Microfiche

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

MAR 2 6 1993

010121

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID# 097601. Propargite. Review of a special cross fostering reproduction study.

TOX CHEM No.: 130I
PC No.: 097601
Barcode No.: D177257
Submission No.: S416530

FROM: John Doherty 3/24/93
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

TO: Linda Propst
Product Manager #73
Special review and Reregistration Division
(H7508W)

THROUGH: Marion Copley, DVM, Section Head
Section IV, Toxicology Branch I
Health Effects Division (H7509C)
Marion Copley 3/24/93

I. CONCLUSION

The special reproduction toxicity study with cross fostering of the litters was reviewed and it was determined that this study does not provide data that will require changes Toxicology Branch's conclusions of the multi-generation reproduction study previously submitted to satisfy the series 83-4 data requirement.

The study, however, does provide useful information which helps define the cause of pup weight decreases during lactation as being related to maternal toxicity of propargite rather than as a result of in utero exposure of the pups. No regulatory action is appropriate based on this submission.

1 of 8

010121

II. ACTION REQUESTED

The Uniroyal Corporation has submitted a special reproduction study that was requested by the California-EPA (refer to letter dated March 4, 1992, Willard F. Cummings to George LaRocca)) from the Uniroyal Co.to help determine if pup body weight decreases observed in the higher dose levels were due to direct effects of the test material on the pups as a result of in utero exposure or as a result of a secondary effect manifested through the dams. This study was reviewed and a copy of the DER is attached.

III. Toxicology Branch Comments

1. The cross fostering study provided a reasonable basis to demonstrate that the effects on body weight in the pups are not a result of exposure of the pups to the test material in utero. In particular, pups born to dams dosed with propargite (i.e. exposed in utero) and fostered by dams not exposed to propargite develop normally with respect to weight gain during lactation. In contrast, pups born to control dams but fostered by dams continuously dosed with 400 or 800 ppm of propargite have decreased body weight gain through lactation. The study confirmed that dams dosed with 800 ppm of propargite and nurse their natural pups, have pups that are also lower in weight. Since there was only a slight difference in the weights of the control pups fostered by the dams dosed with 800 ppm when compared to the pups born to and nursed by the dams dosed with 800 ppm of propargite, the conclusion that the decrease in pup weight gain during lactation is the result of a secondary effect of propargite in the dams is further supported.

2. TB-I previously (HED document No.: 8307, March 26, 1991) determined that the NOEL/LEL for the rat multi-generation reproduction study (MRID No.: 413524-01, Hazleton Labs # 6111-108, January 9, 1990) was 80/400 ppm based on decreases in parental body weight and food consumption. TB-I also acknowledged that there were decreases in pup weight gain during lactation at 400 ppm and at 800 ppm there was a decrease in pup birth weight.

The cross fostering study confirmed that dams dosed with 400 and 800 ppm have pups with deceased weight gain during lactation and that pup weight was decreased in the 800 ppm dose group. Therefore, the cross fostering study does not provide data to justify changes in the original conclusions made for the rat multi-generation reproduction study.

3. The letter (March 4, 1992, Willard F. Cummings to George LaRocca)) from the Uniroyal Co. which accompanied the submission

2

010121

of the study stated that the issue of the cause of the pup weight gain decrease during lactation was not raised by EPA (US). This statement by the registrant is not really true. Or at least the registrant has not interpreted the conclusions made in the DER for this study. In particular, the DER conclusion states that "NOEL (specific reproductive or developmental toxicity) > 800 ppm". This means that TB-I considered that the data generated in the original study provided a reasonable basis to conclude that the effects on body weight in the pups during lactation were an indirect effect resulting from the effects of propargite in the dams.

IV. Study reviewed.

Study Identification	TB-I Comments
83-4. Special cross fostering single generation reproduction study. IRDC, Study No.: 399-113, January 20, 1992 MRID No.: 422306-01. Classification: SUPPLEMENTARY	The data support the hypothesis that the apparent effect of propargite on the body weight of pups is not a direct effect of the test material on the pups but results as secondary effect on the dams. Charles River crl:CD VAF/Plus® strain rats. Dose levels tested 0, 400 and 800 ppm.

3

(83-4. Special cross feeding-Propargite/1992)

Reviewed by: John Doherty 3/24/93
Section IV, Toxicology Branch I (H7509C)
Secondary reviewer: Mario Copley, DVM 3/24/93
Section IV, Toxicology Branch I (H7509C)

010121

DATA EVALUATION REPORT

STUDY TYPE: 83-4. Special cross feeding reproduction study - rats.

