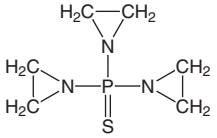
Thiotepa
CAS No. 52-24-4

Known to be a human carcinogen
First Listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

Thiotepa is *known to be a human carcinogen* based on sufficient evidence from studies in humans that indicate a causal relationship between exposure to thiotepa and human cancer. Originally, thiotepa was listed as *reasonably anticipated to be a human carcinogen* but, in 1998, was changed to *known to be a human carcinogen* in the *Eighth Report on Carcinogens.*

Exposure to thiotepa is specifically associated with leukemia in humans. Adamson and Seiber (1981) summarized nine case reports from 1970 to 1978 of secondary development of nonlymphocytic leukemia occurring in cancer patients with primary cancers at other sites who had received thiotepa as the only therapeutic agent. Additional evidence is found in a case-control study examining the development of leukemia as a secondary cancer in patients undergoing chemotherapy compared to surgery alone. Patients treated with thiotepa were significantly more likely to develop secondary leukemia than those undergoing surgery alone (IARC 1990).

The findings in humans are supported by carcinogenicity studies in experimental animals, which demonstrate that thiotepa is carcinogenic at multiple sites in both sexes of mice and rats. In mice, thiotepa administered by intraperitoneal (i.p.) injection caused lymphoma or lymphocytic leukemia and benign lung tumors in both sexes. In rats, i.p. injection of thiotepa caused lymphoma and leukemia in males and malignant mammary and uterine tumors in females (NCI 1978, IARC 1975, 1990). Squamous-cell carcinoma of the skin, preputial gland, and ear canal were observed in male mice, and the same tumor type was found in the skin or ear canal in rats of both sexes (NCI 1978). Rats treated with thiotepa by intravenous (i.v.) injections developed benign and malignant tumors at multiple sites, including the abdominal cavity, mammary gland, blood vessels, bone marrow, lymphatic system, salivary glands, adrenal gland, and testis (IARC 1975, 1987, 1990).

Additional Information Relevant to Carcinogenicity

Thiotepa and its major metabolite, tris(aziridinyl)phosphine oxide (also called TEPA and triethylenephosphoramide), are direct alkylating agents with potent genotoxic activity in a wide variety of prokaryotic, lower eukaryotic, and mammalian *in vitro* and *in vivo* test systems. Thiotepa's ability to induce DNA damage, mutations, micronuclei, and/or chromosomal aberrations in somatic and germ cells sampled from treated rodents, rabbits, and primates, and chromosomal aberrations in peripheral blood lymphocytes sampled from treated humans is consistent with it being a genotoxic carcinogen (IARC 1990).

Properties

Thiotepa belongs to the chemical family of ethyleneimines and is an alkylating agent with a molecular weight of 189.2. It occurs as an odorless, white, crystalline solid or as fine, white, crystalline flakes and is soluble in water, ethanol, diethyl ether, benzene, and chloroform. Its melting point is 51.5°C, and its vapor pressure is 0.007 mm Hg at 70°F (21°C) (AC 1990, HSDB 2003). Thiotepa polymerizes and becomes inactive at temperatures above 2°C to 8°C; however, the bulk drug is stable for up to two years, and dilute aqueous solutions are stable for months at temperatures below 20°C. Thiotepa is stable in alkaline solution; it is unstable in acid and sensitive to light and heat (IARC 1975, 1990). When heated, hazardous decomposition products may include carbon monoxide, carbon dioxide, hydrogen cyanide, and nitrogen oxides (AC 1990). The commercial product is available as an injectable solution containing 15 or 30 mg thiotepa (FDA 2003).

Use

Thiotepa suppresses cell growth and division and was introduced in 1953 for use in cancer chemotherapy to treat lymphomas and a variety of both solid and soft-tissue tumors. It was commonly used in cancer therapy until the early 1970s (only 3 kg were used in 1973). Although thiotepa has largely been replaced by the nitrogen mustards, it still has specific uses, particularly as a component of experimental high-dose chemotherapy regimens. Thiotepa was most effective in treating adenocarcinomas of the breast, ovary, and bladder, malignant lymphomas, bronchiogenic carcinomas, and Wilms' tumor. By the late 1980s, thiotepa also was used at high doses in combination chemotherapy with cyclophosphamide in patients with refractory malignancies treated with autologous bone transplantation (IARC 1975, 1990). As of 2003, thiotepa was used to treat a variety of cancers including bladder, ovarian, breast, lung, brain, and lymphomas (MEDLINEplus 2003).

