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

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

Date: March 3, 2009

SUBJECT: Tetramethrin/Neo-pynamin; Updated Tox DERs

PC Code: 069003
Decision Nos.: 329938, 315642
Petition No.: None
Risk Assessment Type: Tox DERs
TXR No: 0054713
MRID No: (see below)

DP Barcodes: D292301, D234962, D229247, D229511
ID No.: NA
Regulatory Action: None
Case No.: 2660
CAS No.: 7696-12-0
40 CFR: NA

Ver.Apr.08

FROM: Jessica Ryman, Toxicologist 3/4/2009
Risk Assessment Branch IV
Health Effects Division, 7509P

THROUGH: Susan Hummel, Senior Scientist
Risk Assessment Branch IV
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TO: Monica Wait, Chemical Review Manager
Reregistration Branch 3
Special Review and Reregistration Division (7508P)

I. CONCLUSIONS

1) The Executive Summaries and classification information for the Subchronic, Chronic, and Other Toxicity Profile DERs for Tetramethrin (PC Code 069003) that were used for the 2008 RED were updated.

2) There are three DERs that never underwent secondary review (e.g. New DERs). These are MRIDs 44222801, 44083501, and 44096001.

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II. ACTION REQUESTED

Please review and approve these updated DERs and the new DER.

III. BACKGROUND

The Executive Summaries for the DERs used in the final **d-Phenothrin (Sumithrin®)** Risk Assessment for Reregistration Eligibility Decision and Associated Section 3 Reregistration Action (July 2, 2008) were re-formatted and updated as described in each DER SUPPLEMENT.

IV. ATTACHMENTS: SUMMARY TABLE

Guideline	MRID	Comments	File Name
None	44222801	New DER	44222801.DER
None	40275801	Updated DER	40275801.DE1
None	40275901	Updated DER	40275901.DE1
None	42146404	Updated DER	42146404.DE1
None	00114371	Updated DER	00114371.DE1
None	00137658 00137656	Updated DER	00137658.DE1
None	42146403	Updated DER	42146403.DE1
870.3150	41698902	Updated DER	41698902.DE1
870.3200	41995004	Updated DER	41995004.DE1
870.3465	42012101	Updated DER	42012101.DE1
870.3465	41995003	Updated DER	41995003.DE1
870.3700a	42189202 42189201	Updated DER	41289202.DE1
870.3700a	00114369 42014402	Updated DER	00114369.DE1
870.3700b	41995005	Updated DER	41995005.DE1
870.3700b	00114370	Updated DER	00114370.DE1
870.3800	00161842 40777801	Updated DER	00161842.DE1
870.4100a	41723301 40009401 00114365 00143555	Updated DER	41723301.DE1
870.4100b	44083501	New DER	44083501.DER
870.4100b	42189301	Updated DER	42189301.DE1

870.4200a	41723302 00156488 40007501 00114365 00143555	Updated DER	41723302.DE1
870.4300	00158951 40276301	Updated DER	00158951.DE1
870.4300	44096001	New DER	44096001.DER
870.5265	40276001	Updated DER	40276001.DE1
870.5385	42414403 42414402 42414401	Updated DER	42414403.DE1
870.5550	40778401	Updated DER	40778401.DE1
870.6200a	42601501 43152701 42601502	Updated DER	42601501.DE1
870.7485	42448901	Updated DER	42448901.DE1
870.7485	42448902	Updated DER	42448902.DE1

DATA EVALUATION RECORD

TETRAMETHRIN

STUDY TYPE: MOTOR ACTIVITY STUDY IN POSTNATAL MICE – NON-GUIDELINE

MRID 44222801

Prepared for
Health Effects Division, Office of Pesticide Programs
United States Environmental Agency
One Potomac Yard
South Building – Room S-10981
2777 S. Crystal Drive
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830
Work Assignment No. 147-2006

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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory, managed and operated by UT-Battelle, LLC., for the U.S. Dept. of Energy under contract DE-AC05-00OR22725.

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** February 3, 2009
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 1, Health Effects Division (7509P) **Date:** 3/3/09
Template version 02/06

TXR#:0054713

DATA EVALUATION RECORD

STUDY TYPE: Motor Activity Study - Rat; Non-guideline

PC CODE: 069003 **DP BARCODE:** D234962

TEST MATERIAL (PURITY): Tetramethrin (96.2% a.i.)

SYNONYMS: Neopynamin

CITATION: Ivens, I.,J. Pauluhn, G. Schmuck (1996) Motor activity measurements in male and female mice postnatally exposed to TETRAMETHRIN by inhalation. BayerAG, Fachbereich Toxikologie, Friedrich-Ebert-Str. 217-333, D-42096 Wuppertal,Germany. Study number 25749, December 17, 1996. MRID 44222801. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:
In a motor activity study (MRID 44222801), Tetramethrin (96.2% a.i., batch # 30806) was administered via whole body exposure to NMRI mice, 40/sex/dose (10 dams with 4 male and 4 female pups that were 10 days old) at atmospheric concentrations of 0, 1.5, 8 and 40 mg/m3 (equivalent to 0,0.0015, 0.008 and 0.04 mg/L, respectively) 6.3 hours per day for seven days. (Thus, dams with pups were exposed on lactation days 10-16, inclusive). Animals were monitored for clinical signs and body weight. Motor activity testing was performed on male and female offspring when the animals were 17 days and 4 months old with different animals tested at each interval. After each motor activity testing, five males/group were sacrificed and the total muscarinic acetylcholine receptor (mAChR) density in the brain cortex was determined by saturation binding with [^{3}H]-quinuclidinyl bencylate ([^{3}H]-QNB). Non-specific binding was determined by an excess of atropin (atropine). A second technique, displacement of non-specifically bound [^{3}H]-QNB by increasing concentrations of carbachol, was also used as a second endpoint for assessing mAChR receptor density. Acetylcholinesterase (AChE) and choline acetyltransferase (CHAT) enzyme activities were measured to assess any effects of tetramethrin on acetylcholine metabolism, which has also been shown to regulate mAChR receptor density.

No treatment-related effects on mortality, clinical signs or body weight were observed in males or females. At 17 days, there was a significant ($p \leq 0.05$) decrease on horizontal and vertical activity and vertical time in male mice, but no dose-dependent effect was observed in any of these three parameters. No changes were observed in female mice. At 4 months, motor activity was not

affected by treatment in males or females. In 17 day-old male mice, the mAChR density in the cortex of all treated groups was significantly ($p<0.001$) increased in a concentration-dependent manner. Receptor density for controls was 100 ± 11.11 % and was 166.26 ± 9.33, 168.72 ± 8.38, and 202.96 ± 9.4% for atmospheric concentrations of tetramethrin of 1.5, 8, and 40 mg/m^3. However, no treatment-related changes in mAChR density were observed in 40 day-old male mice. Also, AChE and CHAT activities in males were unaffected by treatment at both time points. No results were available on the effects of tetramethrin treatment on mAChR density or acetylcholine metabolism in females at either time point.

The NOAEL for motor activity in males and females was 40 mg/m^3 (0.040 mg/L). A LOAEL was not determined. This study also demonstrated a dose-dependent increase in muscarinic receptor density in the cortex of young males exposed to tetramethrin during postnatal brain development that resolved by adulthood.

This study is classified as acceptable, non-guideline and satisfies the intended purpose of evaluating motor activity in postnatal mice exposed by inhalation to tetramethrin.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality Statements were provided. The study was conducted according to GLP requirements, except for the receptor and enzyme activity measurements.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. **Test material:** Tetramethrin

Description:	White powder
Batch #:	30806
Purity:	96.2% a.i.
Compound stability:	Expiration date: January 24, 1995
CAS # of TGAI:	Not provided
Structure:	Not available

2. **Vehicle:** Polyethylene glycol 400

3. **Test animals (P):**

Species:	Mice
Strain:	NMRI
Age at beginning of treatment:	10 days
Wt. on day 0:	Approximately 6-7 g
Source:	Harlan Winkelmann GmbH Borchen, Germany
Housing:	Dams with pups were housed in type III Makrolon cages; after weaning, pups were housed with littermates of the same sex in type III Makrolon cages
Diet:	Altromin® 1324 meal *ad libitum*
Water:	Tap water *ad libitum*
Environmental conditions:	Temperature: 22.2 ± 2°C Humidity: 55 ± 20% Air changes: Not provided Photoperiod: 12 hrs dark/12 hrs light
Acclimation period:	Two days

B. PROCEDURES AND STUDY DESIGN:

1. **In life dates:** Start: February 20, 1995; End: June 9, 1995

2. **Study schedule:** Postnatal (10 day-old) pups were exposed to targeted atmospheric concentrations of the test material for seven consecutive days. Motor activity was measured when the animals were 17 days and 4 months old. Immediately after motor activity measurements, five mice/group were sacrificed and total muscarinic acetylcholine receptor density in the brain cortex was determined. Acetylcholine cholinesterase (AChE) and choline acetyltransferase (CHAT) enzyme activities were also measured. The methods stated that tissues from both males and females were analyzed for receptor density and enzyme activity, however, only results from males were included in the report.

3. **Animal assignment**: On the first day of the study, 10 dams with 8 pups each (4 males and 4 females) were exposed to the test material by the inhalation route. For the following three days, further sets of the same number of dams and pups were added to the study. The animals

were randomly assigned to the control and treated groups using a computer program (Table 1).

TABLE 1: Study design[a]					
Test group	**Nominal conc. (mg/m^3)**	**Analytical conc. (mg/m^3)**	**MMAD Φm**	**GSD**	**Rats/sex**
Control	0	0	1.76	1.74	40
Low (LCT)	1.5	1.78	1.83	1.76	40
Mid (MCT)	8	7.94	1.81	1.75	40
High (HCT)	40	37.8	1.82	1.77	40

[a] Data obtained from pages 172 and 185-187, MRID 44222801.

4. **Dose selection rationale:** The basis for the selection of atmospheric concentrations was not provided.

5. **Generation of the test atmosphere/chamber description:** The solid test material was first dissolved in the vehicle polyethylene glycol 400. Atmospheres for the inhalation exposures were generated using a modified six-nozzle BGI collision nebulizer type MRE. Following nebulization using 20 L air/min, the atmosphere was fed into the second preseparator/baffle system to eliminate the larger particles. The atmosphere was diluted to approximately 250 L air/min (15 m^3/h) while animals were entering the inhalation chamber. The same concentration of vehicle was present in all chambers with various concentrations of the test material nebulized for the treatment groups. The nominal concentration was calculated from the ratio of the quantity of test material sprayed into the baffle and the total throughput of air through the inhalation chamber. Pilot studies showed that a solution of approximately 7% (w/v) is the maximum stable concentration in the vehicle. Higher concentrations produced crystallization that clogged the nozzles. All air flows were monitored and adjusted continuously by means of calibrated and computer controlled flow-controllers. Temperature and humidity were measured continuously.

