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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 400-UGI
Vitavax - Extra

FROM: William S. Woodrow WSW 6-18-90
E 6/19/90
Precautionary Review Section
Registration Support Branch
Registration Division (H7505C)

TO: Susan Lewis / Stone (PM 21)
Fungicide - Herbicide Branch
Registration Division (H7505C)

APPLICANT: Uniroyal Chemical Co.
74 Amity Road
Bethany, CT 06525

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
carboxin (5,6-dihydro-2-methyl-N-phenyl-1,4-oxathiin-3-carboxamide)	27.2
imazalil (1-(2-(2,4-dichlorophenyl)-2-(2-propenyloxy)-ethyl)-1H-imidazole	2.5
Thiabendazole (2-(4-Thiazolyl)-benzimidazole	2.5
Inert Ingredient(s):	67.8
Total	100.0%

BACKGROUND

The Uniroyal 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 on animal external surfaces.

b. No gravimetric or chemical analytical measurements of the chamber concentration were made.

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's 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 not granted.~~

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 LD_{50}). At present, one dose of 1000 mg/kg (limited), results in the Toxicity Category II - WARNING signal word.

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.

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

Product Manager: (21)
MRID No.: 414918-01
Testing Facility: Food & Drug Res. Labs.
Author(s): E. L. Reagan
Species: Rat, Sprague Dawley
Age: young adult
Weight: (M) M=310.4, F=225.2
Source: Charles River Labs (Wilmington, MA
Test Material: Vitavax-Extra
Quality Assurance (40 CFR §160.12): adequate

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

Observation Days (Post Exposure): (14); other (15)

Conclusion:

1. LD_{50} (mg/kg): Males = ; Females = ; Combined =
2. The estimated LD_{50} is > 2000 mg/kg
3. Tox. Category: III. Classification: Guidelines

Procedure (~~Deviations From §81-1~~): 5M/5F rats were individually dosed with 2000 mg/kg b.w. of test material by gavage. Animals observed for mortality/toxic signs frequently Day 1 of dosing & 2x daily to Day 15. Body weights Days 1 & 15 (& death). All animals subjected to necropsy (gross).

Results:

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: 1/5 incidence of lethargy, 1/5 decreased activity, 1/5 dark material around eyes, 1/5 wet abdomen, 1/5 dark material around eyes.
Necropsy: No gross abnormalities.

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

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Product Manager: (21)
Reviewer:- ~~K. Weller~~ Woodrow
MRID No.: 414918-02
Report Date: 6-18-90
Testing Laboratory: Food & Drug Res. Lab, Report No. 8256A
Author(s): E.L. Reagan
Species: Rabbit, N.Z. White
Sex: 5M+5F Wt.: AVE M 2.47, F 2.47
Test Material: Vitavax-Extra
Quality Assurance (40 CFR §160.12): adequate

Summary:

1. LD_{50} (mg/kg): Males = ~~—~~; Females = ~~—~~; Combined = ~~—~~;
2. The estimated LD_{50} is > 1000 g/kg
3. 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. Site unwiped, animals observed frequently day of treatment, 2x daily to day 15 - Dose necropsied day 15, or at death! Body wt. 0, 8, 15 days

Results:

Reported Mortality

DOSAGE (mg/kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
1000 mg/kg	0/5	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, desribed w. mucous, soft stools, soft stools w. mucous, nasal discharge.

Gross necropsy: No gross abnormalities

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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: Food & Drug Res. Lab. Report No. 8256A
Author(s): J. A. Biesmeier
Species: Rat, Sprague Dawley
Sex: 5M/5F Weight: M&F 221-339 g.
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. LC_{50} (mg/kg): Males = ____; Females = ____; Combined = ____
2. The estimated LC_{50} is not determined
3. Mean Concentration: ____
4. Tox. Category: ____. Classification: Supplementary

Procedure (~~Deviations From §81-2~~): 5M/5F rats exposed for 244 mg (4 hrs 9 min) to aerosol of test material. Animals observed for toxic signs & mortality frequently to 14 dy. All animals subjected to gross necropsy. Body weights 0, 4, & 15 (dayc).

Results:

Reported Mortality

Exposure Concentration (mg/L)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
not Determined	0/5	0/5	0/10

~~Symptomology & Gross Necropsy Findings:~~

Animals exposed in 128 L cannister. Aerosol generated @ 6 L/min. Test material delivered using a Harvard syringe pump to flash evaporator. Aerosol evenly mixed & diluted air to chamber. Nominal concentration determined; wt. test material aborbed ÷ total liters through chamber.

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

Normal concentration determined to be 2-3 mg/L

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, NZ white
Sex: not given Weight:
Source: LaCrosse Industries, Schenectady, N.Y.
Dosage: 0.1 ml
Test Material: Vitavax-Extra, liquid
Quality Assurance (40 CFR §160.12): adequate

Reviewer: Unsigned
Report Date: 6-18-90
Report No. 82564

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 unwashed, 3 treated eyes irrigated = saline beginning 30 sec. after instillation - Eyes examined & scored for irritation @ 1, 24, 48, 72 hrs post treatment, using the Draize system. Also examined every 3 day thereafter if irritation persisted.

Results:

	Observations (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	2/9	0/9	0/9		
Conjunctivae Redness	9/9	9/9	5/9	2/9	2/9	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		

1.0 scores

1.0 scores

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

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5)

Product Manager: (21)
MRID No.: 414918-05
Testing Laboratory: Food & Drug Res. Lab.
Author(s): E. L. Reagan
Species: Rabbit, N Z White
Age: Young adult
Sex: Females
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

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Summary:

The Primary Irritation Index = 0.00

Toxicity Category: IV

Classification: Guidelines

Procedure ~~(Deviations From §81-5):~~ 0.5ml applied to clipped test sites; two sites on dorsal area of each of 6 rabbits. Each test site covered ~ 1" square of gauze & Blenderm tape - 4 hr contact - One-half hour following patch removal, exposure sites examined and scored

Results: 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

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