

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

002852-11  
# 849A

DATE April 17, 1979

SUBJECT CODEX proposal for thiabendazole: tolerances for residues of 0.2 ppm in or on raw grain crops. Caswell #849A.

FROM Edwin R. Budd  
Toxicology Branch, HED TS-769

Budd  
4/17/79 002852

TO Robert Jaeger  
Toxicology Branch, HED TS-769

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SUMMARY

In response to your request for a Toxicology Branch opinion on the CODEX proposal for tolerances of 0.2 ppm of thiabendazole (and its 5-hydroxy metabolite) in or on raw grain crops, Toxicology Branch finds that presently available toxicological data on thiabendazole is adequate to support the proposed CODEX tolerances. Toxicology Branch, therefore, would have no objection to the establishment of these proposed tolerances at this time.

BACKGROUND

1. For the purpose of this request, the term "raw grain crops" was considered to include the following crops and food factor (as described in the memo titled "Food Factors", from R. D. Schmitt, Ph.D. to O.E. Paynter, Ph.D., dated October 4, 1977).

Grain Crops	lbs/week/household	% Diet (Food factor)
Corn	2.38	-
Oats	0.35	-
Rice	0.54	-
Rye	0.002	-
Wheat	10.14	-
Total	13.41	13.70

Total Food Factor for Grain Crops = 13.70%

2. For the purpose of this request, the NOEL used for calculations was 10.00 mg/kg/day which was obtained from a 2-year chronic feeding study in rats (see memo titled "Tolerances for Thiabendazole; Re-assessment of ADI", by R. Engler, Ph.D. to Dr. E. Wilson, dated April 19, 1977).

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3. Based on the above, and a safety factor of 100, the following was obtained:

ADI = 0.100 mg/kg/day  
MPI = 6.000 mg/day/60 kg

Present TMRC\* = 1.3338 mg/day/1.5 kg  
Present %ADI\* = 22.23%

Incremental increase in TMRC\*\*  
due to CODEX proposal = 0.02556 mg/day/1.5 kg  
Incremental increase in %ADI\*\*  
due to CODEX proposal = 0.43%

\* INCLUDES PRESENTLY ESTABLISHED EPA TOLERANCE OF 0.1 ppm  
IN OR ON WHEAT

\*\* INCLUDES INCREMENTAL INCREASE IN WHEAT (FROM 0.1 ppm TO  
PROPOSED 0.2 ppm)

See Computer Printout (attached).

4. Relevant toxicological data on thiabendazole is summarized in the attached memo titled "THIABENDAZOLE (TBZ, MERTECT)".
5. Presently available toxicological data is considered adequate to support the proposed CODEX tolerances which would add only 0.02556 mg/day/1.5 kg to the TMRC and only 0.43% to the %ADI used up (new %ADI of 22.66%).

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CFR 180.242

Triabendazole

1/4/79

Unverified Printout

## ACCEPTABLE DAILY INTAKE DATA

Rat	NOEL	S.F.	ADI	MPI
mg/kg	ppm		mg/kg/day	mg/day/60kg
10.000	200	100	0.100	6.000

## Published Tolerances

CROP	Tolerance	Food Factor	mg/day/1.5kg
Apples (2)	10.000	2.53	0.37950
Citrus Fruits (33)	10.000	3.81	0.57179
Pears (116)	10.000	0.26	0.03832
Bananas (7)	0.400	1.42	0.00852
Squash (191)	1.000	0.11	0.00165
Sugar, cane/beet (154)	0.250	3.64	0.01364
Dairy Products (93)	0.100	28.62	0.04292
Meat, red (90)	0.100	10.31	0.01622
Sweet Potatoes (157)	0.025	0.40	0.00012
Potatoes (127)	3.000	5.43	0.24420
Soybeans (148)	0.100	0.92	0.00138
Wheat (170)	0.100	10.36	0.01554

6.000 MPI

TMRC

% ADI

mg/day/60kg

1.3338 mg/day/1.5kg

22.23

Current Action - CODEX proposal of 0.2 ppm  
in or on raw grain crops.

CROP	Tolerance	Food Factor	mg/day/1.5kg
Grain crops *	0.200 *	13.70	0.04110

(minus contribution of wheat at 0.1 ppm) - 0.01554

Total increase in TMRC = 0.02556

\* includes wheat at 0.2 ppm

MPI	TMRC	% ADI
6.000 mg/day/60kg	1.35936 mg/day/1.5kg	22.66

THIABENDAZOLE (TBZ, MERTECT<sup>®</sup>)Conclusions and Suggestions

A survey of Toxicology Branch files, Chemistry Branch petition files and readily accessible informational resources revealed the following about Thiabendazole.

- (1) Thiabendazole has long been recognized as an anthelmintic against parasitic worms in humans and domestic animals. The maximal daily dose for humans according to The United States Dispensatory (27th edition, 1973), in which it is listed, is 3 grams per day.
- (2) Thiabendazole (and/or its metabolite, 5-hydroxythiabendazole) has tolerances ranging from 0.1 ppm on meats, meat byproducts, fat and milk to 10 ppm on apples, pears citrus fruits and sugar beet tops. See 40 CFR 180.242.
- (3) Relevant toxicological data on Thiabendazole include:

Feeding Studies

- (a) 30-Day Subacute Feeding, Rats  
NOEL < 100 mg/kg/day
- (b) 6-Month Subacute Feeding, Rats  
NOEL = 50-100 mg/kg/day
- (c) 2-Year Chronic Feeding, Rats  
NOEL = 10 mg/kg/day (TB Memo by R. Engler, Ph.D., 4/19/77)  
Negative for oncogenic effects
- (d) 2-Year Chronic Feeding, Rats  
Negative for oncogenic effects
- (e) 2-Year Chronic Feeding, Dogs (Merck)  
NOEL = 20-100 mg/kg/day
- (f) 2 Year Chronic Feeding, Dogs (Woodard)  
NOEL = 50 mg/kg/day
- (g) 14-Week Subacute Feeding  
NOEL < 156 mg/kg/day      lambs  
NOEL = 15-46 mg/kg/day      swine  
NOEL = 89-247 mg/kg/day      calves
- (h) 16-Week Subacute Feeding, Sheep  
NOEL = 10-50 mg/kg/day
- (i) 50-Week Subacute Feeding, Sheep  
NOEL = 30-50 mg/kg/day

