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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Sumithrin (d-phenothrin) - Review of Rat Reproduction Study

Caswell No.: 652B

FROM: William Dykstra, Reviewer *William Dykstra 7/27/89*
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THRU: Edwin Budd, Section Head *Budd 7/27/89*
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The rat reproduction study is acceptable as Core-Guideline.
The NOEL is 1000 ppm, the mid-dose.

At 3000 ppm (HDT), there was decreased body weight (4 to 6%) in F₀ females, increase in absolute and relative liver weight in F₀ females, slight decrease in litter size at day 1 for F₁B litters, decrease in mean body weight (6%) of F₁ adult males, decrease in body weight of F₂B offspring at day 25, decreased absolute heart and kidney weight of F₂B male offspring, an increase in relative liver weight of F₂B male and female offspring, and an increase in absolute and relative spleen weight, decrease in absolute uterine weight, and increase in relative liver weight in F₁ female adults.

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Reviewed By: William Dykstra *William Dykstra 7/17/84*
Section I, Toxicology Branch I - IRS (H7509C)
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*Budd
7/21/84*

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DATA EVALUATION REPORT

Study Type: 83-4; Reproduction - Rat

TOX Chem No.: 652R

Accession No.: N/A

MRID No.: 402764-04
Vol. 1-4

Test Material: d-phenothrin, S2539-F

Synonyms: Sumithrin

Study Numbers: 85/SUM009/331; ET-61-0101

Sponsor: Sumitomo

Testing Facility: Life Science Research, England

Title of Report: Sumithrin: Effects Upon Reproductive Performance of Rats Treated Continuously Throughout Two Successive Generations.

Author: J.M. Tesh, et al.

Report Issued: November 1986

Conclusions:

The NOEL is 1000 ppm (mid-dose). The LEL is 3000 ppm (HDT).

At 3000 ppm (HDT), the effects are decreased body weight (4 to 6%) of F₀ females, increase in absolute and relative liver weight in F₀ females, slight decrease in litter size at day 1 for F₁B litters, decrease in mean body weight (6%) of F₁ adult males, decrease in body weight of F₂B offspring at day 25, decreased absolute heart and kidney weight of F₂B male offspring, an increase in relative liver weight of F₂B male and female offspring, and an increase in absolute and relative spleen weight, decrease in absolute uterine weight, and increase in relative liver weight in F₁ female adults.

Classification: Core-Guideline

Special Review Criteria (40 CFR 154.7): N/A

Review:

- Sumithrin: Effects Upon Reproductive Performance of Rats Treated Continuously Throughout Two Successive Generations (Life Science Research, England; Lab Project ID 85/SUM009/331; Sumitomo #ET-61-0101; November 1986).

A. Materials:

1. Test Material - A 20 kg sample of Sumithrin (Lot No. 21005) was used during the study; Name: d-phenothrin, S2539-F; Purity: 92.9%; Chemical class: synthetic pyrethroid; Appearance: clear yellow viscous liquid; Storage conditions: 4 °C.
2. Test Animals - Species: Rat; Strain: Sprague-Dawley; Age: 24 days; Weight: Males 155 to 243 g, females 130 to 186 g; Source: Charles River, U.K.

B. Study Design:

1. Randomized groups of 30 male and 30 female Sprague-Dawley rats (the F₀ generation) were administered 0, 300, 1000, and 3000 ppm of test material in the diet. Food and water were available ad libitum.

After 13 weeks on the test diets, the F₀ male and female rats were mated to produce the F_{1a} litters. Following weaning up to day 25 and after a 10-day rest period on the diet, the F₀ parents were mated again to produce the F_{1b} litters.

Following weaning, randomized groups of 30 male and 30 female offspring of the F_{1b} litters were selected to form the F₁ parents.

The randomized groups of 30 male and 30 female F₁ parents (F₁ generation) were fed their respective diets for 13 weeks. The F₁ parents were then mated to produce the F_{2A} litters.

