UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

001979

001979 OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: May 30, 1980

SUBJECT: Request for a tolerance of the fungicide Mertect 340 F be established in or White Rice at 0.25 ppm, Rice Bran at 2.5 ppm, Rice Polishings at 2.5 ppm, Rice Hulls at 8.0 ppm, Rice straw at 10 ppm. Caswell No. 849A

FROM: Carlos A. Podriques Carlos A. Podriques 5/30/80
Toxicology Branch/HED (TS-769) WLB 5/30/80.

TO: Henry M. Jacoby, PM 21
Registration Division (TS-767)

Petitions Nos. 9F2216 and 9H5240

Registrant: Merck Sharp & Dohme
P.O. Box 200
Rahway, N.Y. 0765

Recommendations and Conclusions:

1. Toxicology Branch determined by telecon with FDA, dated 5/16/80 that the petitioner has indicated the near submission of mutagenicity studies on this compound. These studies must be submitted to EPA for our review and evaluation. Based on our review, additional mutagenicity studies may be required.

2. Toxicology Branch recommends the establishment of the requested tolerances subject to chemistry considerations and recommendations and based on the chronic toxicity studies submitted which are negative and the incrementally small residue to be contributed to the ADI.

A. Background Information of Mertect 340-F

Mertect 340-F is a flowable (Water dispersible suspension) formulation of Thiabendazole which is the active ingredient. The composition of the formulation is shown below. The established tolerances of this active ingredient are listed in CFR Sec. 180.242.

B. Uses-Application-Rice-reduce severity of rice blast, stem rot sheath blight, and brown leaf spot.

Aerial & Ground Application-Apply at 6.0-12.0 fl. oz per acre per application in sufficient water for coverag (minimum 5 gallons of water per acre for aerial applicatio:). Make two applications per season, the first application at boot initiation followed by a second application 14-21 days later. Use the higher rate when disease infestations are moderate to severe. Do not use in California.

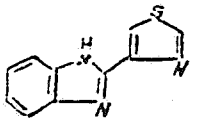
C. Composition of Mertect 340-F

Thiabendazole (2-(4-thiazolyl) benzimidadozole 42.28%

[redacted]

D. Structure

INERT INGREDIENT INFORMATION IS NOT INCLUDED



E. Physical state and selected chemical properties:

White to tan crystaline powder M.P. 304-305°C. Non-volatile at ambient temperature, sublimes at 300°C. Essentially insoluble in water except at low pH's (Solubility data in PP Δ3F1332, Accession No. 093564).

F. Related Petitions: 6F1860, 5F1646, 3F1332, 4F1518, 8F2108, 8F0724

G. Technical Name: Thiabendazole

H. Empirical Formula: $C_{10} H_7 N_3 S$

I. Molecular Weight: 201.6

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

M. Summary of Toxicology Data for Mertect 340-F (42.28% Thiabendazole) Accession No. 23755.

LD_{50} (Acute Oral, mice) = 9.82(7.00-13.60)ml/kg mice)
= 8.92(7.15-11.4)ml/kg(mice)

LD_{50} (Acute Dermal, rabbits) = > 5 ml/kg

LC_{50} (Acute Inhalation, rat) = > 20 mg/l

Toxic signs: preening behavior

Body weight: all animals gained body weight

Organ Pathology: liver-granular surface.
lungs-pale

peribronchial lymph node-enlarged

thymus - red foci

wound behind right shoulder.

nasal turbinates - thickened

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Primary Eye Irritation - slight moderate irritant, slight chemosis. Effects cleared by 72 hours.

Primary Skin Irritation - slight erythema, one rabbit showed slight scaling of the skin on the 8th day, but normal thereafter. The slight erythema disappeared by the 11th day.

N. Summary of Toxicology Data prior to 1978.
(Technical Thiabendazole)

LD_{50} (Acute Oral, rat) = 3.3 g/kg

LD_{50} (Acute Oral, Mice) = 3.81 g/kg

180-Day Subacute Feeding (rat), NOEL = 100 mg/kg, larger dose 200 mg/kg weight gain in male rats, but did not affect the weight gain of females.

