PP6-1615
TAR-746

ENVIRONMENTAL PROTECTION AGENCY

Dr. Baker
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DATE February 10, 1972

JECT: Request for negligible residue tolerances of 5,6-dihydro-2-methyl-1, 4-oxathiin-3-carboxanilide (Vitavax) (Carboxin) and its sulfoxide metabolite, 5,6-dihydro-3-carboxanilido-2-methyl-1,4-oxathiin-4-oxide, a fungicide, of 0.2 ppm on seed harvested from plants grown from treated wheat and peanut seed.

Mr. Drew M. Baker, Chief
Petitions Control Branch
Pesticides Tolerances Division

Pesticide Petition No. 2F1191

Uniroyal Chemical
Bethany, Connecticut 06525

Related Petitions: 9G0819, 0F0939

Tolerances: 21 CFR 180.301 0.2 ppm in or on cottonseed

TOXICOLOGICAL EVALUATION

I. Review of Data Submitted in Previous Petitions

A. PP# 9G0819 (reviewed by Dr. J.L. Svirbely, 6/17/69)

Oral LD_{50} rats	3.82 ± 0.35 g/kg
Dermal LD_{50} rabbits	>8.0 g/kg
96 hour LC_{50} - bluegill sunfish	>562 ppb
rainbow trout	>100 ppb
8 day LD_{50} - bobwhite quail	>5620 ppm
Oral - partridges (no-effect)	2000 mg/kg
15 dermal applications - rabbits (no-effect)	1.5 or 3.0 g/kg
90 day rat feeding study	no-effect level 200 ppm
2 year rat feeding study	no-effect level 200 ppm
2 year dog feeding study	no-effect level 600 ppm
3 generation rat reproduction study	no-effect level 200 ppm

Dr. Svirbely concluded that the data supported the proposed temporary tolerance of 0.2 ppm on small grains (barley, sorghum, and wheat) and peanuts.

B. PP# 0F0939 (reviewed by Dr. J.L. Svirbely, 5/27/71)

96 hour LC_{50}	bluegill sunfish	rainbow trout
Vitavax Seed Protectant	2.9 ppm	4.5 ppm
Vitavax Seed Protectant with Captan	6.6 ppm	11.2 ppm
Vitavax Seed Protectant	0.38 ppm	0.56 ppm

Dr. Svirbely concluded that the data supported the proposed tolerance of 0.2 ppm in cottonseed.

II. Review of New Data

A. Acute Oral Toxicity Studies - Bobwhite Quail (Industrial Bio-Test Laboratories, Inc.; J8584)
Young, adult pen-reared bobwhite quail were fed a single dose of 0, 1.47, 2.15, 3.16, 4.64, 6.81, and 10 g/kg of Vitavax Seed Protectant with Thiram or Vitavax Seed Protectant with Captan with 5 M and 5 F/ group. The birds were observed for 21 days. LD_{50}'s of 2.41 g/kg for the Vitavax with Thiram and >10 g/kg for the Vitavax with Captan were encountered.

B. Acute Dust Inhalation Toxicity Studies (Industrial Bio-Test Laboratories, Inc.; N8586)
5 M and 5 F young adult Charles River albino rats/formulation were exposed in a 70L. chamber for one hour to either Vitavax Seed Protectant with Captan or Vitavax Seed Protectant with Thiram and observed for 14 days.

	Vitavax Captan	Vitavax Thiram
Air flow rate	9.4 L/min.	9.8 L/min.
Avr. nominal dust concentration	94 mg/L	14 mg/L
Filter assay dust concentration	8.3 mg/L	0.51 mg/L

No deaths occurred with either formulation and the only sign noticed was a slight clear nasal discharge after 30 minutes exposure to the Captan formulation.

C. Primary Skin Irritation - Rabbits (Pharmakon Laboratories) 7/22
Six adult New Zealand White albino rabbits/formulation had 0.5 gm of moistened Vitavax (75% active material), Vitavax with Thiram (37.5% Viravax), or Vitavax with Captan (37.5% Vitavax) applied to their clipped intact or abraded backs for 24 hours. The rabbits were observed 24 and 72 hours after application for dermal signs. No apparent irritatnt effect were noted with any of the 3 formulations.

