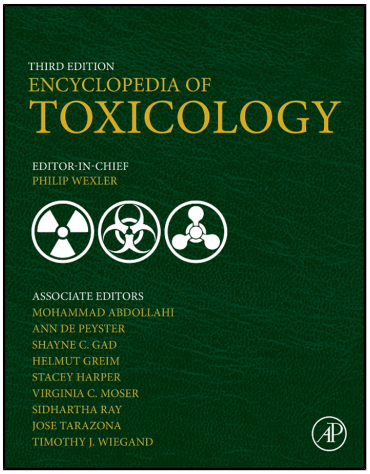

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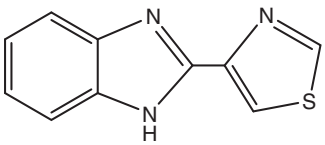
Thiabendazole

GG Dumancas, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA
RS Hikkaduwa Koralege, Oklahoma State University, Stillwater, OK, USA
E-RE Mojica, Pace University, New York, NY, USA
BS Murdianti, Arkansas Tech University, Russellville, AR, USA
PJ Pham, Mississippi State University, MS, USA

- Name: Thiabendazole
- Chemical Abstracts Service Registry Number: 148-79-8
- Synonyms: 2-(4-Thiazolyl)-1H-benzimidazole, 4-(2-Benzimidazolyl)thiazole, 2-(Thiabendazol-4-yl)benzimidazole, Equizole, Mertec
- Chemical/Pharmaceutical/Other Class: Chemical, pharmaceutical
- Molecular Formula: $C_{10}H_7N_3S$
- Molecular Mass: 201.25 g mol^{-1}
- Chemical Structure:



Background

Thiabendazole is a compound with benzimidazole group. It is a white- or cream-colored odorless powder with low solubility in water, but is readily soluble in diluted acid and alkali. Thiabendazole was introduced in 1964 by Merck Chemical Co. as an anthelmintic drug for treating roundworm infestations in humans and livestock and was approved in the United States in 1967.

Thiabendazole was later widely used as a fungicide to control fruits and vegetables diseases. It was first registered as a pesticide in the United States in 1969 by Merck and Company, Inc. The primary registrant of end use products has been Syngenta Crop Protection, Inc. According to the US Environmental Protection Agency (EPA), 62 thiabendazole pesticide products are currently registered.

Thiabendazole also acts as a chelating agent to bind a number of metals, including iron but not calcium, and is used medicinally in treating metal poisoning, such as lead poisoning, mercury poisoning, or antimony poisoning.

Uses

There have been several different uses of thiabendazole, such as a parasiticide, a fungicide, and an angiogenesis inhibitor. As an anthelmintic, the usage of thiabendazole in creeping eruption, an invasion of human skin by larvae of the dog and cat hookworms, was first reported in 1963. Following this initial report, it has been reported that thiabendazole was confirmed to significantly shorten the course of creeping eruption. Thiabendazole is also used as a vermicidal against *Ascaris lumbricoides* (common roundworm), *Strongyloides stercoralis* (threadworm), *Necator americanus*, *Trichuris trichiura* (whipworm), and *Enterobius vermicularis* (pinworm). It also suppresses the subsequent development of those eggs or larvae, which are passed in the feces.

Thiabendazole is used as a fungicide in controlling green mold of artificially inoculated Shamouti and Valencia oranges, and shown to be superior as compared to 2-aminobutane and sodium orthophenylphenate without showing any phytotoxic effect. It also inhibited the colony growth of *Phaeomoniella chlamydospora* and *Phaeoacremonium angustius*, which cause esca disease in grapevines.

Recent work by scientists at the University of Texas at Austin showed that thiabendazole potently inhibits angiogenesis in animal models and human cells. Thiabendazole also shows the ability to slow tumor growth and decreases vascular density in preclinical fibrosarcoma xenografts.

Environmental Fate and Behavior

Thiabendazole does not hydrolyze readily, nor it is metabolized in soil under aerobic or anaerobic conditions. While it photodecomposes in minutes in aqueous solutions, photodecomposition of thiabendazole in soil did not cause more than 40% reduction. Thiabendazole is also only slightly water soluble, and does not migrate in soil. Thus, it is unlikely to contaminate groundwater. If released into the atmosphere, it exists primarily in the particulate phase. In the vapor phase, it will degrade in the atmosphere by reacting with photochemically produced hydroxyl radicals with an estimated half-life of 6 h.

Toxicokinetics

Toxicokinetics studies of thiabendazole showed that rapid absorption after oral dosing in mice, rats, dogs, and humans, with peak plasma levels occurring within 3 h of drug administration. Consequently, the drug was excreted in the urine and feces. Elimination of thiabendazole and its degradation products was more rapid in humans than in mice, rats, and dogs, but metabolism was similar in mice, rats, and humans. Main urinary metabolites include glucuronide and sulfate conjugates of 5-hydroxythiabendazole while the small amounts include unconjugated thiabendazole and the 5-hydroxy derivative.

