

# Methyl and ethyl thiuram monosulfides: Human health tier II assessment



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## Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
<b>Thiodicarbonic diamide [(H<sub>2</sub>N)C(S)]<sub>2</sub>S), tetraethyl-</b>	95-05-6
<b>Thiodicarbonic diamide [(H<sub>2</sub>N)C(S)]<sub>2</sub>S), tetramethyl-</b>	97-74-5

## Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit: [www.nicnas.gov.au](http://www.nicnas.gov.au)

### Disclaimer

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## ACRONYMS & ABBREVIATIONS

## Grouping Rationale

Thiuram (CAS No. 97-74-5, also known as tetramethylthiuram monosulfide or TMTM) and sulfiram (CAS No. 95-05-6, tetraethylthiuram monosulfide or TETM) are structurally similar dithiocarbamate derivatives, which contain either four methyl or ethyl groups, respectively. Each individual chemical is a monosulfide bridged dimer. There are also the disulfide bridged dimers, the thiuram disulfides, such as thiram (CAS No. 137-26-8) and disulfiram (CAS No. 97-77-8). All four chemicals are considered inhibitors of aldehyde dehydrogenase (ALDH). Disulfiram is known to cause adverse reactions with ethanol or delay ethanol elimination in humans, and the other three chemicals have shown similar interactions in vitro and in rats (Mays et al., 1994; Romer et al., 1984).

All share similar uses as rubber accelerators (i.e. speeding the donation of sulfur to rubber to form crosslinks) and fungicides (ACC, 2003; ChemIDplus; NICNASa; NICNASb). Based on their activity, uses, and structural similarity, thiuram (TMTM) and sulfiram are grouped together for purposes of this human health risk assessment. The two thiuram disulfides, with differences in the core structure compared with thiuram monosulfides, are assessed separately (NICNASa; NICNASb).

## Import, Manufacture and Use

### Australian

The chemical TMTM has reported site-limited uses in the manufacture of substances (Sigma-Aldrich SDS).

Both TMTM and sulfiram have non-industrial uses as active constituents of agricultural chemical products (Galleria Chemica).

### International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier; Galleria Chemica; the US National Library of Medicine's ChemIDplus; and Hazardous Substances Data Bank (HSDB).

The chemical TMTM has reported uses in the manufacture of gloves, fingerstall, soles, footwear, treadmills, and large surface articles in flooring, furniture, toys, construction materials. The chemical is also used in manufacture of curtains, leather, paper and cardboard products, and electronic equipment. While these uses of the chemical are commercial and/or site-limited, the articles produced in factories in Australia and elsewhere have domestic uses, and traces of the chemicals can, over time, leach out into the environment during use.

The chemical TMTM has site limited uses in the manufacture of polymers and rubber products, including as a rubber accelerator or a process regulator.

The chemical TMTM and sulfiram have non-industrial uses as agricultural chemicals, bactericides, and fungicides. Sulfiram is also used therapeutically in the treatment of scabies.

## Restrictions

### Australian

No known restrictions have been identified.

### International

The chemical TMTM is listed on the following:

- European Commission (EC) Cosmetics Regulation Annex II (List of substances prohibited in cosmetic products) (CosIng);
- Health Canada Cosmetic Ingredient Hotlist (List of ingredients prohibited or restricted for use in cosmetic products);
- New Zealand Cosmetic Products Group Standard Schedule 4 (Components cosmetic products must not contain) (NZ EPA, 2017); and
- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1 (List of substances which must not form part of the composition of cosmetic products) (ASEAN, 2018).

## Existing Worker Health and Safety Controls

### Hazard Classification

The chemical TMTM is classified as hazardous with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

- Acute toxicity – Category 4; H302 (Harmful if swallowed)
- Skin sensitisation – Category 1; H317 (May cause an allergic skin reaction).

### Exposure Standards

#### Australian

No specific exposure standards are available.

#### International

No specific exposure standards are available.

## Health Hazard Information

No data are available for sulfiram. For hazard endpoints where the data are incomplete or unavailable, read-across information from the respective thiuram disulfides (thiram and disulfiram) is used to indicate the potential toxicity of thiuram monosulfides (TMTM and sulfiram).

