THIOTEPA

This substance was considered by previous working groups, in April 1975 and March 1987, under the title tris(1-aziridinyl)phosphine sulphide (IARC, 1975, 1987). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Chemical and Physical Data

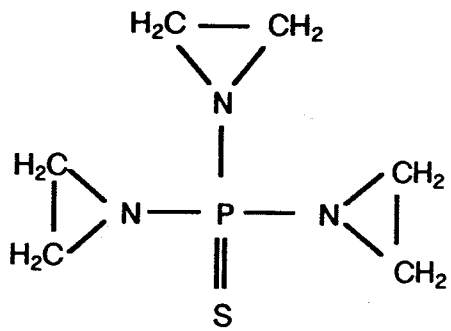
1.1 Synonyms

Chem. Abstr. Services Reg. No.: 52-24-4

Chem. Abstr. Name: Aziridine, 1,1′1″-phosphinothioylidynetris

Synonyms: NSC-6396; phosphoric tri(ethyleneamide); TESPA; thiophosphamide; thiotriethylenephosphoramide; triaziridinylphosphine sulfide; *N,N′N″*-tri-1,2-ethanediylphosphorothioic triamide; *N,N′N″*-tri-1,2-ethanediylthiophosphoramide; tri(ethyleneimino)thiophosphoramide; *meta*-triethylenethiophosphoramide; *N,N′N″*-triethylenethiophosphoramide; *meta*-tris(aziridin-1-yl)phosphine sulfide; triethylenethiophosphorotriamide; tris-(1-aziridinyl)-phosphine sulfide; tris(1-aziridinyl)phosphine sulphide; tris-(ethyleneimino)-thiophosphate; TSPA; WR-45312

1.2 Structural and molecular formulae and molecular weight



$C_6H_{12}N_3PS$ Mol. wt: 189.23

1.3 Chemical and physical properties of the pure substance

From Windholz (1983) and Barnhart (1989), unless otherwise indicated

(*a*) *Description*: White, crystalline solid; fine white crystalline flakes from pentane or ether

(*b*) *Melting-point*: 51.5°C; 52-57°C (Reynolds, 1989)

(*c*) *Solubility*: 1:8 in water; 19 g/100 ml water at 25°C; soluble in ethanol, diethyl ether, benzene and chloroform

(*d*) *Stability*: At temperatures above 2-8°C, thiotepa polymerizes and becomes inactive. The bulk drug is stable (up to two years) at 2-8°C, is unstable in acid and is sensitive to light. Aqueous solutions of 10 mg/ml are stable for five days at 2-8°C. Thiotepa is stable in alkaline solution.

1.4 Technical products and impurities

Trade names: Ledertepa, Onco Thiotepa, Tespamin; Thio-TEPA; Tifosyl

Thiotepa is available in vials containing 15 mg thiotepa, 80 mg sodium chloride and 50 mg sodium bicarbonate; when reconstituted, the pH is 7.6 (Barnhart, 1989).

2. Production, Occurrence, Use and Analysis

2.1 Production and occurrence

Thiotepa has been prepared by the addition of trichlorophosphine sulfide to aziridine and triethylamine (Kuh & Seeger, 1954) and by the addition of aziridine to phosphorus oxychloride (Bestian, 1950). Thiotepa is synthesized in Japan.

Thiotepa is not known to occur naturally.

2.2 Use

Thiotepa is a cytostatic agent. It has been used in the treatment of lymphomas and a variety of solid tumours, such as those of breast and ovary; it has also been used in cases of urinary bladder malignancies, meningeal carcinomatosis and various soft-tissue tumours (Wright *et al.*, 1958; Hollister & Coleman, 1980; Hagen *et al.*, 1987; Reynolds, 1989). Thiotepa is administered intramuscularly, intravenously and intrathecally; other parenteral routes (e.g., intratumoral injections) have also been used. It has been used as instillations in cases of urinary bladder carcinoma (Hollister & Coleman, 1980). Thiotepa has been used recently at high doses in combination chemotherapy with cyclophosphamide in patients with

refractory malignancies treated with autologous bone transplantation (Henner *et al.*, 1987; Lazarus *et al.*, 1987; Williams *et al.*, 1987; Ackland *et al.*, 1988; Eder *et al.*, 1988; Williams *et al.*, 1989).

