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

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

NOV 03 1980

MEMORANDUM

SUBJECT: EPA Reg.#264-~~GUG; Larvin~~ 95% technical; For use in formulating only. CASWELL#900AA

FROM: William Dykstra WMD 10/6/80
Toxicology Branch, HED (TS-769)

TO: Jay Ellenberger (12)
Registration Division (TS-767) WB

Recommendations:

1) The inhalation LC_{50} study (C.M. 42-63) demonstrates that Larvin technical is Toxicity Category I: DANGER (Skull and crossbones). Appropriate labeling should be added. The registration can be supported.

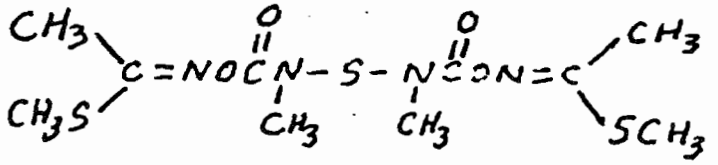
2) The submitted toxicology studies are acceptable as core minimum data or supplementary data.

"CONFIDENTIAL"

Larvin Thiodicarb Insecticide 95% technical

Ingredients	Percent Weight
Thiodicarb	96.0
[redacted]	
	100.0

Structure:



Chemical Name: Ethanimidothioic acid, N.N'-[thio bis[methylimino) carbonyloxy]]bis,-dimethyl ester

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Review:

A. Book II: Toxicology Data

1. Acute Oral Toxicity Study in Male and Female Rats (Hazelton Project No. 400-613; January 21, 1980)

   Reviewed in memo of 2/21/80 from William Dykstra to Charles Mitchell; 1016-EUP-LE; PP#9G2152.

   Results: LD_{50} = 398 (256-620) mg/kg; males
   LD_{50} = 248 (120-511) mg/kg; females
   LD_{50} = 325 (204-516) mg/kg; both sexes

   Toxicity Category II: WARNING

   Classification: Core-Minimum Data

2. Acute Dermal Administration in Rabbits (Hazelton Project No. 400-614; December 17, 1979)

   Reviewed in memo of 2/21/80 from William Dykstra to Charles Mitchell; 1016-EUP-LE; PP#9G2152.

   Results: No deaths, LD_{50} > 6.31 gm/kg

   Toxicity Category III: CAUTION

   Classification: Core-Minimum Data

3. Acute Dermal Toxicity in Rats (CDC Study No. CDC-UC-012-79; November 9, 1979)

   Test Material: UC-51762

   One group of 4 male Sprague-Dawley rats received 640 mg/kg of test material on the intact skin of the fur clipped trunk under an impervious cuff for 24 hours. Observation was for 7 days.

   Results: No deaths, LD_{50} > 640 mg/kg

   Toxic Signs: None observed; P.I. = 0.0

   Body Weight: Weight gain

   Necropsy: Not remarkable

   Classification: Supplementary Data

   (a) only one dose level
   (b) LD_{50} not determined
   (c) females not tested

4. Primary Skin Irritation Study in Rabbits with Larvin Insecticide Technical (UC-51762) (Hazelton Project No. 400-617, November 23, 1979)

   Reviewed in memo of 2/21/80 from William Dykstra to Charles Mitchell; 1016-EUP-LE; PP#9G2152.

   Results: P.I. = 0.0; no erythema, edema or other dermal effects were observed at 24 or 72 hours.

   Toxicity Category IV: CAUTION

   Classification: Core-Guidelines

5. Acute Eye Irritation Study in Rabbits with Larvin Insecticide Technical (UC-51762) (Hazelton Project No. 400-616; November 23, 1979)

   Reviewed in memo of 2/21/80 from William Dykstra to Charles Mitchell; 1016-EUP-LE; PP#9G2152.

   Results: Corneal opacity and conjunctival redness, chemosis and discharge were observed in the washed and unwashed eyes of the test rabbits. All lesions were observed to clear by day 7.

   Toxicity Category II: WARNING

   Classification: Core-Guidelines

6. Acute Inhalation Toxicity Study in Rats with Larvin (UC-51762 technical dust) (Hazelton Project No. 400-615; November 30, 1979)

   Reviewed in memo of 2/21/80 from William Dykstra to Charles Mitchell; 1016-EUP-LE; PP#9G2152.

