United States
Environmental Protection
Agency

Office of Pesticides and Toxic Substances
Office of Pesticide Programs (TS-766C)
Washington, DC 20460

EPA Pesticide Fact Sheet

Name of Chemical: Dimethyl (1,2-phenylene)-bis (iminocarbono thioyl) bis(carbamate)
Reason for Issuance: Registration Standard
Date Issued: 9/86
Fact Sheet Number: 92

I. DESCRIPTION OF CHEMICAL

Common Name: Thiophanate-methyl

Trade Names: NF44, AC 87,844, Topsin M, Cercobin M, Mildothane, Cycosin, Fungo, Fungo 70, Spot-kleen, TD-1771, Thiophanate-methyl

Empirical Formula: $C_{12}H_{14}N_4O_4S_2$

Chemical Abstracts Service (CAS) Number: 23564-05-8

Pesticide Chemical Code (Shaughnessy): 102001

Pesticide Type: Systemic fungicide

Chemical Family: Carbamates

U.S. and Foreign Producers: Agchem Division of the Pennwalt Corporation

II. USE PATTERNS AND FORMULATIONS

Application sites: Thiophanate-methyl is registered for control of plant diseases on almonds, apples, apricots, bananas, beans, celery, cherries, cucumbers, melons, nectarines, onions, ornamentals, pecans, peaches, peanuts, plums, potatoes, pumpkins, soybeans, squash, strawberries, sugar beets, sugarcane, turf, and wheat.

Type of formulations: 94.3% technical grade, dusts (2.5, 5%), granular (1.75, 2.3, 5.5%), wettable powders (1.75, 15, 24.4, 25, 50, 70%), a 19.65% liquid, and a 46.2% flowable.

Types and methods of applications: End use products are applied aerially, banded, broadcasted, and applied over-the-top with ground equipment. Thiophanate-methyl is also used as a post harvest dip for fruits, as a seed piece treatment, as a soil drench for ornamentals, and as a soil furrow spray.

Application rates: 0.26 to 2.8 lb ai/A on crop sites, 0.033 to 0.36 lb ai/1000 sq ft on turf, 0.35 to 0.70 lb ai/100 gal for post-harvest treatments, and 0.175 to 1.16 lb ai/100 gal for seed piece treatments.

Usual carriers: Water, spray oil, or wax.

3. SCIENCE FINDINGS:

Summary science statements: Thiophanate-methyl is readily absorbed by animals and partly metabolized to methyl-2-benzimidazole carbamate (MBC). Eighty to ninety percent of thiophanate-methyl orally administered to laboratory animals is recovered in the excreta within 24 hours as parent compound and metabolites (including MBC).

Thiophanate-methyl did not show any positive effects in oncogenic studies in the rat and mouse. However, the fungicidal activity of thiophanate-methyl depends on its conversion to MBC in the plants. MBC has been shown to cause tumors solely in the mouse liver and has been tentatively classified as a Group C oncogen (possible human oncogen).

No compound-related maternal or fetal effects were observed in a rat teratology study. A mouse teratology study of thiophanate-methyl is incomplete. Therefore, another teratology study must be conducted. In a reproduction study in rats the only signs of toxicity observed were decreased pup and litter weights at birth and during lactation for pups and dams administered the high dose (640 ppm or 32 mg/kg/day). In a study with male mice given 5 consecutive oral daily doses of 192 mg/kg body weight, there was no indication that thiophanate-methyl affected the function of the testes or accesssory sex organs.

Acute toxicity studies of thiophanate-methyl indicate Toxicity Category III based on dermal toxicity. Thiophanate-methyl is virtually non-toxic to avian species and of low to moderate toxicity to freshwater fish with the exception of catfish. Studies conducted with thiophanate-methyl show that it is highly toxic to catfish.

Available data are insufficient to fully assess the residues of thiophanate-methyl and MBC in raw agricultural commodities. Available data are insufficient to fully assess the environmental fate of thiophanate-methyl.

Chemical characteristics: Thiophanate-methyl is a light-tan crystalline powder that has a sulfidic odor at room temperature. Its molecular weight is 342.4. It is stable at neutral pH at 25° C in aqueous solution up to 25 days.

Toxicological characteristics:

Acute toxicology effects of thiophanate-methyl are as follows:

Acute Oral Toxicity: (rat)	male: 7,500 mg/kg body weight female: 6640 mg/kg body weight Toxicity category IV
Acute Dermal Toxicity: (rat)	>10,000 mg/kg body weight Toxicity category III
Dermal Sensitization: (guinea pig)	non-sensitizing

Subchronic toxicology effects of thiophanate-methyl are as follows:

Subchronic Oral (rats)	NOEL = 64 ppm (3 mg/kg/day) LEL = 320 ppm (16 mg/kg/day) (decreased body weight gain)

At the highest dose tested (8000 ppm) thyroid histopathology included decreased coloidal content and epithelial hypertropphy in the follicles.