The initial dosage of thiotepa has generally been 5-40 mg [3-23 mg/m^2] at one- to four-weekly intervals (Wright *et al.*, 1958; Cohen *et al.*, 1986; Hagen *et al.*, 1987); doses up to 75 mg/m^2 have been used in children (Heideman *et al.*, 1989). The dosage is generally adjusted on the basis of changes in leukocyte counts. High-dose therapy has involved daily doses in excess of 1100 mg/m^2 (Lazarus *et al.*, 1987).

2.3 Analysis

Thiotepa has been determined in pharmaceutical preparations by colorimetric titration (US Pharmacopeial Convention, Inc., 1989) and in biological fluids by chromatography (Egorin *et al.*, 1985; Hagen *et al.*, 1985; McDermott *et al.*, 1985) and high-performance liquid chromatography (Sano *et al.*, 1988).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

The carcinogenicity of antineoplastic drugs, including thiotepa, in animals has been reviewed (Berger, 1986).

(*a*) *Intraperitoneal administration*

Mouse: In a screening assay based on the accelerated induction of lung tumours in a strain highly susceptible to development of this neoplasm, three groups of ten male and ten female strain A/He mice, six to eight weeks of age, received intraperitoneal injections of thiotepa (purity, 95-99%) in 0.1 ml of purified tricaprylin three times per week for four weeks (total doses, 19, 47 and 94 mg/kg bw). A group of 80 males and 80 females received 24 injections of 0.1 ml of tricaprylin alone. All mice were killed 24 weeks after the first injection. The incidences of lung tumours in treated mice were 16/20, 10/20 and 11/20 in the groups receiving the high, mid and low doses, respectively, compared to 28% and 20% in male and female controls. The numbers of lung adenomas per mouse were significantly higher in the high-dose (1.50; $p < 0.001$) and mid-dose (0.74; $p < 0.05$) groups in comparison to male (0.24) and female (0.20) controls (Stoner *et al.*, 1973).

Groups of 35 male and 35 female B6C3F1 mice, six weeks of age, received intraperitoneal injections of thiotepa (purity, 98.0 ± 1.0%) at 1.15 or 2.3 mg/kg bw

three times a week for up to 52 weeks and were observed for an additional 34 weeks. Two groups of 15 males and 15 females were untreated or received injections of phosphate-buffered saline vehicle only and served as matched controls. Pooled vehicle controls were also used, by adding 15 animals of each sex taken from a bioassay on another chemical. By 43 weeks, all high-dose females had died, and, by 56 weeks, all high-dose males had died. At weeks 86-87, 15/35 low-dose males, 17/35 low-dose females, 7/15 vehicle-control males and 12/15 vehicle-control females were still alive, at which time the study was terminated. Because of early deaths, statistical analyses were based only on time-adjusted incidences of tumours, eliminating those mice that had died before week 52. The incidences of malignant lymphoma and lymphocytic leukaemia combined were significantly greater in high-dose animals (32/32 females, 26/28 males; $p < 0.001$, Cochrane-Armitage test, Fisher's exact test) in comparison with vehicle and pooled controls (0/14 and 0/29 females; 1/8 and 1/18 males) (National Cancer Institute, 1978). [The Working Group noted the poor survival among the high-dose animals and that the study design involved controls pooled from different studies.]