MRID NO.: 422306-01 (two volumes) **TOX CHEM. NO.:** 130I
PC No.: 097601

TEST MATERIAL: Omite® technical (propargite).

STUDY NUMBER(S): 399-113

SPONSOR: Uniroyal

TESTING FACILITY: International Research and Development Corporation (IRDC), Mattawan, Michigan

TITLE OF REPORT: "A cross-fostering Reproduction Study with Omite® Technical in Rats"

AUTHOR(S): Raymond G. York

REPORT ISSUED: January 20, 1992

STUDY DATES: 10-22-90 to 9-9-91 (dates of inspection as indicated in the QAS).

CONCLUSIONS:

The data support the hypothesis that the apparent effect of propargite on the body weight of pups is not a direct effect of the test material on the pups but results as secondary effect on the dams.

Charles River crl:CD VAF/Plus® strain rats. Dose levels tested 0, 400 and 800 ppm.

Classification: CORE-SUPPLEMENTARY. The study was designed to answer a specific question and did not follow the specified protocol for a series 83-4 multi-generation reproduction study. A study satisfying this requirement already exists.

Quality Assurance Statement: Provided.
Good Laboratory Practice Statement: Provided.

4

REVIEW 010121

Introduction. This is a special study that was conducted at the request of the California EPA to attempt to resolve if the body weight effects noted in the pups during lactation in the multi-generation reproduction study (MRID No.: 413524-01, refer to HED document No.: 008307 dated March 26, 1991) an effect of the test material on the pups or a secondary effect resulting from an effect on the dams. The overall conclusion for the original multi-generation reproduction study as determined by TB-I is as follows:

"NOEL = 80 ppm. LEL = 400 ppm: decreases in parental body weight and food consumption, decreases in pup weight during lactation. 800 ppm: decreased mean pup birth weight. NOEL (specific reproductive or developmental toxicity) > 800 ppm."

Important note: Since cross fostering study was not designed to meet a specific guideline requirement and was not requested by the Agency, the review will present only a summary of the basic study design and results as well as TB-I's interpretation of these results.

Experimental Constants:

Test Chemical: Omite® technical. Stated as being 89.87% purity from batch No.: 010N628 and described as a amber liquid. The remaining 10.13% was not identified. Omite is the commercial name for propargite (2-(p-tert-butylphenoxy)cyclohexyl 2-propynlsulfate).

Test System: Charles River crl:CD VAF/Plus® strain rats obtained from the Charles River Breeding Laboratories Portage, Michigan. They were reportedly 30 days of age on receipt.

Basic Study Design: The basic design for this study consisted of dosing initial groups of control (100/sex, group 1), 400 ppm (30/sex, group 2) and 800 ppm (60/sex, group 3) to serve as parental animals. These groups were dosed for 70 days with their designated diet. After 70 days they were mated (1:1) with an animal from the same treatment level. Treatment continued throughout mating, gestation and lactation. Following parturition, the pups were culled to 8 per litter (four of each sex) and cross fostered according to the following scheme with each group consisting of 20 dams and a culled litter.

Control/Control Groups (2):

Group 4: Untreated dams with natural untreated litters.
Group 5: Untreated dams with cross fostered untreated litters.

5

010121

Control/Treated Groups (2):

Group 6: Untreated dams with cross fostered 400 ppm treated litters.
Group 7: Untreated dams with cross fostered 800 ppm treated litters.

Treated/Control Groups (2):

Group 8: 400 ppm treated dams cross fostered with untreated litters.

Group 9: 800 ppm treated dams cross fostered with untreated litters.

Treated/Treated Group (1):

Group 10: 800 ppm treated dams with natural 800 ppm treated litters.

As best as possible, the cross fostering was done between dams delivering on the same date. Since there was a limited number of control litters (some control dams failed to deliver), there were only 15 dams in Group 1. It was considered a higher priority to assign the untreated litters to groups 5 to 7.

Statistical Methods:

Test	Parameter Evaluated
Analysis of variance (one-way classification) and Bartlett's test for homogeneity of variance and "appropriate" t-test (for equal or unequal variances) as described by Steel and Torrie using Dunnett's multiple comparison tables.	Parental body weight changes during gestation and lactation; mean body weights of pups by sex in groups 1, 2 and 3 at lactation day 0 and mean numbers of liveborn pups per litter.
Hierarchial (nested) design, with post hoc multiple comparisons of group means.	Mean body weight of pups by sex on lactation days 0, 4, 7, 14 and 21.
Mann-Whitney U-test as described by Siegel and Weil.	Pup survival indices

Results

A. Parental Animals.

1. Survival and Clinical reactions. One male dosed with 800 ppm died with no reported signs of reactions. 100% survival was attained in the other groups. No signs of clinical reactions were reported.

