UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

849A

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DATE: March 2, 1979

SUBJECT: Request for a tolerance of the fungicide thiabendazole, (2-(4-thiazolyl) benzimidazole), in or on wheat grain at 0.2 ppm and wheat straw at 1.0 ppm.

FROM: Carlos A. Rodriguez Carlos A. Rodriguez 3/2/79. EL 4-20-79
Toxicology Branch, HED (TS-769)

TO: Henry M. Jacoby
Product Manager#21

001978

PP#8F2103
Caswell#849A

Petitioner: Merck Sharp & Dohme
P.O. Box 2000
Rahway, NJ 07065

Recommendation(s) & Conclusions:

We recommend the establishment of the requested tolerances, however a restriction which prohibits the grazing by lifestock on treated wheat may be placed on the label until such a time residue data is submitted to determine the level of residues which could be ingested by livestock. (Please see RCB recommendation section, PP#8F2103, 1/22/79, A. Smith).

A second oncogenic study (second species) is required for this chemical (See Dr. Reto Engler, April 7, 1977 conclusions, PP#6F1860 and 5F1646). The potential significance of the second onco. study is not serious enough to disqualify these requested tolerances.

A. Residue Chemistry Considerations:

RCB recommends against the proposed tolerance because of the lack of residue data for wheat at the pasture stage. Such data are necessary to determine the level of residues which could be ingested by livestock. As an alternative, restrictions which prohibit the grazing of treated wheat may be placed on the label. (Please see attached computer printout.)

B. Related Petitions: 6F1860, 5F1646, 3F1332, 4F1518, 8F0724

C. Technical Name: Thiabendazole

EPA FORM 1320-6 REV. 3-76)

CFR 180.242 Thiabendazole 5/11/79

File last updated 5/11/79

CP1978

ACCEPTABLE DAILY INTAKE DATA

RAT,Older NOEL mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day/60kg
10.000	200.00	100	0.1000	6.0000

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
Milk&Dairy Products(93)	0.100	28.62	0.04292
Sweet Potatoes(157)	0.020	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
Cattle(26)	0.100	7.18	0.01078
Goats(62)	0.100	0.03	0.00005
Hogs(69)	0.100	3.43	0.00515
Horses(206)	0.100	0.03	0.00005
Sheep(145)	0.100	0.19	0.00029

MPI	TMRC	% ADI
6.0000 mg/day/60kg	1.3339 mg/day/1.5kg	22.23

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Current Action 8F2198

CROP	Tolerance	Food Factor	mg/day/1.5kg
Wheat(170)	0.100	10.36	0.01554

MPI	TMRC	% ADI
6.0000 mg/day/60kg	1.3495 mg/day/1.5kg	22.49

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Empirical Formula: $C_{10}H_7N_3S$

Molecular Weight: 201.6

Description: White to tan, odorless powder.

Stability: Is quite stable as a solid and in aqueous suspension. No change in ultraviolet absorption was found in samples of Thiabendazole stored for 8 days at 100 °C. At pH2, it is stable at room temperature for at least 2 years.

Volatility: Nonvolative at ambient temperatures. Sublimes when heated strongly (300 °C) at atmospheric pressure.

Melting Range: 304° - 305 °C

Solubility: Soluble in a number of solvents; essentially insoluble in water except at low pH values.

D. Formulation: (Mertect-340-F)

Active Ingredient:

2-(4-thiazolyl)-benzimidazole -------42.28%

Inert Ingredients: INERT INGREDIENT INFORMATION IS NOT INCLUDED

[redacted]

E. Uses: Fungicide (Wheat) - Control of Cercosporella foot rot.

Soybeans - reduce the severity of pod and stem blight, anthracnosa and brown spot.

Pome Fruit - (Apples and Pears) - control blue mold rot, bull's eye rot, and gray mold.

Sugar beets - control cercosporella leaf spot.

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Ornamental Bulbs and corms - control fusarium basal rot and penicillum blue mold.

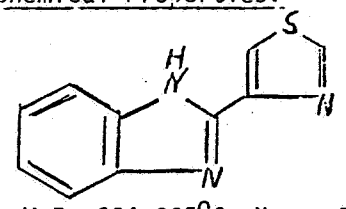
Sweet potato "seedroots" - control black rot, scurf and foot rot.

