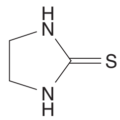
Ethylene Thiourea

CAS No. 96-45-7

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

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

Cancer Studies in Experimental Animals

Oral exposure to ethylene thiourea caused tumors in two rodent species and at two different tissue sites. Administration of ethylene thiourea by stomach tube for three weeks followed by dietary administration for an additional 80 weeks caused liver cancer (hepatcellular carcinoma) in mice of both sexes, and dietary administration of ethylene thiourea caused thyroid-gland cancer (follicular-cell carcinoma) in rats of both sexes (IARC 1974).

Since ethylene thiourea was listed in the *Fourth Annual Report on Carcinogens,* additional studies in rodents have been identified. Studies conducted by the National Toxicology Program compared the effects of adult exposure, perinatal exposure, and combined perinatal and adult exposure to ethylene thiourea in mice and rats (NTP 1992, IARC 2001). Dietary exposure of adult animals to ethylene thiourea caused thyroid-gland cancer (follicular-cell carcinoma) in mice and rats of both sexes, liver cancer (hepatocellular carcinoma) in mice of both sexes, and benign pituitary-gland tumors (adenoma of the pars distalis) in mice of both sexes. Perinatal exposure only (via dietary exposure of pregnant and lactating animals) did not increase the incidence of thyroid-gland tumors. Combined perinatal and adult exposure caused tumors at the same tissue sites as observed for adult-only exposure (except that the incidence of benign pituitary-gland tumors was increased only in female mice). However, combined exposure increased the proliferative effects of ethylene thiourea on thyroid follicular cells in both sexes of both species and may also have been responsible for increased incidences of mononuclear-cell leukemia and Zymbal-gland tumors in rats of both sexes.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to ethylene thiourea. One study of 1,929 rubber-manufacturing workers in the United Kingdom who were potentially exposed to ethylene thiourea reported no cases of thyroid cancer (based on cancer registry records) (IARC 1987). However, the statistical power to detect an effect was inadequate, and no data were provided on exposure, age, sex, length of employment, or duration of follow-up.

Properties

Ethylene thiourea is a heterocyclic compound that exists at room temperature as white to pale-green needle-like crystals with a faint amine odor. It is soluble in water, ethanol, naphtha, and acetic acid, slightly soluble in methanol, ethylene glycol, and pyridine, and insoluble in acetone, chloroform, ligroin, ethyl ether, and benzene (HSDB 2009). It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of ethylene thiourea are listed in the following table.

Property	Information
Molecular weight	102.2[a]
Density	1.417 g/cm^3[b]
Melting point	199°C to 204°C[a]
Boiling point	347°C[c]
Log K_{ow}	–0.66[a]
Water solubility	20 g/L at 30°C[a]
Vapor pressure	2.02×10^{-6} mm Hg at 25°C[c]

Sources: [a]HSDB 2009, [b]Akron 2009, [c]ChemIDplus 2009.

Use

Ethylene thiourea is used primarily as an accelerator for vulcanizing polychloroprene (neoprene) and polyacrylate rubbers (IARC 1974, 2001, HSDB 2009). Neoprene rubbers are used almost exclusively in industrial applications, including industrial and mechanical goods, automotive products, wire and cable production, construction, and adhesives (IARC 1974). Polyacrylate rubbers are used in products such as seals, O-rings, and gaskets for automotive and aircraft applications. Ethylene thiourea is also used in electroplating baths, as an intermediate in antioxidant production, and in dyes, pharmaceuticals, and synthetic resins.

Production

Commercial production of ethylene thiourea was first reported in the United States in 1951 (IARC 1974). In 1977, U.S. production of ethylene thiourea was about 100,000 lb, and U.S. imports totaled about 10,000 lb (HSDB 2009). By 1980, production had fallen to about 1,000 lb. In 2009, ethylene thiourea was available from 24 suppliers worldwide, including 12 U.S. suppliers (ChemSources 2009). No recent U.S. import or export data specifically for ethylene thiourea were found. Combined U.S. production and imports of ethylene thiourea reported to the U.S. Environmental Protection Agency (EPA) in 2015 were the range of 100,000 to 500,000 lb (EPA 2016), similar to production volumes reported in 1986, 1994, 1998, and 2002 (EPA 2004).

