WORKING DRAFT

HAZARD INFORMATION REVIEW

Bis(dimethylthiocarbamyl) Disulfide

THIRAM

IR-220

January 31, 1981

Prepared under EPA Contract No. 68-01-5789 for:
TSCA Interagency Testing Committee

Prepared by:
Enviro Control, Inc.
11300 Rockville Pike
Rockville, Maryland 20852

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CONTENTS

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AN OVERVIEW

CHARACTERISTICS

Bis(dimethylthiocarbamyl) disulfide is a powder that is unlikely to be soluble in water or organic solvents.

PRODUCTION AND USE

The U.S. production of bis(dimethylthiocarbamyl) disulfide has decreased steadily from 1974 to 1977. In 1977 the U.S. production of the compound was estimated to be four million pounds.

Bis(dimethylthiocarbamyl) disulfide is primarily used as an accelerator in compounding rubber. It is also used as a fungicide.

BIOCHEMICAL INFORMATION

Bis(dimethylthiocarbamyl) disulfide is absorbed through all portals. Following absorption after a single dose, this compound is distributed throughout the organism and is eliminated over a period of 2 or 3 weeks.

This compound inhibits the activity of numerous enzymes and interferes with catecholamine, carbohydrate, and lipid metabolism.

TOXICOLOGICAL INFORMATION

Four studies of two animal species demonstrate that bis(dimethylthiocarbamyl) disulfide is not a carcinogen in rats and mice.

Bis(dimethylthiocarbamyl) disulfide has been found to be a mutagen in various test systems, including the Ames test, Rec assay test, and scheduled and unscheduled DNA synthesis tests.

Bis(dimethylthiocarbamyl) disulfide has been found to be a teratogen in hens, hamsters, and mice.

In birds, bis(dimethylthiocarbamyl) disulfide inhibits ovulation and spermatogenesis and delays egg production. In both sexes of rats the compound reduces fertility, and in females it delays both the estrus cycle and the growth of ovarian follicles.

Ingestion of bis(dimethylthiocarbamyl) disulfide by rats in high doses and over long periods of time produced many complications, such as advanced degenerative changes in liver and kidney, reduced weight gain and food consumption, and lymphocytosis and hyperplasia of the lymph follicles.

OBSERVATIONS IN HUMANS

Exposure to bis(dimethylthiocarbamyl) disulfide may result in contact dermatitis. Ingestion of ethanol after exposure to the compound may lead to a violent nonallergic reaction. Chronically exposed individuals may develop cardiovascular and neurological disturbances.

ENVIRONMENTAL RELEASE AND CONCENTRATIONS

There are three possible routes of environmental entry of bis(dimethylthiocarbamyl) disulfide: from manufacturing and processing facilities, from agricultural uses, and from vulcanized rubber products. Analytical methods for detecting the compound have been developed but do not appear to have been used for monitoring.

ENVIRONMENTAL FATE AND EFFECTS

Bis(dimethylthiocarbamyl) disulfide is not expected to persist in any environmental compartment.

The compound does not disrupt nutrient cycling in the soil but is toxic to birds and fish.

SUMMARY OF HAZARD POTENTIAL

The health effects of bis(dimethylthiocarbamyl) disulfide are well studied and are for the most part adverse. Laboratory studies of environmental effects show that the compound is toxic to wildlife. The uses of the compound provide considerable opportunity for environmental release; however, it is unlikely to persist in the environment. No monitoring studies have been conducted to show the existence of the compound in the environment.

CURRENT AND PLANNED ACTIVITY

Bis(dimethylthiocarbamyl) disulfide is currently under preregulatory assessment by EPA for health effects other than oncogenicity.

Bis(dimethylthiocarbamyl) Disulfide

I. CHEMICAL AND PHYSICAL INFORMATION

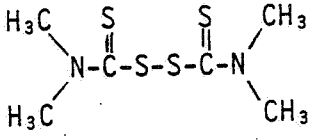
A. IDENTIFICATION

1. CAS No.: 137-26-8
2. NIOSH No.: J01400000
3. Synonyms: Thiram
   Tetramethylthiuram

   Comment: Bis(diethylthiocarbamyl) disulfide (i.e., the ethyl congener of Thiram) is a drug called Antabuse or Disulfiram.

B. FORMULAS AND MOLECULAR WEIGHT

1. Structural Formula



2. Empirical Formula: $C_6H_{12}N_2S_4$
3. Molecular Weight: 240.44

C. PHYSICAL PROPERTIES

1. Description: White to cream powder (IARC, 1976)
2. Melting Point

   155-156°C (recrystallized)
   146°C (commercial grade) (Merck, 1976)

2. Boiling Point: No information available
3. Vapor Pressure: No information available

   Comment: Probably very low

5. Specific Gravity: 1.29

6. Solubility in Water: "Insoluble" (Merck 1976)

7. Solubility in Organic Solvents

This compound has moderate to low solubility (i.e., less than about 3% w:w) in common organic solvents (Merck, 1976).

8. Partition Coefficient

Log P octanol/water is expected to be in the range of -1 to -2 (estimated, Leo et al., 1971).

9. Impurities: No information available

D. CHEMICAL PROPERTIES

1. Hydrolysis

Boiling sulfuric acid releases CS_2 and $(CH_3)_2NH$ from bis dimethylthiocarbamyl) disulfide (Rangaswamy et al., 1970).

2. Homolysis of the S-S Bond

The bond energy of the S-S bond is only about 54 kcal/mol (Roberts and Caserio, 1964). At elevated temperatures or when exposed to ultraviolet light, this bond may break yielding two thio radicals. This is probably the function of bis(dimethylthiocarbamyl) disulfide in the vulcanization process (Pimblott et al., 1979), and photochemical polymerizations (Hosaka et al., 1979).

3. Reduction of the S-S Bond

Bis(dimethylthiocarbamyl) disulfide is reduced to dimethyldithiocarbamate, $(CH_3)_2NCS_2^-$, by stannous chloride (Ghezzo and Magos, 1971).

Comment: The dimethyldithiocarbamate is readily hydrolyzed at low pH to dimethylamine.

E. EXPOSURE ESTIMATES

1. Release Rate: No information available

2. Occupational Exposure

TLV (air): 5 mg/m^3 (ACGIH, 1979)
Estimated number of workers exposed: 179,777 (NOHS, 1980)

3. Production

Bis(dimethylthiocarbamyl) disulfide is believed to be produced commercially in the United States by passing chlorine gas through a solution of sodium dimethyldithiocarbamate (IARC, 1976).

The 1978 U.S. production of bis(dimethylthiocarbamyl) disulfide together with other thiurams equaled 7.66 million pounds (USITC, 1979). The other thiurams include:

- bis(diethylthiocarbamyl) disulfide
- bis(dimethylthiocarbamyl) sulfide
- N,N'-dioctadecyl-N-N'-diisopropyl thiuram disulfide
- mixed methyl-ethyl thiurams

The U.S. production from 1974 through 1977 of bis(dimethylthiocarbamyl) disulfide has decreased (Figure 1) (USITC, 1975-1978).

The U.S. production and importation for 1977 was in excess of 3 million pounds (TSCA Inventory, 1980). For an enumeration of the available production and importation information by manufacturer refer to Enclosure 1.

Figure 1. U.S. Production of bis(dimethylthiocarbamly) disulfide, 1974-1977.

The production for 1977 is an estimate based on the quantity sold. Adapted from data compiled by USITC (1975-1978).

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4. Use

Bis(dimethylthiocarbamyl) disulfide is primarily used as an accelerator in compounding natural and synthetic rubbers, including isobutylene-isoprene, butadiene, styrene-butadiene, synthetic isoprene, and nitrilebutadiene (IARC, 1976). It is also used as a fungicide, mainly as a seed disinfectant (Reed, 1980, Personal communication, FDA). The fungicide is also used on fruits, nuts, vegetables, and ornamental crops, and on paper, polyurethane foam products, and industrial texiles. Other less important uses include animal repellent, bacteriostat in soap, antiseptic sprays, and lube oil additives (IARC, 1976; Merck, 1976).

According to IARC (1976), 97% of bis(dimethylthiocarbamyl) disulfide is used as an accelerator in compounding rubber.

In 1974, 1.3 million pounds of the compound was used as a fungicide (Reed, 1980, Personal communication, FDA). This fungicidal use would have equaled 11% of the 1974 U.S. production of bis-(dimethylthiocarbamyl) disulfide. Thus at most, 89% of the compound could have been used as a rubber accelerator in 1977.