2. Body weight gain and food consumption.

a. Growth period and mating period. Male body weight in the

6

high dose group was deceased ($p < 0.01$) starting at week 1 and continued to be decreased till week 14 when it was about 14% lower. Similarly females in the 800 ppm dose group were also decreased in weight but by week 13 the difference was no longer significant. Typically the females were about 8% lower during weeks 1 to 12.

The 400 ppm male group was not statistically different from the control and only at weeks 11 and 12 were the females (8 to 13%) lower.

Food consumption was up to 20% lower for males and females in the 800 ppm dose group and was also slightly lower in the 400 ppm dose group.

b. Gestation period. Weight gain over the 20 day gestation period was decreased 14% (compare means of 128 ± 33.7 gms for the high dose group with 148 ± 30.5 gms for the control. The intervals for days 7-14 and 14-20 did not show significant differences for the high dose group. No difference in the 400 ppm dose group was evident (mean 148 ± 25.2 gms).

Food consumption during gestation was slightly lower (11% for days 0-20) but not statistically significant.

c. Lactation period. No statistical differences were observed in the bodyweight gains of the dams during lactation for groups 4 to 10. The body weight gains ranged from 24 ± 22.7 gms to 44 ± 23.1 meaning that there were very large standard deviations for this parameter (sometimes as high as 88%). The body weights were essentially equal except that group 10 which started lower and remained lower.

Food consumption during lactation did not demonstrate statistical differences and ranged from 45.3 ± 2.72 gms for the group 10 to 60.3 ± 4.73 gms for group 7 and the control/control group 4 consumed 56.7 ± 5.17 gms.

B. Pup data at parturition.

a. Before cross-fostering, pup body weights for the high dose group male pups were about 1.5% lower in weight ($p < 0.01$, compare 6.5 ± 0.52 gms for the high dose group with 6.6 ± 0.76 for the controls). That for females were also about 1.6% lower ($p < 0.05$ compare 6.1 ± 0.56 with 6.2 ± 0.73 gms). The 400 ppm dose group females was higher (3.2%, $p < 0.01$).

After cross-fostering, only the group 10 females were lower in weight than the naive (control/control group, -4.7%, $p < 0.01$).

C. Pup data during lactation.

010121

There were no statistical differences in body weight during lactation for group 4 (control/control), group 5 (control/CF-pups), group 6 (control/400 ppm pups) or group 7 (control/800 ppm pups). This indicates that pups born to dams dosed with propargite develop normally with respect to weight gain when fostered by control dams. Thus, no effect of the pups resulting from in utero exposure is implied.

Statistically significant decrease in pup body weight during lactation were noted in the pups dosed in group 8 (400 ppm dams/control pups), group 9 (800 ppm dams/control pups) and group 10 (800 ppm dams/800 ppm pups). Table 1 illustrates the body weight of the pups at day 21 of lactation for groups 4, 8, 9, and 10.

Table 1. Pup body weight at day 21 of lactation in the cross fostering study with propargite.

		Body Weight in gms	
Group	Description	Males	Females
Group 4	Control/Control	60.2 ± 6.50	57.8 ± 7.79
Group 5	Control/CF-control	60.6 ± 5.94	57.0 ± 4.78
Group 8	400 ppm/control	52.3 ± 6.10[1](14)	50.2 ± 5.74[1](13%)
Group 9	800 ppm/control	42.4 ± 6.35[1](30%)	40.7 ± 6.11[1](29%)
Group 10	800 ppm/800 ppm	40.8 ± 4.22[2](32%)	39.0 ± 4.01[2](33%)

1. Groups 8 and 9 are compared with group 5 (control/CF-control).
2. Group 10 is compared with group 4 (control/control).
Note: For both 1 and 2 comparisons, the statistical differences were $p < 0.01$.
3. The numerator refers to the dosing status of the dams/the denominator refers to the dosing status of the pups before cross fostering.

Since control pups did not gain weight when nursed by dams being dosed with either 400 or 800 ppm of propargite, the cause of the weight decrease is related to the effect of the propargite in the dams rather than on inherent effect from in utero exposure of the pups. This is supported by the observation that group 10 (800 pp/800 ppm) had essentially the same decrease in body weight as the control pups nursed by the 800 ppm dams.

CONCLUSION. This study is SUPPLEMENTARY. The data support the hypothesis that the apparent effect of propargite on the body weight of pups is not a direct effect of the test material on the pups but results as a secondary effect on the dams.

8

END