UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 002852 #849A

DATE April 17, 1979

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

FROM: Alwin 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 Thiabendazole 1/4/79

Unverified Printout

ACCEPTABLE DAILY INTAKE DATA

~~Dog~~ Rat NOEL mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI 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)	0.200	1.42	0.00852
Squash(191)	1.000	0.11	0.00165
Sugar,Cane&Beet(154)	0.250	3.64	0.01364
Milk&Dairy Products(95)	0.100	28.62	0.04292
Meat, Req(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 mg/day/60kg	TMRC 1.3338 mg/day/1.5kg	% ADI ~~0.00~~ 22.23

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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®)

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 = 20-160 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^3 (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 reason 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 Memos by R. Engler, Ph.D. (dated 4/7/77 and 4/19/77) and by Orville Paynter, Ph.D. (dated 4/19/77)

The U. S. Dispensatory, 27th ed, 1973

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, in 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 times daily, after meals.

Theophylline sodium glycinate, included in N.F. XIII, is an equilibrium mixture of sodium theophylline and glycinoacetic acid in approximately equimolecular proportions buffered with an additional mole of aminoacetic acid, contains, when dried, 49 to 52 percent of anhydrated 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 was 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 4 to 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, and tablet dosage forms are available under the trademarked names *Glynazan* (First Texas), *Synophylate* (Central), and *Theoglycinate* (Brayton).

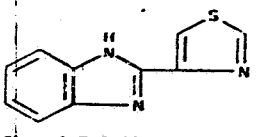
Theophylline monoethanolamine, also called *theophylline olamine*, is a compound of theophylline and monoethanolamine which contains about 75 percent of theophylline (approximately the same as in aminophylline); it is used for the same purposes as aminophylline. Capsule and suppository dosage forms are 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).

Oxtriphylline is *choline theophyllinate*, also called *theophylline cholinate*; 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. Oxtriphylline 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).

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).



Mintezol (*Merck Sharp & Dohme*).

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

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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 xanthesis 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 ascaris, 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.

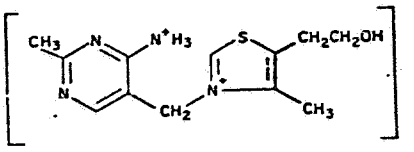
Although studies on animals have failed to reveal evidence of teratogenicity, use of thiabendazole in pregnant women should be undertaken only if the possible beneficial effect outweighs the possibility of damage to the fetus.

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 $C_{12}H_{17}ClN_4OS.HCl$ (337.27). Thiamine mononitrate contains, on the dry basis, not less than 98.0 percent of $C_{12}H_{17}N_5O_4S$ (327.36). The structural formula of the hydrochloride is



Thiamine Hydrochloride: Aneurine hydrochloride; thiamine chloride; vitamin B_1 hydrochloride. *Thiamine Mononitrate:* Aneurine nitrate; thiamine nitrate; vitamin B_1 mononitrate.

Vitamin B_1 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

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

Toleran s are established for negligible res lues of the herbicide 4-(methylsu fonyl) - 2,6 - dinitro - *N*,*N*-dipropyla iline in or on the raw agricultural c mmodities almonds, almond hulls, bra coli, brussels sprouts, cabbage, cau flower, cottonseed, cucurbits, fora legumes, fruiting vegetables, grap s, peanuts, pome fruits, safflower se l, seed and pod vegetables, soybeans dry form), and stone fruits at 0.1 par per million.

[37 FR 13(2, July 12, 1972]

§ 180.238 - Propylbutylethylthiocarbamate; lerances for residues.

Tolera es are established for negligible re dues of the herbicide *S*-propylbu ylethylthiocarbamate in or on the r w agricultural commodities sugar be s (roots and tops) and tomatoes at 0 part per million.

§ 180.239 hosphamidon; tolerances for resid s.

Tolera es (expressed as phosphamidon) r residues of the insecticide phospha idon (2-chloro-2-diethylcarbamoyl-1 methylvinyl dimethyl phosphate) i cluding all of its related cholinestera -inhibiting compounds in or on raw gricultural commodities are establish d as follows:

1 part r million in or on apples.

0.75 p t per million in or on grapefruit, le ons, oranges, tangerines.

0.5 pa per million in or on broccoli, cauliflo r, cucumbers, peppers.

0.25 p t per million in or on cantaloups, w rermelons.

0.1 pa per million in or on cottonseed, p tatoes, sugarcane, tomatoes and wal uts.

§ 180.24 *S*-Propyl dipropylthiocarbamate; tole ances for residues.

Toler nces are established for negligible r idues of the herbicide *S*-propyl propylthiocarbamate in or on the ra agricultural commodities corn grain, rn fodder and forage, fresh corn i cluding sweet corn (kernels plus co 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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Commodity	Parts per million
Horses, meat	0.1
Milk	0.1
Sheep, fat	0.1
Sheep, mbyp	0.1
Sheep, meat	0.1

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

§ 180.243 2 - Chloro - 4,6 - bis(isopropylumino)-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.