Potato - control fusarium tuber rot.

Aerial application - apply 16-24 fluid ounces in 5 gallons of water per acre.

Ground application - apply 16-24 fluid ounces in sufficient water for coverage.

F. Structure & Selected Physical/Chemical Properties:



2-(4-thiazolyl)-benzimidazole

White to tan crystaline powder; M.P. 304-305°C; Non-volatile at ambient temperatures but sublimes at 300°C; essentially insoluble in water except at low pH values, solubility data is shown in PP#3F1332 Accession#093564.

G. Toxicology Data Review: Accession No. 237355.

1. Primary Eye Irritation - Mertect Flowable 340-F, (42.28% Thiabendazole), (Merck Sharp & Dohme Research Laboratories, 78RTS095, June 27, 1978).

0.1 of the undiluted test liquid was instilled into the conjunctival sac of the left eye of 4 male and 5 female albino rabbits, (Buckshire Farm New Zealand) weighing 3.10 to 4.76 kg and 22 to 26 weeks of age. The right eye of rabbit served as an untreated control. Ocular reactions based on the Draize Scoring Method were recorded after 15 minutes, 2 hours, 24 hours and then once daily for 2 weeks.

Results:

Slight to moderate eye irritant, slight chemosis. Effects cleared by 72 hours.

TOX Category: III

Classification: Core-Minimum Data

Washing eye procedure was not done.

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2. Primary Skin Irritation - Mertect Flowable 340-F, (42.28% Thiabendazole), (Merck Sharp & Dohme, Research Laboratories, 78RTS095, June 27, 1978).

0.5 ml of the undiluted material was applied to the intact and abraded skin of each of 3 male and 3 female albino rabbits (Buckshire Farms, New Zealand), weighing 3.52 to 4.54 kg and from 22 to 26 weeks of age. Each test site was covered with a gauze patch and then wrapped with a clear plastic occlusive dressing. The undiluted material was applied to each site by injecting the test liquid through the plastic material beneath the gauze patch. The dressings were removed after 24 hours and the sites examined. The sites were also examined daily thereafter for 14 days.

Results:

Slight erythema. One rabbit slight scaling of the skin on the 8th day, but normal thereafter. Slight erythema disappeared by the 11th day.

TOX Category: III

Classification: Core-Minimum Data

3. Acute Dermal Toxicity - Mertect Flowable 340-F, (42.28% Thiabendazole), (Merck Sharp & Dohme, Research Laboratories, 78RTS095, June 27, 1978).

4 male and 4 female albino rabbit (Buckshire Farms, New Zealand) weighing between 3.05 to 4.08 kg and from 22 to 26 weeks of age, were used to study the percutaneous systemic toxicity of the material. The hair was removed from the back of each rabbit and the test sites of 4 rabbits were abraded, the test sites of the remaining 4 rabbits were left intact. The test site of each rabbit was covered with a clear patch and then wrapped with a clear plastic occlusive material. The undiluted material was applied at a dose of 5 ml/kg by injecting the liquid through the plastic material and beneath the gauze patch with a syringe and needle attached. The animals were observed closely on the day of treatment and then daily for two weeks. The occlusive dressings were removed 24 hours after exposure and the sites examined for dermal change. Individual body weights were taken prior to treatment and at 7 and 14 days.

Results:

No deaths occurred and no systemic effects were observed. Slight erythema on both the intact and abraded test sites. Slight thickening of the skin and loss of hair were seen at the intact and abraded test sites and persisted until the end of the 14-day observation period with the exception of one intact rabbit whose skin appeared normal on the eighth day.

TOX Category: IV

Classification: Core-Minimum Data

4. Acute Oral LD_{50} - Mertect Flowable 340-F, (42.28% Thiabendazole), (Merck Sharp & Dohme, Research Laboratories, 78RTS095, June 27, 1978).

10 male and 10 female albino mice (Carworth CF-1 strain), weighing 19 to 23 grams and 5 to 6 weeks of age, were used in each of five dose levels of 3.33, 5.00, 7.50, 11.25 and 16.875 ml/kg. The undiluted test material was given by gastric intubation. The animals were observed closely on the day of administration and daily thereafter for 14 days.

