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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Tetramethrin; Oral Teratology Study in Rats with Technical Tetramethrin; Guideline Study 83-3; ID # 069003-010308

DP Barcode No.: D174819
Tox.Chem No.: 844
MRID No.: 421892-01, -02
HED Project No.: 2-1495
Submission No.: S412103

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

FROM: William Dykstra, Ph.D., Toxicologist
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William Dykstra 8/24/92

for THRU: Roger Gardner, Section Head, Toxicologist
Review Section 1
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ACTION REQUESTED: Sumitomo Chemical Company has submitted a new rat teratology study with tetramethrin to support reregistration of tetramethrin. The submission included both a range-finding study and a main study. The studies were initiated to fulfill a request by California regulatory authorities. Sumitomo wanted the U.S. EPA to have an equivalent data base to that of California. The studies were not specifically requested by the U.S. EPA. Toxicology Branch has been requested to review the two rat oral teratology studies with technical tetramethrin submitted in support of reregistration.

CONCLUSIONS: The main study is acceptable as core-guideline data and supports reregistration. The maternal NOEL is 500 mg/kg/day and the LEL is 1000 mg/kg/day with decreased body weight gain (42.8%) and decreased food consumption (10.7%) occurring during days 6-9 of gestation. The developmental NOEL is 1000 mg/kg/day (HDT). Dose levels were 0, 150, 500, and 1000 mg/kg/day. A DER is attached.

The results of the previous rat teratology study, which was conducted at doses of 0, 100, 300, and 1000 mg/kg/day by gavage, were: Developmental NOEL: 1000 mg/kg/day and Maternal NOEL = 300 mg/kg/day with decreases in body weight gain and food consumption at the LEL of 1000 mg/kg/day.

Reviewed by: William Dykstra, Ph.D. Toxicologist William Dykstra 3/30/92
Review Section I, Tox. Branch I
for Secondary Reviewer: Roger Gardner, Section Head
Review Section I, Tox Branch I Pamela M. Hurley 11/18/92
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DATA EVALUATION REPORT 009842

STUDY TYPE: 83-3; Rat Teratology

TOX. CHEM NO: 844

MRID NO.: 421892-01, -02

TEST MATERIAL: tetramethrin, technical

SYNONYMS: Neo-Pynamin

STUDY NUMBER: IT-11-0240; IT-11-0241

SPONSOR: Sumitomo Chemical Co., Osaka, Japan

TESTING FACILITY: Bio-Research Labs, LTD., Quebec, Canada

TITLE OF REPORT: An Oral Teratology Study of Neo-Pynamin in the Rat

AUTHOR(S): K. Robison, G. Washer, J. Noveroske

REPORT ISSUED: December 16, 1991

CONCLUSION: The maternal NOEL was 500 mg/kg/day. The LEL was 1000 mg/kg/day (HDT) and the effects were decreased (42.8%, $p < 0.05$) body weight gain and decreased (10.7%, $p < 0.01$) food consumption during days 6-9 of gestation. The developmental NOEL was 1000 mg/kg/day. Doses were 0, 150, 500, and 1000 mg/kg/day during days 6-15 of gestation in Sprague-Dawley rats.

Core Classification: Guideline

Review

1. An Oral Teratology Study of Neo-Pynamin in the Rat (It-11-0241; Bio-Search No. 95219; Dec. 16, 1991).

   Quality Assurance statement was signed by A. Gayne and P. Sidney on Dec. 16, 1991 and a Good Laboratory Practice Statement was signed by the Study Director, K. Robinson, on Dec. 16, 1991.

Test material: Neo-pynamin, Technical grade, Lot No. 90304; coarse white powder; purity of 95.1%.

Vehicle/control substance: High viscosity carboxymethyl cellulose (Code No. 6-5013), Lot No. 38F-05291 was received from Sigma Chemical company, St. Louis, MO.

Animals: One hundred and sixty 10 week old female Sprague-Dawley rats (Crl: COBS VAF CD^{R} (SD)BR) were obtained from Charles River Laboratories, Kingston, N.Y. The rats were acclimated for 21 days. On day of mating (Day 0 of gestation), the 100 females used for the study were 13 or 14 weeks old and weighted 243 to 320 gm. Proven males used for breeding were of the same strain and source. Animals were housed individually under controlled conditions and had free access to pelleted PMI Certified Rodent chow No. 5002 and tap water.

Test Material Suspension Preparation

Test material, finely ground, was suspended in 0.5% (W/V) of aqueous carboxymethylcellulose. Test material was prepared weekly and stored refrigerated. Test suspensions were analyzed for concentration.

Mating

One female was placed with 1 proven male of the same strain and source. The day of positive identification of spermatozoa in the vaginal lavage was termed day 0 of gestation. Females were randomly assigned to the control and test groups.

