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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Review of a 2-generation reproduction study on trifluralin (Treflan EPA Reg 1471-70)

To: Carol Gray, Team 23
Registration Division, TS-767C

From: Marcia van Gemert, Ph.D.
Head, Section III
Toxicology Branch, HED
M. van Gemert 10.22.86

Thru: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch, HED
10-22-86

Chemical: Trifluralin

Proj. No. 2284

Accession No.: 264493

Caswell No: 889

Action Requested: Review submitted data.

Elanco has submitted a 2-generation reproduction study on trifluralin in partial fulfillment of the data requirements as set forth in the recent registration standard.
The study appears well presented and no toxicity was seen in reproductive parameters. The middle and high dose, 0.063 and 0.2%, showed decreases in body weight and some body weight gain, as well as food consumption.

NOEL = 0.02%

LEL = 0.063% based on decreases in body weight.

Core classification = minimum

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Reviewed by: Marcia van Gemert, Ph.D. M van Gemert 10.22.86
Head, Section III Tox. Branch (TS-769C)
Secondary reviewer: Theodore M. Farber, Ph.D.
Chief, Tox. Branch (TS-769C)

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DATA EVALUATION REPORT

STUDY TYPE: 2-generation Reproduction study TOX. CHEM. NO.: 389

ACCESSION NUMBER: 264493 MRID NO.: ?

TEST MATERIAL: Trifluralin

SYNONYMS: EL 152, Compound 36352

STUDY NUMBER(S): RO6384, RI3984

SPONSOR: Elanco

TESTING FACILITY: Toxicology Division, Lilly Research Labs
Greenfield, ind. 46140

TITLE OF REPORT: A One-year two generation reproduction study in CD rats maintained on diets containing trifluralin

AUTHOR(S): J.K. Markham

REPORT ISSUED: Aug. 1986

CONCLUSIONS: SYSTEMIC NOEL = 0.02%

Systemic LEL = 0.063% based on decreased body weights

Reproductive NOEL = 0.2% (HDT)

Classification: core-Minimum

A. MATERIALS:

1. Test compound: trifluralin, Description, not given
Batch # 554AP2, Purity 96.4%, contaminants: list in CBI appendix

2. Test animals: Species: rat, Strain: Crl:CD(SD) Age: not given,
Weight: males-162.6± 1.3gm Source: Charles River Breeding Labs
females-131.7± 1.0gm Portage Mich. 49081

B. STUDY DESIGN:

1. Animal assignment
Animals were assigned randomly to the following test groups:

Test Group	Dose in diet (ppm)	mg/kg	%	# of animals
1 Cont.	0	0	0	25/sex
2 Low (LDT)	200	15	0.02	25/sex
3 Mid (MDT)	630	47	0.063	25/sex
4 High(HDT)	2000	148	0.2	25/sex

2. Diet preparation

Diet was prepared biweekly and stored at room temperature. Samples of treated food were analyzed for stability and concentration 4 times each generation and at initiation of each generation.

Results
Testing showed test article to be stable in the diet for the duration of F_1 and F_2 generations and no changes were seen in nitrosamine content of the diet. Concentration of the test chemical in the diet were found to be present at or slightly below theoretical concentrations.

3. Animals received food and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data:
An accounting of the statistical manipulations of the data can be found on appended pages 1 and 2.

5. Quality assurance was certified in a signed document in the study text.

6. Protocol

A schematic diagram of the protocol is found on appended page 3.

F_0 generation: Test diet was administered to weanling males and females, 25/sex/dose, for 70 days growth period and through 2 breeding trials. Following the 70 day growth period, the corresponding treatment groups were mated. Females kept progeny (F_{1a}) for 21 days postpartum. 25/sex/group of F_{1a} were selected to become F_1 parents. One weanling/sex/litter of the remaining pups was given a gross necropsy. The F_0 parents were again mated at 25 weeks of age and allowed to deliver and rear f_{1b} generation for 21 days postpartum. At weaning, all F_{1b} pups were sacrificed and given a gross necropsy. At 36 weeks of age all f_0 parents were killed and given a gross necropsy. Reproductive tissues and kidneys were collected for histopathological evaluation.

F_1 generation: was similar to F_0 generation except weanlings were kept on diet 69 instead of 70 days pre-mating.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected daily for signs of toxicity and mortality. At least once/week each rat was examined, noting muscle tone, pelage, eyes, teeth, and general condition. Females were observed more frequently close to parturition.

2. Reproductive measurements

The study text indicates that postcoital periods, gestation length, number of live and dead progeny on day of delivery were recorded. All females that didn't deliver during either breeding trial were examined for evidence of pregnancy.

3. Progeny measurements

Surviving progeny were counted on days 1, 4, 7, 14, and 21 postpartum. Sex was determined on day 4 postpartum. Litters were culled to 8 keeping 4/sex if possible. Culling was random. Progeny were weighed as litters on days 1, 7 and 14 postpartum and individual pups were weighed on days 4 and 21 postpartum.