Oncogenic Studies

- (a) See 2-Year Chronic Feeding, Rats (2 studies, above)
- (b) 18-24 Month Oncogenic Study, Mice (In Progress)  
Currently being performed by Merck, Sharpe & Dohme

Teratogenic Studies

- (a) Teratology Study, Rats  
0 and 80 mg/kg/day on days 8-15 of gestation  
Negative for terata

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- (b) Teratology Study, Rabbits  
0, 100, 200, 400 and 800 mg/kg/day on days 8-16 of gestation  
Negative for terata

Reproduction Studies

- (a) Rats, 3-Generations, 2 Litters/Generation  
0, 20, 40 and 80 mg/kg/day  
NOEL = 40 mg/kg/day (?)  
(b) Mice, 5-Generations  
NOEL = 150 mg/kg/day  
(Also negative for terata)

Inhalation Study

- (a) 31-Day Subacute Inhalation Study, Mice  
Fine dust, 6 hours/day, 5 days/week  
Single dosage level of 70 mg/M<sup>3</sup> (or 0.07 mg/L) produced  
no effects.

Metabolism Studies

- (a) Man  
14 or 28 mg/kg orally. 87-100% of dose recovered in urine  
(80-91%) and feces (4-9%) within 48 hours. Nearly all of  
urinary products were metabolites. Major metabolite was  
5-hydroxythiabendazole (with conjugation to glucuronide  
and sulfate)  
(b) Rats, Dogs, Cattle, Sheep, Goats, Swine.  
Findings were very similar to those obtained in man. Tissues  
taken several days after treatment were virtually free of  
thiabendazole and/or metabolites.

- (4) Data gaps for Thiabendazole include:  
Mutagenicity studies

~~There does not appear to be any outstanding reasons why Thiabendazole  
should not be considered a potentially viable alternative for Benomyl.~~

Data Examined

- (1) The United States Dispensatory, 27th edition, 1973, p.p. 1181-2.  
(2) 40 CFR 180.242  
(3) Toxicology Branch Caswell, subject and petition files  
(4) Toxicity Profile (Contractor--dated 10/4/78)  
(5) Registry of Toxic Effects of Chemical Substances 1977 (NIOSH)  
(6) Suspected Carcinogens 1976 (NIOSH)  
(7) Accession #095267, 008323, and 095266

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Attachments

- (1) p.p. 1181-2 of The United States Dispensatory, 27th edition, 1973
- (2) 40 CFR 180.242 (1977)
- (3) Toxicity Profile (Contractor--dated 10/4/78)
- (4) Toxicology Branch Memo by R. Engler, Ph.D. (dated 4/7/77 and 4/19/77) and by Orville Paynter, Ph.D. (dated 4/19/77)

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The U. S. Dispensatory, 27<sup>th</sup> ed., 1943

Thiabendazole

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1181

to do with inadequate absorption and gastric intolerance of the compound. In seeking a solution to these problems, a number of water-soluble salts of theophylline have been prepared.

Mention may be made here of the action of theophylline as a diuretic, of its increase of cardiac output, and of its dilation of afferent renal arterioles (Schroeder, *J.A.M.A.*, 147, 1109, 1951). It is useful in the dyspnea of bronchial asthma; also in paroxysmal dyspnea secondary to acute left ventricular strain, and possibly in angina pectoris and coronary artery disease. Elixir dosage forms of theophylline and its salts are usually well tolerated, rapidly absorbed, and very effective.

**Dose.**—The usual dose of theophylline is 200 mg., 3 or 4 times daily, after meals. The dose for children is 10 mg. per Kg. of body weight daily, subdivided into 2 or 3 portions orally administered.

**Theophylline Derivatives.**—As noted above, many compounds of theophylline have been made in the effort to find better absorbed and better tolerated dosage forms of the drug. The most widely used compound is formed by neutralizing theophylline with ethylene diamine; the product is aminophylline, described elsewhere in this volume. Other compounds are described in the following paragraphs.

**Theophylline sodium acetate**, a hydrated mixture of sodium theophylline and sodium acetate in approximately equimolecular proportions, contains between 55 and 65 percent of anhydrous theophylline; it is included in N.F. XIII. A white, crystalline powder, 1 Gm. dissolves in about 25 ml. of water; it is insoluble in alcohol, chloroform, and in ether. It has the actions and uses of theophylline, but in the past has been used especially as a diuretic. The usual range of dose is 200 to 300 mg., 3 or 4 times daily, after meals.

**Theophylline sodium glycinate**, included in N.F. XIII, is an equilibrium mixture of sodium theophylline and aminoacetic acid in approximately equimolecular proportions buffered with an additional mole of aminoacetic acid, contains, when dried, 49 to 52 percent of anhydrous theophylline. It was synthesized and studied by Krantz *et al.* (*J.A.Ph.A.*, 36, 248, 1947) in a search for a better tolerated theophylline compound, which it has proved to be. It can be given in larger dosage than the more alkaline theophylline preparations; its uses are those of aminophylline. It is administered orally in liquid dosage forms, and also in tablets that need not be enteric-coated; in emergencies intravenous administration may be employed. The usual dose orally for adults is 400 mg., but may be as much as 1 Gm., given every 6 hours; the intravenous dose is 400 mg. in 10 ml., injected slowly to test its effectiveness and the tolerance of the patient, increased to 800 mg. in 20 ml. if necessary, and repeated 3 or 4 times daily until oral therapy can be employed. Elixir, syrup, injection, suppository, 1 tablet dosage forms are available under the trademarked names *Glynozai* (First Texas), *Synophylate* (Central), and *Theoglycinate* (Brayten).

