2,5-Dimercapto-1,3,4-thiadiazole
[CAS No. 1072-71-5]
(and Its Salts and Esters)

Review of Toxicological Literature

January 2005

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Abstract

2,5-Dimercapto-1,3,4-thiadiazole (DMcT) has been used for many years in flame-retardant products, yet there is little available information on potential health effects. It is not a high production volume chemical but is listed in the Toxic Substances Control Act Inventory. It is utilized in a variety of other applications including synthesizing polymers and heavy metal and basic salts; in cross linking halogenated polymers; as an additive in lubricating oils and greases; in electrode compositions; as an intermediate or starting material for pharmaceuticals and dyes; as a chelating agent in the analysis of metals; in purifying and treating waste; and as a biocide. An estimated 1,602 employees were potentially exposed to DMcT in the workplace between 1981 and 1983. Seven cases of allergic sensitization were reported at one manufacturing plant. It can cause chemical conjunctivitis, and eye, skin, respiratory tract, and gastrointestinal irritation in man. It caused moderate acute skin and eye irritation in rabbits. Daily oral doses of an unspecified DMcT reaction product given to rats for 28 days induced hepatocyte hypertrophy in males and females; females also had increased basophilia of the cortical tubules and increased liver and kidney weights. DMcT was not cytotoxic in rat tracheal epithelial cell cultures. It was chemopreventive in some *in vivo* tests (e.g., inhibited lung adenocarcinomas induced by *N,N*-diethylnitrosamine in hamsters and the carcinogenic activity of benzo[*a*]pyrene and *N*-butyl, *N*-(4-hydroxybutyl)nitrosamine in mice). It was also anticarcinogenic in several *in vitro* studies (e.g., for tyrosine kinase inhibition in human leukemic cells, primary human fibroblast inhibition, and for induction of reduced glutathione in buffalo rat liver cells).

Executive Summary

Nomination

2,5-Dimercapto-1,3,4-thiadiazole (DMcT), also known as bismuthiol I, was nominated in 1994 for toxicological studies by a now defunct commercial firm, Chemonics Industries, Inc., which used the compound or its disodium salt as a component of proprietary products for control of forest and wildland fires. Although used in retardant formulations for years, there is little available information on potential health effects. Evidence of continued production and use of this chemical for a variety of industrial processes combined with a lack of toxicity data provides a basis for further consideration.

Nontoxicological Data

General Information

DMcT is produced from the reaction of hydrazine and carbon disulfide. Under the 1990 and 1994 Inventory Update Rule (IUR), an aggregate production volume ranging between >500,000 and 1 million lb (226,800 and 4.5×10^7 kg) was reported. In 1986, 1998, and 2002, 10,000 to 500,000 lb (4535.9 to 226,800 kg) was reported. Producers of DMcT include Aceto Corporation, R.T. Vanderbilt Company, Inc., Alfa Aesar, Austin Chemical, ChemPacific, and Charkit Chemical Corporation. DMcT is used in synthesizing salts of strong bases, heavy metal salts, and polymers; as an ingredient in flame and scorch retardants; in cross linking halogenated polymers; as an additive in lubricating oils and greases; as a corrosion inhibitor; in electrode compositions; in photography; as an adhesion improver; as an intermediate or starting material for pharmaceuticals and dyes; as a chelating agent used to determine metals in samples; in purifying and treating waste; and as a biocide. DMcT is listed in the Toxic Substances Control Act (TSCA) Inventory. No information was available regarding DMcT levels in environmental media or its biodegradability.

Human Exposure

In the National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, an estimated 1,602 employees (130 of these female) were potentially exposed to DMcT in the workplace. Although 335 facilities were surveyed, they represented only two industries and two occupations. Workers manufacturing or using DMcT-containing compositions such as copper corrosion inhibitors, flame retardants, and photographic developers may become sensitized to DMcT. Consumer exposure is possible from use of products containing DMcT such as photographic developers and motor oils.

Toxicological Data

Human Data

DMcT may cause eye irritation, chemical conjunctivitis, skin irritation, respiratory tract irritation, and gastrointestinal irritation, including nausea, vomiting, and diarrhea. DMcT was one of 43 compounds tested in 16 men as an antidote to the skin vesicant lewisite, an arsenic compound. It was not an effective decontaminant of lewisite, producing 14 erythemas compared to 7 induced by 2,3-dimercaptopropanol. In a manufacturing plant, seven cases of industrial allergic sensitization to DMcT were reported.

Acute Toxicity

The inhalation LC_{50} value for DMcT was 3.09 mg/L (503 ppm) in rats. The intraperitoneal (i.p.) LD_{50} for DMcT was 200 mg/kg (1.33 mmol/kg) in mice (strain not provided) and 1387 mg/kg (9.231 mmol/kg) in NMRI/Han mice. An oral LD_{50} of 5000 mg/kg (33.28 mmol/kg) was reported for rats, and a dermal LD_{50} of 2000 mg/kg (13.31 mmol/kg) was reported in rabbits.

Short-term and Subchronic Exposure

When daily oral doses of an unspecified DMcT reaction product (50, 250, or 1000 mg/kg [0.33, 1.66, or 6.656 mmol/kg]) were given to rats for 28 days, no deaths were reported. The mid- and high-dose males

and females exhibited hepatocyte hypertrophy. Additionally, females had increased basophilia of the cortical tubules, predominating in the distal convoluted tubules, as well as increased liver and kidney weights.

Synergistic/Antagonistic Effects

DMcT was not effective as an antidote in isolated kidney tubules from male Sprague-Dawley rats administered arsenic compounds. In *in vivo* studies in mice, DMcT was an effective antidote for nitrogen mustard poisoning. The prophylactic antidote effects of DMcT to mechlorethamine in the animals were increased with a combination of atropine and toxogonin. DMcT was "markedly antihepatotoxic in preventive, preventive-curative, and curative tests" in carbon tetrachloride-treated rats. Additionally, it reduced gastric mucosal lesions in ethanol-treated rats.

Cytotoxicity

DMcT (0.67-67 µM [0.10-10 µg/mL]) was not cytotoxic in rat tracheal epithelial cells. Colony-forming efficiency was ≥80% of control levels.

Anticarcinogenicity

DMcT was positive for chemopreventive properties in several *in vitro* assays (e.g., strong for tyrosine kinase and free radical inhibition in human leukemic cells, for primary human fibroblast inhibition, and free radical inhibition). Additionally, it inhibited cancer-related cell changes in rat tracheal epithelial cells (e.g., benzo[*a*]pyrene [BaP] transformation) and in human foreskin epithelial cells.

In vivo, DMcT inhibited cancer-related cell changes in hamster lung induced by *N,N*-diethylnitrosamine (DEN) and mouse bladder induced by *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine. In mice, DMcT also inhibited carcinogenesis induced by BaP and by *N*-butyl, *N*-(4-hydroxybutyl)nitrosamine. In rats, DMcT was inactive in inhibiting azoxymethane-induced aberrant crypt foci.

Immunotoxicity

New mono- and di-substituted DMcT derivatives showed immunological activity in the popliteal lymph node assay in mice and in several other tests. CUVAN 826, a DMcT derivative used as a corrosion inhibitor and a metal deactivator for copper and other non-ferrous metals, was a contact sensitizer in guinea pigs.

Other Data

DMcT was a potent inhibitor of high-affinity binding of basic fibroblast growth factor in an assay using rat lung tissue membrane from which endogenous growth factor had been removed. It was a weak inhibitor of carbonic anhydrase in an *in vivo* rat study. Additionally, DMcT dose-dependently inhibited endothelin converting enzyme taken from bovine aortic clonal endothelial cell lines; the response was less than that for ethylenediaminetetraacetic acid.

Structure-Activity Relationships

Among the 21 compounds identified in the 1996 edition of *The Merck Index* from a search for *thiadiazol*, 13 had the 1,3,4-thiadiazole substructure, four the 1,2,5-thiadiazole substructure, and two each had the 1,2,4- and 1,2,3-thiadiazole substructures. None of the compounds with the 1,3,4-thiadiazole substructure were derived from DMcT, although a few had the 2- or 5-position occupied by a sulfur atom in a thioether or sulfonyl group. The physiological activities of these compounds included diuretics (acetazolamide, butazolamide, methazolamide); antibacterials (cefazedone, cefazolin, ceftezole, sulfathidole, sulfamethizole); antidiabetics (glybuthiazol[e], glybuzole); insecticide, acaricide (methidathion); herbicide (tebuthiuron [Dow Elanco's Graslan, Spike, and Perflan]); and bacteriostatic and fungistatic compounds (triafur). These compounds possess too many constituent groups to merit any

toxicity discussion in this report. In addition, no toxicity information was found for bismuthiol II, also called 3-phenyl-1,3,4-thiadiazoline-5-thione, potassium salt.

2,5-Bis(*tert*-nonyldithio)-1,3,4-thiadiazole [CAS No. 89347-09-1]

2,5-Bis(*tert*-nonyldithio)-1,3,4-thiadiazole (also known as Amoco 158) is a high volume chemical used as a copper corrosion inhibitor and extreme pressure agent in compositions of finished greases and lubricating oils and as a sulfur deactivator, corrosion inhibitor, and antioxidant in gasoline, heating oil, and Liquefied Petroleum Gas. According to the NIOSH NOES, an estimated 222,864 people (69,002 of these female) were potentially exposed to Amoco 158 in the workplace. In fathead minnows, a 96-hour LC_{50} of >1000 mg/L was determined. In Sprague-Dawley rats, an oral LD_{50} >10 g/kg and inhalation LC_{50} >2.75 mg/L were reported. In rabbits, the dermal LD_{50} was >2 g/kg. Amoco 158 was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 and *Escherichia coli* strain WP2*uvr*A, tested with and without metabolic activation. Additionally, it did not induce chromosome aberrations in Chinese hamster V79 cells.

