



165A

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

008842

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 400-UGI
Vitavax - ExtraFROM: William S. Woodrow WSW 6-18-90
Precautionary Review Section E 6/19/90
Registration Support Branch
Registration Division (H7505C)TO: Susan Lewis / Stone (PM 21)
Fungicide - Herbicide Branch
Registration Division (H7505C)APPLICANT: Universal Chemical Co.
74 Amity Road
Bethany, CT 06525

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
<u>carboxin (5,6-dihydro-2-methyl-N-phenyl-1,4-oxathiazin-3-carboximide)</u>	<u>27.2</u>
<u>imazalil (1-(2-(4-dichlorophenyl)-2-(2-propoxy)ethyl)-1H-imidazole)</u>	<u>2.5</u>
<u>Thiabendazole (2-(4-thiazolyl)-benzimidazole)</u>	<u>2.5</u>
Inert Ingredient(s):	<u>67.8</u>
Total	100.0%

BEST AVAILABLE COPY

BACKGROUND

The Unitoray Chemical Co. submitted acute oral, acute dermal, acute inhalation, primary eye and primary skin irritation studies in support of Vitavax-Extra registration. MRID NOS. used were 414918-01 through 414918-05.

RECOMMENDATIONS

- 1) The acute oral, acute dermal, primary eye and skin irritation studies were acceptable to RSB/PRS, and were graded Core Guideline studies.
- 2) The acute inhalation study was not acceptable to RSB/PRS:
 - a. the only aerosol chamber concentration measurement made was the nominal: which measures only total expended material and does not account for chamber interior - impinged surface material, test material collected at chamber bottom, ^{OR} ~~non~~ animal external surfaces.
 - b. No gravimetric or chemical analytical measurements of the chamber concentration were made.

BEST AVAILABLE COPY

c. No particle size/particle size distribution studies were made

The acute inhalation toxicity study deficiencies listed above resulted in a study grade of Supplementary Data.

The Registrant should carefully examine the "Comments on Standard Evaluation Procedure - Inhalation Toxicology Testing (SEP/Inhalation)", by Dr. Stanley Gross (attached). The NTIS #PB89-124077 publication, page 3 of Dr. Gross' note, provides specific inhalation toxicity study guidance.

~~3) The request for waiver of the requirement to submit a dermal sensitization study, due to apparent lack of frequent dermal exposure, is justified.~~

4) The Registrant may wish to consider submitting a new acute dermal toxicity study; generated using higher doses of test material (at least 2000 mg/kg, preferably 1500, 2000, and 3000 mg/kg to more accurately determine an LD₅₀). At present, one dose of 1000 mg/kg (Vindiol), results in the Toxicity Category II - WARNING signal word.

BEST AVAILABLE COPY

LABELING

- 1) The WARNING signal word is appropriate
- 2) The Precautionary Statements are acceptable.
- 3) The Statement of Practical Treatment is acceptable.

PM NOTE: Upon receipt of an acceptable acute inhalation study, precautionary labeling may require revision.

ADDITIONAL RECOMMENDATION

- 5) The Registrant must submit an acceptable acute inhalation toxicity study, generated using Vitavax-Extra.
- 6) The Registrant must submit an acceptable dermal sensitization study, using Vitavax-Extra. The Agency does not view the system intended for product use as a closed system with consequent little opportunity for repeated exposure.

BEST AVAILABLE COPY

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§81-1)

008842

Product Manager: (21) Reviewer: M. Walter
 MRID No.: 414918-01 Report Date: 6-18-90
 Testing Facility: Food & Drug Res. Labs. Report No. 8256A
 Author(s): E. L. Reagan
 Species: Rat, Sprague Dawley
 Age: young adult Observation Days (Post Exposure): 14; other (5)
 Weight: M 310.4, F 225.2
 Source: Charles River Labs Wilmington, MA
 Test Material: Vitavax-Extra
 Quality Assurance (40 CFR §160.12): adequate

Conclusion:

- LD₅₀ (mg/kg): Males = ; Females = ; Combined =
- The estimated LD₅₀ is > 2000 mg/kg
- Tox. Category: III. Classification: Guidelines

Procedure (~~Deviations From §81-17~~): 5M45F rats were individually

dosed with 2000 mg/kg b.i.d. of test material by gavage.

Animals observed for mortality/toxic signs frequently during dosing

2x daily to Day 15. Body weights drop 5x/5 (or death). All

Results: animals subjected to necropsy (gross).

Reported Mortality

DOSAGE (mg /kg)	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
2000 mg/kg	0/5	0/5	0/10

Symptomology & Gross Necropsy Findings:

All animals gained weight

Clinical: - Females appeared normal. Males: an incidence
of 1/5 exhibited decreased activity, 1/5 diarrhea, 1/5 wet
abdomen, 1/5 dark moistened around eyes.

Necropsy: No gross abnormalities.

BEST AVAILABLE COPY

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

0088

Product Manager: (211)
 MRID No.: 414918-02
 Testing Laboratory: Food & Drug Res. Lab.
 Author(s): E.L. Reagan
 Species: Rabbit, N & White
 Sex: 5M & 5F
 Test Material: Vitavax-Extra
 Quality Assurance (40 CFR §160.12): adequate
 Reviewer: Woodrow Weller
 Report Date: 6-18-90
 Report No. 8256A
 Wt.: M 2.47, F 2.47

Summary:

- LD50 (mg/kg): Males = _____; Females = _____; Combined = _____
- The estimated LD50 is > 1000 mg/kg
- Tox. Category: II Classification: Guidelines

Procedure (Deviations From §81-2): 1000mg applied to clipped backs of 5M & 5F rabbits (intact skin) under occlusive plastic wrap + Stockinette sleeve, secured w/ masking tape. 24 hr contact.