Rat: Groups of 35-39 male and 31-35 female Sprague-Dawley rats, aged 35, 42 or 58 days, received intraperitoneal injections of thiotepa (purity, 98.0 ± 1.0%) at 0.7, 1.4 or 2.8 mg/kg bw three times a week for up to 52 weeks and were observed for additional periods of time. Two groups of ten males and ten females were untreated or received injections of buffered saline alone at 2.5 ml/kg bw and served as controls. A lower-dose group was started 69 weeks after the beginning of the original study, together with two additional control groups. Pooled vehicle controls were also used, by adding ten rats of each sex from bioassays on other chemicals. All high-dose males had died by week 19 and all high-dose females by week 21. Treatment of mid-dose groups was terminated at week 34, and animals were observed until weeks 78-81, at which time all of them had died. All other groups were observed until weeks 82-87. Because of early deaths, statistical analyses were based only on time-adjusted incidences of tumours, eliminating those rats that had died before week 52. Malignant lymphomas, lymphocytic leukaemia and granulocytic leukaemia were observed in 6/34 low-dose (pooled controls, 0/29; $p = 0.020$) and 6/16 mid-dose (pooled controls, 0/30; $p < 0.001$) males. Uterine adenocarcinomas were found in 7/21 mid-dose females (pooled controls, 0/28; $p = 0.001$) and 2/29 low-dose females but not in corresponding lower-dose controls. The incidence of adenocarcinomas of the mammary gland was significantly increased in mid-dose females (8/24; pooled controls, 1/28; $p = 0.006$), but this tumour was also observed in one lower-dose pooled control and in 3/10 lower-dose untreated controls. The incidences of neuroepitheliomas or nasal carcinomas (three in low-dose males, two in low-dose females, two in mid-dose females) were not statistically significantly increased, although they did not occur among

corresponding controls or among the 388 pooled vehicle controls (National Cancer Institute, 1978). [The Working Group noted the high mortality among high- and mid-dose groups, which necessitated the later inclusion of the lower dose-treated group, and that the study design included controls pooled from different studies.]

(*b*) *Intravenous administration*

Rat: A group of 48 male BR46 rats, 100 days of age, received weekly intravenous injections of thiotepa [purity and vehicle unspecified] at 1 mg/kg bw for 52 weeks. A group of 89 untreated males served as controls. Of the treated animals, 30 were still alive when the first tumour appeared, compared to 65 controls. Malignant tumours developed in 9/30 treated animals (two sarcomas of the abdominal cavity, one lymphosarcoma, one 'myelosis', one seminoma, one fibrosarcoma and one haemangioendothelioma of the salivary gland, one mammary sarcoma, one phaeochromocytoma) and in 4/65 controls (three mammary sarcomas, one phaeochromocytoma) ($p < 0.01$). Benign tumours occurred in 5/30 treated and 3/65 control animals (Schmähl & Osswald, 1970; Schmähl, 1975). [The Working Group noted the short latency of tumour induction.]

3.2 Other relevant data

(*a*) *Experimental systems*

(i) *Absorption, distribution, excretion and metabolism*

One hour after intraperitoneal injection of thiotepa at 9.3 mg/kg bw into Sprague-Dawley rats, radioactivity was found in plasma (5.4%), peritoneal fluid (26%), urine (1.9%), kidney (0.7%), liver (3.8%), lung (0.6%) and muscle (25.9%) (Litterst *et al.*, 1982). In another study, 5 min after intravenous or intraarterial injection of labelled thiotepa in Sprague-Dawley rats, slightly higher levels of radioactivity were found in plasma, heart, kidneys and lungs, compared to other organs; 94-98% of radioactivity administered intravenously was excreted in urine within 8.5 h. Most of the urinary radioactivity was associated with unchanged thiotepa; tris(1-aziridinyl)phosphine oxide (tepa) was responsible for about 30% of the radioactivity (Boone *et al.*, 1962).

In female mongrel dogs, 75-85% of an intravenous dose of labelled thiotepa was recovered in the urine; only 0.2-0.3% unchanged thiotepa was found (Mellett *et al.*, 1962). Following intravenous (at 3 mg/kg bw) or oral (at 6 mg/kg bw) administration of thiotepa to dogs, about 13% of the dose was excreted as tepa. The plasma level of tepa was about 1.2 µg/ml 2 h after intravenous injection of thiotepa. The authors concluded that 50% of the administered thiotepa was absorbed (Mellett & Woods (1960).

A biexponential decline in thiotepa concentration in plasma was seen during the first hours after intravenous injection of thiotepa at 5 mg/kg bw in

Swiss-Webster mice. The half-time was 0.21 min for the first phase and 9.62 min for the second (Egorin *et al.*, 1984).

After an intravenous dose of thiotepa to rhesus monkeys, equilibrium with plasma levels in lumbar and ventricular cerebrospinal fluid was obtained rapidly. After intravenous administration, the total body clearance of thiotepa was about 35 ml/min (Strong *et al.*, 1986).

