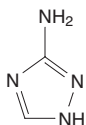


Amitrole

CAS No. 61-82-5

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

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

Cancer Studies in Experimental Animals

Amitrole caused tumors in two rodent species, at two different tissue sites, and by two different routes of exposure. Amitrole caused cancer of the thyroid gland (follicular-cell carcinoma) and liver tumors (hepatocellular tumors) when administered to rats of both sexes in the feed or drinking water and to 7-day-old weanling mice of both sexes by stomach tube for three weeks and in the diet starting at four weeks of age. It also caused liver and thyroid-gland tumors in rats (of unspecified sex) when administered by subcutaneous injection (IARC 1974, Tsuda *et al.* 1976).

Since amitrole was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Dietary administration of amitrole caused cancer of the thyroid gland (follicular-cell carcinoma) in rats of both sexes and marginally increased the incidence of benign pituitary-gland tumors (adenoma) in female rats (IARC 1986, 1987, 2001). Dietary administration of amitrole to female mice nursing pups and then to the weaned offspring caused liver cancer (hepatocellular carcinoma) in the male offspring (IARC 1986).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to amitrole. A small cohort study of Swedish railroad workers who had sprayed herbicides found a statistically significant excess of all cancers among those exposed to both amitrole and chlorophenoxy herbicides, but not among those exposed mainly to amitrole (IARC 1974).

Properties

Amitrole is a triazole compound that is a colorless to white crystalline solid at room temperature (Akron 2009, HSDB 2009). It forms salts with most acids and bases and is a powerful chelating agent (IPCS 1994). It is soluble in water, ethanol, methanol, chloroform, and acetonitrile; sparingly soluble in ethyl acetate; and insoluble in acetone (HSDB 2009). Amitrole is stable under normal temperatures and pressures, but decomposes on exposure to light (Akron 2009). Physical and chemical properties of amitrole are listed in the following table.

Property	Information
Molecular weight	84.1 ^a
Specific gravity	1.14 mg/mL at 20°C ^a
Melting point	159°C ^a
Log K_{ow}	-0.97 ^a
Water solubility	280 g/L at 25°C ^a
Vapor pressure	4.4×10^{-7} mm Hg at 25°C ^a
Dissociation constant (pK _a)	4.2 ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Amitrole was first registered for use as an herbicide in the United States in 1948 but was not commercialized until the 1950s (EPA 1996). In 1958, food-crop use was limited to post-harvest application to cranberries (EPA 1996, IARC 2001). Registrations for use on food crops were cancelled by the U.S. Environmental Protection Agency in 1971, after which amitrole was used primarily as a non-selective terrestrial post-emergent herbicide in outdoor industrial areas, non-agricultural rights of way, and non-agricultural uncultivated areas to treat vines, shade trees, ornamental shrubs and trees, and soil. Amitrole has a wide spectrum of activity against annual and perennial broad-leaf and grass-type weeds. Approved uses on soil were for non-crop land prior to sowing and for inter-row weed control in tree and vine crops, where contact with food plants was avoided (IPCS 1994). Limitations on the use of amitrole included not feeding or grazing animals on land treated with amitrole and not applying it directly to water or wetlands. Amitrole was usually applied by fixed-boom sprayers attached to tractors, trucks, or railroad wagons (EPA 1996, IARC 2001).

Production

Amitrole was first synthesized in 1898 (IARC 2001). At one time, 40 registered pesticide products contained amitrole as an active ingredient; however, no active registered products in the United States now contain amitrole (EPA 2009). Amitrole was not reported to be produced commercially in the United States in surveys conducted in 1978 and 1982 (HSDB 2009). In 2009, amitrole was produced by one manufacturer in Europe and two manufacturers in East Asia (SRI 2009) and was available from 34 suppliers, including 23 U.S. suppliers (ChemSources 2009). Reported U.S. imports of amitrole were 1.2 million pounds in 1978, but had declined to 465,000 lb by 1982 (HSDB 2009). No data on U.S. imports or exports after 1985 were found. A report filed in 1990 under EPA's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of amitrole totaled 10,000 to 500,000 lb (EPA 2004); no inventory update reports were filed for amitrole in 1994, 1998, or 2002.

Exposure

The routes of potential human exposure to amitrole are inhalation, dermal contact, and ingestion (HSDB, 2009). Exposure of the general population could occur through ingestion of contaminated drinking water. Because amitrole is not registered for food-crop uses, there is no known dietary exposure. In 1958 and 1959, amitrole residues were found on cranberries (EPA 1996, HSDB 2009). No amitrole residues were detected in food or water when recommended use practices were followed (IPCS 1994). Exposure could previously have occurred through inhalation near herbicide manufacturing or spraying areas. Large quantities of amitrole previously were used as an herbicide in the United States. In California alone, 82,000 kg (180,000 lb) was used in 1970 and 64,000 kg (141,000 lb) was used in 1972 (IARC 1974). EPA estimated that annual use was 500,000 to 800,000 lb in 1984, declining to between 50,000 and 100,000 lb in 1989 and between 40,000 and 60,000 lb in 1990 (EPA 1996). One death from ingestion of a weed killer containing a mixture of amitrole and ammonium thiocyanate was reported; amitrole was measured in the blood of the victim at 13 mg/L over 12 hours after ingestion (Legras *et al.* 1996).

According to EPA's Toxics Release Inventory, 176 lb of amitrole was released to the environment in 1999, mostly to off-site facilities, and slightly over 100 lb was released in 2007, to off-site facilities. The largest total annual releases were of 265 lb to off-site landfills in 2001 (TRI 2009). When amitrole is released to air, it reacts with photochemically produced hydroxyl radicals, with a half-life of 3 days (EPA

1996, HSDB 2009). It was measured in the air near a manufacturing facility at concentrations as high as 100 µg/m³ (IPCS 1994). In water and soil, amitrole is not expected to hydrolyze, but it is readily biodegraded by soil microorganisms; it is not likely to bioaccumulate in aquatic organisms. Amitrole is moderately persistent under aerobic conditions, with half-lives of 57 days in water and 22 to 26 days in soil, but it is more persistent under anaerobic conditions, with a half-life of over 1 year in water (EPA 1996, HSDB 2009). Amitrole is highly mobile in alkaline or neutral soils and leaches into groundwater, but it can be bound moderately by cation-exchange reactions in acidic soils, resulting in moderate mobility (EPA 1996, IPCS 1994). Concentrations of amitrole in a river downstream from a production plant ranged from 0.5 to 2 mg/L (IPCS 1994). When amitrole was sprayed on a watershed in Oregon for control of weeds, it was detected in the stream 30 minutes after the aerial spray application at a concentration of 155 µg/L, but not after 6 days (detection limit = 2 µg/L) (Marston *et al.* 1968).

Occupational exposure to amitrole could have occurred during its manufacture, packaging, or application as a herbicide. Particulates containing amitrole could have been released during its production (IPCS 1994). Those most likely to have been exposed were pesticide mixers, loaders, and applicators (EPA 1996). In Sweden, railroad workers exposed during spraying of track areas reported both inhalation exposure and dermal exposure due to wet spray on the hands and face (Axelson *et al.* 1980). According to the National Occupational Exposure Survey (conducted from 1981 to 1983), 693 workers potentially were exposed to amitrole, including 24 women (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of amitrole = U011.

Listed as a hazardous constituent of waste.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.2 mg/m³.

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Recommended exposure limit (time-weighted-average workday) = 0.2 mg/m³.

Listed as a potential occupational carcinogen.

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