The two thiuram disulfides show generally similar toxicity, with the methyl and ethyl analogues being quite similar. For this reason, it is considered that the more comprehensive data available for TMTM is applicable to sulfiram. The exception is for skin and eye irritation, where thiram is more irritating than disulfiram and; therefore, irritation results for TMTM are not read across to sulfiram.

## Toxicokinetics

No toxicokinetic studies are available.

Based on their low molecular weight (MW <500) and partition coefficients (log P) of 0.75 and 2.71 (ChemIDplus), TMTM and sulfiram respectively are expected to be absorbed after oral, dermal and inhalation exposure with wide distribution in the body. Metabolism is expected to occur in the liver and excretion via the urine.

## Acute Toxicity

### Oral

The chemical TMTM is classified as hazardous with hazard category and statement 'Acute toxicity – Category 4; H302 – Harmful if swallowed' in HCIS (Safe Work Australia). The available data support this classification. Due to the close structural similarity, it is considered that this classification should also apply to sulfiram (see **Recommendation** section).

Median lethal doses (LD50s) between 413 and 1400 mg/kg were reported in rats and mice for TMTM. Sublethal effects included inhibition, diarrhoea, paresis, hind limb paralysis, convulsions and prolonged sleep time. The liver seemed to be the target organ (Alanis et al., 1982; Sheftel, 1995; US EPA OPPT, 2003; Galleria Chemica; REACH).

In a standard test (Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401 – Acute oral toxicity), the LD50 for TMTM was calculated as 690 mg/kg bw in rats, based on reported mortalities of 0/10, 5/10, 7/10, 8/10 and 10/10 at 100, 500, 1000, 2500 and 3100 mg/kg bw, respectively (REACH).

### Dermal

Based on the available data, TMTM and sulfiram are considered to have low acute dermal toxicity with dermal LD50 >2000 mg/kg bw.

In a standard test (OECD TG 402 – Acute dermal toxicity), no death occurred in rats after dermal application of TMTM under semi-occlusive conditions for 24 hours at 2000 mg/kg bw (REACH).

In rabbits, the LD50 for TMTM was determined to be >2000 mg/kg bw, after a 24-hour occlusive application (US EPA OPPT, 2003; REACH).

### Inhalation

Based on the available data, TMTM has moderate acute inhalation toxicity, warranting hazard classification. Due to the close structural similarity, it is considered that this classification will also apply to sulfiram (see **Recommendation** section).

In a standard test (United States Environmental Protection Agency (US EPA) TG – Acute inhalation toxicity), the LC50 for TMTM was calculated as 4.42 mg/L/4 hours in rats, based on reported mortalities of 1/10, 3/10 and 6/10 at 2.06, 3.36 or 5.04 mg/L, respectively (REACH).

## Corrosion / Irritation

### Skin Irritation

Based on the available data and read-across information from thiram (NICNASa), TMTM is considered to cause skin irritation, warranting hazard classification (see **Recommendation** section). Read-across information from disulfiram (NICNASb) does not support extension of this classification to sulfiram.

In a standard test (OECD TG 404 – Acute dermal irritation/corrosion), New Zealand White rabbits (n=6) were tested with TMTM (500 mg) under occlusive conditions for 24 hours. Erythema and oedema were observed with mean scores of 0.1 and 0.83 at 24 hours, respectively. The scores increased to 4 for both erythema and oedema at 72 hours. Erythema was reversible but oedema was not after 8-day observation (REACH). These skin reactions are considered delayed on three consecutive days, which meet the criteria of Globally Harmonized System of Classification and Labelling of Chemicals (GHS 2009).

### Eye Irritation

Based on the available data and read-across information from thiram (NICNASa), TMTM is considered to cause severe eye irritation, warranting hazard classification (see **Recommendation** section). Read-across information from disulfiram (NICNASb) does not support extension of this classification to sulfiram.

In a standard test (OECD TG 405 – Acute eye irritation/corrosion), TMTM (100 µL) was applied to the conjunctival sac of New Zealand White rabbits (n=6). Maximum mean scores were 4 for corneal opacity, 2 for iritis, 3 for conjunctival redness, and 4 for conjunctival chemosis. The conjunctival effects reversed within 8 days, and no information on reversibility of the corneal and iris effects was reported (REACH).

