MEMORANDUM

SUBJECT: PPA Reg. No./File Symbol 464-AUC

XRM 5164 TC Termite Control Concentrate

FROM: Lucy D. Markarian, 1-4-90
Precautionary Review Section
Registration Support Branch
Registration Division (F75-05C)

TO: Dennis Edwards/Carl Anderson, (PM 3)
Institute - Residua
Registration Division (F75-05C)

APPLICANT: Dow Elanco
9002 Purdue Road
P.O. Box 681428
Indianapolis, IN 4628-

FORMULATION FROM LABEL:

Active Ingredient(s):
Cypermethrin [O,O-Dimethylo-(3,5,6-Trichloro-2-pyridyl)phosphoramidothioate]

6 lb gal.
22.0%

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

Total 100.0%

BEST AVAILABLE COPY
BACKGROUND:

Don Elwood has presented five acute studies in support of their product XRM-S1BA TC under EPA Sympath 461-2013.

XRM-S184 was 22.0% chlorpyrifos as active ingredient and 78.0% inert.

Formerly an oral LD50 study was submitted and accepted as core minimum data. The present package includes three remaining required acute toxicity studies.

RECOMMENDATION:

A. The eye and dermal irritation studies were repeated as core guideline data.

B. The sensitization study is considered core minimum ideal, but accepted the reasons given for the granting one.

1. The guidelines require that the method must be specified when conducting the test. This was not done, it was assumed that the Beekel method was used.

2. The Beekel method includes naive controls as a base for comparison. There were no naive controls used in the test. The positive controls serve to demonstrate the capability of the performing laboratory to induce sensitization and are not used as part of comparison.

3. Only male animals were used. The guidelines require representation of both sexes.
C. The Acute Dermal Toxicity test is considered supplementary data for the following reasons:

1. The animals are overweight. The guidelines specify that the animals used in testing dermal toxicity must be in the 3.0 to 3.5 kg range. The weight is indicative of age. An overweight animal is often older than the required young-adult model. Furthermore, it is established in the principles of toxicology that age and weight are definite variables in toxic responses, and the results obtained from overweight and old animals are not reliable.

2. Animals must not be washed with soap, regardless of how mild it is, to remove residue. Soap adds a variable to the test condition.

D. The subacute study is considered supplementary data for the following reasons:

1. Some of the animals are immature and underweight. A 105 g Fischer rat is not considered a young adult. As discussed before, age and weight have a definite bearing on the toxic response. An immature and/or underweight animal responds differently to a test material than a young adult. Also, result the outcome of the test is not reliable. The females in the test weigh much less than the males and there was a higher incidence of mortality in the females. It cannot be decided if the higher rate of mortality was due to the immature...
RECOMMENDATION: (Cont.)

of the females on the one occasion, no sex difference in the toxicity of XRM 5124. The oral toxicity did not indicate a sex difference.

2. There was more than 20% difference in weight of the animals among the different levels. The guidelines state that "the weight variation of animals in between groups of animals used in the test should not exceed 20% of the mean weight of each sex." The males at 1.40 mg/l were considerably heavier than the females in the 5.69 mg/l group, and 1.30 mg/l group (2.0 to 112 and 134).

3. All dose levels must include same number of males. The lowest level is considered using formulae. The recommendation for using lowest possible number of test groups to contain the use of animals to such a degree as to render the test results irreducible. The objective remains to be safety. The guidelines require that if the limit tests indicate no three level LC₅₀ study five of each sex must be used per level.

4. Statistical analysis is required by the guidelines when a three level LC₅₀ study is conducted. Statistical analysis is not feasible with four or fewer animals at one level.

5. The sampling ratio for the gravimetric analyses in particulate sizing must be monitored.

6. MMAD is expressed as an average, not the whole test (for all levels). This is not acceptable. Information specific
RECOMMENDATION: (cont)

To determine particle size distribution for each level must be provided. The information must include the particle sizes at each stage of the impaction. Their distribution can in weight and percentage, specific MMD for that analysis and the standard geometric deviation.

