestos processing, including milling, manufacturing, and fabrication are about 2,240 pounds per year (U.S. EPA, 1992b). This estimate assumes full compliance with the current National Emission Standards for Hazardous Air Pollutants (NESHAP) (U.S. EPA, 1986, 1990) applicable to asbestos. Occupational exposures to asbestos in air were reported as high as 3×10^{9} fibers/m^3 in 1949 and reduced to 2×10^{8} fibers/m^3 (200 fibers/mL) in 1965 (IPCS, 1998). The current OSHA permissible exposure limit is 0.1 fibers/mL (1×10^{5} fibers/m^3).

An estimated total of 11,264 pounds (about 5.1 metric tons) of asbestos, amounting to about 4.5 percent of the total environmental release, was discharged to the air from manufacturing and processing facilities in the U.S. in 1992 (TRI92, 1994). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Other sources of asbestos release include releases from clutches and brakes on cars and trucks, as well as releases of asbestos from insulation or other building materials. Estimated asbestos emissions from waste disposal from all sources were about 499,000 pounds (about 227 metric tons) per year (U.S. EPA, 1990). If all sources were in full compliance with the NESHAP for asbestos, waste disposal emissions would be reduced to 1,320 pounds (about 600 kilograms) per year (U.S. EPA, 1990a).

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.

An estimated total of 235,900 pounds (about 107 metric tons) of asbestos, amounting to about 95.3 percent of the total environmental release, was discharged to land from manufacturing and processing facilities in the U.S. in 1992 (TRI92, 1994). The Toxics Release Inventory (TRI) data collected by the U.S. EPA should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Water

Asbestos is released to water from a number of sources, including erosion of asbestos-bearing rocks and surficial materials in the watershed, erosion of natural deposits, corrosion from asbestos-cement pipes, and disintegration of asbestos roofing materials with subsequent transport via rainwater into cisterns, and the like. Wastewater from asbestos mining activities and asbestos-related industries as well as atmospheric input also carry significant burdens of asbestos fibers in water (U.S. EPA, 1976). In the U.S.,

asbestos in drinking water has been shown as primarily chrysotile (Millette *et al*., 1981; IPCS, 1998; Speil, 1974). In areas such as San Francisco, Sherbrooke, and Seattle, chrysotile in water supplies has been attributed to erosion from natural asbestos rocks and ores (Millette, 1983). The fibers may remain in suspension in the water for long periods of time. In addition, suspended chrysotile fibers may adsorb organic materials, which eventually cover the entire fiber surface and consequently affect the biological activities of the fiber (Bales and Morgan, 1985; IARC, 1996; IPCS, 1998).

The total amount of asbestos released to water has been estimated to be 1.1×10^5 to 2.2×10^5 pounds (about 50 to 100 metric tons) per year (NAS, 1984). Chrysotile concentrations in lakes and streams have been variable, depending on proximity to source areas and river flow pattern (IPCS, 1998; Schreier, 1989). Concentrations of 1×10^6 to 1×10^8 fibers/L are typical in most rivers draining serpentinic rock formations, with seasonal fluctuations. Concentrations up to 1×10^{13} fibers/L have been reported in a stream draining asbestos-bearing bedrock (IPCS, 1998; Schreier, 1987; 1989). Bishop *et al*. (1985) identified asbestos and glass fibers ranging from about 5 μm in diameter to 50 μm in length in Los Angeles municipal sewage sludges at 10^6 to 10^8 fibers per gram sludge dry weight.

An estimated total of 250 pounds (about 0.11 metric tons) of asbestos, amounting to less than one percent of the total environmental release, was discharged to surface water from manufacturing and processing facilities in the U.S. in 1992 (TRI92, 1994; not an exhaustive list).

Cunningham and Pontefract (1971) reported asbestos in drinking water in Quebec and Ontario in Canada (ranging from 2×10^6 to 1.73×10^8 fibers/L) with the highest levels in unfiltered tap water near a mining area. Asbestos concentrations in drinking water in Austria were higher in an area with natural deposits at the source of the water supply (1.9×10^5 fibers/L) compared to a median of 3.2×10^4 fibers/L from 10 areas with asbestos deposits, or 14 areas with use of asbestos cement pipes, or six control areas. However, a sample of surface water from a cistern showed considerable asbestos contamination and raised concern about the use of water for room air humidification (Neuberger *et al*., 1996). Similar concern was discussed in the U.S. (Webber *et al*., 1988).

Average asbestos concentrations from 0.3 to 1.5 μg/L were measured in eastern U.S. river water samples and chrysotile levels up to 12 μg/L were found in the Jumata and Connecticut rivers (IARC, 1977; Nicholson, 1974; Nicholson and Pundsack, 1973). Cook *et al*. (1974, 1976) reported average asbestos concentrations of about 1.7×10^6 fibers/L in the Great Lakes and Saint Lawrence River bywaters with higher counts along the north shore of Lake Superior between Silver Bay and Duluth, along the Saint Clair River in the U.S., and downstream from Montreal and in the asbestos mining district in Quebec (IARC, 1977). This led to national surveys of asbestos in drinking water in the late 1970s in the U.S., Canada, the United Kingdom, Germany, and other countries that resulted in findings of 10^5 to 10^6 fibers/L in water supplies. Approximately 10 percent of water supplies in the U.S. and five percent in Canada contained 10^8 to 10^9 fibers/L due to naturally occurring asbestos-rich bedrock or asbestos mining activities (IARC, 1977; Millette, 1983; Schreier 1989).

In the U.S., northern California, where asbestos-bearing rocks are abundant, is known for high asbestos levels in water supplies. Because California is a water deficient state and water distribution systems for drinking water and irrigation are extensive and interconnected, this has the potential to compound the degree of asbestos contamination. Once asbestos-rich sediment gets into the system, the fibers are distributed over large areas, thus affecting drinking water quality for a large segment of the population (Hayward, 1984; Jones and McGuire, 1987; Tarter *et al*., 1983). Other areas in the U.S. with high asbestos concentrations in drinking water are the Puget Sound area of Washington, part of the Appalachian Mountains in New York, New Jersey, and Maryland, the Duluth area in Minnesota, and sections of New Mexico (Schreier, 1989). Groundwater in the Rio Grande Valley in New Mexico was also found to contain asbestos (Oliver and Murr, 1977).

In 1973, amphibole asbestos fibers were discovered in the municipal water supply of Duluth, Minnesota ranging from 10^7 to 10^9 fibers/L (Cook *et al*., 1974). The entire city population of 100,000 was exposed from the late 1950s through 1976 at levels of 1×10^6 to 6.5×10^7 fibers/L of water (Sigurdson, 1983; Sigurdson *et al*., 1981).

Drinking water concentrations of asbestos are usually less than 1×10^6 fibers/L for fibers of all sizes, although significantly higher values up to 1×10^9 fibers/L have been found in circumstances where water systems have been in contact with asbestiform minerals or where contamination of the water supply exists (Cotruvo, 1983). The fiber mass concentrations corresponding to these fiber concentrations are usually less than 0.01 μg/L. Thus direct water ingestion usually leads to exposure of less than 0.02 μg/day (U.S. EPA, 1980). Estimated annual doses of ingested asbestos for drinking water in the United States range from $9\text{x}10^5$ to $4\text{x}10^{11}$ fibers, as shown in Table 3.

Reported data suggest that fibers of all lengths at 1×10^6 fibers/L correspond to anywhere from 2×10^{-4} to 2×10^{-3} μg/L, with up to 2×10^8 fibers/L in water systems (IPCS, 1986, 1998; U.S. EPA, 1980). Data on asbestos concentrations from erosion of fibers from asbestos cement cooling tower panels indicate that the mass of 1×10^6 fibers is from 0.01 to 0.2 μg (U.S. EPA, 1980). From 1984 to 2000, asbestos was detected in 80 out of 1933 samples from public drinking water systems in California. The detection limit for purposes of reporting (DLR) was 0.2×10^6 fibers/L or 0.2 MFL as reported by DHS at http://www.dhs.cahwnet.gov/ps/ddwem/chemicals/phgs/mclcomparison.htm (accessed January 21, 2001).

Table 3. Estimated Ingested Dose from Drinking Water in U.S.*

Reference	Concentration in water	Yearly ingested dose (EM fibers[§])
Office of Toxic Substances estimate of asbestos-contaminated water (Bishopville, SC)	547 x 10^6 fibers/L	3.99 x 10^{11}
Natural contamination; geological source (San Francisco, CA)	130 x10^6 fibers/L	9.49 x 10^{10}
Groundwater (ambient)	3.2 x 10^5 fibers/L	2.34 x 10^8
Office of Water Regulations and Standards, Survey of Drinking Water	1 x10^5 to 100 x10^6 fibers/L	7.3 x 10^7 to 7.3x10^{10}
American Water Works estimates (municipal water systems):		
•Memphis District System	1.7 µg/L	4.69 x 10^8
•Providence District System	0.27 µg/L	7.45 x 10^7
•Saginaw Source	0.0032 µg/L	8.83 x 10^5

*Adapted from Rowe (1983).
[§]Yearly dose estimates: OTS, OWRS: conc. in water x 2 L/day x 365 days/yr; AWWA: conc. in water x 2 L/day x EM fibers/µg x 365 days/year.

Food and Other Sources

In the past, filters made from asbestos, and talc containing asbestos as an impurity were employed in the preparation of wines, beers, coated rice, processed sugar, vegetable oil, lard, and other items consumed by humans (IARC, 1977). Asbestos concentrations in British, Canadian and American beer ranged from 1 to 10×10^6 fibers/L and in various sherries, ports, vermouths, and soft drinks ranged from 1.7 to 12.2×10^6 fibers/L (Biles and Emerson, 1968; Cunningham and Pontefract, 1971, 1974; IARC, 1977). Chrysotile fibrils at 13 to 24×10^6 fibers/L were found in spirit filtered with asbestos filters (IARC, 1977; Wehman and Plantholt, 1974). Wines have been shown to contain as much as 64×10^6 fibers/L (U.S. EPA, 1985c). Analysis of 47 brands of sake purchased in Japan during 1983-1985 showed asbestos concentrations from less than the detection limit of 7.8×10^3 fibers/L to 196×10^6 fibers/L (Ogino *et al*., 1988).

The use of asbestos filters in food or pharmaceutical preparations has been discontinued in the U.S. since 1976, and intake of asbestos through foods or drugs is now unlikely. However, asbestos has been found in art supplies such as crayons, probably as a contaminant of the talc used to strengthen the crayons.

METABOLISM AND PHARMACOKINETICS

Asbestos fibers may enter the body after inhalation or oral exposures. It is unlikely that any appreciable uptake of asbestos fibers will occur after dermal exposure. The

deposition and fate of fibers in the lungs is largely dependent upon their size and shape. Fibers deposited in the lungs may be removed from the lungs by mucociliary clearance or by macrophages, or they may be retained in the lung. It has been estimated that 25 to 75 percent of inhaled fibers are cleared from the respiratory tract by the mucociliary escalator, and subsequently swallowed (Lee, 1974).

Longer fibers that are retained in the lung may undergo a number of processes including translocation, dissolution, fragmentation, splitting or protein encapsulation. Long fibers that become encapsulated in protein form what is often referred to as an "asbestos body;" the term "ferruginous body" is used when the nature of the core fiber is not known. These bodies are golden brown in appearance, owing to the presence of iron. The protein coat is rich in ferritin, an iron storage protein, possibly arising from macrophages and giant cells. The formation of asbestos bodies may represent an attempt of macrophages to digest long fibers extracellularly (Koerten *et al*., 1990a,b). Ferruginous coatings form on a population of asbestos fibers that are greater than eight µm. Ferruginous bodies, when seen in lung tissue sections in combination with fibrosis, are important in establishing the diagnosis of asbestosis (Dodson *et al*., 1999).

An intraperitoneal injection in mice of 200 µg UICC crocidolite fibers, about 91 percent of which were shorter than two µm, resulted in clearance by the lymphatic system, producing minimal inflammation and mesothelial cell proliferation. However, for fibers about 60 percent longer than two µm, the injection resulted in accumulation of inflammatory cells, mesothelial cell injury, and proliferation due to fiber persistence up to six months after the treatment, with limited lymphatic clearance (Moalli *et al*., 1987).

Absorption

There is considerable controversy as to whether ingested asbestos fibers can penetrate and pass through the walls of the gastrointestinal tract in sufficient numbers to cause adverse effects (Cook, 1983; Hilding *et al*., 1981; Meek, 1983; Volkheimer, 1973, 1974). While the data are inconclusive, a number of toxicokinetic studies have shown that asbestos fibers do penetrate the gastrointestinal mucosa, and collect in other tissues (Amacher *et al*., 1974; Carter and Taylor, 1980; Cook and Olson, 1979; Craun and Millette, 1977; Epstein and Varnes, 1976; Lee, 1974; Pontefract and Cunningham, 1973; Storeygard and Brown, 1977; Wells, 1975; Westlake *et al*., 1965; Westlake, 1974).

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 the blood, lymph, urine, and other tissues (Carter and Taylor, 1980; Cunningham and Pontefract, 1973; Cunningham *et al*., 1977; Hallenbeck and Patel-Mandlik, 1979; Kaczenski and Hallenbeck, 1984; Ogino *et al*., 1987; Patel-Mandlik and Millette, 1980, 1983; Pontefract and Cunningham, 1973; Sebastien *et al*., 1980; Weinzweig and Richards, 1983). The mechanism by which asbestos fibers pass through the gastrointestinal wall is not known with certainty, but it has been noted that a wide variety of µm-sized particles, e.g., starch granules, cellulose particles, or pollen, can cross the gut by passing between (not through) the cells of the epithelial layer in a process termed persorption. It seems likely that this may account for

uptake of asbestos fibers as well (Volkheimer, 1973, 1974). 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.

Although several researchers have found no clear evidence of transmigration (Davis *et al*., 1974; Holt, 1974; Pooley, 1974), the weight of evidence supports the conclusion that some asbestos fibers do cross the gastrointestinal tract barrier. Data are insufficient to precisely estimate the fraction of ingested fibers which pass through the gastrointestinal wall, but Sebastien *et al*. (1980) estimated that a maximum of 10^{-4} to 10^{-7} times the number of chrysotile or crocidolite fibers introduced to the stomach appeared in the lymph fluid of rats. Cook and Olson (1979), analyzing human urine, detected from 10^{-3} to 10^{-5} of the concentration present in the subject's drinking water. Neither the lymph fluid nor the urine can account for all fibers that may migrate across the gastrointestinal tract mucosa.

Study Limitations

Many of the studies on gastrointestinal penetration by ingested asbestos fibers provide incomplete information for defining analytical sensitivity, fiber recovery, sample contamination, latency period determination, etc. The absence of clear definitions of detection limits and/or positive tissue control samples make the reports of no fiber presence in some studies difficult to evaluate. For example, in the Gross *et al*. (1974) rat study, although clearly most of the ingested asbestos fibers were not absorbed across the gastrointestinal tract, the detection limit information was incomplete, there were no positive controls, and the negative control samples were contaminated. Many of the gut penetration studies entail exposures to chrysotile asbestos, the most common contaminant of water, food and beverages. However, chrysotile asbestos fiber concentrations are the most difficult to estimate because, in addition to having extremely thin diameters that make them difficult to identify, these fibers are readily reduced to individual fibrils.