5. Manufacturers (TSCA Inventory, 1980)

Pennwalt Corp., Wyandotte, Michigan
Goodyear Tire and Rubber Co., Akron, Ohio
Brin-mont Chemicals, Inc., Greensboro, North Carolina
Vanderbilt Chemical Corp., Bethel, Connecticut

Refer to Enclosure 1 for a listing of importers.

F. SCORES FROM 1980 ITC SCORING EXERCISE

1. Occupational and Consumer Exposure

The exposure scores for bis(dimethylthiocarbamyl) disulfide (normalized from 0.0 to 1.0) are as follows:

Occupational Exposure Index: 0.61

Consumer Exposure Index: 0.52

2. Health and Environmental Effects

Health and environmental effects were scored on a scale from 0 to 3 (minus assigned if score is based solely on judgment in the absence of experimental data):

Individual factor scores for bis(dimethylthiocarbamyl) disulfide are as follows:

Mutagenicity:	1.6
Carcinogenicity:	-2.8
Teratogenicity:	3.0
Reproductive effects:	2.7
Acute toxicity effects:	1.0
Other toxic effects:	2.0
Bioaccumulation:	-0.3
Ecological effects:	0.0

Aggregate scores for bis(dimethylthiocarbamyl) disulfide are as follows:

Sum positive:	10.3
Sum negative:	-3.1

II. BIOCHEMICAL INFORMATION

A. METABOLISM

Summary: Bis(dimethylthiocarbamyl) disulfide is absorbed through all portals. Following absorption of a single dose, this compound is distributed throughout the organism and is eliminated over a period of 2 to 3 weeks. One of the metabolites of this compound is carbon disulfide.

1. Absorption

Bis(dimethylthiocarbamyl) disulfide can be absorbed through all portals (CPC, 1955). The compound can be absorbed through the skin (Gaul, 1957), through the lungs (RTECS), and through the gastrointestinal tract (Zhavoronkov and Antiseferov, 1977). The compound can generate the carcinogen N-nitrosodimethylamine in the presence of nitrite at the acid pH of the stomach (Sen et al., 1975; Egert and Greim, 1976a).

2. Distribution and Excretion

In three species studied, bis(dimethylthiocarbamyl) disulfide was found distributed through the body following a single oral dose (Zhavoronkov and Antiseferov, 1977). These authors observed maximum values of bis(dimethylthiocarbamyl) disulfide in blood, kidney, spleen, and liver 1 day after dosing. The compound remains in the system for about 15 days (Table 1).

Table 1. Tissue concentrations of bis(dimethylthiocarbamyl) disulfide after a single oral dose.[a] Values are ranges in mg/kg for various organs.

Species	Dose (mg/kg)	Number of days after administration						
		1	2	4	10	13	15	20
Sheep	150	4-15	--	0.6-5.4	Observed	--	Minimal	Minimal in spleen and kidney
Suckling pig	200	--	0.6-6.9	0.5-2.8	--	--	Trace	Not observed
Hen	300	--[b]	--	--	--	0.5-1	--	Not observed

[a]Compiled from Zhavoronkov and Antiseferov (1977).

[b]Maximum value was observed but not reported.

The excretion by cows of bis(dimethylthiocarbamyl) disulfide was studied by Zhavoronkov and Antiseferov (1977, See Table 2). These authors also observed that bis(dimethylthiocarbamyl) disulfide was not present in the eggs and excrements of hens 15 days after a single oral dose (300 mg/kg).

Table 2. Excretion of bis(dimethylthiocarbamyl) disulfide by cows after a single oral dose of 50 mg/kg.

	Time after administration of dose				
	3 h	1 d	2 d	3 d	15 d
Concentration in Milk	0.33 mg/kg	3.4 mg/kg	0.56 mg/kg	"Decreased"	"Not observed"
Concentration in Urine	0.22 mg/kg	4.9 mg/kg	1.56 mg/kg	"	"

Compiled from Zhavoronkov and Antiseferov (1977).

Comment: Vekstein and Khitsenko (1971) have studied the metabolism of the pesticide Ziram $[(CH_3)_2NCS_2)_2Zn]$ in rats. One of the metabolites of Ziram was bis(dimethylthiocarbamyl) disulfide. This compound was found to be present in the kidney in much greater concentrations than Ziram, its precursor. From day 2 to day 6 of the experiment the tissue concentration of bis(dimethylthiocarbamyl) disulfide in the kidney decreased from 6.7 µg/g to 2.4 µg/g.

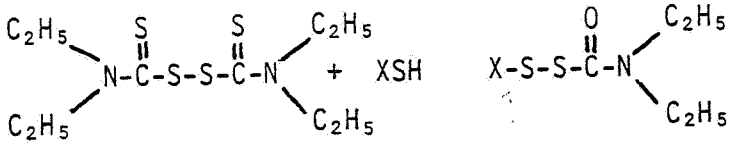
3. Biotransformation

Melson and Weigelt (1967) observed that guinea pigs dosed orally with bis(dimethylthiocarbamyl) disulfide (600 mg/kg) showed carbon disulfide in the blood. One hour after dosing, these authors reported 0.003% of the administered dose was found as carbon disulfide (CS_2) in the blood of the guinea pigs.

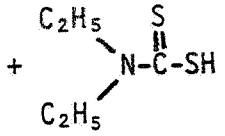
4. Biotransformation of Disulfiram

Further insight into the transformation of bis(dimethylthiocarbamyl) disulfide can be obtained by analogy with the ethyl derivative bis-(diethylthiocarbamyl) disulfide, also known as Antabuse or Disulfiram. Disulfiram is used clinically to induce aversion to alcohol (DeBruin, 1976).

Stromme (1965) has studied the biotransformation of Disulfiram. Free Disulfiram was not found in plasma, liver, or urine. Immediately after absorption, Disulfiram undergoes reactions that generate protein-bound and free diethyldithiocarbamate. Binding of Disulfiram to protein, via disulfide bonds produced by disulfide exchange, is reversible and thus not permanent. These reactions proceed as follows (x = a protein or glutathione residue):



Disulfiram



free diethyldithiocarbamate

Diethyldithiocarbamate is rapidly metabolized at a high rate along several pathways: (1) conjugation with glucuronic acid, (2) oxidation to sulfate, (3) decomposition to carbon disulfide and diethylamine, and (4) some reoxidation to Disulfiram (Stromme, 1965).

Neims et al. (1966) showed that bis(dimethylthiocarbamyl) disulfide competes with Disulfiram for binding to oxyhemoglobin in vitro. Thus, it is likely that bis(dimethylthiocarbamyl) disulfide will bind reversibly to proteins by disulfide exchange following absorption.

B. EFFECTS ON ENZYMES AND OTHER BIOCHEMICAL ASPECTS

Summary: Bis(dimethylthiocarbamyl) disulfide interferes with catecholamine metabolism. The compound inhibits numerous enzymes in vivo and produces an altered pattern of carbohydrate and lipid metabolism.

1. In Vivo Studies

a. Bis(dimethylthiocarbamyl) disulfide (600 ppm) fed to rats for 14 days decreased the redox potential of the liver, as evidenced by the significantly decreased proportions of lactate to pyruvate (Griffaton et al., 1975). These authors concluded that their results indicated an orientation of liver metabolism toward heat production rather than synthesis. They compared this finding to a state of hyperthyroidism.

b. Bis(dimethylthiocarbamyl) disulfide (600 ppm) fed to rats produced the following effects (Faudemay et al., 1975):

- o Hepatic glycogen increased 1.5-fold. Its level was more labile to perturbations such as exercise, glucose injection, and exposure than that of control animals.
- o Hepatic lipids were increased significantly. This effect was attributed to lipid mobilization from peripheral depots.

c. Bis(dimethylthiocarbamyl) disulfide was administered orally (1 g/kg) to rats; controls were left untreated. Sixteen hours later all the animals were dosed (2 g/kg, ipr) with ethanol. Four hours after being dosed with ethanol, the treated rats had 10-fold higher levels of acetaldehyde in the blood than the untreated controls (Freundt and Netz, 1977). Elevation of blood acetaldehyde is putatively the initial step in the alcohol intolerance reaction produced by the analog Disulfiram (De Bruin, 1976).

d. Synthesis of phosphatidyl choline and of ethanolamine in the isolated perfused rat liver was depressed by 33%, 16 hours after oral administration of a dose (1 g/kg) of bis(dimethylthiocarbamyl) disulfide (Leyck and Freundt, 1978).