§ 180.244 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.

§ 180.245 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]

§ 180.246 Daminozide; tolerances for residues.

Tolerances are established for residues of the plant regulator daminozide [butanedioc 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, nectarines, peaches, peanuts, and sweet cherries.

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

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 residuas of the herbicide 2-chloroallyl diethyldithiocarbamate 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]

§ 180.248 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 $C_9H_{19}COOH$)) 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.

1.5 parts per
hulls.

0.75 part pe
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,
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, Fe
15, 1974]

§ 180.250 3-(p
methylurea

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

§ 180.251 Do
metheno-2
tolerances

Tolerances
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oxicity Profile - Thiabendazole

cute Toxicity

nimal	Sex	Route	Formulation	LD_{50} + 95% C.I.
ouse	Female	Oral	Mertect 140-F (42%)	3.05 g/kg (2.23-4.1
	Female	Oral	Mertect 160 (60.6%)*	7.63 g/kg (6.51-8.
	Female	Oral	Mertect 360 (60.6)*	7.60-7.63 g/kg(6.1
at	Male	Oral	Mertect 160 (60.6%)**	-8.10 g/kg
	Male	Oral	Mertect 360 (60.6%)**	5.23->8.10 g/kg
	Male	Oral	Primafresh-24 with TBZ(0.15%)	>5 ml/kg
	Female	Oral	Mertect 160**	>8.10 g/kg
	Female	Oral	Mertect 360**	5.04->8.10 g/kg
	Female	Oral	Primafresh-24 with TBZ(0.15%)	>5 ml/kg
	-	Oral	Metasol MPXP-41 (50%)	13.5 g/kg(12.6-1
abbit	Male & Female	Dermal	Metasol MPXP-41 (50%)	>50 ml/kg
	Male & Female	Dermal	Technical (98.5%)	>4 g/kg

nhalation Toxicity

nimal	Sex	Dosage	Formulation	Exposure	Results
ouse	Female	70mg/M^3	Aerosol	6hrs/day,5 day/ week for 4 weeks + 3days (133 hrs)	very low order o subacute toxicit pulmonary route- sign of respira distress, eye ir fation or genera discomfort
ats	Male & Female	50,200, 500, + 1000 mg/ L	Aerosol (Metasol MPXP-41)	1 hour	no sign of syst toxicity; no dea

rritation Studies

nimal	Sex	Route	Formulation	LD_{50} + 95% C.I.
abbit	-	Eye	Mertect 140F, 160, 360-SP, Primafresh-24 with TBZ(0.15%) and Technical Powder (98.5%)	0.1g or 0.1ml-sli eye irritation; c gone after 24 hou 3 days generally
abbit	-	Dermal	Mertect 140F, 160, 360-SP, Primafresh-24 with TBZ(0.15%) and Technical Powder (98.5%)	0.1g or 0.1ml-sli mild to slight sk irritant with sli edema; no irritat by Primafresh-24 Technical Powder.

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

Two year feeding study-rats: Charles River weanling albino rats were fed thiabendazole (purity unspecified - code no. L-505216-0-40) at 0, 80, 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 15, 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	25/10
80 mg/kg/day	27/8	20/15

* 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-505216-0-40) 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 2% 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.

3. 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-505216-0-40).

At the 20 and 50 mg/kg/day levels, no effects attributable to thiabendazole were noted on survival, weightgain, general condition, organ 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 cell 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 extraneous material in the bile ducts.

One nonsurviving 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 thiabendazole dosage and these signs is uncertain.

tology

50 (Charles River) albino female rats, weighing 260g 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 6th to 15th day of gestation. Purity of thiabendazole 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). Resorption 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 group while control group had 0.4% external and 12.1% internal anomalies, the latter being essentially "skeletal variation.". 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 thiabendazole orally from the 6th through the 18th day of gestation at dose levels of , 100, 200, 400 and 800 mg/kg/day in four different studies. Four to five studies used 17 rabbits with 41 control and 12, 22, 8 and animals at the 100 to 800 mg/kg dose levels. Daily administration of dose was by gavage in a 10% suspension in 1% Methocel followed by a 10 ml Methocel rinse. The greater incidence of sickness and death during these studies is attributed to this stressful administration (stomach tube) rather than to thiabendazole.

b. Body Weight: There was an increasing loss of weight in the pregnant rabbits from day 4 to day 17 of gestation at 200(-5%), 400(-10%) 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 400 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 84% in controls to 60% at 400 mg/kg and the percent dose delivered to those bred varied from 73% in controls to 56-60% in the treatment groups. The mean weighted resorption 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

ale (24) and female (48) mature albino rats (FDRL) were assigned to a control d three treatment groups containing 10 male and 16 female rats of about 0 days of age. They were fed by intragastric doses of 0, 20, 40 and 80 mg/kg dy weight of thiabendazole (purity unspecified) in 0.5% CMC solution to give l solution/kg body weight. Dosage given to both sires through mating, 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 osed until 28 days of age (except through dam's milk up to 21 days). generation females delivered two litters (F_1, Litter 1 and Litter 2) and their pups to weaning (21 days). F_1 generation weaned pups were dosed incorporation of thiabendazole into the basal diet (unspecified) at levels above. Same procedure for F_2, Litter 1 pups. At 100 days of age dietary age was discontinued and dosage was by gastric intubation.

