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FINAL

DATA EVALUATION REPORT

TETRAMETHRIN

Study Type:
21-Day Dermal Toxicity Study in Rats

Study Title:
21-Day Dermal Toxicity Study in Rats with Neo-Pynamin

Prepared for:

Office of Pesticide Programs
Health Effects Division
U.S. Environmental Protection Agency
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Arlington, VA 22202

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Review Section I, Toxicology Branch I (H7509C) 6/11/92

DATA EVALUATION REPORT

Study Type: 82-2: 21-Day Dermal Toxicity Study in Rats
TOX Chem No. 844
MRID No.: 419950-04

Test Material: Tetramethrin

Synonyms: Neo-pynamin; 3,4,5,6-Tetrahydro-phthalimidomethyl (IRS)-cis-trans-chrysanthemate

Study Number: 343-232

Sponsor: Sumitomo Chemical Company, LTD.

Testing Facility: Hazleton Laboratories America, Inc.
1330B Piccard Drive
Rockville, Maryland 20850-4373

Title of Report: 21-Day Dermal Toxicity Study in Rats With Neo-Pynamin

Author: M.R. Osheroff, Ph.D., D.A.B.T.

Report Issued: July 19, 1991

Conclusion: Tetramethrin (neo-pynamin), administered dermally to Sprague-Dawley rats for 21 days at doses of 100, 300 and 1000 mg/kg/day was not associated with any toxic effects. Although, there was a significant increase in the mean hemoglobin level and percent hematocrit in male rats exposed to 300 and 1000 mg/kg/day and a significant decrease in the mean leukocyte, corrected leukocyte, and eosinophil levels of male rats exposed to 1000 mg/kg/day, these findings were not considered toxicologically significant. Exposure to 100 mg/kg/day was not associated with any effects. Although effects were noted at both 300 and 1000 mg/kg/day, the hematologic levels did not increase in a dose-dependent manner. The percentage of change was not reported for any of the effects.

The macroscopic lesions noted in rats exposed to tetramethrin were considered to be unrelated to exposure, because each effect was observed in only 1 of the 10 animals exposed per dose. Most of the macroscopic effects occurred only in animals from the high-dose group; however one animal exposed to 300 mg/kg/day and one exposed to 100 mg/kg/day also exhibited kidney and skin effects, respectively.

Microscopic examination was conducted only on control and Group 4 animals (1000 mg/kg/day). There were several microscopic effects noted in Group 4 animals. These effects were not due to treatment with tetramethrin because most of the effects occurred in one particular animal from Group 4. Also, the incidence of the effects was equal to 1 or to that noted in the control animals. The incidence of effects of the regenerative tubules in the kidneys was slightly elevated in Group 4 males over the controls, but this was not found to be statistically significant by the reviewer.

The no-observed-effect level (NOEL) is 1000 mg/kg/day (HDT).

Core Classification: This study satisfies the Guideline (8202) requirements for a 21-day dermal toxicity study in rats and is classified Core Minimum.

A. Materials, Methods, and Results

1. Test Article Description

Name: tetramethrin

Formula: $C_{19}H_{25}NO_4$

Lot Number: 90304 (received December 21, 1989)

Purity: 95.3%

Physical property: off-white powder

Stability: a 24-hour stability analysis was conducted on samples for the 100 mg/kg/day and 1000 mg/kg/day exposures. The details of the stability analysis are on file with the sponsor and were not included in the report. The compound was reported as stable.

2. Test Article Analyses for Purity and Stability

The test material, which was prepared daily, was dissolved in corn oil (% solution not specified) and tested for homogeneity and stability prior to the 7-day range-finding study and the 21-day exposure. Homogeneity testing consisted of taking three duplicate samples of material from the top, middle and bottom of each

preparation. These samples were then analyzed prior to the initiation of the 21-day exposure. Also, two duplicate samples (not specified whether top, middle, or bottom) for each dose were analyzed on days 1, 8, and 15 of the 21-day exposure regime. Each sample was analytically tested by gas chromatography using a flame ionization detector to verify the concentration in corn oil.