Distribution

Asbestos is reported to be disseminated in the body of experimental animals following its initial primary site of absorption or deposition (Pontefract and Cunningham, 1973; Westlake *et al*., 1965; Volkheimer, 1973, 1974). Asbestos fibers have been detected in blood (Weinzweig and Richards, 1983), lymph (Sebastien *et al*., 1980), human fetuses, and fetuses (Haque *et al*., 2001) 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, asbestos fibers have been detected in lung, kidney, liver, brain, heart, and spleen of rats exposed to asbestos in the diet (Cunningham *et al*., 1977; Pontefract and Cunningham, 1973). Highest levels of fibers were found in the omentum, which is a fold of the peritoneum interconnecting the abdominal viscera, supporting the idea that the fibers were emanating from the gastrointestinal tract. Although the diet fed to the animals was prepared using corn oil to minimize asbestos fiber inhalation, the possibility that some fiber inhalation took place cannot be eliminated (Cunningham *et al*., 1977).

Suzuki and Kohyama (1991) reported that inhaled asbestos can be translocated into extrapulmonary tissues. Masse *et al*. (1980) provided clear evidence of penetration of the gut in animals. Sebastien *et al*. (1980) recovered chrysotile and crocidolite fibers in the lymphatic and blood circulatory systems of rats following both a single dose ingestion and chronic ingestion. Kaczenski and Hallenbeck (1984), in a study on baboons, demonstrated clear evidence of hematogenous migration of chrysotile asbestos after gavage feeding. Webster (1973, 1974) reported finding iron-containing macrophages in the duodenal and ileal mucosa of baboons fed asbestos for up to five years.

Kobayashi *et al*. (1987) reported on the asbestos distribution/burdens in extrathoracic organs of human subjects exposed to chrysotile. Twenty-six male autopsy subjects were subdivided into three groups according to the degree of asbestos bodies (ABs) in the lung. Group I had from 100-1000 ABs/g of wet lung, Group II had ABs ranging from 10 to 99, and group III had no detectable ABs in the lung. The incidence and the number of ABs in extrapulmonary organs usually increased as the pulmonary exposure level rose. The esophagus was one of the preferential sites of exposure. In Group I, ABs were found in the esophagus, spleen, pancreas, bone marrow, and thyroid gland; one or more ABs were identified in at least 54 percent of the examined organs. In group II, 24 percent of the organs had one or more ABs. No extrapulmonary ABs were found in Group III subjects. The authors reported that the Group I subjects had no direct occupational exposure to asbestos.

A few human studies also suggest asbestos uptake from the gastrointestinal tract and its circulation and migration to other organs. Langer (1974) reported concentrations of asbestos bodies and uncoated fibers, in the order from high to low, in lungs, kidneys, pancreas, and liver, for asbestos workmen. Carter and Taylor (1980) detected amphibole asbestos in the lung, liver, and jejunum of autopsied residents of Duluth, Minnesota, with long-term high-level oral exposure to amphibole asbestos through a contaminated water supply. Sixty percent of the 19 persons studied had levels of amphibole fibers greater than 2×10^5 fibers/g in the lung, liver and intestinal wall. Total counts of these amphibole fibers in the drinking water ranged from approximately 2×10^6 to 2×10^8 fibers/L with an average of 2×10^7 fibers/L.

Several authors have described the presence of asbestos fibers and asbestos bodies in tumor tissue (Ehrlich *et al*., 1985; Henderson *et al*., 1975). Henderson *et al*. (1975) found amphibole and chrysotile asbestos fibers in stomach tumors and adjacent gastric mucosa in Japanese men with oral exposure to chrysotile. Not all of the tumor tissue examined contained asbestos fibers. The occupational history of the patients was not known. Other silicates besides asbestos were also found in some of the tissues. In at least one case, asbestos bodies were found in a carcinoma of the colon in an insulation worker with asbestosis (Ehrlich *et al*., 1985).

A group of investigators reported finding many asbestos fibers in electron microscopic analyses of placenta and body tissues taken from some stillborn infants, but very few in placental digests from liveborn infants (Haque *et al*., 1992, 1996, 1998). Haque *et al*. (1998) summarized the results from the study of 82 stillborn and 45 liveborn infants. Twenty-three percent of the placentas of stillborn infants contained asbestos fibers, with mean numbers of about 53,000 fibers per gram in the positive tissues. Fifteen percent of placentas from liveborn infants contained asbestos fibers, but at much lower levels. The

mean level was reported as 19 fibers/g, although this contradicts the reported sensitivity level, where one fiber is equivalent to 11,000 fibers/g. The discrepancy may be due to subtraction of reagent blank readings, which would correspond to a fraction of a fiber per gram. Asbestos fibers were also detected in other tissues of the stillborn infants. The mean fiber counts were highest in the liver (59,000/g), followed by lung (39,000/g) and skeletal muscle (32,000/g). Actual numbers of asbestos fibers counted, based on the indicated conversion factor, ranged from zero to 33 per gram of processed tissue. Fiber sizes in the stillborn infants ranged from 0.5 to 16.8 µm in length and 0.03 to 0.8 µm in width, with a mean length of 1.55 µm and a mean width of 0.098 µm. Eighty-eight percent of the fibers were chrysotile. In the liveborn infants, the fibers tended to be longer and thicker. However, differences in processing and examination between the groups make this finding uninterpretable. A highly significant association was noted between fiber presence and previous abortions ($p<0.007$), and a smaller but still significant association with placental disease ($p<0.04$). The authors postulate that disease processes resulting in a stillbirth might result in increased transfer of maternal fibers to the placenta and infant. They also suggest that rapidly dividing fetal cells may be especially susceptible to the carcinogenic and mutagenic effect of asbestos.

Several studies have demonstrated transplacental transfer of asbestos in animal models. After asbestos fibers were injected intravenously, transplacental transfer of asbestos was shown in rats (Cunningham and Pontefract, 1974). Haque and Vrazel (1998) demonstrated transfer of asbestos fibers to the fetus and placenta within one hour following a single intravenous injection via the tail vein in pregnant mice. The asbestos suspensions contained approximately 345,000 fibers/mL. Histologic examination of sections from fetuses and placentas showed focal areas of coagulative necrosis with mild neutrophil infiltration in some placentas. Electron microscopy of the placental tissue taken from the areas of necrosis showed the presence of very small (100 to 700 nm) asbestos fibers within the cytoplasm and nuclei of placental cells. Asbestos fibers were found in fetal lungs and liver following the injection of one to three mg (one mg/mL water) of chrysotile asbestos fibers into the femoral vein of pregnant Wistar rats at two-day intervals from days 10-14 of gestation (Cunningham and Pontefract, 1974). Total dose varied from four to 12 mg (4×10^5 to 12×10^5 fibers) of asbestos. The highest number of fibers found in fetal liver (27×10^6 fibers/g) and lungs (140×10^6 fibers/g) came from a dam administered four 3-mg injections (total dose = 12 mg or 12×10^5 fibers). In a recent work, Haque *et al*. (2001) demonstrated the transfer of asbestos fibers to the fetus following gavage feeding of pregnant mice with chrysotile asbestos. Groups of mice (6/group) were given two doses of either 50 µg chrysotile suspension in 0.2 ml sterile normal saline (treated) or 0.2 ml saline (control), and were allowed to mate two days later. After pregnancy was confirmed, the treated and control groups received two additional doses of chrysotile asbestos or saline on gestational days 7 and 12. Both groups were allowed to deliver naturally and the pups were sacrificed at 8, 11, 19 or 20 days after birth. The lungs and liver of two pups from each dam were processed for fiber counts using electron microscopy. All pups of the treated group had chrysotile fibers, while none were present in pups from controls. The mean fiber count of the lungs and liver of the treated pups was 780 and 214 fibers/g, respectively. Mean lengths of the fibers in the lung and liver were 18.5 and 18.3 µm, respectively. There was no significant difference in weight gain between the two groups. The postnatal fetal

mortality, 8.2 percent for the treated and 4.5 percent for the control group, was not statistically significant.

Metabolism

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 (Sheshan, 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, 1983). These observations, although limited, suggest that chrysotile fibers undergo some metal ion exchange and alterations in gross structure in biological fluids after oral exposure. Asbestos bodies have been detected in tissues such as the colon (Ehrlich *et al*., 1992), suggesting that encapsulation of asbestos fibers may occur in extrapulmonary tissues as well.

Excretion

It has been demonstrated that ingested fibers are eliminated through the urine and feces. Several authors have reported on the excretion of asbestos fibers in urine (Boatman *et al*., 1983; Cook and Olson, 1979; Hallenbeck and Patel-Mandlik, 1979). Cook and Olson (1979) detected amphibole fibers in the urine of persons with varying exposure to unfiltered drinking water drawn from Lake Superior. In some cases, the urine samples contained more than 10 times the number of fibers corresponding to the detection limits (10 to 40 amphibole fibers/mL urine). A single day's ingestion of water was observed to result in a urine amphibole load of 10^{-3} to 10^{-5} of the number of fibers ingested, with fibers detectable in urine at least 10 days after ingestion. The authors felt this ratio to be remarkably large. Hallenbeck and Patel-Mandlik (1979) reported that chrysotile fibers administered orally to baboons may be recovered in urine. Gross *et al*. (1974), in a study on rats, reported that nearly all ingested asbestos fibers are excreted in the feces. This is essentially complete within 48 hours following a single oral dose.

TOXICOLOGY

Asbestos was suspected to have links with some human cancers as early as 1935 (Lynch and Smith, 1935). A number of authoritative bodies have listed asbestos as a known human carcinogen via the inhalation route. NTP (2000) and IARC (1987) reported that there is sufficient evidence of carcinogenicity of asbestos as well as chrysotile, amosite, anthophyllite, and crocidolite in experimental animals. NAS (1977, 1983, 1984) and ATSDR (1995) are also in agreement with the determination of asbestos carcinogenicity.

There are numerous publications on toxicological evaluations of asbestos, mainly on occupational groups exposed to airborne asbestos. It is well recognized that the greatest risks with occupational exposure to asbestos, mainly through inhalation as well as some through accidental ingestion, are mesothelioma, bronchial carcinoma in the lung, and

asbestosis (IPCS, 1998). Mesothelioma is a primary malignant tumor of the pleura and peritoneum whereas asbestosis is described as a diffuse pulmonary fibrosis. Numerous studies in various animals also support the carcinogenicity of asbestos fibers, especially through inhalation exposure (Reeves *et al*., 1971, 1974; Smith *et al*., 1965; Wagner *et al*., 1974).

However, this PHG technical support document focuses mainly on toxicological data needed for characterization of the risk from ingestion of asbestos in drinking water since the purpose of this document is to develop a health protective concentration of asbestos in drinking water. Special attention has been paid to carcinogenicity and genotoxicity as the supporting evidence for selecting carcinogenicity as the most sensitive toxicity endpoint for deriving a public health protective concentration in drinking water.

Toxicological Effects in Animals

Acute, Subacute, and Chronic Noncancer Effects

Most studies conducted in animals seem to indicate that ingestion of asbestos causes little or no risk of noncarcinogenic injury. No studies were located regarding respiratory, musculoskeletal, hepatic, endocrine, dermal, ocular, metabolic, or other systemic effects in animals after oral exposure to asbestos (ATSDR, 1995; HSDB, 2000).

In the literature search, no studies have been located regarding death in animals after acute, intermediate, or chronic oral exposure to asbestos. Feeding studies in rats and hamsters indicate that ingestion of high amounts in the diet (one percent), equivalent to doses of 500 to 800 mg/kg-d of chrysotile, amosite, crocidolite, or tremolite, does not cause premature lethality, even when exposure occurs for a lifetime (ATSDR, 1995; NTP, 1983, 1985, 1988, 1990a,b,c).

Kidney Effects

Cemerikic (1977) exposed male and female Wistar rats (seven per sex) to chrysotile asbestos in drinking water for 3 months. The ten male and seven female controls received tap water. A suspension of asbestos fibers in drinking water was prepared by shaking 2.5 g of chrysotile asbestos in 500 ml of water; this was allowed to settle for 30 minutes and the top 250 ml, which contained about 9.4×10^9 (1 mg) fibers/ml was drawn off (the technique of Pontefract and Cunningham, 1973). Blood pressure was measured by tail cuff at one or more time points (3, 6, 9, 12, 15 weeks). A moderate increase of blood pressure, evidence of hypertension, was found by the tail cuff procedure in exposed females after 6, 9 and 12 weeks, and in males at 9 and 15 weeks, compared with controls. Arterial pressures measured in the anesthetized animals via cannulation at 12 weeks in females and 15 weeks in males were also shown to be elevated. One male and three females were judged to be hypertensive (blood pressure >two standard deviations above the mean control level). Females were sacrificed after 12 weeks and males after 15 weeks. The organs were measured and the kidneys and bladders examined histopathologically. Pathologic presence of red blood cells and

hyaline casts in the urine sediment of four males indicated damage to the kidneys. Kidneys of experimental females showed only discrete perivascular infiltration. Results were interpreted by the authors as indicating that "asbestos may be nephrotoxic in male and hypertensive in female rats."

Gastrointestinal Effects

A number of researchers have investigated nonneoplastic and biochemical effects of ingested asbestos on the gut wall since the tissue most directly exposed to ingested asbestos is the gastrointestinal epithelium (ATSDR, 1995). In addition, studies in rats by Evans *et al*. (1973) have shown that the gastrointestinal tract receives, via pulmonary clearance, much of the asbestos load of the lung. Several researchers have described significant biochemical or histological alterations at the subcellular level in the gastrointestinal tract after oral exposure to asbestos.

Jacobs *et al*. (1978a) examined the gastrointestinal tract tissues of an unspecified number of rats fed 0.5 or 50 mg of chrysotile per day for one week or 14 months. Light microscopy revealed an accumulation of cellular debris and Alcian blue-positive material in the lumen of the ileum, colon and rectum. There was also marked vacuolation in the surface epithelial cells of the mucosa, and in the loose tissue core of the lamina propria. Analysis by electron microscopy revealed marked separation of cells along the intracellular membrane in the colon and ileum. Loss of the brush border and discharge of the cell contents into the lumen was common, with adherence to the luminal surface. Microvilli were often less compact, organized and evenly stained than those of the control animals, and abnormal blebbing of the surface was present. In addition, mitochondria were swollen in intact cells. The esophagus, stomach, and cecum in treated animals appeared unaffected. Significant alterations, consistent with a mineral-induced cytotoxicity, were found in the lining cells of the rat small intestine in animals fed diets containing chrysotile asbestos (0.5 to 50 mg/day) for 10 months (Jacobs *et al*., 1977), then starved for 24 hours before sacrifice. The DNA content of washings from the small intestine lumen increased and RNA levels decreased in asbestos-treated rats. The level of DNA in the lumen washings of treated animals maintained on both concentrations of asbestos in the diet was twice as high as that found in control animals. Enzyme levels within the lumen were also significantly higher than those found in a similar number of control rats. Levels of DNA, RNA and protein in the mucosal lining cells of the gut remained unchanged, although intracellular enzyme levels were consistently elevated. The higher levels of DNA and enzymes in the intestinal lumen of fasted rats that have previously ingested asbestos may be the result of mineral-induced cellular damage (i.e., cytotoxicity to mucosal cells).