   The inhalation chambers were made of stainless steel, had a volume of approximately 2.2 m^3 and measured 119 x 119 x 137 cm with pyramidal top and bottom sections. Each chamber held 10 cages with one dam and litter per cage. Animals were exposed in two levels (5 cages/level) and each cage position was rotated daily. The pups with their dams were exposed by whole body exposure to the different atmospheric concentrations of the test substance on seven consecutive days for 6.3 hours daily.

   Test atmosphere concentrations were measured in the vicinity of the animal cages using a flow rate of 1 L/min and a total air volume of 10, 20 and 50 L/sample in the top, middle and lowest treatment groups, respectively. Four samples per exposure day were collected in adequately spaced time intervals. The integrity stability of the aerosol generation system was monitored using a RAS-2 real-time aerosol photometer. Samples were taken continuously in the vicinity of the animal cages.

   Particle size distribution was analyzed using a low-pressure critical orifice AERAS cascade impactor. The mass median aerodynamic diameter (MMAD), the geometric standard deviation (GSD) and the relative mass with an aerodynamic diameter of ≤ 3 µm were

determined. The MMAD and GSD values are presented in Table 1 above. The percentage of particles ≤3 µm was 83%, 81%, 82% and 81% in the control, LCT, MCT and HCT groups, respectively.

6. **Statistics:** Body weights of treated groups were compared to the control group using the significance test (U-test) at the significance of $\alpha = 5\%$ or $\alpha = 1\%$ (two-sided tests). Motor activity data were analyzed in a two-factorial (treatment x block) analysis of variance with repeated measures over time. The data for the total receptor activity and for enzyme activity assays were analyzed using the Mann Whitney U-Test.

C. OBSERVATIONS:

1. Observations:

1a. Cageside observations: Animals were inspected for signs of toxicity and mortality twice daily before and after the inhalation period for the first seven days of the study. After termination of the inhalation exposure, the animals were inspected at least twice daily.

1b. Clinical examinations: Detailed examinations of individual animals were conducted once a week.

1c. Body weight: Body weight was recorded at age 10, 12, 14 and 17 days. The weight of mice assigned to the second motor activity evaluation at age 4 months was recorded beginning with study week 2 (age of mice: 3 weeks).

1d. Motor activity testing: Motor activity was evaluated in 17 day-old offspring and 4 month-old adults; different animals were tested at each time. Groups of 18 to 20 mice per concentration and sex were tested on four consecutive days. Mice were tested in activity monitors for 60 minutes in sample intervals of 10 minutes at both ages. Each cage was crossed by 8x14 infra-red light beams for recording horizontal activity and 15 light beams 8 cm above the cage floor to record the vertical activity. No food or water was provided during the testing period. During the first testing, animals were too small to interrupt the vertical sensors by rearing. Therefore, the recordings represent only jumping activity. At 4 months, the vertical parameters were from rearing and jumping.

The following parameters were reported and analyzed. Other parameters were measured but not evaluated statistically.

Horizontal Activity (HA): total number of beam interruptions that occurred in the horizontal sensors during a given sample period.

No. of Movements (NM): each time a break in ambulatory activity occurred for a period greater than 1 second, this parameter was incremented by 1.

No. of Stereotypy (NS): if the animal broke the same light beam (or set of beams) repeatedly this counted as stereotypy. The number of stereotypy incidents corresponded

to the number of times the monitor observed stereotypic behavior in the animal. A break in stereotypy of 1 second or more was required to separate one episode from the next.

Total Distance (TD) (cm): calculation from the position of the interrupted light beams.

Vertical Activity (VA): the total number of beam interruptions that occurred in the vertical sensor during a given sample period.

Vertical Time (VT) (s): time the animal interrupted any vertical light beam.

Movement Time (MT) (s): amount of time the animal was ambulating during a given sample.

Stereotypy Time (ST) (s): the total amount of time that stereotypic behavior is exhibited is accumulated.

2. **Postmortem observations:** After each motor activity testing, five mice per group and sex were sacrificed by injection of an overdose of a barbiturate and perfused with a formaldehyde solution. The brain was removed and the cortex was dissected from both hemispheres. The brain was immediately placed in ice-cold sucrose buffer and homogenized in 20 to 25 volumes of the brain weight in a homogenizer. The homogenate was centrifuged and the synaptosomal P 2 fraction was resuspended in the original volume of ice-cold sucrose. To determine the total unspecific binding of Quinuclidinyl[phenyl-4- ^{3}H] benzilate (QNB), Atropin was given to displace QNB from all specific binding places. The displacement with Carbachol, an unspecific ligand of the cholinergic receptors, was used to record the receptor specific binding curve. Acetyl cholinesterase (AChE) activity was determined according to the Ellman assay. The choline acetyltransferase (CHAT) activity was measured using the Schuberth assay.

3. **Positive and historical control data:** Positive control data for horizontal and vertical activity in males were included with the graphs of these parameters.

II. RESULTS:

A. MORTALITY AND CLINICAL OBSERVATIONS:

One male in the low-dose group was sacrificed in moribund condition; the day of sacrifice and cause of death were not given. No treatment-related clinical signs of toxicity were observed. Wounds resulting from fighting were observed in all groups; those animals with severe wounds were separated from littermates.

B. BODY WEIGHT:

Selected group mean body weight data are summarized in Table 2. No treatment-related changes were observed. Significant increases in body weight were reported at some time periods, mostly in the low- and mid-concentration groups.

TABLE 2. Mean body weight (g ±S.D.)[a]

Age	Atmospheric concentration (mg/m^3)							
	0	1.5	8	40	0	1.5	8	40
	Males				Females			
10 days	6.15	7.00	6.52	6.68	6.36	7.05	6.43	6.77
17 days	8.59	9.61	8.96	9.23	8.75	9.66	9.04	9.30
2 weeks	14.5 ± 3.4	17.6** ± 2.4	19.6** ± 3.8	16.8* ± 2.7	13.9 ± 3.1	16.6** ± 1.7	17.6** ± 2.7	15.6 ± 2.6
9 weeks	37.7 ± 3.0	40.6** ± 2.9	41.3** ± 2.4	39.4 ± 3.5	31.0 ± 2.3	32.5 ± 3.4	32.7 ± 3.2	31.5 ± 3.5
14 weeks	39.9 ± 3.1	43.8** ± 3.5	43.8** ± 2.7	41.8 ± 3.7	33.7 ± 3.1	34.4 ± 4.5	34.6 ± 3.7	34.3 ± 4.4

[a] Data obtained from pages 52-54, MRID 44222801. Standard deviations were not reported for some of the measurements.
* Significantly different from control value, $p<0.05$.
** Significantly different from control value, $p<0.01$.
N = 19-20

C. MOTOR ACTIVITY:

Selected motor activity data for males and females are presented in Tables 3 and 4, respectively, for 17-day old animals and in Tables 5 and 6, respectively, for 4-month old animals. No effect on any parameter was found in either sex on either testing day. Habituation was evident in both sexes on both testing days.

The report noted a significant ($p\leq0.05$) decrease effect of treatment on horizontal activity (HA), vertical activity (VA) and vertical time (VT) in 17 day-old male mice of the HCT group. No dose-dependant effect was observed in any of the three parameters and the decreases in VA and VT were small. No significant changes were observed in female mice. At 4 months of age, repeated measures ANOVA analysis showed a significant effect of treatment in stereotypy time in female mice. This finding is not considered treatment-related since it was the only parameter affected, and it did not occur in male mice or at the earlier testing.

TABLE 3. Mean (±S.E.) motor activity data in 17 day-old male mice [a]				
Interval	Atmospheric concentration (mg/m^3)			
	0	1.5	8	40
Horizontal Activity[b] (no. beam breaks)				
1	2242 ± 119	2498 ± 116	2445 ± 184	2286 ± 96
2	1851 ± 85	1680 ± 74	1728 ± 87	1521 ± 53
3	1525 ± 70	1496 ± 69	1574 ± 83	1302 ± 56
4	1459 ± 71	1509 ± 89	1554 ± 79	1249 ± 73
5	1354 ± 79	1220 ± 81	1471 ± 83	1086 ± 65
6	1185 ± 99	1235 ± 87	1259 ± 87	1014 ± 87
Movement Time (sec)				
1	150 ± 12	180 ± 11	160 ± 13	162 ± 11
2	122 ± 8	114 ± 8	114 ± 9	104 ± 7
3	106 ± 8	106 ± 7	104 ± 7	87 ± 7
4	107 ± 9	113 ± 10	106 ± 8	86 ± 6
5	94 ± 8	86 ± 7	95 ± 11	72 ± 8
6	83 ± 10	95 ± 10	85 ± 9	60 ± 7
Number of Movements				
1	124 ± 6	139 ± 4	130 ± 6	135 ± 3
2	119 ± 5	117 ± 4	116 ± 4	112 ± 4
3	106 ± 6	107 ± 5	118 ± 4	103 ± 5
4	110 ± 5	113 ± 7	115 ± 6	100 ± 7
5	103 ± 5	96 ± 7	107 ± 6	80 ± 7
6	94 ± 8	101 ± 9	96 ± 8	77 ± 8
Number of Stereotypy				
1	66 ± 4	73 ± 4	66 ± 6	67 ± 4
2	60 ± 3	60 ± 3	56 ± 5	58 ± 3
3	52 ± 3	54 ± 3	48 ± 4	51 ± 3
4	47 ± 2	52 ± 3	49 ± 4	45 ± 4
5	48 ± 3	44 ± 3	45 ± 4	42 ± 3
6	43 ± 3	42 ± 3	39 ± 4	39 ± 4
Stereotypy Time (sec)				
1	65 ± 6	69 ± 8	73 ± 11	64 ± 7
2	54 ± 5	57 ± 4	48 ± 6	52 ± 5
3	48 ± 4	53 ± 6	45 ± 5	46 ± 4
4	42 ± 4	48 ± 5	41 ± 5	41 ± 5
5	43 ± 5	41 ± 4	45 ± 6	48 ± 6
6	42 ± 5	37 ± 4	35 ± 5	47 ± 6
Total Distance (cm)				
1	1814 ± 187	2222 ± 219	1954 ± 231	1880 ± 150
2	1283 ± 130	1188 ± 103	1140 ± 122	977 ± 79
3	1009 ± 91	1056 ± 95	994 ± 98	841 ± 75
4	1012 ± 113	1148 ± 120	976 ± 107	802 ± 77
5	914 ± 113	876 ± 98	870 ± 122	656 ± 74
6	797 ± 118	953 ± 132	780 ± 98	537 ± 70
Vertical Activity[b] (no. beam breaks)				
1	50 ± 11	46 ± 9	25 ± 5	56 ± 11
2	100 ± 13	66 ± 12	64 ± 11	73 ± 9
3	101 ± 10	70 ± 8	82 ± 12	80 ± 9
4	125 ± 16	88 ± 13	83 ± 12	104 ± 17

TABLE 3. Mean (±S.E.) motor activity data in 17 day-old male mice [a]				
Interval	Atmospheric concentration (mg/m^3)			
	0	1.5	8	40
5	105 ± 12	61 ± 9	79 ± 13	73 ± 14
6	106 ± 17	71 ± 10	67 ± 12	81 ± 14
Vertical Time (sec)[b]				
1	10 ± 2	9 ± 3	5 ± 1	13 ± 3
2	23 ± 4	15 ± 3	14 ± 3	16 ± 2
3	23 ± 3	14 ± 2	20 ± 4	19 ± 3
4	33 ± 5	20 ± 3	20 ± 4	24 ± 4
5	26 ± 4	14 ± 2	20 ± 4	18 ± 4
6	29 ± 6	17 ± 3	17 ± 4	20 ± 4

[a] Data obtained from pages 57-59, MRID 44222801.

