CASWELL FILE

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

009836

NOV 24 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Tetramethrin; One Year Chronic Toxicity Dog Study; ID# 069003-010308; Miscellaneous Data Submitted for Reregistration

DP Barcode No.: D174421
Caswell No.: 844
Project No.: 2-1371
Submission No.: S411530
MRID No.: 421893-01

TO: Christine Rice, PM Team #52
Registration Branch
Special Review and Reregistration Division (H7508W)

FROM: William Dykstra, Ph.D. William Dykstra 8/24/92
Review Section I, TB-I, IRS
Health Effects Division (H7509C)

for THRU: Roger Gardner, Section Head Pamela M. Hurley 11/17/92
Review Section I, TB-I, IRS
Health Effects Division (H7509C) R.G. 11/17/92 11/13 11/17

Requested Action:

In support of reregistration of tetramethrin, Sumitomo Chemical Company has submitted a new one year chronic toxicity dog study to supplement/replace the present 6-month dog study. Toxicology Branch has been requested to review the new one-year chronic toxicity dog study submitted in fulfillment of Guideline 83-1(B) with tetramethrin.

Conclusion and Recommendation:

The study is acceptable as core-minimum data.

The systemic NOEL = 300 mg/kg/day(HDT). There were no compound-related systemic effects. The findings observed in the study are attributed to the presence of estrus in the female dogs.

The findings at 100 mg/kg/day were gross necropsy findings consisting of ovaries of unequal size, and thickened uterine wall,

increased absolute ovarian and uterine weights (48.2% and 128%, respectively), and histological effects consisting of increased incidences and grades of prominent corpora lutea of ovaries and endometrial glandular proliferation of uterus.

At 300 mg/kg/day (HDT), in addition to the findings at 100 mg/kg/day, there were additional findings. There was a 22% decrease in body weight gain in male dogs, which was not statistically significant and which was not considered compound-related, and there was an increased histological incidence of stromal hypertrophy/edema of the vagina, gross vaginal necropsy findings consisting of thickened wall, and increased relative (BW) ovarian (60%) and uterine (198%) weight.

Also, at 100 mg/kg/day, one female dog was found to be pregnant.

Doses were 0, 10, 30, 100, and 300 mg/kg/day in 4/sex/dose of Beagle Dogs.

A DER is attached.

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Reviewed by: William Dykstra, Ph.D. William Dykstra 11/17/92
Review Section I, Toxicology Branch I (H7509C)
for Secondary Reviewer: Roger Gardner, Section Head Pamela McHurley 11/17/92
Review Section I, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT

Study Type: 83-1(B): Chronic Toxicity Dog — TOX Chem No. 844; MRID No.: 421893-01

Accession Number: N/A

Test Material: Neo-pynamin, technical (Lot No. 90304), 95.3% purity

Synonyms: Tetramethrin

Study Number: IT-11-0242 (HWA 343-235)

Sponsor: Sumitomo Chemical Company, Osaka, Japan

Testing Facility: Hazleton Washington, Inc.
Vienna, VA

Title of Report: Chronic Toxicity Study in Dogs with Neo-Pynamin

Author: D. W. Dalgard, D.V.M.

Report Issued: December 19, 1991

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uterine (198%) weight.

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Classification: Core-Minimum

Special Review Criteria (40 CFR 154.7) N/A

A. MATERIAL:

1. Test compound: Neo-pynamin, Description: white, granular material, Batch # 90304, Purity 95.3%, contaminants: list in CBI appendix

2. Test animals: Species: Dog, Strain: Beagle, Age: 5 months, Weight: males = 5.1 to 7.7 kg; females = 4.7 to 7.6 kg, Source: Hazleton Research Products, Inc., VA.

B. STUDY DESIGN:

1. Animal assignment - Animals were assigned randomly to the following test groups and were individually caged.

Test Group	Dose by Capsule mg/kg/day	Main Study 12 months Male	Female
1. Control	0	4	4
2. Low (LDT)	10	4	4
3. Mid (MDT)	30	4	4
4. Mid (MDT)	100	4	4
5. High (HDT)	300	4	4

2. Diet preparation - test compound was prepared weekly as capsules and stored at room temperature. Samples were not analyzed for stability and concentration.

3. Animals received food (Purina Certified Canine Diet #5007) and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data: Levene's Test, Rank transformation, ANOVA, Dunnett's test; $p<0.05$ was significant by two-tail analysis.