Thiotepa was tested for use as an intermediate in the manufacture of polymeric flame retardants for cotton, and it was shown to be an effective insect chemosterilant. However, these uses were not developed for commercial application because of various problems associated with its application, toxicity, and environmental effects (IARC 1975).

Production

There was one U.S. producer of thiotepa in the early 1970s; but by 1990, it was produced only in Japan (IARC 1975, 1990). As of 2004, the Directory of Chemical Producers listed only one plant in East Asia that manufactured this drug (SRI 2004). In 2003, one U.S. company was identified as a manufacturer of thiotepa; there was at least one supplier and three companies with four U.S. Food and Drug Administration (FDA)-approved products containing thiotepa as the active ingredient (ChemSources 2003, FDA 2003). No data on current or past production, import, or export volumes of thiotepa could be found.

Exposure

Individuals are exposed to thiotepa during its use in cancer therapy. Thiotepa has been administered through various parenteral routes (e.g., intravenous, intramuscular, intrathecal, and intratumoral injection), generally with adjustment of the dosage on the basis of changes in leukocyte counts. Thiotepa is available in injectable form with solutions containing 15 mg or 30 mg per vial (FDA 2003). The initial dosage of thiotepa has typically been 5 to 40 mg (3 to 23 mg/m^2) administered at one- to four-week intervals; doses up to 75 mg/m^2 have been used in children. Daily doses in excess of 1,100 mg/m^2 have been used in high-dose therapy (IARC 1990).

There is a potential of exposure to health-care professionals during the preparation and administration of the compound in cancer therapy. Potential occupational exposure may occur for workers involved in its formulation and packaging. The National Occupational Exposure Survey (1981-1983) indicated that 11,452 workers, including 8,724 women, potentially were exposed to thiotepa (NIOSH 1990).

Regulations

EPA

Resource Conservation and Recovery Act
Listed as a Hazardous Constituent of Waste

FDA

Thiotepa is a prescription drug subject to labeling and other requirements

References

AC. 1990. Material Safety Data Sheet. Thiotepa. American Cyanamid. Lederle Laboratories Division. http://hazard.com/msds2/.

Adamson, R. H. and S. M. Seiber. 1981. Chemically induced leukemia in humans. Environ Health Perspect 39: 93-103.

ChemSources. 2003. Chemical Sources International, Inc. http://www.chemsources.com.

FDA. 2003. The Electronic Orange Book. Food and Drug Administration. http://www.fda.gov/cder/ob/default.htm (then select "Search by Active Ingredient" and type in thiotepa).

HSDB. 2003. Hazardous Substances Database. National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

IARC. 1975. Some Aziridines, *N-*, *S-*, and *O*-Mustards and Selenium. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 9. Lyon, France: International Agency for Research on Cancer. 286 pp.

IARC. 1987. Overall Evaluations of Carcinogenicity. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Supplement 7. Lyon, France: International Agency for Research on Cancer. 440 pp.

IARC. 1990. Pharmaceutical Drugs. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 50. Lyon, France: International Agency for Research on Cancer. 415 pp.

MEDLINEplus. 2003. Drug Information: Thiotepa. National Library of Medicine. Last updated: 1/1/03. http://www.nlm.nih.gov/medlineplus/druginformation.html and search thiotepa. Last accessed: 2/16/04.

NCI. 1978. Bioassay of Thio-TEPA for Possible Carcinogenicity (CAS No. 52-24-4). Technical Report Series No 58. DHEW (NIH) Publication No. 78-1308. Bethesda, MD: National Institutes of Health. 168 pp.

NIOSH. 1990. National Occupational Exposure Survey (1981-83). Unpublished provisional data as of 7/1/90. Cincinnati, OH: U. S. Department of Health and Human Services. http://www.cdc.gov/noes/noes3/empl0001.html (listed as phosphine sulfide, tris(1-aziridinyl).

SRI. 2004. Directory of Chemical Producers. http://dcp.sric.sri.com/Public/ (Visitor Search).