[b] Significantly different from control, $p<0.05$ for treatment effect.

N = 10

TABLE 4. Mean (±S.E.) motor activity data in 17 day-old female mice [a]				
Interval	Atmospheric concentration (mg/m^3)			
	0	1.5	8	40
Horizontal Activity (no. beam breaks)				
1	2191 ± 105	2540 ± 139	2289 ± 111	2508 ± 104
2	1626 ± 74	1877 ± 96	1556 ± 72	1651 ± 50
3	1429 ± 90	1591 ± 69	1477 ± 85	1495 ± 76
4	1326 ± 61	1335 ± 91	1385 ± 82	1373 ± 77
5	1168 ± 82	1282 ± 98	1300 ± 65	1186 ± 57
6	1029 ± 94	1203 ± 121	1062 ± 83	1117 ± 86
Movement Time (sec)				
1	171 ± 11	185 ± 14	162 ± 9	179 ± 7
2	126 ± 9	138 ± 10	110 ± 7	120 ± 7
3	105 ± 9	128 ± 10	106 ± 8	113 ± 7
4	101 ± 7	102 ± 9	104 ± 9	106 ± 9
5	83 ± 9	99 ± 12	93 ± 6	87 ± 8
6	76 ± 11	94 ± 14	76 ± 8	83 ± 8
Number of Movements				
1	133 ± 5	132 ± 5	135 ± 4	137 ± 4
2	116 ± 5	121 ± 5	114 ± 5	116 ± 4
3	104 ± 6	122 ± 6	111 ± 6	110 ± 6
4	105 ± 6	96 ± 6	106 ± 7	102 ± 6
5	86 ± 7	93 ± 9	110 ± 6	90 ± 5
6	78 ± 9	91 ± 9	90 ± 9	88 ± 7
Number of Stereotypy				
1	66 ± 4	79 ± 3	63 ± 5	72 ± 4
2	54 ± 3	62 ± 3	50 ± 4	58 ± 4
3	48 ± 4	51 ± 2	42 ± 3	55 ± 4
4	45 ± 4	47 ± 3	45 ± 4	51 ± 3
5	44 ± 3	44 ± 3	44 ± 4	44 ± 3
6	37 ± 4	40 ± 4	34 ± 4	40 ± 3
Stereotypy Time (sec)				
1	59 ± 5	78 ± 6	60 ± 10	69 ± 7
2	47 ± 3	56 ± 4	44 ± 5	53 ± 5
3	42 ± 5	45 ± 4	38 ± 5	49 ± 7
4	42 ± 5	45 ± 4	40 ± 5	50 ± 4
5	45 ± 5	41 ± 5	39 ± 5	42 ± 5
6	32 ± 4	35 ± 5	33 ± 6	37 ± 3
Total Distance (cm)				
1	2189 ± 199	2310 ± 190	2028 ± 199	2163 ± 161
2	1389 ± 115	1429 ± 116	1198 ± 118	1197 ± 105
3	1090 ± 102	1358 ± 142	1138 ± 110	1069 ± 79
4	1058 ± 73	986 ± 96	1035 ± 106	972 ± 84
5	849 ± 88	975 ± 124	982 ± 88	819 ± 81
6	748 ± 107	959 ± 156	786 ± 97	766 ± 69
Vertical Activity (no. beam breaks)				
1	38 ± 13	62 ± 17	33 ± 9	46 ± 9
2	63 ± 13	92 ± 14	64 ± 15	86 ± 10
3	89 ± 18	103 ± 16	71 ± 16	91 ± 11
4	82 ± 15	91 ± 16	72 ± 16	93 ± 14

TABLE 4. Mean (±S.E.) motor activity data in 17 day-old female mice [a]				
Interval	Atmospheric concentration (mg/m^3)			
	0	1.5	8	40
5	72 ± 13	97 ± 20	63 ± 12	85 ± 14
6	67 ± 16	89 ± 22	63 ± 14	82 ± 13
Vertical Time (sec)				
1	8 ± 3	13 ± 3	7 ± 2	9 ± 2
2	14 ± 3	20 ± 3	14 ± 4	17 ± 2
3	21 ± 5	24 ± 4	17 ± 4	18 ± 2
4	19 ± 4	22 ± 4	17 ± 4	20 ± 3
5	18 ± 4	24 ± 5	15 ± 3	18 ± 3
6	17 ± 4	22 ± 6	16 ± 4	18 ± 3

[a] Data obtained from pages 60-62, MRID 44222801.
N = 10

TABLE 5. Mean (±S.E.) motor activity data in 4-month-old male mice [a]

Interval	Atmospheric concentration (mg/m^3)			
	0	1.5	8	40
Horizontal Activity (no. beam breaks)				
1	4412 ± 585	3285 ± 219	3681 ± 226	3683 ± 352
2	4176 ± 702	2813 ± 177	3097 ± 176	3466 ± 373
3	4004 ± 774	2261 ± 171	2848 ± 183	2938 ± 358
4	3493 ± 782	1823 ± 132	2274 ± 167	2373 ± 325
5	3174 ± 914	1477 ± 169	1908 ± 146	1938 ± 329
6	2745 ± 949	1212 ± 137	1622 ± 169	1611 ± 313
Movement Time (sec)				
1	223 ± 22	180 ± 8	195 ± 10	203 ± 17
2	199 ± 25	144 ± 10	156 ± 10	176 ± 18
3	193 ± 28	117 ± 10	144 ± 11	157 ± 17
4	169 ± 29	96 ± 9	120 ± 11	121 ± 17
5	141 ± 32	78 ± 10	100 ± 11	99 ± 17
6	122 ± 35	57 ± 10	73 ± 9	78 ± 16
Number of Movements				
1	137 ± 8	152 ± 4	153 ± 4	144 ± 4
2	133 ± 8	139 ± 6	146 ± 5	141 ± 5
3	127 ± 9	120 ± 6	138 ± 7	129 ± 4
4	117 ± 9	100 ± 8	123 ± 8	107 ± 7
5	92 ± 8	90 ± 10	109 ± 9	87 ± 8
6	71 ± 9	70 ± 9	89 ± 9	76 ± 10
Number of Stereotypy				
1	96 ± 3	102 ± 2	102 ± 2	104 ± 2
2	99 ± 3	97 ± 3	97 ± 3	97 ± 2
3	92 ± 3	87 ± 3	89 ± 4	94 ± 3
4	84 ± 3	82 ± 4	80 ± 4	90 ± 3
5	76 ± 3	68 ± 5	78 ± 4	78 ± 5
6	64 ± 5	67 ± 5	71 ± 5	66 ± 6
Stereotypy Time (sec)				
1	188 ± 18	167 ± 15	178 ± 14	167 ± 10
2	163 ± 17	143 ± 9	157 ± 13	166 ± 12
3	140 ± 15	115 ± 9	133 ± 13	129 ± 12
4	117 ± 13	102 ± 7	104 ± 9	120 ± 10
5	98 ± 10	77 ± 7	90 ± 8	96 ± 10
6	82 ± 10	77 ± 7	87 ± 10	82 ± 10
Total Distance (cm)				
1	2696 ± 615	1640 ± 94	1781 ± 141	2136 ± 326
2	2975 ± 1007	1289 ± 99	1386 ± 107	1955 ± 448
3	3443 ± 1364	1051 ± 96	1303 ± 109	1693 ± 365
4	3331 ± 1471	836 ± 85	1097 ± 108	1272 ± 302
5	3462 ± 1873	669 ± 90	867 ± 112	1060 ± 310
6	3326 ± 1905	479 ± 77	627 ± 84	874 ± 290
Vertical Activity (no. beam breaks)				
1	246 ± 22	289 ± 18	319 ± 23	295 ± 22
2	252 ± 27	285 ± 18	309 ± 25	301 ± 20
3	232 ± 24	201 ± 15	254 ± 20	235 ± 18
4	192 ± 22	164 ± 20	205 ± 20	185 ± 22

TABLE 5. Mean (±S.E.) motor activity data in 4-month-old male mice [a]				
Interval	Atmospheric concentration (mg/m^3)			
	0	1.5	8	40
5	125 ± 15	117 ± 18	152 ± 21	129 ± 23
6	96 ± 19	86 ± 16	111 ± 17	106 ± 25
Vertical Time (sec)				
1	126 ± 10	145 ± 9	145 ± 8	146 ± 8
2	127 ± 11	150 ± 9	146 ± 9	153 ± 6
3	129 ± 12	123 ± 8	137 ± 10	132 ± 7
4	112 ± 12	106 ± 10	119 ± 11	111 ± 10
5	80 ± 8	79 ± 10	101 ± 13	83 ± 10
6	64 ± 9	60 ± 9	78 ± 11	68 ± 11

[a] Data obtained from pages 63-65, MRID 44222801.
N = 10

TABLE 6. Mean (±S.E.) motor activity data in 4-month-old female mice [a]

