

**TOXICITY SUMMARY FOR
ASBESTOS**

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EXECUTIVE SUMMARY

Asbestos (CAS No. 1332-21-4) is the generic name for a variety of naturally formed hydrated silicates containing metal cations such as sodium, magnesium, calcium, or iron. The two major groups of asbestos are serpentine and amphibole based on their physical/chemical properties. Chrysotile (CAS No. 12001-29-5) is the only asbestos in the serpentine group, whereas the amphibole group is represented by actinolite (CAS No. 13768-008), amosite (CAS No. 12172-73-5), anthophyllite (CAS No. 17068-78-9), crocidolite (CAS No. 12001-28-4), and tremolite (CAS No. 14567-73-8) (U.S. EPA, 1984; ATSDR, 1993). Asbestos fibers are chemically inert, or nearly so. They do not evaporate, dissolve, burn, or undergo significant reactions with other chemicals (ATSDR, 1993).

Asbestos fibers can enter the body after inhalation or oral exposures. Fibers which are deposited in the lung may be removed from the lung by mucociliary clearance or by macrophages, or they may be retained in the lungs (U.S. EPA, 1980; 1984). Some ingested asbestos fibers penetrate the gastric mucosa and a small percentage of the fibers are distributed to other tissues. Ingested fibers are mostly excreted in the feces (Cunningham et al., 1976).

Long-term feeding studies in rats and hamsters indicate that ingestion of high concentrations (1% in the diet or 500-800 mg/kg/day) of chrysotile, amosite, crocidolite, or tremolite does not cause systemic effects (NTP, 1985; NTP 1988a,b,c; NTP, 1990). Other studies reported some histological and biochemical alterations in cells of the gastrointestinal tract in rats receiving up to 50 mg/kg/day of chrysotile for 14-15 months (Jacobs et al., 1978a,b).

Numerous studies in humans have established that long-term inhalation of asbestos fibers causes chronic, progressive pneumoconiosis (asbestosis). The disease is common among occupational groups directly exposed to asbestos fibers such as insulation workers, but also extends to those working near the application or removal of asbestos and family contacts of exposed workers (U.S. EPA, 1980). Asbestosis results from a prolonged inflammatory response stimulated by the presence of fibers in the lungs and is characterized by fibrosis of the lung parenchyma, which usually becomes radiographically discernible 10 years after the first exposure (U.S. EPA, 1985). The main clinical symptom is shortness of breath, often accompanied by rales and cough. In severe cases, impairment of respiratory function may ultimately result in death (ATSDR, 1993). Because asbestos fibers are resistant to breakdown in the lung, the inflammatory response triggered by the fibers is ongoing, even after exposure has ceased. It has been estimated that cumulative exposures of 17-75 fibers-year/mL would result in fibrotic lung lesions and cumulative exposures of 3.5-300 fibers-year/mL would cause death in humans (ATSDR, 1993). Smoking has been shown to increase the risk of asbestosis (Schulz, 1994). Fibrosis has been produced in laboratory animals following subchronic or chronic inhalation exposure to various forms of asbestos (Wagner, 1963; Wagner et al., 1974; Donaldson et al., 1988). Some studies of workers with asbestos-related diseases indicate that the cellular immune system in such patients can be depressed (ATSDR, 1993). Dermal contact with asbestos may result in the formation of warts or corns (Alden and Howell, 1944).

An oral Reference Dose (RfD) or inhalation Reference Concentration (RfC) for asbestos has not been derived (U.S. EPA, 1995).

Several epidemiologic studies suggest that high levels of asbestos in drinking water in certain geographic areas may cause gastrointestinal cancer in humans (Cooper et al., 1979; Conforti, 1983; Kanarek, 1983), whereas other studies failed to find a clear association between ingested asbestos and cancer in humans (Harrington et al., 1978; Polissar, et al., 1983). The evidence for carcinogenicity in orally exposed animals is also equivocal. A series of lifetime feeding studies with rats and Syrian golden hamsters with various forms of asbestos have yielded mostly negative results (NTP, 1985; 1988a,b,c; 1990). An increased incidence of benign adenomatous polyps of the large intestine was observed in male rats exposed to 1% (500 mg/kg/day) intermediate range chrysotile (65% of fibers >10 µm in length) in the diet (NTP, 1985).

Numerous epidemiologic studies have documented an increased incidence of lung cancer and pleural and peritoneal mesothelioma (a tumor involving the lining of the abdomen and chest) as a result of asbestos exposure. All major types of commercial asbestos such as chrysotile, amosite, and crocidolite

have been found to produce asbestos-related cancer among workers occupationally exposed in mining and milling, in manufacturing, and in the use of the materials containing asbestos fibers (U.S. EPA, 1980). Asbestos-related cancer has also been identified, although less frequently, in individuals who had worked near the application or removal of asbestos material; in individuals residing in the vicinity of asbestos plants; and in individuals who had lived in the household of an asbestos worker (IARC, 1977; 1987).

For lung cancer, the magnitude of the carcinogenic risk appears to be a function of a number of factors, including the level and duration of exposure; the time since exposure occurred; the age at which exposure occurred; the smoking history of the exposed person; and the type and size distribution of asbestos fibers. There is a substantial latency period (10-30 years) between onset of exposure to asbestos and the occurrence of lung cancer (ATSDR, 1993). Many reports have documented cases of pleural and peritoneal mesotheliomas resulting from occupational and non-occupational exposures to various types and mixtures of asbestos. It has been estimated that a third of the mesotheliomas occurring in the U.S. may be due to non-occupational exposure (IARC, 1977; 1987). Asbestos exposure and cigarette smoking act synergistically to produce dramatic increases in lung cancer compared with those from exposure to either agent alone (U.S. EPA, 1984). The data for possible interactions between smoking and mesothelioma is not certain, but it appears that smoking does not increase the risk for this cancer (Schulz, 1994).

