UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: January 19, 1979

SUBJECT: Application for Amended Registration, Mertect-340 F (Reg. No. 618-75) for Post-harvest application to Sugar Beets. Caswell No. 849 A

FROM: John E. Preston, Ph.D.
Toxicology Branch

TO: H. M. Jacoby
Product Manager

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Petitioner:

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

Action Requested:

To amend registration of Mertect-340F to include post-harvest application to sugar beets.

Related Petitions:

6F1860, 5F1646, 3F1332, 4F1518

Background Information:

Mertect -340 F is a flowable formulation of Thiabendazole which is the active ingredient. The formulation has the composition shown below. Thiabendazole is a fungicide, its tolerances are shown in CFR 40 § 180.242 and its structure is shown below.

Mertect-340 F Composition of Formulation

CONFIDENTIAL

Thiabendazole, active ingredient 42.28%

[redacted]

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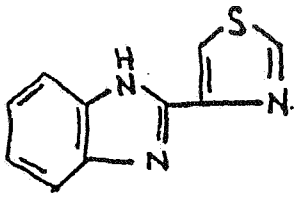
EPA FORM 1320-6 (REV. 3-76) INERT INGREDIENT INFORMATION IS NOT INCLUDED

1 of 3

Structure:



2-(4-thiazolyl) benzimidazole

Physical state & 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 # 3F1332, A # 093564).

Recommendation:

The application for registration of Mertect-340F for use as a fungicide for post-harvest application to sugar beets is toxicologically supported. This recommendation is based on:

1. A review of the toxicity data accompanying the application and prior pertinent toxicological data.

2. Evaluation of proposed label for correct signal words based on use and toxicity category and for other necessary information, e.g. directions and antidote.

It should be noted, however, that this proposed label change should not be made until after the requested tolerance of 6 ppm for post-harvest use on sugar beets is approved. See P.P. 6F1860.

Summary of New Toxicity Data (provided with the application).

Acute Oral Toxicity in Mice. Carworth, CF-1. 10 M & 10 F per dose level. 5 dose levels: 16.875, 11.25 7.5, 5.0 & 3.333 ml/kg. Mertect-340-F formulation was administered by gastric intubation.

Results

LD 50 = 9.82 (7.08-13.6) ml/kg - males

= 8.98 (7.05-11.4) ml/kg - females

Signs: ataxia, bradypnea, ptosis and loss of righting.

Classification: Core-Minimum Data. Toxicity Category IV.

Source: Mertect Flowable 340-F Acute Toxicity Studies. June 27, 1978 Merck & Co.

Acute Dermal Toxicity in Rabbits. Buckshire Farms, New Zealand random. 4 m and 4 f rabbits ($\frac{1}{2}$ intact, $\frac{1}{2}$ abraded) were used at a single dose of 5 ml/kg using Mertect-340-F formulation (undiluted). 24 hour exposure, 14-day observation period.

Results

Acute Dermal LD 50 > 5 ml/kg (Toxicity Category III). No deaths or systemic toxicity were observed during the observation period. All rabbits showed gains in body weight.

Classification: Core-Minimum Data (upgraded from Supplementary, where it was originally categorized due to single dose level). Rationalization--- The lack of any mortalities and of no systemic toxicity at the single relatively high dosage level of 5 ml/kg clearly establishes the acute dermal LD 50 > 5 ml/kg (Toxicity Category III). No gross necropsies or histopathologic examinations were conducted. Toxicology Branch considers the results of this study sufficient to determine the potential dermal toxicity for this formulation- in spite of only 1 dosage level being tested..

Source: As above.

Acute Ocular Irritation in Rabbits. Buckshire Farms, New Zealand random. 4 m & 5 f per dose. One dose: 0.1 ml placed in conjunctival sac. Undiluted 340-F (formulation) was used and the Draize method. 14-day observation period.

Results

Slight to moderate eye irritation, effects cleared at 72 hours. No corneal opacity at any time. Toxicity Category III.

Classification: Core-Minimum Data- effect of washing eye was not done.

Source: As above.

Primary Skin Irritation in Rabbits. Buckshire Farms. 3 M and 3 F per dose level. One dose level: 0.5 ml/test site/rabbit. Undiluted Mertect 340-F formulation. 1 abraded and 1 intact shaved site per rabbit was used. 24 hour exposure. 14 day observation period.

Results

Mild or slight skin irritant. Toxicity Category IV.

Classification: Core-Guidelines

Source: As above.

Acute Inhalation Study in Rats. Sprague-Dawley (albino, CR. COBS) 10 male rats were exposed for 4 hours to 7.98 mg/L of Mertect 340-F aerosol (80% of aerosol was 0.5-3.0μ particle size). A 50% solution of Mertect 340-F (in distilled water) was used.

Results

Acute Inhalation LC 50 > 7.98 mg/L (Toxicity Category III) Males only. No deaths during 14 days of observation. Increased preening behavior. Gross pathology: enlarged peribronchial lymph nodes 7/10; red foci in thymus, 7/10.

Classification: Core-Minimum Data (upgraded from Supplementary, where it was originally categorized due to single dose level and to only 1 sex being used). Rationalization- The lack of any mortalities and the observation of normal appearance and behavior during the 14-day observation period (except for 2 rats with alopecia on the last day) clearly establishes the acute inhalation LC 50 > 7.98 mg/L (Toxicity Category III, males only). Since differences in response by sex were not observed in the acute oral and acute dermal studies described above, a difference in response by sex is not expected in this study. Toxicology Branch considers the results of this study sufficient to determine the potential inhalation toxicity for this formulation- in spite of only 1 dosage level and 1 sex being tested.

Source: 618-75 Mertect Flowable 340-5. Acute Toxicity Studies June 27, 1978 attached to letter of R.R. Buck of Merck Sharpe & Dohme to Dr. E. Wilson of EPA dated 6/6/78.

Summary of Toxicity Data prior to 1978.

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

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 = 40 mg/kg/day, subsequently reduced to 10 mg/kg/day*

Two Year Dog Feeding - NOEL = 50 mg/kg/day

Reproduction, Mouse, - negative at 150 mg/kg 5 generation.

4

The following data were taken from a toxicity profile prepared by R.A. Zimmerman, Ph.D, R.E. Johnson, Ph.D., & R.A. Herin, D.V.M. Ph.D. dated October 4, 1978 also 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 @ 80.4 mg/kg for 7 days: Reproductive capacity and resorption rate was same, test and control group.

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

5