Amacher *et al*. (1974, 1975) conducted several dose-response studies in rats to measure DNA synthesis by tritiated thymidine uptake in tissues. In the first study, three groups of five Charles River rats were gavaged with 5, 100, or 500 mg/kg chrysotile. There were 21 control animals. Two weeks following administration of the 5 mg/kg dose, DNA synthesis was significantly increased in the colon and small intestine and significantly reduced in the liver. At the 500 mg/kg dose, DNA synthesis was significantly reduced in the small intestine two weeks following administration. No significant changes were

noted in the stomach or liver. Increases in DNA synthesis were noted in the stomach and small intestine at one and two days respectively, and in the colon from 23-68 days following administration of 100 mg/kg chrysotile to five groups of five rats. An additional study (Amacher *et al*., 1975) was conducted in which five groups of five rats were administered 0.5, 5.0, 25.0, 50.0 and 100 mg/kg chrysotile by gavage following fasting for 24 hours. At three days, incorporation of tritiated thymidine was significantly elevated in the whole stomach, duodenum, and jejunum in the 5-100 mg/kg dose range; incorporation in the liver was reduced.

Increased numbers of aberrant crypt foci (ACF), preneoplastic lesions of colon cancer, were induced in rats one month following bolus administration of either a single dose (70 mg/kg-day) of chrysotile, a single dose (40, 80 or 160 mg/kg-day) of crocidolite, or three doses (33 mg/kg-day) of crocidolite over a 5 day period (Corpet *et al*., 1993). Rats given any asbestos (any form or dose) had more ACF in the colon than water treated controls. Chrysotile (70 mg) induced as many ACF as crocidolite (80 mg). No aberrant crypt foci were seen in the controls ($p < 0.05$ with each one of the four treated groups). No dose response was noted however, since increasing doses of crocidolite did not induce increasing numbers of ACF (all different from control, all $p<0.05$, but no difference between treated groups). The aberrant crypt foci were distributed primarily in the middle colon and rectum in all groups. Mice administered either a single dose (100 mg/kg) of chrysotile or three doses (50 mg/kg-day) of crocidolite did not show any increases.

Delahunty and Hollander (1987) exposed an unspecified number of Sprague-Dawley rats to 0.5 g/L chrysotile asbestos in their drinking water, approximately seven mg/day ingested, for 1.5 years. *In vivo* intestinal permeability studies showed that asbestos treatment resulted in a significant reduction in the ability of the intestine to absorb the non-metabolizable sugars lactulose and mannitol in comparison to control animals, as determined by significant decreases in the urinary elimination. However, no decrease was found in the elimination of rhamnose, another non-metabolizable sugar. Previous experiments by the authors showed that the permeability function of rat intestine could be monitored by the oral administration of non-metabolizable compounds (permeability probes) such as lactulose, rhamnose, and polyethylene glycol. The entire intestinal mucosal surface of each animal was removed and examined macroscopically for obvious lesions. Multiple representative sections of the small and large intestines of asbestos-treated and control animals were processed for light microscopy and assessed for any abnormalities. No specific findings of these examinations were reported except the absence of asbestos fibers in the sections. There were no differences in the weight or appearance of the treated rats, compared to controls.

No excess non-neoplastic lesions of the gastrointestinal epithelium have been detected in a number of other animal feeding studies (Bolton *et al*., 1982; 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, 1983, 1985, 1988, 1990a,b,c).

Body Weight Effects

An NTP toxicology/carcinogenesis study reported decreased (15-37 percent) body weight gain in rats exposed to amosite asbestos in the diet (NTP, 1990b). Amosite (target concentration of 10,000 ppm, one percent by weight of study diet) was given to two groups of male and female rats. One group (amosite group) was exposed from weaning throughout life. The second group received chrysotile asbestos (by mistake) beginning at birth by preweaning gavage and then amosite in feed from weaning throughout the lifespan (amosite + PW group). Group sizes varied from 100-250. Litter size was the same, but the offspring from mothers exposed to amosite asbestos were smaller at weaning than those from non-exposed mothers, and remained smaller throughout their life. Changes in food consumption do not explain the decreased body weight gain since treated rats had slightly higher food intakes than controls. This did not appear to negatively effect the survival of amosite-exposed rats since they show enhanced survival compared with the non-exposed rats. Effects on body weight gain have generally not been observed in other studies (Gross *et al*., 1974; NTP, 1983, 1985, 1988, 1990a,c; Delahunty and Hollander, 1987). The significance of this finding is therefore uncertain.

Immunological and Lymphoreticular Effects

Asbestos exposure has been associated with changes in both humoral and cellular immune functions in experimental animals *in vivo* as well as *in vitro*. For example, the chronic inflammatory response after asbestos exposure represents a complex immunological process initiated by fiber deposition which involves multiple types of immune cells (Luster and Rosenthal, 1993; Rosenthal *et al*., 1998, 1999).

An intraperitoneal injection of 200 μg UICC crocidolite fibers (about 60 percent of which were longer than two μm) in mice resulted in accumulation of inflammatory cells, mesothelial cell injury and proliferation (Moalli *et al*., 1987). Repeated weekly intraperitoneal injection of 200 μg UICC crocidolite in mice for 3 to 42 weeks resulted in inflammation and submesothelial fibrosis associated with fiber clusters after 6 to 12 weekly injections. Mesothelial cell proliferation with thymidine incorporation increased progressively over 42 weekly injections. Mesothelial cell proliferation was dissociated spatially and temporally from the development of submesothelial fibrosis (MacDonald and Kane, 1993).

Choe *et al*. (1999) assessed the effects of *in vitro* and *in vivo* asbestos exposure on the adhesion of rat pleural leukocytes (RPLs) to rat pleural mesothelial cells (RPMCs). Exposure for 24 hours to either crocidolite or chrysotile at 1.25 to 10 $\mu g/cm^2$ increased the adhesion of RPLs to RPMCs in a dose-dependent fashion, an effect that was potentiated by interleukin-1beta (particulates were added to RPMC cultures at concentrations ranging from 1.25-10.0 $\mu g/cm^2$). Crocidolite or chrysotile plus interleukin-1beta (IL-1beta) also upregulated vascular cell adhesion molecule-1 mRNA and protein expression in rat pleural mesothelial cells, and the binding of rat pleural leukocytes to asbestos-treated rat pleural mesothelial cells was also abrogated by anti-vascular cell adhesion molecule-1 antibody. In the *in vivo* experiments, rat pleural leukocytes exposed by intermittent inhalation to crocidolite for two weeks manifested

significantly greater binding to RPMCs than did RPLs from sham-exposed animals. The time weighted exposure concentration for crocidolite in this experiment was 10.5 $\pm$ 2.3 (SE) mg/m^3. These exposure levels were comparable with historic asbestos dust concentrations recorded in the workplace environment of asbestos mines and mills. The ability of asbestos fibers to upregulate RPL adhesion to RMPCs may play a role in the induction and/or potentiation of asbestos-induced pleural injury.

Asbestos may cause pathological lesions via an autocrine-like process in which the response evoked by fibers acts to enhance subsequent interactions of asbestos with tissue (Xie *et al*., 2000). Exposure of rat alveolar macrophages *in vitro* to crocidolite increases the production of tumor necrosis factor alpha (TNF-alpha) and IL-1beta (Mongan *et al*., 2000). The role that cytokine TNF-alpha and chemokine macrophage inflammatory protein-2 (MIP-2) play in asbestos-induced inflammation in the lung has been reviewed recently (Driscoll, 2000). Asbestos fibers stimulate TNF-alpha production by macrophages, and TNF-alpha is released from alveolar macrophages after phagocytosis of fibers. TNF-alpha initiates adhesion molecule expression and production of chemotactic cytokines that ultimately results in the infiltration of inflammatory cells to a site of infection or tissue injury in the respiratory tract. MIP-2 produced by macrophages and epithelial cells mediates the neutrophilic inflammatory response of the rodent lung to crocidolite. Expression of the MIP-2 gene in rat lung epithelial cells is dependent on the transcription factor (NF), NF-kappaB, and is regulated partially by oxidative stress induced by asbestos exposure (Driscoll, 2000). TNF-alpha increases epithelial fiber binding by an NF-kappaB-dependent mechanism, while macrophage TNF-alpha production acts to enhance subsequent tissue fiber interactions (Xie *et al*., 2000). The stimulus for pleural macrophage recruitment after chrysotile or crocidolite exposure is the induction of monocyte chemoattractant protein-1 (MCP-1) synthesis by pleural mesothelial cells, as shown by both *in vivo* and *in vitro* experiments (Tanaka *et al*., 2000).

Asbestos-induced binding to epidermal growth factor receptor initiates signaling pathways responsible for increased expression of protooncogene c-fos and the development of apoptosis. Crocidolite abolished binding of epidermal growth factor to its receptor in rat pleural mesothelial cells *in vitro*. Crocidolite interacts with the epidermal growth factor receptor and stimulates steady state mRNA levels and synthesis of epidermal growth factor receptor protein. Stimulation of epidermal growth factor receptor phosphorylation by asbestos is linked to the induction of c-fos, but not of c-jun. Inhibition of signaling through this pathway with tyrphostin AG-1478, but not with the nonspecific tyrphostin A-10, decreases apoptosis *in vitro* (Zanella *et al*., 1999).

Neurological Effects

No histological or clinical evidence of neurological injury was detected in rats or hamsters chronically exposed to high doses (500 and 830 mg/kg-day, respectively) of chrysotile, amosite, crocidolite, or tremolite in the diet (NTP, 1983, 1985, 1988, 1990a,b,c).

Reproductive Effects

Limited evidence from animal studies suggests that chronic ingestion of asbestos does not injure reproductive tissues, and that exposure during gestation does not reduce fertility (NTP, 1983, 1985, 1988, 1990a,b,c). No histopathological changes in reproductive organs or effects on fertility were observed in Syrian hamsters exposed to chrysotile, amosite, crocidolite, or tremolite (500 and 830 mg/kg-day, respectfully) in the diet during breeding, gestation, and lactation (NTP, 1983, 1985, 1988, 1990a,b,c).

Developmental Effects

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 (500 and 830 mg/kg-day, respectively) during gestation (NTP, 1983, 1985, 1988, 1990b,c). However, decreased body weight at birth and later in life was noted in some of the studies (McConnell *et al*., 1983a; NTP, 1985, 1990a). No teratogenic effects were seen in CD-1 mice given doses up to 33 mg/kg-day of chrysotile in their drinking water, or 143 mg chrysotile asbestos per mL, during days 1-15 of gestation (Schneider and Maurer, 1977). Studies carried out with blastocyst exposure to chrysotile in drinking water found some decrease in postimplantation survival (Hall and Rumack, 2000).

Genotoxicity

Regulation of DNA synthesis, measured via the uptake of tritium labeled thymidine, was altered in the stomach, small intestine, and liver of the young adult male Charles River CD rats gavaged with chrysotile suspensions (mainly between five and 120 μm in diameter) in normal saline at 5, 100, and 500 mg/kg doses (Amacher *et al*., 1974, 1975). Epstein and Varnes (1976) also demonstrated changes in DNA metabolism in tissues lining the gastrointestinal tract and other body organs in rats gavaged with 5 to 100 mg/kg chrysotile. These investigators concluded that asbestos penetrates the mucosal layer of the gut and either enhances mitosis by interaction with nuclear DNA, or causes accelerated cell death and thus stimulates a mitotic burst of replacement cells.

Inclusion of 0.5 to 50 mg chrysotile in the diet of rats initiated changes in the small intestinal lumen content of DNA and RNA, and produced changes in both lysosomal and brush-border enzymes (Jacobs *et al*., 1977). The asbestos-induced cytotoxicity in the mucosal cells lining the small intestine in rats exposed for one week or for five to 15 months was confirmed using electron microscopy (Jacobs *et al*., 1978a). The incorporation of tritium-labeled thymidine into DNA was significantly increased in the small intestine, colon, rectum, stomach, and spleen, but was decreased in the liver (Jacobs *et al*., 1978b).

DNA fingerprint analysis of rat peritoneal tumors induced by intraperitoneal injections of crocidolite or benzo(a)pyrene revealed similar mutational frequencies by crocidolite (14.8 percent) and benzo(a)pyrene (18.2 percent). Only deletions of bands were observed in the DNA from asbestos-induced tumors, whereas the alterations in the benzo(a)pyrene-induced tumors were exclusively additional bands (Kociok *et al*., 1999).

Asbestos fed to male mice in doses of 20 mg/kg-day for 60 days did not result in genotoxic effects on sperm and germinal cells (Rita and Reddy, 1986). An intraperitoneal injection of 10 mg asbestos per CBA mouse induced micronuclei in polychromatic bone marrow erythrocytes and the combination of radiation increased the mutagenic effect (Frash *et al*., 1999).

Yamaguchi *et al*. (1999) reported an increase of 8-hydroxyguanine in DNA and its repair activity in the lung of Syrian hamsters or Wistar rats after intratracheal instillation of crocidolite asbestos, indicating a type of oxidative DNA damage. Crocidolite induced activator protein (AP-1) transactivation in the pulmonary and bronchial tissues of transgenic mice at two days after intratracheal instillation. It also caused a dose-and time-dependent induction of AP-1 activation in cultured JB6 cells persisting for at least 48 hours, indicating cell proliferation (Ding *et al*., 1999). The upregulation of the protooncogenes c-myc, fra-1, and egfr monitored at different stages of asbestos-induced carcinogenesis in rats showing the mRNA expression patterns was demonstrated by suppression subtractive hybridization and array assay. A possible role of fra-1 as one of the dimeric proteins generating the AP-1 transcription factor was substantiated by its dose-dependent expression in mesothelial cells treated with asbestos *in vitro* (Sandhu *et al*., 2000).

Drosophila melanogaster fed asbestos induced aneuploidy in germinal cells. Chrysotile, nonfibrous tremolite, and amosite induced aneuploidy in the fruit flies but crocidolite did not induce significant chromosomal changes (Osgood, 1994; Osgood and Sterling, 1991).

There are many reviews (Daniel, 1983; IARC, 1973, 1977, 1980, 1987, 1989, 1996; IPCS, 1986, 1998; Jaurand, 1991, 1996, 1997) that summarize the use of *in vitro* genotoxicity and cell transformation assays to evaluate the potential carcinogenicity of fibers. Some of these studies are described below.

Mutagenicity

Chamberlain and Tarmy (1977) found negative gene mutation results of chrysotile, crocidolite, amosite, anthophyllite, and man-made vitreous fibers in *Salmonella typhimurium* TA1535 and TA1538 as well as several strains of *Escherichia coli*. However, an alkali-rich analogue of tremolite induced a significant number of mutants in *Escherichia coli* CSH50 with exogenous liver homogenate S9 fraction (Cleveland, 1984). Jaurand (1989) postulated that this might be due to the test fiber being ground just prior to adding to the bacterial cultures and new sites being opened on the fiber surfaces for the formation of mutagenic oxidants. Using *Salmonella typhimurium* TA102, which is sensitive to oxygen free-radical DNA damage, Faux *et al*. (1994) found that UICC crocidolite, but not UICC chrysotile, produced gene mutations. Athanasiou *et al*. (1992) did not observe gene mutations with tremolite in TA102. With the addition of hydrogen peroxide, asbestos-induced lipid peroxidation leading to DNA adduct formation in *Salmonella typhimurium* TA104 and rat lung fibroblasts was observed. Howden and Faux (1996) concluded that the DNA damage might be related to the amount of iron mobilized from the fibers.