Chronic toxicology effects of thiophanate-methyl are as follows:

Thyroid histopathology similar to that observed in the subchronic rat feeding study was found in the long-term studies in male rats (32 mg/kg/day) and female dogs (250 mg/kg/day). Decreased body weight gain in female rats and testicular histopathology in male rats was noted at the 640 ppm (32 mg/kg/day) diet. NOEL's with respect to these effects were 8 mg/kg/day in rats. A NOEL of 50 mg/kg/day in dogs was based on decreased weight gain in males and changes in thyroid histology in females.

Oncogenic effects of thiophanate-methyl are as follows:

There were no compound related effects or tumor incidence in mice after two years of feeding diets containing 0, 40, 160, or 640 ppm (0, 1.5, 6, 24, or 96 mg/kg/day) thiophanate-methyl (a MTD was not reached in this mouse study). No oncogenic potential was observed in the rat study at the dietary levels up to 32 mg/kg/day, which did approach a MTD.

Teratogenic effects of thiophanate-methyl are as follows:

No compound-related maternal or fetal effects were observed in a limited teratology study in rats. In a second study, pregnant rats received thiophanate-methyl in their diets during gestation, and no fetal effects were observed. This study was limited because the palatability of diets containing the

highest dose was decreased by the fungicide. The highest dose tested (1000 mg/kg/day) in a mouse study did not cause toxicity in the dams or their fetuses. However, the report was incomplete and, therefore, a teratology study in a second species is needed.

Reproductive effects of thiophanate-methyl are as follows:
In a three-generation reproduction study in rats, there was no effect on fertility, viability, gestation, or lactation indices. There was a decrease in pup and litter weights at the 640 ppm diets. The NOEL for this effect was 8 mg/kg/day.

Mutagenic effects of thiophanate-methyl are as follows:

In mutagenicity tests, thiophanate-methyl did not induce reverse mutations in bacteria or affect fertility.

Major routes of human exposure:

Dermal, ocular, and inhalation exposures to workers may occur during application. Exposure from mixing, handling, and application of the dusts, granulars and wettable powders is expected to be mainly dermal.

Physiological and biochemical behavioral characteristics:

Translocation: Thiophanate-methyl is mobile in the xylem and the phloem.
Mechanism of pesticidal action: Thiophanate-methyl inhibits the growth of plant pathogens.

Environmental characteristics: Available data are insufficient to fully assess the environmental fate of thiophanate-methyl and the potential exposure of humans and nontarget organisms. An aerobic soil metabolism study is the only environmental fate study available for thiophanate-methyl. In order to assess the environmental fate and transport of, and the potential exposure to thiophanate-methyl, the Agency is requiring a full range of environmental fate studies.

Ecological characteristics: Available data indicate that thiophanate-methyl has very low toxicity to birds, is slightly toxic to sunfish and trout, and very highly toxic to catfish. MBC has been shown to be highly toxic to fish. Thiophanate-methyl has been shown to be moderately toxic to aquatic invertebrates.

Aquatic invertebrate toxicity:	
Daphnia magna	27 ppm
96 hour fish toxicity:	
Bluegill sunfish	15.8 - 58 ppm
Rainbow trout	8.3 - 25.2 ppm
channel catfish	0.030 ppm

Avian dietary toxicity:

Mallard duck	>10,000 ppm
Bobwhite quail	>10,000 ppm

Potential problem for endangered species:
A review by the Agency indicates that two endangered catfish species inhabit areas where soybeans are grown and which may be treated with thiophanate-methyl.

Tolerance Reassessment:

Listed below are tolerances which have been established for residues of thiophanate-methyl on a wide range of raw agricultural products listed in 40 CFR 180.371.

The most appropriate NOEL's for this tolerance reassessment are those from the chronic and reproduction studies in rats (160 ppm or 8 mg/kg/day). There were no effects in any other study that evaluated doses at or below that NOEL. Using a safety factor of 100 and the 8 mg/kg/day NOEL, the ADI for humans was calculated as 0.08 mg/kg/day. The maximum permissible intake (MPI) for a 60 kg adult is 4.8 mg/1.5 kg diet.

To date the tolerances granted have accounted for approximately 22.85% of the acceptable daily intake with a theoretical maximum residue contribution (TMRC) to the daily diet of 1.0969 mg/day (for an average 1.5 kg daily diet).

