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Asbestos

CAS No. 1332-21-4

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Asbestos and all commercial forms of asbestos are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Studies in humans have shown that exposure to asbestos causes respiratory-tract cancer, mesothelioma of the lung and abdominal cavity (pleural and peritoneal mesothelioma), and cancer at other tissue sites. Case reports and epidemiological studies have found that occupational exposure to chrysotile, amosite, anthophyllite, mixtures containing crocidolite, and various complex mixtures of asbestos increases the risk of lung cancer (the various forms of asbestos are identified and described below, under Properties). The risk of lung cancer was increased up to sixfold in vermiculite miners exposed to tremolite and actinolite. Mesothelioma and digestive-tract cancer were observed in workers occupationally exposed to crocidolite, amosite, and chrysotile; however, the results for digestive-tract cancer were inconsistent among studies. An excess of laryngeal cancer was reported in studies of shipyard workers, chrysotile miners, insulation workers, and other workers exposed to asbestos. People living near asbestos factories or mines or living with asbestos workers also developed mesothelioma. However, no clear association was found between cancer risk and exposure to asbestos in drinking water. Co-exposure to asbestos and tobacco smoking increased the risk of lung cancer in a synergistic manner (i.e., the effects of co-exposure on risk were multiplicative, rather than additive). The International Agency for Research on Cancer concluded that there was sufficient evidence for the carcinogenicity of asbestos in humans (IARC 1977, 1987).

Since asbestos was listed in the *First Annual Report on Carcinogens*, the evidence for the carcinogenicity of asbestos has been reevaluated by the Institute of Medicine (IOM) of the National Academy of Sciences in 2006 (NAS 2006) and by IARC in 2009 (Straif *et al.* 2009). IARC concluded that exposure to all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) was associated with an increased risk of lung cancer and mesothelioma. In addition, it concluded that there was sufficient evidence from epidemiological studies that asbestos also caused cancer of the larynx and ovary, as well as limited evidence that it caused cancer of the colorectum, pharynx, and stomach. In general, these conclusions were consistent with the IOM evaluation, which found sufficient evidence that exposure to asbestos caused cancer of the larynx and suggestive evidence that it caused cancer of the pharynx, stom-

ach, and colorectum (NAS 2006). The IOM did not review studies on lung cancer and mesothelioma.

Cancer Studies in Experimental Animals

All commercial forms of asbestos have been shown to cause cancer in several species of experimental animals by various routes of exposure (IARC 1977, 1987). Inhalation exposure to chrysotile, crocidolite, amosite, anthophyllite, or tremolite caused mesothelioma and lung cancer (carcinoma) in rats. Intrapleural injection of various types of asbestos caused mesothelioma in rats and hamsters, and intraperitoneal injection of chrysotile, crocidolite, or amosite caused peritoneal tumors, including mesothelioma, in mice and rats. The incidence of abdominal tumors was increased by intraperitoneal injection of crocidolite in hamsters and actinolite or tremolite in rats. When filter material containing chrysotile was added to the diet of rats, the overall incidence of malignant tumors (including kidney, lung, and liver tumors) was increased. Oral administration of amosite, tremolite, or crocidolite did not cause tumors in rats, nor did oral administration of amosite or chrysotile in hamsters (NTP 1985, IARC 1987). Dietary administration of chrysotile asbestos fibers of short or intermediate lengths did not cause tumors in female rats, but dietary exposure to the intermediate-length fibers resulted in a low incidence of benign adenomatous polyps of the large intestine in male rats (NTP 1985).

Asbestos and the polycyclic aromatic hydrocarbon benzo[*a*]pyrene administered alone by intratracheal injection did not cause tumors in rats, but when co-administered caused lung tumors and mesothelioma (IARC 1977). Synergistic effects on tumor induction also were observed following co-administration of asbestos and benzo[*a*]pyrene or asbestos and *N*-nitrosodiethylamine to hamsters (IARC 1987).

IARC (1977, 1987) concluded that there was sufficient evidence in experimental animals for the carcinogenicity of asbestos, including the following forms: actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite. Since asbestos was reviewed for listing in the *First Annual Report on Carcinogens* and by IARC, intrabronchial instillation of chrysotile has been shown to cause pulmonary and pleural mesothelioma in rats (Fasske 1988).