Interval	Atmospheric concentration (mg/m^3)			
	0	1.5	8	40
Horizontal Activity (no. beam breaks)				
1	4582 ± 238	4195 ± 281	4779 ± 224	5008 ± 591
2	3753 ± 253	3373 ± 227	3694 ± 139	4413 ± 631
3	3225 ± 220	3115 ± 262	3249 ± 188	4130 ± 696
4	2764 ± 196	2856 ± 330	2917 ± 220	3871 ± 676
5	2372 ± 204	2424 ± 326	2377 ± 180	3256 ± 648
6	2053 ± 170	2098 ± 310	2200 ± 211	2895 ± 665
Movement Time (sec)				
1	228 ± 11	233 ± 16	223 ± 10	255 ± 25
2	183 ± 11	190 ± 17	183 ± 9	225 ± 26
3	158 ± 11	175 ± 17	167 ± 13	218 ± 29
4	135 ± 9	163 ± 23	155 ± 15	205 ± 32
5	114 ± 12	141 ± 24	127 ± 14	175 ± 32
6	97 ± 9	123 ± 21	118 ± 17	148 ± 30
Number of Movements				
1	155 ± 3	144 ± 5	155 ± 3	140 ± 8
2	149 ± 3	138 ± 5	150 ± 3	134 ± 8
3	141 ± 4	133 ± 5	137 ± 4	124 ± 8
4	130 ± 5	122 ± 8	129 ± 4	120 ± 8
5	114 ± 8	110 ± 9	108 ± 5	103 ± 9
6	101 ± 8	94 ± 9	100 ± 6	89 ± 8
Number of Stereotypy				
1	104 ± 2	104 ± 2	105 ± 2	106 ± 2
2	102 ± 2	100 ± 2	101 ± 2	101 ± 3
3	95 ± 2	94 ± 3	97 ± 3	93 ± 3
4	93 ± 3	86 ± 3	91 ± 2	88 ± 3
5	86 ± 3	80 ± 4	85 ± 3	84 ± 4
6	78 ± 3	74 ± 4	80 ± 4	74 ± 5
Stereotypy Time (sec)[b]				
1	219 ± 14	179 ± 11	226 ± 11	185 ± 14
2	184 ± 14	136 ± 10	170 ± 11	161 ± 13
3	153 ± 12	123 ± 9	140 ± 10	134 ± 13
4	125 ± 10	109 ± 8	121 ± 10	128 ± 14
5	111 ± 9	95 ± 8	106 ± 7	109 ± 12
6	99 ± 8	84 ± 7	98 ± 7	93 ± 11
Total Distance (cm)				
1	2220 ± 142	2537 ± 364	2135 ± 123	2403 ± 297
2	1803 ± 135	2010 ± 268	1825 ± 158	2057 ± 293
3	1541 ± 120	1981 ± 328	1784 ± 246	2109 ± 337
4	1411 ± 119	2046 ± 523	1707 ± 276	1953 ± 376
5	1196 ± 131	1829 ± 526	1385 ± 242	1551 ± 318
6	981 ± 96	1483 ± 434	1328 ± 285	1236 ± 242
Vertical Activity (no. beam breaks)				
1	260 ± 24	275 ± 30	299 ± 28	280 ± 32
2	275 ± 28	282 ± 32	343 ± 35	306 ± 36
3	242 ± 27	297 ± 32	312 ± 48	317 ± 45
4	226 ± 26	263 ± 43	265 ± 53	297 ± 62

TABLE 6. Mean (±S.E.) motor activity data in 4-month-old female mice [a]				
Interval	Atmospheric concentration (mg/m^3)			
	0	1.5	8	40
5	184 ± 28	214 ± 43	201 ± 46	273 ± 70
6	148 ± 25	165 ± 32	220 ± 59	206 ± 50
Vertical Time (sec)				
1	138 ± 9	143 ± 10	150 ± 11	138 ± 12
2	153 ± 10	160 ± 13	171 ± 10	150 ± 9
3	149 ± 10	163 ± 10	161 ± 13	162 ± 13
4	144 ± 10	153 ± 14	154 ± 12	151 ± 13
5	126 ± 13	120 ± 15	123 ± 14	137 ± 16
6	117 ± 16	104 ± 13	122 ± 15	112 ± 13

[a] Data obtained from pages 66-68, MRID 44222801.
[b] Significantly different from control, $p<0.05$ for treatment effect.
N = 10

D. POSTMORTEM RESULTS

1. **Total muscarinic acetylcholine receptor (mAChR) density:** The total amount of mAChR was determined by the difference between the [^{3}H]QNB binding alone and the [^{3}H]QNB binding under a high concentration of Atropin (10^{-4} M). In young (17 day-old) male mice, the specific binding of QNB in the cortex of the treated groups increased with concentration (Table 7). No changes in specific binding of QNB were observed in adult male mice. Although the methods stated that brain tissue was processed for both males and females, only results for males were given in the report.

Table 7: Mean (%) (± S.D.) muscarinic acetylcholine receptor (cortex) in male mice[a]				
Time	Atmospheric concentration (mg/m^3)			
	0	1.5	8	40
17 days	100 ± 11.11	166.26** ± 9.33	168.72** ± 8.38	202.96** ± 9.4
4 months	100 ± 5.2	99.55 ± 11.81	95.16 ± 8.2	103.95 ± 8.84

[a] Data obtained from page 219, MRID 44222801.
** Significantly different from control value, $p<0.001$, Mann Whitney U-Test.
N = 10

2. **Acetyl cholinesterase (AChE) and choline acetyltransferase (CHAT) activity:** No treatment-related changes were observed in either AChE or CHAT (Table 8). Only results from males were reported.

TABLE 8: Mean (%) (± S.D.) AChE and CHAT activity in male mice[a]				
Time	Atmospheric concentration (mg/m^3)			
	0	1.5	8	40
AChE				
17 days	100 ± 9.72	87.1 ± 13.33	10.45 ± 12.42	84.19 ± 15.22
4 months	100 ± 7.66	85.21 ± 16.55	91.04 ± 9.31	94.21 ± 19.92
CHAT				
17 days	100 ± 12.26	87.1 ± 13.33	106.45 ± 12.42	84.19 ± 15.22
4 months	100 ± 11.67	114.17 ± 8.38	125.42 ± 16.15	122.92 ± 12.68

[a] Data obtained from page 219, MRID 44222801.
N = 10

III. DISCUSSION and CONCLUSIONS:

A. INVESTIGATORS CONCLUSIONS: The study author concluded that the inhalation exposure of postnatal male mice to tetramethrin for seven days resulted in an increase in the number of receptors and possibly changes in horizontal activity, immediately after treatment. The study author considered the treatment-related differences adaptive in nature, showing a functional status during or shortly after inhalation and not as an adverse effect. At four months of age, changes were no longer present. No treatment-related effects were observed on the enzymes AChE and CHAT.

B. REVIEWER COMMENTS: The study was conducted in response to literature reports that the density of muscarinic receptors and motor activity were changed when mice were treated with pyrethroids during postnatal brain development. At the maximum stable nominal atmospheric concentration of tetramethrin (40 mg/m^3), no evidence of systemic toxicity was present. No treatment-related deaths, clinical signs of toxicity or body weight effects were observed. During motor activity testing, significant decreases in horizontal activity (HA), vertical activity (VA) and vertical time (VT) were observed in 17 day-old male mice in the HCT group. However, a dose-response effect was not observed with any of the three parameters and the decreases in VA and VT were small. No treatment-related effects were observed in 17 day-old females or in either sex during the 4-month motor testing. Therefore, the reviewer disagrees with the study author and does not think that treatment had any effect on motor activity on either testing day.

The total muscarinic acetylcholine receptor (mAChR) density was significantly increased in a concentration-dependent manner in all treated groups of 17 day-old male mice, but returned to the control level by 4 months of age. No treatment-related effects were observed on the AChE and CHAT enzyme activities.

C. STUDY DEFICIENCIES:

1. The study report stated that receptor and enzyme activity measurements were done in male and female mice; however, only data from male mice were included.

2. The study report stated that the brain was weighed at sacrifice but these data were not reported.

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/4/09
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/4/09

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0006386

STUDY TYPE: ***In vitro* Genotoxicity (mammalian cells and salmonella)-*non guideline***

PC CODE: 069003 **DP BARCODE:** D292301

TXR#: 0054713

TEST MATERIAL (PURITY): Tetramethrin (72%, industrial grade).

SYNONYMS: Neopynamin

CITATION: Ding, C., Yu, Y., Jiao, Zhang,, I., Cai, A., Chen, X. Genotoxicity of Tetramethrin in Mammalian Cells and Salmonella Typimurium. Department of Pathophysiology, Zhejiang Medical University. May 11, 1987. Lab Report No. IT-51-0208. MIRD 40275801. Journal of the Zhejiang University of Medicine, Vol 14 (1): 1-4.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In an unscheduled DNA synthesis assay (MRID 40275801), human amnion FL cells and primary rat hepatocyte cultures were exposed to industrial grade tetramethrin (72% a.i, Lot No. not provided) dissolved in dimethyl sulfoxide (DMSO) at concentrations of 0 0.005, 0.05, or 0.5 µg/ml for 5 h in the presence or absence of S9 from rats treated with polychlorinated biphenyls.

It was stated that tetramethrin was tested up to cytotoxic concentrations in the absence of S9 and that there was no toxicity when S9 was present, but the cytotoxicity endpoint was not defined (or quantified). The positive controls did induce the appropriate responses. **There *was* evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures *was* induced, both in the presence and absence of S9.**

In a reverse gene mutation assay in bacteria (MRID 40275801), strains TA100, TA98, and TA97 of *S. typhimurium* were exposed to tetramethrin (72% a.i., Lot No. not available) at 5, 50, or 500 µg/plate (10-fold below the toxic concentration of 5000 µg/plate) in the presence and absence of S9. The plate incorporation method was used for these studies. In a separate study using the fluctuation method, strain TA97 only was exposed to tetramethrin at 5, 50, or 500 µg/ml in the presence and absence of S9. The positive controls induced the appropriate responses in the corresponding strains. **There *was* evidence of induced mutant colonies in the presence and absence of S9 activation via**

the fluctuation method (TA97) and in the absence of S9 via the plate incorporation method (TA97, weak at 3-fold over background).

This study is classified as acceptable, non-guideline and does not satisfy the guideline requirement for Test Guideline OPPTS 870.5550; OECD 482/486 for unscheduled DNA synthesis in mammalian cells in culture. This study was not designed to meet this guideline requirement. Rather, this study was designed to provide information regarding genotoxicity in both bacterial and mammalian cell lines, and in the case of mammalian cells, an unconventional double isotope method was employed.

COMMENTS:

1) This DER has been updated with a new Executive Summary and classification information.

2) None of the other conclusions of the previous DER were altered.

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** March 4, 2009
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/4/09

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0006386, 0054562

STUDY TYPE: ***In vitro* Mammalian Cytogenetics-*nonguideline***

PC CODE: 069003 **DP BARCODE:** D292301

TXR#: 0054713

TEST MATERIAL (PURITY): Neo-pynamin, T.G. (93.4%)

SYNONYMS: Tetramethrin

CITATION: Kogiso, S., Hara, M., Yoshitake, A., et al. (1986). In Vivo Chromosomal Aberration Test of Neopynamin in Mouse Bone Marrow Cells. Laboratory of Biochemistry and Toxicology, Takarazuka Research Center, Sumitomo Chemical Co., Ltd, Japan. March 26, 1986. MRID 40275901. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a mammalian cell cytogenetics assay for chromosome aberration (MRID 40275901), male ICR mice 6/dose were exposed to tetramethrin (93.4%, Lot No. 90508) by i.p. injection (10 ml/kg in a corn oil vehicle) at doses of 0, 1200, 2400, or 5000 mg/kg for 6, 24, or 48 hours. The positive control was mitomycin c (4 mg/kg) and was administered at 6, 24, and 48 h prior to sacrifice. Following sacrifice, bone marrow cells in both femurs of each mouse were used to make chromosomal slide preparations.