Observations: animals observed frequently during treatment, 2x daily to day 15. Gross necropsies of 15, or at death. Body wt. 0, 8, 15 days

Reported Mortality

DOSAGE (mg/kg)	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
1000 mg/kg	9/5	1/5	1/10

Symptomology & Gross Necropsy Findings:

Av. weights: Slight loss in wt at day 8, av. regain in wt. to initial wt by day 15.

Clinical: Prominent in life - anorexia, decreased activity, diarrhea, diarrhea = mucous, soft stools, soft stools = mucous, nasal discharge.

Gross necropsy: No gross abnormalities

BEST AVAILABLE COPY

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: (21) Reviewer: W. Woodrow
 MRID No.: 414918-03 Report Date: 6-18-90
 Testing Laboratory: Eppley Dryg Res. Lab. Report No. 8256A
 Author(s): J. A. Bissmaier
 Species: Rat, Sprague Dawley
 Sex: SM, 15F Weight: MAF 221-303g.
 Source: Charles River Labs, Wilmington, MA
 Test Material: Vitavax-Extra, liquid
 Quality Assurance (40 CFR §160.12): adequate

Summary: No gravimetric measurements, no analytical (chemical) measurements, no particle size distribution studies

1. LC₅₀ (mg/kg): Males = _____; Females = _____; Combined = _____
2. The estimated LC₅₀ is not determined
3. Mean Concentration: _____
4. Tox. Category: ____ Classification: Supplementary

Procedure (~~Deviations From §81-2~~): SM & 15F rats exposed for 245 min (4 h to 9 min) to aerosol of test material. Animals observed for toxic signs & mortality frequently to 11/14/90. All animals subjected to gross necropsy. Body weights 0.4, 5 & 15.1 (Rats).

Results:

Reported Mortality

Exposure Concentration (mg/L)	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
<u>not determined</u>	<u>0/5</u>	<u>0/5</u>	<u>0/10</u>

~~Symptomology & Gross Necropsy Findings:~~

Animals exposed in 128 L series Chamber Total airflow @ 65L/min. Test material delivered using a Harvard syringe pump to protect 1/4 atomizer. Aerosol evenly mixed & coming out to chamber. Nominal concentration determined; test material stopped - total flow through chamber.

BEST AVAILABLE COPY

No toxic symptoms for animals. All animals gained weight. No gross abnormalities revealed during necropsies.

Nominal concentration determined to be 2-3 mg/L

BEST AVAILABLE COPY

DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (§81-4)

00884

Product Manager: (21)
 MRID No.: 414918-04
 Testing Laboratory: Food & Drug Res. Labs.
 Author(s): E. L. Reagan
 Species: Rabbit, No 2 white
 Sex: not given
 Source: La Crosse Industries, Schenectady, N.Y.
 Dosage: 0.1 ml
 Test Material: Vitavax-Extra, liquid
 Quality Assurance (40 CFR §160.12): adequate

Reviewer: M. Waller
 Report Date: 6-18-90
 Report No. 8256A

Summary:

Tox. Category: III Classification: Guidelines

Procedure (Deviation From §81-4): 0.1 ml test material instilled in
 1 eye of each of 9 rabbits. Lids gently held together 1 second. Treated
 eyes of 6 rabbits remained unexamined, 3 treated eyes irrigated w/
 Saline beginning 30 sec. after instillation. Eyes examined &
 Results: Scores for irritation @ 1, 24, 48, 72 hrs post treatment using
 the Draize system. Also examined every 3 days thereafter if
 irritation persisted.

	(number "positive"/number tested)							
	Hour	Days						
	1	1	2	3	4	7	14	21
Cornea								
Opacity	0/9	0/9	0/9	0/9	0/9	0/9		
Iris	4/9	5/9	4/9	3/9	0/9	0/9		
Conjunctivae								
Redness	9/9	9/9	5/9	3/9	3/9	0/9		
Chemosis	9/9	3/9	1/9	0/9	0/9	0/9		
Discharge	9/9	1/9	0/9	0/9	0/9	0/9		

Comments: All 9 treated eyes included; very little difference in treated/
 not rinsed eyes. No corneal involvement. Conjunctival
 irritation through day 4, was absent by day 7.

BEST AVAILABLE COPY

DATA REVIEW FOR SKIN IRRITATION TESTING (981-5)

Product Manager: (21)
 MRID No.: 414918-05
 Testing Laboratory: Food & Drug Res. Lab.
 Author(s): E. L. Reagan
 Species: Rabbit, N 2 White
 Age: young adult
 Sex: Female
 Weight: 3.00 - 4.20 Kg
 Dosage: 0.5ml
 Test Material:
 Quality Assurance (40 CFR §160.12): adequate

Reviewer: Woodrow
 Report Date: 6-18-90
 Report No.: 8256A

008812

Summary:

The Primary Irritation Index = 0.00

Toxicity Category: IV

Classification: Guidelines

Procedure (Deviations From 981-5): 0.5ml applied to clipped test sites: two sites on dorsal areas of each of 6 rabbits. Each test site covered $\approx$ 1" square of gauze & Band-Aid tape. 4 hr contact. One-half hour following patch removal, exposure sites examined and scored for erythema/edema (0-4 scale) - examined at 24, 28, 52, 76 hours post dose.

Results: As outlined above, Dermal test sites examined at 24, 28, 52, and 76 hours, post dosing. No erythema and no edema was recorded for any of the scoring periods - throughout the observation period.

Special Comments:

P.I. Index = 0.00

BEST AVAILABLE COPY