The major urinary metabolite in rats, rabbits and dogs following a single intravenous injection of ^{32}P-thiotepa was tepa, which is also an alkylating agent. Most of the radioactivity in mouse urine, however, was recovered as inorganic phosphate. In mice and rats, a small proportion of radioactivity was detected in most tissues nine days after an intravenous injection of thiotepa; higher levels were detected in blood of rats (Craig *et al.*, 1959).

After addition of thiotepa to sera from patients and healthy individuals, about 10% was bound to protein (Hagen & Nilsen, 1987).

(ii) *Toxic effects*

The LD_{50} of thiotepa in rats was about 9.5 mg/kg bw by intravenous injection and about 8.8 mg after intraarterial injection (Boone *et al.*, 1962). The LD_{50} in mice was 400 mg/kg bw 24 h after an intraperitoneal injection. The acute lethality after 1 h and 24 h was markedly increased by intraperitoneal injection of 60 mg/kg bw pentobarbital shortly after the thiotepa injection (Munson *et al.*, 1974). Pre-treatment of mice with 40 mg/kg bw SKF525A also enhanced the acute lethality of thiotepa (Mellett & Woods, 1960).

Thiotepa caused a dose-dependent inhibition of the growth of P388 murine leukaemia cells in culture (Miller *et al.*, 1988).

(iii) *Effects on reproduction and prenatal toxicity*

When rats were given thiotepa at 4 mg/kg bw by intraperitoneal injection on gestation day 12, teratogenic effects occurred in the offspring (Murphy *et al.*, 1958). [The Working Group noted that the details given in the paper were insufficient to assess the significance of the effect.]

In an extensive study of the effects of thiotepa in pregnant mice, Tanimura (1968) demonstrated both dose-related and time-related effects. Prenatal mortality was most pronounced following intraperitoneal injection of 5-10 mg/kg bw on days 7.5 and 8.5 of gestation, and fetal growth was suppressed after injection on days 10.5-12.5 of gestation. The lowest single teratogenic dose was shown to be 1.0 mg/kg bw; the dose that caused 100% incidence of malformed fetuses was 10.0 mg/kg. The malformations observed were exencephaly, spina bifida, cleft palate, kinky tail and digit alterations.

(iv) *Genetic and related effects*

Thiotepa was mutagenic to *Salmonella typhimurium* TA1535 (Benedict *et al.*, 1977a) and TA100 (Pak *et al.*, 1979) but gave contradictory results in TA98 (Bruce & Heddle, 1979; Pak *et al.*, 1979) in the absence of an exogenous metabolic system. Rats perfused with thiotepa produced urine that was mutagenic to *S. typhimurium* (Pak *et al.*, 1979). In the host-mediated assay in mice, thiotepa was mutagenic to *S. typhimurium* TA1535 (Arni *et al.*, 1977) and G46 (Devi & Reddy, 1980).

Thiotepa induced forward mutations to 8-azaguanine resistance in *Aspergillus nidulans* (Bignami *et al.*, 1982) and chromosomal aberrations (Kihlman, 1975; Sturelid & Kihlman, 1975; Popa *et al.*, 1976) and sister chromatid exchange (Kihlman, 1975) in root meristem cells of *Vicia faba*. It induced sex-linked recessive lethal mutations in *Drosophila melanogaster* (Lüers & Röhrborn, 1965; Fahmy & Fahmy, 1970) and dominant lethal mutations in *Aedes aegypti* (Rodriguez & Rodriguez, 1985).

Thiotepa induced unscheduled DNA synthesis in unstimulated human peripheral lymphocytes (Titenko, 1983). It induced mutations at the *hprt* locus in Chinese hamster V79 cells (Paschin & Kozachenko, 1982), and, in a host-mediated assay with mice and mouse lymphoma L5178Y cells, it induced resistance to thymidine and methotrexate (Lee, 1973).