Tetramethrin was not mutagenic under the conditions of this assay. The percentage of cells with aberrations ranged from 0.3-2.3% for tetramethrin and for 0.7-2.0% for corn oil controls, while the percentage of aberrations for the positive control (mitomycin c) ranged from 9.0-60.0%.

There was no evidence of chromosomal aberration induced over background levels at any dose.

This study is classified as **Acceptable, Nonguideline.**

This study is classified as **Acceptable, Nonguideline** and does not satisfy the guideline requirement for Test Guideline *In vitro* mammalian cytogenetics chromosomal aberration OPPTS 870.5375; OECD 473 for *in vitro* cytogenetic mutagenicity data because only males were tested.

COMMENTS:

1) This DER has been updated with a new Executive Summary and classification information.

2) The original classification was unacceptable, non-guideline because there was no evidence that tetramethrin reached the bone marrow (unacceptable) and only males were tested (non-guideline). However, a similar study performed with radiolabelled tetramethrin (MRID 42917702, TXR 0054562) showed that tetramethrin indeed reaches the bone marrow by both ip injection and oral routes of exposure. Therefore, this study is acceptable. It remains non-guideline because only males were tested. This classification is consistent with the RED for tetramethrin (June 18, 2008).

3) None of the other conclusions of the previous DER were altered.

EPA Reviewer: Jessica P. Ryman, Ph.D. **Signature:**
Reregistration Branch 4, Health Effects Division (7509P) **Date:** December 10, 2008
EPA Secondary Reviewer: Abdallah Khasawinah, Ph.D. **Signature:**
Reregistration Branch 4, Health Effects Division (7509P) **Date:** Dec. 10, 2008

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0009640

TXR#: 0054713

STUDY TYPE: One month Oral Toxicity-feeding-rats; *Non-guideline*

PC CODE: 069003 **DPBARCODE:** D292301

TEST MATERIAL (PURITY): Neo-Pynamin-Forte (935% a.i.)

SYNONYMS: Neopynamin, tetramethrin

CITATION: Hosokawa, S. (1982). One Month Oral Subacute Toxicity Study with Neopynamin-Forte in Rats. Laboratory of Biochem. And Tox., Hyogo, Japan. Lab Report No. IL-20-0188. September 9, 1982. MRID 42146404. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a 1 month oral toxicity study (MRID 42146404) Neo-Pynamin Forte (93.5% a.i., Lot No. 0042) was administered to CRJ: CD (SD) rats 10/sex/dose in the diet at dose levels of 0, 300, 3000, or 10,000 ppm (equivalent to M/F 0, 30.0/30.6, 289/294, 964/941 mg/kg bw/day).

There was one death that was not considered treatment-related (one 3000 ppm male on Day 22). Total mean body weight gain was statistically ($p<0.05$) decreased in females at 300 ppm (↓9.1%), 3000 ppm (↓16.7%) and 10,000 ppm (↓22.1 %), and was considered biologically significant at 3000 and 10,000 ppm. Food consumption was significantly decreased for 10,000 ppm males and females during Week 1 and was significantly increased for 10,000 ppm males during Weeks 2 to 5. Water intake was also significantly increased in 10,000 ppm males from weeks 2 to 5.

There were no treatment-related ophthalmological effects. Absolute and relative liver weights increased in 3,000 and 10,000 ppm males and females and was accompanied by enlarged livers. Histology of the liver showed focal necrosis and panlobular and hepatocellular hypertrophy in 3000 ppm females and in 10,000 ppm males and females. Cytoplasmic vacuolization of the liver was present in 3000 ppm males and in 10,000 ppm males and females. There were also histopathologic changes in the kidneys that were considered treatment-related at 10,000 ppm in

males that were described as an increased incidence in the severity of the grade of the lesion known as eosinophilic body in tubular epithelial cells. Treatment-related clinical chemistry parameters considered both biologically and statistically significant included increased cholesterol in 3000 and 10,000 ppm males and females, increased serum glutamic pyruvate transaminase (SGPT) in 10,000 ppm males and females, and increased SGPT in 3000 ppm males.

The LOAEL is 289/294 mg/kg/day M/F (3000 ppm), based on decreased body weight gain in females, increased absolute and relative liver weight with enlarged livers in males and females with focal necrosis and panlobular and heptocellular hypertrophy in females and cytoplasmic vacuolization in males, increased cholesterol in both sexes and increased SGPT in males. The NOAEL is 30.0/30.6 mg/kg/day M/F (300 ppm).

This 1 month oral toxicity study in the rat is Acceptable/Non-guideline. It does not satisfy any guideline requirement, nor was it designed to do so. Rather, the purpose was to provide useful information on the effects of a 1 month dietary exposure to the compound. This objective was accomplished and so the study is acceptable.

COMMENTS:

1) This DER has been updated with a new Executive Summary.

2) None of the other conclusions of the previous DER were altered. However, NOEL and LEL were changed to NOAEL and LOAEL and the basis for setting the LOAEL was clarified.

3) Actual ingested doses of compound for males and females, instead of calculated or approximate values of 30, 300, and 1000 mg/kg/day were used.

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/3/09
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/3/09

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0003660

STUDY TYPE: Perinatal and Postnatal Study – rats
Non-guideline

PC CODE: 069003 **DP BARCODE:** D292301

TXR#: 0054713

TEST MATERIAL (PURITY): Neopynamin (% a.i. not provided)

SYNONYMS: tetramethrin

CITATION: Sato, T., Tagawa, G., Narama, K. (1982). Reproduction Test of Neopynamin: Part 4. Perinatal and Postnatal Study in Rats. Hamamatsu Seigiken Research, Shizuoka, Japan. Lab Report No. IT-01-0078. (Translation: unpublished study received Sept. 20, 1982 under 10308-1; prepared by Sumitomo Chemical Company, Ltd., Japan). MRID 00114371. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a 2-generation reproduction study (MRID 00114371), neopynamin (% a.i. not provided, Lot No. 90508) was administered to the P generation of pregnant female Slc:SD rats (SPF) 20/dose by gavage (0.5% carboxymethylcellulose vehicle) at dose levels of 0, 100, 300, and 1000 mg/kg bw/day from gestation day 7 to postnatal day 21 (GD7 – PND21). Litters were standardized to 8 to 10 pups per dam on PND 4. Dams and all but 2/sex/dam were sacrificed on PND 21 for organ weights and necropsy (dams) or skeletal examinations (pups). The 2/sex/dam (F1 generation) were allowed to mature and grow, emotional state (open field test), motor coordination (rota rod test), and learning ability (water filled T-maze test) were measured. The F1 generation was mated to produce the F2 generation, with delivery by cesarean on GD20 and assessment of cesarean parameters.

There were no unscheduled deaths or clinical signs in P females. Also, no dose-related changes in body weight were reported. P females did show signs of liver swelling and increased relative liver weight at 300 mg/kg (+7%) and 1000 mg/kg (14.4%). These changes are considered treatment-related. There were no effects of the compound on cesarean parameters.

The maternal systemic LOAEL is 1000 mg/kg bw/day based on increased liver weight. The maternal NOAEL is 300 mg/kg bw/day.

There were no treatment-related effects on body weight, organ weights, or skeletal malformations in the F1 or F2 generations. There were no effects of the compound on growth, emotional state, motor coordination, or learning ability in the F1 generation. There were no effects of the compound on fertility or cesarean parameters in the F1 generation.

The offspring LOAEL was not established. The offspring NOAEL is 1000 mg/kg bw/day in the F1 generation.

The reproductive LOAEL was not established. The reproductive NOAEL is 1000 mg/kg bw/day in the F1 generation.

This study is acceptable, non-guideline and does not satisfy the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800); OECD 416 in rats because the test material was not administered through two (or more) successive generations. This study cannot be upgraded.

COMMENTS:

1) This DER has been updated with a new Executive Summary.

2) LOEL and NOEL changed to LOAEL and NOAEL.

3) The conclusions are consistent with the previous DER and the RED for tetramethrin (June 2008).

4) A reproductive LOAEL/NOAEL was not mentioned in the RED for tetramethrin (June 2008) or the original DER. It has been added to the present DER to comply with the new format.

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** February 3, 2009
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/3/09

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT

STUDY TYPE: One generation reproduction and fertility effects – rats
Non-guideline

PC CODE: 069003 **DP BARCODE:** D292301

TXR#: 0054713

TEST MATERIAL (PURITY): Neopynamin (% a.i. not provided, 100% a.i. assumed)

SYNONYMS: tetramethrin

CITATION: Rutter, H. (1974). One-generation Reproduction Study—Rats: Neopynamin. Hazleton Laboratories America, VA. Lab Report No. 343-106, IT-41-0042. (Unpublished study received April 30, 1982 under 10308-1; prepared by Hazleton Laboratories, Inc). MRID 00137658. Unpublished.

Rutter, H. (1980). One-generation Reproduction Study—Rats: Neopynamin: Individual Animal Data. Hazleton Laboratories America, VA. Lab Report No. 343-106, IT-01-0081. (Unpublished study received April 30, 1982 under 10308-1;Submitted by Sumitomo Chemical Company, Ltd., MD). MRID 00137656. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a one-generation reproduction and fertility effects study (MRIDs 00137658 and 00137656), neopynamin (% a.i. not available, 100% a.i. assumed; lot number not available) was administered to Charles River Sprague Dawley cesarean-derived rats in the diet at dose levels of 0 (20 males/40 females) or 1000, 3000, or 6000 ppm (15 males/30 females per dose, calculated to be equivalent to 0, 50, or 300 mg/kg bw/day for males/females). Dosing of the parental (P) generation began prior to mating (study report does not state how long animals were dosed prior to mating). Dosing continued throughout mating, gestation, and throughout weaning of the F1 generation (study report does not state exactly when dosing terminated upon weaning).

No clinical signs of toxicity were observed in the P generation. Decreases in body weight gain

were observed in females at 3000 ppm and 6000 ppm. There was a decrease in the fertility index at 3000 ppm and 6000 ppm (86.7% at both levels, compared to 95% in controls), but this decrease was not statistically significant. There were no other compound-related effects on fertility or gestation.

The paternal/systemic LOAEL is 150 mg/kg bw/day (3000 ppm) based on decreases in body weight gain. The paternal/systemic NOAEL is 50 mg/kg bw/day (1000 ppm).