5. Quality assurane statement was signed by Karen E. Butler and dated 12/19/91.

C. METHODS AND RESULTS:

1. Observations - Animals were inspected twice daily for signs of toxicity and mortality. Weekly physical examinations were also performed during weighings.

Results

There were no mortalities and no significant illnesses in any of the dogs during the study. The incidence of soft stools was slightly increased in treated dogs in comparison to controls and unabsorbed test material was occasionally seen in the feces of, primarily, dogs of the 100 and 300 mg/kg/day groups. These findings had no apparent effect on the health of the dogs.

2. Body weight - They were weighed weekly for 52 weeks.

Results -

Body Weight (Kg) Males

Dose	Week			
(mg/kg/day)	1	13	27	52
0	7.0	10.2	11.5	11.5
10	7.3	10.4	11.5	12.2
30	7.1	10.8	12.1	12.5
100	6.7	10.0	11.4	11.9
300	7.1	9.7	10.6	11.1
B.W. gain % at 300 ppm		-18.8	-22.2	-11.1

There was a decrease in body weight gain (up to 22% decrease) in high-dose males in comparison to controls. It does not appear that the mean decreased body weight gain was due to an outlier. The 22% decreased body weight gain is not toxicologically significant. None of the measured values were statistically significant for either mean body weights at any time period or for mean body weight gains for specified time periods and the difference between the mean body weights of the high-dose males and the controls was generally not less than 90% for any time period measured. Since there was up to a 22% decrease in body weight gain at the highest dose level, this finding may be close to an LEL for body weight gain. Other treated male groups and all treated female groups were comparable to their respective controls.

3. Food consumption and compound intake - Food consumption was measured weekly.

   Results - There were no compound-related effects in food consumption. Weekly measurements were comparable between male treated and control groups and female treated and control groups. On an ad libitum basis, females consumed less food than males. Food efficiency was comparable between treated and control dogs.

4. Ophthalmological examinations were performed prior to study, and during weeks 26 and 52 on all animals.

   Results - There were no compound-related ophthalmological findings between eyes of treated dogs and their respective controls as determined by Dr. Steven K. Kahlman at week 26 and week 52. All observations were considered incidental.

5. Blood was collected before treatment (week -2) and at weeks 4, 13, 26, 39, and 52 for hematology and clinical analysis from all animals. The CHECKED (X) parameters were examined.
   a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*		Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)*		Mean corpusc. volume (MCV)
X	Platelet count*		Reticulocyte count
X	Prothrombin time	X	Cell morphology
X	Reticulocyte count	X	Activated partial thromboplastin
X	Corrected leukocyte count		

   Results - Mean prothrombin time was decreased in males at 300 mg/kg/day at weeks -2, 4 and 13 but not thereafter. Hemoglobin was decreased in females at 300 mg/kg/day at 52 weeks, but this was unaccompanied by decreases in HCT, and RBC. Findings at 100 mg/kg/day in males and females did not occur at 300 mg/kg/day and were therefore not dose-related. These consisted of increased RBC, HGB, HCT and reticulocytes at week 39 in females, decreased platelets at week 52 in males, and increased WBC and corrected WBC at week 4 in females (no concurrent increases in neutrophil or lymphocyte count).

   In summary, there were no consistent, time-related or dose-related effects on hematological parameters in treated male and female dogs in comparison to controls.

b. Clinical Chemistry

X		X	
	Electrolytes:		Other:
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
X	Phosphorous*	X	Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	Enzymes	X	Total bilirubin
X	Alkaline phosphatase (ALK)	X	Total Protein
	Cholinesterase (ChE)#	X	Triglycerides
	Creatinine phosphokinase*^	X	Creatine kinase
X	Lactic acid dehydrogenase (LAD)		
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		
X	Leucine aminopeptidase		
X	Phospholipid		

Results - The following clinical chemistry parameters were without statistically significant effects:

Males: glucose, BUN, Creatinine, total cholesterol, AST, ALT, LDH, SAP, Albumin, A/G ratio, Calcium, total bilirubin, creatine kinase, P, Na, K, Cl, LAP, Phospholipid.

Females: glucose, BUN, total cholesterol, AST, ALT, LDH, total protein, globulin, A/G ratio, calcium, total bilirubin, creatine kinase, triglycerides, P, Na, K, LAP, Phospholipid.

The following parameters were statistically significantly changed, but the findings were not time-related or dose-related and were not considered compound-related:

Males: at week -2, decreased total protein and globulin at 100 mg/kg/day, increased triglycerides at week 26 and 52 at 100 mg/kg/day.