Most *in vitro* mutagenesis studies have revealed negative results (Kelsey *et al*., 1986; Kenne *et al*., 1986; Oshimura *et al*., 1984; Reiss *et al*., 1980, 1982). However, Huang

et al. (1978), using Chinese hamster lung cells, reported a weak mutagenicity of chrysotile, crocidolite, or amosite at the hypoxanthine guanine phosphoribosyl transferase (hprt) locus with 6-thioguanine as the selective agent (Huang, 1979). On the other hand, no mutagenic response was observed 1) at the hprt locus in adult rat liver cells treated with chrysotile, crocidolite, or amosite (Reiss *et al*., 1982); 2) at the hprt and Na^+/K^+ ATPase locus in Syrian hamster embryo cells treated with chrysotile or crocidolite (Oshimura *et al*., 1984) or 3) at the hprt locus in Chinese hamster ovarian (CHO) cells treated with crocidolite (Kenne *et al*., 1986). Hei *et al*. (1991, 1992, 1995) have shown that both chrysotile and crocidolite fibers are highly mutagenic to mammalian cells in culture, and induce large chromosomal deletions in a dose-dependent manner in the A_L hamster-human hybrid cell line by DNA analysis. A significant rate of mutation was detected at the S1 locus in A_L hamster-human cell hybrids with chrysotile or crocidolite. No mutagenic response was observed at the hprt locus in A_L hamster-human cell hybrids with chrysotile or crocidolite (Hei *et al*., 1992), or tremolite or erionite (Okayasu *et al*., 1999b).

At a dose of 50 µg/mL, chrysotile was mutagenic in the autosomal HLA-A locus in human peripheral lymphocytes but 400 µg/mL crocidolite or erionite was not (Both *et al*., 1994). Crocidolite did not increase mutation frequency in the HLA-A locus in a mesothelioma cell line (Both *et al*., 1995). Loss of heterozygosity was detected in human lymphocytes treated with crocidolite or erionite (Both *et al*., 1994), as well as in mesothelioma cells treated with crocidolite (Both *et al*., 1995) but not with chrysotile (Both *et al*., 1994). As demonstrated by the protective effect of the antioxidant enzyme, manganese superoxide dismutase, in A_L hamster-human cell hybrids, asbestos-induced mutagenesis may be caused by oxygen-derived molecules (Hei *et al*., 1995).

Clastogenicity

There is general agreement about the ability of asbestos fibers, mainly chrysotile and crocidolite, to induce chromosomal mutations including aneuploidy, polyploidy, and aberrations in a variety of mammalian cells (Athanasiou *et al*., 1992; Babu *et al*., 1980; Barrett, 1991; Chamberlain and Tarmy, 1977; Donaldson and Golyasnya, 1995; Dopp *et al*., 1995; Emerit *et al*., 1991, 1995; Hart *et al*., 1992; Hesterberg and Barrett, 1985; Hesterberg *et al*., 1993; Huang *et al*., 1978; Jaurand *et al*., 1983, 1986; Jaurand, 1989; Kelsey *et al*., 1986; Kenne *et al*., 1986; Kodama *et al*., 1993; Korkina *et al*., 1992; Lavappa *et al*., 1975; Lechner *et al*., 1985; Lu *et al*., 1994; Oshimura and Barratt, 1986; Oshimura *et al*., 1984, 1986; Palekar *et al*., 1987; Pelin *et al*., 1995a, 1995b; Price-Jones *et al*., 1980; Rieder *et al*., 1991; Sincock and Seabright, 1975; Sincock *et al*., 1982; Valerio *et al*., 1980, 1983; Verschaeve and Palmer, 1985; Yegles *et al*., 1993). There is also agreement that asbestos can cause chromosome breaks and other chromosomal aberrations (Jaurand *et al*., 1986; Kelsey *et al*., 1986; Kenne *et al*., 1986; Korkina *et al*., 1992; Valerio *et al*., 1983). Several authors have reported that asbestos fibers increase the frequency of sister chromatid exchanges (SCEs) *in vitro* (Babu *et al*., 1980; Fasy, 1991; Livingston *et al*., 1980). Casey (1983) reported SCEs in Chinese hamster ovary K1 cells, human fibroblasts, and lymphoblastoid cells exposed *in vitro* to asbestos. Chrysotile exhibited clastogenic and aneuploidogenic effects in Chinese hamster lung fibroblast V79 cells (Lu *et al*., 1994).

Dopp and Schiffman (1998) investigated mitotic disturbances caused by amosite, crocidolite, and chrysotile in Syrian hamster embryo fibroblasts. All three fiber types induced a significant increase of micronuclei in Syrian hamster embryo cells. The micronuclei formation occurred in a dose-dependent manner. Amosite was the most potent fiber, with the highest micronuclei frequency at the lowest fiber concentration. Asbestos fibers also induced disturbances during mitosis in the absence of spindle fiber damage, misaggregation of chromosomes, and changes in chromatin structure. Chrysotile induced micronuclei in Chinese hamster lung fibroblast V79 cells (Keane *et al*., 1999). Exposing Syrian hamster embryo fibroblasts to one μg chrysotile per cm^2 for 66 hours induced micronuclei ($p < 0.05$), and kerosene soot enhanced the clastogenicity (Lohani *et al*., 2000).

Structural chromosomal aberration was induced in human embryo lung cells exposed to 5 μg/mL chrysotile for 24 hours (Wang *et al*., 1999). Structural chromosomal aberrations in human lymphocytes were reported due to reactive oxygen/nitrogen species, probably generated by monocytes present in the incubation medium (Korkina *et al*., 1992). The occurrence of chromosomal aberrations in human lymphocytes following treatment with conditioned medium from chrysotile-treated mesothelial cells was judged to confirm the role of reactive oxygen/nitrogen species in asbestos clastogenicity. In this study, neither a cell-free nor an asbestos-free control conditioned medium produced chromosome damage. The addition of catalase and manganese superoxide dismutase to the culture medium of asbestos-treated mesothelial cells reduced the clastogenic potency of the resultant conditioned medium (Emerit *et al*., 1991, 1995).

Other Genetic and Preneoplasm Damages

Several researchers have shown that asbestos causes specific mitotic disturbances resulting in chromosome breaks and/or micronucleus formation (Ault *et al*., 1995; Dopp *et al*., 1995, 1997). Ault et al. (1995), in a study using lung epithelial cells of the newt *Taricha granulosa*, reported that crocidolite fiber-chromosome contact induced chromosome breaks, and in one instance, led to displacement of the chromosome. Phagocytized crocidolite asbestos fibers caused a break in both chromatids during mitosis in a living cell. During anaphase, the resultant acentric chromosome fragment, consisting of both chromatids, was left behind at the equatorial plate of the spindle. The fragment ended up in the cytoplasm of one of the daughter cells. Dopp and Schiffmann (1998) investigated mitotic disturbances caused by amosite, crocidolite and chrysotile in Syrian hamster embryo (SHE) fibroblasts. All three fiber types induced micronuclei in SHE cells with a high frequency (up to 200 MN/2000 cells; dose range: 0.1 –5.0 μg/cm^2) in a dose-dependent manner. Asbestos fibers caused both loss as well as breakage of chromosomes in the absence of direct interaction with spindle fibers (spindle deformation was observed in cells with disturbed meta-and anaphases while the spindle fiber morphology appeared unchanged).

DNA damage by asbestos fibers has been indicated by the occurrence of DNA repair in rat pleural mesothelial cells (Renier *et al*., 1990); nick translation in rat embryo cells (Libbus *et al*., 1989); and DNA nicks in C3H10T1/2 cells (Turver and Brown, 1987). Crocidolite caused DNA single strand breaks in human mesothelial cells (Ollikainen

et al., 1999). Kinnula *et al*. (1994) reported no single-strand breaks in MeT-5A cells treated with amosite. Erionite enhanced DNA repair in C3H10T1/2 cells (Poole *et al*., 1983), but chrysotile did not induce DNA repair in hepatocytes (Denizeau *et al*., 1985). Poly(ADP)ribosylation induced by DNA breaks has been observed in rat pleural mesothelial cells treated with chrysotile and crocidolite (Dong *et al*., 1995).

A radiosensitive DNA repair-deficient xrs-5 cell line exposed to chrysotile for 24 hours gave significantly lower cell survival accompanied by a cell growth delay, as well as a higher number of DNA double strand breaks compared with wild-type Chinese hamster ovary cells (Okayasu *et al*., 1999a). Chrysotile asbestos was significantly more cytotoxic to A_L hamster-human cell hybrids than tremolite or erionite, but erionite exhibited mutagenicity comparable to chrysotile (Okayasu *et al*., 1999b).

Several authors have reported that crocidolite or erionite induces the release of free-radical reactive oxygen/nitrogen species (Gormley *et al*., 1985; Hansen and Mossman, 1987; Takeuchi and Morimoto, 1994; Vallyathan *et al*., 1992; Xu *et al*., 1999). Goodglick and Kane (1986) showed that the toxicity of crocidolite against macrophages could be prevented by a hypoxic environment. Reactive oxygen/nitrogen species induce many kinds of DNA damage, including DNA strand breaks and base modifications, and reactive oxygen species have been reported to play an important role in asbestos-related damage (Floyd, 1990; Goodglick and Kane, 1986; Kamp *et al*., 1992; Zoller and Zeller, 2000). Decreased levels of antioxidants and increased levels of lung tissue injury parameters in asbestos-treated Wistar rats, both 24 hours and three months after exposure, suggest involvement of reactive oxygen intermediates in the mechanism of asbestos lung disease development (Kaiglova *et al*., 1999).

Crocidolite and amosite have been found to enhance 8-hydroxydeoxyguanosine, a marker for mutagenic oxidative DNA damage, in calf thymus DNA (Adachi *et al*., 1992; Faux *et al*., 1994). In the Takeuchi and Morimoto (1994) study, crocidolite induced the release of reactive oxygen species in neutrophils and macrophages. A marker for mutagenic oxidative DNA damage, 8-hydroxydeoxyguanosine, was induced in the cellular DNA of a human promyelocytic leukemia cell line, HL60, when incubated with crocidolite. The authors propose that the 8-hydroxydeoxyguanosine increase induced by crocidolite is due, not to an increase of reactive oxygen/nitrogen species released from the cells, but to the generation of hydroxyl radicals by crocidolite internalized in the cells close to DNA. Xu *et al*. (1999) demonstrated that reactive oxygen species mediate crocidolite-induced DNA mutagenesis in A_L hamster-human cell hybrids in a concentration-dependent manner. Crocidolite induced increases in oxidative DNA damage in A_L cells.

In vitro cytotoxicity of various types of asbestos in tissue culture cell lines including Syrian hamster peritoneal macrophages and Chinese hamster lung V79-4 cells has been reported (Bey and Harington, 1971; Brown *et al*., 1978; Chamberlain and Brown, 1978). An Indian variety of chrysotile induced cytotoxicity in rat hepatocytes with lipid peroxidation and intracellular glutathione depletion (Aslam *et al*., 1992). Chrysotile from India produced cytotoxic and cytogenetic effects of cytoplasm vacuolization, cell flattening with increased size, and chromosomal aberrations *in vitro* on CHO cells (Babu *et al*., 1980).

Chrysotile induced cytotoxicity in human erythrocytes (Kennedy *et al*., 1989). Hemolysis by chrysotile may be related to an adsorption of the red blood cell membranes on the fibers (Jaurand *et al*., 1983). The hemolytic activity of asbestos on red blood cells *in vitro* has been correlated with its surface charge as indicated by its zeta potential (Light and Wei, 1977a,b). A correlation between asbestos-induced production of reactive oxygen metabolites and red blood cell hemolysis was observed (Hendenborg and Klockars, 1987).

Cell Transformation and Other Changes

Treatment of either human or rodent cells with asbestos produces damage to cellular DNA, which can lead to neoplastic cell transformation (Barrett, 1992; Barrett *et al*., 1989; Jaurand, 1989). Asbestos did not cause morphologic transformation of C3H10T1/2 cells (Brown *et al*., 1983; Hei *et al*., 1985, 1991), but transformed BALB/c#3T3 cells (Hesterberg and Barrett, 1984; Hesterberg *et al*., 1986; Lu *et al*., 1988). Chrysotile or crocidolite has been shown to induce morphological and neoplastic transformations of Syrian hamster embryo fibroblasts (Hesterberg and Barrett, 1984; Mikalsen *et al*., 1988). Cell transformation assays have demonstrated a greater carcinogenic potential of long versus short fibers (Jaurand, 1996).

The effects of asbestos fibers on cell proliferation, cell activation, and gene expression have been studied (Driscoll, 1996), as well as short-term animal tests for detecting inflammation, fibrosis and pre-neoplastic changes induced by fibers (Donaldson, 1996). The changes in cell number and tissue volumes in response to asbestos exposure have been quantified by morphometry or stereology, and more recently by assessing the incorporation of tritiated deoxythymidine or 5-bromo-2'-deoxyuridine into cells. An intraperitoneal injection in mice of 200 µg UICC crocidolite long fibers (approximately 60 percent greater than two µm), not readily cleared by lymphatics and persistent for six months, resulted in accumulation of inflammatory cells, mesothelial cell injury, and proliferation (Moalli *et al*., 1987). Three to 42 weekly intraperitoneal injections of 200 µg UICC crocidolite in mice led to progressively increased inflammation as well as mesothelial cell injury and proliferation (MacDonald and Kane, 1993).

Chromosomal aberrations were seen in Chinese hamster cells cultured in a medium containing 0.01 mg/mL of either chrysotile or crocidolite asbestos (Sincock and Seabright, 1975). No chromosomal aberrations were seen in culture with coarse glass fibers or with control media.

Cancer

Asbestos as a Carcinogen

A number of researchers have reported increases, some statistically significant, in neoplastic response at one or more tissue sites (mostly gastrointestinal) following dietary exposure to asbestos (Donham et al., 1980; Gibel et al., 1976; McConnell et al., 1983a, 1983b; Smith et al., 1980; Ward et al., 1980). There is some evidence that acute oral

exposure may induce precursor lesions of colon cancer and that chronic oral exposure may lead to an increased risk of gastrointestinal tumors (Chouroulinkov, 1989; NTP, 1985; Truhaut and Chouroulinkov, 1989).

Early animal studies on gastrointestinal cancer from ingested asbestos were mostly inconclusive or negative (Cunningham *et al*., 1977; Gross *et al*., 1974; Wagner *et al*., 1977), although some studies yielded increases in tumor frequency that were not statistically significant (Bolton *et al*., 1982; Donham *et al*., 1980; Smith *et al*., 1980; Ward *et al*., 1980). However, rats fed powdered chrysotile filter materials including 47 percent non-asbestos materials had a significant excess incidence of malignant tumors (Gibel *et al*., 1976). Except for the studies by Donham *et al*. (1980) and Smith *et al*. (1980), these studies were conducted with relatively small numbers of animals. Additionally, some of the studies were conducted for insufficient time periods for adequately testing the carcinogenic potential of ingested asbestos. In the case of the Gross *et al*. (1974) study, systematic histological examination was conducted on only 53 of over 200 animals. Zaidi (1974) cited major differences between the stomachs of rats and humans and emphasized the need for suitable animal models to correlate with results in humans. The author suggested that the role of the mucous barrier in preventing absorption of asbestos from the gastrointestinal tract of rats might account for the lack of neoplastic response seen in most animal studies.