F1 generation pup body weights were similar among all of the treatment groups at 24 h for both sexes, but were significantly ($p<0.05$) decreased compared to controls at weaning for both males and females at 3000 and 6000 ppm. The lactation index was significantly ($p<0.05$) decreased at 6000 ppm. Also, at 6000 ppm, there was an increased incidence of smaller pups.

The offspring LOAEL is 150 mg/kg bw/day (3000 ppm), based on decreased pup body weight. The NOAEL is 50 mg/kg bw/day (1000 ppm).

This study is acceptable, non-guideline. It does not satisfy the guideline requirements for a reproduction and fertility effects study (OPPTS 870.3800); OECD 416 in rats because the test material was not administered through two (or more) successive generations. This study cannot be upgraded.

COMMENTS:

1) This DER has been updated with a new Executive Summary.

2) LOEL and NOEL changed to LOAEL and NOAEL.

3) The original DER could not be found, but the classification and other information is consistent with the RED for tetramethrin (June 2008).

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** February 3, 2009
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/3/09

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT

STUDY TYPE: One generation reproduction and fertility effects – rats
Non-guideline

PC CODE: 069003 **DP BARCODE:** D292301

TXR#: 0054713

TEST MATERIAL (PURITY): Neopynamin (% a.i. not provided, 100% a.i. assumed)

SYNONYMS: tetramethrin

CITATION: Rutter, H. (1974). One-generation Reproduction Study—Rats: Neopynamin. Hazleton Laboratories America, VA. Lab Report No. 343-106, IT-41-0042. (Unpublished study received April 30, 1982 under 10308-1; prepared by Hazleton Laboratories, Inc). MRID 00137658. Unpublished.

Rutter, H. (1980). One-generation Reproduction Study—Rats: Neopynamin: Individual Animal Data. Hazleton Laboratories America, VA. Lab Report No. 343-106, IT-01-0081. (Unpublished study received April 30, 1982 under 10308-1;Submitted by Sumitomo Chemical Company, Ltd., MD). MRID 00137656. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a one-generation reproduction and fertility effects study (MRIDs 00137658 and 00137656), neopynamin (% a.i. not available, 100% a.i. assumed; lot number not available) was administered to Charles River Sprague Dawley cesarean-derived rats in the diet at dose levels of 0 (20 males/40 females) or 1000, 3000, or 6000 ppm (15 males/30 females per dose, calculated to be equivalent to 0, 50, or 300 mg/kg bw/day for males/females). Dosing of the parental (P) generation began prior to mating (study report does not state how long animals were dosed prior to mating). Dosing continued throughout mating, gestation, and throughout weaning of the F1 generation (study report does not state exactly when dosing terminated upon weaning).

No clinical signs of toxicity were observed in the P generation. Decreases in body weight gain

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/3/09
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/3/09

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0003660

STUDY TYPE: Perinatal and Postnatal Study – rats
Non-guideline

PC CODE: 069003 **DP BARCODE:** D292301

TXR#: 0054713

TEST MATERIAL (PURITY): Neopynamin (% a.i. not provided)

SYNONYMS: tetramethrin

CITATION: Sato, T., Tagawa, G., Narama, K. (1982). Reproduction Test of Neopynamin: Part 4. Perinatal and Postnatal Study in Rats. Hamamatsu Seigiken Research, Shizuoka, Japan. Lab Report No. IT-01-0078. (Translation: unpublished study received Sept. 20, 1982 under 10308-1; prepared by Sumitomo Chemical Company, Ltd., Japan). MRID 00114371. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a 2-generation reproduction study (MRID 00114371), neopynamin (% a.i. not provided, Lot No. 90508) was administered to the P generation of pregnant female Slc:SD rats (SPF) 20/dose by gavage (0.5% carboxymethylcellulose vehicle) at dose levels of 0, 100, 300, and 1000 mg/kg bw/day from gestation day 7 to postnatal day 21 (GD7 – PND21). Litters were standardized to 8 to 10 pups per dam on PND 4. Dams and all but 2/sex/dam were sacrificed on PND 21 for organ weights and necropsy (dams) or skeletal examinations (pups). The 2/sex/dam (F1 generation) were allowed to mature and grow, emotional state (open field test), motor coordination (rota rod test), and learning ability (water filled T-maze test) were measured. The F1 generation was mated to produce the F2 generation, with delivery by cesarean on GD20 and assessment of cesarean parameters.

There were no unscheduled deaths or clinical signs in P females. Also, no dose-related changes in body weight were reported. P females did show signs of liver swelling and increased relative liver weight at 300 mg/kg (+7%) and 1000 mg/kg (14.4%). These changes are considered treatment-related. There were no effects of the compound on cesarean parameters.

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/4/09
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/4/09

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0006786

STUDY TYPE: Subchronic Oral Toxicity-feeding-dogs; OPPTS 870.3150 [§ 82-1b]; OECD 409.

PC CODE: 069003 **DP BARCODE:** D292301

TXR#: 0054713

TEST MATERIAL (PURITY): Neopynamin (94.6% a.i.)

SYNONYMS: Tetramethrin

CITATION: Pence, D.H., Hagan, W.H., Alsaker, R.D., Dawkins, B.G., Marshall, P.M., Tacey, R.L. (1981). Subchronic Toxicity in Dogs Neopynamin. Hazleton Laboratories America, Inc., Vienna, VA. Lab. Report No. 343-147. July 17, 1981. MRID 41698902. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a 26-week oral toxicity study (MRID 41698902) neopynamin (94.6% a.i., Lot 00208) was administered to purebred beagle dogs 6/sex/dose in the diet at dose levels of 0, 1250, 2500, or 5000 ppm (equivalent to 0, 31.25, 62.5, 125 mg/kg bw/day). Blood analysis (hematology and clinical chemistry) and urinalysis were conducted at weeks 0,4,8.13,17, 21, and 26.

There were no unscheduled deaths. No effects on body weight gain or food consumption were observed. No treatment-related effects in ophthalmologic examinations were noted. Behavioral effects of nervousness, tremors, and or jerky movements were not observed in male or female controls. However, 2500 ppm in 1/6 males and 1/6 females demonstrated this signs, which increased to 3/6 males and 4/6 females at 5000 ppm. No effects on hematology or urinalysis were observed, however, possible dose-related deviations in BUN, glucose, Ca^{++}, total protein, albumin, albumin/globulin ration, Cl^{-}, and bilirubin were observed. However, deviations in bilirubin, Cl^{-}, Ca^{++}, glucose, BUN, and total protein were not consistent. The albumin content was decreased for the 5000 ppm males at weeks 4-26 (↓22%) and for the 5000 ppm females at

weeks 8-21 (↓17%). The cholesterol content for all dogs was higher than for controls, but dose-response relationships were not evident and statistical significance was only occasionally attained. Absolute liver weights were significantly (↑51%) in males at 2500 ppm. At 5000 ppm, absolute liver weights were significantly increased in males (↑60%) and females (↑16%). Relative liver weights were also significantly increased at this dose in males (↑30%). For females, absolute and relative ovary weights were significantly decreased at 5000 ppm (↓49% and ↓45%, respectively). Also, these 5000 ppm females did not have corpora lutea in the ovaries, indicating that recent ovulation had not occurred.

The LOAEL is 62.5 mg/kg/day (2500 ppm), based on increased liver weight in males and increased nervousness, tremors, and/or jerky movements in males and females The NOAEL is 31. mg/kg/day (1250 ppm) in males and females.

This 6-month oral toxicity study in the dog is acceptable, guideline and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409) in dogs.

COMMENTS:

1) This DER has been updated with a new Executive Summary and classification information.

2) LOEL and NOEL changed to LOAEL and NOAEL.

3) This DER was originally classified as core reserved, pending submission of a pathology addendum. This addendum was received September 1, 1981 and the study was upgraded to acceptable.

4) None of the other conclusions of the previous DER were altered.

EPA Reviewer: Jessica P. Ryman, Ph.D. **Signature:**
Reregistration Branch 4, Health Effects Division (7509P) **Date:** December 10, 2008
EPA Secondary Reviewer: Abdallah Khasawinah, Ph.D. **Signature:**
Reregistration Branch 4, Health Effects Division (7509P) **Date:** Dec. 10, 2008

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT

Previous TXR: 0010285

TXR#: 0054713

STUDY TYPE: 28-Day Dermal Toxicity - rat; OPPTS 870.3200 [§82-2] (rodent); OECD 410.

PC CODE: 069003 **DP BARCODE:** D292301

TEST MATERIAL (PURITY): Tetramethrin (95.3% a.i., powder)

SYNONYMS: Neopynamin

CITATION: Osheroff, M.R. (1991). 21-Day Dermal Toxicity Study in Rats. Hazleton Laboratories America, Rockville, MD. Lab Report No. 20850-4373. July 19, 1991. MRID 41995004. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a 21-day dermal toxicity study (MRID 41995004), tetramethrin (95.3% a.i., Lot No. 90304) was applied to the dorsal shaved skin of Sprague Dawley rats (Crl: CD BR) 5/sex/dose at dose levels of 0, 100, 300, or 1000 mg/kg bw/day (in a corn oil vehicle), 6 hours/day during a 21-day period. At the end of each dosing period, skin was wiped with gauze moistened with distilled water.

There were no treatment-related toxic effects at doses up to and including 1000 mg/kg/bw day. 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 300 and 1000 mg/kg/day, the hematological levels did not increase in a dose-dependent manner. The percentage of change was not reported for any of the effects.

Macroscopic lesions were observed in animals exposed to tetrmethrin, but were considered to be

unrelated to exposure, because each effect was observed only in 1 of the 10 animals exposed per dose. Most of the macroscopic effects occurred only in animals from the high-dose group. These effects were a pale area on the liver, a dark area on the stomach, and lesions in the urinary bladder (calculus lumen, thickened wall, prominent vessel, distention, raised area of the mucosa). One animal exposed to 300 mg/kg/day exhibited a dilated pelvis and two exposed to 100 mg/kg/day also exhibited skin effects (one incidence of alopecia and one sore, respectively).

Microscopic examination was conducted only on control and 1000 mg/kg/day animals. There were several microscopic effects noted in 1000 mg/day/day animals that were absent in controls. These effects were: chronic active pyelitis and hyperplasia of the urothelium in the kidney, focal necrosis and microgranuloma in the liver, hyperplasia of the mucosa in the urinary bladder, necrosis of the stomach, acanthosis of tetramethrin treated and untreated skin, and necrotic debris on the surface of tetramethrin-treated skin. However, each of these effects were not due to treatment with tetramethrin because all occurred in one particular animal. The incidence of effects of regenerative tubules in the kidneys was slightly elevated in 1000 mg/kg/day males at 3/5 compared to controls (1/5), but this was not found to be statistically significant by the reviewer.