Following weaning and a 10-day rest period on diet the F₁ parental rats were again mated to produce the F_{2B} offspring.

Randomized groups of F_{2B} offspring were fed their respective diets for 13 weeks (F₂ generation).

All animals were observed daily for toxic signs. Any animals found dead or killed in extremis were given a thorough gross necropsy.

2. Diet Preparation - Diet was prepared once every 2 weeks and stored at room temperature. Samples of treated food were analyzed for stability and concentration at each preparation.

Results

- a. F₀ Generation - Dietary analysis of the F₀ diets during the study showed that the achieved concentrations of test material in the diet were acceptable. They ranged from 268 to 336 ppm for the low dose, 924 to 1120 ppm for the mid dose, and 2690 to 3210 ppm for the high dose.
- b. F₁ Generation - Dietary analysis of the concentration of test material in the diet showed ranges of 101 to 108 percent for the 300 ppm group, 95 to 111 percent for the 1000 ppm group, and 93 to 101 percent for the 3000 ppm group in comparison to intended concentrations.
- c. F₂ Generation - Dietary analysis of the F₂ prepared rodent diet showed low-dose levels ranging from 101 to 108 percent, mid-dose levels ranging from 95 to 111 percent, and high-dose levels ranging from 91 to 101 percent of the intended concentrations.
3. Animals received food (Spratt's Laboratory Diet No. 2, ground, now marketed as Scientific Feeds Laboratory Animal Diet No. 2) and water ad libitum.
4. Statistics - The following procedures were utilized in analyzing the numerical data: Student's t-test and Dunnett's t-test were used for body weight and organ weight; Mann-Whitney U-test was used for precoital interval and gestation length; Chi-Square and Fischer's Exact Test were used for mating and reproductive indices and sex ratio.

C. Methods and Results:

1. Observations - Animals were inspected daily for signs of toxicity and mortality.

Results

F₀ Generation - There were no compound-related effects in toxic signs during the F₀ generation. During week 21 of the study, about 60 percent of all males (both control and treated) showed signs typical of infection by an SDA-type virus. The infection did not affect the study.

F₁ Generation - There were no compound-related toxic signs.

F₂ Generation - There were no compound-related toxic signs.

Mortality

F₀ Generation - There were no compound-related effects on mortality.

F₁ Generation - There were no compound-related effects. Two control females and one high-dose female died, but necropsy did not reveal any compound-related effects.

F₂ Generation - There were no compound-related effects. One control male and one control female died during the 13-week feeding period.

2. Body Weight - Body weight was measured weekly for the F₀, F₁, and F₂ parental rats.

Results

F₀ Parents - Analysis of group mean body weight of the F₀ males during the growth phase showed no compound-related effects.

Analysis of group mean body weight of the F₀ females during the growth phase, before pairing, showed a statistically significant decrease (4 to 6%) in the high-dose group in comparison to controls. This high-dose decrease in body weight in parental females is considered compound-related (see Figure 3, attached, from the report).

F₁ Parents - Mean body weight of high-dose males during the growth phase was about 6 percent less than control, but this decrease was not statistically significant. However, this decrease is considered compound-related (see Figure 19, attached, from the report).

Mean body weight of treated females was comparable to controls.

F₂ Parents - There were no compound-related effects in body weight.

3. Food Consumption, Food Efficiency, and Water Intake - Food consumption was determined weekly, water consumption daily, and mean daily diet consumption was calculated. Efficiency and compound intake were calculated from the food consumption and body weight gain.

Results

F₀ Generation - There were no compound-related effects in food consumption or food efficiency in F₀ males and females during the growth phase.

There were no compound-related effects in water intake during the F₀ growth phase in males and females.

F₁ Generation - Food consumption and food conversion efficiency was comparable between control and treated groups for both sexes.

Water intake was comparable for male and female treated groups in comparison to controls.