Donham *et al*. (1980) fed 189 weanling F344 rats a diet containing 10 percent chrysotile over their lifetime to determine the effects of ingested asbestos on the colon. Control groups were fed a diet containing 10 percent nonnutritive cellulose (n = 197) or a standard laboratory rat diet (n =115). The cumulative risk for development of any colon-associated lesion (neoplastic plus non-neoplastic lesions) was greatest for asbestos-fed rats (17.9 percent) compared to 13.6 percent for those fed the fiber-controlled diet and 8.2 percent for those fed the standard control diet. Chrysotile fibers were seen by electron microscopy in six out of ten ashed colon specimens of rats fed the asbestos diet. Additionally, levels of two cyclic nucleotides, adenosine 3'-5'-cyclic monophosphate (cAMP) and guanosine 3',5'-cyclic monophosphate (cGMP), were analyzed in the colon tissues of an unspecified number of rats fed the diet for 24 months and killed at 33 months. The levels of cAMP in the asbestos-fed animals were significantly less than in the control groups. For cGMP, the levels in the asbestos-fed animals were similar to the normal diet control group. The authors concluded that the cAMP results suggest a serious cell-regulator defect related to asbestos ingestion.

Gibel *et al*. (1976) reported a statistically significant ($p < 0.01$) increase in malignant tumors in the lung, kidney, liver and reticuloendothelial system, but no increase in intestinal neoplasia, in Wistar rats fed asbestos filter material (20 mg/day) containing 53 percent chrysotile asbestos for a lifetime. The chrysotile fiber was extracted from a commercial filter pad used to purify beverages; the composition of the remainder of the material was unspecified. One lung carcinoma, four kidney carcinomas, three reticular cell sarcomas, and four liver-cell carcinomas were reported. One lung adenoma, two cholangiomas, two papillomas of the forestomach, and two mammary fibroadenomas were also observed. There were two liver cell carcinomas in the control group of 50 animals. The total number of animals with tumors in each group was not reported.

In a study by McConnell *et al*. (1983a), groups of 100 to 250 male and female Fischer 344 rats were administered amosite or tremolite asbestos at a concentration of one percent in pelleted diet for the lifetime of the rats, starting with the dams of the test animals. One group of amosite rats also received chrysotile by gavage during lactation at a dose level of 0.47 mg/kg-day. The offspring from dams exposed to tremolite or amosite asbestos were smaller at weaning than those from untreated mothers, and remained smaller throughout their life. Significant increases ($p<0.05$) in the incidence of C-cell carcinomas of the thyroid and mononuclear cell leukemia in male rats were observed in amosite-exposed groups. C-cell hyperplasia was increased in amosite female groups. No toxicity or increase in neoplasia was observed in the tremolite-exposed rats compared to the controls.

McConnell *et al*. (1983b) reported a significant increase in adrenal cortical tumors ($p < 0.05$) in male and female Syrian golden hamsters fed a pelleted diet over their lifetime with one percent intermediate range (IR) chrysotile asbestos, and in males treated with short range (SR) chrysotile asbestos when compared with pooled controls. Statistical significance was lost, however, when these dosed groups were compared to their temporal controls. A variety of neoplasms was observed in asbestos-exposed and control hamsters. The proportion of control male or female hamsters bearing primary tumors was not statistically different among the four control groups. Thus, statistical comparisons were made with pooled controls as well as with temporal controls.

Ward *et al*. (1980) administered 1 mg amosite asbestos in saline by gavage to six-week old F344 weanling rats ($n = 50$) three times per week for 10 weeks, and observed the animals for 95 weeks. Seventeen tumors (16 carcinomas of the colon, one carcinoma of the ileum) were reported in 49 animals examined. No controls were included but the incidence greatly exceeded that of the one percent reported in historical controls (0/21 tumors by saline, 0/21 untreated). The same dosing regimen administered to 21 rats observed for 34 weeks duration produced no malignant tumors.

Although Bolton *et al*. (1982) did not report any adverse effects following the prolonged ingestion of asbestos in laboratory rats, an examination of the benign tumors showed a clear excess of mesenteric hemangiomas in the chrysotile-treated group ($p < 0.01$). The authors suggest that an increased occurrence of proliferative vascular lesions might be related to vascular dissemination of the fibers.

Smith *et al*. (1980) exposed groups of 30 male and female hamsters for a lifetime to 0.5, 5 or 50 mg/L amosite asbestos and taconite tailings in drinking water. Filtered water from Lake Superior was also given to 120 control animals. In the low and intermediate amosite exposure groups, four malignancies, one pulmonary carcinoma, one peritoneal mesothelioma , and two early squamous cell carcinomas of the nonglandular stomach were found, but the incidence was not statistically significant ($p < 0.05$). No malignancies were found in the highest amosite exposure group.

Wagner *et al*. (1977) fed groups of 32 Wistar rats 100 mg/day chrysotile asbestos or Italian talc in malted milk powder for five days per week for 100 days over a six-month period. The 16 control rats were fed malted milk. One gastric leiomyosarcoma was observed in an animal fed chrysotile and one was observed in an animal fed talc. No tumors occurred in the controls.

A series of large scale, lifetime carcinogenesis studies (feed studies) have been performed by the NTP. These studies have yielded mostly negative results, although some suggestive increases in tumor frequencies did occur (Table 4). The 1985 NTP feed studies of chrysotile asbestos in F344/N rats did show some evidence of carcinogenicity. In this study, male and female rats (88-250/group) were administered a concentration of 1 percent short-range (SR) or intermediate-range (IR) chrysotile asbestos in pelleted diet (500 mg/kg-day) for the lifetime of the rats, starting with the dams of the test animals. Subgroups of 100 male and 100 female IR chrysotile-exposed rats also received 0.47 mg/g IR chrysotile asbestos in water by gavage during lactation (preweaning, PW). Feed consumption and survival were comparable among the SR and IR chrysotile asbestos groups and controls. No neoplastic or nonneoplastic disease was associated with SR chrysotile exposure. However, benign epithelial neoplasms (adenomatous polyps), described by NTP as being "grossly visible", were observed in the large intestine of IR chrysotile asbestos male rats (9/250, 3.6 percent). Although not statistically significant (p=0.08) compared with concurrent controls (0/85), the incidence of these neoplasms was highly significant (p=0.003) when compared with the incidence of epithelial neoplasms (benign and malignant combined) of the large intestine in the pooled male control groups of all the NTP oral asbestos lifetime feeding studies (3/524, 0.6 percent). These lesions are uncommon in standard 2-year carcinogenesis studies. The biologic importance of this finding was further supported by the observation of lesions of similar morphology in the small intestine or glandular stomach of four additional IR chrysotile male rats and by a low incidence (2/100, 2.0 percent) of adenomatous polyps in the large intestine of male rats in the IR/PW group.

In addition to the above findings (NTP, 1985), a significant increase (P>0.05) in keratoacanthomas of the skin was observed in male IR (19/250, 7.6 percent) and IR/PW (8/100, 8 percent) chrysotile-exposed rats compared with the concurrent controls (1/88, 1.1 percent). An apparent increase in the incidence of clitoral gland neoplasms in female IR (18/250, 7.2 percent) and IR/PW (4/100, 4.0 percent) chrysotile-exposed rats compared with that in the concurrent controls (1/88. 1.1 percent) was also observed. The biologic significance of these findings was discounted, however, because of a lack of statistical significance when compared with the pooled male and female control groups, respectively, from all other NTP oral asbestos studies.

The introduction of high concentrations of asbestos and other durable fibers into the pleura (Reeves *et al*., 1971; Smith *et al*., 1965; Stanton and Wrench, 1972; Wagner *et al*., 1973, 1977), or peritoneum (Davis, 1974; Englebrecht and Burger, 1973; Krajnow *et al*., 1998; Miller *et al*., 1999; Pott *et al*., 1976; Reeves *et al*., 1971; Shin and Firminger, 1973) of rats, mice, hamsters, and rabbits resulted in malignant neoplasms. Fiber length, dissolution, and biopersistence influenced the production of mesothelioma in the peritoneal cavity by intraperitoneal injection of amosite in male SPF Wistar rats (Miller *et al*., 1999). Fibers that are long and thin appear to be more carcinogenic than fibers that are short and thick (Stanton *et al*., 1977).

Table 4. Summary of NTP Lifetime Studies on Asbestos in Feed

Asbestos type	Species	Median length (μm)	Size distribution	Carcinogenic effects	Conclusion	Reference
Amosite	Rat	4.37	74% > 6μm	Increased C-cell carcinoma (males) Increased leukemia (males)	Not considered treatment related Questionable biological and statistical significance.	NTP, 1990b
Amosite	Syrian hamster	4.37	74% > 6μm	None	No carcinogenic response	NTP, 1983
Crocidolite	Rat	10	73% > 8μm	None	No carcinogenic response	NTP, 1988
Tremolite	Rat	No data	22%>5μm	None	No carcinogenic response	NTP, 1990c
Chrysotile (short range)	Rat	0.66	30% > 4.5μm	None	No evidence of carcinogenicity	NTP, 1985
Chrysotile (intermediate range)	Rat	0.82	60% > 5.4μm	Benign interstitial polyps (males) Clitoral gland neoplasm (females)	Some evidence of carcinogenicity, NS vs. concurrent controls; highly significant vs. historical controls) No evidence of carcinogenicity	NTP, 1985
Chrysotile (short range)	Syrian hamster	0.66	30% > 4.5μm	Adrenal cortical adenomas (males)	No evidence of carcinogenicity (NS vs. historical controls)	NTP, 1990a
Chrysotile (intermediate range)	Syrian hamster	0.82	60% > 5.4μm	Adrenal cortical adenomas (males and females)	No evidence of carcinogenicity	NTP, 1990a

Abstracted from ATSDR (1995), Table 2-4.
NS = not significant

Asbestos as a Co-carcinogen or a Promoter

It has been shown that there is a synergistic interaction for the risk of lung cancer in humans between exposure to asbestos and smoking (NAS, 1984). Topping and Nettesheim (1980) demonstrated that asbestos increased the incidence of carcinomas induced by 7,12-dimethyl-benz(a)anthracene in the rat tracheal transplant model, whereas asbestos alone induced a low incidence of tumors. Furthermore, the presence of asbestos particles enhances by several-fold the carcinogenic and genotoxic potential of benzo(a)pyrene (Eastman *et al*., 1983; Fournier and Pezerat, 1986; Reiss *et al*., 1983). A number of observations indicate that asbestos induces cellular and biochemical changes such as hyperplasia, metaplasia, DNA synthesis and stimulation of oxygen-free radicals, which are typical of known tumor promoters (IARC, 1996; Mossman and Marsh, 1989; Walker *et al*., 1992).

In light of the equivocal evidence for carcinogenicity of ingested asbestos, it is conceivable that the high adsorption capability of asbestos fibers creates the possibility of comutagenic or cogenotoxic action with adsorbed organic micropollutants which are carcinogens, such as polycyclic aromatic hydrocarbons, trihalomethanes, and others (Eastman *et al*., 1983; Fournier and Pezerat, 1986; Reiss *et al*., 1983). Varga *et al*. (1996a) found a dose-dependent increase in the frequency of SCE in the bone marrow cells of Fischer 344 rats gavaged with benzo(a)pyrene-coated crocidolite fibers at 50 mg/kg with 2.5 μg/mL of benzo(a)pyrene. Untreated fibers as well as fibers treated at lower concentrations of 0.25, 0.5, and 1 μg/mL of benzo(a)pyrene did not cause alterations.

In a second study, Varga *et al*. (1996b) demonstrated that anthophyllite asbestos fibers are able to adsorb benzo(a)pyrene molecules from extremely low concentration aqueous solutions of 0.25, 0.5, 1, and 2.5 μg/mL, but were less effective than crocidolite fibers in inducing cytogenetic alterations in the bone marrow cells of rats. The authors felt this discrepancy was due to differences in fiber diameter; of the amphibole types of asbestos, crocidolite tends to have the thinnest fibers and anthophyllite the thickest. Anthophyllite fibers pretreated with the benzo(a)pyrene solutions caused dose-dependent increases in the SCE frequencies in gavaged rats. As before, untreated fibers did not cause alterations, and serum and urinary mutagenicity using *S. typhimurium* TA98 and TA100 was not observed during these and follow-up studies (Varga *et al*., 1996a,b, 1998).

Varga *et al*. (1999) gavaged F-344 female rats with 50 mg/kg untreated crocidolite and anthophyllite fibers, and fibers that had been allowed to adsorb benzo[a]pyrene from an aqueous solution of 2.5 μg/ml (n = 3/group). Peritoneal macrophages and intestine, parietal, peritoneum and omentum samples were obtained from the animals after 24 hours. High levels of DNA strand breaks were observed in cells prepared from the omentum and intestine. A significant potentiating effect of the adsorbed carcinogen on the induction of DNA damage in the omentum was also observed. The authors concluded that the results of this study support the molecular model of asbestos co-carcinogenesis, including both asbestos-induced deletions and mutations caused by a mutagen carried by the same fibers.

Toxicological Effects in Humans: Oral Exposure

Exposure to asbestos by the oral route may occur through drinking water, recreational water, foods and beverages contaminated with asbestiform fibers, or through swallowing fibers cleared from the respiratory tract via the mucociliary escalator. It has also been postulated that inhaled asbestos may migrate from the lung and circulate in the lymph to other organs in the body. The vast majority of human studies entail ingestion exposure via asbestos-contaminated drinking water. Most studies of asbestos in drinking water are ecologic, and potential confounders such as diet, smoking, and occupation could not be adequately controlled.

Acute, Subacute, and Chronic Noncancer Effects

Asbestos may cause irritation of the gastrointestinal tract due to mechanical action of the fibers. There is no evidence of any acute or subchronic systemic effect from oral exposure to asbestos (Hall and Rumack, 2000). There are a number of toxicological endpoints for which there are no data in humans orally exposed to asbestos. These endpoints include death, immunotoxicity, neurotoxicity, reproductive or developmental effects, and genotoxicity (ATSDR, 1995).

Cancer

Epidemiological Data

Epidemiological data seem to be equivocal on the probability of an increase in cancer incidence in populations exposed to asbestos-fiber contaminated drinking water. A number of epidemiological studies have reported increases, some statistically significant, in cancer death or tumor incidence rates at one or more tissue sites (mostly gastrointestinal) in populations exposed to elevated levels (usually in the range of 1×10^6 to 3×10^8 fibers/L) of asbestos in their drinking water (Andersen *et al*., 1993; Conforti, 1983; Conforti *et al*., 1981; Howe *et al*., 1989; Kanarek, 1983, 1989; Kanarek *et al*., 1980; Levy *et al*., 1976; Polissar *et al*., 1982, 1984; Sigurdson *et al*., 1981; Toft and Meek, 1983; Toft *et al*., 1981, 1984; Wigle, 1977). A review of thirteen of these epidemiological studies in five areas of the U.S. and Canada concluded that the number of positive findings for neoplasms of the esophagus, stomach, pancreas, and prostate was unlikely to be due to chance alone (Marsh, 1983). Kanarek *et al*. (1980) noted that there were relatively consistent findings for increased stomach cancer and pancreatic cancer among the studies. The stomach is an obvious site for concern as the cancer rate at this site has been shown to be elevated in several studies of occupationally-exposed workers. However, Cantor (1997), in a review of the evidence, concluded that the epidemiological drinking water studies were not adequate for quantitative risk assessment.