D. Acute Dermal Application - Rabbits (Pharmakon Laboratories)
Four adult New Zealand White albino rabbits/dosage level/formulation had 0.316, 1.0, 3.17, or 10 g/kg of Vitavax (75% active material), Vitavax with Thiram, or Vitavax with Captan moistened with water and applied to their clipped (2 abraded, 2 intact/group) skin for 24 hours. The rabbits were observed for toxic signs at 0, 1, 4, and 24 hours and daily for 14 days. They were observed for dermal effects at 24 hours and daily thereafter. The only signs noted were a slight to moderate erythema which occurred in the rabbits treated with Vitavax and the Captan formulations and which disappeared by the second day.

E. Acute LD_{50} - Rats (Oral) (Pharmakon Laboratories)
Five M and five F Carworth, Inc. (CFE) albino rats/dosage level were fed either 200, 400, 800, 1200, 1600, or 2000 mg/kg of Vitavax or 200, 400, 800, 1000, 1200, or 1600 mg/kg of the Thiram or Captan formulations. The rats were observed at 0, 1, and 4 hours and daily for mortality and toxic effects. No apparent toxicological or pharmacological effects were noted that were attributable to the chemicals.

F. Draize Eye Irritation - Rabbits (Pharmakon Laboratories)
0.1 ml of Vitavax, Vitavax with Thiram, or the Captan formulation was placed in the conjunctival sac of the left eye of 9 M and F New Zealand White albino rabbits/formulation. Three eyes in each group were irrigated with lukewarm tapwater after 2 seconds, 3 after 4 seconds, and 3 were not irrigated and held closed for 1 second. The eyes were examined at 1, 2, 3, 4 and 7 days for signs of inflammation. Terminal flourescein examinations were conducted on day 7 for indications of corneal damage.

Formulation	Group 2 second	4 second	Non-irrigated
Vitavax	conjunctival redness 3/3 24 hr. 0/3 48 hr.	conjunctival redness 1/3 24 hr. 0/3 48 hr.	conjunctival redness 3/3 24 hr. 0/3 48 hr.
Vitavax with Thiram	no signs	1/3 discharge 48 hr.	conjunctival redness* 3/3 24 hr. 1/3 48 hr. 0/3 72 hr.
Vitavax with Captan	no signs	conjunctival redness 1/3 24 hr. 0/3 48 hr.	conjunctival redness* 3/3 24 hr. 1/3 48 hr. 0/3 72 hr.

*1/3 chemosis @ 24 hr.
The terminal fluorescein examinations performed on all the rabbits were negative.

CONCLUSIONS

In the evaluation of PP No. 8G0819 (memo Dr. J.L. Svirbely, 6/17/69) the no-effect levels of Vitavax (carboxin) were estimated to be: 200 ppm (2-year rat feeding study), 600 ppm (2-year dog feeding study), and 200 ppm (3-generation [2 litters/generation] rat reproduction study). Utilizing the 100-fold safety margin and the lowest no-effect level, 200 ppm (2-year rat feeding study), residue levels of Vitavax of 6 mg/1500 gm average daily diet/60 kg man.

Wheat, peanuts, and cottonseeds (21 CFR 180.301) form approximately 8.83% of the daily diet and a tolerance of 0.2 ppm on these crops would allow a maximum of 0.02649 mg of Vitavax in the daily diet. Label restrictions prohibit the use of the treated seed for food, feed, or oil and prohibit grazing on hay grown from treated seed. Vitavax is considered safe at this level when label restrictions are followed.

Two of the commercial formulations of Vitavax, Vitavax-200 Seed Protectant and Vitavax-300 Seed Protectant, contain pesticides, Captan (21 CFR 180.103) or Thiram (21 CFR 180.132), for which tolerances on wheat and peanuts do not exist. Utilization of these two formulations is dependent upon establishing tolerances for Captan and Thiram on these crops.

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RECOMMENDATION

The proposed tolerance of 0.2 ppm of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (carboxin) (Vitavax) on seed harvested from plants grown from treated wheat and peanut seed is considered safe. We would recommend, however, that the tolerance be granted on grain harvested from plants grown from treated wheat and peanut seed. This is essentially a no-residue situation as the petitioner claims that 0.2 ppm is the sensitivity of the method for detection of Vitavax residues.

We defer to Chemistry Branch regarding (1) the nature of the residue and possible metabolities and (2) the transfer of residues to meat, milk, poultry, and eggs.

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cc: OGFitzhugh
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Division Reading File
Branch Reading File
PP# 2F1191

RD/init; CHWilliams: 2/4/72

WEP;ss;2/11/72; init:CHWilliams

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