MATERIAL SAFETY DATA SHEET
THIOPLEX® thiotepa

MANUFACTURED BY:
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FOR:
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SEATTLE, WA 98101

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1. PRODUCT and COMPANY IDENTIFICATION

PRODUCT NAME: THIOPLEX® thiotepa

USE/SIZE....: Anti-cancer drug/Bulk active & 15 mg/vial

PRODUCT NO...: 04651

CAS No......: [52-24-4]

SYNONYMS....: Triethylenetriphosphoramide; tris(1-aziridinyl)phosphine sulfate; N,N',N"-Triethylenetriphosphoramide; 1,1'1"-Phosphinothioylidinetrisaziridine; TESA; TSPA; CL-8,206

TRADE NAMES.: THIOPLEX®

2. COMPOSITION/INFORMATION ON INGREDIENTS

<table>
<thead>
<tr>
<th>No.</th>
<th>INGREDIENT NAME/SYNONYMS</th>
<th>CAS No.</th>
<th>% WEIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Thiotepa USP</td>
<td>[52-24-4]</td>
<td>100</td>
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</tbody>
</table>

3. HAZARDOUS IDENTIFICATION

DANGER! HIGHLY TOXIC. POISON B.
TOXIC IF SWALLOWED, INHALED OR ABSORBED THROUGH THE SKIN.
CAN CAUSE SEVERE EYE IRRITATION.
CAN CAUSE BLOOD DISORDERS.
MAY CAUSE KIDNEY, LIVER, SPLEEN, LUNG, GASTROINTESTINAL
AND HEART DAMAGE.
MAY CAUSE CANCER.
MAY IMPAIR FERTILITY. MAY CAUSE HARM TO THE UNBORN CHILD.

Continued....
3. HAZARDOUS IDENTIFICATION

POTENTIAL HEALTH EFFECTS:

PRIMARY ROUTE(S) OF EXPOSURE/ENTRY:

Inhalation of dusts or vapors; eye or skin contact. Absorption of toxic amounts through the skin may be expected. Although not an expected route of industrial exposure, Thiotepa would also be expected to be absorbed reasonably well (~50%) from the gastrointestinal tract.

ACUTE EFFECTS:

INHALATION: Based on information available on its toxicity profile via the intravenous (IV) and intraperitoneal (IP) routes, it is expected that thiotepa would be highly toxic by the inhalation route.

INGESTION.: Although not an expected route of exposure in the workplace, accidental ingestion may be harmful; see systemic adverse effects discussed below under "MEDICAL CONDITIONS ....".

SKIN.......: May cause skin irritation. May be absorbed through the skin in toxic amounts.

EYE.......: Can cause severe eye irritation with reversible opacity of the cornea.

TARGET ORGAN EFFECTS (SUBCHRONIC/CHRONIC):

Bone marrow, kidneys, liver, heart, lungs, spleen, blood system, eyes, gastrointestinal system, and reproductive system.

CARCINOGENIC EFFECTS:

IARC's evaluation of the data, and classification of thiotepa as a human carcinogen, was based on review of several clinical case reports of leukemia following treatment with thiotepa alone, as well as a single case-control study in which there was a strong association between risk for leukemia and treatment with thiotepa in ovarian cancer. Two other studies that showed no increased risk for second malignancies subsequent to thiotepa treatment for colorectal or breast cancer were considered by the IARC Working Group to be too small to provide useful information.

REPRODUCTIVE/TERATOGENIC EFFECTS:

FDA PREGNANCY CATEGORY D. Thiotepa has significant embryotoxic and teratogenic properties in animals. Thiotepa can cause fetal harm when administered to a pregnant woman. Since this material may affect the developing fetus, females of childbearing potential and pregnant women should avoid exposure. There are no adequate and well-controlled studies in pregnant women. It is not known whether thiotepa is excreted in human milk. Therefore, it is advisable for nursing mothers to avoid exposure.

Continued...
3. HAZARDOUS IDENTIFICATION (CONTINUED...)

CARCINOGENICITY STATUS:

Thiotepa is considered by the National Toxicology Program (NTP) to be a known human carcinogen (Group A). The International Agency for Research on Cancer (IARC) considers thiotepa to be a known human carcinogen (Group I). Thiotepa is regulated as a chemical hazard by the Occupational Safety and Health Administration (OSHA). American Home Products Company have classified thiotepa as a category A carcinogen, material known to produce carcinogenic effects in humans.