Following the findings of amphibole asbestiform fibers in the Duluth, Minnesota, municipal water in 1973, a number of epidemiological studies focusing on cancer risk were conducted to determine the toxicological risk posed by asbestos contamination in

drinking water. Several studies covered asbestos contamination of industrial source water (Masson *et al*., 1974; Levy *et al*., 1976; Sigurson *et al*., 1981) and natural source water (Conforti *et al*., 1981; Kanarek *et al*., 1980; Neuburger *et al*., 1984; Polissar *et al*., 1982, 1983a,b, 1984; Toft *et al*., 1981; Wigle, 1977). Others evaluated contamination of drinking water through asbestos cement distribution pipes (MacRae, 1988), or where water was collected from asbestos tile roof run-off (Andersen *et al*., 1993; Harrington *et al*., 1978; Howe *et al*., 1983; Meigs, 1983; Meigs *et al*., 1980; Millette, 1983; Millette *et al*., 1983; Sadler *et al*., 1984).

Some of these studies suggested elevated cancer incidence as a consequence of ingestion exposure (Andersen *et al*., 1993; Conforti *et al*., 1981; Kanarek *et al*., 1980; Polissar *et al*., 1982). Kanarek *et al*. (1980) found elevated peritoneal and stomach cancer in an ecological study of cancer incidence for 1969 to 1971 related to natural chrysotile fiber contamination of drinking water in the San Francisco Bay area. Conforti *et al*. (1981) found elevated digestive tract, esophageal, stomach, and pancreatic cancer incidence during 1969 to 1974 in an ecological study of the San Francisco Bay area. In both of these reports the study area was the San-Francisco-Oakland Standard Metropolitan Statistical Area (SMSA) and the unit of observation was the census tract. Polissar *et al*. (1982) found suggestive (elevated but not statistically significant) small intestine cancer when they examined natural contamination by chrysotile asbestos fibers in community water supplies in an ecological cancer incidence study from 1974 to 1977 in Washington's Puget Sound area. Odds ratios for tumors of the small intestine were consistently elevated in both sexes, as were those for neoplasms of the thyroid, eye, testis and prostate in males. The increased risk of prostate cancer found in this study has also been found in the study by Wigle (1977). Although consistent in direction, most of the odds ratios for these sites are not statistically significant. Andersen *et al*. (1993) found elevated stomach cancer in a Norwegian cohort study of male lighthouse keepers who ingested drinking water collected from runoff over asbestos-cement roof tiles. The study population was confined to 690 men alive at the beginning of the follow-up period January 1, 1960. They were followed for cancer morbidity and total mortality to the end of 1991. The five-year age-specific incidence rates for each year from 1960-1991 were used to estimate the expected number of cancer cases. As all of the lighthouses are located in districts with a low population density, expected numbers are therefore based on rates of the rural Norwegian population.

Table 5 summarizes results from a number of these epidemiological studies. The associations summarized in Table 5 represent one or more epidemiological studies that have shown some relationship to asbestos in water for neoplasms of the following sites: rectum (Mason *et al*., 1974), stomach (Mason *et al*., 1974; Levy *et al*., 1976; Wigle, 1977; Conforti *et al*., 1981), pancreas (Mason *et al*., 1974; Levy *et al*., 1976; Wigle, 1977; Meigs *et al*. 1980; Conforti *et al*., 1981), lung (Wigle, 1977), peritoneum (Conforti *et al*., 1981), esophagus (Conforti *et al*., 1981) and pleura (Conforti *et al*., 1981). All of these epidemiological studies, whether or not significant results were found, suffered major flaws or limitations. Many of the studies were ecological and thus had unknown or undocumented exposure; many were without size distribution characterization for the asbestos fibers (Conforti *et al*., 1981; Harrington *et al*., 1978; Kanarek *et al*., 1980; Masson *et al*., 1974; Meigs *et al*., 1980; Millette, 1983; Neuberger *et al*., 1984; Nicholson, 1983; Polissar *et al*., 1982; Sadler *et al*., 1984; Sigurson *et al*., 1981; Toft

et al., 1981; Valic and Beritic-Stahuljak, 1993; Wigle, 1977). Most of the studies did not measure personal risk factors or other potentially confounding factors so that exposure-risk relationships could be adequately characterized. Studies of industrial contamination in Duluth (Masson *et al*., 1974) and natural contamination in the San Francisco Bay area (Kanarek *et al*., 1980) had their periods of mortality follow-up extended with inconsistent results between follow-up periods (Levy *et al*., 1976, and Sigurdson *et al*., 1981 for Duluth; Conforti *et al*., 1981 for the San Francisco Bay area). Other problems included too small a sample size or an inadequate cancer latency period. Although Levy *et al*. (1976) did not find an excess of gastrointestinal malignancies in Duluth residents through 1974, too few years had elapsed since the start of the oral amphibole exposure of the Duluth residents to draw any conclusions about risk. The paucity of positive findings from Connecticut (Harrington et al., 1978; Meis et al., 1980) could be due both to the low concentration of asbestos in the water, and the relatively short duration of exposure in some areas of the state (Craun et al., 1977). Another limitation of all the studies to date is that specific asbestos exposures are imputed to the population in an entire geographic region. There may be a confounding effect from other factors that vary geographically, and there may be misclassification of exposures due to recent in-migration into the study area (Polissar, 1980).

Because the evidence for the carcinogenicity of oral asbestos exposure in animals is equivocal, the question has arisen whether apparent increased cancer risk in some epidemiological studies indicates health effects of organic micropollutants accumulated by the fibers. Organic (and inorganic) chemicals clearly can bind to asbestos fibers. *In vivo* studies have shown that ingested amphibole fibers are genotoxic (e.g., Varga *et al*., 1996a,b). Inhalation studies clearly demonstrate the role of adsorbed polycyclic aromatic hydrocarbons in asbestos carcinogenesis (Hammond *et al*., 1979). The large surface area of the fibers creates the possibility of co-genotoxic action with adsorbed water-borne organics. Studies by Varga *et al*. (1998, 1999) have demonstrated that asbestos fibers are able to adsorb benzo[a]pyrene molecules from aqueous solutions, and consider potential co-genotoxicity of these materials. At present, data are inadequate to fully address this possible tumorigenic mechanism.

Table 5. Summary of Studies of Cancer Risk from Asbestos in Drinking Water, by Neoplasm Site*

	Area/First Author						
Neoplasm Site	**Duluth/**		**Quebec/ Wigle**	**Connecticut/**		**California/ Conforti**	**Puget Sound/ Polissar**
	Mason	**Levy**		**Harrington**	**Meigs**		
Colon	00	00	00	00	00	00	00
Rectum	MF	00	00	00	00	00	00
Stomach	MF	M0	M0	00	00	MF	00
Pancreas	0F	MF	0F	--	B	MF	00
Lung	--	--	M0	--	00	00	00
Peritoneum	--	00	--	--	--	0F	--
Esophagus	00	00	--	--	--	MF	00
Gall Bladder	00	00	--	--	--	00	00
Pleura	--	--	--	--	--	0F	--
Small Intestine	--	00	--	--	--	00	MF
Brain	--	--	00	--	--	00	MF
Leukemia	--	--	00	--	--	00	MF
Thyroid	--	--	--	--	--	00	M0
Eye	--	--	--	--	--	--	M0
Prostate	--	--	M	--	--	00	M

*Table adapted from Polissar *et al*. (1982)
M= association in males (i.e. association between water asbestos levels and risk in one or both sexes); F= association in females; B= association in both sexes combined; 00= no association; -- = not studied.

Toxicological Effects in Humans: Inhalation and Other Exposures

Acute, Subacute, and Chronic Noncancer Effects

Asbestos may cause irritation of the eyes, skin, and respiratory tract due to mechanical action of the fibers. There is no evidence of any acute or subchronic systemic effect from inhalation exposure to asbestos (ATSDR, 1995). Chronic exposure to asbestos through inhalation has been reported to cause various diseases including asbestosis, genotoxicity, and reproductive effects (Hall and Rumack, 2000). There have been a number of studies on immune system changes in humans exposed to asbestos by inhalation.

Immunological and Lymphoreticular Effects

Research over the past three decades has shown that the human immune system can be altered directly or indirectly by occupational exposure to asbestos (Rosenthal *et al*., 1998). An immunogenetic predisposition towards developing asbestosis has been indicated (Rosenthal *et al*., 1998). Although the mechanisms are not well understood, the inhalation studies indicate that the immune system has been affected in individuals who have developed clinical signs of injury, such as asbestosis or cancer (DeShazo *et al*., 1983; Kagan *et al*., 1977a,b; Pernis *et al*., 1965; Sprince *et al*., 1991, 1992). Cell stress induced by crocidolite appears to injure cells via the production of the pro-inflammatory cytokine interleukin IL-8 (Tsuda *et al*., 1999).

Asbestos exposure has been associated with changes in both humoral and cellular immune functions in humans. For example, the chronic inflammatory response preceding the development of asbestosis represents a complex immunological process initiated by fiber deposition that involves multiple types of immune cells. This inflammatory response, along with evidence of peripheral immune changes following asbestos exposure, has long been implicated in the pathogenesis of asbestos-related disease (Rosenthal *et al*., 1999).

Asbestos exposures suppress pulmonary and systemic immunity, and alter host resistance to infectious agents or tumor cells. Impairment in cell-mediated immunity in humans by asbestos is characterized by decreases in delayed hypersensitivity responses, the numbers of circulating T cells, and T-cell proliferation (Rosenthal *et al*., 1999). Disturbances in cell-mediated immune responses are indicated by asbestosis patients' impaired lymphocyte response to phytohaemagglutinin mitogen (Kagan *et al*., 1977a), as well as by low numbers of circulating peripheral blood leucocytes and T lymphocytes (Wagner *et al*., 1979). The responses of normal peripheral blood mononuclear cells, mainly the lymphoid nonadherent population, to phytohaemagglutinin are also depressed when exposed to asbestos *in vitro* (Barbers *et al*., 1982).

Effects on humoral immunity are also revealed by the increased prevalence of autoantibodies and elevations in serum immunoglobulin levels in these patients (Kagan *et al*., 1977b). Asbestosis patients present hyperactive T-cell responses. These are often manifested by elevations of serum immunoglobulins IgA, IgG, IgM, and IgE and secretory immunoglobin IgA, and the presence of autoantibodies such as antinuclear antibody and rheumatoid factor (Doll *et al*., 1983; Kagan *et al*., 1977b; Lange *et al*., 1974; Luster and Rosenthal, 1993; Pernis *et al*., 1965; Rosenthal *et al*., 1998).

Tsang *et al*. (1988) studied peripheral blood lymphocytes in 20 malignant mesothelioma patients, 375 long-term asbestos workers without neoplasia, and 118 healthy control subjects. The absolute numbers of total T cells and T helper cells were normal in asbestos workers without tumors; these cells were significantly reduced in cancer patients. On the other hand, T suppressor cells remained unchanged in cancer patients but were significantly elevated among the asbestos workers without neoplasia. This imbalance of T cell subsets resulted in a marked reduction in T helper to T suppressor ratio in mesothelioma patients and in asbestos workers (Tsang *et al*., 1988). The addition of chrysotile to human peripheral blood lymphocyte cultures, stimulated with concanavalin A and phytohaemagglutinin, resulted in a significant increase in the

mitogenic response. The binding of the mitogen to the reactive sites on the lymphocyte surface is thought to be indispensable. Chrysotile and crocidolite fibers have been shown to stimulate and bind to immature B lymphocytes to go into mitosis, but not to mature B cells (Ueki *et al*., 1984).

In direct response to asbestos, the inflammatory cytokines interleukin IL-6 and IL-8 are produced by lung epithelial cells *in vitro*. This response is controlled by changes in the cellular oxidative state induced by iron present in the fiber through Fenton-type chemistry. As a result of this oxidative stress, the redox sensitive nuclear transcription factors (NF), NF-kappaB and NF-IL-6, which help regulate cytokine gene expression, are activated (Luster and Simeonova, 1998). *In vitro* exposures of macrophages, fibroblasts, alveolar epithelial cells, or pleural mesothelial cells to amosite, chrysotile, or crocidolite produce bioactive lipid chemokines, e.g., interleukin IL-8, or growth factor protein, e.g., platelet-derived growth factor (Driscoll, 1996).

Asbestos stimulation triggers cytokine release *in vitro* from both normal human monocytes and alveolar macrophages as determined by the upregulation of mRNAs for cytokines and activation of the p38 kinase, but there is a block in translation of cytokine mRNAs in the macrophages (Geist *et al*., 1999). Chrysotile or crocidolite upregulates expression of the urokinase-type plasminogen activator receptor on the surface of human mesothelial cells as indicated by binding of radiolabeled activator (Perkins *et al*., 1999). Inhibition or delay of cytokinesis by chrysotile or crocidolite can result in bi- or trinucleation through the loss of midbody or intercellular bridge proteins that are required for completion of cytokinesis in human mesothelial cells (Jensen and Watson, 1999).

The production of proinflammatory cytokines such as TNF-alpha is an important mediator of the pathologic responses of asbestosis. Asbestos-induced TNF-alpha gene expression is mediated through a process that involves NF-kappaB activation and metal-mediated free radical reactions. Exposures of lung macrophages to crocidolite *in vitro* cause increases in TNF-alpha production and NF-kappaB activation; this activation can be inhibited by NF-kappaB inhibitors and free radical scavengers (Cheng *et al*., 1999).

Chrysotile B fibers induce apoptosis of human peripheral blood mononuclear cells. The alteration of gene expression at the mRNA level during *in vitro* cultures reveals upregulation of Flice and Apaf-1 genes and downregulation of TNF receptor 1 and Bid genes. The process may be mediated by the Fas-related apoptotic pathway (Ma *et al*., 1999).

Genotoxicity

Chrysotile has been shown to induce an increased frequency of SCE *in vitro*. Therefore the effect of occupational exposure to chrysotile was evaluated on SCEs in 45 workers versus 45 controls in Korea. There was a marginally significant increase, after controlling for the effects of age and smoking by multiple regression analysis (Lee *et al*., 1999). Takahashi *et al*. (1997) studied the relationship between asbestos exposures and the level of 8-hydroxydeoxyguanosine (8-OHdG) in DNA of peripheral blood leukocytes as a biological marker of asbestos exposure in workers at a Chinese asbestos-material plant. Among the 20 workers and 19 controls in a large scale asbestos plant in China producing brake linings, asbestos rubber, and textiles using chrysotile, the geometric

mean 8-OhdG level showed a positive gradient in relation to increasing grades of asbestosis (exposed worker 2.39, control 1.78, $p = 0.01$), with a significant difference between the control and definite-asbestosis subgroups ($p<0.05$). The authors concluded that the 8-OHdG level in leukocytic DNA is related to grade of asbestosis and may serve as a biologic marker reflecting the status of oxidative DNA damage by asbestos.

Oxidative DNA damage in man caused by exposure to asbestos has been judged to play a role in the formation of malignant tumors (Marczynski *et al*., 2000a, 2000b). The 8-hydroxy-2'-deoxyguanosine (8-OHdG) adduct level of asbestos-exposed workers was significantly increased ($p < 0.001$) compared to that in the control group in all three years of the study period between 1994 and 1997. DNA from white blood cells of the exposed group contained between 1.7 and 2.0 times the level of oxidative damage found in control samples (Marczynski *et al*., 2000b). A second study by Marczynski *et al*. (2000a) examined the association between the 8-OHdG levels in white blood cell DNA of workers highly exposed to asbestos fibers at the workplace and clinical data, occupational and non-occupational confounding factors, and cancer. The mean DNA-adduct level was significantly higher ($p<0.01$) for patients suffering from respiratory cancer, cancer of the GI, mouth/larynx/pharynx, and urogenital tract than for controls, but not significantly higher ($p>0.05$) than that for asbestos-exposed patients without tumors. The authors findings support the hypothesis that oxidative DNA damage in man caused by asbestos fibers plays a role in the formation of malignant tumors

Molecular epidemiologic studies have associated asbestos exposure with a k-ras somatic mutation at the tumor suppressor loci p53 in adenocarcinoma of the lung. For the 84 male lung cancer patients evaluated by Nelson *et al*., (1999), the prevalence of mutation at k-ras codon 12 was higher among those with a history of occupational asbestos exposure after adjustment for age and pack-years of cigarettes smoked (adjusted odds ratio 6.8, 95 percent confidence interval 1.7 to 28.6). An index score that weights both the dates of exposure and the estimated intensity of exposure indicated that those with the mutation had significantly greater asbestos exposure than those without the mutation (Nelson *et al*., 1999). Mutations of the p53 gene were also detected in seven of 10 cases of lung adenocarcinoma in China (Fu *et al*., 1997).