The samples taken from preparations for exposure Groups 2, 3, and 4 (see Table 1), of the 21-day dermal study, had mean deviations of <1%, <6%, and <10% from their respective target doses. A second homogeneity analysis was conducted in which the mean deviations from the target doses for these samples were <5%, <8%, and <2%, respectively.

The samples taken from preparations for exposure Groups 2, 3, and 4 on days 1, 8, and 15 of the 21-day dermal study had deviations of ±3.9-13% (days 1-15), 0-2.7% (days 1-15), and 1-5.7% (days 1-15), respectively.

Rats were grouped (5/sex/dose) using a computerized program which allowed random grouping by body weight. The dosage levels and assigned animals per group are shown in Table 1. A group of 5 corn oil-treated rats was used as the control.

Electric clippers were used for hair removal from the entire trunk of each rat 1 week and then 1 day prior to treatment with tetramethrin or corn-oil and, thereafter, when necessary. Plastic collars were used to prevent each rat from contacting the application site. In addition to a 5-day acclimation period, the collars were worn throughout the study (18 hours a day) except during the 6-hour exposure period.

Exposures were conducted by spreading the test material or the vehicle control with a glass rod over a 5 cm x 5 cm area on the trunks of each rat. Gauze was used to cover the treated area and rubber damming was taped over the gauze; after a 6-hour exposure period the wrapping was removed. After exposure to the test material, the area was wiped with gauze moistened with distilled water.

3. Animals

Twenty-eight-day-old Sprague-Dawley (Crl:CD®BR) rats (122/sex) were received from Charles River Laboratories, Raleigh, N.C. Animals were housed in hanging, stainless-steel wire-mesh cages (one animal per cage) in a room with a 12-hour light/12-hour dark cycle and with temperature and humidity controls set at 72°± 6°F and 50% ± 20%, respectively. Water and food were provided ad libitum. All animals were acclimated to the described environment for 17 days prior to initiation of testing. At the time of exposure, the male body weights ranged from 198.0 to 240.4 g and those of the females ranged from 152.0 to 183.6 g.

TABLE 1. Group Assignment and Dosage Levels

Group Number (Description)	Dosage Level (mg/kg/day) (in 2.0 ml/kg/day)	Animals Assigned per Group (5 animals/dose/sex)	
		Males	Females
1 (Control)	0	9750-9754	9755-9759
2 (Low)	100	9560[a]-9764	9765-9769
3 (Moderate)	300	9770-9774	9775-9779
4 (High)	1000	9780-9784	9780[b]-9789

[a]This value was incorrectly reported on p. 14 of the report: 9560 should be 9760 (see the table, p. 14, and Appendix 4, p. 142, of the report).

[b]This value was incorrectly reported on p. 14 of the report: 9780 should be 9785 (see the table, p. 14, and Appendix 4, p. 143, of the report).

4. General Observations

Analysis of variance using a 5.0% two-tailed probability level was performed to determine the statistical significance of data from treated groups as compared to the controls for each sex. Statistical analyses were performed on the following data:

Absolute mean body weight change (weeks 0 and 3)
Mean body weight change (weeks 0-3)
Total food consumption (weeks 1-3)
Mean clinical pathology values
Mean terminal body weight
Mean organ weight

In cases of variance heterogeneity, a series of transformations was used or analysis of variance was conducted on rank-transformed data to achieve variance homogeneity.

The observation schedule was as follows:

Parameter Observed	Observation Schedule
Mortality	Twice/day (morning and afternoon)
Moribundity	Twice/day (morning and afternoon)
Toxic effects	Once/day
Clinical examinations	Once/week
Dermal responses	Once/day (immediately prior to application of test material)
Body weights	Prior to initiation of the study Once/week, during the exposure period Upon termination of the study
Food consumption	Once/week

(a) Mortality/moribundity/survival

There was neither mortality nor moribunditiy in animals prior to termination of the study.