Teratology (rats), negative at 80 mg/kg/day, (highest dose level tested) 8-15 day pregnancy.

Teratology Study (rabbit) - negative up to 800 mg/kg (highest dose level tested)

Two Year Rat Feeding, NOEL = 10 mg/kg/day, the next higher dose (40 mg/kg/day) some growth depression occurred.

Reproduction Study (rat), NOEL = 20 mg/kg bw per day. At higher dose (40 mg/kg/day) smaller prostate gland weights when compared to controls, 40 and 80 mg/kg/day, statistically smaller body weights of the F2 females.

Two year dog feeding NOEL = 50 mg/kg, and the higher dose of 125 mg/kg death of 2 of 6 dogs occurred slightly weight loss, slight reduction in hemoglobin, increase frequency of urinary albumin, moderate chronic inflammatory liver changes and slight liver glycogen depletion in the treated dogs.

Reproduction study, mouse, 5 generation negative at 150 mg/kg (highest dose tested).

Lifetime Carcinogenic Study in Mice - not oncogenic in this mouse feeding study. Females given (0.2% and 0.33%) and males given (0.2% and 0.066%) had lower average weight gains compared to controls during the study. NOEL = 0.0066% lowest dose tested.

The rate and degree of absorption, distribution, excretion and metabolic fate of thiabendazole were determined orally in man and other species (rat dog, sheep, goat, cattle and swine). Peak plasma levels were found 1 to 2 hours after oral administration of 1.0 g of thiabendazole-C^{-14}. Thereafter the plasma levels declined essentially to zero in 24 to 48 hours. Thiabendazole was rapidly metabolized by man with nearly all of the urinary excretion products appearing as metabolized drug. The urinary radioactivity totaled 80% of the administered dose in 24 hours. Nearly 50% of the labeled material in the urine was found to be compounds which could be measured by the chemical assay procedures. Less than 1% was excreted unchanged and most of the dose was detected in the urine, as the glucuronide (25%) and as the sulfate ester of 5-hydroxythiabendazole (13%). Four to nine percent was excreted in the feces.

In a study with larger dose of unlabeled thiabendazole (2g) in fasting human subjects, maximum drug concentration appeared in plasma about 3 hours after dosage.

After administration of radioactivity thiabendazole to the animal species in many respects the findings were similar to those obtain for man. Tissues taken from the laboratory and from animals and analized after thiabendazole treatment were virtually free of radioactivity.

0. ADI, MPI, and MTE

Based on the rat 2-year study the ADI for man (100 x safety factor) is 0.1 mg/kg body weight per day which is an MPI for a 60 kg man of 6 mg/day.

P. Thiabendazole tolerances are established for the following RACs (180.242):

Commodity	Parts per million
Apples	10.00
Citrus fruits	10.00
Pears	10.00
Bananas	0.40
Squash	1.00
Sugar, cane and 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 are 1.356 mg/kg or 22.53% of the ADI. The requested increase in rice contribute an additional 0.0248 mg/kg/1.5 kg (or 0.41%) to the daily diet. This increase is supported by existing toxicity data. (Please, see attached computer printout.)

CFR 180.[redacted]2 Thiabendazo[redacted] 6/3/80 001979

File last updated 6/3/80

ACCEPTABLE DAILY INTAKE DATA

RAT,Older NOEL mg/kg	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	5.64	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(158)	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(260)	0.100	0.03	0.00005
Sheep(145)	0.100	0.19	0.00029

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

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Unpublished,Tox Approved PP8F2106,9E2263

CROP	Tolerance	Food Factor	mg/day/1.5kg
Wheat(170)	0.100	10.36	0.01554
Papayas(109)	5.000	0.03	0.00225

MPI	THRC	% ADI
6.0000 mg/day/60kg	1.3517 mg/day/1.5kg	22.53

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Current Action PP9F2216/9H5240

CROP	Tolerance	Food Factor	mg/day/1.5kg
Rice(137)	3.000	0.55	0.02483

MPI	THRC	% ADI
6.0000 mg/day/60kg	1.3765 mg/day/1.5kg	22.94

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