Cancer

The carcinogenicity of inhaled asbestos is well established. A number of researchers have concluded that exposure to inhaled asbestos fibers leads to an increased incidence of tumors of the lung, mesothelial membrane in the coelomic cavity, esophagus, gastrointestinal tract, larynx, gastric cardia, breast, kidney, ovary, pancreas, tunica vaginalis, testis, and penis (Churg, 1988, 1998; Clemmesen and Jensen, 1981; Cocco *et al*., 1998; Doll and Peto, 1985; Edelman, 1988; Elmes and Simpson, 1971; Enterline and Kendrick, 1967; Finkelstein, 1983; Goodfellow *et al*., 1999; Goodman *et al*., 1999; Jarvholm, 1988; Kang *et al*., 1997; Karunaharan, 1986; Keal, 1960; MacLure, 1987; McDonald *et al*., 1971, 1980; McLure and Poole, 1990; Morgan *et al*., 1985; Ness and Cottreau, 1999; Newhouse and Berry, 1976; Newhouse and Wagner, 1969; Nicholson *et al*., 1982; Parent *et al*., 2000; Peto, 1980; Peto *et al*., 1982; Plas *et al*., 1998; Prescott *et al*., 1988; Raffn and Korsgaard, 1987; Raffn *et al*., 1996; Sali and Boffetta, 2000;

Selikoff *et al*., 1964, 1979; Serio *et al*., 1992; Stell and McGill, 1973; Tyagi, 1989; Vasama-Neuvonen *et al*., 1999; Weiderpass *et al*., 1999). A rare case of malignant pericardial mesothelioma in a 27-year-old Japanese man suggests the involvement of asbestos exposure (Watanabe *et al*., 1999).

Enterline and Kendrick (1967), as well as Newhouse and Wagner (1969) demonstrated an associated increase in gastrointestinal neoplasms with occupational exposure to asbestos. They observed a large excess of gastrointestinal cancers but not of other nonrespiratory cancers in a study of U.S. asbestos workers. An excess of laryngeal cancer was also observed in some groups of exposed workers. Keal (1960) reported an association between asbestosis and abdominal neoplasms in workers. Asbestos workers exposed to crocidolite, amosite, chrysotile, or mixed fibers containing crocidolite, were reported to suffer an excess risk of gastrointestinal cancers (Selikoff *et al*., 1964). Doll and Peto (1985) reviewed the results of the Selikoff *et al*. (1964) study and subsequent studies by plotting the relative risks separately for gastrointestinal and other sites against the relative risk for lung cancer, which was used as a surrogate measure of intensity of asbestos exposure in the absence of adequate exposure data. Similar, yet weak, correlations were seen with lung cancer risk for both gastrointestinal and other cancers, excluding the Selikoff *et al*. (1964) results (Doll and Peto, 1985).

Mesothelioma has been reported in children in the U.S., Austria, Brazil, Canada, Czechoslovakia, Denmark, France, Germany, India, Israel, Italy, Poland, Romania, Spain, Turkey, USSR, and Taiwan (Fraire *et al*., 1988; Kauffman and Stout, 1964; Lin-Chui *et al*., 1989; Wassermann *et al*., 1980). A pleural mesothelioma was reported in a 19-month-old infant (Reals *et al*., 1950). A congenital papillary peritoneal mesothelioma was found in a six-week-old infant (Siberstein *et al*., 1985). The possible involvement of asbestos in these rare cases of mesothelioma in infancy and childhood suggests the possibility of transplacental transfer of asbestos from mother to fetus (Fraire *et al*., 1988; Wassermann *et al*., 1980). A three-year-old daughter of a ceramics engineer who worked in a Pennsylvania insulation plant handling chrysotile and amosite was diagnosed with pleural mesothelioma (Lieben and Pistawka, 1967). A 17-year-old Texas girl with asbestos exposure earlier in school in Ohio was reported with pleural mesothelioma (Fraire *et al*., 1988). Stein and Henker (1986) reported a case of mesothelioma of the testicle in a child.

The carcinogenic effect of asbestos appears to require exposure of epithelial surfaces, such as in the lung, pleura, larynx, esophagus, peritoneum, and the continuation of the peritoneal lining into the scrotal sac. Fiber type and length seems to be the primary determinant of its disease-causing property (Boffetta, 1998). Schneiderman (1974), after conducting a literature review of digestive cancer among persons subjected to occupational inhalation of asbestos particles, concluded that human data show a dose-response relationship between exposure to asbestos and subsequent development of gastrointestinal neoplasms.

Kang *et al*. (1997) found an association between asbestos exposure and some gastrointestinal cancer in 12 occupations with elevated proportionate mortality ratios (PMRs) for mesothelioma. Elevated PMRs for mesothelioma were used to identify occupations with potentially high exposure to asbestos. When high asbestos exposure occupations were analyzed as a group, the PMRs for esophageal, gastric, and colorectal

cancer were significantly elevated at 108 (95 percent confidence interval 107 to 110), 110 (106 to 113), and 109 (107 to 110), respectively. A total of 15,524 cases of gastrointestinal cancer in the 12 occupations with elevated PMRs for mesothelioma were identified. However, a consistently elevated PMR for gastrointestinal tract cancer did not appear for each occupational group individually, and in particular for insulation workers, which comprised the highest PMR for malignant mesothelioma.

Frumkin and Berlin (1988) performed a meta-analysis of 31 cohort studies of asbestos workers and concluded that significant asbestos exposure, as indicated by a lung cancer standardized mortality ration (SMR) of at least 200, was associated with higher mortality from gastrointestinal cancer. The authors sought to use lung cancer SMR as a surrogate for measure of asbestos exposure because prior research had found lung cancer SMR to be linearly related to dose levels in exposed cohorts (Liddell and Hanley, 1985). The meta-analysis by Homa *et al*. (1994) reported similar results for colorectal cancer stratified according to lung cancer SMR, but found no dose-response relationship with asbestos dust levels.

Henderson *et al*. (1975) found amphibole and chrysotile asbestos fibers in stomach tumors and adjacent gastric mucosa in Japanese men with oral exposure to chrysotile. Not all of the tumor tissue examined contained asbestos fibers. The occupational history of the patients was not known. Other types of silicates, in addition to asbestos, were also found in some of the tissues.

Adenomatous polyps of the colon are generally accepted as precursor lesions for most cases of colorectal carcinoma. Neugut *et al*. (1991) conducted a case-control study of colorectal neoplasia on male subjects aged 35 to 84 years who underwent colonoscopy. The study consisted of 51 colorectal cancer case patients, 153 adenomatous polyp case patients, and 195 control subjects. All biopsy specimens were reviewed by the study pathologist. A questionnaire was used to ascertain each subject's degree of exposure to asbestos. Although the sample sizes were small for both case groups, an elevated risk for adenomatous polyps and colorectal cancer was observed for those subjects with a history of significant exposure to asbestos.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

A number of noncarcinogenic effects have been reported in laboratory animal studies. Noncarcinogenic effects of asbestos include: potential genotoxicity, adverse effects on the gastrointestinal system (Corpet *et al*., 1993; Delahunty and Hollander, 1987; Jacobs *et al*., 1977, 1978a), immune system (MacDonald and Kane, 1993; Moalli *et al*., 1987) kidney (Cemerikic, 1977), and body weight (NTP, 1990b). Most of these studies are inadequate for risk assessment purposes due to incomplete/missing data, the use of experimental exposure routes, and/or the lack of a frank effect. In the case of the NTP (1990b) study, the authors concluded that the marked decreases in body weight, which persisted over the course of the animals' lifetime, did not adversely affect survival.

In many instances, the effect of oral asbestos exposure on individual tissues/organ systems has not been studied. No studies were located regarding the respiratory, cardiovascular, musculoskeletal, hepatic, endocrine, dermal, ocular, metabolic or other systemic effects in animals after oral exposure to asbestos (ATSDR, 1995; HSDB, 2000). In the literature search, no studies have been located regarding death in animals after acute, intermediate, or chronic oral exposure to asbestos.

Cemerikic (1977) exposed male and female Wistar rats (7/sex) to chrysotile asbestos in drinking water for 12 to 15 weeks. The 10 male and 7 female controls received tap water. A suspension of asbestos fibers in drinking water was prepared by shaking 2.5 g of chrysotile asbestos in 500 ml of water; this was allowed to settle for 30 minutes and the top 250 ml, which contained about 9.4×10^9 (1 mg) fibers/ml was drawn off (the technique of Pontefract and Cunningham, 1973). Because fibers could continue to settle out, the fiber concentration and dose actually delivered to the animals cannot be accurately estimated; it might be higher or lower, depending on the design and orientation of the water bottles and drinking tubes. Females were sacrificed after 12 weeks and males after 15 weeks. The organs were measured and the kidneys and bladders examined histopathologically. Pathologic presence of red blood cells and hyaline casts in the urine sediment of four males indicated damage to the kidneys. Kidneys of experimental females showed only discrete perivascular infiltration. A marked increase of indirect pressure, evidence of hypertension, was found in exposed females after 6 and 12 weeks, compared with controls. U.S. EPA (1988c) has estimated that mature male Wistar rats consume 0.032 L/day of drinking water, and females 0.025 L/day. The level at which adverse effects were seen in the kidneys of the male rats was about 107 mg/kg-day ((1 mg/mL x 32 ml/day)/0.3 kg) and in females was about 167 mg/kg-day ((1 mg/ml x 25 mL)/0.15 kg), based on their body weights at the start of the exposures.

The other animal studies showed non-cancer effects at higher doses or with more poorly-defined experimental paradigms. The NTP (1990b) chronic rat feeding study, for example, showed only decreased body weight gain at 500 mg/kg-day.

Carcinogenic Effects

Carcinogenic potency of asbestos fibers depends on mechanical stability and durability, insolubility in aqueous solution, fiber strength, fiber length, fiber diameter, fiber geometry, chemical composition, surface reactivity, and biopersistence of the fiber (IARC, 1996; McDonald, 1998). Asbestos carcinogenesis appears to be a multistage process even though the exact molecular mechanisms leading to the development of cancer after asbestos exposure are poorly understood (Abidi *et al*., 1999; Kamp and Weitzman, 1999). The consensus of a group of invited experts (IARC, 1996) was that asbestos carcinogenesis may be initiated by the ability of fibers to cause:

1) altered expression or function of key genes arising from genetic or epigenetic alterations with enzyme imbalance;
2) altered cell proliferation;
3) altered regulation of apoptosis and immune responses at molecular levels; or
4) chronic, persistent inflammation.

In the IARC report, Kane *et al*. (1996) summarized five proposed mechanistic hypotheses for fiber carcinogenicity as:

1) fibers generate free radicals that damage DNA;
2) fibers interfere physically with mitosis;
3) fibers stimulate proliferation of target cells;
4) fibers provoke a chronic inflammatory reaction leading to prolonged release of reactive oxygen/nitrogen species from macrophages; or
5) fibers act as co-carcinogens or carriers of chemical carcinogens to the target tissue.

Further research is needed to elucidate evidence in favor of or against any of these proposed mechanisms.

The carcinogenic potency of asbestos by inhalation can readily be derived from epidemiologic data. However, the estimation of oral potency is more complicated. The NAS estimated oral cancer risk from inhalation studies of asbestos workers (NAS, 1983). These studies and increased cancer rates are shown in Table 6. The potency calculations involved a series of steps including estimation of the proportion of inhaled particles deposited in the lung, cleared, and swallowed. The proportion was assumed to be 0.3, based on animal models (Evans *et al*., 1973; Morgan *et al*., 1975), plus a human model (Dement and Harris, 1979) that estimated that 28 percent of inhaled chrysotile fibers are deposited in the lung. The models assumed that no asbestos is directly swallowed, and that virtually all deposited fibers are eventually cleared. Because of the change in methods of quantitating asbestos fibers, a conversion factor was also needed to estimate the potency based on the older data using light microscopy, versus the newer data using TEM. TEM was assumed to be about 50 times as sensitive, based upon the work of Lynch *et al*. (1970).

Based on these assumptions, a relative risk of gastrointestinal tract cancer for a person who has swallowed inhaled asbestos fibers was calculated by NAS. These calculations indicated that lifetime ingestion of 1.1×10^{6} TEM fibers/L of water corresponded to an excess gastrointestinal tract cancer risk of 10^{-4}.

Unfortunately, OEHHA was not able to provide an audit trail on all the figures used by NAS (1983) in their calculations. Indeed, the NAS (1983) reported that "The committee adjusted the relative risks to refer only to gastrointestinal cancer" and "shows estimates derived either from the published studies or from personal communication with the authors." Lacking the ability to confirm the values and assumptions used by the NAS in their evaluation of the five occupational inhalation studies, OEHHA considers the reported evaluation to be too unreliable to use in establishing a PHG. In addition, the complex calculations and multiple assumptions make it difficult to duplicate the analysis, and would provide a relatively weak basis for a quantitative risk assessment.

Table 6. Results of Five Cohort Studies of Gastrointestinal Tract Cancers in Asbestos Workers (Abstracted from NAS (1983), Table III-2)

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

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

U.S. EPA has concluded that the animal studies provide the best data for cancer risk estimation from ingestion exposure (U.S. EPA, 1988b). Animal toxicology, based upon the NTP (1985) chronic feeding studies, was used to estimate excess human cancer risk at the 10^{-6} level as approximately 7.1 MFL or 7.1×10^{6} fibers/L by the U.S. EPA (1991a). OEHHA concurs that this approach provides the most credible method to calculate the human risk of oral exposures to asbestos in drinking water. These calculations are shown in the derivation of a proposed PHG for carcinogenic effects below.

CALCULATION OF PHG

Noncarcinogenic Effects

Based on a subchronic study in rats reported by Cemerikic (1977), a LOAEL of 107 mg/kg-day ($1x10^{12}$ fibers/kg-day) for nephrotoxicity was selected for calculation of a

public health-protective concentration for noncarcinogenic effects of asbestos in drinking water. Calculation of a health-protective concentration (C, in µg/L) for noncarcinogenic endpoints follows the general equation:

$$C = \frac{LOAEL \times BW \times RSC}{UF \times L_{eq}/day}$$

where,

LOAEL	=	lowest-observed-adverse-effect level (kidney effects);
BW	=	adult body weight, a default of 70 kg for adults;
RSC	=	relative source contribution (a default of 20 percent to 80 percent);
UF	=	combined uncertainty factor (typical defaults are 10 for estimation of a NOAEL from a LOAEL, 10 to account for the uncertainty in inter-species extrapolation, and 10 for human variability); and
L_{eq}/day	=	adult daily water consumption rate (a default rate of 2 L/day, plus additional equivalent amounts where applicable to account for inhalation and dermal exposures from use of contaminated tap water.