Exposure

Evidence that the U.S. general population is exposed to ethylene thiourea comes from the National Health and Nutrition Examination Survey for 2007–2008, which found that the 95th-percentile concentration of ethylene thiourea in urine was 0.430 μg/mL, based on a sample of 2,571 individuals of all ages, both genders, and all race and ethnicity groups (CDC 2018).

The routes of potential human exposure to ethylene thiourea are inhalation, ingestion, and dermal contact (HSDB 2009). The primary source of these exposures is the use of ethylenebisdithiocarbamate (EBDC) fungicides (e.g., amobam, mancozeb, maneb, metiram, nabam, and zineb), of which ethylene thiourea is an environmental degradation product, metabolite, and impurity (IARC 2001). Ethylene thiourea content in EBDC fungicides depends on the pesticide storage conditions and increases with increasing temperature, moisture, and length of storage (Camoni *et al.* 1988). EPA has grouped these pesticides based on the common mechanism of formation of ethylene thiourea (EPA 2005b), and EPA's reregistration eligibility decisions for mancozeb, maneb, and metiram are based on ethylene thiourea as a metabolite, environmental degradate, and cooking by-product of these fungicides (EPA 2005c,d,e). About 7.5 million pounds of mancozeb, 2.5 million pounds of maneb, and 0.9 million pounds of metiram are used annually, including use on food crops, ornamental plants, and sod.

Ethylene thiourea has been measured in food products, where it is believed to be a metabolite of EBDC fungicides (Houeto *et al.* 1995). Ethylene thiourea was found in beer at concentrations of 0.026 to 0.07 ppm and in wine at 0.037 ppm. The U.S. Food and Drug Administration's Total Diet Study found ethylene thiourea in 27 different products, at concentrations ranging from 0.003 ppm (the limit of quantitation) to 0.276 ppm; the highest concentrations were found in spinach and collards (FDA 2006). In kale and lettuce treated with maneb at a rate of 1.09 kg of active ingredient per acre, ethylene thiourea residues were initially 0.6 mg/kg, decreasing to undetectable levels within seven days after application (IARC 1974). Ethylene thiourea has been detected on apples sold for human consumption at concentrations of 0.018 to 0.044 mg/kg. It can also be formed when foods treated with EBDC fungicides are cooked (NIOSH 1978). A high concentration of 71 mg/kg was measured in spinach sprayed four times in the field with mancozeb and canned without washing (Lentza-Rizos 1990). In a study conducted in Germany, ethylene thiourea was measured in market samples of pears (0.205 ppm) and lamb's lettuce (0.367 ppm) (Dubey *et al.* 1997). Ethylene thiourea concentrations were much lower in the fruits than in the leaves of eggplants treated directly with ethylene thiourea (Kumar and Agarwal 1993). Ethylene thiourea has also been identified in cigarette smoke (IARC 2001); burning cigarettes were reported to produce 16 μg of ethylene thiourea per gram of tobacco (Houeto *et al.* 1995).

Since 2005, only commercial uses of EBDC fungicides have been permitted (EPA 2005a). The U.S. EPA estimated exposure of the general population to ethylene thiourea from past use in residential and other non-occupational scenarios, such as use of mancozeb on home gardens, golf courses, and lawns, to be below the level of concern (EPA 2005b).

Although the curing of rubber converts ethylene thiourea to other compounds, trace amounts of ethylene thiourea are present in cured rubber products (IARC 1974). Testing of a specific neoprene stock indicated that 0.01 mg of unchanged ethylene thiourea per square inch of surface could be extracted by water at 57°C over a period of seven days. Consumer products containing neoprene include shoes and closures for containers (e.g., aerosol dispensers).

According to EPA's Toxics Release Inventory, the largest total releases of ethylene thiourea were reported in 2006, when more than 29,000 lb was released, mostly to off-site non-hazardous-waste landfills. In 2009, 1,945 lb of ethylene thiourea was released to the environment from one facility, nearly all to an off-site non-hazardous-waste landfill (TRI 2009). Ethylene thiourea released to air will exist in the vapor phase and will be degraded by photochemically produced hydroxyl radicals, with a half-life of 2 hours (HSDB 2009). When released to water, it will remain in the water column and will not be likely to adsorb to sediments or to volatilize. It is unlikely to bioaccumulate in aquatic organisms. In soil, it will be highly mobile but will be rapidly biodegraded, especially near the soil surface.