Commodity	Tolerance (ppm)
Almonds pre-H	0.2
Almonds (hulls) pre-H	1.0
Apples (pre- and post-H)	7.0
Apricots (pre- and post-H)	15.0
Bananas (pre-H)	2.0
Bananas, pulp (pre-H)	0.2
Beans (snap and dry) pre-H	2.0
Bean (forage and hay) pre-H	50.0
Cattle, fat	0.1
Cattle, kidney	0.2
Cattle, liver	2.5
Cattle, meat byproducts (exc. kidney and liver)	0.1
Cattle, meat	0.1
Celery (pre-H)	3.0
Cherries (pre- and post-H)	15.0
Cucumbers	1.0
Eggs	0.1
Goats, fat	0.1
Goats, kidney	0.2
Goats, liver	2.5
Goat, meat byproducts (exc. kidney and liver)	0.1

Commodity	Tolerance (ppm)
Goat, meat	0.1
Hogs, fat	0.1
Hogs, liver	1.0
Hogs, meat byproducts(exc. liver)	0.1
Hogs, meat	0.1
Horses, fat	0.1
Horses, liver	1.0
Horses, meat byproducts (exc. liver)	0.1
Horses, meat	0.1
Melons	1.0
Milk	1.0
Nectarines (pre- and post-H)	15.0
Onion, dry	3.0
Onion, green	3.0
Pecans (pre-H)	0.2
Peaches (pre- and post-H)	15.0
Peanuts pre-H	0.2
Peanuts (hulls) pre-H	2.0
Peanuts (forage and hay) pre-H	15.0
Plums (pre- and post-H)	15.0
Potatoes (seed treatment)	0.05
Poultry, fat	0.1
Poultry, liver	0.2
Poultry meat byproducts (exc. liver)	0.1
Poultry, meat	0.1
Prunes (pre- and post-H)	15.0
Pumpkins	1.0
Sheep, fat	0.1
Sheep, kidney	0.2
Sheep, liver	2.5
Sheep, meat byproducts (exc. kidney and liver)	0.1
Sheep, meat	0.1
Soybeans (pre-H)	0.2
Squash	1.0
Strawberries (pre-H)	5.0
Sugar beets (roots pre-H)	0.2
Sugar beets (tops pre-H)	15.0
Sugarcane (seed piece treatment pre-H)	0.1
Wheat, grain	0.05
Wheat, hay	0.1
Wheat, straw	0.1

Problems known to have occurred with use:

The Pesticide Incident Monitoring System (PIMS) did not identify any incidents involving agricultural/domestic uses of thiophanate-methyl from 1966 to present.

4. SUMMARY OF REGULATORY POSITION AND RATIONALE:

Based on the review and evaluation of all available data and other relevant information on thiophanate-methyl, the Agency has made the following determinations:

a. The Agency will not place thiophanate-methyl and its metabolite MBC into Special Review [Section 162.11(a) of CFR 40].

Thiophanate-methyl was previously placed in Special Review by the Agency in December, 1977, because of its potential adverse effects on nontarget organisms and because its metabolite, MBC, had the potential to cause mutagenic effects. It was removed from the special review process in October, 1982 because it was determined that the risks were not unreasonable and were exceeded by the benefits associated with the use of thiophanate-methyl products.

MBC has been classified as a Group C oncogen (possible human oncogen). The current risk analysis performed for thiophanate-methyl, based on its metabolite MBC, is of the same order of magnitude as those calculated in the PD 4 for benomyl (i.e. 10^{-4} to 10^{-5}).

Although MBC is associated with liver tumors in Swiss and Swiss derived mice (CD-1), MBC is not associated with liver tumors in NMRKf strain of mouse , which has a low background incidence of liver tumors. MBC was not oncogenic in the rat and only weakly mutagenic as a possible result of inhibition of the cellular spindle apparatus rather than direct gene mutation or alteration of DNA repair.

The Agency has concluded that the risks to humans posed by thiophanate-methyl are minimal and of the same magnitude as estimated in the 1982 decision. The Agency has also reviewed the benefits of thiophanate-methyl and has concluded that the benefits have not changed significantly since the 1982 decision. The benefits of thiophanate-methyl outweigh its risks with the protective measures on the label. Hence initiation of an additional special review is not necessary at this time.

b. The Agency does not intend to establish new food additive regulations pursuant to Section 409 of the Federal, Food, Drug, and Cosmetic Act (FFDCA). The Agency is deferring action on the presently established food additive regulations until receipt and evaluation of comments in response to a Federal Register notice discussing this issue. This notice

c. The Agency is not requiring a reentry interval for currently registered uses of thiophanate-methyl. The acute toxicity for thiophanate-methyl is low (Category IV) except for dermal irritation (Category III). Additionally, exposure and the resultant risks to field workers are not expected to be significant because thiophanate-methyl is expected to be poorly absorbed dermally. The SAP is being asked if a dermal absorption study should be required.

d. The Agency is imposing labeling restrictions on rotational crops. The extent of the restrictions will be reconsidered when additional data are submitted and reviewed. The restrictions will serve to protect the public from impermissable residues in food and feed. In addition this restriction will protect subsequent planted crops from possible effects due to persistent residues of thiophanate-methyl in the soil.

e. The Agency has determined that the available data are insufficient to fully assess the environmental fate of thiophanate-methyl. Preliminary laboratory data show that thiophanate-methyl and its degradate MBC are moderately mobile in Lakeland sand and Sultan silt loam columns.