### Observation in humans

In a standard Draize test, TMTM at 1 % caused moderate skin reactions in humans (Galleria Chemica).

## Sensitisation

### Skin Sensitisation

The chemical TMTM is classified as hazardous with hazard category and statement 'Skin sensitisation – Category 1; H317 – May cause an allergic skin reaction' in HCIS (Safe Work Australia). The available data, including human case reports for both TMTM and sulfiram, are sufficient to support this classification for both members of the group.

In a guinea pig maximisation test (GPMT), TMTM produced positive responses in 5/8 guinea pigs (62.5 %), following intradermal and topical induction exposure at 5 % and topical challenge exposure at 2 % (Li et al., 1995).

In an occlusive epicutaneous Buehler test, TMTM was sensitising to 3/12 (25 %) and 9/12 (75 %) guinea pigs, following induction exposure at 104 mg/mL and challenge exposure at 10.4 or 104 mg/mL, respectively (REACH).

### Observation in humans

#### TMTM:

In a repeated insult patch test, positive reactions were reported in 5/50 human volunteers challenged with TMTM at 50 % after 15 induction applications and a two-week rest period (Monsanto, 1992a; REACH).

In occupational settings, thiurams (particularly thiram and TMTM) in rubber gloves are the most frequently reported allergens with sensitisation rates of 72 % (Heese et al., 1991; HSDB). A case of allergic contact dermatitis has been reported in a packing worker (47-year-old man) after exposure to rubber bands containing TMTM. The worker did not use any protective gloves (Corazza et al., 2007).

The chemicals TMTM, thiram and disulfiram were observed to show cross sensitisation (HSDB).

#### **Sulfiram:**

A case of toxic epidermal necrolysis caused by skin hypersensitivity to sulfiram was observed in a 47-year-old housewife with scabies. She had previously developed rubber dermatitis while working in a munitions factory. She showed positive eczematous responses on patch-testing with thiram at 48 and 96 hours after application, and sulfiram at three hours after application (Copeman, 1968).

Contact dermatitis following use of sulfiram soap was reported in a 47-year-old female office cleaner, who had also acquired thiuram sensitivity from contact with rubber (Dick & Adams, 1979).

## **Repeated Dose Toxicity**

### **Oral**

Although limited data are available, TMTM may cause harm following repeated oral exposure. Target organs are liver and central nervous system. Given the oral systemic toxicity effects in these organs are similar between thiuram monosulfide (TMTM) and thiuram disulfides (thiram and disulfiram), hazard classification of TMTM is warranted (see **Recommendation** section).

There are insufficient data to warrant classification of sulfiram following repeated exposure; however, its effects on the target organs cannot be ruled out.

Sulfiram, TMTM, and thiuram disulfides showed ALDH inhibitory activities in the hepatic metabolism of ethanol (Mays et al., 1994; Romer et al., 1984) (see **Grouping rationale** section). The chemicals TMTM, thiram and disulfiram similarly produced sedative effects on rats and mice motility. In the mouse, TMTM also increased hexobarbital narcosis similar to disulfiram, and increased ethanol narcosis similar to thiram (Poitou et al., 1978) (see **Neurotoxicity** section). In the rat, TMTM had reported toxicity effects on liver, kidney and blood parameters similar to those of thiram. The lowest observed adverse effect level (LOAEL) for TMTM was 26 mg/kg bw/day and for thiram 38 mg/kg bw/day (NICNASa).

Wistar rats were administered TMTM at gavage doses of 26, 520 or 867 mg/kg bw/day, five days/week for four weeks. Erythrocyte count and haemoglobin content were decreased at 26 mg/kg bw/day. Histologically, generalised swelling of liver cells and renal tubular epithelia were observed at this dose. The chemical also prolonged sleep time with increasing doses, suggesting an inhibition of microsomal aliphatic hydroxylation in the liver (Alanis et al., 1982; US EPA OPPT, 2003; HSDB).

