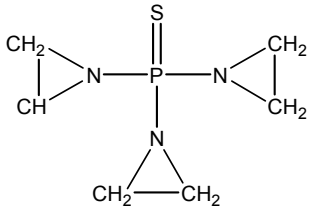
THIOTEPA
CAS No. 52-24-4

First Listed in the *Second Annual Report on Carcinogens* as *Reasonably Anticipated to be a Human Carcinogen* -- changed to *Known to be a Human Carcinogen* in the *Eighth Report on Carcinogens*



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 (IARC 1990).

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 and 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 cancer patients undergoing chemotherapy compared to surgery alone. Patients undergoing chemotherapy were significantly more likely to develop secondary leukemia than those undergoing surgery alone, and in some of these patients, thiotepa was the only chemotherapeutic agent given (IARC 1990).

Thiotepa is carcinogenic at multiple sites in both sexes of mice and rats. In mice, thiotepa administered by intraperitoneal (i.p.) injection induced lymphoma or lymphocytic leukemia in both sexes and squamous-cell carcinoma of the skin and associated glands of males. In rats, i.p. injection of thiotepa induced squamous-cell carcinoma of the skin or ear canal in both males and females and neoplasms of the hematopoietic system in males (NCI 1978). Other rodent studies using i.p. or intravenous (i.v.) routes of exposure also found thiotepa to be carcinogenic. The incidence of lung tumors in both male and female mice was significantly increased by i.p. injections of thiotepa, and rats treated with thiotepa by i.v. injections developed benign and malignant tumors at multiple sites (IARC 1990).

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

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. Its 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 thiotepa being a genotoxic carcinogen (IARC 1990).

PROPERTIES

Thiotepa occurs as an odorless, white, crystalline solid or as fine white crystalline flakes. It is soluble in water, ethanol, diethyl ether, benzene, and chloroform. At temperatures above 2 to 8°C, thiotepa polymerizes and becomes inactive. Thiotepa as a bulk drug is stable for up to two years at 2 to 8°C, and aqueous solutions of 10 mg/mL are stable for five days at 2 to 8°C. Thiotepa is stable in alkaline solution; it is unstable in acid and is sensitive to light (IARC 1990, HSDB 2000). When heated, hazardous decomposition products may include carbon monoxide, carbon dioxide, hydrogen cyanide, phosphorus oxides, sulfur oxides, and nitrogen oxides (American Cyanamide 1990, NTP 2001). The commercial product is available in vials containing 15 mg thiotepa, 80 mg sodium chloride, and 50 mg sodium bicarbonate (IARC 1990).

USE

Thiotepa is an alkylating agent that was introduced in 1953 for use in cancer chemotherapy and was used to treat lymphomas and a variety of both solid and soft-tissue tumors (NCI 1978, IARC 1990). It was commonly used in cancer therapy until the early 1970s (only 3 kg were used in 1973), and has largely been replaced by the nitrogen mustards (IARC 1975, NTP 2001). Thiopeta was most effective in treating adenocarcinomas of the breast and ovary, malignant lymphomas, bronchiogenic carcinomas, and Wilm's tumor (IARC 1975). By the late 1980s, thiotepa was also used at high doses in combination chemotherapy with cyclophosphamide in patients with refractory malignancies treated with autologous bone transplantation.

Thiopeta 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; by 1990, it was produced only in Japan (IARC 1975, 1990). The 1998 Chemical Buyers Directory identified two U.S. suppliers of thiotepa (Tilton 1997). No data on current or past production, import, or export volumes of thiotepa could be found.

EXPOSURE

The general population is not likely exposed to thiotepa because of its limited use in cancer therapy. Thiopeta was administered through various parenteral routes (e.g., intravenous, intramuscular, intrathecal, and intratumoral injection) and the dosage was generally adjusted on the basis of changes in leukocyte counts. The initial dosage of thiotepa was typically 5 to 40 mg (3 to 23 mg/m^2) administered over one- to four-weekly intervals; doses up to 75 mg/m^2 have been used in children. High-dose therapy involved daily doses in excess of 1,100 mg/m^2 (IARC 1990). Potential exposure of health professionals may have occurred 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). This estimate was derived from observations of the use of the actual compound (41% of total observations) and trade name products (59%) (IARC 1990).

REGULATIONS

EPA designates thiotepa as a hazardous constituent of wastes and regulates it under the Resource Conservation and Recovery Act (RCRA).

FDA regulates thiotepa under the Food, Drug, and Cosmetic Act (FD&CA) as a prescription drug. It was approved with the warning that dosing must be adapted carefully. Labeling must identify the drug as a carcinogen. Thiotepa has been listed as an unofficial drug and obtained original FDA approval in 1959.

OSHA regulates the compound under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 173.

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