There are inconsistent reports of excess cancer incidences or mortality from cancers at other sites among workers exposed to asbestos. They include cancers of the gastrointestinal system (esophagus, stomach, colon, bile duct, and rectum), laryngeal cancer, kidney cancer, and ovarian cancer, and cancer affecting the lymphopoietic and hematopoietic systems (IARC, 1977; Schulz, 1994). However, the risk of these cancers appears to be significantly lower than those for lung cancer and mesothelioma in similarly exposed cohorts (Schulz, 1994).

Several types of asbestos were shown to induce tumors in rats, including mesotheliomas and lung adenomas/carcinomas following inhalation of 9.7-14.7 mg/m³, 7 hours/day, 5 days/week for up to 24 months (Wagner et al., 1974). Intrapleural administration of asbestos induced mesotheliomas in rats and hamsters, and intraperitoneal administration induced abdominal tumors including mesotheliomas in rats and mice and abdominal tumors in hamsters (IARC, 1977; 1987).

Based on U.S. EPA guidelines, asbestos was assigned to weight-of-evidence group A, human carcinogen (U.S. EPA, 1995). Slope factors for oral or inhalation exposure are not available at this time. The inhalation unit risk for asbestos is 2.3E-1 (fibers/mL)⁻¹ (U.S. EPA, 1995).

1. INTRODUCTION

Asbestos (CAS No. 1332-21-4) is the generic name for a variety of naturally formed hydrated silicates containing metal cations such as sodium, magnesium, calcium, or iron. The two major groups of asbestos are serpentine and amphibole based on their physical/chemical properties. Chrysotile (CAS No. 12001-29-5) is the only asbestos in the serpentine group, whereas the amphibole group is represented by actinolite (CAS No. 13768-008), amosite (CAS No. 12172-73-5), anthophyllite (CAS No. 17068-78-9), crocidolite (CAS No. 12001-28-4), and tremolite (CAS No. 14567-73-8). Since chrysotile, amosite, crocidolite, and tremolite are of primary commercial importance, most data exists for these fiber types (U.S. EPA, 1984, 1985; ATSDR, 1993). The essential characteristic of asbestos minerals is their fibrous nature. The gross fibers which are visible to the naked eye are actually bundles of much finer fibrils that are submicroscopic in size (U.S. Bureau of Mines, 1980). Asbestos fibers are chemically inert, or nearly so. They do not evaporate, dissolve, burn, or undergo significant reactions with other chemicals (ATSDR, 1993). Amphibole asbestos is generally resistant to acid; however, chrysotile is highly susceptible to attack by mineral acids. Chrysotile is almost completely destroyed within 1 hour in 1 N hydrochloric acid at 95°C (Lindell, 1972). The comparative solubility as defined by resistance to acids is chrysotile << amosite < actinolite < crocidolite < anthophyllite < tremolite (U.S. EPA, 1985).

Asbestos has been widely used because it is noncombustible, nonconducting, and has a relatively high chemical resistance (U.S. EPA, 1985). Chrysotile is the major type of asbestos used in asbestos products (U.S. EPA, 1980). Asbestos was introduced in the late 1800s to make heat- and acid-resistant fabrics. It is now used in a variety of applications such as in the building industry to strengthen cement and plastics; for heat insulation and sound absorption; in break shoes and clutch plates; and as asbestos cloths for fire protection, including the cladding of structural steel beams. Asbestos also has valuable filtration properties (IARC, 1973). In 1991, A U.S. federal court overturned an EPA regulation that banned most uses of asbestos by 1997 (U.S. Bureau of Mines, 1992). Presently, only asbestos-containing products that were not being manufactured, imported, or processed after July 1989, remain subject to the prohibition requirements of the EPA regulation (U.S. EPA, 1992). Specific products which will remain subject to the rule will be documented by EPA.

Humans may be exposed to asbestos from a variety of sources, including ambient air, drinking water, food, occupational settings, and consumer products (U.S. EPA, 1985). Asbestos fibers in air may arise from natural sources such as weathering of asbestos-containing ores, but many come from the wear or breakdown of asbestos-containing materials such as insulation or automobile brakes. Typical concentrations of asbestos in ambient air range from 1 to 200 ng/m³ to over 100 ng/m³ near specific industrial sources. Asbestos in water comes mainly from erosion from natural deposits of asbestos or from erosion of pipes made with asbestos-containing cement. In most water supplies, concentrations of asbestos are less than 1 million fibers/liter (MFL), but may exceed 100 MFL in some cases. Asbestos has been identified in at least 54 of the 1350 hazardous waste sites on EPA's National Priority List (NPL) (ATSDR, 1993).

2. METABOLISM AND DISPOSITION

Asbestos consists largely of insoluble fibers and does not undergo absorption, distribution, and metabolism similar to most other non-fibrous chemicals.

2.1. ABSORPTION

Animal studies have shown that most ingested asbestos fibers are not absorbed from the gastrointestinal tract (Gross et al., 1974). However, some fibers penetrate into the gastrointestinal epithelium and may pass through the gastrointestinal wall to blood, lymph, and other tissues.