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE:

Thiotepa will cause bone marrow depression (a decrease in the ability of the bone marrow to form mature blood cells). Consequently, overexposure may cause leukopenia (a decrease in the number of circulating, formed white blood cells), thrombocytopenia (decrease in the number of platelets), and anemia (decrease in red blood cells). Clinically reported adverse reactions include nausea, vomiting, loss of appetite, dizziness, headache, amenorrhea (abnormal absence or suppression of the menstrual discharge), and interference with spermatogenesis. Death from septicemia (bacterial infection in the blood) and hemorrhage (bleeding) has occurred as a direct result of the depression of bone marrow caused by THIOTEPA.

In clinical-use, THIOTEPA is contraindicated in-patients with a known hypersensitivity (allergy) to the preparation and a history of liver, kidney, or bone marrow damage.

4. FIRST AID MEASURES

INHALATION: Remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Call a physician.

INGESTION: Induce vomiting immediately as directed by medical personnel. Never give anything by mouth to an unconscious person. Never induce vomiting in an unconscious person. Call a physician.

SKIN: Promptly washes with soap and cool running water. Remove contaminated clothing. Contaminated clothing should be washed before reuse. Destroy contaminated leather items (shoes, belts, etc.). Contact a physician if irritation occurs.

EYES: Immediately flush eyes with plenty of cool, low-pressure water for at least 20 minutes. Contact a physician.
4. FIRST AID MEASURES

Continued...

NOTE TO PHYSICIAN: No specific antidote to THIOTEPA intoxication exists. Monitoring of hemograms and white blood cell counts may be helpful in assessing the level of overall toxicity to the hematopoietic system. Generally, induction of vomiting with Syrup of Ipecac produces a mean recovery of only 30% of the ingested dose, but may still be useful in management of the poisoned patient. Save the initial emesis for analysis of THIOTEPA.

5. FIRE FIGHTING MEASURES

FLASH POINT: Not available     METHOD: N/A

AUTOIGNITION TEMP.: Not available

FLAMMABILITY LIMITS: Not available
  LOWER: N/A
  UPPER: N/A

UNUSUAL FIRE AND EXPLOSION HAZARDS:
  Pure thiotepa has an exothermic onset at 86°C with a large heat release and rapid gas evolution. Toxic emissions may be given off in a fire. See decomposition products in section 10-Stability and Reactivity. Pure thiotepa is a Class 1 dust.

COMMON EXTINGUISHING METHODS:
  Water, Carbon dioxide, Dry chemical, Foam.

FIRE FIGHTING PROCEDURES:
  Wear NIOSH/MSHA approved positive pressure, self contained breathing apparatus and full protective turn out gear. Use caution in approaching fire. Use water to keep fire-exposed containers cool. Protective clothing and equipment must be decontaminated if contact with the liquid or vapor has occurred.

6. ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED:
  Review Section 3-Hazards Identification, and Section 8-Exposure Controls/Personal Protection before proceeding with the clean up. Shut off the source of spill or leak. Eliminate possible ignition sources. Use appropriate containment to avoid environmental contamination. Scoop or shovel spilled material into a labeled container for disposal. Avoid creating airborne dust. Close container and move it to a secure holding area. Clean spill area thoroughly with water and detergent. Collect wash with an absorbent material and transfer to labeled container for treatment and disposal. Check area for residual material and repeat clean up if detected.

Continued...
6. ACCIDENTAL RELEASE MEASURES

Continued:

TREATMENT AND DISPOSAL:
Decontaminate or dispose of all protective clothing and equipment. Disposes of in accordance with recommendations in section 13-Disposal Considerations.

REPORTING REQUIREMENTS:
The United States Environmental Protection Agency (USEPA) has not established a Reportable Quantity (RQ) for releases of this material. State and Local regulations vary and may impose additional reporting requirements.

7. HANDLING AND STORAGE

Maintain good housekeeping and personal hygiene procedures.

Store under refrigeration at 2 – 8°C (36 – 46°F). Handle and store away from acidic substances.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

EXPOSURE GUIDELINES:

<table>
<thead>
<tr>
<th>INGREDIENT NAME</th>
<th>OSHA PEL/STEL</th>
<th>ACGIH TLV/STEL</th>
<th>AHPC-OEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiotepa USP</td>
<td>Not est.</td>
<td>Not est.</td>
<td>0.0014 mg/m³</td>
</tr>
</tbody>
</table>

VENTILATION:
Use closed-system handling, laboratory bench hood or local exhaust ventilation to control dusts or mist.

RESPIRATORY PROTECTION:
If the OEG is exceeded, wear an approved, full-face or supplied-air respirator.

PROTECTIVE GLOVES:
Wear 2 pairs of latex surgical gloves should be worn to prevent contact with the skin and should be changed frequently.