Other in vivo inhibitory effects of the compound are summarized in Table 3.

2. In Vitro Studies: See Table 4.

Results from in vitro studies indicate that this compound binds to cytochrome P-450 and inhibits cellular respiration, glycolysis, and the activity of D-amino acid oxidase.

Table 3. In vitro inhibitory effects of bis(dimethylthiocarbamyl) disulfide.

Enzyme	Source	Dose (mg/kg)	Time of observation after start of dosing	Inhibition (%)	Reference
Monoamine oxidase	Guinea pig brain	300 mg/kg orl	4 h	68.2	Nelson and Weigelt, 1967
Alcohol dehydrogenase	Guinea pig liver	300 mg/kg orl	4 h	34.5	Nelson and Weigelt, 1967
Dopamine-β-hydroxylase	Hamster heart and adrenal	125 mg/kg ipr	4 h	89-100	Lippmann and Lloyd, 1971
γ-Glutamyl peptidase	Rabbit plasma	1 mg/kg/day for 15 d. Then 100 mg/kg on 20th day orl	15 d[a]	100	Orecchio et al., 1978
Leucine aminopeptidase	Rabbit plasma	"	15 d[a]	30	Orecchio et al., 1978
Alkaline phosphatase	Rabbit plasma	"	23 d[a]	30	Orecchio et al., 1978
Aniline hydroxylase	Rat liver microsomes	1,000 mg/kg orl	24 h	42[b]	Zemaitis and Greene, 1979
Carboxyl esterase	Rat liver microsomes	1,000 mg/kg orl	24 h	35[b]	Zemaitis and Greene, 1979
Aldehyde dehydrogenase	Rat liver	80 mg/kg orl	43 h	16	Lamboeuf et al., 1974
Aldehyde dehydrogenase	Rat gastric mucosa	80 mg/kg orl	43 h	22	Lamboeuf et al., 1974
Dopamine-β-hydroxylase	Rat heart and adrenal	125 mg/kg ipr	1 h	98-100	Lippmann and Lloyd, 1971

[a]Time of maximum inhibition.

[b]Cytochrome P-450 activity unchanged.

Table 4. In vitro inhibitory effects of bis(dimethylthiocarbamyl) disulfide.

Activity assayed	Source	Inhibitory concentrations (mM)	Inhibition (%)	Remarks	Reference
Enzymes					
Diamino acid oxidase	Hog kidney	7×10^{-3}	100	--	Neims et al., 1966
N-Ethylmorphine dimethylase	Rat liver microsomes	0.1	18	Test compound binds to Cyt P-450	Zemaitis and Greene, 1979
Aniline hydroxylase	Rat liver microsomes	0.1	19	Test compound binds to Cyt P-450	Zemaitis and Greene, 1979
Other					
Cellular respiration	Brush border cells from rat intestinal epithelium	1.9×10^{-2}	100	--	Derache et al., 1970
Glycolysis	Brush border cells from rat intestinal epithelium	9.5×10^{-5}	100	--	Derache et al., 1970

III. TOXICOLOGICAL INFORMATION

A. CARCINOGENICITY

1. Summary Comment

Four studies of two animal species indicated that bis(dimethylthiocarbamyl) disulfide (synonym, Thiram) is noncarcinogenic in rats and mice. In two other studies the experimental procedure was not adequate enough to obtain a valid negative response.

2. Evidence

Thiram was tested for carcinogenicity in rats (Lee et al , 1978*). Thiram did not alter the occurrence or latency period of spontaneous tumors in rats.

E.I. du Pont De Nemours and Co. (unpublishing report cited by Lehman, 1965) conducted chronic feeding studies of Thiram in rats. Each test and control group consisted of 12 male and 12 female rats. Feeding levels of the test compound were 0, 100, 300, 1,000, and 2,500 ppm for a period of 2 years. No difference in incidence of tumors in treated and control animals was observed.

C57BL mice (number not stated) were given weekly doses of 300 mg/kg of Thiram by gavage for 5 weeks and were killed at intervals of up to 9 months after the last dose. Of 51 mice killed at 9 months, 2 had lung adenomas (Chernov et al., 1972; cited by IARC, 1976). The duration of the experiment was inadequate (IARC, 1976). The incidence of tumors in untreated controls is not given.

Innes et al. (1969*) tested Thiram for carcinogenicity in two hybrid strains of mice. Groups of 18 male and 18 female mice of both hybrid strains received 10 mg/kg of Thiram in gelatin at 7 days of age by stomach tube and the same amount daily up to 4 weeks of age. Thereafter, mice were given 26 mg/kg of Thiram in the diet. Tumor incidence was not significantly greater for any tumor type in any sex/strain/subgroup or in the combined sexes of either strain (Innes et al., 1969; BRL, 1968).

Groups of 18 male and 18 female mice of two hybrid strains received single subcutaneous injections of 46.4 mg/kg Thiram in 0.5% gelatin on the 28th day of life. Tumor incidence was compared with that in untreated or vehicle injected controls. Tumor incidence was not increased for any tumor type in any sex/strain/subgroup or in the combined sexes of either strain (BRL, 1968*).

Brieger and Hodes exposed rabbits to inhalation of Thiram. Rabbits failed to develop tumors (Brieger and Hodes, 1948 ; cited in PHS-149; refer to Enclosure 2).

*An asterisk attached to a reference denotes that a Toxicological and Ecological Summary of the study is given in Section VII.

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Comment on Brieger and Hodes (1948): The duration of the experiment was inadequate.

For cancer incidence in humans refer to Section IV. Observations in Humans.

3. Comment

Thiram can react with nitrite under mildly acid conditions, simulating those in the human stomach, to form N-nitrosodimethylamine, which has been shown to be carcinogenic in several animal species (IARC, 1976). Thiram can also react with nitrous acid to form carcinogenic dialkylnitrosamine (Elespuro and Lijinsky, 1973).

B. MUTAGENICITY

Thiram has been found to be a mutagen in various test systems, such as the Ames test, the Rec assay, and scheduled and unscheduled DNA synthesis, and mutation induction. A large amount of data exists on the mutagenicity of this compound. Selected literature was reviewed and is summarized in Table 5.

C. TERATOGENICITY, EMBRYOTOXICITY, AND FETOTOXICITY

Summary: Thiram is teratogenic in hens, hamsters, and mice.

Evidence: The results of teratogenic studies of Thiram are summarized in Table 6.

Table 6. Teratogenic and embryotoxic effects of Thiram in laboratory animals.

Animal	Route	Test group	Control group	Dose	Observations	References
Hen	orl	10-15 F/pen[a] 2 M/pen	10-15 F/pen[a] 2 M/pen	10, 20, or 40 ppm	Teratogenic.(exophthalmia and shortened femurs).	Page, 1975
Hamster	orl	7 F 4 F	14 F 14 F	250 mg/kg, suspended in carboxymethyl cellulose, given once on 7th or 8th d of gestation	Teratogenic and embryotoxic. When Thiram was dissolved in DMSO, teratogenicity was additive.	Robens, 1969*
Mice	orl NMR strain SW strain	16-25 F 12-24 F	23 F 15 F	5-30 mg/kg, given between 6 and and 17th days of pregnancy	Teratogenic. Micrognathia, cleft palate, wavy ribs, curved limb. Most susceptible when given on day 12 of embryonic development.	Roll, 1971*
Mice	orl	20-25 F	20-25 F	10, 20, 20 mg per animal from days 5 to 15 of pregnancy	Teratogenic, Cleft palate, micrognathia, wavy ribs, distorted wavy bone extremities. At a dose of 30 mg on days 12 and 13 of gestation the number of individual malformations was greatest.	Mettiaschk, 1973

[a] 3 pens/trial

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Table 5. Mutagenicity of Thiram in various test systems.