Many inhaled asbestos fibers are deposited on the epithelial surface of the respiratory tract. The number of deposited fibers and the location within the airway are a function of the aerodynamic properties of the fibers (ATSDR, 1993). Timbrell (1982) reported that in humans the fibers deposited in the upper airway consist of relatively thick fibers (>3 µm), with thinner fibers being carried deeper into the airways. Rats exposed by inhalation to chrysotile, amosite, or crocidolite retained about 30-40% of the fibers, with most of these (60%) being deposited in the upper airways (nose, throat, and trachea) (Evans

et al., 1973; Morgan et al., 1975). Inhalation of asbestos is accompanied by ingestion of many fibers cleared from the respiratory tract by mucociliary action. Thus, the amount of inhaled asbestos which is eventually ingested is an important consideration for the estimation of gastrointestinal cancer risk (see Section 4) (U.S. EPA, 1980).

Asbestos fibers can penetrate the skin (Alden and Howell, 1944), but no information was available showing that asbestos fibers can pass through the skin into the blood stream.

2.2. DISTRIBUTION

Following ingestion of asbestos, some of the fibers may penetrate the gastrointestinal epithelium and distribute to other tissues such as the lymphatic system or bloodstream, resulting in widespread body distribution. Phagocytosis of asbestos by macrophages, monocytes, or other phagocytic cells is probably involved in its uptake and subsequent distribution (U.S. EPA, 1984). Amphibole asbestos fibers, resembling those found in Duluth, MN, drinking water were detected in the liver, jejunum, and lung specimens from deceased Duluth residents (Carter and Taylor, 1980). Since amphibole fibers were not found in air samples, it was concluded that the presence of asbestos in these tissues indicated transmucosal uptake from ingestion of drinking water. Asbestos fibers also have been detected in lungs, kidneys, liver, brain, heart, and spleen of rats that had been exposed to asbestos in the diet (Pontefract and Cunningham, 1973; Cunningham et al., 1977).

Most of the asbestos fibers which are deposited in the lung during inhalation are transported by mucociliary action to the pharynx, where they are swallowed, but a small fraction remains in the lungs for long periods of time. Only a small fraction of inhaled fibers penetrate through the epithelial layer of the lungs (ATSDR, 1993). In a study on the retention of asbestos fibers in the lungs of three crocidolite sprayers and two asbestos product workers, Tossavainen et al. (1994) estimated a clearance half-time of \$10 years for deposited asbestos fibers. The fibers were cleared from the lungs to some extent, because they were present in "high" quantities in lymph nodes, parietal pleura, and kidneys of exposed workers.

Musselman et al. (1994) evaluated the biopersistence of crocidolite fibers in rat lungs following nose-only exposure of rats to 10 mg/m³ of long-fibered crocidolite, 6 hours/day for 5 days. The fiber diameter and length were \$0.5 μm and >20 μm, respectively. Of the fibers retained in the pulmonary region at day 1, approximately 40% remained through 545 days. Little if any dissolution or breakage of fibers had occurred since the percentage of fibers of diameter <0.5 μm or \$5 μm was relatively constant from day 90 on.

Following intravenous injection of chrysotile fibers into pregnant rats, fibers were detected in the fetuses of exposed dams, indicating that placental transfer can occur (Cunningham and Pontefract, 1974).

2.3. METABOLISM

Asbestos fibers which are retained in the gastrointestinal or respiratory tracts do not undergo metabolism per se. The physical and chemical properties of ingested fibers of chrysotile and crocidolite have been shown to be altered when exposed to simulated gastric juice (Seshan, 1983) and chrysotile fibers with altered appearance and X-ray diffraction patterns were detected in the urine of baboons gavaged with chrysotile (Hallenbeck and Patel-Mandlik, 1979).

While amphibole fibers deposited in the lung do not appear to undergo major changes, chrysotile fibers undergo a breakdown or alteration. Longer asbestos fibers which are retained in the lungs may undergo any number of processes including dissolution, fragmentation, splitting, or protein encapsulation, forming what is referred to as an "asbestos body" (ATSDR, 1993). Short chrysotile fibers are cleared preferentially to longer ones (Coin et al., 1992). Long (>16 μm) chrysotile fibers deposited in rat lungs undergo longitudinal splitting, so that their number actually increases over time, possibly increasing their potential for biological effects. However, substantial leaching of magnesium from chrysotile fibers up to 30 days after deposition was not observed (Coin et al., 1994).

2.4. EXCRETION

Although most inhaled or directly ingested asbestos particles which pass through the gastrointestinal tract are excreted in feces (Cunningham et al., 1976), some fibers are eliminated through the urinary tract. Cook and Olson (1979) demonstrated the presence of amphibole fibers in human urine originating from ingestion of contaminated drinking water. Boatman et al. (1983) reported that the content of chrysotile fiber in the urine of long-term (24 years) residents of the Puget Sound area was significantly higher than the chrysotile fiber content of short-term (1.5-2.8 years) residents.

3. NONCARCINOGENIC HEALTH EFFECTS

3.1. ORAL EXPOSURES

3.1.1. Acute Toxicity

3.1.1.1. Human

Information on the acute oral toxicity of asbestos in humans was not available.

3.1.1.2. Animal

A single oral administration of 5 to 100 mg/kg of chrysotile to rats has produced an increase of thymidine in the stomach, duodenum, and jejunum (Amacher et al., 1975). The authors suggested that an immediate response of cellular proliferation and DNA synthesis may be stimulated by chrysotile ingestion.

