

Thiophanate Methyl

Dimethyl-4-4'-(o-phenylene)-bis(3-thioallophanate)

Thiophanate methyl is a broad-spectrum fungicide used on food and feed crops, turf, ornamental plants and seed treatments. In 2009, 89,463 pounds were used in California. Top uses included pistachios (20,105 pounds), almonds (15,982 pounds), strawberries (12,643 pounds), and landscape maintenance (13,345 pounds). Pesticide applicators and the general public can be exposed.

Thiophanate methyl passed the animal data screen, underwent a preliminary toxicological evaluation, and is being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

Epidemiological data

No cancer epidemiology studies were identified.

Animal carcinogenicity data

- Long-term diet studies
 - 24-month studies in male and female Fischer 344 rats: U.S. EPA (1999)
 - *Increase (by pairwise comparison and trend) in thyroid follicular cell adenomas, carcinomas, and adenomas and carcinomas combined in male rats*
 - *Increase (by trend) in thyroid follicular adenomas in female rats*
 - 18-month studies in male and female CD-1 albino mice: U.S. EPA (1999)
 - *Increase (by pairwise comparison and trend) in liver adenomas and combined adenomas, carcinomas, and hepatoblastomas in male mice*
 - *Increase (by pairwise comparison and trend) for liver adenomas in female mice*

Other relevant data

- Genotoxicity
 - *In vitro* unscheduled DNA synthesis in primary rat hepatocytes (*negative*): U.S. EPA (1999)
 - Reverse mutation in *Salmonella typhimurium* (*negative*): U.S. EPA (1987)
 - Mutation in *Bacillus subtilis* (*negative*): U.S. EPA (1987)
 - Mitotic gene conversion in *Saccharomyces cerevisiae* (*negative*): U.S. EPA (1987)
 - Dominant lethal mutations in mice (*negative*): U.S. EPA (1987)

- Clastogenicity *in vitro* (*negative*): U.S. EPA (1999)
 - Chromosome aberration in Chinese hamster ovary cells (*negative*) U.S. EPA (1999)
 - Chromosome aberration (somatic cells) in Swiss albino mice (*positive*): (Barale et al. 1993 as reviewed in U.S. EPA, 1999)
 - *In vitro* cell transformation BALB/c3T3 (*positive*): (Perocco et al. 1997 as reviewed in U.S. EPA, 1999)
 - Mammalian preincubation microsome gene mutation assay equivocal when tested in *Salmonella typhimurium* strains TA 98 and TA100: (Zeiger et al. 1992 as reviewed in U.S. EPA, 1999)
- Mechanistic considerations
 - Interference with thyroid–pituitary homeostasis: U.S. EPA (1999, p. v)
 - Methyl-2-benzimidazolecarbamate (MBC) is a common metabolite of both benomyl and thiophanate methyl. All three compounds are inducers of aneuploidy: U.S. EPA (1999, p 20).
 - Structure activity considerations
 - Structural similarity to benomyl and methyl-2-benzimidazole, both of which are aneugenic and cause hepatocellular tumors in mice but no thyroid effects. Thiophanate methyl has structural similarities to propylthiouracil, a known inducer of thyroid tumors in rats and mice: U.S. EPA (1999)

References¹

U.S. EPA, 1987. Memorandum.

U.S. EPA, 1999. Cancer Assessment Review Committee. *Evaluation of the carcinogenic potential of Thiophanate Methyl*. Final report. Health Effects Division, Office of Pesticide Programs HED Doc No 013688.

¹ Excerpts or the complete publication have been provided to members of the Carcinogen Identification Committee, in the order in which they are discussed in this document.