F₂ Generation - There were no compound-related effects in food consumption, food conversion efficiency, and water intake in male and female rats.

4. Evaluation of Mating and Reproductive Indices - Analysis of the mating and reproductive performance consisted of determining the following indices:

$$\text{Mating Index} = \frac{[\text{Females mated}]}{[\text{Females placed for mating}]} \times 100$$

$$\text{Fertility Index} = \frac{[\text{Pregnant females}]}{[\text{Females placed for mating}]} \times 100$$

$$\text{Conception Rate} = \frac{[\text{Pregnant females}]}{[\text{Females mated}]} \times 100$$

Maternal performance was determined as:

$$\text{Gestation Index} = \frac{[\text{Rats with live pups}]}{[\text{Pregnant rats}]} \times 100$$

Litter data were assessed by the following indices:

$$\text{Viability Index} = \frac{[\text{Live pups on day 4*}]}{[\text{Live pups on day 0}]} \times 100$$

$$\text{Survival Index} = \frac{[\text{Live pups on day 7* or 14*}]}{[\text{Live pups on day 4*}]} \times 100$$

$$\text{Lactation Index} = \frac{[\text{Live pups on day 21*}]}{[\text{Live pups on day 7*}]} \times 100$$

*Postpartum day.

Additionally, pup body weight, sex ratio, physical and visual function were also investigated.

Results

F₀ Generation - There were no compound-related effects in F₀ female estrus cycles.

There were no compound-related effects in precoital interval, mating, conception rate, and fertility index in the F₀ generation during the F₁A or F₁B litters.

The fertility index for males of the F₁A litters was 83, 90, 83, and 93 percent for the control, low-, mid-, and high-dose groups, respectively.

The fertility index for females of the F₁A litters was 90, 90, 83, and 93 percent for the control, low-, mid-, and high-dose groups, respectively.

The fertility index for males of the F₁B litters was 90, 97, 90, and 90 percent for the control, low-, mid-, and high-dose groups, respectively.

The fertility index for females of the F₁B litters was 90, 97, 90, and 90 percent for the control, low-, mid-, and high-dose groups, respectively.

There were no compound-related effects in gestation length or gestation index in female rats during the F₁A and F₁B litters.

The majority of females in all groups littered after a gestation period of 22 to 23 1/2 days and there was no evidence of dystocia.

For the F₁A litters, the gestation index was 100, 100, 100, and 96 percent for control, low-, mid-, and high-dose females, respectively.

For the F₁B litters, the gestation index was 96, 96, 100, and 100 percent for control, low-, mid-, and high-dose females, respectively.

There were no compound-related effects in appearance or general behavior of F₁A and F₁B offspring up to weaning.

With respect to litter sizes at day 1, there were no compound-related effects in the F₁A litters.

For the F₁B litter, there was a slight decrease in litter size at day 1 in the high-dose group.

The day 1 mean litter sizes for the F₁A litters were 12.5, 12.3, 13.3, and 12.2 pups for the control, low-, mid-, and high-dose groups, respectively.

The day 1 mean litter sizes for the F₁B litters were 13.0, 13.6, 12.7, and 11.9 pups for the control, low-, mid-, and high-dose groups, respectively. The slight decrease in the litter size of high-dose pups in the F₁B litters may be compound-related.

There were no compound-related effects in live birth index, viability index, or lactation index for the F₁A and F₁B litters. All indices were between 94 to 100 percent and there were no dose-related trends in either litter.

There were no compound-related effects in pup mean body weight at postpartum days 1, 4, 10, 14, 21, and 25 for the F₁A and F₁B litters. Additionally, sex ratio of the F₁A and F₁B litters showed no compound-related effects.

With respect to the F₁B litters, there were no compound-related effect in the rate of physical development, as indicated by pinna unfolding, hair growth, tooth eruption, eye opening, or auditory and visual function.