Male rabbits were treated with TMTM in diet at 20 mg/kg bw/day for 3–4 months. The mortality rate was 50 % and changes in liver, lungs and blood parameters were observed. Histopathological analysis revealed pulmonary oedema and marked dystrophy of the liver and kidneys (Sheftel, 1995; REACH).

### **Dermal**

No data are available.

### **Inhalation**

Limited data are available for TMTM and no data are available for sulfiram. Given similarities in the acute and systemic toxicity effects for TMTM after oral and inhalation exposure, as well as the read-across information from oral systemic toxicity effects,

hazard classification of TMTM is warranted (see **Recommendation** section).

There are insufficient data available to warrant classification of sulfiram following repeated exposure; however, its effects on the target organs cannot be ruled out.

A reported lowest observed adverse effect concentration (LOAEC) in rats was 0.4 mg/L, following repeated inhalation exposure to TMTM, two hours/day for 15 days. Gross necropsy findings were degenerative changes in the liver and kidneys of the exposed animals (US EPA OPPT, 2003; REACH). No additional information was provided.

## Genotoxicity

Based on the available data, TMTM is considered mutagenic in vitro and genotoxic in vivo, warranting hazard classification. On structural grounds, this classification should apply to both members of the group (see **Recommendation** section).

In vitro, TMTM was:

- positive in a bacterial reverse mutation test (OECD TG 471) in *Salmonella typhimurium* TA1535, TA1537, TA98, TA100, and TA102, with and without metabolic activation (REACH);
- positive in *S. typhimurium* TA1535 and TA100, particularly in the presence of metabolic activation (Alanis et al., 1982);
- positive in a sister chromatid exchange assay in Chinese hamster ovary cells, without metabolic activation (Donner et al., 1983);
- negative in a gene mutation assay in mouse lymphoma L5178Y cells, with and without metabolic activation (US EPA OPPT, 2003);
- negative in a gene mutation assay in Chinese hamster lung fibroblasts (V79), with and without metabolic activation (Donner et al., 1983);
- negative in a cell transformation assay in BALB/c 3T3 mouse fibroblasts, without metabolic activation (REACH).

In vivo, TMTM was:

- positive in a bone marrow chromosome aberration test (OECD TG 475) in male SD rats at 1300 mg/kg, although the result was reported possibly due to artefacts of poor cell preparation (US EPA OPPT, 2003). Regarding cytotoxicity, TMTM induced mitotic index depression with time (24 % at 6 hours, 33 % at 24 hours, and 56 % at 48 hours) (Monsanto, 1992b; US EPA OPPT, 2003; REACH);
- positive in a erythrocyte micronucleus assay in bone marrow of Chinese hamsters (Donner et al., 1983); and
- negative in a sex-linked recessive lethal test in *Drosophila melanogaster* (Donner et al., 1983).

## Carcinogenicity

Based on one mouse study and read-across information, TMTM and sulfiram are not considered to be carcinogenic.

In an 18-month study, B6C3F1 and B6AKF1 mice (18/sex/dose) were administered TMTM either by gavage (100 mg/kg bw/day) on days 7–28 then in the diet thereafter, or by a single subcutaneous injection (dose not specified) on day 28. No significant carcinogenic effects were observed (US EPA OPPT, 2003; REACH).

The International Agency for the Research of Cancer (IARC) has classified the two analogues thiram and disulfiram as 'Not classifiable as to its carcinogenicity to humans' (Group 3), based on inadequate evidence in humans and inadequate or limited in experimental animals (IARC, 1987; 1991).

## Reproductive and Developmental Toxicity

Limited data are available for TMTM and no data are available for sulfiram.

Based on the read-across information, TMTM and sulfiram are not expected to cause reproductive or developmental toxicity.

Mice were subcutaneously administered TMTM at doses of 46.4 mg/kg bw/day on gestation day (GD) 6–14 (BL6 strain) or 100 mg/kg bw/day on GD 6–15 (AXR strain). No maternal toxicity or teratogenic effects were observed on GD 18 (sacrificed) (US EPA OPPT, 2003; REACH).