Females: at week 4, increased creatinine at 10 mg/kg/day; at week 39, increased SAP at 300 mg/kg/day, increased albumin at 30 mg/kg/day at weeks 13, 26, and 39 and at 100 mg/kg/day at week 39, increased Na at 10 and 30 mg/kg/day at week 4.

6. Urinalysis

Urine was collected from fasted animals at same time as blood collections. The CHECKED (X) parameters were examined.

X		X	
X	Appearance*	X	Glucose*
X	Volume*	X	Ketones*
X	Specific gravity*	X	Bilirubin*
X	pH	X	Blood*
X	Sediment (microscopic)*		Nitrate
X	Protein*	X	Urobilinogen

Results - Urinalysis were comparable between control and treated dogs of both sexes.

7. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

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

Results

a. Organ weight

Organ Weight

Dose (mg/kg/day)	0	10	30	100	300
Ovary (g)	0.87	0.81	0.98	1.29*	1.74*
(%)				+48.2	+100.0
Uterus (g)	4.87	4.15	4.28	11.11	18.95*
(%)				+128	+289.1

Organ to Body Weight Ratios

Dose (mg/kg/day)	0	10	30	100	300
Ovary %	0.010	0.010	0.010	0.014	0.016*
%					+60
Uterus %	0.059	0.049	0.042	0.120	0.176*
%					+198.3

* $p<0.05$

There were significant increases in absolute ovarian and uterine weight at 100 and 300 mg/kg/day. Additionally at 300 mg/kg/day, the relative (BW) weights of ovary and uterus were significantly increased. These findings are not considered to be treatment-related, because they are indications that the dogs are in estrus.

b. Gross Pathology

Gross Necropsy Findings

Dose (mg/kg/day)	0	10	30	100	300
No. Examined	4	4	4	4	4
Ovary					
Unequal size	0	0	0	2	1
Uterus					
Wall, thickened	0	0	0	2	3
Mass	0	0	0	1	0
Distended	0	0	0	0	1
Vagina					
Wall, thickened	0	0	0	0	2

At 100 and 300 mg/kg/day, there were gross findings in ovaries and uterus, and at 300 mg/kg/day, the vagina wall thickening was increased. The mass located in the uterine wall of female # G28242 of the 100 mg/kg/day was representation of a placenta indicating the dog was pregnant. These findings are not considered treatment related, because they are indications that the dogs are in estrus.

c. Microscopic pathology

(1) Non-neoplastic

Non-neoplastic lesions

Dose (mg/kg/day)	0	10	30	100	300
No. Examined	4	4	4	4	4
Ovary					
corpora lutea, prominent	0	1	0	2	3
Follicle, prominent (early corpora lutea)	0	0	0	0	1
Uterus					
endometrial glandular prolif.	1[a]	1[b]	0	2[c]	4[d]
placental implant site	0	0	0	1	0
fetal tissue (nucleated red cells)	0	0	0	1	0
Vagina					
stromal hypertrophy/ edema	0	0	0	0	2

a = grade was minimal
b = grade was minimal
c = grades were moderate, slight
d = grades were slight, slight, moderate, moderate

Histological findings were present at 100 and 300 mg/kg/day in the ovary and uterus, and at 300 mg/kg/day in the vagina. The tissue mass observed at 100 mg/kg/day was an implantation site. These findings are not

considered treatment-related, because they are indications that the dogs are in estrus.

(2) Neoplastic

There were no tumors of any type observed in dogs in the study.

DISCUSSION: There were no clear-cut results which demonstrated that the findings observed in this study were compound-related. The 22% decrease in body weight gain in high-dose males was not statistically significant, but may represent a borderline finding for body weight gain. The organ weight, gross necropsy and microscopic changes observed were due to the dogs being in estrus. It should be noted that one dog was pregnant, which throws some doubts on the conduct of the study. However, the study is acceptable for regulatory purposes. Since the results of the 6-month dog study show signs of a decrease in estrus at 5000 ppm (125 mg/kg/day) when compared to controls, the results of this study of increased signs of estrus in the mid- and high-dose groups suggest that these findings are unrelated to treatment. Also, there were no compound-related reproductive effects in the rat reproduction study with tetramethrin.

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Chemical:	**Tetramethrin**
PC Code:	**069003**
HED File Code	**13000 Tox Reviews**
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