CASWELL FILE

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

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MAY 31 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Avermectin - Correction in Conclusion of Rabbit Teratology Study

Caswell No. 63AB

FROM: William Dykstra, Reviewer *William Dykstra 5/19/89*
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

TO: George T. LaRocca, PM 15
Insecticide-Rodenticide Branch
Registration Division (H7505C)

THRU: Edwin R. Budd, Section Head *ERB acting 5/19/89* *ERB 5/25/89*
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

The previous conclusion regarding the avermectin rabbit teratology study (TT#82-706-01) was incorrect.

The correct conclusions are the following:

Teratogenic NOEL = 1.0 mg/kg/day

Teratogenic LEL = 2.0 mg/kg/day
(cleft palate and clubbed foot)

Developmental toxicity NOEL = 1.0 mg/kg/day

Developmental toxicity NOEL = 2.0 mg/kg/day
(incompletely ossified sternebrae, metacarpals and forefoot phalanges)

Maternal toxicity NOEL = 1.0 mg/kg/day

Maternal toxicity LEL = 2.0 mg/kg/day
(decreases in body weight, food consumption and water consumption)

after normalizing for nonparameteric data. When necessary, a covariance analysis was used to adjust for the effects of Day 6 weights on maternal body weight changes.

Results: One rabbit died in the 3.0 mg/kg/day group on day 16 of gestation.

Four rabbits aborted. One in the 1.0 mg/kg/day group on day 20 of gestation, one in the 2.0 mg/kg/day group on day 27 of gestation, and two in the 3.0 mg/kg/day group on days 26 and 27 of gestation.

Toxic signs and decreased body weight were observed in females from the 2.0 mg/kg/day group only. Increased body weight was noted in the 1.0 mg/kg/day group.

Conclusion: Maternal LEL is 3.0 mg/kg/day. Maternal NOEL is 2.0 mg/kg/day. The abortions noted in the 1.0 and 2.0 mg/kg/day groups in study are not considered treatment-related due to the small sample size.

Classification: Supplementary data.

b. Oral Teratogenic Study in Rabbits (TT #82-706-01).

Test material: MK-0936; 94% purity; Lot No. L-767, 863-00V50.

Groups of 18 impregnated New Zealand white rabbits were orally gavaged with doses of 0, 0.5, 1.0 and 2.0 mg/kg/day of test material on days 6-27 of gestation.

The rabbits were sacrificed on day 28 of gestation. The parameters evaluated were toxic signs, body weight and pregnancy status. Corpora lutea, implantations and resorptions were counted. All fetuses were given exteranl examination, sexed, weighed and examined for visceral and skeletal abnormalities.

Statistical analyses of maternal body weight changes, live fetal weights, percent preimplantation loss, rate of resorptions, number of implants per pregnant female, and number of live and dead fetuses per pregnant female in the teratogenic study were performed using an IBM 370 computer. Statistical significance at $P = 0.05$ was based on an analysis of variance or covariance using a least significant difference procedure after normalizing for nonparameteric data. When necessary, a covariance analyais was used to adjust for the effects a Day 6 weights on maternal body weight changes and the effects of litter size on live fetal weight.

Results: The following number of live pregnant rabbits were available for evaluation in the study: 15 (control), 13 (low-dose), 11 (mid-dose), and 15 (high-dose).

One non-pregnant rabbit at 0.5 mg/kg/day died on day 26, one non-pregnant rabbit at 1.0 mg/kg/day died on day 27, and one pregnant rabbit at 2.0 mg/kg/day was sacrificed in poor condition on day 20 of gestation. Abortions occurred as one (control), two (low-dose), one (mid-dose), and one (high-dose) but are not considered treatment-related since there was no dose-response relationship.

The following number of rabbits were alive but not pregnant: 2 (control), 2 (low-dose), 5 (mid-dose), and 1 (high-dose).

Treatment-related decreases in body weight, food consumption and water consumption were noted in most rabbits of the 2.0 mg/kg/day group.

Implants, percent implantation loss and resorptions were unaffected by treatment. The number of fetuses available for evaluation were 97 (control), 90 (low-dose), 95 (mid-dose) and 121 (high-dose). Five dead fetuses at the mid-dose (1.0 mg/kg/day) group were significantly increased above control (0), but were not considered treatment-related since there was no dose-related relationship in this parameter. Sex-ratio and fetal body weight were not affected by treatment.