Experimental Design

Group	Dosage (mg/kg/day)	Concentration (mg/ml)	No. of Mated Females
1	0	0	25
2	150	15	25
3	500	50	25
4	1000	100	25

Dosing was performed on days 6-15 of gestation consecutively. Doses for the main study were based on the results of a range-finding study conducted at doses of 0, 500, 750, 1000, and 1500 mg/kg/day during days 6-15 of gestation in 6 Sprague-Dawley rats/dose. Results showed a transient weight loss during the treatment period for the 1500 mg/kg/day group. Prestudy dose preparation for this current study for dosages of 150, 500, and 1500 mg/kg/day also provided samples with concentrations below specifications at the high-dose level. After repeating these preparations and analyzing a range of concentrations, the high-dose level was decreased to 1000 mg/kg/day to provide a concentration at which accurate dose preparation was possible. Further, the 1000 mg/kg/day dose level met the U.S. EPA requirements (83-3) for a limit dose and was thought it may produce an effect upon body weight.

The dosage volume was 10 ml/kg/day. Individual dose volumes were calculated according to the animal's body weight on Day 6 of gestation.

Methods

Clinical examinations were conducted twice daily during days of acclimatization and gestation. Body weight of individual females were measured once each week during acclimatization and on days 0, 3, 6, 9, 12, 15, 18 and 20 of gestation. Food consumption was measured on days 0-3, 3-6, 6-9, 9-12, 12-15, 15-18 and 18-20 of gestation.

On day 20, female rats were killed using CO_2 asphyxiation followed by exsanguination and given a complete gross necropsy examination. Abnormal tissues were preserved in 10% formalin. The reproductive tract was dissected out, ovaries removed and corpora lutea counted. Gravid uterus was weighed, uterine contents examined, and the number and location of live fetuses, dead fetuses, and early, middle, and late resorption were recorded. The uterus of non-pregnant animals was stained with 10% aqueous (V/V) ammonia sulfide solution and examined for implantation sites.

Each fetus was weighed, sexed, examined externally and killed by subcutaneous injection of T61 euthanasia solution. Visceral examination was performed on 1/2 of the fetuses of each litter with a dissecting scope by evisceration. The heads of these fetuses were removed and placed in Bouin's Fluid for examination by Wilson technique. The remaining 1/2 of the fetuses in each litter were eviscerated. These fetuses and the bodies of those examined viscerally were placed in 85% ethanol/15% methanol for subsequent staining with Alizarin Red S (using a modified Dawson technique) and skeletal examination.

Abnormalities were classified as major malformations, minor visceral or skeletal anomalies or common skeletal variants.

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Statistical Analyses

Means were calculated and analyzed statistically.

Statistical analysis of body weight, food consumption, pregnant females, uterine weight was performed using ANOVA (one-way) and where F values were less than $p<0.05$, Dunnett's test was used to analyze for differences between control and test groups.

For reproductive data, statistical analysis was performed using the Kruskal-Wallis test and where the "H" value was of significance ($p<0.05$), the Mann-Whitney "U" test was used to analyze differences between control and test groups.

Fetal weights were analyzed by ANOVA (one-way) and Dunnett's test.

Fetal malformations and anomalies, were evaluated by either Chi-Square (with Yates correction) or Fisher's Exact Test (using cumulative probabilities). Fetal skeletal variants were analyzed by Kruskal-Wallis and Mann-Whitney "U" tests.

Results

Analysis of Test Material and Suspensions of Dosing Solutions

Analysis of technical at the beginning of the study was 96.6% (mean) and at the end of the study was 93.6% (mean). Analysis of dosing solutions of 15, 50 and 100 mg/ml were 94.7%, 99.4% and 98.5% on 7/23/91; 90.0%, 93.7% and 91.1% on 8/1/91 and 95.4%, 103.8% and 95.5% on 12/8/91 for the low, mid, and high-dose dosing solutions, respectively.

Mortality and Clinical Signs

There were no deaths and no compound-related toxic signs. Incidental findings included areas of alopecia in one control dam and three dams at the low-dose. One high-dose dam had red discharge of the left periorbital region throughout gestation.

Body Weight

Body weight gain was significantly ($p<0.05$) decreased (42.8%) between days 6-9 of high-dose dams in comparison to controls. Although body weight gain from days 3-6 were significantly increased at the high-dose (28.2%) in comparison to controls, the decreased weight gain at the high-dose is considered compound-related. Mid and low-dose groups were comparable to controls.

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The following table illustrates the differences in body weight gain during gestation.

Body Weight Gain (Grams) During Gestation

	Dose (mg/kg/day)			
Days	0	150	500	1000
0-3	20.0	20.1	19.8	18.4
3-6	16.3	16.2	18.4	20.9* (28.2%)
6-9	11.2	11.6	8.3 (25.9%)	6.4* (42.8%)
9-12	18.8	22.2	21.8	21.9
12-15	19.3	20.0	18.8	19.6
15-18	43.3	46.4	44.4	45.2
18-20	37.7	39.4	38.3	38.4
6-15	49.4	53.8	48.9	47.8

Corrected Body Weight Gain (grams): Days 6-20 of Gestation

	Doses (mg/kg/day)		
0	150	500	1000
43.68	42.04	40.38	41.80

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Food Consumption

Food consumption was significantly decreased ($p<0.01$) during days 6-9 of high-dose group (10.7%) in comparison to controls. Mid and low-dose groups were comparable to controls. The following table illustrates the food consumption during gestation.