Results

F₁ Generation - Estrus cycles of the treated females were comparable to controls.

For the F₂A and F₂B litters, adult male and female fertility indices were comparable between control and treated groups.

For the F₂A mating, the fertility index in males was 63, 67, 63, and 77 percent for the control, low-, mid-, and high-dose groups, respectively. The fertility index in females was 77, 77, 77, and 90 percent for control, low-, mid-, and high-dose groups, respectively.

For the F₂B mating in males, the fertility index was 69, 66, 77, and 79 percent for control, low-, mid-, and high-dose groups, respectively. For the F₂B mating, the fertility index for females was 72, 66, 80, and 83 percent for control, low-, mid-, and high-dose groups, respectively.

The length of gestation was 22 to 23 1/2 days for females of the F₂A and F₂B litters and there were no compound-related effects in gestation length.

There were no compound-related effects in litter size for the F₂A and F₂B litters.

There were no compound-related effects in live birth index, viability index, and lactation index for F₂A and F₂B litters.

For all groups of the F₂A litters, live birth indices ranged from 96 to 98 percent, viability index at day 4 ranged from 87 to 97 percent, and lactation indices ranged from 92 to 99 percent.

For all groups of the F₂B litters, live birth indices ranged from 99 to 100 percent, viability index at day 4 ranged from 87 to 94 percent, and lactation indices ranged from 90 to 100 percent.

Group mean body weights of the F₂A pups were comparable between control and treated groups during lactation.

For F₂B pups, the mean body weight of the high-dose group was slightly decreased in comparison to controls on day 25 (control, 71.1 g; high dose, 66.0 g). The decreased body weight was not statistically significant but may be compound-related, nevertheless.

Sex ratio was unaffected by treatment for F₂A and F₂B litters.

For the F₂B litters, there were no compound-related effects in pinna unfolding, hair growth, tooth eruption, eye opening, or auditory and visual responses.

5. Sacrifice and Pathology - All animals that were sacrificed on schedule were subject to gross pathological examination. The following checked (X) tissues from parental animals and pups were examined histologically. The (XX) organs in addition were weighed.

<u>X</u>	Digestive system	<u>X</u>	Cardiovasc./Hemat.	<u>X</u>	Neurologic
	Tongue		Aorta*	XX	Brain*
	Salivary glands*	XX	Heart*		Periph. nerve*
X	Esophagus*	X	Bone marrow*		Spinal cord (3 levels)
X	Stomach*	X	Lymph nodes	XX	Pituitary*
X	Duodenum*	XX	Spleen*	X	Eyes (optic n.)*
X	Jejunum*	X	Thymus*		Glandular
X	Ileum*		Urogenital	XX	Adrenals*
	Cecum*	XX	Kidneys*		Lacrimal gland
	Colon*	X	Urinary bladder*		Mammary gland
X	Rectum*	XX	Testes*		Parathyroids*
XX	Liver*	XX	Epididymides	XX	Thyroids*
	Gallbladder*	XX	Prostate		Other
X	Pancreas*	XX	Seminal vesicle		Bone*
	Respiratory	XX	Ovaries		Skeletal muscle*
X	Trachea*	XX	Uterus*		Skin
XX	Lung*			X	All gross lesions and masses

*Recommended by Subdivision F (October 1982) guidelines for chronic studies.

Results

F₀ Generation - Necropsy of F₀ parental animals did not reveal any compound-related findings.

Analysis of absolute and relative organ weights of F₀ parental animals showed a statistically significant increase in the relative kidney weight of high-dose and mid-dose male rats and an increase in absolute and relative liver weight of high-dose female rats. However, there were no histopathological findings in these organs.

The increase in absolute and relative liver weight in high-dose F₀ females is considered compound-related, since increased relative liver weight was also seen in F₁ females and F₂B male and female weanlings. Individual data for the F₀ females showed that only one control female had an absolute liver weight exceeding 15 g, whereas 12 high-dose females had absolute liver weights exceeding 15 g.