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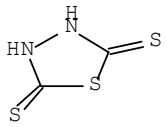
1.0 Basis for Nomination

2,5-Dimercapto-1,3,4-thiadiazole (DMcT), also known as bismuthiol I, was nominated in 1994 for toxicological studies by a now defunct commercial firm, Chemonics Industries, Inc., which used the compound or its disodium salt as a component of proprietary products for control of forest and wildland fires. Although used in retardant formulations for years, there is little available information on potential health effects. Evidence of continued production and use of this chemical for a variety of industrial processes combined with a lack of toxicity data provides a basis for further consideration.

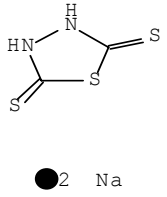
2.0 Introduction

DMcT, its salts, and an ester for which six or more Chemical Abstracts records were found are pictured below (see also Appendix B). Compounds I and IV are available commercially. Synthesis of compound VIII is described in Section 3.0 and its use is described in Section 5.0. Compounds mentioned in Section 5.0 are II and V for photography, III for lubricating oils and photography, VI for electrode compositions, and VII for flame retardants.

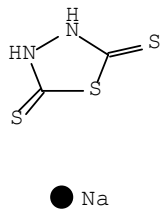
2,5-Dimercapto-1,3,4-thiadiazole (I)
[1072-71-5]



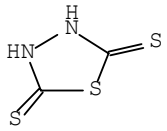
2,5-Dimercapto-1,3,4-thiadiazole disodium salt (II)
[55906-42-8]



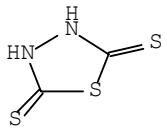
2,5-Dimercapto-1,3,4-thiadiazole monosodium salt (III)
[50530-45-5]



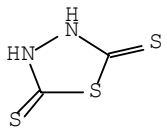
2,5-Dimercapto-1,3,4-thiadiazole dipotassium salt (IV)
[4628-94-8]



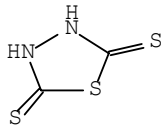
2,5-Dimercapto-1,3,4-thiadiazole monopotassium salt (V)
[54092-09-0]



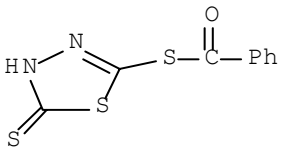
2,5-Dimercapto-1,3,4-thiadiazole dilithium salt (VI)
[140481-31-8]



2,5-Dimercapto-1,3,4-thiadiazole zinc salt (VII)
[63813-27-4]

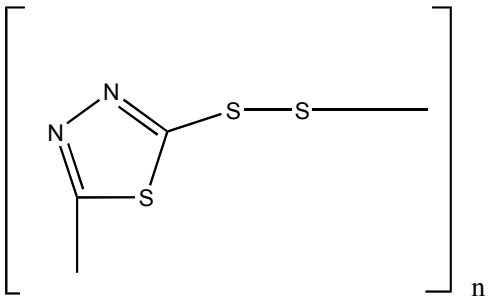


2,5-Dimercapto-1,3,4-thiadiazole monobenzoate ester; ECHO A; ECHO S (VIII)
[51988-14-8]



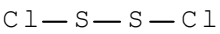
DMcT polymers pictured below were found in Chemical Abstracts records (see Appendix B). Syntheses of compounds IX and X are described in Section 5.0 under Synthesizing Other Chemicals. Use of compound XI in electrode compositions is also noted in the section. The synthesis of compound XII is described in Section 2.2, and its use is described in Section 5.0 under Lubricating Oils and Greases Additive.

Poly(1,3,4-thiadiazole-2,5-diyldithio) (IX)
[79509-46-9]

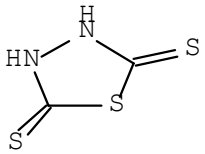


1,3,4-Thiadiazolidine-2,5-dithione, polymer with sulfur chloride (X)
[174672-51-6]

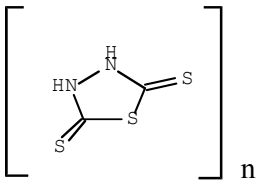
CM 1 structure



CM 2 structure

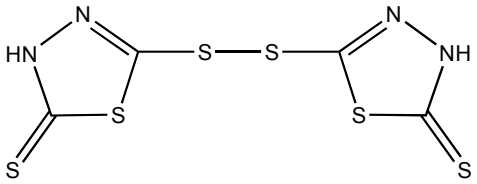


2,5-Dimercapto-1,3,4-thiadiazole homopolymer (XI)
[30555-21-6]



[Note: Actual structure not given in Registry record.]

2,5-Dimercapto-1,3,4-thiadiazole dimer (XII)
[72676-55-2]



2.1 Chemical Identification and Analysis

2,5-Dimercapto-1,3,4-thiadiazole (DMcT) [($C_2H_2N_2S_3$); mol. wt. = 150.25] is also called:

1,3,4-Thiadiazole-2,5-dithiol
1,3,4-Thiadiazolidine-2,5-dithione
2,5-Dimercaptothiadiazole
AI3-18635
Bismuthiol
Bismuthiol I
D 2
Dimercaptothiadiazole
DMTD
EINECS 214-014-1
NSC 4645
PY 61H
USAF A-8354
Vanchem DMTD

1,3,4-Thiadiazole-2,5-dithiol, disodium derivative (6CI) [($C_2H_2N_2S_3$•2Na); mol. wt. = 196.23] is also called:

2,5-Dimercapto-1,3,4-thiadiazole disodium salt

1,3,4-Thiadiazolidine-2,5-dithione, monosodium salt (9CI) [($C_2H_2N_2S_3$•Na); mol. wt. = 173.24] is also called:

2,5-Dimercapto-1,3,4-thiadiazole monosodium salt

1,3,4-Thiadiazolidine-2,5-dithione, dipotassium salt (9CI) [($C_2H_2N_2S_3$•2K); mol. wt. = 228.45] is also called:

1,3,4-Thiadiazole-2,5-dithiol, dipotassium salt (8CI)
1,3,4-Thiadiazole-2,5-di(potassiomercaptide)
2,5-Dimercapto-1,3,4-thiadiazole dipotassium salt

1,3,4-Thiadiazolidine-2,5-dithione, monopotassium salt (9CI) [($C_2H_2N_2S_3$•K); mol. wt. = 189.35]

1,3,4-Thiadiazolidine-2,5-dithione, dilithium salt (9CI) [($C_2H_2N_2S_3$•2Li); mol. wt. = 164.13] is also called:

2,5-Dimercapto-1,3,4-thiadiazole dilithium salt

1,3,4-Thiadiazolidine-2,5-dithione, zinc salt (2:1) (9CI) [($C_2H_2N_2S_3$•$^1/_2$Zn); mol. wt. = 182.95]

2,5-Dimercapto-1,3,4-thiadiazole monobenzoate ester [($C_9H_6N_2OS_3$); mol. wt. = 254.35] is also called:

Benzenecarbothioic acid, *S*-(4,5-dihydro-5-thioxo-1,3,4-thiadiazol-2-yl) ester (9CI)

Poly(1,3,4-thiadiazole-2,5-diyldithio) (9CI) [$(C_2N_2S_3)_n$; sru wt. = 148.24$_n$] is also called:

2,5-Dimercapto-1,3,4-thiadiazole-disulfur dichloride copolymer, sru [sru means Structural Repeating Unit.]

1,3,4-Thiadiazolidine-2,5-dithione, polymer with sulfur chloride (S_2Cl_2) (9CI) [$(C_2H_2N_2S_3•Cl_2S_2)_n$; mol. wt. = 285.29$_n$] is also called:

2,5-Dimercapto-1,3,4-thiadiazole-disulfur dichloride copolymer

Sulfur chloride (S_2Cl_2), polymer with 1,3,4-thiadiazolidine-2,5-dithione (9CI)

2,5-Dimercapto-1,3,4-thiadiazole homopolymer [$(C_2H_2N_2S_3)_n$; mol. wt. = 150.25$_n$] is also called:

1,3,4-Thiadiazole-2,5-dithiol, polymers (8CI)

Poly(2,5-dimercapto-1,3,4-thiadiazole)

2,5-Dimercapto-1,3,4-thiadiazole dimer [($C_4H_2N_4S_6$); mol. wt. = 298.48] is also called:

1,3,4-Thiadiazole-2(3*H*)-thione, 5,5'-dithiobis- (9CI)

1,3,4-Thiadiazole-2-thiol, 5,5'-dithiobis- (7CI)

Sources: ChemIDplus (2002); Registry (2002)

Solid-phase vibrational spectroscopy has been used to identify DMcT and derivatives in a polyaniline composite cathode in a secondary lithium cell (Pope and Oyama, 1998; Pope et al., 1997).