Thiotepa induced sister chromatid exchange in mouse cells (Andersen, 1983), a cloned hamster cell line (Banerjee & Benedict, 1979), Chinese hamster cells (Chebotarev & Selezneva, 1979; Chebotarev *et al.*, 1980; Selezneva *et al.*, 1982) and peripheral lymphocytes of rhesus monkeys (Kuzin *et al.*, 1987) and humans (Littlefield *et al.*, 1979; Mourelatos, 1979; Chebotarev & Listopad, 1980; Listopad & Chebotarev, 1982; Shcheglova & Chebotarev, 1983a). It induced chromosomal aberrations in a cloned hamster cell line (Benedict *et al.*, 1977b), in Chinese hamster CHO cells (Maier & Schmid, 1976; Sturelid, 1976), in peripheral lymphocytes of rabbits (Bochkov *et al.*, 1982) and in human peripheral lymphocytes *in vitro* (Hampel *et al.*, 1966; Bochkov & Kuleshov, 1972; Bochkov *et al.*, 1972; Chebotarev, 1974; Kirichenko, 1974; Kirichenko & Chebotarev, 1976; Yakovenko & Nazarenko, 1977; Bochkov *et al.*, 1979; Wolff & Arutyunyan, 1979; Yakovenko & Kagramanyan, 1982; Shcheglova & Chebotarev, 1983a). Thiotepa induced morphological transformation of C3H/10T½ cells (Benedict *et al.*, 1977b).

Thiotepa induced DNA cross-links in chick embryos (McCann *et al.*, 1971). It induced sister chromatid exchange (Shcheglova & Chebotarev, 1983b) and chromosomal aberrations (Malashenko & Surkova, 1974a,b, 1975; Sram, 1976; Leonard *et al.*, 1979; Malashenko & Surkova, 1979; Shcheglova & Chebotarev, 1983b) in bone marrow of mice treated *in vivo*. It induced micronuclei in the bone marrow of rats (Setnikar *et al.*, 1976) and mice (Maier & Schmid, 1976; Ioan *et al.*, 1977; Bruce & Heddle, 1979; Leonard *et al.*, 1979) and chromosomal aberrations in

peripheral lymphocytes of rabbits (Bochkov *et al.*, 1982) and rhesus monkeys (Kuzin *et al.*, 1987) *in vivo*. Treatment of pregnant mice with thiotepa led to chromosomal aberrations in embryonic liver cells (Korogodina *et al.*, 1979; Korogodina & S'yakste, 1981).

Thiotepa induced dominant lethal mutations (Machemer & Hess, 1971; Epstein *et al.*, 1972; Setnikar *et al.*, 1976; Sram, 1976; Semenov & Malashenko, 1981) and chromosomal aberrations in spermatogonia (Malashenko & Beskova, 1988) and spermatocytes [one dose] (Devi & Reddy, 1980; Meistrich *et al.*, 1982) in mice *in vivo*. Treatment of male mice with thiotepa led to chromosomal aberrations in preimplantation embryos [one dose] (Malashenko *et al.*, 1978a; Semenov & Malashenko, 1979). Thiotepa also induced sperm abnormalities (Bruce & Heddle, 1979) and heritable translocations [one dose] (Malashenko & Surkova, 1974b; Semenov & Malashenko, 1977; Malashenko *et al.*, 1978b; Malashenko & Goetz, 1981) in mice *in vivo*. Thiotepa produced liver protein variants in F_1 fetuses derived from treated male mice [one dose] (Paschin & Ambrossieva, 1984).

(*b*) *Humans*

(i) *Pharmacokinetics*

Because of acid instability, absorption of thiotepa after oral administration is erratic and incomplete (Mellet *et al.*, 1962). After an intravenous bolus injection of thiotepa at 12 mg/m^2, a biexponential disappearance from the plasma was observed; the second-phase half-time was 73.7 min (Egorin *et al.*, 1985). Disappearance half-times of 1.3-2.1 h were reported in further studies (McDermott *et al.*, 1985; Cohen *et al.*, 1986; Hagen *et al.*, 1987; Henner *et al.*, 1987; Hagen *et al.*, 1988; Heideman *et al.*, 1989) after intravenous or intramuscular administration. At dose levels in excess of 25 mg/m^2 (Heideman *et al.*, 1989), 180 mg/m^2 (Henner *et al.*, 1987) and 4.8 mg/kg (Ackland *et al.*, 1988), the plasma clearance of thiotepa was reported to decline with increasing dose. However, in one study with high doses (45-1215 mg/m^2), no dose-dependence of kinetics was reported (Lazarus *et al.*, 1987). The volume of distribution of thiotepa has been reported to be approximately 50 l (Cohen *et al.*, 1986; Henner *et al.*, 1987; Hagen *et al.*, 1988; Heidemann *et al.*, 1989).