Test system	Species/strain/ tissue	Mutagenicity	Remarks	Reference
Reverse mutations	*Salmonella typhimurium*/ TA1535, TA100, TA1538, TA98	+	In TA1535 and TA100, mutations were induced without metabolic activation. TA1538 and TA98 required metabolic activation. Cysteine and glutathione abolished mutagenic activity in all strains. Rat liver microsome fraction abolished mutagenic activity in TA1535 and TA100.	Zdzienicka et al., 1979*
	S. typhimurium/ TA1535, TA1537, TA1538, TA98, TA100	+	Thiram was found to be one of the most potent directly acting mutagens. Mutagenic effects were found on the base-substitution-sensitive strains TA1535 and TA100. Addition of a metabolizing system induced slight increase in the number of mutants in TA100.	Hedenstedt, et al., 1979
	S. typhimurium/ TA1535, TA100, TA1537, TA1538, TA98	+	Mutagenic in TA1535 and TA100. Number of revertants were at least double the control mean.	Andrews et al., 1980
	S. typhimurium/ TA1535, TA1537, TA98, TA100; *Escherichia coli*/ WP2 *her*	+	Mutagenic in TA100; not mutagenic in frameshift strains TA1537, TA1538, and TA98.	Moriya et al., 1978
	Saccharomyces cerevisiae	-	Thiram was nonmutagenic when tested in strains of *S. cerevisiae* using reversion from histidine and methionine auxotrophy as a measure of the induced mutation.	Guerzoni et al., 1976
	Escherichia coli/ WP2 *try*$^-$ (*her*$^+$ and *her*$^-$ strains)	-	Reversion to prototrophy was not significantly different from that of control.	Nagy et al., 1975
DNA synthesis (scheduled and unscheduled)	Rat/thymocytes	+	Exerted a marked inhibition of cell repair process after UV irradiation.	Rocchi et al., 1980*
	Human/lymphocytes	-	No damage induced to human lymphocyte DNA.	"
Rec assay	*Bacillus subtilis*/ H17 *Rec*$^+$, M45 *Rec*$^-$	+	Zone of inhibition in Rec$^+$ and Rec$^-$ were 0 and 2.0 mm, respectively, following exposure to a concentration of 2 µg/disk.	Kada et al., 1974; Shirasu et al., 1976 Shirasu, 1976
Multinucleation test	MO cell line	?	Thiram was toxic to MO cell line (an epithelioid-type C3H mouse embryo cell line).	Deßrabander et al., 1976
Mutation induction	*Alternaria mali* (fungus)	+	Two variants were obtained when 20,000 homokaryotic conidia were exposed to Thiram. Variants were morphologically distinguishable on 5 different media on the basis of colony size, texture, and color.	Slifkin, 1973
Chromosomal aberrations and visible mutations	Hard spring wheat (Khar'kovskaya-46)	-,+	In the first generation, no significant influence on the frequency of chromosomal rearrangement was observed following seed treatment with melted powder, aqueous solution, or 20% suspension. However, slight but reliable increase in the frequency of visible mutations in a number of traits in the second and third generations was observed.	Logvinenko and Shkvarnikov, 1974
	"	+	Frequency of chlorophyll mutations in the progeny of treated seeds increased (compared to control).	Mamalyga et al., 1974
	Mice	+	Mice, given Thiram ipr at 100 mg/kg, developed 2.5 times more chromosomal aberrations in their bone marrow cells than did mice given the same dos intragastrically.	Kurinnyi and Kendratenko, 1972
	Barley (*Hordeum vulgare*)		Thiram induced chromosome breaks which gave more than 15% fragments at metaphase. Anaphase bridges and anaphase fragments were also induced at a concentration of 250 ppm.	George et al., 1970
MISCELLANEOUS				
Nitrosamine formation		+	Nitrosation of Thiram in the presence of nitrites under conditions which resemble those found in stomach, yielded 16% dimethylnitrosamine. Dimethylnitrosamines are carcinogenic and mutagenic when tested against *E. coli* K_{12} strain in the presence of metabolizing test system.	Egert and Greim, 1976b

Prenatal effects of Thiram were studied in male and female offspring of Wistar rats. Thirty-four to 36-day-old Wistar rats were obtained from mothers that had been treated orally with 25 mg/kg of the test compound during pregnancy. Two groups consisting of 8 rats each were used as controls. Prenatal treatment with Thiram caused interference with the pattern of weight gain but did not affect behavioral deviations (Hinkova and Vergieva, 1976).

Aleksandrov (1974) studied the embryotoxic effects of vulcanization accelerators in rats. Thiram exerted embryotoxic effects (increased incidence of total preimplantation and postimplantation lethality, decreased weight of offspring) in rats when administered immediately before the onset of pregnancy and on the 4th and 11th days of pregnancy. No mention of dose levels and control animals is made.

D. SPECIAL STUDIES

1. Reproductive Effects

Results of reproductive studies of Thiram in laboratory animals are discussed in Table 7.

For reproductive effects of Thiram in humans refer to Section IV. Human Observations.

2. Toxicity of Thiram in Young Domestic Fowl

Chicks given Thiram (178 mg/kg) became lame, and their long bones developed greatly swollen epiphyses. This was due to abnormal endochondral ossification, giving rise to a thickened cartilaginous epiphyseal plate (Rasul and Howell, 1974).

3. Sedative Effects

Poitou et al. (1978) found that bis(dimethylthiocarbamyl) disulfide had a sedative effect on rats and mice. This effect in rats inhibits the conditioned avoidance response and causes hypothermia. The effect in mice is not noticeable after narcosis induced by ethanol.

4. Immunological Effects

Inhibition of immunogenesis was observed in rats after 3 months of treatment with 1/50 LD_{50} (LD_{50} not stated) bis(dimethylthiocarbamyl) disulfide (Olefir, 1978).

Perelygin et al. (1971) report that with rabbits and mice in a 6-month experiment daily intragastric administration of bis-(dimethylthiocarbamyl) disulfide:

- did not cause any stable changes in immunological reactivity at 0.1 mg/kg dose.
- reduced the phagocytic activity of leukocytes, the formation of antibodies, and the protective properties of the serum at 0.5 mg/kg
- produced a considerable and progressive decline of immunological reactivity at 1,0 mg/kg.

E. ACUTE TOXICITY

Table 8 contains a summary of data on the acute toxicity of bis(dimethylthiocarbamyl) disulfide. Table 9 contains a summary of data on the acute toxicity of a related compound, bis(diethylthiocarbamyl) disulfide (Disulfuram).

F. SHORT-TERM TOXICITY (Subacute)

Summary in Table 10.

G. LONG-TERM STUDIES (Chronic)

Summary in Table 11.

Table 7. Reproductive effects of Thiram in laboratory animals.

Animal	Route	Test group	Control group	Dose	Observations	Reference
Quail	orl	--[a] F	-- F	8.8 mg/kg·d in diet	Inhibits ovulation, 50% decrease in egg production, decrease in serum calcium level (which is estrogen controlled), alternation in the normal maturation pattern of the ova in treated birds.	Wedig et al., 1968
Quail	orl	-- F	-- F	50 ppm in diet	Decreased egg production and impaired reproduction.	Egberts et al., 1972
Quail	orl	-M -F	--	20 g Thiram/ 10 kg	Caused immediate blockade of egg laying and regression of secondary sexual characteristics in males. Histology indicated blockade of germinal line at the stage of spermatogonias and spermatocytes, total absence of spermatozoids, and regression of interstitial tissue. All the effects were reversible upon removal of the fungicide from diet.	Lorgue et al., 1975
Partridge	orl	--	--	1.6 g/kg added to feed	Inhibited egg laying within 48 h. At 4-fold lower doses, Thiram significantly increased the incidence of embryonic mortality.	Lorgue and Soyez, 1976
Dove	orl	-- M	--	1 g/kg	Inhibition of spermatogenesis.	Kuznetsov, 1974
Domestic fowl	orl	7 M	7 M	56 mg/kg, 6 d/wk as a 10% emulsion in light liquid paraffins	Retardation of testicular development, degeneration in the seminiferous epithelium of mature bird (see Enclosure 3)..	Rasul and Howell, 1974
Hen	orl	-- F	--	1/180 LD_{50}	Decreased fertility, impaired the development of chicks produced by treated hens.	Zhavoronkov et al., 1973
Hen	orl	--	--	10, 20, 40 ppm	Decreased egg production, reduced hatchability, and resulted in soft-shelled eggs.	Page, 1975
Rat and mice	ihl	- F	--	0.45-3.8 mg/m³; 6 hr/d, 5 x wk for 4.5 mo	Disturbances in estrous cycle, reduction in fertility, and lower fetus weights.	Davydova, 1973, 1974
Rat	orl	-- M	--	52 mg/kg·d; 80 wk	No effect on reproductive organs.	Lee et al., 1978*
				132 mg/kg·d; for 13 wk	Moderate tubular degeneration of the testes with atypical spermatids in the epididymis.	"
Rat	orl	20 M	--	132 mg/kg, 13 wk, daily	Causes infertility in male rats, interferes with reproduction only at doses that produced toxicity to dam.	Short et al., 1976*
Rat	orl	20 F	--	96 mg/kg daily for 14 d	Delays estrous cycle.	"
Rat	orl	20 F	--	136 mg/kg during organogenesis	Reduces litter size.	"
Rat	orl	-- F	8	Mothers received 25 mg/ kg	No specific action on the reproductive function. Increase in the number of resorptions, embryos with hematomas, and a fall in the body weight of embryos were noted only if the doses were toxic to maternal body.	Vasilos et al., 1978
Rat	orl	12 M-F	12 M-F	0, 100, 300, 1,000, and 25,000 ppm/ 2 yr	No effect on reproduction through 3 generations at 100 ppm (E.I. du Pont, 1955).	Cited by Lehman, 1965
Rat	orl	-- F	--	80 mg/kg, given at 2-wk terval	Decreased growth rate and the weight of the uterus and ovaries. The duration of the proestrus, estrus, and metestrus was decreased, and that of diestrus increased.	Ghizelea and Ozeranschi, 1973
Rat	ihl	-- F	--	3.8 mg/m³ for 2 mo	Delayed development of ovarian follicles and caused hemorrhaging in the ovarian stroma. After 4.5 months inhalation Thiram inhibited follicle development, caused degeneration of the mature follicles, induced collagenization of the ovarian stroma.	Pivenshtein and Davydova, 1974
Rat	ihl	-M -F	--	.1 mg/m³, 4 mo	Decrease in number of ovarian follicles, ovocytes and growing and maturing follicles. Males showed decrease in the index of spermatogenesis and sperm mobility.	Vaitekuniene, 1973
						"