(b) Clinical observations

Clinical observations were not considered to be treatment related by the author. Alopecia and lacrimation were both noted in only one female rat from Group 4 (Table 2). However, alopecia was

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TABLE 2. Summary of the Incidence of Clinical Signs in Rats During 21-Day Dermal Exposure to Tetramethrin

Clinical Observations (week of exposure)	Incidence of Effects							
	Group 1 (0 mg/kg/day)		Group 2 (100 mg/kg/day)		Group 3 (300 mg/kg/day)		Group 4 (1000 mg/kg/day)	
	Male	Female	Male	Female	Male	Female	Male	Female
Alopecia of the eyelid (2)	0	0	0	0	0	0	0	1
Lacrimation (1)	0	0	0	0	0	0	0	1
Body sores (2)	2	1	1	0	0	0	0	0

also observed by macroscopic examination in a Group 2 male (Table 7). The incidence of bodily sores in treated groups was not greater than in controls (Table 2).

(c) Dermal irritation observations

There were no treatment related dermal irritation effects observed. Based upon the Draize scale, desquamation occurred in one Group 2 male and one control group female on days 15-17 of the study. The Group 2 male also exhibited this effect on day 14. No data were presented in the report for these effects other than in the discussion of the results.

(d) Body weights/food consumption

Body weights--There were no significant effects on body weight or body weight gain.

Food consumption--There were no significant effects on food consumption.

5. Clinical Pathology

Animals were fasted overnight but had access to water ad libitum. Animals were then anesthetized by intramuscular injection with ketamine hydrochloride, and blood samples were taken from the orbital sinus.

(a) Hematology: The checked (X) parameters were examined.

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*
Reticulocyte count (RETIC)
Red cell morphology
X Leukocyte differential count*
X Corrected Leukocyte count (COR WBC)
Mean corpuscular HGB (MCH)
Mean corpuscular HGB concentration (MCHC)
Mean corpuscular volume (MCV)
Coagulation: thromboplastin time (PT)

* = Recommended by Subdivision F (November 1984) Guidelines

Statistically significant, but not dose-dependent, hematological effects (i.e., increased mean hemoglobin level and percent hematocrit) were noted in male rats of Groups 3 and 4 (Table 3). In addition, male rats from Group 4 exhibited significantly depressed mean leukocyte, corrected leukocyte, and eosinophil levels. None of these effects was considered by the author to be exposure related, but were thought to be secondary effects due to stress from wrapping during exposure. The low magnitude of the changes and the lack of significant decreases in segmented neutrophils or lymphocytes (two primary leukocytes) were also given as reasons

TABLE 3. Selected Clinical Hematology Data for Rats Following 21-Day Dermal Exposure to Tetramethrin

Hematological Parameters Measured (Week #4)	Mean Level of Effect (SD) (N=5 dose/sex)							
	Group 1 (0 mg/kg/day)		Group 2 (100 mg/kg/day)		Group 3 (300 mg/kg/day)		Group 4 (1000 mg/kg/day)	
	Male	Female	Male	Female	Male	Female	Male	Female
Erythrocytes (red blood cells) (mi/µl)	8.03 (.179)	8.16 (.368)	7.98 (.249)	8.25 (.335)	8.36 (.212)	8.32 (.386)	8.27 (.292)	8.12 (.345)
Hemoglobin (g/dl)	15.9 (.35)	16.4 (.41)	16.3 (.51)	16.5 (.62)	16.6* (.29)	16.7 (.53)	16.5* (.36)	16.6 (.60)
Hematocrit (%)	46.9 (1.05)	47.9 (1.55)	47.8 (1.40)	48.3 (1.24)	49.2* (.92)	49.2 (1.68)	48.7* (1.10)	48.6 (1.99)
Leukocytes (white blood cells) (th/µl)	11.8 (2.22)	7.5 (3.47)	9.7 (1.05)	7.2 (1.98)	11.2 (1.99)	9.4 (3.48)	8.1* (2.40)	8.4 (2.56)
Corrected leukocyte count (th/µl)	11.8 (2.22)	7.5 (3.47)	9.7 (1.05)	7.2 (1.98)	11.2 (1.99)	9.4 (3.48)	8.1* (2.40)	8.4 (2.56)
Segmented neutrophils (th/µl)	2.4 (2.36)	1.0 (.45)	2.2 (.43)	.8 (.26)	1.5 (.48)	1.2 (.56)	1.6 (.86)	.8 (.44)
Lymphocytes (th/µl)	9.1 (1.38)	6.6 (3.14)	7.3 (1.12)	6.4 (2.13)	9.5 (1.74)	8.1 (3.38)	6.4 (2.62)	7.5 (2.83)
Eosinophils (th/µl)	.2 (.13)	.0 (.00)	.0 (.05)	.1 (.08)	.1 (.12)	.1 (.09)	.0* (.00)	.0 (.05)