After an intravenous injection of thiotepa in paediatric patients, the cerebrospinal fluid:plasma ratio of thiotepa was 0.92 (Heideman *et al.*, 1989). After intraventricular administration of thiotepa, the ratio of thiotepa concentrations in cerebral ventricular fluid:plasma was almost 1000 (Strong *et al.*, 1986); in another, similar study, it was approximately 200 (Grochow *et al.*, 1982). The urinary excretion of unchanged thiotepa is complete usually within 8 h of the injection, and less than 1.5% of the dose is excreted in the urine unchanged (Egorin *et al.*, 1985; Hagen *et al.*, 1985; Cohen *et al.*, 1986; Hagen *et al.*, 1987). Five minutes after an intravenous

injection of thiotepa, tepa was observed in the blood; after 120 min, the concentration of tepa in the blood was higher than that of thiotepa. The proportion of thiotepa in urine was 1.5%, and that of tepa was 4.2%; other alkylating metabolites represented another 23.5% of the dose administered (Cohen *et al.*, 1986).

(ii) *Adverse effects*

The toxic effect of thiotepa that limits the dose that can be given is myelosuppression, characterized by granulocytopenia and thrombocytopenia; disturbances in hepatic and renal function, neurotoxicity, nausea and vomiting were uncommon at dose levels of approximately 75 mg/m^2 or less (Wright *et al.*, 1958; Heideman *et al.*, 1989). In high-dose therapy with autologous bone-marrow transplantantion, central nervous system disturbances, hepatic damage, infections, nausea, vomiting, diarrhoea, mucositis, skin rashes, haemorrhagic cystitis and cardiomyopathy may be severe (Lazarus *et al.*, 1987; Williams *et al.*, 1987, 1989). Severe myelosuppression has also been described after intravesicular instillations of thiotepa (Bruce & Edgcomb, 1967; Watkins *et al.*, 1967; Hollister & Coleman, 1980).

(iii) *Effects on reproduction and prenatal toxicity*

Use of thiotepa in the third trimester of pregnancy had no adverse effect on the progeny (Nicholson, 1968; Sweet & Kinzie, 1976). In a report of the effects of treatment of women with stage-II and stage-III Hodgkin's disease with radiotherapy and chemotherapy with TVPP (thiotepa, vinblastine, vincristine, procarbazine and prednisone), menstrual function ceased in two of four women aged 35-44 years but continued in all 30 women under 35 years of age. Ten of the women had a total of 12 babies, all with normal development (Lacher & Toner, 1986).

As reported in an abstract, transient azoospermia occurred in a man treated with thiotepa; the effect was reversed when the dose interval was increased from monthly to three-monthly dosing (Bayar *et al.* 1978).

(iv) *Genetic and related effects*

Five patients who received a total dose of thiotepa at 40-100 mg had 9.5 $\pm$ 1.07% aberrant cells in peripheral lymphocytes 24 h after the last treatment, compared with 1.4 $\pm$ 0.1% in a control group (Selezneva & Korman, 1973).

3.3 Case reports and epidemiological studies of carcinogenicity to humans

Many case reports have been made of cancer occurring following treatment with thiotepa (IARC, 1975; Nakanuma *et al.*, 1976; Anon., 1977; Hollister & Coleman, 1980; Sheibani *et al.*, 1980; Easton & Poon, 1983; Silberberg & Zarrabi,

1987). All report the occurrence of nonlymphocytic leukaemia, and usually thiotepa was the only chemotherapeutic agent administered.