2.2 Physical-Chemical Properties

Property	Information	Reference(s)
	2,5-Dimercapto-1,3,4-thiadiazole (I)	
Physical State	Solid	Fisher Scientific Canada/Acros Organics (2000)
Color	Slightly yellow	MDL Information Systems, Inc. (2001)
Odor	Irritating	Fisher Scientific Canada/Acros Organics (2000)
Melting Point (°C)	162	Registry (2002)
Flash point (°C)	112	Fisher Scientific Canada/Acros Organics (2000)
Water Solubility (mol/L)	≥1 @ pH 7	Registry (2002)
	3% w/w	Fisher Scientific Canada/Acros Organics (2000)
Log of the octanol-water partition coefficient (log K_{OW})	0.204±0.783 @ pH 7	Registry (2002)
Ultraviolet spectrum in methanol	329 nm, 259 nm	HODOC (1989)
	2,5-Dimercapto-1,3,4-thiadiazole dimer (XII)	
Water Solubility (mol/L)	≥ 1 @ pH 7	Registry (2002)
log K_{OW}	1.712±1.059 @ pH 7	Registry (2002)

DMcT alkali salts precipitate heavy metals as insoluble DMcT salts from solutions of their water-soluble salts (Krzikalla and Pohlemann, 1956). In the copolymerization of DMcT with mono-, di-, and trivalent metal cations, divalent cations were found to form linear polymers, while trivalent aluminum cations formed branched polymers (Ortega et al., 1997). The cobalt, zinc, and cadmium DMcT complexes are tetrahedral; the nickel complex is octahedral; and the copper complex is square planar (Osman et al., 1980). Both thiocarbonyl (C=S) and deprotonated thiol groups act as bidentate bridging ligands. Tested as an *in vitro* chelator of copper, starch dialdehyde 2,5-dimercapto-1,3,4-thiadiazone had a metal-binding capacity of 1.25 mmol/g (Andersen et al., 1989).

DMcT degrades rapidly in acetone and methyl ethyl ketone but is stable at 2% in analytical grade methanol when freshly made (O'Driscoll et al., 1990 abstr.). Between ambient temperature and 800 °C, thermolysis of DMcT yields isothiocyanic acid, carbon disulfide, and hydrogen cyanide (Hipler et al., 2002).

Several studies were found that described DMcT reactions at electrodes due to the strong research interest in electrodes for lithium secondary batteries. The polymerization/ depolymerization reactions provide the "excellent charge-storage capabilities of electrodes based on the DMcT family of compounds" (Pope and Oyama, 1998). DMcT etched copper electrodes formed the dimer XII (Matsumoto et al., 1999). The processes of DMcT polymerization and depolymerization at electrodes do not occur with the same coulombic efficiency—that is, more electrons are consumed during polymerization than during depolymerization. Oxidation leads to polymerization via -S-S- bonds, while overoxidation and degradation of the polymer occur in its deposit on the electrode (Naoi et al., 1995). Picart and Genies (1996) studied the polymerization and depolymerization of DMcT at a polyaniline-modified electrode and characterized the redox potentials of the dithiol (dimercapto), thiolate, dithiolate, and dimer forms. During oxidation, the thiyl radical is formed, which dimerizes to the disulfide. Oxidation of the dithiolate gives the dithiolate of the dimer; further oxidation gives oligomers. Pope and Oyama (1998) studied the redox character of DMcT during polymerization and depolymerization; careful control of the protonation state avoids the electrochemical irreversibility characteristic of the processes. The electrochemical reduction of poly[dithio-2,5-(1,3,4-thiadiazole)] is accompanied by cleavage of the disulfide bond, while oxidation leads to formation of disulfide bonds; the authors concluded that the redox reaction was "quasi-reversible" (Shouji and Oyama, 1996). The presence of acid accelerates the electrochemically driven cleavage of the disulfide bond (Shouji et al., 1996). Deprotonation of DMcT by pyridine (single deprotonation) or triethylamine (double deprotonation of the thiol groups) in acetonitrile facilitates electrochemical oxidation leading to disulfide-containing dimers and polymers (Shouji et al., 1997).

Yamada et al. (2000) described a system in which DMcT was photopolymerized and deposited on the electrode. Zayed et al. (1991) studied the photolysis of DMcT in the presence and absence of singlet oxygen in methanol; three disulfides were identified.

2.3 Commercial Availability

Under the 1998 Inventory Update Rule (IUR), Aceto Corporation and R.T. Vanderbilt Company, Inc. were listed as companies reporting production information to the Environmental Protection Agency (EPA). Under the 2002 IUR, R.T. Vanderbilt Company, Inc. was the only company

reporting figures (U.S. EPA, 1998, 2002b). Other suppliers of DMcT include Alfa Aesar, a Johnson Matthey Company, Austin Chemical, which provides industrial grade DMcT, ChemPacific, and Charkit Chemical Corporation, which both offer DMcT in laboratory and/or bulk quantities (Austin Chem, undated; Block, 2002; Chem. Week, 2003; CHEMCATS, 1999-2001).

Most sources of DMcT and its dipotassium salt (IV), according to the CHEMCATS (1999-2001) database of chemical catalogs, either offer package sizes of ≤250 g (Acros Organics [Fisher Sci. USA], Aldrich, Chem Service, Fluka, ICN Pharmaceuticals, Lancaster Synthesis, TimTec, and University of Florida) or do not provide amounts (Otsuka Chem., H.W. Sands Corp., Spectrum, TCI America, Waco Chem., and Wilshire Chem.). Purities usually given are 98-99%. Pfaltz and Bauer provide amounts up to 1000 g of 95% pure DMcT.

3.0 Production Processes

DMcT is produced from hydrazine and carbon disulfide. A high yield (82.6%) was obtained by refluxing hydrazine sulfate with carbon disulfide and potassium hydroxide in ethanol for three hours (Gao et al., 1997). In a Hercules Inc. patent, DMcT was produced similarly and benzoylated with benzoyl chloride to give VIII (Richwine, 1979c).

4.0 Production and Import Volumes

In 1977, 2000 to 20,200 lb (907 to 9162.6 kg) of DMcT was produced or imported into the United States (R.T. Vanderbilt Co., Inc., 1980a). Under the 1990 and 1994 IUR, an aggregate production volume ranging between >500,000 and 1 million lb (226,800 and 4.5×10^5 kg) was reported. In 1986, 1998, and 2002, 10,000 to 500,000 lb (4535.9 to 226,800 kg) was reported (U.S. EPA, 2002a).

5.0 Uses

Synthesizing Other Chemicals

DMcT is used to synthesize salts and polymers. Treating DMcT with amines or alkalis readily produces salts of strong bases. For example, treating DMcT with ammonia or pyridine generates monoammonium and monopyridine salts, while treating DMcT with hydrazine or hydrazine hydrate gives both mono- and dihydrazine salts (Kuodis et al., 2000). Heavy metal salts may be prepared by treating DMcT with the metal salt in a polar solvent such as ethanol. The products are polymeric complexes (Gao and Yin, 1998). Polymers may be produced by treating DMcT with a sulfur chloride such as S_2Cl_2 in strongly aqueous alkaline solution at temperatures up to 100 °C (X) (Graf et al., 1996). Oxidative polymerization of DMcT gives poly(1,3,4-thiadiazole-2,5-diyldithio) (IX) [CAS Nos. 30555-21-6 and 79509-46-9]. Thus, DMcT in tetrahydrofuran "was oxidized in an N-purged system with dropwise addition of SO_2Cl_2" in an exothermic reaction that gave the polymer as a precipitate (Zisman and Williams, 1993).

Flame and Scorch Retardants

Publications on flame and fire retardants were specifically sought in CAPLUS. Chemonics Fire-Trol, Inc., USA patented fire retardant compositions for wildland fire suppression that are based on salts of thiosulfuric acid and contain DMcT [presumably as a stabilizer or the corrosion inhibitor] (Crouch, 1998). Chemonics Industries, Inc., USA, patented colored liquid fire retardant compositions for aerial application to vegetation. The compositions were apparently

based on ammonium polyphosphate and contained DMcT (Crouch and Burchert, 1996). DMcT or its sodium or other metal salts were used as a viscosity stabilizer for the galactomannan gum thickener for a fire retardant composition based on ammonium phosphate and/or ammonium sulfate. [A typical composition would provide about 17,000 lb DMcT per million gallons water after dilution of the concentrate] (Kegeler and Vandersall, 1986). Polte and Heuwer (1986) in a patent assigned to a German firm described concentrates for fire-resistant hydraulic fluids containing DMcT in low concentrations. [The preferred amount of DMcT in the formulation represented a concentration of 0.3%.] DMcT is used as a corrosion inhibitor (e.g., for aluminum) in fire retardant compositions (Vandersall and Kegeler, 1999, 2002a,b).

Occidental Chemical Corporation patented DMcT salts of barium, cobalt, nickel, manganese, copper, chromium, iron, and zinc as flame retardants for nylon; 20 parts DMcT zinc salt (VII) in 80 parts nylon 66 gave good fireproofing results (Chao and Scharf, 1983). Courtaulds PLC, UK patented a smoke suppressant additive for polyurethane foam (PUF); the final PUF contained about 6% DMcT derivative (Marriott et al., 1988). DMcT monobenzoate provided antiscorching protection to halogen-containing polymers (Richwine, 1977).

Cross Linking Halogenated Polymers

Several DMcT derivatives are patented for use in cross linking (also called curing or vulcanizing) elastomers, including the following:

- chlorinated polyethylene—The monobenzoate was used by Aarts et al. (1992); Class (1995a-c); Flynn et al. (1989). Dollinger and Davis (1992) used DMcT amine salts.
- polychloroprene—Graf et al. (1996) used the DMcT polymers.
- hexafluoropropylene-vinyl fluoride—Amine salts were used by Richwine (1978, 1979a)
- poly(vinyl chloride)—Richwine (1979b) used amine salts.
- acrylic rubber compositions—Barnes (1997) and Venkataswamy (1997) used DMcT monobenzoate.
- epichlorohydrin-ethylene oxide copolymer—Richwine (1977) used the monobenzoate; in 1981, he used amine salts.
- chlorosulfonated polyethylene—Tsujimura et al. (1999) used DMcT + zeolite to trap HCl
- nitrile rubber-poly(vinyl chloride)—see Tsujimura et al. (1999) above.
- thermoplastic polyamides and polycarbonates—DMcT or its monobenzoate were used by Venkataswamy (1997).