Food Consumption of Pregnant Rats (grams/animal)

	Dose (mg/kg/day)			
Days	0	150	500	1000
0-3	80.9	79.5	84.3	81.7
3-6	85.7	86.1	90.0	87.2
6-9	88.9	87.5	83.8	79.3** (10.7%)
9-12	89.4	94.4	93.6	89.2
12-15	92.1	96.4	96.5	97.6
15-18	101.0	104.3	104.5	107.1
18-20	66.3	68.0	69.0	68.8

Gross Pathological Findings

There were no compound-related gross pathological findings in treated dams in comparison to controls.

Uterine Findings

The pregnancy rate was 100, 100, 96 and 100% for the control, low, mid, and high-dose groups. There were no dead fetuses in any group and there were no compound-related effects in sex ratio, early, middle or late resorptions, total resorptions, pre-implantation loss, post-implantation losses, weight of gravid uterus and fetal body weight.

Cesarean Section Observations:

Table III: Cesarean Section Observations[a]

	Control	LDT	MDT	HDT
Dose:	0	150	500	1000
#Animals Assigned	25	25	25	25
#Animals Mated/Inseminated	25	25	24	25
Pregnancy Rate (%)	100	100	96	100
Maternal Wastage				
#Died	0	0	0	0
#Died/pregnant	0	0	0	0
#Non pregnant	0	0	1	0
#Aborted	0	0	0	0
#Premature Delivery	0	0	0	0
Corpora Lutea/Dam	19.4	19.8	19.0	18.4
Implantations/Dam	16.4	18.0	17.9	17.0
Live Fetuses/Dam	15.3	17.2	16.5	15.9
Resorptions/Dam	1.1	0.8	1.5	1.0
Early	1.0	0.7	1.2	0.9
Late	0.1	0.1	0.3	0.1
Total Dead Fetuses	0	0	0	0
Mean Fetal Weight (gm)	3.82	3.82	3.69	3.81
Preimplantation Loss(%)	14.3	8.4	5.7	8.4
Postimplantation Loss(%)	7.6	4.5	7.6	6.2
Sex Ratio (% Male)	49.6	47.0	48.2	52.1

[a] = Data extracted from study.

There were no statistically significant differences between control and treated groups with respect to uterine findings.

Major Malformations

The number of externally examined fetuses (litters) was 383(25),

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428(25), 395(24), and 398(25) for the control, low, mid and high-dose groups, respectively. The major malformations which were observed were unrelated to treatment. In the controls, one fetus (dam 160) had spina bifida; in the low-dose, there were no malformations; in the mid-dose, four fetuses (dam 369) had exencephaly, cleft palate and micrognathia and one fetus (dam 354) had stenosis of the pulmonary trunk; in the high dose, two fetuses (dam 455 and 458) had umbilical hernia.

Minor External and Visceral Anomalies

The number of fetuses (litters) with minor external and visceral anomalies were 2(2), 1(1), 2(2), and 2(2) for the control, low, mid, and high-dose groups, respectively.

The incidental anomalies included intra and extra ocular hemorrhage, moderate dilation of the ventricles of the brain and dilation of ureters. None of the findings in the treated groups were dose related.

Minor Skeletal Anomalies

The number of fetuses with minor skeletal anomalies was decreased in the low and high-dose group in comparison to controls. The fetuses (litters) affected for the different groups were 112 (25) for controls, 85** (24) for the low dose, 92 (23) for the mid-dose, and 87* (23) for the high-dose. The number of fetuses with irregular ossification of the supra-occipital bone was decreased in the low and high-dose groups in comparison to controls. Similarly, the number of fetuses with ossification centers on 1st lumbar of 14th thoracic vertebrae was decreased in all treated groups in comparison to controls.

None of these findings showed a dose-related occurrence in treated groups.

Common Skeletal Variants

Common skeletal variants including thoracic centrum, sternebra 1 to 4, and sternebrae 5 and xiphisternum were unaffected by treatment.

Addendum: Review of the oral range finding teratology study was not considered necessary (MRID No. 421892-01) in light of the significant maternally toxic effects at 1000 mg/kg/day in the main study (MRID No. 421892-02). Doses for the main study were based on the results of a range-finding study conducted at doses of 0, 500, 750, 1000, and 1500 mg/kg/day during days 6-15 of gestation in 6 Sprague-Dawley rats/dose. Results showed a transient weight loss during the treatment period for the 1500 mg/kg/day group.

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