Exposure Routes and Pathways

Typically, birds and mammals can be exposed to such pesticide applied as foliar sprays or granulars by a variety of routes,

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including ingestion, dermal contact, and inhalation. For thiabendazole, which is applied indoors as a seed treatment for wheat, wildlife exposure is not relevant until treated seeds are planted back in the fields. By then, ingestion might become an exposure route, as seed-eating birds and small granivorous mammals uncover and consume the treated seeds. However, seeds planted deep into the ground would yield insignificant threat to wildlife. Indoor uses, which include applications to and treatment of mushrooms, pose minimal risks to birds and mammals. Terrestrial wildlife exposure from direct injection of thiabendazole and its salt into trees may occur but is expected to be of minimal means of exposure.

Based on current use patterns, handlers (mixers, loaders, and applicators) may also be exposed to thiabendazole applications in agricultural and other settings such as in thiabendazole-treated carpets and paints.

Acute and Short-Term Toxicity or Exposure

Animal

Acute toxicity on both male and female mice includes oral, intravenous, and intraperitoneal routes with LD_{50} values of 2400–3810, 150, and 430 mg kg^{-1} bw^{-1}, respectively. Male and female mice given gavage doses of 0, 250, or 500 mg kg^{-1} bw^{-1} day^{-1} thiabendazole (purity 98.5%) in olive oil were killed after dosing for 1, 3, 5, or 7 days. In a 6 week pilot study, Charles River CD-1 (HaM/ICR) mice given with 0, 50, 150, 300, 600, or 900 mg kg^{-1} bw^{-1} day^{-1} thiabendazole via the diet showed no clinical signs or mortality. Food intake and weight gain were observed to be depressed in males at 600 and 900 mg kg^{-1} bw day^{-1}, respectively. Acute LD_{50} values for orally, intravenously, and intraperitoneally administered thiabendazole in rats were reported as 3330–3600, 130, and 1850 mg kg^{-1} bw^{-1}, respectively. LD_{50} for inhalation in rats was reported to be >397 mg m^{-3}. Rats administered with thiabendazole by gavage at dosage levels of 0, 100, 400, 800, 1200, or 1600 mg kg^{-1} bw^{-1} day^{-1} during a 30 day experimental period showed a decreased food intake and gradual loss of weight in the 800 mg kg^{-1} bw^{-1} day^{-1} group. Acute LD_{50} values in rabbits via oral and dermal routes were reported as 3850 and >2000 mg kg^{-1} bw^{-1}. In a short-term toxicity study, rabbits receiving dermal doses of thiabendazole (purity 98.9%) showed no evidence of local or systemic toxicity. In sheep and goats, acute LD_{50} values were 2000 and >2000 mg kg^{-1} bw^{-1}, respectively.

Signs of toxicity due to large doses of thiabendazole by oral or intraperitoneal routes generally caused lethargy and stupor while intravenous administration of a large dose of thiabendazole hydrochloride produced narcosis and death occurred due to respiratory failure.

Human

Thiabendazole has a low acute toxicity via the oral and dermal routes, and it is not an eye or dermal irritant nor a dermal sensitizer. There is a negligible risk of inhalation exposure to vapor or aerosol during the use of thiabendazole since it has a low potential to vaporize or aerosolize. Primary studies on eye and skin irritation concluded thiabendazole to be nontoxic. The primary target organs of thiabendazole are the thyroid and liver.

A group of male volunteers who received a single oral dose of 250 mg of thiabendazole (average dosage, 3.3 mg kg^{-1} day^{-1}) and another set who received a single dose of placebo were studied during a 6 month period for their physiological parameters. The single-dose no observed effect level (NOEL) for clinical signs and symptoms and blood chemistry changes in humans was 3.3 mg kg^{-1} day^{-1}.

Chronic Toxicity or Exposure

Animal

The principal effects of chronic exposure to thiabendazole in laboratory animals include thyroid toxicity, hepato/biliary toxicity, anemia, and atrial thrombosis. The NOEL for inflammatory liver changes, depletion of liver glycogen, hemosiderosis, and histopathological changes in the urogenital tract of dogs were 10 mg kg^{-1} day^{-1}. Beagles given with oral thiabendazole (99.1% pure) daily for 104 weeks at 0, 20, 100, or 200 mg kg^{-1} day^{-1} resulted in reduced body weights, red blood cell counts, hematocrits, and hemoglobin. In rats, the lowest observed effective level for mild anemia was 100 mg kg^{-1} day^{-1}, with a NOEL of 50 mg kg^{-1} day^{-1}. Thiabendazole did not show a significant effect on the incidence of thyroid follicular cell carcinomas, but had a combined incidence of carcinomas and adenomas in rats. The NOEL for adaptive liver response in rats was found to be 10 mg kg^{-1} day^{-1}. There has not been any indication of thiabendazole-related oncogenicity in mice. Male mice exhibited atrial thrombosis at 278 mg kg^{-1} day^{-1}, with a NOEL of 92 mg kg^{-1} day^{-1}.