3.1.2. Subchronic Toxicity

Information on the subchronic oral toxicity of asbestos in humans or animals was not available.

3.1.3. Chronic Toxicity

3.1.3.1. Human

Information on the chronic oral toxicity of asbestos in humans was not available.

3.1.3.2. Animal

Groups of male and female F344/N rats and male and female Syrian Golden hamsters were administered short-range and intermediate-range fiber length chrysotile at a concentration of 1% in the diet for life (NTP, 1985; 1990). The estimated daily intake corresponds to 500 or 830 mg/kg/day for rats or hamsters, respectively (ATSDR, 1993). Using similar protocols, groups of male and female F344/N rats were exposed to 1% dietary concentrations of crocidolite, amosite, or tremolite asbestos for life (NTP, 1988a,b,c). None of the various asbestos forms affected survival or induced overt signs of toxicity.

Rats were fed a diet containing 0.5 or 50 mg of chrysotile daily for 14 months, and the gastrointestinal tract was examined following cessation of exposure (Jacobs et al., 1978a). No effects were noted in the esophagus, stomach, or cecum, but structural changes in the villi of the ileum were seen at both doses. Jacobs et al. (1978b) found a significant increase in [³H]-thymidine incorporation in the small intestinal mucosa, colon, rectum, spleen, and stomach of rats following ingestion of 50 mg/kg/day of chrysotile for 5 to 15 months. It was suggested that asbestos interferes with DNA metabolism in rat tissue.

Bolton et al. (1982) fed Wistar rats margarine containing 5 mg amosite, crocidolite, or chrysotile/g of margarine *ad libitum* for 25 months. The asbestos intake averaged 250 mg/rat/week. Rats given access to margarine with or without asbestos consumed less standard diet and weighted more than rats not given access to margarine. Obesity, however, did not appear to affect morbidity or mortality. No damage to gastrointestinal tissue was found. Although occasional asbestos fibers were seen in several tissues (examined by light and electron microscopy), no lesions or effects of treatment were seen.

3.1.4. Developmental and Reproductive Toxicity

3.1.4.1. Human

Information on the developmental and reproductive toxicity of asbestos in humans following oral exposure was not available.

3.1.4.2. Animal

Two types of chrysotile asbestos, short-range (98% of fibers <10 μm in length) and intermediate-range (65% of fibers >10 μm in length) were administered to male and female F344/N rats at a concentration of 1% in the diet (500 mg/kg/day) for life, starting with the dams of the test animals (NTP, 1985). Neither type of fiber adversely affected the fertility of the dams or the litter size of the F₁ animals. In a similar study, a 1% concentration of crocidolite asbestos was administered in feed to male and female F344/N rats, beginning with exposure of the dams before and during gestation (NTP, 1988a). Ingestion of crocidolite did not adversely affect the fertility of the dams or the litter size of the F₁ animals, but the average weight gain of the offspring at weaning from exposed mothers was 19% lower than the offspring of nonexposed mothers. Slightly lower body weight of offspring of asbestos-exposed mothers has been a finding in two other NTP studies, having been observed in similar exposure protocols with amosite asbestos (NTP, 1988b) and tremolite asbestos (NTP, 1988c).

No teratogenic effects were seen in mice given doses up to 33 mg/kg/day of chrysotile during gestation (Schneider and Maurer, 1977).

3.1.5. Reference Dose

An oral Reference Dose (RfD) for asbestos has not been derived (U.S. EPA, 1995).

3.2. INHALATION EXPOSURES

Note: Comparison of quantitative data in asbestos inhalation studies are complicated by the fact that a number of different methods have been employed to measure asbestos concentrations in air. Currently, air concentrations are expressed in terms of phase contrast microscopy (PCM) fibers/mL (f/mL). A particle visible under PCM is counted as a fiber if it is $\geq 5 \mu\text{m}$ long and has a length/thickness ratio of $\geq 3:1$. Other studies report airborne levels in terms of mass/volume (e.g., mg/m³). For a rough conversion, it is assumed that 1 mg/m³ = 33 f/mL. Older occupational studies measured dust exposure in million particles per cubic foot (mppcf). A number of studies found that asbestos-related health effects correlate with cumulative exposure [the product of concentration (PCM f/mL) multiplied by years of exposure]. Therefore, human exposures can be expressed as PCM f-yr/mL (ATSDR, 1993).

3.2.1. Acute Toxicity

3.2.1.1. Human

Temporary breathing difficulties have been reported in individuals exposed to high concentrations of asbestos dust (U.S. EPA, 1980).

3.2.1.2. Animal

Rats exposed by inhalation to asbestos for 14 days (no further details provided) developed local inflammatory lesions in the terminal bronchioles. Progressive fibrosis followed within a few weeks of the first exposure to dust (Holt et al., 1964).

3.2.2. Subchronic Toxicity

3.2.2.1. Human

Although most asbestos-related health effects have been reported to occur after long-term exposure, one study described an increased incidence of radiological abnormalities indicative of pulmonary fibrosis in amosite workers after relatively brief exposure period (6 months) (Ehrlich et al., 1992). In another study, obstructive airflow abnormalities were observed in 12/23 individuals examined 1.5 months

following an "intense" 5-month exposure to chrysotile. Eight months following exposure, 17/23 exhibited air flow obstruction. Of the 17 affected individuals, 12 were nonsmokers, current light smokers, or ex-light smokers (Harless et al., 1978).