It is recommended that Dow Elanco present new data in:

1. Dermal Toxicity - using the right species, sex, and not introduced variable conditions.

2. Inhalation Toxicity - using animals in the right species and weight range, in a quiet environment.

3. Include information about particle size and distribution as required.

4. Provide statistical analysis of confidence limits as required by the guidelines.

Label:

As the tests stand now the signal word is "caution". The precautionary statement must include:

Harmful if swallowed or absorbed. Through skin or inhalation, delete "causes moderate eye irritation"

"Handle contents in a ventilated area"

"Wear protective clothing & Chemically resistant gloves when handling"

The statement of practical treatment is also satisfactory. The label may have to be revised after the receipt & review of the revision claim.
DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

Product Manager: L. Markarian
MRID No.: 516401-01
Testing Laboratory: Tox. Research Div. Chemical
Author(s): N.M. Bondarec, D.F. Schulte, B.L. Yano
Species: Rabbit, New Zealand white (Harlan Sheep, Breeders, Inc. Harlan, IN)
Sex: 50♂ & 50♀
Wt.: 3.1 - 3.6 kg
Test Material: Chrysotherix (CHM-263-1) ACR 121770 (XRM S12) included
Quality Assurance (40 CFR §160.12): included

Summary:
1. LD₅₀ (mg/kg): Males = ______; Females = ______; Combined = ______;
2. The estimated LD₅₀ is ______;
3. Tox. Category: ______. Classification: Supplementary

Procedure (Deviations From §81-2): The test material was applied to the backs of rabbits, held in restraint without freedom of movement and untreated. The rabbits were then observed for 1 hr. The rabbits were then observed for mortality and morbidity. Observations were made on a daily basis. The rabbits were sacrificed on day 3. The necropsy was performed on all rabbits. CG of the deceased was recorded.

Results:

<table>
<thead>
<tr>
<th>Dosage (mg/kg)</th>
<th>(Number Killed/Number Tested)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
</tr>
<tr>
<td>20000</td>
<td>0/5</td>
</tr>
</tbody>
</table>

Symptomology & Gross Necropsy Findings:

There were no deaths. No systemic toxicity was observed.

Dermal toxicity was expressed as erythema (1%) with two rabbits showing exposure at the application site.

Duration of erythema not specified. No product related gross pathology was observed at Terminal necropsy.
DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: (12) Reviewer: L. Markarian
MRID No.: 4626-03 Report Date: 10/31/90
Testing Laboratory: Tox. Res. Inc., 307-18th St., Cartoon, N.Y.
Author(s): C.J. Bradley, G. B. Befleicher, W. E. Brennan
Species: Rat, Fischer 3-44
Sex: Male = 15, Female = 15
Weight: Male = 110-115 g, Female = 80-85 g
Source: Charles River Breeding Laboratories, Inc., Kingwood, N.J.
Test Material: Chlorpyrifos (CAS-63-51, Lot # 233176) (ERM-5114) pre-catalized
Quality Assurance (40 CFR §160.12): Included

Summary:

1. LC50 (mg/kg): Males = ___________; Females = ___________
   Combined = ___________
2. The estimated LC50 is ___________
3. Mean Concentration: ___________
4. Tox. Category: ___________
   Classification: ___________

Procedure (Deviations from §81-2): The test animals were exposed to atmospheric concentrations of the test material in an exposure area of a chamber. The test material was allowed to remain in the chamber for 4 hours. Air flow was maintained for 2 hours. At the end of the exposure period, the air flow was determined using a method described in the report. The exposure temperature and humidity were recorded at 30 minute intervals. Geometric means of concentrations were calculated.

Results:

<table>
<thead>
<tr>
<th>Exposure Concentration (mg/L)</th>
<th>(NUMBER KILLED/NUMBER TESTED)</th>
<th>Males</th>
<th>Females</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.84 (4.78-5.87)</td>
<td>5/5</td>
<td>5/5</td>
<td>10/10</td>
<td></td>
</tr>
<tr>
<td>1.19 (1.77-1.93)</td>
<td>1/5</td>
<td>0/5</td>
<td>2/10</td>
<td></td>
</tr>
<tr>
<td>1.14 (0.95-1.25)</td>
<td>-</td>
<td>0/5</td>
<td>0/5</td>
<td></td>
</tr>
</tbody>
</table>

were made. Three times during the exposure, the exposure from the breathing zone was not specified. Particle size distribution was not specified. The exposure was specified from the breathing zone. Sampling and determination at unspecified sampling time. MAMAD was determined as 1.90 cm with standard deviation of 0.13 as an average for the three levels. No individual MAMAD or particle size distribution was specified.

Animals were observed during exposure and once daily thereafter. Body weights were recorded at initiation and on days 2, 4, 8, 11 and 15, except females at 1.14 mg/L. The weights were not recorded on day 2.
Necropsy was performed on all animals at death or at termination.

Results

At 5.0 mg/L, the effect was visual. Conjunctival toxicity included
salivation, eye摩擦, eye roughness, and tearing. Through the
process of autolysis, there was a smell of formaldehyde.

Necropsy revealed pulmonary congestion, with some hemorrhage
in the lungs and in the major blood vessels. The liver was
flushed red and the heart was congested. The kidneys were
red and swollen.