No increased risk of second malignancies was found among 470 patients with colorectal cancer randomized to low-dose (four doses of 0.2 mg/kg bw) adjuvant therapy with thiotepa, followed for 3102 person-years (30 second noncolorectal malignancies observed, 31.4 expected; Boice *et al.*, 1980). No increased risk of second malignancies was found among 90 patients with breast cancer randomized to adjuvant therapy with thiotepa for one year (at 0.8 mg/kg bw in divided doses followed by 0.2 mg/kg bw weekly maintenance); after an average follow-up of approximately five years, five nonskin, nonbreast cancers had occurred in 5819 person-years among 90 treated subjects compared with six in 4746 person-years among the 77 nonexposed patients (Kardinal & Donegan, 1980). [The Working Group considered these two studies to be too small to provide useful information.]

Kaldor *et al.* (1990) compared 114 cases of leukaemia that developed in patients previously diagnosed with ovarian cancer, with 342 controls with ovarian cancer who had survived as long as the cases and who were matched by age and year of diagnosis of ovarian cancer. Chemotherapy (without radiotherapy) was associated with a relative risk of 12 (95% confidence interval, 4.4-32) compared to treatment by surgery only. For nine cases and 11 controls, the only chemotherapy was thiotepa; 21 cases and 187 controls had had no chemotherapy. The matched relative risks were 8.3 and 9.7 in a lower- and a higher-dose group, and these were significantly different from 1.0 ($p < 0.01$). In the same study, four other alkylating agents known to be carcinogenic (melphalan, chlorambucil, cyclophosphamide and treosulphan; see IARC, 1987) were independently associated with significantly increased risks for leukaemia.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Thiotepa is a cytostatic agent that has been used in the treatment of malignant lymphomas and solid tumours, in a wide range of doses.

4.2 Experimental carcinogenicity data

Thiotepa was tested for carcinogenicity by intraperitoneal administration in mice and rats and by intravenous administration in male rats. In mice, it induced an increased incidence of lung tumours and lymphoproliferative malignancies in mice of each sex. In rats, intraperitoneal administration induced an increased incidence of lymphoproliferative malignancies in males and of uterine adenocarcinomas and

mammary carcinomas in females. Intravenous administration to male rats induced tumours at a variety of sites.

4.3 Human carcinogenicity data

Several cases of leukaemia following treatment with thiotepa alone have been reported. One case-control study has shown a strong association between risk for leukaemia and treatment with thiotepa.

4.4 Other relevant data

In one study, there was no evidence that thiotepa therapy adversely affected subsequent fertility in women. Thiotepa is embryotoxic to mice and rats, and embryo- and fetolethality and gross structural abnormalities were induced during organogenesis after single intraperitoneal injections.

Thiotepa is converted to alkylating metabolites *in vivo*. It suppresses the bone marrow in humans.

In one study, increased frequencies of chromosomal aberrations were observed in peripheral lymphocytes of patients receiving thiotepa.

Thiotepa induced chromosomal aberrations in germ cells, sperm abnormalities and dominant lethal mutation in mice *in vivo*. It induced micronuclei in the bone marrow of rats and mice, chromosomal aberrations in bone-marrow cells and liver cells of mice and in peripheral lymphocytes of rabbits and rhesus monkeys and sister chromatid exchange in bone-marrow cells of mice *in vivo*. Thiotepa induced DNA damage in chick embryos. It induced chromosomal aberrations in cloned hamster cells, in Chinese hamster cells and in human cells, sister chromatid exchange in human, mouse, Chinese hamster and rabbit cells, gene mutations in Chinese hamster cells and unscheduled DNA synthesis in human peripheral lymphocytes *in vitro*. It induced cell transformation in mouse cells. Thiotepa induced sex-linked recessive lethal mutations in *Drosophila* and sister chromatid exchange and chromosomal aberrations in *Vicia faba*. It induced gene mutations in *Aspergillus nidulans* and *Salmonella typhimurium*. (See Appendix 1.)

4.5 Evaluation[1]

There is *sufficient evidence* for the carcinogenicity of thiotepa in humans.

There is *sufficient evidence* for the carcinogenicity of thiotepa in experimental animals.

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[1]For description of the italicized terms, see Preamble, pp. 26–29.

Overall evaluation

Thiotepa *is carcinogenic to humans (Group 1).*

5. References

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