3.2.1.2. Animal

Diffuse pulmonary fibrosis was observed in rats exposed by inhalation to 330 f/mL of asbestos, 7 hours/day, 5 days/ week for 15 weeks (Donaldson, 1988). Male and female rats exposed by inhalation to 9.06 mg chrysotile/m³, 7 hours/day, 5 days/week for 3 months exhibited considerable cellular changes in the alveolar epithelial and interstitial cells (Barry et al., 1983). There was a 57% increase in the number of type II epithelial cells and a 90% increase in their average cellular volume. A 58% increase in the number of interstitial cells and a 40% increase in their average cellular volume were also observed. Infiltration with macrophages accounted for nearly all the increases in interstitial cell numbers. Most of the cells that contained chrysotile were macrophages; eventually the fibers were calcified and cellular inclusions were formed.

3.2.3. Chronic Toxicity

3.2.3.1. Human

Numerous studies in humans have established that long-term inhalation of asbestos fibers causes chronic, progressive pneumoconiosis (asbestosis). The disease is common among occupational groups directly exposed to asbestos fibers such as insulation workers, but also extends to those working near the application or removal of asbestos and family contacts of exposed workers (U.S. EPA, 1980). Asbestosis results from a prolonged inflammatory response stimulated by the presence of fibers in the lungs and is characterized by fibrosis of the lung parenchyma, which usually becomes radiographically discernible 10 years after the first exposure (U.S. EPA, 1985). Characteristically, X-ray radiographs show small, irregular opacities, usually in the lower and middle lung fields (U.S. EPA, 1980). The main clinical symptom is shortness of breath, often accompanied by rales and cough. In severe cases, impairment of respiratory function may ultimately result in death (ATSDR, 1993). In addition to pulmonary fibrosis, three pleural diseases, fibrotic pleural plaques, pleuritis, and diffuse pleural thickening have been attributed to asbestos exposure (Schulz 1994). Because asbestos fibers are resistant to breakdown in the lung, the inflammatory response triggered by the fibers is ongoing, even after exposure has ceased. Some studies of workers with asbestos-related diseases indicate that the cellular immune system in such patients can be depressed. However, it is not known whether the alterations in immune function are the cause or result of asbestos-induced disease (ATSDR, 1993). Epidemiological evidence has also shown that the risk of chronic pulmonary fibrosis is significantly higher in individuals that smoke than in nonsmoking individuals with similar asbestos exposures (Schulz, 1994).

The toxicity of asbestos is dependent on exposure intensity and duration and on the physical/chemical properties of the asbestos fibers. While most studies with humans involve exposure to chrysotile asbestos, available evidence indicates that all forms of asbestos are fibrogenic (ATSDR, 1993). A factor in determining the pathogenic potential of asbestos is the fiber-length distribution; it is generally believed that asbestos fibers shorter than 5 μm are not pathogenic (ACGIH, 1991). The British Occupational Hygiene Society (BOHS, 1968) estimated that exposure to airborne asbestos for <50 years at an exposure level of 2 fibers/cm³ (>5 μm) would cause development of asbestosis in no more than 1% of the exposed group. This estimate was based on the incidence of asbestosis (diagnosed by the presence of high-pitched rales in the basal portions of the lung) in a population of asbestos textile workers. Estimates by ATSDR (1993) indicate that cumulative exposures of 17-75 fibers-year/mL result in fibrotic lung lesions in humans and death has been reported with cumulative exposures of 3.5-300 fibers-year/mL.

3.2.3.2. Animal

Wagner (1963) exposed guinea pigs and Vervet monkeys to chrysotile and amosite dust at average concentrations of 30,000 particles/mL, respectively, for 8 hours/day, 5 days/week for 49 weeks/year. Exposure to chrysotile produced pulmonary fibrosis, interstitial pneumonitis, metaplasia of the epithelium of the alveolar ducts, and cor pulmonale in guinea pigs. Similar but more rapidly developing lesions were observed in guinea pigs exposed to amosite. Three monkeys died after 7, 10, and 22 months of exposure

to chrysotile dust and three monkeys exposed to amosite dust died after 4, 22, and 14 months of exposure (total number of animals not reported). Pathological findings included lung fibrosis and cor pulmonale. In a later study, Wagner et al. (1974) exposed Wistar rats to amosite, anthophyllite, crocidolite, and chrysotile dust for 3, 6, 12, or 24 months at concentrations of 9.7-14.7 mg/m³, 7 hours/day, 5 days/week. Overall, the severity of asbestosis (fibrosis and production of type II pneumocytes) increased with exposure. Amosite caused less severe asbestosis than the other asbestos dusts tested.

3.2.4. Developmental and Reproductive Toxicity

Information on the inhalation developmental and reproductive toxicity of asbestos in humans or animals was not available.

3.2.5. Reference Concentration

An inhalation Reference Concentration (RfC) for asbestos has not been derived (U.S. EPA, 1995).

3.3. OTHER ROUTES OF EXPOSURE

3.3.1. Acute Toxicity

3.3.1.1. Humans

Alden and Howell (1944) reported formation of small warts or corns in workers installing amosite insulation in ships after dermal contact with asbestos. Nearly 60% of the workers developed one or more of these lesions, mostly on the hands. The lesions were associated with penetration of the skin by asbestos fibers. Corns developed within 10 days and were painful at first.

3.3.1.2. Animals

Information on the acute toxicity of asbestos in animals by other routes of exposure was not available.