Properties

Asbestos is the generic name for a group of six naturally occurring fibrous silicate minerals, including the fibrous serpentine mineral chrysotile and the five fibrous amphibole minerals actinolite, amosite, anthophyllite, crocidolite, and tremolite. Asbestos minerals possess a number of properties useful in commercial applications, including heat stability, thermal and electrical insulation, wear and friction characteristics, tensile strength, the ability to be woven, and resistance to chemical and biological degradation. The forms are ranked from greatest to least tensile strength as follows: crocidolite, chrysotile, amosite, anthophyllite, tremolite, and actinolite. Their ranking from greatest to least acid resistance is tremolite, anthophyllite, crocidolite, actinolite, amosite, and chrysotile. The forms that have been used commercially are chrysotile, anthophyllite, amosite, and crocidolite (IARC 1977, ATSDR 2001, HSDB 2009).

Chrysotile, the most abundant form of asbestos in industrial applications, occurs naturally in fiber bundle lengths ranging from several millimeters to over 10 cm (Virta 2002a). Chrysotile has an idealized chemical composition of $\text{Mg}_3\text{Si}_2\text{O}_5(\text{OH})_4$ and occurs as a curled sheet silicate, which wraps around itself in a spiral, forming a hollow tubular fiber. The hydroxyl group may, rarely, be replaced by oxygen, fluorine, or chlorine. In addition, small amounts of iron, aluminum, nickel, calcium, chromium, manganese, sodium, or potassium may be present as impurities. Natural chrysotiles occur with a range of phys-

ical properties. Chrysotiles may be white, gray, green, or yellowish, with a silky luster. Although chrysotile fibers are more flexible than the amphiboles, fibers from different geological locations may differ in flexibility. Chrysotile fibers have a net positive surface charge and form a stable suspension in water. The fibers degrade in dilute acids (IARC 1973, 1977, IPCS 1986).

The amphibole forms of asbestos consist of chain structures, with nine structural sites that accommodate cations. Amphibole crystals consist of two chains based on Si_4O_{11} units, linked by a band of cations. The principal cations are magnesium, iron, calcium, and sodium, and their ratios determine the mineral species. The chemical composition and physical properties vary over a wide range, and the chemical composition of a field sample seldom matches the idealized formula. Amphibole fibers do not divide into fibrils as small in diameter or as symmetrical as chrysotile fibers, and they do not have a hollow central core. They have a negative surface charge in water (IPCS 1986, HSDB 2009).

Amosite is ash gray, greenish, or brown and is somewhat resistant to acids. It tends to occur with more iron than magnesium, at a ratio of approximately 5.5 to 1.5. The fibers are long, straight, coarse, and somewhat flexible (less so than chrysotile or crocidolite) (IARC 1973, 1977, IPCS 1986).

Anthophyllite is grayish white, brown-gray, or green and is very resistant to acids. It is relatively rare and occasionally occurs as a contaminant in talc deposits. The fibers are short and very brittle (IARC 1973, 1977, IPCS 1986).

Crocidolite is lavender or blue and has good resistance to acids, but less heat resistance than other asbestos fibers. Its fibers typically are shorter and thinner than those of other amphiboles, but not as thin as chrysotile fibers. The fibers have fair to good flexibility and fair spinnability. Crocidolite usually contains organic impurities, including low levels of polycyclic aromatic hydrocarbons (IARC 1973, 1977, IPCS 1986).

Tremolite is a calcium-magnesium amphibole, and actinolite is an iron-substituted derivative of tremolite. Both occur in asbestos and non-asbestos forms. Tremolite is a common contaminant in chrysotile and talc deposits, and actinolite is a common contaminant in amosite deposits. Tremolite is white to gray, and actinolite is pale to dark green. Both are brittle; tremolite is resistant to acids, but actinolite is not (IARC 1977, IPCS 1986).

Use

Although asbestos use dates back at least 2,000 years, modern industrial use began around 1880. Use of asbestos peaked in the late 1960s and early 1970s, when more than 3,000 industrial applications or products were listed. Asbestos has been used in roofing, thermal and electrical insulation, cement pipe and sheets, flooring, gaskets, friction materials, coatings, plastics, textiles, paper, and other products (ATSDR 2001, HSDB 2009). The U.S. Consumer Product Safety Commission banned use of asbestos in general-use garments, but asbestos may be used in fire-fighting garments if they are constructed to prevent release of asbestos fibers (HSDB 2009). Domestically used asbestos fibers are classified into seven quality categories or grades. Grades 1, 2, and 3 include the longer, maximum-strength fibers and generally are used in the production of textiles, electrical insulation, and pharmaceutical and beverage filters. Grades 4, 5, and 6 are medium-length fibers used in the production of asbestos-cement pipes and sheets, clutch facings, brake linings, asbestos paper, packaging, gaskets, and pipe coverings. Grade 7 includes short fibers generally used as reinforcers in plastics, floor tiles, coatings and compounds, some papers, and roofing felts (OSHA 1986).