Relevant information was found in trade literature database records. R.T. Vanderbilt Company, Inc. developed improved DMcT cure systems for chlorinated polymers (Elastomerics, 1992). [DMcT itself cross links polymers with labile chlorine or bromine atoms rapidly, but the product has poor scorch resistance.] Some DMcT derivatives improve scorch safety (Ohm, 1998). Thiadiazole-based cure systems with DMcT have allowed the wide use of chlorinated polyethylene in cables and hoses (Rubber World, 1986). Rubber World (1995) described Echo A (which the Registry file gives as a synonym for DMcT monobenzoate) as a blend of DMcT esters. The Hercules product is used with an amine accelerator and a basic metal oxide as acid acceptor and cure activator. New peroxide/coagent cure systems are said to give better heat-aging characteristics in hose and belting than traditional sulfur/accelerator systems such as

DMcT monobenzoate. The new systems can be used with chlorosulfonated polyethylene and polychloroprene (White, 2000).

Lubricating Oils and Greases Additive

A large number of lubricant additives contain hydrazine-based sulfur compounds such as DMcT (Arch Hydrazine, 2002). DMcT and several derivatives are frequently claimed in patents for lubricants. Treating DMcT monosodium salt (III) with the reaction product of an olefin and a sulfur halide gave a product used as a lubricant additive (Caspari, 1978). In 1986, trade publications announced that Cortaulds Chemicals and Plastics' Sulphur Chemicals Group had begun to produce tonnage quantities of nitrogen/sulfur heterocyclic compounds, including a derivative of DMcT for the lubricating oil industry (Chem. Br., 1986; Chem. Mark. Rep., 1986). DMcT derivatives are used as the metal deactivator in lubricating oils and additives for synchromesh-type manual transmissions (Gahagan and O'Connor, 2003). In combustion engines, they serve as the silver protective agents for the lubricating oil (Hutchison and Moore, 1992). Lubricants patented by Bridgestone Corp., Japan that are suitable for use in drawing steel filament and cord for tire manufacture included DMcT monocation salts (Fukushima and Kondo, 2002). A 1991 patent assigned to a German company described a biodegradable lubricating grease containing DMcT derivatives for motor vehicles (Huber and Fischer, 1991). Showa Shell Sekiyu K.K. and Toyota Motor Corp. were awarded a Japanese patent for a lubricating grease composition that included DMcT dimer (Saito et al., 2001). Wei et al. (1995) investigated antiwear, antioxidation, and anticorrosion behavior of DMcT derivatives.

Other Corrosion Inhibitor Applications

Standard Oil Co. patented alkyl derivatives of DMcT as inhibitors of sulfur corrosion of copper (Blaha, 1973). Hori and Ueda (1990) reported use of monosodium, monopotassium, or monoethanolamine salts of DMcT for inhibition of corrosion of brass and steel plated with tin, nickel, or chromium. The diallylamine salt of DMcT is useful as a corrosion inhibitor and stabilizer for antifreeze solutions and engine coolants (Karol and Donnelly, 1997). DMcT and its dimer were used in pigment-grade corrosion-inhibiting compositions for metal coatings and paints (Sinko 1999, 2000).

Electrode Compositions

Published reviews (e.g., Battery EV Technol., 1997 and Freemantle, 1995) described research efforts in Japan on the development of high-energy, rechargeable secondary batteries with lithium anodes. DMcT homopolymer (XI) and DMcT lithium salts (VI) have been mentioned in several patents and articles for use in electrode compositions for lithium secondary batteries, electrochromic devices, and other electronic uses (e.g., Lampert et al., 1993, 1994). Many of the recent patents have been assigned to Matsushita Electric Industries. For example, Nakagiri and Eda (2001) described electrode compositions with DMcT, its dilithium salt, or a palladium salt useful for lithium batteries, electrochromic displays, sensors, and memory devices. Work at the University of Wyoming described oxidative intercalation of DMcT dimer into thin films of vanadium pentoxide (Shouji and Buttry, 1999a,b, 2000). Numerous additional publications and patents are available on this use of DMcT.

Photography

DMcT is a general photographic chemical (Charkit Chem. Corp., undated). The following examples of DMcT use in photography do not represent an exhaustive search: DMcT and its disodium salt (II) were used to form silver salts that stabilized photographic layers (Evva, 1967). DMcT (up to 1%) was used in the composition of a silver halide nuclear emulsion (Ilford Imaging Ltd., 2000). Fuji Photo Film Co., Ltd. holds a patent for the use of DMcT monopotassium salt (V) or DMcT dithiocarbamate in silver-based photographic materials for metal reliefs, printed circuits, and printing plates (Inoue et al., 1974). DMcT was mentioned as a component of the novel ascorbic acid developer liquid for silver halide film processing in a more recent Fuji Photo Film Co. patent (Okutsu et al., 1997). In another Fuji patent, a gold- and chalcogen- (e.g., selenium-) sensitized silver halide emulsion was developed by compositions containing mercaptothiadiazoles (including DMcT) and 2-mercaptobenzimidazoles (Ozeki, 1997). Eastman Kodak Co. patented a silver halide photographic material that used DMcT or its monosodium salt to release a photographic development inhibitor to reduce interlayer interimage effects (Poslusny et al., 1992). Photodimerization of DMcT in solution with deposition of the polymer on an electrode has potential as writing images (Yamada et al., 2000).

Adhesion Improver

DMcT salts (monopotassium, monosodium, or monodicyclohexylamine) were used in compositions to improve heat-resistant adhesion between steel cord and rubber in tires (Fujiki, 1997). Use of DMcT monobenzoate as the cross linking agent improved compositions for bonding and sealing chlorinated polyethylene roofing membranes used for flat roofs (Jones and Warren, 1993).

Chemical Intermediate or Starting Material

DMcT and derivatives are used as intermediates or starting materials in the synthesis of pharmaceuticals (frequently antibacterials) and dyes (e.g., Amiel et al., 1995; Labeeuw and Salhi, 1983; Morita et al., 1987; and Shudo and Ichikawa, 1995a,b), as well as other materials. DMcT was among the heterocyclic compounds used to produce aphidocolane derivatives to be tested as antineoplastic agents (Hiramitsu et al., 1994). Hoechst A.-G. patented immunostimulant and cytostatic compounds produced from sulfur-containing heterocyclic compounds, including DMcT (Scheunemann et al., 1986). Supuran et al. (1996) used DMcT to produce 1,3,4-thiadiazole-2,5-bissulfonamide, "the lead molecule for designing important classes of pharmacological agents, such as benzothiadiazine diuretics." Fields (1984) produced an antimicrobial, rust-inhibiting, surfactant derivative by C8 alkylation of DMcT followed by peroxide oxidation. DMcT and polymers were also used to produce nanocomposite films with high electrical activity (Gong et al., 1998).

Analytical Reagent

DMcT is a chelating agent that is used to determine metals in industrial, environmental, and biological samples (e.g., Ahmed and Mosaddeque, 2001 [lead]; Ahmed et al., 2002 [copper]; Ben-Bassat and Alony, 1976 [lead]; Chiang et al., 1989 [aluminum, arsenic, nickel, and selenium]; and Li et al., 1988 [cadmium and zinc]). Maxwell and Smyth (1996) reported satisfactory use in the determination of cadmium, lead, and zinc in river waters by anodic stripping voltammetry.

Purification and Waste Treatment

Buckl (1984) patented compositions containing DMcT salts and bentonite or zeolite sorbents for heavy metal ion removal from industrial and municipal wastewaters. Hudson et al. (1986) described a potential wastewater treatment process for cadmium removal by complexation and polymerization with DMcT. Lessi et al. (1996) used the complexing property to remove trace metal contamination (cadmium, cobalt, iron(III), lead, nickel, and zinc) from commercial ethanol for use as engine fuel. DMcT has also been employed as a trapping agent for sulfonic acids from penicillin (Micetich et al., 1985).

Biocides

Domenico (1999, 2000) patented biocidal compositions in which antimony, arsenic, or bismuth is complexed with certain thiol compounds such as DMcT. The biocidal compositions were said to be useful as a disinfectant, a preservative, and bactericidal, bacteriostatic, antibiofilm, antifungal, and antiviral agents. Hasegawa et al. (1973) patented thiadiazole fungicides, such as DMcT monobenzoate, active against leaf blight of rice and canker of oranges. Mollin et al. (1986) discussed the relation of antimycobacterial activity to complex formation, and DMcT was indexed in the EMBASE record. Somers (1958) studied plant tissue and fungal spore uptake of DMcT and its C_1-C_8 *n*-alkyl thioethers. Thorn and Ludwig (1958) reported that such compounds are effective fungicides but appear to be too toxic to the infected plants to be used practically.

Miscellaneous Uses

The polycarbonate Lexan 145 was protected from yellowing during gamma-ray sterilization by a stabilizing composition containing DMcT and 2-mercaptobenzothiazole (Avakian, 1989). DMcT dipotassium salt has been added as a brightener to baths for electrolytic deposition of copper (Borhani, 1981). DMcT dimer, trimer, and tetramer were useful as brightening-leveling additives for copper-plating electrolytic baths (Valiuliene and Rutavicius, 1999). In an early patent, colorants for leather, soap, paper, plastics, and spin-dyed fibers contained heavy metal salts of DMcT (Krzikalla and Pohlemann, 1956). DMcT monopotassium salt will prevent browning of fresh-cut fruits and vegetables (Subaric et al., 2000). DMcT dimer and oligomers may be used in smudge-proof aqueous inks (Takagishi, 2000). Metal complexes of DMcT can be used for the treatment of sepsis and septic shock (Domenico and Saha, 1999).

6.0 Environmental Occurrence and Persistence

No data were available.