**Theophylline monoethanolamine**, also called *theophylline ethanamine*, is a compound of theophylline and monoethanolamine which contains about 75 percent of theophylline (approximately the same as in aminophyl-

line); it is used for the same purposes as aminophylline. Capsule and suppository dosage forms are available under the trademarked name *Monotheamin* (Lilly); a single-dose unit for rectal administration of the drug is also available (*Fleet*).

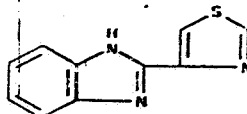
**Dyphylline**, also called *hyphylline*, is 7-(2,3-dihydroxypropyl)theophylline, and contains about 70 percent of anhydrous theophylline. It is a white, amorphous powder, freely soluble in water and sparingly soluble in alcohol; its aqueous solution is essentially neutral. When administered orally it produces less nausea than aminophylline and other alkaline theophylline compounds; therefore it can be given in larger doses than aminophylline. Dyphylline has the peripheral vasodilator, bronchodilator, diuretic, and myocardial stimulant actions of aminophylline and other theophylline derivatives. It may be administered orally or intramuscularly. The usual oral dose for adults is 200 mg. 3 or 4 times daily, which may be increased to 800 mg. 3 times daily when necessary. For treatment of an acute asthma attack or cardiac dyspnea, 500 mg. may be injected intramuscularly, very slowly, and repeated if necessary. The oral dose for children is 14 mg. per Kg. of body weight daily, given in 3 or 4 divided doses. Dyphylline is available in elixir, injection, and tablet dosage forms under the trademarked names *Dilor* (Savage), *Lufyllin* (Mallinckrodt), and *Neothylline* (Lemmon).

**Oxytriphylline** is *choline theophyllinate*, also called *theophylline choline*; it is a combination of molecular equivalents of theophylline and choline and contains about 64 percent of theophylline. It is a white, crystalline powder, very soluble in water and freely soluble in alcohol; its aqueous solution is alkaline. Reports of improved gastrointestinal absorption and tolerance, compared to aminophylline, have been published, but a comparison with other theophylline compounds has not come to our attention. Oxytriphylline is administered orally in conditions for which aminophylline and other theophylline derivatives may be used. The usual range of dose for adults is 100 to 400 mg., 4 times daily, after meals and at bedtime. The dose for children 2 to 12 years of age is 3.6 mg. per Kg. of body weight 4 times daily. Oxytriphylline is available in tablets containing 100 and 200 mg., under the brand name *Choledyl* (Warner-Chilcott).

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# Thiabendazole

Thiabendazole is 2-(4-thiazolyl)benzimidazole and contains, on the anhydrous basis, not less than 98.0 percent of  $C_{10}H_7N_3S$  (201.25).



Mintrol (Merck Sharp & Dohme).

Thiabendazole may be prepared by interactions involving *o*-nitroaniline and 4-thiazolecarbonyl chloride as

the principal reactants (Brown *et al.*, *J.A.C.S.*, 83, 1764, 1961; U.S. Patent 3,017,415, issued in 1962).

**Description.**—White to practically white powder; odorless or practically odorless. Practically insoluble in water; 1 Gm. dissolves in about 150 ml. of alcohol and 300 ml. of chloroform; very slightly soluble in ether. Melts between 296° and 303°.

**Actions and Uses.**—Thiabendazole is an anthelmintic active against a variety of helminths. It is useful in the treatment of ascariasis (large roundworm infection), creeping eruption or cutaneous larva migrans (infection of the skin of man caused by the larvae of the dog and cat hookworm, *Ancylostoma brasiliense*, and *A. caninum*), enterobiasis or oxyuriasis (*Enterobius vermicularis* or pinworm infection), strongyloidiasis (*Strongyloides stercoralis* or threadworm infection), trichinosis (*Trichinella spiralis* infection), trichuriasis (*Trichuris trichiura* or whipworm infection), and uncinariasis or ancylostomiasis (hookworm disease due to *Necator americanus* or *Ancylostoma duodenale*). Thiabendazole is the drug of choice in the treatment of creeping eruption and strongyloidiasis. It is considered highly effective against *Enterobius vermicularis* infection. It reduces symptoms of trichinosis but it does not appear that it will eliminate the adult *Trichinella spiralis*. In the treatment of hookworm disease due to *Necator americanus*, thiabendazole appears to be as effective as tetrachloroethylene; against *Ancylostoma duodenale*, thiabendazole may be more effective and less toxic than tetrachloroethylene. In the treatment of *Trichuris trichiura* infections variable effectiveness is reported but it is considered a preferred drug. Results in the treatment of ascariasis (*Ascaris lumbricoides* infection) have been variable unless high dosage is used; piperazine citrate may be the drug of choice in this infection (Plorde *et al.*, in *Harrison's Principles of Internal Medicine*, 6th ed., 1970).

Thiabendazole is rapidly absorbed from the gastrointestinal tract; maximum plasma levels are attained 1 to 3 hours after oral administration, and within 48 hours about 90 percent of the metabolites of the drug have been excreted in the urine. Food in the digestive tract is claimed not to have any effect on the action of the drug, and purgation prior to treatment is not necessary.

**Untoward Effects.**—Dizziness, anorexia, nausea, and vomiting occur the most frequently; diarrhea, fever, abdominal distress, flushing, chills, angioneurotic edema, pruritus, lethargy, perianal rash, skin rash, and headache occur less frequently. Tinnitus, hypotension, and collapse, and also numbness, hyperglycemia, and xanthosis have been reported. It is possible that some untoward effects occur as a result of sudden destruction of large numbers of parasite and absorption or released toxic organic material. Also, some of the effects may be caused by penetration of the gut by the parasite and migration into the lung as a result of stimulation by thiabendazole; this may occur with ascariasis, necessitating close supervision of patients with ascariasis.

**Warnings and Precautions.**—The hepatotoxic potential of thiabendazole requires that it be used with caution in patients with liver disease or impaired liver function.