Histopathological evaluation of 20 control and 20 high dose male and female F₀ parental rats did reveal two unusual findings in females, but none in males.

A statistically significant increase in the high-dose in comparison to controls of cystic thyroglossal duct remnants in the thyroid and yellow pigment in suspensory

ligament of the uterus was observed in females. The following table shows the incidence of these findings:

	F ₀ Female Rats				
	Group (ppm)	0	300	1000	3000
<u>No. Examined</u>		20	0	0	20
<u>Thyroid</u>					
Cystic thyroglossal duct remnants		4	0	0	12*
<u>Uterus</u>					
Yellow pigment in suspensory ligament		10	0	0	19**

*p < 0.05

**p < 0.01

In contrast, histological evaluation of the thyroid and uterus of F₁ adult female rats did not confirm these findings. An incidence of 11/19 in the controls compared to 13/20 in the high-dose for cystic thyroglossal duct remnants in the thyroid and an incidence of 12/19 in the controls compared to 8/20 in the high-dose for pigment in suspensory ligament in the uterus was observed in the F₁ females.

In light of the findings in the F₁ adult females, the histological findings in the F₀ females may not be compound-related.

Necropsy of the offspring of the F₁A and F₁B litters did not show any compound-related effects. The most frequent necropsy observation was the absence of milk or food in the stomach and the incidence of this finding was comparable among groups of the F₁A and F₁B litters.

Results

F₁ Generation - There were no compound-related effects in gross necropsy observation in the weanlings of the F₂A and F₂B litters.

Terminal body weight and absolute heart and kidney weight of the male high-dose group were statistically significantly decreased in comparison to controls.

With respect to relative organ weight, high-dose males had a statistically significant increase in relative liver and brain weight in comparison to controls.

In female F₂B offspring, the high-dose group had a statistically significant increase in relative liver weight in comparison to controls.

Histopathological evaluation of F₂B offspring did not show any compound-related effects in high-dose male and female offspring in comparison to controls.

The decreased body weight and decreased absolute heart and kidney weight in high-dose males and the increase in relative liver weight in high-dose male and female offspring are considered compound-related.

Gross necropsy of F₁ adult males and females did not reveal any compound-related macroscopic findings.

Analysis of absolute and relative organ weights of F₁ adult male rats did not show any compound-related effects.

In female F₁ adult rats, there was a statistically significant increase in absolute spleen weight at the high dose and statistically significant decrease in absolute uterus weight at the mid and high dose in comparison to controls.

The mean absolute uterine weights of the control, low-, mid-, and high-dose groups were 0.72, 0.68, 0.60 and 0.60 g, respectively. Relative uterus weight was statistically significantly decreased in mid-dose but not high-dose females.

Relative spleen and liver weights were increased in high-dose females in comparison to controls.

At the high-dose, the decrease in absolute uterine weight and the increase in absolute and relative spleen and relative liver weights in F₁ female rats are considered compound-related.

The reasons for this conclusion are: 1) For the uterus, both the mid and high dose absolute weights were decreased; 2) both the absolute and relative spleen weights were increased; and 3) the increase in relative liver weight was observed in F₀ females and both male and female F₂B weanlings.

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The NOEL for the study is the mid-dose group of 1000 ppm.

Histopathological evaluation of control and high-dose male and female F₁ adult rats did not reveal any compound-related effects.

Results

F₂ Generation - There were no compound-related effects in gross necropsy, absolute or relative organ weight, or histopathology in male and female F₂ adult rats.

Attachments

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R: 56533:Dykstra:C.Disk:KENCO:4/21/89:rw:vo:jh:rw:vo:AS:EK:AS
R: 57229:Dykstra:C.Disk:KENCO:7/19/89:AS:vo:de:rw

Sumithrin toxicology review dated 7/27/89

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Pages 15 through 21 are not included in this copy.

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