a.--Number of animals not stated.

Table 8. Acute toxicity of bis(dimethylthiocarbamyl) disulfide (i.e., Thiram) in laboratory mammals.

Animal	Route	Test group	Dose (95 confidence limits)	Effects	Reference
Mouse	orl	--	LD_{50}: 1,350 mg/kg	--	RTECS[a]
"	orl	8-16 M	LD_{50}: 4,000 mg/kg (3,500-4,500)	Ataxia and hyperactivity followed by inactivity, loss of muscular tone, and alopecia after high doses; labored breathing and clonic convulsions before death; most deaths occurred 2-7 days after dosing.	Lee et al., 1978
		8-16 F	LD_{50}: 3,800 mg/kg (3,300-4,400)		
"	ipr	10 M/10 F	LD_{50}: 205 mg/kg (95-115)	--	Poitou et al., 1978
"	ipr	--	LD_{50}: 200 mg/kg	--	NTIS AD277-660 cited by RTECS
"	scu	--	LDLo: 46 mg/kg	--	NTIS PB223-159 cited by RTECS
Rat	orl	10 F	LD_{50}: 560 mg/kg (329-952)	--	Weiss and Orzel, 1967
"	orl	8-16 M	LD_{50}: 4,000 mg/kg (3,000-5,400)	See effects of mouse above.	Lee et al., 1978
		8-16 F	LD_{50}: 1,900 mg/kg (1,400-2,500)	"	"
"	orl	50 M	LD_{50}: 640 mg/kg (533-768)	Survival time: minimum 42 h, maximum 8 d	Gaines, 1969
"	orl	50 F	LD_{50}: 620 mg/kg (500-769)	Survival time: minimum 42 h, maximum 11 d	"
"	orl	10 M	LD1[b]: 225 mg/kg	--	"
"	orl	10 F	LD1[b]: 232 mg/kg	--	"
"	orl	10 M	LDLo: 400 mg/kg	--	"
"	orl	10 F	LDLo: 400 mg/kg	--	"
"	ipr	10 M/10 F	LD_{50}: 138 mg/kg (103-167)	--	Poitou et al. 1978
"	skn	10 M	LD_{50}: >2,000 mg/kg	--	Gaines, 1969
"	"	10 F	LD_{50}: >2,000 mg/kg	--	"
"	skn	10 M	LDLo: 2,000 mg/kg	2 of 10 rats died.	"
"	"	10 F	LDLo: 2,000 mg/kg	2 of 10 rats died.	
Rabbit	orl	--	LD_{50}: 210 mg/kg	Ingestion of high doses of Thiram and Disulfuram [LD_{50}: 2,050 mg/kg] produced definite and mostly advanced degenerative changes in liver and kidneys, while inflammatory changes were less marked and not regular. Very high doses of Disulfuram produced excessive leukopenia or aleukia, with very marked hypoplasia or aplasia of the bone marrow. On account of the higher toxicity, Thiram could not be given in correspondingly high doses, but there was also evidence of a trend of leukopenia in rabbits poisoned by high doses of Thiram. The lymphocytes were affected predominantly, and the lymph follicles of the spleen were found amotropic. With lower doses, rather a lymphocytosis and hyperplasia of the lymph follicles were observed.	Spiegel, 1947
"	orl	--	LD(min): 350 mg/kg	Gradual depression with ataxia and paralysis; fall of body temperature slowed respiration and pulse.	Hanzlik and Irvine, 1931
Cat	orl	1	LDLo: 230 mg/kg	--	"

[a] RTECS cites Hygiene and Sanitation 29: 37, 2964 as the source; however, the chemical was not found in the article.

[b] LD1 is the dose that is expected to be lethal to 1% of the animals.

[c] Indicates that no information is available.

Table 9. Acute toxicity of bis(diethylthiocarbamyl) disulfide (i.e., Disulfuram) in laboratory mammals.

Animal	Route	Dose (95% Confidence limits)	Effects	Reference
Mouse	orl	TDLo: 3,600 mg/kg, for 78 wk	Carcinogenic	RTECS
	ipr	LD_{50}: 75 mg/kg	--	RTECS
	scu	TDLo: 1,000 mg/kg	Neoplastic	RTECS
Rat	orl	LD_{50}: 1,300 mg/kg	--	RTECS
	ipr	LD_{50}: 483 mg/kg (400-541)	--	Poitou et al., 1978
Rabbit	orl	LD_{50}: 2,000 mg/kg	--	Brieger, 1947

[a]The RTECS (1980) number for bis(diethylthiocarbamyl) disulfide is J01225000.

Table 10. Short-term toxicity of bis (dimethylthiocarbamyl) disulfide in laboratory mammals.

Animal	Route	Test group (control)	Dose	Effects	Reference
Rat	orl	20 M (20 M)	30 mg/kg·d, 13 wk	Significantly reduced weight gain and food consumption (81, 64, and 229, respectively, % of control at 3 dose levels, 30, 58, and 132 mg/kg·d).	Lee et al., 1978
"	orl	20 M (20 M)	58 mg/kg·d, 13 wk	In addition to above, mild increase in blood urea nitrogen.	"
"	orl	20 M (20 M)	132 mg/kg·d, 13 wk	In addition to above, 1 death, mild elevations of fasting glucose, serum glutamic oxaloacetic transaminase, and serum glutamic pyruvic transaminase; moderate tubular degeneration of the testes with atypical spermatids in the epididymis.	"
"	orl		225, 300, 450, 600, 900, and 1,200 ppm (mg/kg diet), 29 d	The 21 parameters studied had distinctly different sensitivities to the chemical; the most sensitive parameters were the weights of the epididymal and perirenal fat pads, which were decreased by a 130-184 ppm diet, i.e., a dosage unable, or just able, to decrease food intake. The no-effect level, as derived from the weights of epididymal fat pads and considering the part of the effect not linked to the lowering of food intake by the compound itself, was estimated at 48 ppm. For liver enlargement in particular, the no-effect level was estimated as 184 ppm.	Lowy et al., 19

Table 11. Long-term toxicity of bis(dimethylthiocarbamyl) disulfide in laboratory mammals.

Animal	Route	Test group (control)	Dose	Effects	Reference
Rat	orl	24 M 24 F	Males: 5, 20, and 52 mg/kg·d, 80 wk Females: 6, 26, and 67 mg/kg·d, 80 wk	Weight gain was reduced starting at 5 mg/kg in males and 26 mg/kg in females; food consumption was reduced in proportion to the reduced weight gain; females fed 67 mg/kg·d developed alopecia and ataxia, which led to paralysis of the hind limbs; males had more severe incidence of squamous metaplasia in the thyroid and fatty infiltration in the pancreas than control males; reduced incidence of spontaneous nephritis in both males and females; periodic hematologic examination and terminal clinical blood tests did not reveal any severe changes; no alteration in the occurrence or latent period of the spontaneous tumor seen in controls was detected.	Lee et al., 1978

IV. OBSERVATIONS IN HUMANS

A. SUMMARY COMMENT

Contact dermatitis may develop in individuals exposed to bis(dimethylthiocarbamyl) disulfide. A violent nonallergic reaction may develop in individuals who ingest ethanol following exposure to bis(dimethylthiocarbamyl) disulfide. Cardiovascular and neurological disturbances have been exhibited by chronically exposed individuals.