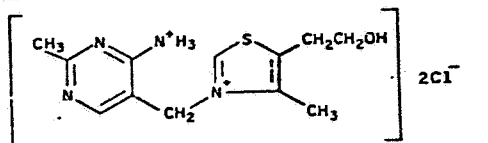
Although studies on animals have failed to reveal evidence of teratogenicity, use of thiabendazole in pregnant women should be undertaken only if the possible beneficial effect outweighs the possibility of damage to the fetus.

**Dose.**—The usual dose, given orally, is 25 mg. per Kg. of body weight twice daily. This dosage is given for 1 or 2 days in the treatment of strongyloidiasis, uncinariasis, and ascariasis. In trichuriasis the same dosage is given for 2 to 4 days, in cutaneous larva migrans for 2 days, in enterobiasis for 1 day and repeated in 7 days, and in trichinosis for 2 to 4 days. The maximal daily dose is 3 Gm.

**Dosage Form.**—Suspension containing 500 mg. in 5 ml.

### Thiamine Hydrochloride Thiamine Mononitrate

Thiamine hydrochloride contains, on the dry basis, not less than 98.0 percent of  $C_{12}H_{17}ClN_4OS \cdot HCl$  (337.27). Thiamine mononitrate contains, on the dry basis, not less than 98.0 percent of  $C_{12}H_{17}N_4O_3S$  (327.36). The structural formula of the hydrochloride is



Thiamine Hydrochloride: Aneurine hydrochloride; thiamine chloride; vitamin B<sub>1</sub> hydrochloride. Thiamine Mononitrate: Aneurine nitrate; thiamine nitrate; vitamin B<sub>1</sub> mononitrate.

Vitamin B<sub>1</sub> was first isolated in crystalline form from rice bran by Jansen and Donath, in 1926, who named it *aneurin*. Its empirical formula was determined by Windaus and his collaborators in 1932 and Williams and Cline in 1936 announced its synthesis (*J.A.C.S.*, 58, 1504, 1936). For a method of synthesizing the pyrimidine and thiazole moieties of thiamine, and of combining them, see Cline *et al.* (*J.A.C.S.*, 59, 1052, 1937).

Thiamine hydrochloride and thiamine mononitrate represent two different types of salts of thiamine. In the hydrochloride, 1 molecule of thiamine is combined with 2 chloride ions; in the mononitrate, 1 molecule of thiamine is combined with 1 nitrate ion. The reason is that in the hydrochloride the  $NH_2$  of the pyrimidine moiety is positively charged by acceptance of a proton, and since the thiazole nitrogen is quaternary, 2 chloride ions are required for the doubly-charged cation. In the mononitrate, the only charge is on the thiazole nitrogen, and a single nitrate ion suffices for electrostatic neutralization. An important difference in the properties of the salts is that the hydrochloride is acid in solution, the pH being about 3, while the mononitrate is practically neutral, the pH being close to 7.

**Description.**—Thiamine Hydrochloride: Small, white crystals or crystalline powder, usually having a slight, characteristic odor. When exposed to air, the anhydrous

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§ 180.242

## Chapter I. Environmental Protection Agency

§ 180.237 (Methylsulfonyl) - 2, 6-dinitro-*N,N*-dipropylaniline; tolerances for residues

Tolerances are established for negligible residues of the herbicide 4-(methylsulfonyl) - 2, 6-dinitro - *N,N*-dipropylaniline in or on the raw agricultural commodities almonds, almond hulls, broccoli, brussels sprouts, cabbage, cauliflower, cottonseed, cucurbits, forage legumes, fruiting vegetables, peanuts, pome fruits, safflower seed, seed and pod vegetables, soybeans (dry form), and stone fruits at 0.1 part per million.

(37 FR 1302, July 12, 1972)

§ 180.238 Propylbutylethylthiocarbamate; tolerances for residues.

Tolerances are established for negligible residues of the herbicide *S*-propylbutylethylthiocarbamate in or on the raw agricultural commodities sugar beets (roots and tops) and tomatoes at 0.1 part per million.

§ 180.239 Phosphamidon; tolerances for residues.

Tolerances (expressed as phosphamidon) for residues of the insecticide phosphamidon (2-chloro-2-diethylcarbamoyl-methylvinyl dimethyl phosphate) including all of its related cholinesterase-inhibiting compounds in or on raw agricultural commodities are established as follows:

1 part per million in or on apples.  
0.75 part per million in or on grapefruit, lemons, oranges, tangerines.  
0.5 part per million in or on broccoli, cauliflower, cucumbers, peppers.  
0.25 part per million in or on cantaloupes, watermelons.  
0.1 part per million in or on cottonseed, potatoes, sugarcane, tomatoes and walnuts.

§ 180.240 *S*-Propyl dipropylthiocarbamate; tolerances for residues.

Tolerances are established for negligible residues of the herbicide *S*-propyl dipropylthiocarbamate in or on the raw agricultural commodities corn grain, corn fodder and forage, fresh corn including sweet corn (kernels with husk removed), peanuts,

peanut forage, peanut hay, potatoes, soybean forage, soybean hay, soybeans, and sweet potatoes at 0.1 part per million.

(37 FR 2839, Feb. 8, 1972)

§ 180.241 *S*-(*O,O*-Diisopropyl phosphorodithioate) of *N*-(2-mercaptoethyl) benzenesulfonamide; tolerances for residues.

Tolerances are established for negligible residues of the herbicide *S*-(*O,O*-diisopropyl phosphorodithioate) of *N*-(2-mercaptoethyl) benzenesulfonamide including its oxygen analog *S*-(*O,O*-diisopropyl phosphorodithioate) of *N*-(2-mercaptoethyl) benzenesulfonamide in or on the raw agricultural commodities, carrots, cottonseed, cucurbits, fruiting vegetables, leafy vegetables, and onions (dry bulb) at 0.1 part per million.

§ 180.242 Thiabendazole; tolerances for residues.