The Agency determined that two endangered catfish species inhabit areas where soybeans may be grown. To protect these species, endangered species labeling is required.

Site: The Agency has not proposed changes in thiophanate-methyl's uses.

Specific Label Warning Statements:

The following required label statements must appear on the labels of all products in channels of trade within two years [April 30, 1988] of issuance of this Standard. After review of data to be submitted under this Standard, the Agency may impose additional label requirements or take further regulatory actions as necessary.

1. Manufacturing-Use Product Statements

All products intended for formulation into EPs must bear the following environmental hazard statement:

"Do not discharge effluent containing this product directly into lakes, streams, ponds, estuaries, oceans or public waters unless this product is specifically identified and addressed in a National Pollutant Discharge Elimination System (NPDES) permit. Do not discharge effluent containing this product into sewer systems without previously notifying the sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of the Environmental Protection Agency."

2. End-Use Product Statements

The following environmental hazard statement must appear on all EP's:

"This pesticide is toxic to catfish. Do not apply directly to water or wetlands (swamps, bogs, marshes, and pot holes). Drift and runoff from treated areas may be hazardous to catfish in adjacent areas. Do not contaminate water by cleaning of equipment or disposal of wastes."

--for granular products add "cover or incorporate spills."

Restrictions on Rotational Crops

"Do not plant food or feed crops in thiophanate-methyl treated fields for 18 months after the last application unless thiophanate-methyl is registered for use on those crops."

Endangered Species Information for use on Soybeans
The following must appear on all EP's registered for use on Soybeans:

"ENDANGERED SPECIES RESTRICTIONS

The use of any pesticide in a manner that may kill or otherwise harm an endangered or threatened species or adversely modify their habitat is a violation of federal laws. The use of this product is controlled to prevent death or harm to endangered or threatened species that occur in the following counties or elsewhere in their range.

STATE Species	COUNTY
OHIO Scioto madtom	CHAMPAGNE FRANKLIN LOGAN MADISON PICKAWAY UNION
TENNESSEE Yellowfin madtom	CLAIBORNE HANCOCK
VIRGINIA Yellowfin madtom	LEE RUSSELL SCOTT

Before using this pesticide in these counties you must obtain the EPA Cropland Endangered Species Bulletin (EPA/ES-CROP). The use of this pesticide is prohibited in these counties unless specified otherwise in the Bulletin. The EPA Bulletin is available from either your County Agricultural Extension Agent, the Endangered Species Specialist in your State

Wildlife Agency Headquarters, or the appropriate Regional Office of either the U.S. Fish and Wildlife Service (FWS) or the U.S. Environmental Protection Agency (EPA). THIS BULLETIN MUST BE REVIEWED PRIOR TO PESTICIDE USE."

5. SUMMARY OF MAJOR DATA GAPS:

The toxicological studies are required on the following dates:

Acute Inhalation Toxicity - rat	January 31, 1987
Eye Irritation - rabbit	January 31, 1987
Dermal Irritation - rabbit	January 31, 1987
Teratogenicity	April 30, 1987
Oncogenicity - mouse	June 30, 1990
Structural Chromosomal Aberration	April 30, 1987
Mechanisms of Mutagenicity	April 30, 1987
Dermal Absorption Study	April 30, 1987

The environmental fate data are required on the following dates:

Hydrolysis	January 31, 1987
Photodegradation in water and on soil	January 31, 1987
Anaerobic Soil	July 31, 1988
Leaching and Adsorption/Desorption	April 30, 1987
Volatility (lab)	April 30, 1987
(field)	July 31, 1987
Soil dissipation	July 31, 1989
Accumulation - rotational crops (confined)	July 31, 1989
- rotational crops (field)	June 30, 1990
- fish	April 30, 1987

The ecological effects data are required on the following dates:

Acute Avian Oral Toxicity	January 31, 1987
Avian Subacute Dietary Toxicity - waterfowl	January 31, 1987
Acute Toxicity to Aquatic Invertebrates	January 31, 1987

The residue chemistry data are required on the following dates:

Nature of residue (animal metabolism)	October 31, 1987
Residue Analytical Methods	October 31, 1987
Storage Stability Data	July 31, 1987
Residue studies on crops, processed food/feed commodities	April 30, 1988

Product chemistry data required within a year of issuance of standard.

6. CONTACT PERSON AT EPA

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