B. CONTACT DERMATITIS

Contact dermatitis may appear first as an eczematous pruritic (itchy) eruption, which may become widespread. In severe cases, the skin may become scaly and fissured. Contact dermatitis has been observed in nonoccupationally exposed individuals who had contact with rubber products (Gaul, 1957), soaps, and fungicides (Shelley, 1964) containing bis(dimethylthiocarbamyl) disulfide. Shelley (1964) describes the case of an individual who developed an eczematous pruritic eruption after taking up golf. This individual had previously regularly used a soap containing bis(dimethylthiocarbamyl) disulfide. Contact with this compound present in the fungicide used to spray the lawn precipitated severe eruptions. The eruptions cleared at the end of the season. Dzhogan (1972) has observed an allergy to bis(dimethylthiocarbamyl) disulfide which occurred with asthma and urticaria. Positive skin test

reactions from this compound were observed in 11 of 135 patients (8%) in Kenya (Verhagen, 1974,).

C. REACTION TO ALCOHOL

A 38-year-old floriculturist dusted his plants with approximately 1 kg each of bis(dimethylthiocarbamyl) disulfide and Ortocide on a hot night, wearing mouth protection but only short pants and a shirt. Before retiring, he consumed a half-liter of beer. After a restless night, he arose with nausea, gastric pains, vomiting, and alternating sensations of heat and cold. He was hospitalized with hyperirritability, a fine tremor of the fingers and tongue, blood pressure of 150/85, slight fever, and moderate leucopenia. There were no complications on follow-up (Reinl, 1966).

In a study conducted in the Pacific Northwest, 15% of reforestation workers who were exposed to seedlings treated with bis(dimethylthiocarbamyl) disulfide reported some degree of intolerance to alcohol. Seven percent of another group also exposed to this compound in nursery work reported the same disturbance. Environmental sampling demonstrated that levels of atmospheric bis(dimethylthiocarbamyl) disulfide were within existing accepted federal standards (less than 5 mg/m^3). The amount of the compound found on the trees to which workers were exposed varied considerably. A route of exposure contributing to alcohol intolerance is likely to be by way of skin contact followed by poor hygienic practices (Apol and Thoborn, 1977).

Comment: The mechanism of the alcohol reaction has not been fully elucidated. The initial step seems to be accumulation of acetaldehyde due to inhibition of aldehyde dehydrogenase by the bis(dialkylthiocarbamyl) disulfide, followed by disturbances in biogenic amine metabolism (De Bruin, 1976).

D. OCCUPATIONAL HYGIENE

The majority of 195 persons who had had occupational exposure to bis-(dimethylthiocarbamyl) disulfide at seed control laboratories and seed farms complained of irritation of the upper air passages, headaches, fatigue, and pains in the head region. The most frequent changes observed were myocardial dystrophy (21.5%) and hepatobiliary disturbances (22%). In 7.5% of the examinees thyroid pathology was noted, including hyperplasia, diffuse enlargement, and one case of cancer. In persons working with bis(dimethylthiocarbamyl) disulfide hematologic changes were observed, including moderate hypochromic anemia and leucopenia (Kaskevich and Bezuglyi, 1973).

Investigation of the cardiovascular system in persons contacting bis(dimethylthiocarbamyl) disulfide revealed clinical forms of myocardial dystrophy in 22.4% of the persons; subclinical forms as judged from electrocardiograms were found in 53% (Kaskevich et al., 1974).

A variety of disorders of the nervous system plus cirrhosis and increased urinary excretion of adrenaline and noradrenaline have been observed in workers exposed to bis(dimethylthiocarbamyl) disulfide.

A health hazard evaluation conducted by NIOSH determined that bis-(dimethylthiocarbamyl) disulfide poses a toxic hazard to both nursery workers and tree planters in the reforestation industry in the Pacific Northwest. Environmental sampling yielded nontoxic air levels of the compound but demonstrated a considerable variation in the amount of bis(dimethylthiocarbamyl) disulfide to be found on the trees to which the workers were exposed. Clinical histories of the workers showed that the most frequent complaint involved skin problems, 45% among nursery workers and 28% among tree planters. Planters who extended their workweek beyond 5 days showed a greater incidence of systemic symptoms (headache, nausea) and alcohol intolerance (Apol and Thoburn, 1977).

The current threshold limit value in air (TLV-air) in the United States is 5 mg/m^3 of bis(dimethylthiocarbamyl) disulfide (ACGIH, 1979). The TLV in the German Democratic Republic is 1 mg/m^3. Workers exposed to this level of the chemical excrete carbon disulfide in the urine at a concentration of 300 ng/ℓ of urine (Grunewald, 1975). On the basis of animal tests, Zhilenko et al. (1976) in the U.S.S.R. recommended a TLV of 0.5 mg/m^3.

The lowest concentration in air to produce toxic effects in humans (TCLo) for bis(dimethylthiocarbamyl) disulfide is 30 $\mu g/m^3$ by inhalation over a period of 5 years (RTECS).

E. ACCEPTED LEVELS IN FOOD

The World Health Organization (WHO) recommended an acceptable daily intake (for humans, of bis(dimethylthiocarbamyl) disulfide as pesticide residue in food) of 5 µg/kg. This corresponds to a 350 ppb (µg/kg) diet for an average adult male eating 1 kg of food daily (WHO, cited by Lowy, 1979).

V. ENVIRONMENTAL INFORMATION

A. ENVIRONMENTAL RELEASE AND CONCENTRATIONS

1. Environmental Entry

There are three possible routes of environmental entry of bis-(dimethylthiocarbamyl) disulfide: from manufacturing and processing facilities, from agricultural uses (e.g., Ragunath, 1978; Odeyemi, 1979), and from vulcanized rubber products (Ganeva, 1971; Shurupova and Vlasyak, 1971).

According to the FDA (Reed, 1980,Personal communication), the pesticide use of bis(dimethylthiocarbamyl) disulfide was 0.6 million kilograms in 1974. The main use was for seed treatment for cereal grains. There were minor uses for apples, vegetables, and ornamental plants.

2. Environmental Concentrations

a. Observations

Theune and Bravenboer (1975) report that residues of bis-(dimethylthiocarbamyl) disulfide on greenhouse-grown lettuce can reach levels of 50 ppm under some treatment regimens. However, 1 to 3 ppm was a more typical range.

Comment: FDA apparently monitors for thiocarbamate pesticides on food crops, but compilations of data are not readily available (Reed, 1980, Personal communication).

b. Analytical Methods

The usual method used to monitor for dithiocarbamate pesticides on food crops and seeds is not specific, since it involves hydrolysis of the pesticides to carbon disulfide (Ghezzo and Magos, 1971; Rangaswamy et al., 1970). This method simultaneously detects a variety of pesticides, including: Thiram, Ziram, Ferbam, Maneb, Nabam, and Zineb.

There is also a compound-specific gas chromatographic method (Bowman and Beroza, 1970), but it does not appear to have been used for monitoring. A thin-layer chromatographic method has also been mentioned (Ganeva, 1971).

B. ENVIRONMENTAL FATE

Because of its pesticide uses, bis(dimethylthiocarbamyl) disulfide has been subjected to many studies relevant to its environmental fate. However, no overall projection was found. From the work reported in the literature and its physical and chemical properties, we project its environmental fate in the following comments.

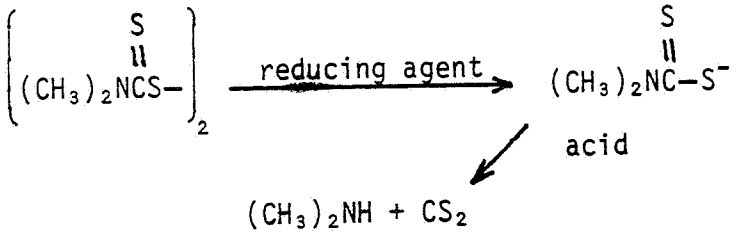
1. Partitioning Among Environmental Compartments

The low solubility and low volatility of this compound suggest that most of it will move around in the environment as solid particles. The particles will slowly dissolve in water. Also, there may be leaching from discarded rubber products into water (Ganeva, 1971).