Because ethylene thiourea is very soluble and moderately mobile in the environment, it potentially could be found in drinking water from both surface water and groundwater sources. It was measured at 0.21 ppb in the raw water from one public drinking-water well. However, it was not detected in any of 84 sampled finished drinking water sources, and a targeted study did not detect ethylene thiourea in surface water (detection limit = 0.1 ppb (EPA 2005b,c,d). Ethylene thiourea was detected in 1 of 183 tested U.S. groundwater wells at a concentration of 0.7 mg/L, and it has been estimated that 0.1% of rural wells in the United States are contaminated with ethylene thiourea.

Ethylene thiourea has been measured in the urine of the general population in Italy at concentrations as high as 61.4 μg/g of creatinine (Aprea *et al.* 1996, 1997, Colosio *et al.* 2006). The higher concentrations were attributed to wine consumption greater than 500 mL per day by rural male individuals.

Potential occupational exposure to ethylene thiourea is greatest for workers involved in metal fabrication, manufacture of machinery, manufacture of rubber and rubber products, and manufacture, formulation, and application of EBDC pesticides (IARC 2001). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 3,500 workers potentially were exposed to ethylene thiourea during the manufacture of rubber products (NIOSH 1978). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 10,749 workers, including 1,804 women, but not including agricultural workers, potentially were exposed to ethylene thiourea (NIOSH 1990). Samples taken in an ethylene thiourea manufacturing facility in 1976 found concentrations in personal air samples of up to 330 μg/m^3 and background levels in the range of 10 to 240 μg/m^3 (Smith 1984). In a second ethylene thiourea manufacturing facility, sampled in 1980, concentrations in personal samplers ranged from 120 to 160 μg/m^3. Among workers in Italy producing commercial formulations of mancozeb, the urinary concentration of ethylene thiourea was highest in workers formulating pesticide in powder form (median = 55.4 μg/g of creatinine), reflecting the higher concentrations found in the air (1.9 μg/m^3), in the hand-wash residue (36.9 to 194.3 μg), and in pads attached to the workers' necks (15 to 96 ng/cm^2) in the area of the plant where the pesticide powder was formulated (Aprea *et al.* 1998).

Among agricultural workers in Italy who regularly handled EBDC pesticides, pre-exposure urinary concentrations ranged from 0.5 to 2.1 μg/L and post-exposure concentrations from 1.9 to 8.2 μg/L (Sottani *et al.* 2003). In another study in Italy, workers had pre-exposure concentrations of less than 1.6 μg/g of creatinine and a post-exposure median concentration of 8.5 μg/g, with a maximum of 40.1 μg/g (Fustinoni *et al.* 2005). A third study in Italy confirmed these findings (Corsini *et al.* 2005). Ethylene thiourea was measured at a mean concentration of 58 ppb in the urine of 49 agricultural workers in Mexico who applied EBDCs in backpack sprayers to tomatoes and at 12 ppb in 14 owners of the farms, but was not detected in the urine of 31 unexposed control subjects. Ethylene thiourea was measured in the blood and urine of banana plantation workers in the Philippines; in directly exposed workers, mean concentrations were 4.4 ppb in blood and 378.3 ppb in urine, compared with 0.3 ppb in the blood and 26.3 ppb in the urine of control subjects (Panganiban *et al.* 2004). Ethylene thiourea was also measured in the breathing zone of workers exposed to EBDCs in potato fields and pine nurseries; concentrations of up to 1.81 μg/m^3 were measured in the area where the pesticide was weighed and mixed (Kurttio and Savolainen 1990). The mean level of ethylene thiourea in 24-hour urine samples ranged from 498 ng for the pine-nursery weeders to 3,746 ng for the potato-field workers (Savolainen *et al.* 1989, Kurttio and Savolainen 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

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

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 codes for which the listing is based wholly or partly on the presence of ethylene thiourea = U116, K123, K124, K125, K126.

Listed as a hazardous constituent of waste.

Guidelines

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

Listed as a potential occupational carcinogen.

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