## Other Health Effects

### Neurotoxicity

In rats and mice, TMTM and thiram disulfides were reported to have effects on the central nervous system by decreasing motor activity two hours after administration and inducing sleep time. TMTM enhanced hexobarbital induced narcosis as seen for disulfiram, and enhanced ethanol induced narcosis as seen for thiram (Poitou et al., 1978).

## Risk Characterisation

### Critical Health Effects

The critical health effects of TMTM and sulfiram for risk characterisation include harmful systemic effects, particularly neurotoxicity, following repeated exposure and dermal sensitisation. The chemicals may have some genotoxic potential and can also cause systemic acute effects (from oral and inhalation exposure).

The chemical TMTM is also a skin and eye irritant.

### Public Risk Characterisation

The chemical TMTM has reported uses in gloves, footwear, and as large surface articles in flooring, furniture, toys, leather and cardboard products overseas. The general public could be exposed through the skin or inhalation when using these domestic articles containing the chemicals. However, these effects are known to manufacturers, and care is taken to ensure that the traces or impurities of the chemicals in these products are sufficiently low to prevent harmful or sensitising effects. Therefore, the risk to public health is not considered to be unreasonable.

### Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term, systemic acute and local health effects, these chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal, ocular and inhalation exposure are implemented. These chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The available data support an amendment to the hazard classification in the HCIS (Safe Work Australia) (see **Recommendation** section).

## NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by



the relevant state or territory.

## Regulatory Control

### Work Health and Safety

The chemicals are recommended for classification and labelling in alignment with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below.

The classifications for skin and eye irritation, and specific target organ toxicity (STOT) following repeated exposure are applicable to TMTM (CAS No. 97-74-5) only.

This assessment does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS) <sup>a</sup>	GHS Classification (HCIS) <sup>b</sup>
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302) Harmful if inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Not Applicable	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Not Applicable	May cause damage to the liver and nervous system through prolonged or repeated exposure - Cat. 2 (H373)
Genotoxicity	Not Applicable	Suspected of causing genetic defects - Cat. 2 (H341)

<sup>a</sup> Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

<sup>b</sup> Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

\* Existing Hazard Classification. No change recommended to this classification

### Advice for consumers

Products containing the chemicals should be used according to the instructions on the label.

### Advice for industry

#### Control measures

Control measures to minimise the risk from oral, dermal, ocular and inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using hazardous chemicals depend on the physical form and the manner in which they are used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemicals from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

#### ***Obligations under workplace health and safety legislation***

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that safety data sheets (SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of these chemicals has not been undertaken as part of this assessment.

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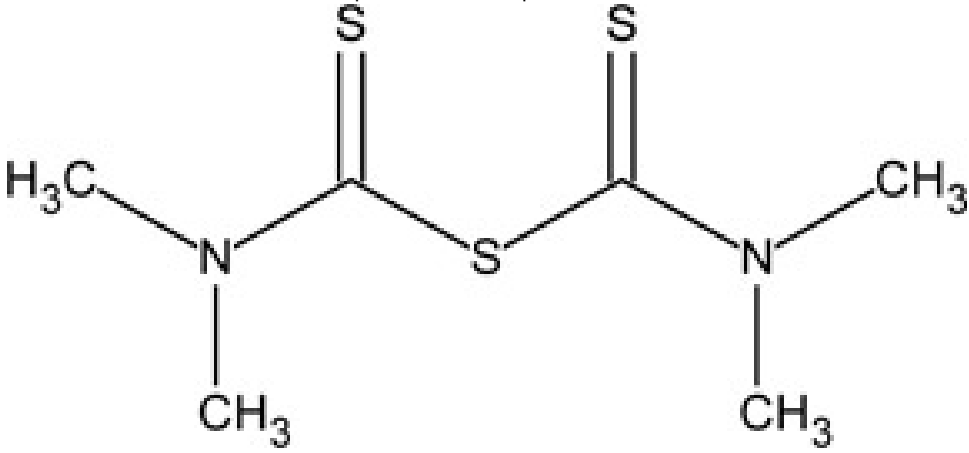
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Structural Formula	 <chem>CN(C)C(=S)SC(=S)N(C)C</chem>
Molecular Formula	C <sub>6</sub> H <sub>12</sub> N <sub>2</sub> S <sub>3</sub>
Molecular Weight	208.37

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