The LOAEL was not determined. The NOAEL is 1000 mg/kg/day in males and females, and is both the highest dose tested and the limit dose.

This 28-day dermal toxicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a 21/28-day dermal toxicity study (OPPTS 870.3200 ; OECD 410) in rats.

COMMENTS:

1) This DER has been updated with a new Executive Summary.

2) None of the other conclusions of the previous DER were altered. However, NOEL and LEL were changed to NOAEL and LOAEL.

EPA Reviewer: Jessica P. Ryman, Ph.D. **Signature:** Jessica P. Ryman Ph.D.
Reregistration Branch 4, Health Effects Division (7509P) **Date:** March 4, 2009
EPA Secondary Reviewer: Abdallah Khasawinah, Ph.D. **Signature:** A. Khasawinah
Reregistration Branch 4, Health Effects Division (7509P) **Date:** March 4, 2009
Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0010285

STUDY TYPE: Subchronic Inhalation Toxicity – rats; OPPTS 870.3465 [§ 82-4]; OECD 413.

PC CODE: 069003 **DP BARCODE:** D292301

TXR# : 0054713

TEST MATERIAL (PURITY): tetramethrin (95.3% a.i., white solid)

SYNONYMS: Neo-pynamin

CITATION: Kawaguchi, S. (1991). Three-month Inhalation Toxicity Study of Neo-Pynamin in Rats. Environmental Health Science Laboratory, Sumitomo Chemical Co., Inc., Osaka, Japan. Lab Report No. 2189. August 9, 1991. MRID 42012101. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a subchronic inhalation toxicity study (MRID 42012101) tetramethrin (95.3% a.i., Lot No. 90304) was dissolved in corn oil administered to Crj: CD (Sprague-Dawley) SPF rats 10 sex/concentration by dynamic whole body exposure at concentrations of 0 (atomized corn oil), 20.3, 134, or 824 mg/m^3 (0.0203, 0.134, or 0.824 mg/L) for 6 hours per day, 5 days/week for a total of 13 weeks plus 3 days into Week 14.

There were no unscheduled deaths. Clinical signs included irregular respiration and bradypnea in males and females at 0.134 and 0.824 mg/L. At 0.824 mg/L, decreased spontaneous activity, focal loss of hair, nasal discharge, dark red substance surrounding the snout, red tear, salivation, and urinary incontinence were noted in both sexes. Ophthalmological examinations revealed no differences.

There was no effect of the test compound on food consumption. At 0.824 mg/L, body weights were significantly decreased in males on Days 8, 43, and 89 and in females on Day 89. Body weight gains were significantly decreased in males throughout the treatment period at 0.824 mg/L and at Days 43 and 89 in females.

Administration of 0.134 or 0.824 mg/L tetramethrin was also associated with changes in hematology, clinical chemistry, and urinalysis parameters, and decreases in body weight gains.

In males, monocyte count was decreased at 0.134 and 0.824 mg/L. In females, mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were decreased at 0.824 mg/L. In males and females at 0.824 mg/L, mean corpuscular hemoglobin concentration (MCHC) was decreased and prothrombin time (PT), activated partial thromboplastin time (APPT), and fibrinogen were increased. Clinical chemistry in males showed a significant increase in total protein at all concentrations of tetramethrin and at 0.824 mg/L only in females. Glucose was decreased in females at 0.134 and 0.824 mg/L, while total cholesterol was increased in males and females at 0.824 g/L and in males at 0.134 mg/L. Gamma glutamyl transpeptidase (GTP), phospholipids, and inorganic phosphorus were increased in males at 0.134 and 0.824 mg/L, while beta-globulin was increased at 0.824 mg/L. In females, GTP and phospholipids were increased at 0.824 mg/L and beta-globulin was increased at 0.134 and 0.824 mg/L. Bilirubin levels were increased in the 0.134 mg/L females and in 0.824 mg/L males and females. Urobilinogen was also increased in 0.824 mg/L males and females.

Gross findings in the livers of 0.134 and 0.824 mg/L males and females consisted of soft livers and/or enlarged livers and dark-red discoloration. Hepatocellular hypertrophy was noted at both 0.134 and 0.824 mg/L in both sexes. Focal necrosis of the liver was seen in 0.824 mg/L males. The pathological changes in the liver correlated with an increase in absolute and relative liver weights. An increased incidence of hyaline droplets in renal tubules was present in 0.134 and 0.824 mg/L males. The presence of hyaline droplets in the renal tubules corresponded to an increase in relative kidney weights at these concentrations. Absolute and relative kidney weights were increased in females at all doses. Significant increase in relative liver weights was seen at all doses in males and females. There were no macroscopic or microscopic lesions in the 0.0203 mg/L males or females.

The LOAEL was 134 mg/m^3/day (0.134 mg/L/day), based on increased clinical signs in males and females, changes in hematology, clinical chemistry, and urinalysis in males and females, macroscopic and microscopic liver changes in males and females, microscopic kidney changes in males, and increased absolute and relative kidney weights and relative liver weights in males and females. The NOAEL is 20.3 mg/m^3/day (0.0203 mg/L/day) in males and females.

This subchronic inhalation toxicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a subchronic inhalation study OPPTS 870.3465; OECD 413.

COMMENTS:

1) This DER has been updated with a new Executive Summary and classification information. This study was originally classified as unacceptable, guideline because the exposure atmosphere was characterized on only 2/5 exposure days/week. In a March 8, 1994 Memorandum to Kathryn Davis from William Dykstra, this study was upgraded to acceptable, guideline due to a low coefficient of variation and no significant differences in atmospheric concentration between characterized exposure days. This new classification is consistent with the RED for tetramethrin (June 18, 2008).

2) None of the other conclusions of the previous DER were altered. However, NOEL and LEL were changed to NOAEL and LOAEL.

EPA Reviewer: Jessica P. Ryman, Ph.D. **Signature:**
Reregistration Branch 4, Health Effects Division (7509P) **Date:** December 10, 2008
EPA Secondary Reviewer: Abdallah Khasawinah, Ph.D. **Signature:**
Reregistration Branch 4, Health Effects Division (7509P) **Date:** Dec 10, 2008

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXRs: 010285

TXR# : 0054713

STUDY TYPE: Subchronic Inhalation Toxicity – rats; OPPTS 870.3465 [§ 82-4]; OECD 413.

PC CODE: 069003 **DP BARCODE:** D292301

TEST MATERIAL (PURITY): tetramethrin (95.3% a.i., white solid)

SYNONYMS: Neo-pynamin

CITATION: Kawaguchi, S. (1991). Three-month Inhalation Toxicity Study of Neo-Pynamin in Rats (Determination of the No Observed Effect level). Environmental Health Science Laboratory, Sumitomo Chemical Co., Inc., Osaka, Japan. Lab Report No. 2279. August 9, 1991. MRID 41995003. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a subchronic inhalation toxicity study (MRID 41995003) tetramethrin (95.3% a.i., Lot No. 90304) was dissolved in corn oil administered to Crj: CD (Sprague-Dawley) SPF rats 10 sex/concentration by dynamic whole body exposure at concentrations of 0 (atomized corn oil), 1.9 ± 0.19, 4.4 ± 0.60, 19.8 ± 1.16 mg/m^3 or 0.0019 ± 0.00019, 0.0044 ± 0.00060, 0.0198 ± 0.00116 mg/L for 6 hours per day, 5 days/week for a total of 13.5 weeks.

Ophthalmological examinations were not performed. There was no treatment-related mortality and no concentration-related clinical signs. Wet fur, indicating deposition of the test substance and vehicle on the coat, was observed in all animals. Consequently, dermal and oral exposure could also result via grooming. No compound-related effects on food consumption were observed in males or females, and no effects on water intake were observed in females. In males, water consumption increased with tetramethrin concentration up to 20.5%, but was not statistically significant compared to vehicle or air controls.

There were no compound-related effects on hematology, clinical chemistry, or urinary parameters in the exposed rats. However, there were significant differences between vehicle and air-only controls on hematology and clinical chemistry. The only organ weights recorded were liver and

kidney. There were no treatment-related effects on the kidneys. The absolute and relative liver weights of all vehicle-containing animals were higher than air-only controls, indicating an effect of the corn oil vehicle. At 19.8 mg/m^3 (0.0198 mg/L), relative liver weights were increased 8.7% in females.

A LOAEL was not established. The NOAEL is 19.8 mg/m^3/day (0.0198 mg/L/day, the highest dose tested).

This subchronic inhalation toxicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a subchronic inhalation study OPPTS 870.3465; OECD 413.

COMMENTS:

1) This DER has been updated with a new Executive Summary and classification information. This study was originally classified as **Unacceptable/Guideline** because the exposure atmosphere was characterized on only 2/5 exposure days/week. In a March 8, 1994 Memorandum to Kathryn Davis from William Dykstra, this study was upgraded to acceptable, guideline due to a low coefficient of variation and no significant differences in atmospheric concentration between characterized exposure days. This new classification is consistent with the RED for tetramethrin (June 18, 2008).

2) None of the other conclusions of the previous DER were altered. However, NOEL and LEL were changed to NOAEL and LOAEL.

EPA Reviewer: Jessica P. Ryman, Ph.D. **Signature:**
Reregistration Branch 4, Health Effects Division (7509P) **Date:** December 10, 2008
EPA Secondary Reviewer: Abdallah Khasawinah, Ph.D. **Signature:**
Reregistration Branch 4, Health Effects Division (7509P) **Date:** Dec. 10, 2008

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0009842

TXR#: 0054713

STUDY TYPE: Prenatal Developmental Toxicity Study - Rat; OPPTS 870.3700a [§83-3a]; OECD 414.

PC CODE: 069003 **BARCODE**: D292301

TEST MATERIAL (PURITY): Neo-Pynamin (95.1% a.i., technical grade), (Tetramethrin)

SYNONYMS: Tetramethrin, Neopynamin Forte

CITATION: Robinson, K., Washer, G., Noveroske, J. (1991). An Oral Teratology Study of Neo-Pynamin in the Rat. Bio-Research Labs, LTS, Quebec, Canada. Lab report No., IT-11-0240 & IT-11-0241. December 16, 1991. MRID 42189201, 42189202. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRIDs 42189201 and 42189202), Neo-Pynamin (95.1%, Lot No. 90304) was administered to pregnant Crl: COBS VAF CD^R SD BR rats at 25 rats/dose by gavage (0.5% w/v carboxymethylcellulose vehicle) at dose levels of 0, 150, 500, or 1000 mg/kg bw/day (limit dose) from days 6 through 15 of gestation (GD 6-15). Doses were in 10 ml/kg, adjusted for body weight on GD 6. Animals were sacrificed on Day 20. (Doses were based on a range finding study in 6 Sprague-Dawley rats at doses of 0, 150, 500, and 1500 mg/kg day on GD 6-15, in which it was found that the dose concentration was not within specifications at 1500 mg/kg).