7.0 Human Exposure

According to the National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, an estimated 1602 workers (130 of these female) were potentially exposed to DMcT in the workplace. Although 335 facilities were surveyed, they represented only two industries and two occupations (NIOSH, 1983; cited by RTECS, 2001). Workers manufacturing or using DMcT-containing compositions such as copper corrosion inhibitors, flame retardants, and photographic developers may be exposed to DMcT (O'Driscoll et al., 1990 abstr.). Consumer products that might contain DMcT include photographic developers and motor oils. Analytical chemists may use DMcT in methods for the determination of heavy metals. No studies specifically quantifying human exposure levels were located.

8.0 Regulatory Status

DMcT is listed in the TSCA Inventory (CHEMLIST, 2002). Announcements of receipts of R.T. Vanderbilt Company, Inc. premanufacturing notices (PMNs) for DMcT derivatives have appeared several times in the *Federal Register*.

9.0 Toxicological Data

9.1 General Toxicology

9.1.1 Human Data

DMcT may cause eye irritation, chemical conjunctivitis, skin irritation, respiratory tract irritation, and gastrointestinal irritation with nausea, vomiting, and diarrhea (Fisher Scientific Canada/Acros Organics, 2000). During acute inhalation exposure, it can produce irritation to mucous membranes and the upper respiratory tract, and upon short-term exposure, it can cause skin irritation and severe eye irritation (MDL Information Systems Inc., 2001).

DMcT (0.4 M in propylene glycol) was one of 43 compounds tested in 16 men as an antidote to the skin vesicant lewisite, an arsenic compound. It was not an effective decontaminant of lewisite, producing 14 erythemas compared to 7 induced by 2,3-dimercaptopropanol (Thomson et al., 1947). In a manufacturing plant, seven cases of industrial allergic sensitization to DMcT were reported (O'Driscoll et al., 1990 abstr.). In patch tests with an unspecified DMcT derivative formulated on amorphous silica, a worker had an allergic skin reaction to the covered test and a mild reaction to the uncovered test, while another individual had a mild reaction to the occluded patch test (R.T. Vanderbilt Co., Inc., 1995).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

No data were available.

9.1.3 Acute Exposure

Acute toxicity values for DMcT are presented in **Table 1**.

Table 1. Acute Toxicity Values for DMcT

Route	Species (sex and strain)	LC_{50}/LD_{50}	Reference(s)
inh	Rat (sex and strain n.p.)	LC_{50} = 3.09 mg/L (503 ppm)	R.T. Vanderbilt Co., Inc. (2001)
i.p.	Mouse (sex and strain n.p.)	LD_{50} = 200 mg/kg (1.33 mmol/kg)	NTIS (1977, cited by RTECS, 2001)
	Mouse (sex n.p.; NMRI/Han)	LD_{50} = 1387 mg/kg (1256-1531 mg/kg) (9.231 [8.359-10.19 mmol/kg])	Joos (1971); Rauen et al. (1971a)
p.o.	Rat (sex and strain n.p.)	LD_{50} = 5000 mg/kg (33.28 mmol/kg)	R.T. Vanderbilt Co., Inc. (2001)
Dermal	Rabbit (sex and strain n.p.)	LD_{50} = 2000 mg/kg (13.31 mmol/kg)	R.T. Vanderbilt Co., Inc. (2001)

Abbreviations: inh = inhalation; i.p. = intraperitoneal; LC_{50} = lethal concentration for 50% of test animals; LD_{50} = lethal dose for 50% of test animals; n.p. = not provided; p.o. = *per os* (oral)

DMcT caused moderate acute skin and eye irritation in rabbits (R.T. Vanderbilt Co., Inc., 2001). In another study, DMcT (100 mg [0.665 mmol]) produced severe irritation in the eyes of the animals. Application, followed by a 30-second rinse, yielded the same effect (R.T. Vanderbilt Co., Inc., 1980b).

9.1.4 Short-term and Subchronic Exposure

When daily oral doses of an unspecified DMcT reaction product (50, 250, and 1000 mg/kg [0.33, 1.66, or 6.656 mmol/kg]) were given to rats for 28 days, no deaths were reported. The mid- and high-dose males and females exhibited hepatocyte hypertrophy. Additionally, females had increased basophilia of the cortical tubules, predominantly in the distal convoluted tubules, as well as increased liver and kidney weights (R.T. Vanderbilt Co., Inc., 1991).

9.1.5 Chronic Exposure

No data were available.

9.1.6 Synergistic/Antagonistic Effects

Details of the following studies are presented in **Table 2**.

In Vitro Studies

DMcT was not effective as an antidote in isolated kidney tubules from male Sprague-Dawley rats administered arsenic compounds (Mückter et al., 1993).

In Vivo Studies

DMcT was an effective antidote for nitrogen mustard [mechlorethamine hydrochloride or *N,N*-bis(2-chloroethyl)methylamine] poisoning in mice (Rauen et al., 1971a). The prophylactic antidote effects of DMcT to mechlorethamine in the animals were increased with a combination of atropine and toxogonin (Rauen et al., 1971b). It, however, was unable to suppress cadmium absorption in mice (Andersen et al., 1989). DMcT was "markedly antihepatotoxic in preventive, preventive-curative, and curative tests" in carbon tetrachloride-treated rats (Rauen et al., 1973a,b). Additionally, it reduced gastric mucosal lesions in ethanol-treated rats (Kusterer and Szabo, 1987).

9.1.7 Cytotoxicity

DMcT (0.67 to 67 μM [0.10-10 μg/mL]) was not cytotoxic in rat tracheal epithelial cells. Colony-forming efficiency was ≥80% of control levels (Steele et al., 1990).

9.2 Reproductive and Teratological Effects

No data were available.

9.3 Carcinogenicity

No data were available.

9.4 Initiation/Promotion Studies

No data were available.

Table 2. Synergistic/Antagonistic Studies with DMcT

Species, Strain, and Age, Number, and Sex of Animals, or Substrate and Source	Chemical Form, Purity, Route, Dose, Duration, and Observation or Incubation Period for DMcT	Chemical Form, Purity, Route, Dose, Duration, and Observation or Incubation Period for Other Chemical	Results/Comments	Reference
***In Vitro* Studies**				
Kidney tubule cell suspension from Rats, Sprague-Dawley, age and sex n.p., 4-6 per dose	DMcT, concentrated stock solution in 0.1 mol/L $NaHCO_3$, at pH 7.4	A mixture of arsenite or oxophenylarsine (0.1 mL of stock solution) was added to cell suspension (10 mg protein/mL). A control received buffer only. Gluconeogenesis proceeded for 1 h at 37 °C. After 30 min., DMcT was added. Glucose and cell viability was measured every 10 min.	DMcT was not an effective antidote to either arsenite or oxophenylarsine. DMcT and arsenite produced glucose formation 17.5 ± 4.5% controls; DMcT and oxophenylarsine-produced glucose formation 6.2 ± 5.6% controls.	Mückter et al. (1993)
***In Vivo* Studies**				
Mice, NMRI/Han, age n.p., 8-12M per dose	DMcT, purity n.p., once i.p., 470 mg/kg (3.13 mmol/kg)	Mechlorethamine HCl, purity n.p., i.p. Increasing doses were used against a constant dose of DMcT.	DMcT was an effective antidote to mechlorethamine HCl. The DRF was 2.8. DRF = $\frac{LD_{50}\text{ mechlorethamine HCl with DMcT}}{LD_{30}\text{ mechlorethamine HCl without DMcT}}$	Rauen et al. (1971a)
Mice, NMRI/Han, age n.p., 8-12M per dose	DMcT, purity n.p., once i.p., 470 mg/kg (3.13 mmol/kg)	Mechlorethamine, purity n.p., i.p., in 0.2 M phosphate buffer at pH 7.2. DMcT was given with and without 2 mg atropine and 72 mg/kg toxigonin/mouse i.m. 15 min before dosing.	DMcT was a more effective antidote with atropine and toxigonin than without them. The DRF was 2.75 (2.5-3.2) without atropine and toxigonin. The DRF was 2.9 (2.6-3.15) with atropine and toxigonin.	Rauen et al. (1971b)
Mice, NMRI, age n.p., 10M per dose	DMcT in 0.5 percent $NaHCO_3$ at pH 7.4, 0.01 mL/g, i.p.; Control: 10 mL/kg saline, s.c.	Arsenite, 0.2 mmol As/kg, s.c., 30 min before antidote administration.	No animals survived. There was no significant difference in survival time in hours between experimental and control.	Mückter et al. (1993)

Table 2. Synergistic/Antagonistic Studies with DMcT (Continued)