3.3.2. Subchronic Toxicity

Information on the subchronic toxicity of asbestos in humans or animals by other routes of exposure was not available.

3.3.3. Chronic Toxicity

Information on the chronic toxicity of asbestos in humans or animals by other routes of exposure was not available.

3.3.4. Developmental and Reproductive Toxicity

Information on the developmental and reproductive toxicity of asbestos in humans or animals by other routes of exposure was not available.

3.4. TARGET ORGANS/CRITICAL EFFECTS

3.4.1. Oral Exposures

3.4.1.1. Primary Target Organs

Gastrointestinal tract: Histological and biochemical alterations in cells of the gastrointestinal tract were observed in rats after chronic exposure to chrysotile.

3.4.1.2. Other Target Organs

No other target organs were identified.

3.4.2. Inhalation Exposures

3.4.2.1. Primary Target Organs

Lungs: Long-term inhalation of asbestos fibers causes chronic, progressive pneumoconiosis (asbestosis) in humans. The disease is characterized by fibrosis of the lung parenchyma, which usually becomes radiographically discernible 10 years after the first exposure. The main clinical symptom is shortness of breath, often accompanied by rales and cough. In severe cases, impairment of respiratory function may ultimately result in death. In addition to pulmonary fibrosis, three pleural diseases, fibrotic pleural plaques, pleuritis, and diffuse pleural thickening have been attributed to asbestos exposure.

3.4.2.2. Other Target Organs

Immune system: Depressed immune function has been observed in some workers with asbestos-related diseases.

3.4.3. Other Routes of Exposure

Skin: Dermal contact with asbestos fibers may produce small warts or corns.

4. CARCINOGENICITY

4.1. ORAL EXPOSURES

4.1.1. Human

Several epidemiological studies have been conducted to determine if the cancer incidence is higher than expected in geographical areas with high levels of asbestos in drinking water. Most of the studies had weaknesses such as lack of statistical power due to inadequate study design, exposure level and duration, exposure to other risk factors, and a number of other confounding factors. In a study on the cancer incidence of the San Francisco Bay area, Cooper et al. (1979) reported statistically significant trends for the incidence of several cancer types, including stomach, gallbladder, esophageal, and peritoneal cancer, when census tracts were analyzed on a gradient of low to high concentrations of asbestos in municipal drinking water. Later studies confirmed the association between asbestos concentrations in drinking water and cancer in the Bay area (Conforti, 1983; Kanarek, 1983). However, Harrington et al. (1978) found no association between the use of asbestos-cement pipe for municipal water supplies in Connecticut and the incidence of gastrointestinal cancer. In the Everett, Washington area, the presence of chrysotile asbestos in the drinking water (200×10^6 fibers/L) was not clearly associated with an increased cancer risk (Polissar et al., 1983). Marsh (1983) reviewed eight independent studies of asbestos in drinking water in five geographic areas. He concluded that even though one or more studies found an association between asbestos in water and cancer mortality (or incidence) due to tumors in various organs, no individual study or aggregation of studies exists that would establish risk levels from ingested asbestos. In a later review of several independent epidemiological studies, Kanarek (1989) concluded that there were relatively consistent findings for increased stomach and pancreatic cancer among the studies. However, according to IARC (1987), no clear excess of cancer has been associated with the presence of asbestos in drinking water.

4.1.2. Animal

Gibel et al. (1976) found a significantly increased incidence ($p > 0.01$) of malignant tumors and an earlier tumor induction time compared with controls in a group of 50 Wistar rats fed asbestos filter material containing 52.6% chrysotile fibers. The filter material was administered for life at an estimated daily dose of 50 mg/kg. Among 42 animals available for evaluation, there were 12 malignant tumors with metastases (4 kidney carcinomas, 1 lung carcinoma, 3 reticulum-cell sarcomas, and 4 liver carcinomas). Also observed were 1 lung adenoma, 2 cholangiomas, 2 papillomas of the forestomach, and 2 mammary fibroadenomas.

Ward et al. (1980) administered 10 mg amosite 3 times/week for 10 weeks by gavage to 50 male F344 rats. Following a 78-79 week observation period, a total of 17 colon carcinomas were observed.

The tumor incidence was statistically significantly increased compared with historical controls, but no concurrent controls were maintained.

More recently, NTP performed a series of feeding studies with rodents. Groups of male and female F344/N rats and male and female Syrian Golden hamsters were administered short-range and intermediate-range fiber length chrysotile at a concentration of 1% in the diet for life (NTP, 1985; 1990). The estimated daily intake was 500 or 830 mg/kg/day for rats or hamsters, respectively (ATSDR, 1993). Using similar protocols, groups of male and female F344/N rats were also exposed to 1% dietary concentrations of crocidolite, amosite, or tremolite asbestos for life (NTP, 1988a,b,c). The studies yielded mostly negative results for carcinogenicity although some suggestive increases in tumor incidences did occur. Male rats exposed to chrysotile fibers of intermediate length exhibited an increased incidence of benign adenomatous polyps of the large intestine. These tumors were not observed in female rats or in hamsters (NTP, 1985). The data were interpreted as providing "some evidence" of carcinogenicity for chrysotile fibers of intermediate length. An increased incidence of tumors of the adrenal cortex was observed in both male and female hamsters exposed to the short-range chrysotile fibers. NTP suggested that the biological significance of adrenal tumors in the absence of target organ (gastrointestinal tract) neoplasia was questionable.