The four commercially important forms of asbestos have been chrysotile, amosite, anthophyllite, and crocidolite (IARC 1973); however, commercial use of anthophyllite was discontinued by the 1980s (IPCS 1986, HSDB 2009). Chrysotile, amosite, and particularly crocidolite all have extremely high tensile strengths and are used extensively as reinforcers in cements, resins, and plastics. Although chrysotile is most adaptable to industrial use, crocidolite and amosite are particularly useful in combination with chrysotile for adding specific properties, such as rigidity (OSHA 1986). By the 1990s, chrysotile accounted for more than 99% of U.S. asbestos consumption (ATSDR 2001). By 2008, chrysotile was the only type of asbestos used in the United States (Virta 2008); 64% of chrysotile used was categorized as grade 7 asbestos (with fiber lengths less than 3 mm), followed by grades 4, 5, and 3 (Virta 2002a, 2009).

In 1973, when U.S. consumption of asbestos was at its peak, the major markets included asbestos cement pipe (24%), flooring (22%), roofing (9%), friction products, such as automobile brakes and clutches (8%), and packing and gaskets (3%) (Virta 2002a). In 2009, roofing products accounted for about 65% of U.S. consumption; the remaining 35% was attributed to "other uses" (USGS 2010).

Production

U.S. demand for asbestos increased dramatically from 1900 to the early 1970s. By 1950, the United States was the world's largest user of asbestos. However, asbestos demand declined rapidly after 1973 as health and liability issues became apparent (Virta 2002a). Before the 1980s, asbestos was produced in California, Arizona, North Carolina, and Vermont; however, most of these facilities suspended mining operations in the 1970s, and the last U.S. asbestos mine closed in 2002 (ATSDR 2001, Virta 2002b). U.S. production of asbestos decreased from a high of 136,000 metric tons (300 million pounds) in 1973 to 2,720 metric tons (6 million pounds) in 2002 (USGS 2009). U.S. asbestos consumption declined from a maximum of 803,000 metric tons (1.8 billion pounds) in 1973 to 715 metric tons (1.6 million pounds) in 2009 (USGS 2009, 2010). In 2010, two U.S. suppliers of asbestos were identified (ChemSources 2009). Most of the asbestos used in the United States is imported from Canada (Virta 2008). U.S. imports of asbestos peaked in 1973, at 718,000 metric tons (1.6 billion pounds) and totaled 715 metric tons (1.6 million pounds) in 2009 (USGS 2009, 2010). U.S. asbestos exports peaked in 1981 at 64,400 metric tons (142 million pounds), declining to 55 metric tons (121,000 pounds) in 2009.

Exposure

The primary routes of potential human exposure to asbestos are inhalation and ingestion. Dermal absorption of asbestos is minimal, but dermal contact may lead to secondary ingestion or inhalation of dust. Asbestos fibers vary with respect to size (length and diameter) and chemical composition. These differences are known to affect deposition, movement, and clearance from the body and carcinogenic potency. Fiber diameter is the most important factor affecting penetration and deposition in the lungs. Thin fibers have the greatest inhalation potential and deposit deep within the lungs. Fiber length, surface chemistry, and other properties affect biological activity. Fibers longer than 8 μm with a diameter of less than 1.5 μm are the most potent carcinogens (IPCS 1986).