* Significantly different from control value, $p \leq 0.05$.

for not considering these effects to be of toxicological importance. These explanations do not appear to be valid, particularly since the controls were also wrapped and there were significant changes in the eosinophil levels which are also considered to be primary leukocytes. No significant hematological effects occurred in the treated females (Table 3).

(b) Blood (clinical) chemistry: The checked (X) parameters were examined.

Electrolytes	Other
X Calcium*	X Albumin*
X Chloride*	Albumin/globulin ratio
Magnesium	X Blood creatinine*
X Phosphorus*	X Blood urea nitrogen*
X Potassium*	Cholesterol
X Sodium*	X Globulins
	X Glucose*
Enzymes	X Total bilirubin*
	Direct bilirubin
Alkaline phosphatase (ALP)	X Total protein*
Cholinesterase	Triglycerides
Creatinine phosphokinase	
Lactic acid dehydrogenase	
X Serum alanine aminotransferase (SGPT)*	
X Serum aspartate aminotransferase (SGOT)*	
Gamma glutamyltransferase (GGT)	

* = Recommended by Subdivision F (November 1984) Guidelines

There were no significant changes in any of the serum parameters tested in the animals treated with tetramethrin. However, in one male control animal, there were abnormally high alanine and aspartate aminotransferase levels. No explanation was given for these observations.

6. Sacrifice and Pathology

No animals died during the study. All animals were humanely sacrificed upon termination of the study and necropsies were performed on the carcasses. The external surface of the body, all orifices, the nasal cavity and paranasal sinuses, the abdominal cavity and viscera, the thoracic cavity and viscera, the pelvic cavity and viscera, the cervical tissues and organs, the external surface of the brain, and the cranial cavity of each animal were examined.

For animals in the control and high-dose groups, histological examination of those organs checked (X) was conducted after tissue fixation in 10% neutral-buffered formalin. A double-check (XX) denotes organs that were also weighed.

Digestive System	Cardiovascular/Hematologic	Neurologic
Tongue	Aorta	X Brain
Salivary glands	Heart	Peripheral nerve (sciatic nerve)
Esophagus	Bone marrow	Spinal cord (three levels)
Stomach	Lymph nodes	Pituitary
Duodenum	Spleen	Eyes (Optic nerve)
Jejunum	Thymus	
Ileum		
Cecum	Urogenital	
Colon		
Rectum	XX Kidneys*	Glandular
XX Liver*	Urinary bladder	
Gallbladder	XX Testes**	Adrenals
Pancreas	Epididymides	Lacrimal gland
	Prostate	Mammary gland
Respiratory	Seminal vesicle	Thyroids
	Ovaries	Parathyroids
Trachea	Uterus	Harderian glands
Lung		

Other

Bone (sternum and femur)
Skeletal muscle
X Skin (treated and untreated)*
X All gross lesions and masses*

* = Recommended by Subdivision F (November 1984) Guidelines
**This organ was not examined histologically

(a) Macroscopic

There were no apparent treatment related changes noted in rats exposed to tetramethrin. The observed effects shown in Table 4 are not likely to be due to exposure since they were only noted in 1 of the 10 animals per dose. However, there were no statistical analyses conducted for any of these effects and therefore, it cannot be verified whether the effects are treatment related.

Two animals (i.e., one from Group 3 and one from Group 4) each had dilated pelvis of the kidney and dark areas of the stomach. However, these effects are not likely to be due to exposure to tetramethrin since the Group 4 rat (#9789) had numerous lesions in addition to those of the kidney and stomach. Rat #9789 exhibited the majority of the lesions that are noted in Tables 4 and 5 for Group 4 animals.