External examination showed a treatment-related increase at 2.0 mg/kg/day (maternally toxic level) in malformations in comparison to controls and other groups. Cleft palate (12 fetuses, 1 litter), omphalocele (2 fetuses, 1, litter), clubbed forefeet (5 fetuses, 3 litters) occurred in the high-dose group, whereas omphalocele (1 fetus, 1 litter) were present in the control. Additionally, clubbed forefoot was present in 2 fetuses (1 litter) from the 1.0 mg/kg/day group.

Visceral examination did not show any treatment-related effect. However, there was a slight increase in the number of fetuses with variation of lung lobation in the 0.5 (2), 1.0 (2) and 2.0 mg/kg/day groups (3) in comparison to controls (1).

With respect to skeletal malformations, the number of litters (fetuses) with skeletal malformations was 0(0) in controls, 3 (4) in the low-dose, 1(2) in the mid-dose and 3(5) in the high-dose.

At the low dose, 2 fetuses had caudal vertebrae malformations, one fetus had fused ribs, and one fetus had both branched ribs and thoracic vertebrae malformation. At the mid-dose, one fetus had craniostenosis and another had verterbral malformation. These malformations at 2.0 mg/kg/day occurred in litters and in fetuses that displayed treatment-related external abnormalities also. However, it should be noted that 2.0 mg/kg/day is a maternally toxic dose level.

Fetotoxicity at 2.0 mg/kg/day was evident as incompletely ossified sternbrae, metacarpals, and forefoot phalanges.

Conclusion: The findings at 2.0 mg/kg/day of external and skeletal malformations ocurred at a level which produced maternal toxicity. Therefore the malformations at this level can be attributed to maternally toxic effects. The NOEL for maternal toxicity is 1.0 mg/kg/day.

However, the low dose of 0.5 mg/kg/day, four-fold less than the high-dose level, produced 3/13 litters with skeletal terata in comparison to 0/15 litters in the control and 3/15 litters in the high-dose.

The results at the low dose are suggestive of compound related effects.

However, the narrow dose range and the high toxicity of the chemical make a clear separation of maternal effects and fetal effects at lower doses very difficult to assess in a species as variable as rabbits. The NOEL for fetotoxicity is 1.0 mg/kg.

Classification: Supplementary data. (a) Historical control data for maternal and fetal effects are required to be submitted for complete evaluation of the study.

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3/7/85

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Avermectin B1; 618-EUP-10; PP# 4F3065; 50658- EUP-R; 618-0G; Historical control data for rat and rabbit teratology studies
Caswell #: 63AB
Accession #: 073303

TO: George LaRocca
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and

Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

THRU: Robert P. Zendzian, Ph.D. 3/8/85
Acting Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: William Dykstra, Ph.D. William Dykstra
Toxicology Branch
Hazard Evaluation Division (TS-769) 3/7/85

Recommendations:

1. The submitted historical control data are acceptable. The rat and rabbit teratology studies can be upgrated from supplementary to core minimum data.

Review:

1. Rat teratology Study. In the rat teratology study (TT# 82-705-1) the increased incidence of lumbar rib in fetuses was considered to be a fetotoxic effect. Lumbar rib occurred in 22% of fetuses and 67% of litters.

The overall historical data for increased lumbar ribs was 14% in fetuses and 57% of litters. However, the single study with highest incidence of increased lumbar ribs was 29% of fetuses and 87% of litters.

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In light of these data the finding of increased lumbar ribs in the rat teratology study is not considered a fetotoxic effect.

Conclusion:

The rat teratology study can be upgraded from supplementary to core minimum data.

The study was negative for terata maternal, toxicity, and fetotoxicity at 1.6 mg/kg/day (HDT).

Classification:

e Minimum Data.

2. bit teratology study. In the rabbit teratology study (-706-01) the incidence of skeletal terata at the low-do 0.5 mg/kg/day was considered suggestive of a teratogenic effe

ne low-dose had 3/13 litters and 4 fetuses with caudal vertebrae malformations; one fetus had fused ribs, and one fetus had both branched ribs and thoracic vetebrae malformations. The control data in the study did not have any fetuses or litters (0/15) with skeletal defects.

The submitted historical control data shows an overall incidence of skeletal malformations, of the type observed in the study, to be comparable in the percent incidence of skeletal findings in the reviewed study.

The control group in the reviewed study did not have any fetuses or litters affected. The absence of findings in the control group are considered unusual and not representative of the historical control data.

The rabbit teratology study can be upgraded from supplementary to core minimum data.

Conclusion:

Avermectin was negative for terata at 2.0 mg/kg (HDT). The findings in the low-dose group (0.5 mg/kg/day) are not considered compound-related.

Classification:

Core minimum data.

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