9-13-84

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP#4F3096/4H5414: EPA File Symbol 43813: Request registration of Fungaflor 50 EC for postharvest treatment of pome fruits at 7 ppm and apple pomace (wet/dry) at 10 ppm. CASWELL No. 497AB.

TO: Mr. Henry M. Jacoby, PM #21
Herbicide-Fungicide Branch
Registration Division (TS-767)

THRU: David L. Ritter, Acting Section Head
Review Section #1
Toxicology Branch/HED (TS-769)

FROM: Carlos A. Rodriguez
Review Section #1
Toxicology Branch/HED (TS-769)

INFORMATION IS NOT INCLUDED

Recommendations:

1. TOX Branch defers to RCB as to whether the level of secondary residues will exceed the established milk and meat tolerances.

2. Components of the inerts ingredients [redacted] and [redacted] must be identified and cleared under 40 CFR 180.100(c).

3. Toxicology Branch cannot support these permanent tolerances in pome fruits and apple pomace because the deficiencies outlined under conclusions.

Bases for Conclusions:

1. Mouse teratology study is deficient because:

a. The per cent of pregnancies in the control group (60%) is too low for a statistical evaluation and valid conclusions. Pregnancy rate above 80% is needed in the control and dose groups for adequate statistics values.

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b. The fetuses were not examined further for skeletal and soft tissue anomalies.

2. We have no information on the formulation inerts [redacted] and [redacted] components of these materials must be cleared under 40 CFR 180.1001(c). [redacted] must also be cleared under 180.1001(c).

3. Data Supporting Proposed Tolerance (Reviewed by R. Bruce Jaeger, memo 4/30/82).

2 Year Chronic Feeding (rat)
NOEL = 3 mg/kg
LEL = 12.1 mg/kg (rel. liver wt. increase)

2 Year Feeding (Dog)
NOEL = 1.25 mg/kg
LEL = 5 mg/kg (decreased body weight gain)

Oncogenicity (Rat)
Negative at 40 mg/kg (HDT)

cogenicity (Mouse)
Negative at 40 mg/kg (HDT)

3-Generation Reproduction (Rat)
NOEL = 800 ppm (HDT)
(40 mg/kg)

Teratology (Rat)
NOEL = 800 ppm (HDT)
(40 mg/kg)

Mutagenicity (Dominant Lethal - mouse)
Negative at 160 mg/kg (HDT)

Micronucleus test (Rat)
No structural chromosomes
mutations induced at 160 mg/kg (HLT)

Metabolism (Rat) no retention in fatty tissues; little tissue retention.

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Review of Label/Data:

A. Label

Proper precautionary labeling for Fungaflor 50 EC must bear the signal word "Danger" in close proximity to the stacement "Keep Out of Reach of Children" on the front panel label.

The precautionary statements on the left panel of the label must contain the precautionary labeling statements required for Toxicity Category I (eye) and II (skin) as specified in Criteria and Policy Notice 2161.2 dated 3/31/82. Skull and crossbones are not required.

B. Toxicity Data Submitted

Oral Embryotoxicity and Teratogenicity Study in Cobs Mice, (Janssen Le Brun Research Lab., Study Protocol No. N-657,11/28/83).

Sexually mature (Cobs-Charles River) virgin female mice weighing between 23-36 grams were used in this study. Each group of 3 females were mated with one adult male from the same strain. The occurrence of copulation was determined by daily vaginal inspection for mucous plug. The day that mucous plug was found was considered to be day one of gestation. The test material was administered in arabic gum 5% suspension orally by gavage from days 6 through 15 of gestation to four groups of 20 bred female Cob-Charles River mice at levels of 0, 2.5, 10 or 40 mg/kg/day of base. The control group received the vehicle agent less the test material. The test article was given orally as a suspension, one ml per 100 g of body weight. Animals were observed daily for behavior, appearance and signs of toxic and pharmacological response. Body weights were recorded on days 1, 6, 14 and 19 of gestation. Food consumption was recorded on the 1st and 19th days of gestation. On day 19th the animals were sacrificed by decapitation. Autopy was performed and any macroscopic pathological changes recorded. The number of implantations, resorptions, dead and viable fetuses, fetal birth weight and anomalies were recorded. All of the fetuses were preserved in formalin (10%).

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Results from Laboratory Report:

Two mortalities occurred in the control group. No mortalities were observed in any of the dose groups.

Administration of technical Imazalil during the period of organogenesis did not affect the maternal body weight gain in any of the experimental groups. There was a slightly significant decreased of food consumption in the groups receiving 10 mg/kg and 40 mg/kg of base.

The conception rate was comparable between the control group and the various dosage groups.

No differences were observed in the distribution of embryos and fetuses in each uterine horn. Litter size, viable fetuses, dead and resorbed fetuses per litter were comparable between control and treated groups.

No significant difference in the mean birth weight of the pups was observed between the control group and dosed group.

Abnormalities observed consisted of an exencephalia in one stillborn in the control group and talipes valgus* in all groups. This incidence was comparable between the control group and treated groups.

*Laboratory reports that spontaneous incidence of anomalies of this type are common in Cobs-control mice and considered to be of no importance.

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Formulation of Fungaflor 50 EC: (Confidential)

Active Ingredient:

Imazalil Base----------45.8%

Inert Ingredients:

[redacted]

Total 100.0%

* Components of these must be cleared under 40 CFR 180.1001(C).

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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Conclusions:

The teratology study as submitted is found unsatisfactory for the following rea ons:

1. The per cent of pregnancy in the control group (60%) is too low. Pregnancy rate above 80% is needed in both the control and dose groups for adequate statistics values.

2. The study should be repeated using at least 20 pregnant mice at each dose level and control group to permit a meaningful evaluation of the teratogenic potential of the test subtance.

3. The fetuses were not examined further for skeletal and soft tissue anomalies.

4. TOX Branch concludes that a teratology study correcting these discrepanceis must be submitted in order to determine whether or not the test material is teratoge to Cobs-Charles River mice.

Classification of Study: Supplementary.

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