MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol

400-UG

Vitavax - Extra

FROM: William S. Woodrow

Precautionary Review Section
Registration Support Branch
Registration Division (H7505C)

TO: Susan Lewis

Fungicide - Herbicide Branch
Registration Division (H7505C)

APPLICANT: Union Chemical Co.

24 Amity Road

Bethany, CT 06525

FORMULATION FROM LABEL:

<table>
<thead>
<tr>
<th>Active Ingredient(s):</th>
<th>% by wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxin (5,6-dihydro-2-methyl-N-phenyl-1,4-oxathiin-3-carboxamide)</td>
<td>77.2</td>
</tr>
<tr>
<td>Imazethapyr (2-chloro-3-(2,6-dichlorophenyl)-2-(3-pyridyl)ethyl)</td>
<td>2.0</td>
</tr>
<tr>
<td>Thiodan 70EC (5,7-(4-thiazolyl)-benzimidazole)</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Inert Ingredient(s): .............................

Total 100.0%

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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. NMP ID 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 expanded material and does not account for chamber interior impaired surface material, test material collected at chamber bottom or animal external surfaces.

b. No gravimetric or chemical analytical measurements of the chamber concentration were made.
6. 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 NIOSH PB89-124077 publication, page 3 of Dr. Gross' note, provides specific inhalation toxicity study guidance.

7. The request for waiver of the requirement to submit a dermal sensitization study due to apparent lack of frequent adverse effects is justified.

8. 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 LID50). At present, one dose of 1000 mg/kg (uncodified) 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 Regisant must submit an acceptable acute inhalation toxicity study, generated using Vitavax-Extra.
6) The Regisant 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)

Product Manager: (21)  
MRID No.: 414918-01  
Review:  
Author(s):  
Species: Rat, Sprague-Dawley  
Weight: Young adult  
Source: Charles River Labs, Wilmington, MA  
Test Material: Vitavax Extra

Quality Assurance (40 CFR §160.12): adequate

Conclusion:

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

Procedure (Deviations from §81-1): 5M9F/Ea/72 were individually dosed with 2000 mg/kg b.i.d of test material by gavage. Animals observed for mortality/toxic signs frequently 24, 48, and 72 hours. Results:

<table>
<thead>
<tr>
<th>DOSAGE (mg/kg)</th>
<th>(NUMBER KILLED/NUMBER TESTED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000 mg/kg</td>
<td>Males</td>
</tr>
<tr>
<td></td>
<td>0%</td>
</tr>
</tbody>
</table>

Symptomology & Gross Necropsy Findings:

All animals gained weight.

Clinical:
- Females appeared normal. Male: Anorexia of 1/5 exhibited decreased activity, 1/5 decreased, 1/5 wet bedding, 1/5 darkened around eyes.
- Necropsy: No gross abnormalities.

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

Product Manager: (21) Reviewer: M. Weller
MRID No.: 414918-02 Report Date: 6-18-90
Testing Laboratory: Fed.-Drug Res. Lab., Report No. 8256A
Author(s): C. Reagan
Species: Rabbit W & Female
Sex: EMSE Wt.: M 2.47, F 2.47
Test Material: Vitaxen-Extra
Quality Assurance (40 CFR §160.12): Adequate

Summary:

1. LD50 (mg/kg): Males = __________; Females = __________; Combined = __________

2. The estimated LD50 is __________ mg/kg.

3. Tox. Category: 11 Classification: Guidelines

Procedure (Deviations From §81-2):

1. 1000 mg/kg applied to clipped back of 5-10 g. rabbits (intact skin) under occlusive plastic wrap. To remove excess, secured with masking tape. 24 hr. contact.

2. 3rd, 7th, 14th, and 28th days monitored.

Results:

15 days - None survived

30 days - Died 3rd day, 3, 5 days.

Reported Mortality

<table>
<thead>
<tr>
<th>DOSAGE (mg/kg)</th>
<th>(NUMBER KILLED/NUMBER TESTED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 mg/kg</td>
<td>Males</td>
</tr>
<tr>
<td></td>
<td>1/5</td>
</tr>
</tbody>
</table>

Symptomology & Gross Necropsy Findings:

At necropsy: None Survived.