Species, Strain, and Age, Number, and Sex of Animals, or Substrate and Source	Chemical Form, Purity, Route, Dose, Duration, and Observation or Incubation Period for DMcT	Chemical Form, Purity, Route, Dose, Duration, and Observation or Incubation Period for Other Chemical	Results/Comments	Reference
Mice, NMRI, age n.p., 10M per dose	DMcT in 0.5 percent $NaHCO_3$ at pH 7.4, 0.01 mL/g, i.p.; Control: 10 mL/kg saline, s.c.	Oxophenylarsine, 0.02 mmol As/kg, s.c., 30 min before antidote administration.	No animals survived. There was no significant difference in survival time in hours between experimental and control groups.	Mückter et al. (1993)
Mice, CBA/bom, 7- to 8-wk-old, 8 per dose, sex n.p.	Starch dialdehyde DMcT was produced from DMcT, purity n.p., and starch dialdehyde, purity n.p., condensed in the presence of HCl. Dose: 2 g/kg (13 mmol/kg) by stomach tube.	$CdCl_2$, purity n.p., 0.27 mmol/kg once by stomach tube 15 min before starch dialdehyde DMcT administration. Animals were weighed and counted on days 1, 2, 3, 4, 7, and 10. Surviving animals were killed on day 10.	DMcT was unable to suppress Cd absorption. One animal died. The intestinal Cd absorption was 104% of control. Brain, lungs, heart, testes, spleen, kidneys, liver, stomach with duodenum, and the rest of the gastrointestinal tract were evaluated for Cd absorption. DMcT increased the distribution of Cd to the heart and lungs relative to controls as expressed as % of residual whole body burden. **Organs** / **Experimental (%)** / **Controls (%)** Heart / 0.38 ± 0.09 / 0.27 ± 0.07 Lungs / 0.34 ± 0.06 / 0.17 ± 0.06	Andersen et al. (1989)
Rats, strain, age, number, and sex n.p.	DMcT, purity n.p, i.p.; 235 mg/kg (1.56 mmol/kg) 15 min before CCl_4 administration; 120 mg/kg (0.799 mmol/kg) 1 h after CCl_4 administration; and 50 mg/kg (0.33 mmol/kg) 2 and 7 h after CCl_4 administration.	CCl_4, purity, route, and doses n.p.	DMcT was antihepatoxic. The protective/curative effect was based on decreases in serum enzyme activities of glutamate-oxalacetate transaminase, glutamate-pyruvate transaminase, and cholinesterase. The suggested mechanism was that thiol groups trapped $\bullet CCl_3$.	Rauen et al. (1973a)
Rats, Wistar, "adult" (age n.p.), M, number n.p.	DMcT, purity n.p., i.p.; 470 mg/kg (3.13 mmol/kg)	CCl_4, purity n.p., by gavage, (2.5 mL) 1:1 mineral oil.	DMcT inhibited phosopholipid peroxidation in rat liver endoplasmic reticulum. The suggested mechanism was that thiol groups trapped radicals.	Rauen et al. (1973b)

Table 2. Synergistic/Antagonistic Studies with DMcT (Continued)

Species, Strain, and Age, Number, and Sex of Animals, or Substrate and Source	Chemical Form, Purity, Route, Dose, Duration, and Observation or Incubation Period for DMcT	Chemical Form, Purity, Route, Dose, Duration, and Observation or Incubation Period for Other Chemical	Results/Comments	Reference
Rats, Sprague-Dawley, age and number n.p., F	DMcT, purity n.p., once s.c., 60 mg (0.40 mmol) per 100g ethanol	Absolute ethanol, (1 mL for 150-200 g rats and 0.5 mL for 50-80 g rats), injected 30 min after DMcT. The rats were killed 1 h later.	Hemorrhagic mucosal lesions were measured by computerized planimetry. Glandular stomach sections were processed for histologic examination. DMcT reduced ethanol-induced gastric mucosal lesions by 59%. It was twice as protective as 2-amino-5-mercapto-1,3,5-thiadiazole.	Kusterer and Szabo (1987)

Abbreviations: CCl_4 = carbon tetrachloride; DRF = dose reduction factor; F = female(s); h = hour; i.m. = intramuscular; i.p. = intraperitoneal; M = male(s); min = minute(s); n.p. = not provided; s.c. = subcutaneous; wk = week(s)

9.5 Anticarcinogenicity

Details of the following studies, except where noted, are presented in **Table 3**.

In Vitro Studies

DMcT was reported to inhibit cancer-related cell changes in the rat tracheal epithelial cell assay and the human foreskin epithelial cell assay. [No study details were provided] (Kelloff et al., 1993). DMcT inhibited benzo[*a*]pyrene (BaP) transformation of cultured rat tracheal cells (Steele et al., 1990). It was also positive for chemopreventive properties in six *in vitro* assays (Sharma et al., 1994).

In Vivo Studies

DMcT inhibited cancer-related cell changes in two tests: hamster lung and mouse bladder induced by *N,N*-diethylnitrosamine (DEN) and *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine, respectively. [No study details were provided] (Kelloff et al., 1993). In mice, DMcT inhibited carcinogenesis induced by BaP (Kallistratos, 1975) and by *N*-butyl, *N*-(4-hydroxybutyl)nitrosamine (Steele et al., 1994). In rats, DMcT was inactive in inhibiting azoxymethane-induced aberrant crypt foci (Barnes et al., 1993 abstr.; Pereira et al., 1994). In hamsters, DMcT inhibited carcinogenesis induced by DEN (Steele et al., 1994).

9.6 Genotoxicity

No data were available.

9.7 Cogenotoxicity

No data were available.

9.8 Antigenotoxicity

No data were available.

9.9 Immunotoxicity

Kowalczyk-Bronisz et al. (1995) reported that new mono- and di-substituted DMcT derivatives showed immunological activity in the popliteal lymph node assay in mice and in several other tests. No details were provided in the abstract. CUVAN® 826 [CAS No. 159250-69-8], a DMcT derivative used as a corrosion inhibitor and a metal deactivator for copper and other non-ferrous metals, was a contact sensitizer in guinea pigs, according to the Buehler test (R.T. Vanderbilt Co., Inc., undated, 2001). The induction phase was done with 15% w/v CUVAN® 826 in mineral oil; the challenge was made with 5% CUVAN® 826 solution; and rechallenges were made with 2.5% and 1% CUVAN® 826 (Pestic. Toxic Chem. News, 1996).

9.10 Other Data

DMcT was found to be ineffective in inhibiting *in vitro* RNA alkylation by tris-(2-chloroethyl)-amine (Sznicz et al., 1981). It, however, was a potent inhibitor of high-affinity binding of basic fibroblast growth factor in an assay using rat lung tissue membrane from which endogenous growth factor had been removed (Herblin and Barbera, 1995). DMcT inhibited jack bean urease in a dose-dependent manner, and its effectiveness was enhanced slightly by hydrogen peroxide; the reaction was partially reversible (Gould et al., 1978). It was a weak inhibitor of carbonic anhydrase in an *in vivo* study in rats (Kusterer and Szabo, 1987). Additionally, DMcT dose-

Table 3. Anticarcinogenicity Studies of DMcT

Species, Strain, and Age, Number, and Sex of Animals, or Cell Source and Assay	Chemical Form, Purity, Route, Dose, for DMcT	Other Chemical Form, Purity, Route, Dose, and Duration or Observation Period	Results/Comments	Reference
***In Vitro* Studies**				
Human leukemic HL-60 cells (inhibition of tyrosine kinase test)	DMcT, purity n.p., (0.0001, 0.001, 0.01, 0.1, or 1.0 mM), with 5 % CO_2	TPA (0.1 μM) to induce tyrosine kinase added immediately before the addition of DMcT or biochanin A as a positive control (0.001 M). Incubation period: 24 h at 37 °C.	DMcT classified as "strongly inhibitory" of tyrosine kinase activity because it met one of the following: dose-dependent inhibition, all doses inhibitory, or two doses showed 100% inhibition; or three doses showed inhibition greater than 50%.	Sharma et al. (1994)
2C5 cells from rat tracheal epithelium, (inhibition of ornithine decarboxylase assay)	DMcT, purity n.p., (0.0001, 0.001, 0.01, 0.1, or 1.0 mM)	TPA (0.5 μM) or TPA plus DMcT or DFMO (10 μM) as a positive control of ornithine decarboxylase inhibition. Incubation period: 5 h at 37 °C.	DMcT was listed as "highly" positive for ornithine decarboxylase inhibition, because it exhibited dose-dependent inhibition or inhibition at all doses.	
Primary human fibroblasts (inhibition of PADPR assay)		Propane sultone (41 nM) alone or with a positive inhibitor, 3-aminobenzamide (5 mM), or DMcT for 18 h at 37 °C with 5% CO_2.	DMcT was classified as a strong inhibitor of PADPR because all doses showed either > 20% inhibition or three doses showed > 60% inhibition.	
BEAS-2B cells from human bronchial epithelium (carcinogen-DNA binding assay)		[^{3}H]B[*a*]P (1 μM) alone for 4 h at 37 °C or after pretreating with DMcT or with ellagic acid (0.1 mM) for 2 h at 37 °C.	DMcT was classified as strong inhibitor of carcinogen-DNA binding. A compound was classified as a strong inhibitor if either 3 doses showed > 20% inhibition or 2 doses showed > 40% inhibition.	
Buffalo rat liver (BRL3a) cells (glutathione assay)		DMcT was added to the cells to induce GSH. The mixture was incubated for 24 h.	DMcT tested positive for induction of reduced GSH because one dose induced > 10% of media control.	
Primary human fibroblasts or HL-60 cells (free radical inhibition assay)		TPA (8 μM) was added to the cells to induce free radical formation, followed by addition of DMcT and cytochrome c (160 μM). The mixture was incubated for 20 min at 37 °C. Controls: Bovine serum albumin was a blank, and superoxide dismutase was a positive inhibitor.	DMcT tested 'highly' positive for free radical inhibition, rated so because either all doses were inhibitory or two doses showed > 30% inhibition.	