Asbestos is released to the environment from both natural and anthropogenic sources and has been detected in indoor and outdoor air, soil, drinking water, food, and medicines. Because asbestos products were used so widely, the entire U.S. population potentially is exposed to some degree; however, the potential for exposure continues to decline, because asbestos mining has stopped, and asbestos products are

being eliminated from the market. Releases from asbestos materials in buildings and vehicle brake linings account for substantial emissions of asbestos into the air. Demolition of buildings with asbestos insulation or fireproofing may cause high atmospheric concentrations for relatively short periods. Environmental asbestos concentrations vary widely; therefore, it is not possible to accurately calculate human exposure levels except on a site-by-site basis. People may be exposed to higher-than-average levels of asbestos in air if they live near asbestos-containing waste sites or asbestos-related industries, if they use asbestos-containing products, or if they live or work in buildings with deteriorating asbestos insulation or that have undergone poorly performed asbestos removal (ATSDR 2001). In the past, families of asbestos workers potentially were exposed to high fiber levels from contaminated clothing brought home for laundering. People living in households with asbestos workers were found to have significantly elevated lung burdens of asbestos, often in the same range as found in individuals occupationally exposed to asbestos, such as shipyard workers. The asbestos-fiber burdens of occupants of a building containing asbestos insulation, on the other hand, were comparable to those of individuals with no known occupational exposure to asbestos (IARC 1977, Roggli and Longo 1991).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, almost all environmental releases of asbestos are to landfills. Reported releases declined about 80% from 1988 to 1997, then increased between 1998 and 2001, when 18.2 to 24.4 million pounds was released to landfills annually. Releases returned to lower levels after 2002. In 2007, 30 industrial facilities (mostly waste-management companies) reported releasing or disposing of about 10.5 million pounds of friable (readily crumbled) asbestos (TRI 2009).

In the past, occupational exposure occurred primarily during the mining and milling of asbestos, during the manufacture of all asbestos products, and in the construction and shipbuilding industries. Occupational exposure still occurs among workers who use asbestos end products, such as asbestos insulation workers, brake repair and maintenance workers, building demolition workers, and asbestos abatement workers (IARC 1977, ATSDR 2001, HSDB 2009). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 215,265 workers, including 9,727 women, potentially were exposed to asbestos and that 92,033 workers, including 13,262 women, potentially were exposed to chrysotile (NIOSH 1990). In 1990, the U.S. Occupational Safety and Health Administration estimated that about 568,000 workers in production and services industries and 114,000 workers in construction industries potentially were exposed to asbestos (ATSDR 2001). No more recent occupational exposure estimates were found.

Regulations

Consumer Product Safety Commission (CPSC)

Consumer patching compounds containing intentionally added respirable, free-form asbestos are banned.

Artificial emberizing materials (ash and embers) containing respirable free-form asbestos are banned.

General-use garments containing asbestos (other than those needed for personal protection and constructed so that asbestos fibers will not become airborne) are banned.

Certain household products containing intentionally added asbestos that release asbestos fibers are subject to cautionary labeling requirements.

Department of Transportation (DOT)

Asbestos is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 7 million fibers per liter.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 7 million fibers per liter for fibers longer than 10 μm .

Toxic Substances Control Act

Rules have been established for identifying, analyzing, and disposing of asbestos found in schools, and prohibitions on the manufacturing and import of asbestos products have been established.

Mine Safety and Health Administration

Permissible exposure limit (PEL) for miners (surface and underground coal, metal, and nonmetal mines): Full-shift limit = 0.1 fiber/cm³ (8-h time-weighted average); excursion limit = 1 fiber/cm³ (30-min sample).

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Ceiling concentration = 1 fiber/cm³ (excursion limit) as averaged over a sampling period of 30 min. Permissible exposure limit (PEL) = 0.1 fiber/cm³ for fibers longer than 5 μm having a length-to-diameter ratio of at least 3 to 1.

Comprehensive standards for occupational exposure to asbestos have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.1 respirable fiber/cc (cm³).

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

Recommended exposure limit (REL) = 0.1 fiber/cm³ (fibers longer than 5 μm).

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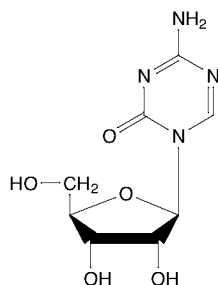
Azacitidine

CAS No. 320-67-2

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)

Also known as 5-azacytidine, 5-aza-C, or Vidaza (a registered trademark of Celgene Corporation)



Carcinogenicity

Azacitidine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to azacitidine by injection caused tumors at several different tissue sites in mice and rats. Intraperitoneal injection of azacitidine caused cancer of the hematopoietic system (lymphocytic or histiocytic lymphoma or granulocytic leukemia or sarcoma) in female mice and skin and lung tumors in mice of both sexes. Prenatal exposure of mice to azacitidine caused leukemia, lymphoma, and tumors of the lung and liver (NCI 1978, Luz and Murray 1988, IARC 1990). In male rats, intraperitoneal injection of azacitidine caused skin cancer (squamous-cell carcinoma) and tumors of the testis (interstitial-cell neoplasia) (IARC 1990).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to azacitidine.