   Results: No deaths; LC_{50} > 5.3 mg/L (nominal)
   LC_{50} > 0.32 mg/L (gravimetric)

   Toxicity Category II: WARNING

   Classification: Core-Minimum Data

7. Acute and 9-Day Dust Inhalation Study on Rats with UC-51762 technial (Carnegie-Mellon Project No. 42-63; July 5, 1979)

   Test Material: UC-51762 technical

   Acute Study: Groups of 6 male and 6 females were exposed for 4 hours to dust concentrations of 48 mg/m^3, 126 mg/m^3, 150 mg/m^3, 163 mg/m^3, and 195 mg/m^3. Observation for 14 days.

Results: LC_{50} = 126.6 (121.14-132.35) mg/m^3 (males)
LC_{50} = 115.50 (109.38-121.98) mg/m^3 (females)
LC_{50} = .126 mg/L (males) and
LC_{50} = .115 mg/L (females)

Toxic Signs: Toxic signs indicative of cholinesterase inhibition.

Body Weight: Not reported.

Necropsy: Dark red foci in lungs, intestines gas filled, liver mottled.

Classification: Core-Minimum Data

Toxicity Category I: DANGER

Nine-Day Dust Inhalation: Groups consisting of 10 male and 10 female Hilltop Sprague-Dawley rats each were subjected for 6 hours per day, for 9 days, to repeated inhalation of UC-51762 technical particulates at mean measured atmospheric concentrations of 59.5, 17.7, and 4.8 mg/m^3 for males and 54.0, 19.6, and 4.8 mg/m^3 for females. Control groups inhaled chamber air that did not contain UC-51762 technical particulates. Body weight per se and as a change from pre-exposure values, liver, lung, kidney and brain weight per se and as a percentage of body weight, food consumption and plasma, RBC, and brain cholinesterase per se and as a percentage of the control mean were compared to evaluate toxic response.

Conclusion: A NOEL was not observed for inhalation of UC-51762 technical dust in this study. At the lowest level tested (4.8 mg/m^3), two clinical signs typically associated with cholinesterase effects, pinpoint pupils and tremors, were observed in both males and females. Other than a slight significant decrease in absolute kidney weight, no statistically significant effects (such as body weight changes seen as the 20 ang 60 mg/m^3 target concentrations) were observed in the 4.8 mg/m^3 target concentration animals. In addition no statistically significant effects were observed for any cholinesterase measurement at the 4.8 mg/m^3 or the 20 mg/m^3 target concentrations.

Classification: Core-Minimum Data

8. Acute Delayed Neurotoxicity Study in Hens (IRDC Report No. 369-047; September 2, 1980)

Test Material: Larvin thiodicarb insecticide; UC-51762; analytical grade; Shipment No. 20-ARD-98; Register No. 511-01-1812; white powder.

Fifty-five adult (8-12 months old) white leghorn hens were selected for this study. Prior to receipt, the hens were vaccinated against Marek's disease, Newcastle disease, Avian Encephalomyelitis, and Bronchitis.

The hens were individually identified by leg band and individually housed in suspended wire mesh cages arranged in a stepwise fashion on a metal A-frame stand. They were maintained in temperature-, humidity-, and light-controlled (12 hours light and 12 hours dark) quarters. Water and Purina Lab Cage Layer Chow was available ad libitum except for a period 19-20 hours, prior to study initiation when food but not water was withheld.

During the conditioning period each hen was observed daily for signs of ill health and disease. Only hens which were found to be in good health, free of disease and within body weight requirements were considered for randomization and subsequent placement on study. 50 hens selected, from the 55 were randomly distributed into the treatment groups as shown below:

Material	Dosage Level	Number of Hens
corn oil (vehicle control)	10 ml/kg	10
*TOTP (positive control)	1200 mg/kg	10
Larvin (test group)	660 mg/kg	30

Thirty minutes prior to the administration of the test and control articles each hen was administered atropine sulfate as a solution in deionized water at a dosage level of 25 mg/kg.

*Tri-o-tolyl phosphate

Observations for pharmacotoxic, and neurotoxic signs and mortality were made at 1, 2 1/2, and 4 hours following dosing and twice daily thereafter (AM and PM) for 21 days.

Body weights were obtained twice weekly throughout the pretest period, immediately prior to administration and twice weekly during the study period.

At the conclusion of the experimental period, all surviving hens from each group were sacrificed with sodium pentobarbital injected into a wing vein.