Human

Thiabendazole can cause hepato/biliary toxicity in humans. Four doses of oral injections of 25 mg kg^{-1} of thiabendazole over an 8 day period to treat a helminthic infestation caused severe and protracted intrahepatic cholestasis, which was associated with nausea, intense pruritus, and a generalized rash.

In Vitro Toxicity Data

Mutagenicity for thiabendazole was reported in *Salmonella typhimurium* strain 98. However, three other studies using the same strain (TA98) did not show any mutations. Genetic toxicology studies on thiabendazole showed that it is nonmutagenic in *in vitro* assays.

Immunotoxicity

The effect of thiabendazole on the mammalian immune system was reported to be immunosuppression of the inflammatory reactions, which play a prominent role in the pathophysiology of helminth infections. Another study on mice indicated that thiabendazole was responsible for causing significant augmentation of cellular immune responses. However, the net

effect of thiabendazole on the immune system is not clearly understood.

Reproductive and Developmental Toxicity

In a reproduction study, mice dosed with thiabendazole at concentrations of 0, 0.02, 0.1, or 0.5% in the diet for five generations had an approximate NOEL of 150 mg kg^{-1} day^{-1} for reduced numbers of mice born and weaned per litter, as well as reduced weanling weight. In a two-generation rat reproduction study with thiabendazole (99% purity) at 0, 10, 30, or 90 mg kg^{-1} day^{-1} (based on food consumption data), the NOEL for decrement in parental weight gain was 10 mg kg^{-1} day^{-1} and the NOEL for reduced pup weights in rats was 30 mg kg^{-1} day^{-1}.

Thiabendazole had shown major malformations of the skeletal system in mice, rabbits, and rats in some studies. Pregnant rats exposed to thiabendazole in the diet showed increased skeletal variations and a significant increase in major malformations of the skeletal system, including cleft palates and the absence of the os hyoideum. The estimated no effect level for mice was 26 mg kg^{-1} day^{-1}, based on skeletal abnormalities. In rabbits, the NOEL for developmental toxicity was 24 mg kg^{-1} day^{-1} based on fetal resorption and hydrocephaly. Based on decrement in food consumption and body weight gain, the maternal NOEL in rabbits was 120 mg kg^{-1} whereas in rats the NOEL for decreased maternal food consumption was 10 mg kg^{-1}.

Genotoxicity tests were generally negative. In one of three *S. typhimurium* reverse-mutation assays, positive results were obtained in strain TA98 only. Further investigation showed that an impurity in some batches was responsible for the mutagenic activity. The manufacturer indicated that no positive results had been obtained in tests on several hundred further batches. In one laboratory, micronuclei were induced in mouse bone marrow and abnormal anaphase–telophase figures were increased in cultured Chinese hamster ovary cells. The effects were seen only at relatively high levels and may be indicative of the tubulin-binding activity characteristic of benzimidazoles. A range of other assays for mutation, DNA damage, and cytogenetic activity were clearly negative.

Carcinogenicity

The US EPA has classified thiabendazole as likely to be carcinogenic at doses high enough to cause a disturbance of the thyroid hormone balance. It is not likely to be carcinogenic at doses lower than those, which could cause a disturbance of this hormonal balance. A two-year feeding study with rats at levels of 10–160 mg kg^{-1} produced no cancer-related effects attributable to thiabendazole. There is no evidence of carcinogenic effects in humans from exposure to thiabendazole.

Clinical Management

Accidental ingestion of thiabendazole may be damaging to the health of the individual. Although the material is not thought to be an irritant, direct contact with the eye may cause momentary discomfort characterized by tearing or conjunctival redness (as with windburn). Slight abrasive damage to the skin may also result. The material is not thought to produce adverse health effects or skin irritation following contact (as classified using animal models). Nevertheless, good hygiene practice requires that exposure be kept to a minimum and that suitable gloves be used in an occupational setting. The material is not thought to produce either adverse health effects or irritation of the respiratory tract following inhalation (as classified using animal models). Nevertheless, adverse effects have been produced following exposure of animals by at least one other route, and good hygiene practice requires that exposure be kept to a minimum and that suitable control measures be used in an occupational setting. If swallowed, do *not* induce vomiting. If vomiting occurs, lean patient forward or place on left side with head down to maintain open airway and prevent aspiration. Treat patient symptomatically. Pre-existing liver or kidney disease may be aggravated by exposure.

Exposure Standards and Guidelines

The allowable daily intake from the US EPA is 0.1 and 0.3 mg kg^{-1} day^{-1} from the World Health Organization. The Office of Pesticide Programs recommends a reference dose of 0.1 mg kg^{-1} day^{-1}. The Occupational Safety and Health Administration permissible exposure limit, National Institute of Occupational Safety and Health recommended exposure limits, and the American Conference of Governmental Industrial Hygienists threshold limit value have not yet been established. People may be exposed to residues of thiabendazole through the diet. Tolerances or maximum residue limits have been established for agricultural and livestock commodities by the US EPA.

See also: Federal Insecticide, Fungicide, and Rodenticide Act, US; Pesticides.

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