4.2. INHALATION EXPOSURES

4.2.1. Human

Numerous epidemiologic studies have documented an increased incidence of lung cancer and pleural and peritoneal mesothelioma (a tumor involving the lining of the abdomen and chest) as a result of asbestos exposure.

All major types of commercial asbestos such as chrysotile, amosite, and crocidolite have been found to produce asbestos-related cancer among workers occupationally exposed in mining and milling, in manufacturing, and in the use of the materials containing asbestos fibers (U.S. EPA, 1980). Asbestos-related cancer has also been identified, although less frequently, in individuals who had worked near the application or removal of asbestos material; in individuals residing in the vicinity of asbestos plants; and in individuals who had lived in the household of an asbestos worker (IARC, 1977; 1987).

For lung cancer, the magnitude of the carcinogenic risk appears to be a function of a number of factors, including the level and duration of exposure; the time since exposure occurred; the age at which exposure occurred; the smoking history of the exposed person; and the type and size distribution of asbestos fibers (ATSDR, 1993). There is a substantial latency period (10-30 years) between onset of exposure to asbestos and the occurrence of lung cancer. After a sufficient time (e.g., 20 years), the risk of lung cancer in exposed workers is generally observed to increase in proportion to the cumulative exposure (f-yr/mL) (ATSDR, 1993). Epidemiological evidence has shown that asbestos exposure and cigarette smoking act synergistically to produce dramatic increases in lung cancer compared with those from exposure to either agent alone (U.S. EPA, 1984). The data for possible interactions between cigarette smoke and mesothelioma is not certain, but it appears that smoking does not increase the risk for this cancer (Schulz, 1994).

There is strong evidence that long fibers are more carcinogenic than short fibers (ATSDR, 1993). Although all types of asbestos are known to cause lung cancer, there may be differences in the carcinogenic potential of the different asbestos forms. It has been suggested that crocidolite has the greatest potential to induce lung cancer, chrysotile the lowest, with amosite occupying an intermediate position (ACGIH, 1991). In a study of 1348 retirees from the asbestos industry, the respiratory cancer rate of men exposed only to chrysotile was 2.3 times the expected, whereas this rate was 5.3 times the expected for men who had been exposed to a combination of chrysotile and crocidolite (Enterline and Henderson, 1973). A similar difference was noted in the asbestos cement industry. Workers exposed to chrysotile and cement (shingles and sheets) had a respiratory cancer rate 1.4 times the expected, whereas workers exposed to chrysotile and crocidolite in combination with cement (asbestos cement pipes), had a respiratory cancer rate 6.1 times the expected (Enterline and Henderson, 1973).

Selikoff (1976) reported 59 cases of lung cancer and 31 cases of mesothelioma among 1249 asbestos insulation workers followed prospectively for 11 years. A retrospective cohort mortality study of

17,800 U.S. and Canadian asbestos insulation workers followed over a 10-year period reported an increased incidence of cancer at all sites [319.7 expected vs. 995 observed, SMR (standard mortality ratio) = 311] and lung cancer (105.6 expected vs. 486 observed, SMR = 460). A modest increase in deaths from gastrointestinal cancer was reported along with 175 deaths from mesothelioma (none expected). The years of exposure ranged from <10 to >45 (Selikoff et al., 1979). In other epidemiologic studies, the increase of lung and pleural cancer has ranged from a low of 1.9 times the expected rate in asbestos factory workers in England (Peto et al., 1977) to a high of 28 times the expected rate in female asbestos textile workers in England (Newhouse et al., 1972).

Many reports from a number of countries have described cases of pleural and peritoneal mesotheliomas in relation to occupational exposures to various types and mixtures of asbestos. However, mesotheliomas also have been reported in household contacts and in non-occupationally exposed individuals living in the neighborhood of industrial sources of asbestos (IARC, 1977). It has been estimated that a third of the mesotheliomas occurring in the U.S. may be due to non-occupational exposure (IARC, 1987). A case-control study with 83 patients with mesothelioma reported that 53% had occupational exposure to asbestos or lived with asbestos workers compared with 12% of the controls. Of the remaining patients, 31% lived within half a mile of an asbestos factory compared with 8% of controls (Newhouse and Thompson, 1965).

The relation between asbestosis and lung cancer is not clear. An assessment of epidemiologic data by Schulz (1994) indicates that the risk of lung cancer is considerably higher in workers with radiographic evidence of asbestosis, but there is no proof that asbestosis is a necessary precursor for lung cancer or that asbestosis progresses to lung cancer. The results of a recent case-referent study with 271 patients with a confirmed diagnosis of primary lung cancer and 678 referents (279 with other respiratory disease and 399 with cardiac disease) suggest that asbestos is associated with lung cancer even in the absence of radiologically apparent pulmonary fibrosis (Wilkinson et al., 1995).

In addition to lung cancer and mesothelioma, there are inconsistent reports of excess cancer incidences or mortality from cancers at other sites among workers exposed to asbestos. They include cancers of the gastrointestinal system (esophagus, stomach, colon, bile duct, and rectum), laryngeal cancer, kidney cancer, and ovarian cancer, and cancer affecting the lymphopoietic and hematopoietic systems (IARC, 1977; Schulz, 1994). Gastrointestinal cancers occurred at an increased incidence in workers exposed to crocidolite, amosite, chrysotile, or mixed fibers containing crocidolite, although not all studies were consistent in this respect (IARC, 1987). The risk of the above listed cancers appears to be significantly lower than those for lung cancer and mesothelioma in similarly exposed cohorts (Schulz, 1994).