2. Aquatic Chemistry

The half-life of bis(dimethylthiocarbamyl) disulfide in sterile and nonsterile sewage, stream water, and soil (starting concentration, 50-100 mg/ℓ) was found to be only a few days. In seawater (initial concentration, 50 mg/ℓ), the concentration decreased rapidly for a few days but then leveled off at about 15 mg/ℓ and persisted in sterile seawater for months. In nonsterile seawater, there was a slow degradation of the last portion of the compound (Odeyemi, 1979).

An explanation for the results in seawater may be as follows: The first step in degradation is reduction of the S—S bond to yield N,N-dimethyldithiocarbamate. This reaction may proceed abiotically (with appropriate reducing agents), biologically, or with cell-free extracts of certain organisms (Sud and Gupta, 1972). The second step is a pH-dependent hydrolysis of the dithiocarbamate to dimethylamine (Ayanaba et al., 1973) and carbon disulfide (Ghezzo and Magos, 1971).



If it is assumed that Odeyemi's (1979) experimental design for sterilized sewage, soil, and stream water allowed for a sufficient level of "reducing agent" to reduce all the applied bis(dimethylthiocarbamyl) disulfide while his experimental design for sterilized seawater did not allow for a sufficient level of "reducing agent,"

then his observations can be explained. Odeyemi's data might also be explained if the seawater had limited "acid content." Of course, in the ocean the supply of "reducing agent" and "acid" is not a limiting factor, and decomposition of this compound is not expected to level off at any particular concentration.

Dithiocarbamates have the ability to selectively complex copper (Kumaraswamy and Raghu, 1976). The role of dithiocarbamates in mobilizing copper in soil and in vivo is not well understood, but it does play a role in the toxic effects of these compounds (Ragunath, 1978).

3. Atmospheric Chemistry

Bis(dimethylthiocarbamyl) disulfide is not expected to enter the atmosphere except as dust. In this form, little chemical conversion is expected.

4. Biodegradation

The sensitivity of various organisms to toxicity by bis(dimethylthiocarbamyl) disulfide is linked to their ability to reduce the disulfide linkage. Sud and Gupta (1972) showed that crude cell-free extracts of sensitive organisms reduced the disulfide compounds to the dithiocarbamates more rapidly than did extracts from resistant organisms.

Subsequently, the dithiocarbamates are readily hydrolyzed to CS_2 and $(CH_3)_2NH$ (Ayanaba et al., 1973). This reaction is pH dependent and probably does not involve enzymes.

5. Bioconcentration

Bis(dimethylthiocarbamyl) disulfide is not expected to bioconcentrate because of its low octanol/water partition coefficient and rapid degradation.

6. Summary

The projected environmental fate of bis(dimethylthiocarbamyl) disulfide is shown in Figure 2.

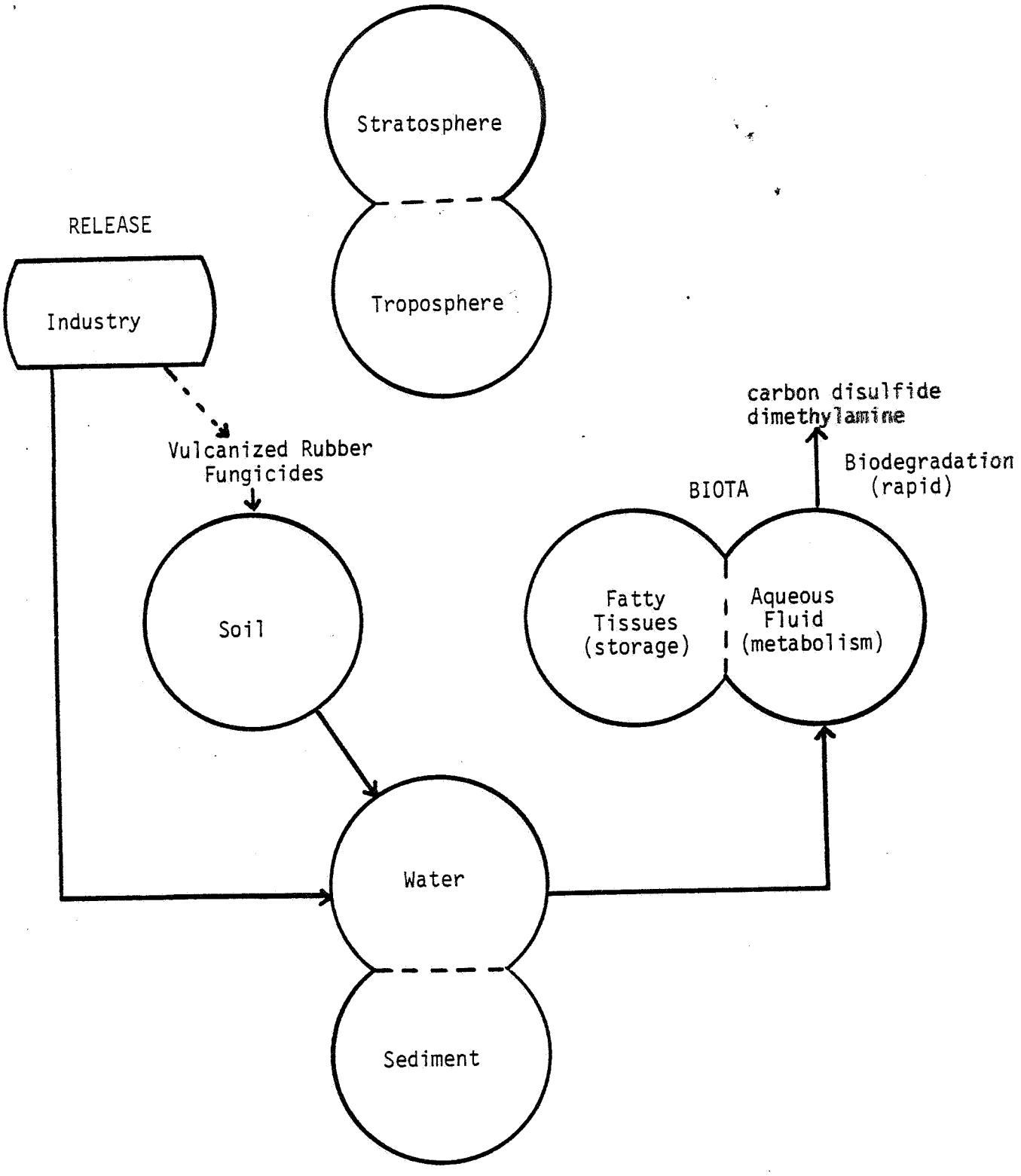


Figure 2. Projected environmental fate of bis(dimethylthiocarbamyl) disulfide. This compound is not expected to persist in any environmental compartment.

C. ECOLOGICAL EFFECTS

1. Terrestrial Ecology

Comment: The studies that establish that bis(dimethylthiocarbamyl) disulfide is fungicidal (McIntosh, 1971; Wangikar and Kodmelwar, 1977; Kochman and Macias, 1974; Tu, 1979; etc.) do not address the question as to whether the compound has irreversible deleterious effects on the terrestrial ecology. These studies will not be discussed here because they merely establish the acknowledged fungicidal properties of bis(dimethylthiocarbamyl) disulfide. However, the questions that remain unanswered from these studies, such as the effects on species diversity, the effects on nitrogen fixation, and the effects on the sulfur cycle (S-cycle), will be discussed.

a. Species Diversity

Summary Comment on Species Diversity: The diversity and growth of soil fungi were reduced after exposure to bis(dimethylthiocarbamyl) disulfide. The number of soil bacteria increased while the number of soil fungi decreased.