(a) Tolerances are established for residues of the fungicide thiabendazole (2-(4-thiazolyl) benzimidazole) in or on the following raw agricultural commodities:

Commodity	Parts per million
Apples (post-h)	10
Bananas (post-h)	3
Bananas, pulp (post-h)	0.4
Beets, sugar without tops (pre-h)	0.25
Beets, sugar, tops	10
Citrus fruits (post-h)	10
Pears (post-h)	10
Potatoes (pre and post-h)	3
Soybeans	0.1
Squash, Hubbard	1
Wheat, grain	0.1
Wheat, straw	0.2

(b) Tolerances are established for combined residues of thiabendazole and its metabolite 5-hydroxythiabendazole in the following raw agricultural commodities:

Commodity	Parts per million
Cattle, fat	0.1
Cattle, mbyp	0.1
Cattle, meat	0.1
Goats, fat	0.1
Goats, mbyp	0.1
Goats, meat	0.1
Hogs, fat	0.1
Hogs, mbyp	0.1
Hogs, meat	0.1
Horses, fat	0.1
Horses, mbyp	0.1

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## § 180.243

Commodity	Parts per million
Horses, meat.....	0.1
Milk.....	0.1
Sheep, fat.....	0.1
Sheep, mby.....	0.1
Sheep, meat.....	0.1

[42 FR 32783, June 28, 1977, as amended at 42 FR 44812, Sept. 7, 1977]

§ 180.213 2-Chloro-4,6-bis(isopropylamino)-s-triazine; tolerances for residues.

A tolerance of 0.25 part per million is established for negligible residues of the herbicide 2-chloro-4,6-bis(isopropylamino)-s-triazine in or on the raw agricultural commodities sorghum grain, forage, and fodder.

§ 180.211 Basic zinc sulfate; tolerances for residues.

A tolerance of 30 parts per million is established for residues of the fungicide basic zinc sulfate, calculated as elemental zinc, in or on the raw agricultural commodity peaches.

§ 180.215 Streptomycin; tolerances for residues.

Tolerances of 0.25 part per million are established for negligible residues of the fungicide streptomycin in or on the raw agricultural commodities celery, peppers, and tomatoes from treatment of the seedling plants before transplanting; potatoes from treatment of seed pieces; and pome fruits.

[38 FR 31539, Nov. 15, 1973]

§ 180.216 Daminozide; tolerances for residues.

Tolerances are established for residues of the plant regulator daminozide [butanediol acid mono (2,2-dimethylhydrazide)] in or on raw agricultural commodities as follows:

55 parts per million in or on sour cherries.

50 parts per million in or on plums (fresh prunes).

40 parts per million in or on tomatoes.

30 parts per million in or on apples, pectarines, peaches, peanuts, and sweet cherries.

20 parts per million in or on brussels sprouts, peanut hay, and pears.

## Title 40—Protection of Environment

10 parts per million in or on grapes and peanut hulls.

3 parts per million in or on melons.

2 parts per million in poultry kidney.

1 part per million in or on peppers.

0.2 parts per million in the meat, fat and meat byproducts of cattle, goats, hogs, horses, poultry (except poultry kidney), and sheep.

0.2 part per million in eggs.

0.02 part per million (negligible residue) in milk.

[36 FR 22540, Nov. 25, 1971, as amended at 38 FR 28937, Oct. 18, 1973; 40 FR 19476, May 5, 1975; 40 FR 42357, Sept. 12, 1975]

§ 180.247 2-Chloroallyldiethyldithiocarbamate; tolerances for residues.

Tolerances are established for negligible residues of the herbicide 2-chloroallyldiethyldithiocarbamate in or on raw agricultural commodities bean vines, broccoli, brussels sprouts, cabbage, cantaloups, cauliflower, celery, chicory, collards, corn (kernels plus cob with husk removed), corn fodder and forage, corn grain, cucumbers, endive (escarole) kale, lettuce, lima beans, mustard greens, okra, potatoes, snap beans, soybeans, soybean forage and hay, spinach, tomatoes, turnip greens, turnips, and watermelons at 0.2 part per million.

[36 FR 22540, Nov. 25, 1971, as amended at 38 FR 3511, Feb. 7, 1973]

§ 180.218 Neodecanoic acid; tolerances for residues.

A tolerance of 1 part per million is established for negligible residues of the desiccant and defoliant neodecanoic acid (a mixture of 10-carbon trialkyl acetic acids (calculated as C<sub>10</sub>H<sub>19</sub>COOH)) in or on the raw agricultural commodity cottonseed.

§ 180.249 Alachlor; tolerances for residues.

Tolerances are established for combined residues of the herbicide alachlor (2-chloro-2',6'-diethyl-N-(methoxymethyl) acetanilide) and its metabolites (calculated as alachlor) in or on raw agricultural commodities as follows:

3 parts per million in or on peanut forage and hay.

## Chapter I—En

1.5 parts per hulls.

0.75 part per bean forage.

0.2 part per due) in or on corn grain, co hay of peas an

0.1 part per due) in or on lima beans, l mined on pea: present when

0.05 part pe due) in or on cluding sweet with husk ren

0.02 part pe due) in milk, and meat by: hogs, horses,

[38 FR 32909, 39 FR 7422, Feb 15, 1974]

§ 180.250 3-(p-methylurea

A tolerance established f cide 3-(p-br-methylurea) tural commo

§ 180.251 Doc metheno-2 tolerances

Tolerances ticide dodec: metheno-27: in or on raw are establish

0.1 part p due) in the goats, hog: sheep.