4. Mortality

All animals that died on test were subjected to gross necropsy. All pups dying before day 4 postpartum were decapitated and the heads were preserved in Bouin's solution for later examination.

5. Indices measured

Mating index, fertility index, liveborn index

6. Cumulative indices based on the two breedings in each generation

female fertility index
male fertility index

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Results: Toxicity/Mortality (survival)

1. Parental mortality:

one F_0 male of the 0.02% group died with urolithiasis at 126 days on test. No other parental mortality was noted.

2. Parental clinical observations:

There were no treatment-related signs of clinical toxicity evident in the parents other than yellow-colored urine which was light, medium and dark in the low, medium and high doses respectively.

3. Mating Performance:

There were no treatment-related differences in fertility, mating performance and postcoital periods between groups. Mating indices ranged from 84-100% while male and female fertility indices ranged from 88-100%.

4. Reproductive parameters:

There were no treatment-related differences in number of pregnant females with liveborn progeny, gestation length, gestation survival or liveborn litter size.

5. Progeny Survival:

Survival was excellent throughout the study. No treatment-related decreases in progeny survival were evident.

6. Sex distribution:

No treatment-related changes in sex distribution were evident.

7. Progeny clinical observations:

In the combined four breeding trials, 0, 1, 3 and 4 litters of the 0, 0.02, 0.063 and 0.2% doses groups respectively had small progeny, approximately 1/2 the size of littermates. This may be treatment-related, and would be part of the picture of decreased body weights seen throughout the study. Another observation that appeared to be treatment-related was the occurrence of yellow fat in the weanling progeny of the 0.2% group. This was attributed to the high fat solubility of the trifluralin metabolites, some of which exhibit a yellow color. There was a slight increase in microphthalmia in the high dose (4 effected animals vs. 1 in controls). However, three of these came from one mother, and should not necessarily be considered treatment-

related. No additional treatment-related phenomen were seen.

2. Body weight

Animals were weighed weekly during the growth periods. Males were weighed monthly and prior to necropsy. Females were weighed weekly during the mating periods until copulation was confirmed. Mated females were weighed on gestation days 0, 7, 14, and 21. Females with litters were weighed on postpartum days 7, 14, and 21. All females were weighed prior to necropsy.

Results: see appended pages for results:

Males: F_o
In the F_o generation there was a significant ($p > 0.05$) decrease in body weight and body weight gain which occurred during the growth and reproduction periods in the 0.2% group.

Males: F_1
In the F_1 generation there was a significant drop in body weight at the 0.063% and 0.2% groups during the growth period but body weight gain was only effected in the 0.2% group. During the reproduction period only the 0.2% group was effected significantly at 99 and 127 days on test. They appeared to catch up somewhat to the control group in weight as the study progressed.

Females:
In both F_o and F_1 generations there was a significant decrease at 0.2% dose level in body weight and body weight gain during the growth, both gestations,both lactational periods, and both breeding trials, and at termination. No decrease in body weight gain was seen in the gestation period and second breeding trial of the F_1 generation. During the second breeding trial of the F_o generation there was also a significant decrease in body weight, but not body weight gain in the 0.063% group.

Progeny:

Postpartum body weights of both breeding trials of the F_1 and F_2 progeny were similar to controls on day 1 postpartum. However, However, all 0.2% groups started to show decreases from controls at various times starting with the F_{2a} which showed decreased body weight by days 4 postpartum; F_{1b} by day 7 and all were decreased significantly ($p > 0.05$) by days 14 and 21.

3. Food consumption and compound intake

Consumption was determined and mean daily diet consumption was calculated. Efficiency and compound intake were calculated from the consumption and body weight gain data.
Food consumption/Food Efficiency/Compound Intake

Results:
During the 70-day growth period on trifluralin, there was a

significant ($p > 0.05$) decrease in food consumption in both males and females on day 69 in the 0.2% groups. Additionally in the F_1 generation there was a decrease in food consumption in the 0.063% male group. NO decrease occurred in lactating females. Additionally in the 0.2% group of the F_o generation that was a significant decrease ($p > 0.05$) in food efficiency during the growth period. These data are appended for reference.

4. Pathology

All F_o and F_1 generation parents and animals dying on test were subjected to gross necropsy.

The following list of tissues was examined histopathologically in the control and high dose groups:

vagina, uterus, ovaries, mammary glands in females, testes, epididymus, seminal vesicles, prostate, kidneys and all gross lesions.

Results:

One low dose male died of urolithiasis with an acute urinary tract infection. The 0.2% groups showed pale yellow adipose tissue at necropsy, however, histopathology of the adipose tissue revealed normal tissue. No other treatment-related gross or histopathological lesions could be attributed to test compound.

5. Discussion:

Body weights at the 0.063% and 0.2% groups appear to be the only treatment-related effects noted in this study.

NOEL = 0.02%

LEL = 0.063% based on decreased body weight

Trifluralin Science Reviews

Page _____ is not included in this copy.

Pages __8__ through _22__ are not included in this copy.

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