EYE PROTECTION:
The use of Safety Glasses/Goggles is required.

OTHER PROTECTIVE MEASURES:
Minimize excess handling. Keep container closed when not in use. Wash hands, face and exposed body parts at lunch and breaks, and at end of shift.
9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AND ODOR: White lyophilized cake or powder.

MELTING POINT: 52 – 57°C  
BOILING POINT: No data available

SPECIFIC GRAVITY/DENSITY: Not applicable

VAPOR DENSITY: Not applicable  
VAPOR PRESSURE: 0.007 torr @ 20°C

SOLUBILITY:
WATER............: Thiotepa is soluble in water to about 19% (19 g/100 ml) @ 25°C.
OTHER SOLVENTS: Thiotepa is freely soluble in ethanol; soluble in ether, benzene, and chloroform.

DECOMPOSITION TEMPERATURE: Decomposes upon heating above 86°C

VISCOITY: Not applicable

pH: 5.8 – 7.5 (0.02% solution)

EVAPORATION RATE: <0.0002 mg/min @ 23°C

10. STABILITY AND REACTIVITY

STABILITY: Stable up too 40°C  
POLYMERIZATION: Will not occur.

HAZARDOUS DECOMPOSITION PRODUCTS:
Emits toxic fumes of carbon monoxide, carbon dioxide, nitrogen oxides, and, possibly, hydrogen cyanide. Phosphorous-, and sulfur-containing products may also be generated.

CONDITIONS TO AVOID............: Contact with acidic substances. Decomposes at elevated temperatures (86°C) with a large heat release and evolution of gas.

INCOMPATIBLE MATERIALS............: Acidic substances

DUST HAZARD INFORMATION:
Explosibility Classification – A/B Test...: No data available
Minimum Ignition Energy (MIE)....................: No data available
Minimum Ignition Temperature (MIT)............: No data available
Hazard Dust Class (St value)....................: 1

11. TOXICOLOGICAL INFORMATION

ACUTE/SUBCHRONIC/CHRONIC DATA:
The oral LD50 values for THIOTEPA were 22 to 46 mg/kg in mice, 14.5 to 55 mg/kg in rats, and > 2 mg/kg in dogs. The

Continued...
11. TOXICOLOGICAL INFORMATION

ACUTE/SUBCHRONIC/CHRONIC DATA CONTINUED....

intraperitoneal (IP) and intravenous (IV) LD50s in mice and rats were in the
range of 8.4 to 9.8 mg/kg, respectively. Signs of toxicity seen in mice, rats,
and dogs included depression, diuresis (excessive urination), tremors, body
weight loss, dyspnea (abnormal breathing), bloody nostrils, and white blood
cell depression (dogs). Thiopeta has been reported to be a severe, but
reversible eye irritant when instilled in the rabbit eye. Although it was
toxic by dermal contact (dermal LD50 in guinea pigs was 45 mg/kg/24 hr), it was
not a skin irritant (based on the signs of toxicity seen in guinea pigs after
dermal exposure, which included general depression, diarrhea, and salivation).

The short-term and subchronic toxicity studies have been conducted,
mostly by injection, in mice, rats, and dogs. In mice, five day, multiple-
dose, oral and IP LD50s for Thiopeta were ~35 and 18 mg/kg/day, respectively.
In rats, the IP LD50 for Thiopeta ranged from 3.48 to 3.9 mg/kg/day for 5-6
days, whereas subcutaneous doses of 0.5 mg/kg/day for 14 days were tolerated.
Target organs affected were bone marrow and kidneys. In dogs, doses of 0.5
mg/kg/day orally or IV for 14 days were tolerated, while doses of 1 or 2
mg/kg/day resulted in the death of some animals. Target organs affected were
blood, spleen, gastrointestinal tract, lungs, heart, and liver.

CARCINOGENIC EFFECTS DATA:

Thiopeta has also been shown in several studies to cause cancer in both
sexes of rats and mice when administered by injection (intravenous and/or
intraperitoneal). In mice, repeated IP administration of thiopeta at doses of
1.15 or 2.3 mg/kg 3 times/week for 52 or 43 weeks, respectively, produced a
significant increase in the combined incidence of squamous-cell carcinomas of
the skin, preputial gland, and ear canal, and combined incidence of lymphoma
and lymphocytic leukemia. In other studies in mice, repeated IP
administration of thiopeta (4 or 8 mg/kg 3 times/week for 4 weeks followed by
20-week observation period or 1.3 mg/kg 3 times/week for 4 weeks followed by
35-week observation period) resulted in an increased incidence of lung tumors.
In rats, thiopeta was administered at doses of 0.7 or 1.4 mg/kg 3 times/week
for 52 or 34 weeks, respectively. A significant increase in the incidence of
squamous-cell carcinomas of the skin or ear canal, combined hematopoietic
neoplasms, and uterine adenocarcinomas. Thiopeta given IV to rats at dose of 1
mg/kg once/week for 52 weeks, produced an increased incidence of malignant
tumors (abdominal cavity sarcoma, lymphosarcoma, myelosis, seminoma,
fibrosarcoma, salivary gland hemangioendothelioma, mammary sarcoma,
pheochromocytoma) and benign tumors.