0.1 part p flecting neg

0.1 part p due) in eggs

0.01 part due) in or o

modities (e and the f

horses, poul

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Toxicity Profile - ThiabendazoleAcute Toxicity

Animal	Sex	Route	Formulation	LD <sub>50</sub> ± 95% C.I.
Mouse	Female	Oral	Vertect 140-F (42%)	3.05 g/kg (2.23-4.1)
	Female	Oral	Vertect 160 (60.6%) <sup>A</sup>	7.63 g/kg (6.51-8.8)
	Female	Oral	Vertect 360 (60.6%) <sup>A</sup>	7.40-7.63 g/kg (6.1)
Rat	Male	Oral	Vertect 160 (60.6%) <sup>A</sup>	8.10 g/kg
	Male	Oral	Vertect 360 (60.6%) <sup>A</sup>	5.23-8.10 g/kg
	Male	Oral	Primafresh-24 with TBZ (0.15%)	>5 ml/kg
	Female	Oral	Vertect 160 <sup>A</sup>	8.10 g/kg
	Female	Oral	Vertect 360 <sup>**</sup>	5.04-8.10 g/kg
	Female	Oral	Primafresh-24 with TBZ (0.15%)	>5 ml/kg
Rabbit	Male & Female	Dermal	Metasol EPXP-41 (50%)	13.5 g/kg (12.6-14)
	Male & Female	Dermal	Metasol EPXP-41 (50%)	>50 ml/kg
	Male & Female	Dermal	Technical (93.5%)	>4 g/kg

Inhalation Toxicity

Animal	Sex	Dosage	Formulation	Exposure	Results
Mouse	Female	70mg/m <sup>3</sup>	Aerosol	6hrs/day, 5 day/week for 4 weeks + 3days (133 hrs)	very low order of subacute toxicity; pulmonary route - signs of respiratory distress, eye irritation or general discomfort
Rats	Male & Female	50,200, 500, + 1000 mg/1000 l	Aerosol (Metasol EPXP-41)	1 hour	no signs of systemic toxicity; no death

Irritation Studies

Animal	Sex	Route	Formulation	LD <sub>50</sub> ± 95% C.I.
Rabbit	-	Eye	Vertect 140F, 160, 360-EP, Primafresh-24 with TBZ (0.15%) and Technical Powder (93.5%)	0.1g or 0.1ml - slight eye irritation; none after 24 hours 3 days generally
Rabbit	-	Dermal	Vertect 140F, 160, 360-EP, Primafresh-24 with TBZ (0.15%) and Technical Powder (93.5%)	0.1g or 0.1ml - mild to slight irritation with slight edema; no irritation by Primafresh-24 or Technical Powder.

Administered as a 20% concentrate in 1% aqueous methylcellulose.  
Administered as a 40% concentrate in 1% aqueous methylcellulose.

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Two year feeding study-rats: Charles River weanling albino rats were fed thiabendazole (purity unspecified - code no. L-585216-0-40) at 0, 10, and 120 mg/kg/day bodyweight in the diet to 35 male and 35 female rats in each group. Thiabendazole causes statistically significant growth depression in male rats at both dietary levels (at 13, 27 and 50 weeks) and in female rats at the high dose level at the same time periods. Hematology: Mean hematological values at 5, 31, 53, 77 and 101 weeks were comparable for the control and the 120 mg/kg/day dose level. Pathology: Statistically significant decreases in mean absolute adrenal weights of males at both dose levels and increases in mean absolute thyroid weights of males at the 120 mg/kg/day dose level occurred. Histopathology: On the basis of histopathological observations, there were no apparent significant differences between the control and treated groups (aside from neoplasia). For neoplasms, there was no apparent difference between the control and treated groups in regards to the frequency of pituitary adenomas, but there was a greater frequency of other tumors in the controls than observed in treated rats. This study showed a high mortality at all dose levels after 2 years and includes animals sacrificed in a moribund condition.

	Dead/Alive*	
	Male	Female
Control	25/10	20/15
120 mg/kg/day	30/5	25/12
80 mg/kg/day	27/8	20/15

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- \* About 59% of deaths and animals sacrificed in moribund condition occurred after 70 weeks of the study and was attributed to the age of the rats.

Two year feeding study-rats: Charles River rats were fed thiabendazole (purity unspecified - code no. L-585216-0-40) in the diet to 35 male and 35 female rats to give concentrations of 0, 10, 40, and 160 mg/kg/day, starting one week after weaning, for 103-107 weeks. This is a study similar to the one above. No effects were noted which were attributable to the thiabendazole for survival, time of death in non-survivors, neoplasm incidence or location and tissue histopathology. At either the 10 and 40 mg levels, there were no effects on weight gain, food consumption, or hemograms. At the 160 mg level, there was a 29% reduction in weight gain corresponding to the reduced food consumption and slightly reduced hemoglobin and microhematocrit values; these were the only effects attributable to thiabendazole administration.

- Two year feeding study-dogs: Purebred beagle dogs were fed by gelatin capsules, 0, 20, 50, and 125 mg/kg daily for 101 weeks to 3 males and 3 females in each dose level. Purity of thiabendazole was unspecified (Code L-585216-0-40).

At the 20 and 50 mg/kg/day levels, no effects attributable to thiabendazole were noted on survival, weightgain, general condition, gross weights, hematological or clinical chemistry values and histopathological observations. In two dogs at the 50mg level, a small amount of inspissated material was found adhering to the gall bladder mucosa.

At the 125 mg/kg level, two of six dogs died and there was slight weight loss, slight to moderate reduction in hemoglobin and packed volume, increased frequency of urinary albumin, moderate chronic inflammatory liver changes, slight liver glycogen depletion, and inspissated material adhering to the gall bladder mucosa with no evidence of extrahepatic material in the bile ducts. 002852

One non-surviving dog exhibited cirrhosis of the liver of a type not due to biliary obstruction. Prior to death this animal had elevated blood urea nitrogen, serum alkaline phosphatase, and serum glutamic oxaloacetic transaminase values. The relationship between thiazendazole dosage and these signs is uncertain.