Table 3. Anticarcinogenicity Studies of DMcT (Continued)

Species, Strain, and Age, Number, and Sex of Animals, or Cell Source and Assay	Chemical Form, Purity, Route, Dose, for DMcT	Other Chemical Form, Purity, Route, Dose, and Duration or Observation Period	Results/Comments	Reference
Rat tracheal epithelial cells	DMcT (98% purity (according to CHEMCATS, 2001), 0.67 to 67 µM, dose n.p.	B[*a*]P (10 µg) was administered to 20,000 viable cells/60-mm dish on day 1 for 24 hours. The chemical was removed, then DMcT was added twice, 14 days apart. Cultures were maintained at 5% CO_2 in air incubator at 37 °C. On day 30, cultures were fixed and stained with methylene blue. The experimental cultures were compared with cultures with B[*a*]P only and to cultures with solvent only.	DMcT scored positive for effectiveness in B[*a*]P transformation because % of transformation was –7.79% (less than 80%). Formula: % B[*a*]P transformation = $\frac{\text{(\% agent + B[a]P) - \% solvent transformation}}{\text{\% B[a]P transformation - \% solvent transformation}}$	Steele et al. (1990)
***In Vivo* Studies**				
Mice, NMRI, 4- to 5-wk-old, 28-30 F per dose	DMcT (20 mg), purity n.p., s.c.	3,4-B[*a*]P (2.52 mg) and DMcT, once s.c. Mice were observed for more than 7 mo.	DMcT strongly inhibited carcinogenesis. In the experimental group, 3 of 28 mice died in 7 mo. After 345 days 23 of 28 mice were still alive. In the 3,4-B[*a*]P only group, all 30 mice had tumors in 7 mo, and all died ~200 days. There were no tumors or deaths among the control group.	Kallistratos (1975)
Mice, BDF mice, 50-days-old, number n.p., M	DMcT, purity, route and dose, n.p.	OH-BBN, purity n.p., 7.5 mg/kg twice each wk for 8 wk by intragastric instillation.	DMcT was positive for chemoprevention measured as percent reduction in incidence of transitional cell carcinomas of the bladder compared with controls treated with OH-BBN.	Steele et al. (1994)
Rats, Fischer 344, age and number n.p., M	DMcT, purity and dose n.p., administered in the diet until sacrifice	AOM (15 mg/kg), purity n.p., was administered s.c. twice, 1 wk apart, beginning 1 wk after DMcT administration began. The colons from the rats were examined 4 wk later.	DMcT was inactive in inhibiting aberrant crypt foci induced by azoxymethane.	Barnes et al. (1993 abstr.)

Table 3. Anticarcinogenicity Studies of DMcT (Continued)

Species, Strain, and Age, Number, and Sex of Animals, or Cell Source and Assay	Chemical Form, Purity, Route, Dose, for DMcT	Other Chemical Form, Purity, Route, Dose, and Duration or Observation Period	Results/Comments	Reference
Rats, Fischer 344, 7-wk-old, number n.p., M	DMcT, 98% purity (according to CHEMCATS, 2001), 2 and 4 mg/kg in diet for 35 days.	AOM, purity n.p., 15 mg/kg, s.c. on days 7 and 14. Control groups received saline solution. Animals were killed on day 35.	DMcT did not have an effect on the yield of foci in the colon. Values are expressed as percent inhibition. **Dose** / **Foci/colon** / **Crypts/focus** 2.0 g/kg DMcT / 82.1±9.94 / 1.59±0.04 4.0 g/kg DMcT / 96.4±8.07 / 1.58±0.05 Control diet / 85.3±10.2 / 1.67±0.05	Pereira et al. (1994)
Rats, Sprague-Dawley rats, 50-days-old, number n.p., F	DMcT, purity, route and dose n.p.	MNU, purity n.p., 50 mg/kg, pH 5.0, once i.v. Rats were followed for 120 days.	DMcT did not induce a statistically significant decrease in mammary adenocarcinomas, or multiplicity or latency compared with the carcinogen-treated controls at one or more dose levels.	Steele et al. (1994)
Hamsters, Syrian golden, 7- to 8-wk-old, number n.p., M	DMcT, purity and dose n.p., administered in the diet from 1 wk before carcinogen administration to 180 days after carcinogen administration	DEN, purity n.p., 17.8 mg/kg twice each wk for 20 wk, s.c.	DMcT inhibited DEN-induced lung adenocarcinomas.	Steele et al. (1994)

Abbreviations: AOM = azoxymethane; B[*a*]P = benzo[*a*]pyrene; BEAS-2B cells = human bronchial epithelial cells ; 2C5 cells = rat tracheal epithelial cells; CO_2 = carbon dioxide; DEN = *N,N*-diethylnitrosamine; DFMO =difluoromethyl ornithine; F= female; GSH = reduced glutathione; HL-60 cells = human leukemic cells; i.v. = intravenous(ly); M = male; MNU = *N*-methyl-*N*-nitrosurea; mo = month(s); n.p. = not provided; OH-BBN = *N*-butyl, *N*-(4-hydroxybutyl)nitrosamine; PADPR = primary human fibroblasts; s.c. = subcutaneous; TPA = 12-*O*-tetradecanoylphorbol-13-acetate; wk = week(s)

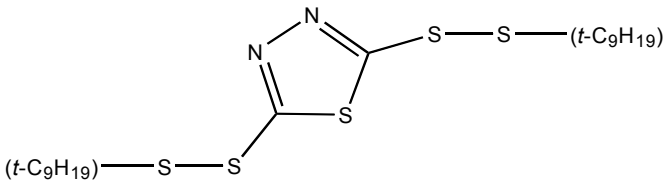
dependently inhibited endothelin converting enzyme taken from bovine aortic clonal endothelial cell lines; the response was less than that for ethylenediaminetetraacetic acid (EDTA) (Ashizawa et al., 1994).

10.0 Structure-Activity Relationships

Among the 21 compounds in the 1996 edition of *The Merck Index* resulting from a search for *thiadiazol* were 13 with the 1,3,4-thiadiazole substructure, four with the 1,2,5-thiadiazole substructure, and two each with the 1,2,4- and 1,2,3-thiadiazole substructures (Budavari, 1996). None of the compounds with the 1,3,4-thiadiazole substructure were derived from DMcT, although a few had the 2- or 5-position occupied by a sulfur atom in a thioether or sulfonyl group. The physiological activities of these compounds included diuretics (acetazolamide, butazolamide, methazolamide); antibacterials (cefazedone, cefazolin, ceftezole, sulfathidole, sulfamethizole); antidiabetics (glybuthiazol[e], glybuzole); insecticide, acaricide (methidathion); herbicide (tebuthiuron [Dow Elanco's Graslan, Spike, and Perflan]); and bacteriostatic and fungistatic compounds (triafur). These compounds possess too many constituent groups to merit any toxicity discussion in this report.

No toxicity information was found for bismuthiol II, also called 3-phenyl-1,3,4-thiadiazoline-5-thione, potassium salt.

2,5-Bis(*tert*-nonyldithio)-1,3,4-thiadiazole [CAS No. 89347-09-1]



2,5-Bis(*tert*-nonyldithio)-1,3,4-thiadiazole (also known as Amoco 158) is a high volume chemical with annual U.S. production >1 million lb (Environ. Defense, 2004; Registry, 2004). It is used as a copper corrosion inhibitor and extreme pressure agent in compositions of finished greases and lubricating oils and as a sulfur deactivator, corrosion inhibitor, and antioxidant in gasoline, heating oil, and Liquefied Petroleum Gas (Am. Chem. Council Petroleum Additives Panel, 2003a). According to the NIOSH NOES, conducted between 1981 and 1983, an estimated 222,864 people (69,002 of these female) were potentially exposed to Amoco 158 in the workplace (NIOSH, 1990).

Amoco 158 is registered on the Domestic Substances List (DSL) in which under the Canadian Environmental Protection Act, 1999, assessment of whether it is toxic or is capable of becoming toxic is needed; it is in the pilot phase for evaluation to determine whether it poses a risk to humans or the environment (Environ. Canada, 2001, 2004). It was found to not be readily biodegradable; it biodegraded by 2-5% in 28 days using the biochemical oxygen demand test and high-performance liquid chromatography. In fathead minnows (*Pimephales promelas*), a 96-hour LC_{50} of >1000 mg/L was determined; the no observed effect level was 1000 mg/L. In Sprague-Dawley rats, an oral LD_{50} >10 g/kg and inhalation LC_{50} >2.75 mg/L were reported. In rabbits, the dermal LD_{50} was >2 g/kg. In the oral study, decreased motor activity and diarrhea were observed at the dose level, and one male had a spleen with dark red edges. In the inhalation

study, nasal discharge, red encrustation around the nose and eyes, and salivation were observed during the four-hour exposure period. A few animals had spongy lungs and/or brown foci through lung lobes (Am. Chem. Council Petroleum Additives Panel, 2003a,b).

Amoco 158 (up to 5000 µg/plate) was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 and *Escherichia coli* strain WP2*uvr*A, tested with and without metabolic activation (S9). Additionally, Amoco 158 (up to 20 µg/mL) did not induce chromosome aberrations in Chinese hamster V79 cells in the presence or absence of S9 (Am. Chem. Council Petroleum Additives Panel, 2003a,b).