Observations: In view of the adverse effects of bis(dimethylthiocarbamyl) disulfide to soil fungi, Kuthubutheen and Pugh (1979) monitored the fungal species exposed to the compound to determine successional patterns and to distinguish between tolerant and recolonizing species. Bis(dimethylthiocarbamyl) disulfide was sprayed onto soil every 28 days for 12 consecutive months at an application rate of 6.7 kg/ha. Immediately after the first application, bis(dimethylthiocarbamyl) disulfide reduced the number of fungal propagules in soil by 36% compared with the control. Throughout the sampling period, the fungal numbers in soils treated with the compound did not recover sufficiently to reach control levels. The mean number of species isolated from soils treated with bis(dimethylthiocarbamyl) disulfide was 7 at the time of application and 9 thereafter, whereas the mean number of species isolated from the control was 11. A breakdown of the effects of bis(dimethylthiocarbamyl) disulfide on specific species is as follows:

Tolerant: Cladosporium cladosporioides, Mortierella minutissima Trichocladium asperum, Trichoderma hamatum, Zygorhynchus moelleri, Apiosordaria verruculosa. Initially Intolerant (recolonizer): Trichoderma viride, Penicillium spp. Intolerant: Botryotrichum piluliferum, Gliocladium roseum, Humicola fusco-atra and Sepedonium chrysospermum

After treatment of soil with 50 ppm of bis(dimethylthiocarbamyl) disulfide, the microbial balance in soil changed; the number of bacteria increased, while the number of fungi decreased (Anonymous, 1971).

b. Nitrogen Fixation

Summary Comment on Nitrogen Fixation: Bis(dimethylthiocarbamyl) disulfide does not inhibit symbiotic nitrogen fixation. Conflicting evidence leaves the question of the compound's inhibitory effects on nonsymbiotic nitrogen fixation unresolved. Studies have indicated that nitrogen-fixing organisms can be inhibited by bis(dimethylthiocarbamyl) disulfide; but at concentrations equivalent to fungicidal application rates, it is unlikely that the organisms would be severely inhibited. Nonetheless, studies measuring the process of nitrogen fixation have provided evidence indicating both inhibitory and non-inhibitory effects. This may be a result of different soil types, the state of nitrogen in the soil, the species of nitrogen-fixing organisms, etc.

Observations

Fisher (1976) studied the effect of growth and nitrogen-fixing capacity of the bacterium *Rhizobium trifolii*, symbiont with white clover, after exposure to bis(dimethylthiocarbamyl) disulfide. After applying 10, 50, 100, and 200 ppm of bis(dimethylthiocarbamyl) disulfide to plates inoculated with *R. trifolii*, the author found that radial growth expressed as percent of control was 100, 100, 90, and 90, respectively. He found that the total nitrogen content of white clover plants grown in symbiotic relationship with *R. trifolii* and exposed to 250 ppm and 500 ppm of bis(dimethylthiocarbamyl) disulfide in the soil did not significantly differ from the control ($p = 0.05$). Similarly, the effect of the same soil concentrations of bis(dimethylthiocarbamyl) disulfide on the nitrogen-fixing capacity of the excised root nodules of the white clover as determined by monitoring for ethylene was not significantly different from the control ($p = 0.05$).

Sud and Gupta (1972) reported that the nitrogen-fixing microorganisms, *Rhizobium* spp. and *Azotobacter chroococcum*, are sensitive to bis(dimethylthiocarbamyl) disulfide and to its breakdown product, dimethyl dithiocarbamate. They studied the effects of the microorganisms treated with 0.003%, 0.03%, 0.3%, and 3.0% concentrations of the compounds at varying pH. At pH 7, most bacteria were sensitive to bis(dimethylthiocarbamyl) disulfide at a 0.3% concentration and to dimethyl dithiocarbamate at a 0.03% concentration, whereas at a pH above or below 7, the bacteria were less sensitive to the compounds by an order of magnitude. *A. chroococcum* was generally more sensitive than the *Rhizobium* spp.

Hutber et al. (1979) exposed two unicellular and two filamentous cyanobacteria (blue-green algae) to bis(dimethylthiocarbamyl) disulfide concentrations in the range of 0.01 to 1,000 ppm under conditions of optimal photoautotrophic growth. The concentrations of the compound at which exponential growth was reduced by 50% and 100% of the control are listed in Table 12.

Table 12. Concentration of bis(dimethylthiocarbamyl) disulfide causing inhibition of the photoautotrophic growth of some cyanobacteria. The cyanobacteria were exposed to the compound for the mean generation of photoautotrophic growth.

Percent Inhibition	*Aphanocapsa* 6714	*Aphanocapsa* 6308	*Anabaena variabilis*	Nostoc strain Mac
50% Inhibition	50 ppm	100 ppm	50 ppm	100 ppm
100% Inhibition	>100 ppm	100 ppm	100 ppm	>100 ppm

Adapted from Hutber et al. (1979)

Tu (1979) reported that bis(dimethylthiocarbamyl) disulfide does not inhibit nonenzymatic nitrogen fixation in organic soil. The author determined whether nitrogen fixation was inhibited in soil samples treated with the compound at rates of 5 µg/g and 10 µg/g by monitoring the reduction of C_2H_2 to C_2H_4 after 2 and 7 days. Tu (1979) found no significant difference between the reduction of C_2H_2 to C_2H_4 in this treatment and that of the control ($p = 0.05$). Tu (1978) reported similar results in an identical experiment using sandy loam instead of organic soil. Contrarily, Govindaraju et al. (1975) found that bis(dimethylthiocarbamyl) disulfide applied at normal field application rates inhibited nonsymbiotic nitrogen fixation and nitrogen mineralization in sandy alluvium and loam soils. However, it had little effect on the bacterial count or the total biological activity (detected by CO_2 evolved) of the soils.

c. S-cycle

Bis(dimethylthiocarbamyl) disulfide had little deleterious effect on the oxidation of elemental S in soil (Wainwright, 1979). Triplicate soil samples were treated with 50 µg/g soil of the compound and a 1% dry-soil concentration of elemental S. At 7-day intervals, the concentrations of $S_2O_3^{2-}$, $S_4O_6^{2-}$, and SO_4^{2-} were monitored. An increase in SO_4^{2-} concentration and parallel decrease in $S_2O_3^{2-}$ concentration would indicate that the S-cycle has not been disrupted. The experimental results from bis(dimethylthiocarbamyl) disulfide-treated soil paralleled those from the control.

Comment on Wainwright (1979): The author suggests that, if inhibition of the S-cycle occurred, then the compound would be inhibiting the growth of *Thiobacilli* or S-oxidizing heterotrophic microorganisms. Since bis(dimethylthiocarbamyl) disulfide did not inhibit the S-cycle, then the compound does not inhibit the growth of *Thiobacilli* and S-oxidizing heterotrophic microorganisms to a noticeable extent.

d. Vascular Plant Toxicity

Kochman and Macias (1974) tested a formulation containing a 50% concentration of bis(dimethylthiocarbamyl) disulfide as its active ingredient for toxicity to onions. The authors applied bis(dimethylthiocarbamyl) disulfide to five different soil types at a rate of 300 kg/ha. The compound was phytotoxic in sand, peat, clay, and sandy soil but not in compost.

Comment on Phytotoxic Effects: The application rate of bis(dimethylthiocarbamyl) disulfide used by Kochman and Macias (1974) is comparable to application rates used for the compound's fungicidal soil drench uses. To avoid phytotoxic effects, a farmer applies the fungicide 1-4 weeks before planting or sowing a crop (Ragunath, 1978).

Woody species are probably tolerant to bis(dimethylthiocarbamyl) disulfide.

e. Bird Toxicity

Bis(dimethylthiocarbamyl) disulfide disrupts reproductive processes in birds (Refer to Section III.D.1.).

2. Aquatic Ecology

a. Summary Comment

Bis(dimethylthiocarbamyl) disulfide is very toxic to fish. However, in view of the degradability and low solubility of the compound in water the toxic effects are expected to be minimal.

b. Acute Fish Toxicity

Tooby et al. (1975) determined 24-hour, 48-hour, and 96-hour LC_{50} values of a formulation containing 80% bis(dimethylthiocarbamyl) disulfide as the active ingredient to the harlequin fish, *Rasbora heteromorpha* D., to be 0.02 mg/ℓ 0.012 mg/ℓ, and 0.007 mg/ℓ, respectively. This compound was among the most toxic of the 102 pesticides analyzed.

Comment on Tooby et al. (1975): Acetone was used as a carrier to dissolve the compound in water. This method may have influenced the LC_{50} values.

The 72-hour LC_{50} for channel catfish to bis(dimethylthiocarbamyl) disulfide was 0.79 ppm (Anonymous, 1971).

C. Arthropod Toxicity

Bis(dimethylthiocarbamyl) disulfide applied at a concentration of 1,000 ppm to water remained mostly on the surface and had little or no effect upon Trichogramma female adults exposed for 10 hours (Anonymous, 1971).