Similarly, the same effect was noted at 1.0 mg/L.

The one male died on the 11th day. On the 11th day, the male had a dislocated
foot, interpreted as evidence of renal thrombosis. Gross pathology
was also similar to the higher dose level except that the
renal female showed no abnormalities.

Weight loss was noted at this level on day 7 (10%) and
the animals continued to lose weight to termination.

At 1.4 mg/L, aching of feet, breathing through mouth, redness
at nose & regurgitation of food were noted. However, all were
normal by day 6. 9% loss in body weight was noted on day 4,
but the animals regained weight at termination.

Necropsy revealed no abnormalities.
DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (§81-4)

Product Manager:  (12)  
MRID No.:  416401-03  
Reviewer:  Lucy J. Mackinney  
Testing Laboratory:  Tox. Research, Dow Chemical  
Report Date:  10/18/80  
Author(s):  N. M. Berdasco  
Report No.:  M-005124-003-C  
Species:  Rabbit, New Zealand White  
Weight:  3.9 - 3.45g  
Dosage:  0.1 ml  
Test Material:  Chlorpyrifos (G433.2653-3, A6E 28,770) XRM-5124 (clear liquid)  
Quality Assurance (40 CFR §160.12):  included

Summary:
Tox. Category:  IV  
Classification:  Core G340/380

Procedure (Deviation From §81-4):  The test material was instilled in the conjunctiva of preanesthetized right eyes. All were examined immediately with good light at 1,2, 4, 6, and 24 hrs after instillation. Grading was done according to Draize.

Results:

<table>
<thead>
<tr>
<th>Observations (number &quot;positive&quot;/number tested)</th>
<th>Hour:</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cornea Opacity</td>
<td>0/6</td>
<td>0/6</td>
</tr>
<tr>
<td>Iris Conjunctivae Redness</td>
<td>0/6</td>
<td>0/6</td>
</tr>
<tr>
<td>Chemosis</td>
<td>0/6</td>
<td>0/6</td>
</tr>
<tr>
<td>Discharge</td>
<td>0/6</td>
<td>0/6</td>
</tr>
</tbody>
</table>

Comments:  Animals over 3.0 kg must not be used. They are not considered young adults at that weight.
DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5)

Product Manager: (12)  
MRID No.: 416401-04  
Testing Laboratory: I.C. Research, DuPont Chemical  
Author(s): N.M. Berchiano  
Species: Rabbit, New Zealand White Male, 12 months, Prednisolone, AZ, Denver  

Age: Not specified  
Sex: 3 males  
Weight: 2.7 - 3.1 kg  
Dosage: 0.5 ml  
Test Material: Chlorpyrifos G44, 21525347, 160-51-8, formulated  
Quality Assurance (40 CFR §160.12): 160-51-8, formulated  

Summary:  
The Primary Irritation Index = 0  
Toxicity Category: 14  
Classification: Core guideline  

Procedure (Deviations From §81-5):  
The shaved back of rabbit was given 4x4 cm piece of cloth twice. The cloth was covered with absorbent bandage to form a top. After 24 hours, the wrapping were removed. The reaction was evaluated at 3, 24, and 48 hours after removal of product.  

Results:  
No irritation was observed at any of the sites at any time.  

Special Comments:
DATA REVIEW FOR SKIN SENSITIZATION TESTING (§81-6)

Product Manager: (12)  
Reviewer: Lucy D. Mackaman  
MRID No.: 44601-05  
Report Date: 10/31/90  
Testing Laboratory: Tor. Genova, Drexel Chemical  
Report No. M.304-178  
Author(s): N. M. Beardsley  
Species: Guinea Pig, Hartley  
Sex: Male  
Weight: 400-450  
Source: Charles River Breeding Laboratory, Inc., Kingston, N.Y.  
Test Material: Chlorinated GPH 333-3 (KRM-5284) Skin Irritant  
Positive Control Material: 10% DER 333-3  
Quality Assurance (40 CFR §160.12): Included  

Method: not specified, assumed to be Positive

Summary:
1. This product is not a dermal sensitizer.
2. Classification: Core Mammal

Procedure (Deviation From §81-6): A pretreatment chamber was used before each application. The chamber was filled with the test material. The chamber was then filled with the positive control material. After 24 hours at the end of the induction period, the test chamber was placed on the treated area of the back. The chamber was then removed at the end of the induction period.

Results:
No irritation was noted after any of the induction applications or at 24 or 48 hrs after challenge with the test material.

DER 333-3 resulted in mild irritation at 70% after the first injection. An challenge at 70% was positive. At 90% 1/10 were positive.