Results:

$AOLD_{50}$ = 9.82 (7.00 - 13.6) ml/kg (male mice)

8.98 (7.05 - 11.4) ml/kg. (female mice)

Toxic Signs: ataxia, decreased activity, bradypnea, ptosis, loss of righting. All death occurred in the first five days. Loss of weight was noticed the first week of observation, but no weight loss was noted in 14 days. No difference in toxicity was noted between sex.

TOX Category: IV

Classification: Core-Minimum Data

5. Acute Rat Inhalation Toxicity Study - Mertect 340-F (Hazelton Laboratories America, Inc; Project No. M167-123, June 12, 1978).

10 male Sprague-Dawley albino rats (Charles River, COBS), weighing between 200 and 300 grams were used for this study. They were exposed under dynamic conditions in a 100 liter glass and stainless steel inhalation chamber at a target nominal concentration of 20 mg/liter of air for 4 hrs. Following exposure all animals were observed for mortality, signs of toxicity and/or abnormal behavior throughout the exposure, immediately after exposure and daily for 14 days after the termination of the exposure. The animals were sacrificed on the fifteenth day for gross organ pathology. All animals were weighed prior and after exposure.

Results:

LC_{50} = >20 mg/L (male rat)

Toxic Signs: preening behavior.

Body weight: all animals gained body weight.

Organ pathology: liver - granular surface.
lungs - pale.
Peribronchial lymph nodes - enlarged.
Thymus - red foci
Wound - behind right bladder.
Nasal turbinates - thickened

Classification: Core-Minimum Study

TOX Category: IV

Conclusion: This study is reclassified from Supplementary to Minimum because the extremely low degree of toxicity at a dosage level of 20 mg/L, well above the exposure level. Female testing should not be required.

H. Summary of Toxicity Data prior to 1978.

LD_{50} (acute oral, rat) = 3.33 g/kg

LD_{50} (acute oral, mouse) = 3.81 g/kg

Subacute feeding, rat-NOEL = 100 mg/kg

Teratology - negative at 80 mg per kg per day

Two Year Feeding, Rat - NOEL = 10 mg/kg/day

Two Year Dog Feeding - NOEL = 50 mg/kg

Reproduction, mouse, 5 generation - negative at 150 mg/kg

The above data were extracted from the memo of Dr. Reto Engler to Dr. E. Wilson of April 7, 1977 on the subject "Tolerance for Thiabendazole (of) 4.0 ppm on Sugar Beets".

The data below were taken from a Toxicity Profile prepared by Drs. R.A. Zimmerman, R.E. Johnson, & R.A. Herin dated October 4, 1978 and from PP#5F1646.

Teratology Study in Rats. CR albino. Pregnant rats were given thiabendazole by gavage, 80.4 mg/kg (8 rats) each day from 8th to 15th day of gestation Thiabendazole (purity not given).

Results:

Not teratogenic at 80.4 mg/kg for 7 days. Reproductive capacity & resorption rate were the same, test & control group.

*Per memo of Dr. Reto Engler to Dr. E. Wilson of April 19, 1977.

ADI, MPI, and MTE

Based on the rat 2-year feeding study the ADI for man (100 X safety factor) is 0.1 mg/kg b.w./day which results in a MPI for 60 kg of 6 mg/day.

Tolerance for thiabendazole are established for the following rac (180.242):

Commodity	Parts per million
Apples	10.00
Citrus fruits	10.00
Pears	10.00
Bananas	0.40
Squash	1.00
Sugar, cane & beet	0.25
Milk and Dairy Products	0.10
Sweet Potatoes	0.02
Potatoes	3.00
Soybeans	0.10
Wheat	0.10
Cattle	0.10
Goats	0.10
Hogs	0.10
Horses	0.10
Sheep	0.10

The residues in the daily 1.5 kg human diet for the established tolerances is 1.334 mg/day or 22.23% of the ADI. The requested increase in the wheat tolerance will contribute an additional 0.0155 mg/day/1.5 kg (or 0.26%) to the daily diet. This increase is supported by existing toxicity data.

TOX/HED:ssr