It was assumed for the calculation that other sources of asbestos would be significant, so a 20 percent (0.2) default relative source contribution of asbestos from drinking water was chosen. Uncertainty factors of 10 each would be applicable to account for extrapolation of a LOAEL to a NOAEL, interspecies extrapolation, and human variability. In addition, an uncertainty factor of 3 was applied to account for subchronic to chronic study duration extrapolation. We interpret this as requiring the maximum uncertainty factor of 3,000, in accordance with U.S. EPA (1991c) guidelines and theoretical considerations (Gaylor and Kodell, 2000).

$$C = \frac{107 \text{ mg/kg-d} \times 70 \text{ kg} \times 0.2}{3{,}000 \times 2 \text{ L/d}} = 0.25 \text{ mg/L } (250 \text{ µg/L})$$

Thus the public health protective concentration for asbestos in drinking water based on noncarcinogenic effects is proposed to be 250 µg/L, which is equivalent to 2.4×10^9 fibers/L, or 2350 MFL at the indicated fiber concentration of 9.4×10^9 fibers/mg.

Carcinogenic Effects

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. The NAS calculations indicated that lifetime ingestion of 1.1×10^6 TEM fibers/L of water corresponded to an excess gastrointestinal tract cancer risk of 10^{-4} (NAS, 1983). This is equivalent to a 10^{-6} excess cancer risk level of 0.01 MFL or 1×10^4 fibers/L for oral exposures. However, the NAS risk assessment is difficult to follow, and impossible to reproduce. The difficulties are based in part on their undocumented personal communications with authors of some of the five studies. Other considerations include the nature of the occupational cohort studies used to determine the potency, with difficulties in estimation of inhalation exposures and calculation of oral doses. In addition, many of the assumptions used to derive the potency estimate (e.g. that no inhaled asbestos is directly swallowed, and that virtually all deposited fibers are eventually cleared) have been shown to be incorrect. OEHHA considers the NAS potency estimate based on inhalation studies to be too problematic to use in establishing a proposed PHG.

The U.S. EPA, in its cancer risk evaluation (1991a, 1994) chose to use the rat NTP study for determination of safe drinking water levels, although in its IRIS file it has declined to identify any oral risk level (U.S. EPA, 2000). The ATSDR (1995) also selected the NTP (1995) study as the most appropriate basis for a risk estimate, without commenting upon the much lower extrapolations from occupational inhalation studies.

OEHHA acknowledges the 700-fold more potent risk assessment based on the earlier NAS evaluation, but concurs with the U.S. EPA and ATSDR that the rat oral exposure data (NTP, 1985) provide a more suitable basis for estimating a public-health-protective level of asbestos in drinking water. The human occupational studies indicating excess risk of gastrointestinal cancer from inhalation exposures to asbestos are considered to provide a supporting qualitative basis for concern about total exposures to asbestos.

Risk Estimate Based on Animal Data

In a lifetime feeding study in rats, exposure to intermediate length chrysotile fibers (65 percent > 10 μm in length) led to an increased incidence of intestinal polyps in the large intestine of male rats (NTP, 1985). The incidence of these benign epithelial neoplasms (9/250, 3.6 percent) was significantly increased ($p = 0.003$) compared to the incidence of combined benign and malignant epithelial neoplasms of the large intestine in the pooled control groups (male) of all the NTP oral asbestos lifetime studies. The approach shown below, including interspecies extrapolation, follows that used in the U.S. EPA (1988b) Drinking Water Criteria Document for Asbestos, pp. VIII-11 through VIII-15:

In the NTP (1985) study, asbestos fibers were mixed into the diet rather than suspended in the drinking water. This presumably provides a more uniform exposure, but requires the assumption that the asbestos in the dry diet would have the same effect as asbestos in water. A single dose of one percent asbestos (by weight) was used, estimated to be equivalent to 500 mg/kg-day.

Based on measurements of transmission electron microscope (TEM) performed at the Illinois Institute of Technology Research Institute, the fiber counts

were ~ 0.129 x 10^9 f/mg with a median fiber aspect ratio (length divided by diameter) of 8.435 (NTP, 1985). The daily dose of asbestos can be recalculated in terms of fiber exposure as:

$$500 \text{ mg/kg} \times 0.129\text{x}10^9 \text{ f/mg} = 6.45\text{x}10^{10} \text{ f/kg}$$

In order to determine human equivalent dose, the U.S. EPA procedure has been to assume dosage equivalency on a dose/surface area basis. This is roughly equal to equivalency on a dose/(body weight)$^{2/3}$. Thus, the equivalent dosage for a 70 kg human, calculated from the average dose in a 0.38 kg rat, is:

$$(6.45\text{x}10^{10} \text{ f/kg})/(70/0.380)^{1/3} = 1.13\text{x}10^{10} \text{ f/kg}$$

A 70 kg human is assumed to drink 2 liters of water/day. The f/kg dose can be restated in terms of drinking water concentration as:

$$1.13\text{x}10^{10} \text{ f/kg} \times 70 \text{ kg/2 L} = 4.0\text{x}10^{11} \text{ f/L}$$

Since there was only a control and one dose level, the usual linearized multistage model is reduced to a single dose or one-hit model. U.S. EPA, using the standard multistage model, has determined the maximum likelihood estimate (MLE) of potency to be:

$$q_1 = 7.7\text{x}10^{-14} \text{ (f/L)}^{-1}$$

with a 95 percent upper-limit potency of:

$$q_1^* = 1.4\text{x}10^{-13} \text{ (f/L)}^{-1}$$

The health protective concentration is calculated for a one in one million cancer risk level as:

$$C = \frac{R}{q1^*} = \frac{10^{-6}}{1.4\text{x}10^{-13} \text{ (f/L)}^{-1}} = 7.1\text{x}10^6 \text{ f/L}$$

For a lifetime individual risk of gastrointestinal cancer of one in a million, the 95 percent lower confidence limit on concentration of asbestos fibers in drinking water is therefore 7.1x10^6 f/L. This value is much less than the noncancer risk level estimated above, and therefore should be protective against all noncancer effects. The proposed PHG is rounded to 7x10^6 f/L, also expressed as 7 MFL.

RISK CHARACTERIZATION

Epidemiological studies of the risk associated with ingestion of asbestos in drinking water, either by themselves or in the aggregate, are unsatisfactory for quantitative risk evaluation. Most of these studies are ecological in design, and hence lack individual measures of exposure. Consumption exposures are assumed due to contamination of municipal drinking water. These studies cover natural contamination, contamination through industrial pollution, and contamination through the use of asbestos-cement distribution pipes. Often the duration and level of contamination is not known. In addition, the asbestos fibers are not well characterized by size distribution.

Given the problems associated with this data source, other studies must be relied upon to provide a basis for risk assessment. These other studies involve extrapolation across exposure modalities or extrapolation across species.

Human inhalation exposure has provided one basis for extrapolating to oral particle exposure because the inhaled particles deposited in the lungs are cleared through the mucociliary escalator and swallowed (Evans *et al*., 1973). Other processes, including migration of fibers through mucosal and other tissues (Pontefract and Cunningham, 1973; Westlake *et al*., 1965), and blood or lymphatic transport of fibers away from the site of entry (Kanazawa *et al*., 1970; Roe *et al*., 1967), have been experimentally established (Amacher *et al*., 1974; 1975). Gastrointestinal tract cancer is the most likely target carcinogenicity endpoint. The U.S. EPA has based one model of carcinogenic risk for ingested asbestos on data from occupational inhalation cohort studies. This work is presented in a National Research Council (NAS, 1983) analysis of five worker cohorts presented in four reports (Selikoff *et al*., 1979; Seidman *et al*., 1979; Newhouse and Berry, 1979; Henderson and Enterline, 1979; see also Seidman, 1984) (see Table 6). Based upon these five studies, NAS (1983) established a 10^{-6} excess cancer risk level as 0.01 MFL or 1×10^{4} fibers/L for oral exposures.

However, for its regulatory standards, the U.S. EPA has relied on an extrapolation from the NTP (1985) chronic rat study. OEHHA has also chosen this approach because it is a more straightforward risk assessment. The NTP (1985) study in rats found "some evidence of carcinogenicity" in male rats exposed to intermediate range (IR) chrysotile asbestos as indicated by an increased incidence of adenomatous polyps in the large intestine (9/250, 3.6 percent). Although not statistically significant compared with concurrent controls, the incidence of these neoplasms was highly significant (P=0.003) when compared with the incidence of epithelial neoplasms (benign and malignant combined) of the large intestine in the pooled male control groups of all the NTP oral asbestos lifetime studies. The biologic significance of this finding was supported by the observation of lesions of similar morphology in the small intestine or glandular stomach of four additional IR chrysotile male rats, whereas none were found in the concurrent control group. NTP concluded that the observed effect in the large intestine of the male IR chrysotile asbestos group was "quite unlikely to be due to chance alone," because adenomatous polyps are uncommon in standard 2-year carcinogenesis studies. It is noteworthy that the other NTP asbestos studies were carried out at the same laboratory, conducted using an overlapping time frame, and used animals that were received from the same source and exposed to the same environmental conditions. The post-mortem examinations were conducted with an identical protocol by the same technicians; the histopathologic examination used the same morphologic classification; and every neoplasm was reviewed by the NTP Quality Assurance contractor and the NTP Pathology Working Group. For these reasons, more credence than usual was given to the historical data. Although no malignant epithelial neoplasms were observed in the large intestine in this study, this progression occurs with known intestinal carcinogens.

It is plausible that the true value of the human oral cancer potency for asbestos in drinking water has a lower bound of zero based on statistical and biological uncertainties. Part of this uncertainty is due to limited suggestive evidence to support a genotoxic mechanism. However, due to the absence of specific scientific information explaining

why the animal tumors are irrelevant to humans at environmental exposure levels, a standard health protective approach was taken to estimate cancer risk. The OEHHA proposed public health goal uses the calculations derived by the U.S. EPA (1991a) in establishing the federal MCL. The proposed PHG is considered to contain an adequate margin of safety to protect against the potential genotoxicity as well as noncarcinogenic effects including adverse effects on the gastrointestinal system, immune system, kidney, and body weights. Sensitive subpopulations should also be protected against adverse effects.

REGULATORY STANDARDS

Maximum Contaminant Level (MCL) and Drinking Water Standards

The U.S. EPA (1991a, 1994) and approximately nine states have set 7 or 7.1 MFL as a drinking water standard (ATSDR, 1995). The ATSDR (1995) also selected the 7.1 MFL as an appropriate risk estimate without commenting upon the much lower extrapolations from occupational inhalation studies.

In 1991, U.S EPA (1991a, 1994) adopted an MCL and an MCLG of 7 MFL or 7×10^6 fibers/L for asbestos fibers exceeding 10 μm in length (40 CFR 141.51), based upon evidence of benign polyps occurring in the large intestine of Fischer 344/N male rats following the oral administration of intermediate range, longer than 10 μm size chrysotile fibers (NTP, 1985). Similar lifetime carcinogenesis studies of chrysotile asbestos in male and female Syrian golden hamsters did not cause any tumors when ingested at the one percent level in the diet (NTP, 1990a).

Although asbestos has been shown to be a human carcinogen through inhalation exposure and is classified by the U.S. EPA as a Group A human carcinogen, asbestos in water is classified as a Category II contaminant based on evidence from the NTP dietary and drinking water ingestion studies. Based on a daily consumption of two liters of drinking water and considering the risk level of 10^{-6}, the corresponding interim Ambient Water Quality Criteria (AWQC for ingesting water and organisms) established by the U.S. EPA (1980) was 3×10^4 or 30,000 fibers/L using preliminary NTP data.

DHS (1991) proposed, but never finalized, that a Recommended Public Health Level (RPHL) for California be set at 7×10^6 fibers/L for fibers exceeding 10 μm in length, that is, the U.S. EPA's MCL. California, Kansas, and Minnesota established a drinking water quality standard of 7.1×10^6 fibers/L for asbestos. Arizona, Florida, Oklahoma, Rhode Island, Utah, and Wisconsin established a drinking water quality standard of 7×10^6 fibers/L for asbestos (ATSDR, 1995).

Other Regulatory Standards

Because of the potential for asbestos to cause adverse health effects in exposed people, numerous regulations and advisories have been established for asbestos by various

international, national, and state agencies. Such regulations and advisories control asbestos in air and water, and how it is contained, handled, and disposed.

In addition to the Safe Drinking Water Act, U.S. EPA regulates asbestos under the Clean Air Act, Clean Water Act, Comprehensive Environmental Response, Compensation, and Liability Act, Resource Conservation and Recovery Act, Superfund Amendments and Reauthorization Act, and Toxic Substances Control Act. The U.S. Food and Drug Administration regulates the use of asbestos in indirect food additives, adhesives, components of coatings, and polymers, as well as the use of asbestos filters in the manufacture of drugs and drug ingredients under the Food, Drug, and Cosmetic Act. The Consumer Product Safety Commission (CPSC) has banned garments containing asbestos for general use since 1978, and since October 1986, has required labeling of all consumer products containing intentionally added asbestos that are likely to release fibers. The CPSC has banned the use of asbestos in patching compounds and in gas fireplaces. U.S. manufacturers of hand-held hair dryers cooperated with CPSC in ceasing to use asbestos liners (NTP, 2000).

The National Institute for Occupational Safety and Health (NIOSH, 1994) has recommended that asbestos be treated as a potential human carcinogen since 1972. The NIOSH recommended exposure limit is 0.1 fibers/mL for fibers greater than 5 μm in length as a time-weighted average (TWA) concentration for up to an 8-hour workshift, 40-hour workweek (NIOSH, 1997). The federal Occupational Safety and Health Administration (OSHA) established a workplace Permissible Exposure Limit in 1994 of 0.1 fibers per mL of air averaged over an 8-hour work shift based on a count of fibers greater than 5 μm in length, for both general industry and construction. The excursion or short-term limit is 1 fiber/mL averaged over a sampling period of 30 minutes (OSHA, 1994). Fiber is defined as a particulate form of asbestos, tremolite, anthophyllite, or actinolite, 5 μm or longer, with a length-to-diameter ratio of at least three to one (29 CFR 1910.1001). The American Conference of Governmental Industrial Hygienists (ACGIH) has designated asbestos as an A1 suspected human carcinogen. ACGIH has set a threshold limit value (TLV) of 2 fibers/mL for chrysotile, 0.5 fiber/mL for amosite, 0.2 fiber/mL for crocidolite, and 2 fibers/mL for other forms, as a TWA for a normal 8-hour workday and a 40-hour workweek (NIOSH, 1997).

Most states have adopted and enforce the regulations and guidelines set by national agencies. For example, with regard to air emission standards, most states follow the National Emission Standards for Hazardous Air Pollutants (NESHAP) established by U.S. EPA (1990) for asbestos emissions. States may establish their own standards, but they must be comparable to or more stringent than the ones set forth by U.S. EPA, OSHA, and similar agencies. In addition, states may establish regulations for asbestos when federal regulations do not exist for a particular scenario (Kaplan, 1993). In California, asbestos is regulated as a carcinogen under California's Toxic Air Contaminant (TAC) program, and OEHHA has conducted a quantitative risk assessment (QRA) for the inhalation route. The Minnesota Department of Health has set its Clean Indoor Air Standard at 0.01 fibers/mL.

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