MUTAGENIC EFFECTS DATA:

Thiopeta was mutagenic in in vitro assays in S. typhimurium, E. coli, Chinese
hamster lung cells and human lymphocytes. Chromosomal aberrations and sister
chromatid exchanges were observed in vitro with thiopeta in bean root tips,
human lymphocytes, Chinese hamster lung cells, and monkey lymphocytes. It was
also positive in vivo in the mouse micronucleus test with IP dose of > 1 mg/kg
and in the mutation assay in mouse at oral dose of > 2.5 mg/kg.

Continued....
11. TOXICOLOGICAL INFORMATION

MUTAGENIC EFFECTS DATA CONTINUED...:
Other positive in vivo chromosomal aberration or mutation assays included Drosophila melanogaster, Chinese hamster bone marrow cells, murine bone marrow cells, monkey lymphocyte, and murine germ cells.

Thiotepa is a highly toxic chemical that exerts its effect by alkylating DNA (i.e., binding to the molecules that control the genetic make-up of cells). This binding disrupts the synthesis of DNA in rapidly multiplying cancerous cells, causing cell death and, hence, affecting its therapeutic action. However, thiotepa will also alkylate DNA in rapidly multiplying normal cells (e.g., bone marrow cells, developing sperm, etc.), killing them, too.

REPRODUCTIVE/TERATOGENIC EFFECTS DATA:
Thiotepa impaired fertility in male mice at oral or IP doses of ≥ 0.7 mg/kg. Mice and rats receiving IP injections of thiotepa produced pups with malformations at low doses, and malformations and fetal loss at high doses. In another fertility-related study, thiotepa at 0.5 mg inhibited implantation in female rats when instilled into the uterine cavity prior to mating. Implantation was completely suppressed in the right horn for 2 months after treatment; the left horn was unaffected. Thiotepa interfered with spermatogenesis in mice and hamsters at IP doses of ≥ 0.5 mg/kg and 1 mg/kg, respectively. Thiotepa given IP was teratogenic in mice at doses of ≥ 1 mg/kg. It was also teratogenic in rats at IP doses of ≥ 3 mg/kg. In rabbits, a dose of 3 mg/kg of thiotepa on days 6-8 of gestation prevented implantation.

12. ECOLOGICAL INFORMATION

ECOTOXICOLOGICAL INFORMATION: No data available

CHEMICAL FATE INFORMATION...: No data available

13. DISPOSAL CONSIDERATIONS

DISPOSAL RECOMMENDATIONS:
Place collected material into a plastic bag and place into an approved disposal container. Label and dispose of in accordance with all Federal, State, and local regulations. Dispose of contaminated garments in a like manner. Incineration is recommended at a permitted facility.

RCRA WASTE #. . . . . . . . . .  :
This is not a RCRA regulated hazardous waste.
14. TRANSPORT INFORMATION

U.S. DEPARTMENT OF TRANSPORTATION (DOT)......:
  Proper Shipping Name..: Toxic organic, solid, n.o.s. (Thiotepa); UN2811
  Hazard class/Division.: 6.1
  Package Group.........: II

INTERNATIONAL AIR TRANSPORT ASSOCIATION (IATA):
  Proper Shipping Name..: Toxic organic, solid, n.o.s. (Thiotepa); UN2811
  Hazard class/Division.: 6.1
  Package Group.........: II

15. REGULATORY INFORMATION

USEPA.............: Not regulated.

OSHA.............: OSHA has not developed a Permissible Exposure Limit (PEL) for
  THIOTEPA (See Section 8).

SARA TITLE III: Thiotepa is not reportable under Section 313 and contains no
  constituents which are reportable under this section.

16. OTHER INFORMATION

PREPARATION AND REVISION INFORMATION

Preparer.............: Hesham M. Soliman/Toxicologist/Scientific Consultant
Approver.............: S. Rera/Certified Industrial Hygienist/Safety Engineer
  A. Moran/Director Safety Services

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determine the suitability of this information for their particular purposes.