#### Toxicology

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50 (Charles River) albino female rats, weighing 240g at initiation of experiment, were administered oral doses of 0 (19 rats) and 50.4 (6 rats) mg/kg by gavage as 10% suspension at volume of 1ml/200g live weight from 10th to 15th day of gestation. Purity of thiazendazole unspecified.

a. Body weight: Not specified.

b. Reproduction and viability: Reproductive capacity of both groups were normal. Mean implantation was slightly higher in control (14.2) than in treated group (13.5) and live litter size was slightly higher in control (13.3) than in treated group (12.7). Absorption rates were the same for both groups.

c. Fetal observations: Average fetal weights the same. Sex distribution not noted but no external or internal anomalies observed for treated groups while control group had 0.4% external and 12.1% internal anomalies, the latter being essentially "skeletal variations". Total absence of embryotoxic effects.

An oral dose of 50.4 mg/kg for 7 days during gestation in Charles River albino rats was not teratogenic.

Pregnant New Zealand albino female rabbits were administered thiazendazole orally from the 8th through the 16th day of gestation at dose levels of 0, 100, 200, 400 and 800 mg/kg/day in four different studies. These four studies used 120 rabbits with 40 control and 12, 22, 22 and 24 animals at the 100 to 800 mg/kg dose levels. Daily administration of drug was by gavage in a 10% suspension in 1% Methocel followed by a 10% Methocel slurry. The greater incidence of sickness and death during these studies are attributed to this stressful administration (stomach tube) rather than to thiazendazole.

a. Body weight: There was an increasing loss of weight in two pregnant rabbits from day 4 to day 17 of gestation at 200(-5%), 400(-6%) and 800(-15%) mg/kg/day dose levels and a 10% weight gain for both the control and 100 mg/kg dose level. In two studies, the post-treatment weight changes (day 17 to 29 and 30), especially at the 200 mg/kg level, were markedly higher than the controls. The net result of weight changes from day 4 to 29 and 30 of gestation were not appreciably different between control and treated groups.

- b. Reproduction and viability: Although not stated to be significant, the percent animals surviving to those bred varied from 94% in controls to 60% at 300 mg/kg and the percent dose delivered to those bred varied from 73% in controls to 56-56% in the treatment groups. The mean weighted conception rate for the control was 6.6 and average for treatments 11.5 which was found not to be statistically significant. Average number of implants / animal was the same in control and average weight of viable fetuses slightly lower in treatment groups.
- c. Fetal observations: Average weight of viable fetuses was slightly lower in treatment groups but insignificant. Primary anomalies noted were skeletal variations but these abnormalities were similar in controls and common to rabbit colony. Abnormalities not related to treatment and there was a lack of dose response.

Thiabendazole does not appear to have teratogenic properties at dosages used.

### Three Generation Reproduction

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Male (42) and female (48) mature albino rats (F0) were assigned to a control and three treatment groups containing 10 male and 10 female rats of about 90 days of age. They were fed by intragastric dosage 0, 20, 40 and 80 mg/kg body weight of thiabendazole (purity unspecified) in 0.5% CMC solution to give 1 solution/kg body weight. Dosage given to both sides through gavage, station and weaning of the first litter and to males through mating and the females through weaning of the second litter. The pups were not fed until 28 days of age (except through dam's milk up to 21 days). F1 generation females delivered two litters (L1, Litter 1 and Litter 2) and raised their pups to weaning (21 days). F1 generation weaned pups were dosed with incorporation of thiabendazole into the basal diet (unspecified) at levels above. Same procedure for F2, Litter 1 pups. At 100 days of age dietary age was discontinued and dosage was by gastric incubation.

- a. Body weight: For durations of 10 weeks, both body weight gain and food intake were lower in dietary treatments than in controls of males in both F1 and F2 generation and only in females in the F2. However, efficiency of food utilization were similar in all groups. Final body weights of F3 rats at 28 days of age were similar in all groups.
- b. Hematology: Hematological data all normal for F1 and F2 rats compared to pre-treatment F0 rats at 100 days of age and F3 at 28 days of age at different treatment levels.
- c. Urinalysis: No significant differences between the generations nor drug dose levels for specific gravity or pH.
- d. Reproduction and viability: No abnormalities of pups observed in any of the dose levels for Litter 1 and 2 of F0, F1 and F2 generations nor were there any apparent differences in other reproduction and lactation responses attributable to thiabendazole.
- e. Pathology: Prostate gland weight increase of 23 and 75% as percent of body weight and 20 and 75% on gross weight basis, respectively, and 10 and 30 mg/kg dose levels in F1 and F2 generation rats.

reverse was true in the  $F_2$  generation where smaller prostate gland weights were statistically different from the control on a weight basis but not on percent of body weight basis. In  $F_2$ , testes weights in all three treatments were significantly larger on a percent of body weight basis. This data may reflect the statistically significant smaller body weights of the  $F_2$  males at the 40 and 80 mg/kg dose levels.

- c. Histopathology: The differences cited under Pathology did not indicate biological difference since no significant structural changes were revealed. No treatment related pathological manifestations were found in rats given thiaabendazole.

Doses of 20, 40 or 80 mg/kg body weight over  $F_0$  to  $F_3$  generation indicates thiaabendazole is not a teratogen.

\* Food and Drug Research Labs, Hespeth, N.Y.

#### Data Gaps

#### Mutagenicity

#### Reference

EPA files Acc. Nos. 050171, 001522, 022912, 004138, 220007, 101573, 110571, 227763, 227778, 100853, 100637, 050040, 123717, 001791, 001730  
Delacour, et.al. Actualite Therapeutique (Comparative), Bull. Soc. Sci. Vet. et Med. 76(2):147-154 (1974). Translated from French, p. 126-144.

October 4, 1973

Robert A. Zimmerman, Ph.D.

Richard L. Johnson, Ph.D.

Reginald A. Herin, D.V.M., Ph.D.

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8491H  
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Egler  
002852

SUBJECT: Tolerance for Thiabendazole 4:0 ppm on Sugarbeets  
(from post harvest application).

DATE: APR 7 1977

FROM: Toxicology Branch (Eng/rr)

TO: J. C. Wilson  
Product Manager  
Food Chemistry Branch

Pesticide Petition: 6F1860 and 5F1646

Petitioner: Merk Co.