Studies on Mechanisms of Carcinogenesis

In an initiation-promotion study, partially hepatectomized male rats were administered *N*-nitrosodiethylamine followed by chronic administration of azacitidine by intraperitoneal injection. The incidence of liver tumors and the combined incidence of skin and lung tumors were increased; all surviving rats developed hyperplastic liver nodules (Carr *et al.* 1988, IARC 1990).

Azacitidine in the absence of mammalian metabolic activation is genotoxic in a wide variety of prokaryotic, lower eukaryotic, and mammalian *in vitro* test systems. It caused DNA damage and base-pair substitution mutations (but not frame-shift mutations) in prokaryotic systems and mitotic recombination, gene conversion, chromosomal aberrations, and gene mutations in somatic and germ

cells of lower eukaryotes (yeast, fruit flies, and plants). In cultured rodent cells, azacitidine inhibited DNA synthesis and caused sister chromatid exchange, chromosomal aberrations, gene mutations (in some but not all studies), and morphological cell transformation. In cultured human cells, azacitidine caused DNA damage and gene mutations; studies on sister chromatid exchange and chromosomal aberrations gave conflicting results. Azacitidine did not cause dominant lethal mutations in male mice exposed *in vivo* (IARC 1990).

The carcinogenic or tumor-enhancing activity of azacitidine has been postulated to result directly or indirectly from its ability to inhibit DNA methylation (Harrison *et al.* 1983, Riggs and Jones 1983, Kerbel *et al.* 1984, 1986, Takenaga 1986, Glover and Leyland-Jones 1987, Glover *et al.* 1987, IARC 1990, Jones and Buckley 1990, Haaf 1995). Altered levels of DNA methylation can affect gene expression (Cedar 1988, IARC 1990, Fajkus *et al.* 1992, Velge *et al.* 1995), and hypomethylation is associated with the expression of genes that are normally silent or downregulated. DNA hypomethylation is somatically heritable, causing alterations in gene expression that are maintained in daughter cells as the affected cells proliferate (Holliday 2006). In pBOR-II-3 mice, which are transgenic for the interleukin-3 (IL-3) gene (expression of which is driven by a long-terminal repeat), injection of azacitidine increased the incidence of thymic lymphoma over that observed in nontransgenic controls. The authors concluded that increased expression of IL-3, resulting from demethylation of the transgene long-terminal repeat by azacitidine, was responsible for the increased incidence of lymphoma (Saavedra *et al.* 1996). There is no evidence to suggest that the mechanisms by which azacitidine causes tumors in experimental animals would not also operate in humans.

Properties

Azacitidine is a pyrimidine analogue of cytidine that exists at room temperature as a white crystalline powder (IARC 1990). It is soluble in warm and cold water, 0.1 N hydrochloric acid, 0.1 N sodium hydroxide, 35% ethanol, and dimethyl sulfoxide, and slightly soluble in acetone, chloroform, and hexane. Azacitidine is stable under normal temperatures and pressures (Akron 2009), but is very unstable in aqueous solution, breaking down to complex products within hours (IARC 1990). Its stability in aqueous solutions depends on pH; in neutral and alkaline solutions, it has a half-life of 4 hours, but in Ringer's solution (pH 6.2), its half-life is 65 hours (Glover and Leyland-Jones 1987). Physical and chemical properties of azacitidine are listed in the following table.

Property	Information
Molecular weight	244.2 ^a
Melting point	228°C to 230°C (decomposes) ^a
Log <i>K</i> _{ow}	-3.83 ^b
Water solubility	89 g/L at 25°C ^b
Vapor pressure	4.1 × 10 ⁻¹² mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Azacitidine is a cytostatic anticancer drug that has been used in the United States since 1970. (NCI 1978). One product containing azacitidine as the active ingredient has been approved by the U.S. Food and Drug Administration; it is available in 100-mg vials for subcutaneous injection (FDA 2009). Azacitidine is approved to treat chronic myelomonocytic leukemia and myelodysplastic syndromes. It is also used to treat acute myeloblastic leukemia, breast cancer, colon cancer, melanoma, and ovarian cancer (IARC 1990, Santini *et al.* 2001, Celgene 2010). Azacitidine is also used in clinical trials in combina-