TABLE 4. Selected Pathological Effects in Rats Following 21-Day Dermal Exposure to Tetramethrin

Affected Organ/ Effect Noted	Incidence of Effect (N=5 dose/sex)							
	Group 1 (0 mg/kg/day)		Group 2 (100 mg/kg/day)		Group 3 (300 mg/kg/day)		Group 4 (1000 mg/kg/day)	
	Male	Female	Male	Female	Male	Female	Male	Female
Kidney								
Dilated pelvis	0	0	0	0	1	0	0	1
Liver								
Pale area	0	0	0	0	0	0	0	1
Mass	1	0	0	0	0	0	0	0
Mottled	1	0	0	0	0	0	0	0
Urinary bladder								
Calculus lumen	0	0	0	0	0	0	0	1
Thickened wall	0	0	0	0	0	0	0	1
Prominent vessel	0	0	0	0	0	0	0	1
Distended	0	0	0	0	0	0	0	1
Raised area of the mucosa	0	0	0	0	0	0	0	1
Glandular stomach								
Dark area	0	0	1	0	0	0	0	1
Skin								
Alopecia	0	0	1	0	0	0	0	0
Sore	0	0	1	0	0	0	0	0

(b) Organ weights and body weight ratios

There were no statistical differences in absolute and relative kidney, liver, or testis weights in treated rats compared to controls.

(c) Microscopic

Histopathology was conducted only on rats from the control and high-dose groups. In these animals, the lesions that were noted do not appear to be due to treatment with tetramethrin. However, there were no statistical analyses conducted for any of the effects noted and therefore, it cannot be verified whether the effects are treatment related.

There was a slightly elevated incidence of regenerative tubules of the kidneys, which is indicative of nephropathy, in the males of the high-dose group compared to the controls (Table 5). This lesion was reported as "slight" to "minimal" in the control animals and as "minimal" in the Group 4 animals. The reviewer found that the increased incidence in the male rats receiving 1000 mg/kg/day was not statistically significant ($p<0.05$) when compared to the incidence observed in the untreated male controls using the Fisher's Exact Test of statistical analysis. One explanation, which was offered by the author of the study, for the appearance of this lesion in the controls, is that the legion occurs spontaneously in this strain of rat.

As discussed above, one female rat from Group 4 (#9789) exhibited numerous lesions that were not noted in other treated animals: urothelium hyperplasia of the kidney, stomach necrosis,[1] necrotic debris on the epidermal surface, and acanthosis of treated skin (Table 5). This rat also exhibited moderate unilateral chronic-active pyelitis with moderately severe hyperplasia of the urinary bladder; these latter effects are reported by the author to occur spontaneously in this strain of rat.

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The Reviewer has no other comments regarding the materials and methods sections.

A description of the statistical analysis employed was included in the report.

A signed Good Laboratory Compliance Statement, a signed Quality Assurance Statement, and a list of Quality Assurance Inspections were included.

[1] This was the only rat examined for this effect.

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TABLE 5. Histological Effects in Rats Following 21-Day Dermal Exposure to Tetramethrin

Affected Organ/ Effect Noted	Incidence of Effect[a,b]			
	Group 1 (0 mg/kg/day)		Group 4 (1000 mg/kg/day)	
	Male	Female	Male	Female
Kidney				
regenerative tubules	1	2	3	3
microconcretion of tubules	0	1	0	0
chronic-active pyelitis	0	0	0	1
mononuclear infiltrate	1	2	1	1
hyperplasia, urothelium	0	0	0	1
Liver				
infarction	1	0	0	0
focal necrosis	0	0	1	0
microgranuloma	0	0	0	1
Urinary Bladder				
hyperplasia of the mucosa	0	0	0	1[c]
Stomach				
necrosis	0	0	0	1[c]
Skin, untreated				
acanthosis	0	0	0	1
Skin treated				
acanthosis	0	0	0	1
necrotic debris on epidermal surface	0	0	0	1

[a] The total number of rats per sex per dose is 5, unless specified otherwise.

[b] Rats from Groups 2 and 3 were not examined.

[c] The total number of rats examined is 1.