At necropsy, an examination was made of the external body surface, orifices and the different body cavities from each hen for any gross abnormalities. Each hen was then perfused systemically using 4% paraformaldehyde followed by 5% glutaraldehyde thru a needle inserted into the aorta (using masterflex pump). The entire spinal cord and distal end of both sciatic nerves were then taken and preserved in 10% neutral buffered formalin. From each control and treated bird, multiple longitudinal and transverse sections of the cervical, thoracic, and lumbar spinal cord, plus sections of the distal ends of both sciatic nerves were stained with hematoxylin and eosin, luxol fast blue, PAS (for myelin) and Bielschowskis (for axon) for microscopic evaluation.

Results:

Following administration of the negative control article all hens in this group remained normal for the duration of the observation period.

No signs of acute toxicity were noted, however, classical clinical signs of the delayed neurotoxicity syndrome were observed in all hens in the TOTP positive control group. All hens in both the negative and positive control groups survived the study period. Pharmacotoxic signs of acute toxicity following administration of the test article were seen in the test article group including the death of 13 of 30 hens in this group.

All of the negative control hens showed body weight gains during the study period while 9 of 10 TOTP positive control hens exhibited body weight losses. In the test article group 7 of 17 survivors exhibited body weight losses. The 10 hens in the test article group showing body weight gains exhibited gains of a lesser amount than shown by the negative control group.

Gross necropsy of the 13 hens receiving the test article, which died on study, did not reveal compound related pathologic lesions.

Grossly, no significant lesions were found in hens sacrificed at terminal necropsy. Results of the microscopic evaluation of sections of the spinal cord and sciatic nerve from hens in the negative control group were essentially normal. Hens receiving the positive article TOTP, exhibited lesions which were neurologically considered directly related to the administration of the positive test article. In the test article group, five hens exhibited slight ataxia ranging up to 11 days. All of the affected hens had recovered by day 12, most by day 5. All but one of the five hens had focal interstitial lymphocytic infiltrates of the sciatic nerve. Lymphocytic infiltrates of the sciatic nerve were present in hens of both the vehicle control and positive control, although the vehicle control hens did not show any ataxia. The lesions and ataxia in the test article

hens could be the results of acute cholinesterase toxicity (ataxia) and Marek's disease (lesions). No compound related morphological alterations involving the spinal cord or sciatic nerves were observed in hens receiving Larvin Thiodicarb.

Conclusion:

Larvin Thiodicarb was not a delayed neurotoxic agent in this study.

Classification: Core-Minimum Data

9. Pilot Teratology Study in Rats with UC-51762 (IRDC Report No. 369-028, September 10, 1979)

Reviewed in memo of 2/21/80 from William Dykstra to Charles Mitchell; 1016-EUP-LE; PP#9G2152.

Conclusion:

Due to high maternal toxicity a dosage level of 40 mg/kg/day is considered excessive for a teratology study.

Classification: Supplementary Data

10. Teratology Study in Rats with UC-51762 (IRDC Report No. 369-029; December 20, 1979)

Reviewed in memo of 2/21/80 from William Dykstra to Charles Mitchell; 1016-EUP-LE; PP#9G2152.

Conclusion:

The test material produced signs of maternal and fetal toxicity as evidenced by dose-related decreases in mean maternal body weight gain and mean fetal body weight and dose-related increases in reduced fetal ossification. The test material was not teratogenic when administered to pregnant rats at dosages up to 30 mg/kg/day. However, the NOEL for fetotoxicity was not established in the study.

Classification: Core-Minimum Data

11. Rat Teratology Studies with UC-51762 (Carnegie-Mellon Institute for Research, Project Report No. 42-48, June 1, 1979)

Reviewed in memo of 5/2/80 from William Dykstra to Charles Mitchell; 1016-EUP-LE; PP#9G2152.

Conclusion:

UC-51762 was not teratogenic at dosages up to 100 mg/kg/day given during gestation days 6-15 or 0-20. The fetotoxic NOEL is 3 mg/kg/day.

Classification: Core-Minimum Data

12. Pilot Teratology Study in Mice (IRDC#396-030, August 29, 1979)

Reviewed in memo of 2/21/80 from William Dykstra to Charles Mitchell; 1016-EUP-LE; PP#9G2152.

Conclusion:

A dosage level greater than 200 mg/kg/day for a teratology study would produce excessive maternal toxicity.

Classification: Supplementary Data

13. Teratology Study in Mice with UC-51762 (IRDC Report#369-031)

Reviewed in memo of 2/21/80 from William Dykstra to Charles Mitchell; 1016-EUP-LE; PP#9G2152.

Conclusion: The NOEL for maternal toxicity is 100 mg/kg/day. UC-51762 is not teratogenic or fetotoxic at 200 mg/kg/day or less.

TS-769:th:TOX/HED:LCHITLIK:10-2-80

8