4.2.2. Animal

A number of inhalation studies have been conducted with experimental animals; some of the more pertinent studies are summarized below.

Lung tumors (17 adenocarcinomas, 4 squamous cell carcinomas, and 7 fibrosarcomas) were observed in 24/72 white rats exposed to 86 mg chrysotile dust/m³, 30 hours/week for 16 months (Gross et al., 1967). No lung tumors were found in 39 control rats. Wagner et al. (1974) exposed male and female Wistar rats to amosite, crocidolite, anthophyllite, or Canadian or Rhodesian chrysotile asbestos at concentrations of 9.7-14.7 mg/m³ for 1 day or for 3, 6, 12, or 24 months for 7 hours/day, 5 days/week. All forms of asbestos produced an increased incidence of lung tumors, (ranging in severity from adenomas to squamous carcinomas) and mesotheliomas after 3 months. Rats exposed to Rhodesian chrysotile did not develop mesotheliomas. A positive association between asbestosis and lung tumors was reported.

AxC F₁ mice were exposed to chrysotile dust (150-300 million particles/mL), 8-12 hours/day, 5 days/week for 17 months (Lynch et al., 1957). Although a higher incidence of pulmonary adenomas was reported in the exposed group (58/127) than in controls (80/222), the increase was not statistically significant.

Rats, mice, rabbits, guinea pigs, and gerbils were exposed to various forms of asbestos at mean concentrations of about 50 mg/m³, 4 hours/day, 4 days/week for up to 24 months (Reeves et al., 1974).

Dusts of chrysotile, crocidolite, and amosite were prepared by ball-milling, a process noted for destroying much of the fibrous character of asbestos. The fiber counts were 54 fibers/mL for chrysotile, 864 fibers/mL for amosite, and 1105 fibers/mL for crocidolite. Tumors were detected only in rats and mice. Rats exposed to crocidolite, chrysotile, or amosite developed lung tumors in 5/46, 3/43, or 3/46 animals, respectively. In a later study, Reeves (1976) exposed rats to the same three forms of asbestos for 2 years, using the same exposure protocol. Crocidolite, with the highest fiber count, also induced the highest number of lung tumors (7/50), while chrysotile (3/54) and amosite (3/61) induced fewer tumors in treated animals.

4.3. OTHER ROUTES OF EXPOSURE

4.3.1. Human

Information on the carcinogenicity of asbestos in humans by other routes of exposure was not available.

4.3.2. Animal

Asbestos has also been tested by intrapleural administration and intraperitoneal injection in several species. As reviewed in IARC (1977; 1987), chrysotile, crocidolite, amosite, and anthophyllite produced mesotheliomas in rats and hamsters after intrapleural administration. Given by the same route, mesotheliomas were also observed in rats exposed to tremolite. The various forms of asbestos were usually administered as single doses at concentrations ranging from 0.5 to 67 mg of asbestos. Synergistic effects were noted following intratracheal administration of chrysotile and benzo[*a*]pyrene in rats and hamsters.

Intraperitoneal administration of chrysotile, crocidolite, and amosite at doses ranging from 2 to 100 mg/animal induced abdominal tumors including mesotheliomas in rats and mice; crocidolite produced abdominal tumors in hamsters; and tremolite and actinolite produced abdominal tumors in rats (IARC, 1977; 1987).

4.4. EPA WEIGHT-OF-EVIDENCE

Classification -- A - human carcinogen (U.S. EPA, 1995)

Basis -- Observations of increased mortality and incidence of lung cancer, mesotheliomas, and gastrointestinal cancer in occupationally exposed workers are consistent across investigators and study populations. Inhalation studies in two strains of rats showed similar findings for lung cancer and mesotheliomas. Animal evidence for carcinogenicity via ingestion is limited (male rats fed intermediate-range chrysotile fibers; i.e., >10 μm length, developed benign polyps), and epidemiologic data are inadequate.

4.5. CARCINOGENICITY SLOPE FACTORS

4.5.1. Oral

Although slope factors have been derived in the past based on oral studies with animals and extrapolation from human inhalation studies (U.S. EPA, 1985), a slope factor is not available at this time (U.S. EPA, 1995).

4.5.2. Inhalation

SLOPE FACTOR: Not available

UNIT RISK: $2.3\text{E-}1$ (f/mL)⁻¹ (U.S. EPA, 1995); the estimated air concentrations which would result in lifetime cancer risks of 10^{-4} , 10^{-5} , and 10^{-7} are $4\text{E-}4$, $4\text{E-}5$, and $4\text{E-}6$ f/mL, respectively.

PRINCIPAL STUDIES: The unit risk has been calculated based on inhalation response data from 15 occupational exposure studies. Details of the derivations are provided in U.S. EPA (1986).

COMMENT: Risks have been calculated for males and females according to smoking habits for a variety of exposure scenarios (U.S. EPA, 1986). The unit risk value was calculated for the additive combined risk of lung cancer and mesothelioma, and was calculated as a composite value for males and females. The epidemiologic data show that cigarette smoking and asbestos exposure interact synergistically for induction of lung cancer, but do not interact synergistically with regard to mesothelioma. The unit risk value was based on risks calculated using U.S. general population cancer rates and mortality patterns without consideration of smoking habits. The unit risk was based on fiber counts made by phase contrast microscopy (PCM) and should not be directly applied to measurements made by other analytical techniques such as transmission electron microscopy (TEM).

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