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 F_1 and F_2 generation and only in females in the F_2. However, efficiency of food utilization were similar in all groups. Mean body weights of F_3 rats at 28 days of age were similar in all groups.

b. Hematology: Hematological data all normal for F_1 and F_2 rats compared to pre-treatment F_0 rats at 100 days of age and F_3 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 litters 1 and 2 of F_0, F_1 and F_2 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 25% as percent of body weight and 21 and 25% on gross weight basis between [illegible] and 40 and 80 mg/kg dose levels in [illegible]

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, tested 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.

f. 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 thiabendazole.

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

* Food and Drug Research Labs, Maspeth, N.Y.

Data Gaps

Mutagenicity

Reference

EPA files Acc. Nos. 050171, 091622, 022912, 004138, 222097, 101473, 110571, 227762, 227778, 108853, 100637, 050048, 123797, [illegible], 091739
Delatour, et.al. Actualite Therapeutic (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. Hoxie, D.V.M., P

8441H

Engler

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

002852

SUBJECT: lerance for Thiabendazole 4.0 ppm on Sugarbeets DATE: APR 7 1977
rom post harvest application).

FROM: oxicology Branch (Engler)

TO: . E. Wilson
oduct Manager
d Chemistry Branch

sticide Petition: 6F1860 and 5F1646

etitioner: Merk Co.

onclusion: Th requested tolerance on sugarbeets and the previously equested tolerance of 0.1 ppm on soybeans can be established, provided hat an assurance is obtained from the petitioner that a second ncogenicity study (second species) will be submitted within a reasonble time span, and interim reports of this study will be submitted s they become available. (The usual time required for such an ncogenicity study is 2.5 to 3 years). Furthermore, mutagenicity esting must be carried out, or initiated at the time when requirements ecome 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 eproduction, 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.

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

eview

o new toxicity data were submitted. We refer to our reviews of eptember 2, 1975, and October 28, 1976 (PP 5F1646). For convenience he toxicity tests are listed below; thiabendazole also has a history s antihelmintic drug.

LD_{50} (rat	3.33 g/kg
LD_{50} (mouse)	3.81 g/kg
Subacute feeding (rat)	NEL 100 mg/kg; dose finding study 30, and 180 days, 30% deaths at 800 mg/kg
Teratology (rats)	Negative at 80 mg/kg/day; 8-15th day of pregnancy

2-year rat feeding	NEL 49 mg/kg/day — 10 mg/kg/day
2-year dog feeding	NEL 50 mg/kg/day
5-generation reproduction (mouse)	negative at 150 mg/kg

ADI, MPI, 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 MPI for a (60) kg man of 24 mg/day. changed See Engler memo of 4/19/77 (attached)

Tolerances for thiabendazole are established for the following rac (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 MPI, the ADI is therefore not exceeded.

Leto Engler, Ph.D.
Toxicology Branch
Registration Division

RE for ccP 4/13/77

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Engler

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 NEL 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 NEL since some growth depression occured at this level. The NEL was thus set at the next lower feeding level, namely 10 mg/kg/day. This will reduce the ADI from 0.4 mg/kg/day to 0.1 mg/kg/day and the MPI 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 MPI respectively is not exceeded by the existing and the proposed tolerances which result in a maximal theoretical exposure of roughly 1.0 mg/day.

Carlo Engler

Carlo Engler, Ph.D.
Toxicology Branch
Registration Division

002852

...31 10, 1977

...ponse to Briefing Memo for Thiabendazole - tolerance ...f 0.1 ppm in/on Soybeans (5F1636)

...f (Payter)
To...icology Branch (TOX-567)

...Wilson (PM #21)
...gistration Division (TOX-567)

THRU: ...ociate Director for Scientific Review
...gistration Division (TOX-567)

This memo addresses two points in your briefing memo concerning the ...pm tolerance in soybeans for thiabendazole: 1) demonstration of "safety" of proposed tolerance and 2) the need for delayed neurotoxicity 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 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 MPI of 6 mg/day. A tolerance of 0.1 ppm on soybeans is calculated to produce a TMRC to the average daily diet of 0.003 mg/day (0.1 X 1.5 X 0.02). The TMRC of this tolerance and existing tolerances is approximately 1 mg/day. This is below the MPI 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 addaa 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.

3) Thiabendazole contains no organic phosphate or carbamate 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.

...ille C. Payter, Ph.D.

...t:ryter/ccw 3/10/77