11.0 Online Databases and Secondary References

11.1 Online Databases

Chemical Information System Files
TSCATS (Toxic Substances Control Act Test Submissions)

National Library of Medicine Databases
ChemIDplus
EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files

AGRICOLA	CIN	MSDS-OHS
BIOSIS	CSNB	NIOSHTIC
BIOTECHNO	DDFU	NTIS
CA	EMBASE	PASCAL
CABA	ESBIOBASE	PIRA
CANCERLIT	HODOC	PROMT
CAPLUS	HSDB	Registry
CEN	IPA	RTECS
CHEMCATS	LIFESCI	TOXCENTER
CHEMLIST	MEDLINE	

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSHTIC®	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM

Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

Databases Available on the Internet
Code of Federal Regulations (CFR), National Archives and Records Administration

In-House Databases
Current Contents on Diskette®
The Merck Index, 1996, on CD-ROM

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Appendix A. Units and Abbreviations

°C = degrees Celsius
µg/L = microgram(s) per liter
µg/m^3 = microgram(s) per cubic meter
µg/mL = microgram(s) per milliliter
µM = micromolar
BaP = benzo[*a*]pyrene
DEN = *N,N*-diethylnitrosamine
EPA = Environmental Protection Agency
F = female(s)
g = gram(s)
g/mL = gram(s) per milliliter
h = hour(s)
i.p. = intraperitoneal(ly)
IUR = Inventory Update Rule
i.v. = intravenous(ly)
kg = kilogram(s)
L = liter(s)
lb = pound(s)
LC_{50} = lethal concentration for 50% of test animals
LD_{50} = lethal dose for 50% of test animals
M = male(s)
mg/kg = milligram(s) per kilogram
mg/m^3 = milligram(s) per cubic meter
mg/mL = milligram(s) per milliliter
min = minute(s)
mL/kg = milliliter(s) per kilogram
mm = millimeter(s)
mM = millimolar
mmol = millimole(s)
mmol/kg = millimoles per kilogram
mo = month(s)
mol = mole(s)
mol. wt. = molecular weight
NIOSH = National Institute for Occupational Safety and Health
nm = nanometer(s)
n.p. = not provided
ppb = parts per billion
ppm = parts per million
p.o. = peroral(ly), *per os*
s = second(s)
s.c. = subcutaneous(ly)
TSCA = Toxic Substances Control Act
yr = year(s)

Appendix B. Summary of March 2002 Literature Searches on Bismuthiol I (1072-71-5; ILS Code L720), Its Salts, and Polymers

Search Description

Databases searched simultaneously included the following (number in parentheses is the number of records after automated duplicate identification and removal):

MEDLINE	(5)	ESBIOBASE	(0)	PASCAL	(49)
CANCERLIT	(3)	CABA	(3)	NTIS	(8)
AGRICOLA	(0)	IPA	(0)		____
NIOSHTIC	(0)	BIOSIS	(7)		
EMBASE	(14)	TOXCENTER	(67)	Total	(156)
BIOTECHNO	(0)	LIFESCI	(0)		

Before duplicate removal, the numbers of records associated with the synonyms and CASRNs were the following

2,5-Dimercapto-1,3,4-thiadiazole	103
1072-71-5	71
1,3,4-Thiadiazole-2,5-dithiol	31
DMTD (not all were for compd. of interest)	26
Dimercaptothiadiazole	18
Bismuthiol I	16
1,3,4-Thiadiazolidine-2,5-dithione	10
55906-42-8 (DMTD disodium salt)	4
4628-94-8 (DMTD dipotassium salt)	2

Because bismuthiol I is not a common synonym, DMTD will be used for brevity in this discussion. (DMTD is also used as a synonym for methoxychlor and a dimethylthiadiazole). Another acronym frequently encountered is DMcT, where the Mc stands for the mercapto group.

Four additional TOXCENTER records were retrieved by use of CASRNs for 17 other related compounds, primarily salts.

REGISTRY file full records retrieved up to 10 of the most recent CA records for each of the 17 related compounds, many of which were also indexed for DMTD.

The RTECS record presented only results of acute studies.
The TSCATS search found studies on three microfiche submitted by R.T. Vanderbilt Chemical Co.

Other databases searched with the CASRN and a few synonyms included TOXLINE (18 records), DART (1 record), and EMIC (2 records), which are available from NLM on the Internet, and CHEMCATS (28 U.S. companies), CHEMLIST, HODOC, MSDS-OHS, DDFU (12 records), PIRA (1 record), CEN (1 record), CIN (11 records), CSNB (1 record), and PROMT (9 records), which were searched on the STN International system.

A targeted CAPLUS search found two records associated with adverse effects and seven in the environmental pollution sections (all because of the use of bismuthiol I in the analysis or trapping of heavy metals). There were eight records found when the CASRN was combined with the terms "fire OR flame OR firefighting."

Internet searches found little company product literature and nothing on NCI preclinical trials as an antineoplastic agent (a few publications were identified, however, in the database searches).

The following compounds are in the TSCA Inventory (number of CAPLUS records in parentheses):

DMTD [1072-71-5]	(803 + 41 CAOLD)
DMTD disodium salt [55906-42-8]	(23 + 2 CAOLD)
DMTD dipotassium salt [4628-94-8]	(29)
DMTD monosodium salt [50530-45-5]	(6)
DMTD monobenzoate; ECHO A; ECHO S [51988-14-8]	(20)

Other DMTD derivatives of interest include these salts and polymers:

DMTD dilithium salt [140481-31-8]	(18)
DMTD monopotassium salt [54092-09-0]	(8)
DMTD zinc salt [63813-27-4]	(7) [CASRNs for several other heavy metal salts were identified.]
DMTD dimer [72676-55-2]	(33 + 2 CAOLD)
DMTD-S_2Cl_2 copolymer [79509-46-9] (no chlorine atoms in product)	(11)
DMTD homopolymer [30555-21-6]	(48)

The analog bismuthiol II [6336-51-2] is the monopotassium salt of the 3-phenyl derivative of DMTD.

There was no HSDB record, and no published general reviews were identified.

Appendix C. History of the Online Search Sessions on STN International Conducted in October 2004

Files MEDLINE, CANCERLIT, AGRICOLA, NIOSHTIC, EMBASE, BIOTECHNO, ESBIOBASE, CABA, IPA, BIOSIS, TOXCENTER, LIFESCI, PASCAL, and NTIS were searched simultaneously on STN International on October 7 and 18, 2004. The search and retrievals on October 7-8 were primarily directed toward structural analogs.

October 7, 2004

```
L21           1 S 50530-45-5
L22         295 S 51988-14-8 OR ECHO(W)(A OR S)
L23           3 S 51988-14-8
L24           0 S 140481-31-8
L25           1 S 54092-09-0
L26           1 S 63813-27-4
L27           1 S 72676-55-2
L28           0 S 79509-46-9
L29           0 S 30555-21-6
L30         297 S L22 OR L23 OR L25 OR L26 OR L27
                SET DUPORDER FILE
L31         231 DUP REM L30 (66 DUPLICATES REMOVED)
             44 ANSWERS '1-44' FROM FILE MEDLINE
              3 ANSWERS '45-47' FROM FILE CANCERLIT
              2 ANSWERS '48-49' FROM FILE AGRICOLA
             35 ANSWERS '50-84' FROM FILE EMBASE
              2 ANSWERS '85-86' FROM FILE ESBIOBASE
              2 ANSWERS '87-88' FROM FILE CABA
             22 ANSWERS '89-110' FROM FILE BIOSIS
             10 ANSWERS '111-120' FROM FILE TOXCENTER
              1 ANSWER '121' FROM FILE LIFESCI
             78 ANSWERS '122-197' FROM FILE PASCAL
             34 ANSWERS '198-231' FROM FILE NTIS
L32          21 S L31 AND (2002-2004)/PY
L33          21 SORT L32 1-21 TI
L34           5 S L21 OR L23 OR L25 OR L26 OR L27
L35           5 DUP REM L34 (0 DUPLICATES REMOVED)
                ANSWERS '1-5' FROM FILE TOXCENTER
L36          34 S BISMUTHIOL(W)(II OR 2)
L37           4 S 6336-51-2
L38          38 S L36 OR L37
L39          33 DUP REM L38 (5 DUPLICATES REMOVED)
              1 ANSWER '1' FROM FILE MEDLINE
              1 ANSWER '2' FROM FILE EMBASE
              4 ANSWERS '3-6' FROM FILE BIOSIS
             14 ANSWERS '7-20' FROM FILE TOXCENTER
             13 ANSWERS '21-33' FROM FILE PASCAL
L40          33 SORT L39 1-33 TI
                SAVE L40 PHDMCT/A
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October 18, 2004

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L1           91 S 2(W)5(W)DIMERCAPTO(W)1(W)3(W)4(W)THIADIAZOLE
L2           95 S 1072-71-5
L3           26 S 1(W)3(W)4(W)THIADIAZOLE(W)2(W)5(W)DITHIOL
L4           31 S DMTD NOT (METHOXYCHLOR OR DIMETHYLTHIADIAZOLE OR
                  DIMETHYL(3A)THIADIAZOLE
L5           20 S DIMERCAPTOTHIADIAZOLE
L6           25 S BISMUTHIOL(3A)(I OR 1)
L8           13 S 1(W)3(W)4(W)THIADIAZOLIDINE(W)2(W)5(W)DITHIONE
L9          193 S L1 OR L2 OR L3 OR L4 OR L5 OR L6 OR L8
L10         101 S DMCT
L11          89 S L10 NOT L9
L13          44 S L11 NOT (DEMETHYLCHLORTETRACYCLIN? OR
                  DEMETHYL(2A)TETRACYCLI?)
L14          39 S L13 NOT DEHYDROMONOCROTALIN?
L15         232 S L9 OR L14
L16           6 S 55906-42-8 OR 4628-94-8
L17         234 S L15 OR L16
                  SET DUPORDER FILE
L18         192 DUP REM L17 (42 DUPLICATES REMOVED)
              8 ANSWERS '1-8' FROM FILE MEDLINE
              3 ANSWERS '9-11' FROM FILE CANCERLIT
             14 ANSWERS '12-25' FROM FILE EMBASE
              4 ANSWERS '26-29' FROM FILE CABA
              8 ANSWERS '30-37' FROM FILE BIOSIS
             90 ANSWERS '38-127' FROM FILE TOXCENTER
              2 ANSWERS '128-129' FROM FILE LIFESCI
             55 ANSWERS '130-184' FROM FILE PASCAL
              8 ANSWERS '185-192' FROM FILE NTIS
L19         192 SORT L18 1-192 TI
L20          30 S L17 AND (2001-2004)/PY
L21          20 DUP REM L20 (10 DUPLICATES REMOVED)
              2 ANSWERS '1-2' FROM FILE MEDLINE
              1 ANSWER '3' FROM FILE CABA
              4 ANSWERS '4-7' FROM FILE TOXCENTER
             13 ANSWERS '8-20' FROM FILE PASCAL
                  SAVE L17 DMCTALLDATES/A
L22          20 SORT L21 1-20 TI
                  SAVE L22 DMCT200104/A
```