Conclusion: The requested tolerance on sugarbeets and the previously requested tolerance of 0.1 ppm on soybeans can be established, provided that an assurance is obtained from the petitioner that a second oncogenicity study (second species) will be submitted within a reasonable time span, and interim reports of this study will be submitted as they become available. (The usual time required for such an oncogenicity study is 2.5 to 3 years). Furthermore, mutagenicity testing must be carried out, or initiated at the time when requirements become finalized. This conclusion is reached because:

- The studies submitted previously show that thiabendazole is not oncogenic for the rat, is not a teratogen, and does not affect reproduction, and

- The requested tolerances on sugarbeets and soybeans will not add an appreciable amount, if any, to the dietary burden of man; see also determination of ADI and maximal theoretical exposure (MTE) calculation in review.

Notes: The previous recommendation, not to establish the soybean tolerance (memo of October 28, 1976) was based solely on the concept of a data gap with respect to proposed data requirements.

Review

New toxicity data were submitted. We refer to our reviews of September 2, 1975; and October 28, 1976 (PP 5F1646). For convenience the toxicity tests are listed below; thiabendazole also has a history as an antihelmintic drug.

LD<sub>50</sub> (rat)  
LD<sub>50</sub> (mouse)  
Subacute feeding (rat)

Teratology (rats)

3.33 g/kg  
3.81 g/kg  
NEL 100 mg/kg; dose finding  
study 30, and 120 days,  
30% deaths at 800 mg/kg  
Negative at 80 mg/kg/day;  
8-15th day of pregnancy

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- 2 -

2-year rat feeding  
2-year dog feeding  
5-generation reproduction  
(mouse)

NEL 40 mg/kg/day  
NEL 50 mg/kg/day  
negative at 150 mg/kg

mg /kg /day

### ADI, NPI, and MTE

Based on the rat 2-year feeding study the ADI for man (100-X safety factor) is 0.4 mg/kg b.w./day which results in a NPI for a 70 kg man of 24 mg/day.

*changed*

*See Engler*

*MEMO 4/19/77*

*(attached)*

Tolerances for thiabendazole are established for the following residues (180.242):

- 10 ppm apples, citrus, pears, sugarbeet tops
- 3 ppm bananas (0.4 ppm in pulp)
- 1 ppm hubbard squash
- 0.25 ppm sugarbeets
- 0.1 ppm milk; meat, fat and meat byproducts, cattle, goats, hogs, horses and sheep.
- 0.02 ppm sweet potatoes.

Using the appropriate food factors the MTE (maximum theoretical exposure) of man is calculated to be 0.982 mg/day or about 4% of the NPI, the ADI is therefore not exceeded.

*Rob Engler*

Rob Engler, Ph.D.  
Toxicology Branch  
Registration Division

*12 for OCP 4/17/77*

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

002852

DATE: April 19, 1977  
SUBJECT: Tolerances for Thiabendazole; Re-assessment of ADI.

FROM: Toxicology Branch (Engler)

TO: Dr. E. Wilson  
Product Manager  
and  
Chemistry Branch

Pesticide Petition: 6F1660 and 5F1646

The previous calculation of the ADI and thus the maximum permissible intake for man was based on a MEL of 60 mg/kg/day in a rat study. Discussions between the petitioner and officials of FDA however established that this level was in fact not a true MEL since some growth depression occurred at this level. The MEL was thus set at the next lower feeding level, namely 10 mg/kg/day. This will reduce the ADI from 0.3 mg/kg/day to 0.1 mg/kg/day and the MRL from 24 mg/day to 6 mg/day. This change, however, does not affect our previous conclusion about the safety of the proposed tolerances since this lowered ADI and MRL respectively is not exceeded by the existing and the proposed tolerances which result in a maximum theoretical exposure of roughly 1.0 mg/day.

*Engler*  
John Engler, Ph.D.  
Toxicology Branch  
Registration Division

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March 10, 1977

002852

Response to Briefing Memo for Thiabendazole - tolerance  
of 0.1 ppm in/on Soybeans (SF16-56)

Ch. of (Paynter)  
Toxicology Branch (MH-567)

E. Wilson (PI #21)  
Registration Division (MH-567)

MEMO: Associate Director for Scientific Review  
Registration Division (MH-567)

This memo addresses two points in your briefing memo concerning the  
0.1 ppm tolerance in soybeans for thiabendazole: 1) demonstration  
of "safety" of proposed tolerance and 2) the need for delayed neuro-  
toxicity tests.

- 1) Sufficient toxicological data has been submitted by the  
petitioner to satisfy the requirements for tolerances prior  
to the need for mutagenic and an additional (second)  
oncogenic studies. Thiabendazole is used in veterinary  
medicine at high levels of intake. No evidence, of which  
the TOX Branch is aware, has implicated the compound as  
producing an unreasonable adverse effect on humans in at  
the current tolerance levels. On the basis of long term  
rat feeding study we have established a NOEL of 50 mg/kg/day  
and an ADI of 0.1 mg/kg/day. This gives a RPI of 6 mg/day.  
A tolerance of 0.1 ppm on soybeans is calculated to produce  
a "RPI" to the average daily diet of 0.003 mg/day ( $0.1 \times 1.5 \times 0.02$ ).  
The "RPI" of this tolerance and existing tolerances  
is approximately 1 mg/day. This is below the RPI and the  
ADI. It is the opinion of the TOX Branch that the added  
0.003 mg/day add by the requested soybean tolerance will  
not add a significant risk to man, even without the second  
oncogenicity study. The second onco. study is not being  
waivered and is required. The potential significance of  
the second onco. study is not serious enough to disqualify  
this soybean tolerance.
- 2) Thiabendazole contains no organic phosphate or carbonate  
moiety, and therefore a delayed neurotoxicity test is not  
required by Sec. 3 regulations. In addition, we know of  
no theoretical grounds on which to suspect that thiabendazole  
would cause delayed neurotoxicity. The study in the opinion  
of the TOX Branch is unnecessary.

Dr. Hille E. Paynter, Ph.D.

Paynter/ccw 3/10/77

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