Clinical: No change in life-span, no death, no incidence of deaths.

Gross necropsy: No gross abnormalities.
DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: (21) Reviewer: W. Woodrow
MRID No.: 414918-03 Report Date: 6-15-90
Testing Laboratory: Elyx Drug Res. Lab Report No. E256A
Author(s): R. A. Biermer
Species: Rat Sprague-Dawley
Sex: Male
Weight: Male 221-2629
Source: Charles River Lab, Wilmington, MA
Test Material: Vitavax-Ester Liquid
Quality Assurance (40 CFR §160.12): Adequate
Summary: No geometric measurements, no analytical (chemical) measurement, no particle size distribution studies
1. LC50 (mg/kg): Males = ______; Combined = ______; Females = ______
2. The estimated LC50 is not determined
3. Mean Concentration: __________
4. Tox. Category: _______. Classification: Supplementary

Procedure (Deviation From §81-2): 514 mg/kg delivered at 7.4 L/min (405 min) to exhaust of test chamber. Animals observed for
signs of mortality, frequent weighing. All animals
subjected to gross necropsy. Body weight: 0.45 ± 0.05 (± SD).

Results:

<table>
<thead>
<tr>
<th>Exposure Concentration (mg/L)</th>
<th>(# NUMBER KILLED/NUMBER TESTED)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
</tr>
<tr>
<td>not determined</td>
<td>%</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

Symptomology & Gross Necropsy Findings:

Animals respirated in 1781 cubic chamber, 72°F atmosphere @ 650 min. Test mixture delivered using Harvard syringe
pump to Model 471 anesthesia. Record every minute for
respirations to chamber. Non-invasive concentration determined, but test
mixture adjusted to total liters through chamber.

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No toxic symptoms found in animals. All animals gained weight. No gross abnormalities revealed during necropsy.

Brain concentration determined to be 2-3 mg/l.
DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (§81-4)

Product Manager: (21)  
MRID No.: 414918-04  
Testing Laboratory: Food & Drug Res. Labs.  
Author(s): E. L. Reagan  
Species: Rabbit, N° 2 white  
Sex: not given  
Weight:  
Source: Lactose Industries, Schenectady, N.Y.  
Dosage: Oral  
Test Material: NaCl - 5% extra liquid. Water  
Quality Assurance (40 CFR §160.12): adequate  

Summary:

Tox. Category: III  
Classification: Guidelines

Procedure (Deviation from §81-4): Oral test material instilled in each of 5 rabbits, lidosqually blindfolded (second test) and 6 rabbits remained unweighted. Treated eye irritation to determine beginning on or and after installimation. Examinations 1, 24, 48, 96 hours post-treatment.

Results: No irritation @ 1, 24, 48, 96 hrs post treatment swelling in the Dziek system also examined every 3 days thereafter. 4!

<table>
<thead>
<tr>
<th>Observations</th>
<th>Hour 1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>7</th>
<th>14</th>
<th>21</th>
</tr>
</thead>
</table>

Comments: All treated eyes included, may be difference in results from eyes not rinsed eyes. No chemosis involvement. Conjunctival irritation through 24 hrs was absent 9 days later.

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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: 3.00-3.30 Kg  
Dosage: 0.5 ml  
Test Material:  
Quality Assurance (40 CFR §160.12): adequate  

Summary:  
The Primary Irritation Index = 0.00  
Toxicity Category: IV  
Classification: Guidelines  

Procedure (Deviation From §915):  
A 1 cm2 area of clipped test site. Two sites on dorsal area of each of 6 rabbits. Each test site coated with 24 ml of a 24+h contact - 1:10 blend of Bovine tape. No patch removal, exposed 4 x 4 cm and scored 76 hours post dose.  

Results:  
No erythema, edema, or scaling observed at 24, 28, 52, and 76 hours post dosing. No irritation or eosinopenia was recorded for any of the scoring periods throughout the observation period.  

Special Comments:  
P.I. = 0.00