There was no mortality and no clinical signs of toxicity were observed. Body weight gain (not corrected for gravid uterine weight) was significantly decreased (↓42.8%) in 1000 mg/kg bw/day dams during GD 6-9. This was accompanied by a decrease in food consumption (↓10.7%). There were no differences in weight gain or food consumption at any other time, however. There were no effects on pregnancy rate, nor were there abortions. No effects on gross pathology or cesarean parameters were observed.

The maternal LOAEL is 1000 mg/kg bw/day, based on decreased body weight gain and food consumption during GD 6-9. The maternal NOAEL is 500 mg/kg bw/day.

There were no dead fetuses, and there were no treatment-related effects on major malformations, minor external and visceral abnormalities, or minor skeletal anomalies.

The developmental LOAEL was not established. The developmental NOAEL is 1000 mg/kg bw/day (the higest dose tested).

The developmental toxicity study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided.

COMMENTS:

1) This DER has been updated with a new Executive Summary.

2) LOEL and NOEL changed to LOAEL and NOAEL.

3) None of the other conclusions of the previous DER were altered.

EPA Reviewer: Jessica P. Ryman **Signature:** Jessica P. Ryman
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** February 3, 2009
EPA Secondary Reviewer: Marquea D. King **Signature:** Marquea D. King
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/3/09

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0003660,0008795

STUDY TYPE: Prenatal development – rats
OPPTS 870.3700a [§ 83-3]/ DACO 4.5.2/ OECD 414

PC CODE: 069003 **DP BARCODE:** D292301

TXR#: 0054713

TEST MATERIAL (PURITY): Neopynamin (% a.i. not provided)

SYNONYMS: tetramethrin

CITATION: Sato, T., Narama, K. (1982). Reproduction Test of Neopynamin: Part 2. Teratology Study in Rats. Hamamatsu Seigiken Research, Shizuoka, Japan. Lab Report No. IT-01-0076. (Translation: unpublished study received Sept. 20, 1982 under 10308-1; prepared by Sumitomo Chemical Company, Ltd., Japan). MRID 00114369. Unpublished.

Sato, T., Narama, K. (1980). Reproduction Test of Neopynamin: Part 2. Teratology Study in Rats. Hamamatsu Seigiken Research, Shizuoka, Japan. Lab Report No. IT-01-0076. June 14, 1980. MRID 42014402. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a teratology study in Slc:CD (SPF) rats (MRIDs 00114369, 42014402) neopynamin (>90% , Lot No. 90508) was administered to pregnant females 30/dose by stomach tube (0.5% carboxymethylcellulose vehicle) at dose levels of 0, 100, 300, and 1000 mg/kg bw/day from gestation day 7 to 17 (GD7 –17). Twenty dams were sacrificed on GD 20 and subjected to cesarean section (c-section), while the remaining 10 were allowed to deliver naturally and were sacrificed two weeks after delivery. Pups were subjected to a series of tests to determine any adverse effects of *in utero* exposure. A subset of pups was reared to 11 weeks of age and mated to assess fertility.

There were no unscheduled deaths and no clinical signs of toxicity in the dams. There were

small but statistically significant decreases in body weight at 1000 mg/kg bw/day and a tendency for reduced food consumption and increased water consumption after administration of the test material. For dams that were sacrificed and subjected to c-section, no significant differences in cesarean parameters were observed, however, the relative liver weights were 4% and 12% higher at 300 and 1000 mg/kg bw/day, respectively. Also for the 1000 mg/kg bw/day group, kidney weights were 7.3% higher and ovary weights were 9.3% higher. No changes in organ weights were observed for dams that delivered naturally.

The maternal systemic LOAEL is 1000 mg/kg bw/day based on decreased body weight and increased liver, kidney, and ovary weights. The maternal NOAEL is 300 mg/kg bw/day.

There were no treatment-related effects on organ weights, or skeletal malformations in the pups. Also, there were no effects of the compound on growth and development or motor coordination (rota rod), emotionality (via open field test), or learning ability (water-filled T maze). There were no effects of the compound on fertility or cesarean parameters in the F1 generation, except that higher numbers of corpora lutea, implantations, and surviving fetuses were noted in the 1000 mg/kg bw/day dose group. Also in the 1000 mg/kg bw/day subset of animals mated in the F1 generation, body weights were significantly increased.

The offspring LOAEL was not established. The offspring NOAEL is 1000 mg/kg bw/day.

This study is classified as acceptable, guideline, and satisfies the guideline requirements for Prenatal Developmental Toxicity Study in rats [OPPTS 870.3700a/ DACO 4.5.2/ OECD 414].

COMMENTS:

1) This DER has been updated with a new Executive Summary.

2) LOEL and NOEL changed to LOAEL and NOAEL.

3) The RED for tetramethrin (June 2008) classifies this study as acceptable, nonguideline because the dams were not dosed according to present guidelines (from implantation to the day prior to cesarean). However, this study was classified as core guidelines at the time it was performed (TXR 003660) because it followed the dosing guidelines at the time, which only had to cover organogenesis. Therefore, this study is acceptable, guideline and the classification remains unchanged.

EPA Reviewer: Jessica P. Ryman, Ph.D. **Signature:**
Reregistration Branch 4, Health Effects Division (7509P) **Date:** December 10, 2008
EPA Secondary Reviewer: Abdallah Khasawinah, Ph.D. **Signature:**
Reregistration Branch 4, Health Effects Division (7509P) **Date:** Dec. 10, 2008

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0010285

TXR: 0054713

STUDY TYPE: Prenatal Developmental Toxicity Study - Rabbit; OPPTS 870.3700b [§83-3b]; OECD 414.

PC CODE: 069003 **DP BARCODE:** D292301

TEST MATERIAL (PURITY): tetramethrin (95.1% a.i., powder

SYNONYMS: Neopynamin

CITATION: Robinson, K., Washer, G., Noveroske, J. 1995. An Oral Teratology Study of Neo-Pynamin in the Rabbit. Bioresearch Laboratories, Ltd., Montreal, Canada. Lab Report No. 95088. July 18, 1991. MRID 41995005. Unpublished.

SPONSOR: Sunitomo Chemical Company Ltd., Osaka, Japan.

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 41995005) tetramethrin (95.1% a.i., Lot No. 90304) was administered to 20 pregnant New Zeland White rabbits/dose by gavage in a 0.5% w/v carboxymethylcellulose vehicle at nominal dose levels of 0, 30, 100, 300, or 500 mg/kg bw/day from days 7 through 19 of gestation (GD 7-19). The actual dose of the 500 mg/kg bw/day animals was 420 mg/kg bw/day. Other doses were within 93-103% of nominal values. Animals were sacrificed on GD 29. It was stated that there was no apparent relationship between the test material and five unscheduled deaths (one at 100 mg/kg on GD 17, two at 300 mg/kg on GD 7 and GD18, and two at 500 mg/kg on GD 7 and GD 18). All of these deaths were attributed to gavage dosing. There was one abortion on GD 23 in the 30 mg/kg group. Maternal toxicity, observed at 300 and 420 mg/kg bw/day, was manifested as a non-significant but substantially decreased body weight gain during dosing (↓20%) and gestation (↓10%) periods. This was accompanied by decreases in corrected body weight gain.

The maternal LOAEL is 300 mg/kg bw/day, based on non-significantly decreased body weight gain. The maternal NOAEL is 100 mg/kg bw/day.

Developmental toxicity was not observed in this study.

The developmental LOAEL was not established. The developmental NOAEL is 420 mg/kg bw/day.

The developmental toxicity study in the rabbit is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rabbits.

COMMENTS:

1) This DER has been updated with a new Executive Summary.

2) None of the other conclusions of the previous DER were altered. However, NOEL and LEL were changed to NOAEL and LOAEL.

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/3/2009
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/3/09

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0003660

STUDY TYPE: Prenatal development – rabbits
OPPTS 870.3700b [§ 83-3]/ DACO 4.5.3/ OECD 414

PC CODE: 069003 **DP BARCODE:** D292301

TXR#: 0054713

TEST MATERIAL (PURITY): Neopynamin (% a.i. not provided)

SYNONYMS: tetramethrin

CITATION: Sato, T., Narama, K. (1982). Reproduction Test of Neopynamin: Part 2. Teratology Study in Rabbits. Hamamatsu Seigiken Research, Shizuoka, Japan. Lab Report No. IT-01-0077. (Translation: unpublished study received Sept. 20, 1982 under 10308-1; prepared by Sumitomo Chemical Company, Ltd., Japan). MRID 00114370. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a prenatal development study (MRID 00114370) in white rabbits described as "Japanese white rabbits", neopynamin (% a.i. not provided, Lot No. 90508) was administered to pregnant females 10/dose by stomach catheter (in a 0.5% carboxymethylcellulose vehicle) at dose levels of 0, 50, 150, or 500 mg/kg bw/day from gestation day 8 to 18 (GD6 –18). Dams were sacrificed on GD29 and pups delivered by cesarean.

No obvious signs of toxicity were noted in the dams with regard to survival, body weight, and food consumption (only minor changes in the high dose group at best), behavior, necropsy, or organ weight changes. Cesarean parameters revealed an equivocal increase in fetal deaths per implantation (1.4, 4.0, 5.4, and 6.0) that did not distinguish between pre-dosing or post-dosing deaths.

The maternal systemic LOAEL is 500 mg/kg bw/day based on transient decreases in body weight gain and food consumption. The maternal NOAEL is 150 mg/kg bw/day.

The number of live fetuses increased from the control to high dose groups (70, 73, 80, and 82).

There was a significant decrease in pup body weights at 1000 mg/kg bw/day, but this finding was considered equivocal, since the body lengths and placental weights appeared smaller at 1000 mg/kg bw/day.

The offspring LOAEL was not established. The offspring NOAEL is 500 mg/kg bw/day.

This study is acceptable, guideline and satisfies the guideline requirements for a Prenatal Developmental Toxicity Study in rabbits [OPPTS 870.3700b/ DACO 4.5.3/ OECD 414].

COMMENTS:

1) This DER has been updated with a new Executive Summary.

2) LOEL and NOEL changed to LOAEL and NOAEL.

3) The RED for tetramethrin (June 2008) classifies this study as acceptable, nonguideline because the dams were not dosed according to present guidelines (from implantation to the day prior to cesarean). However, this study was classified as core guidelines at the time it was performed (TXR 003660) because it followed the dosing guidelines at the time, which only had to cover organogenesis. Therefore, this study is acceptable, guideline and the classification remains unchanged.

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** February 3, 2009
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/3/09

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0007306

STUDY TYPE: Reproduction and Fertility Effects Study – rats OPPTS 870.3800 [§ 83-4]; OECD 416.

PC CODE: 069003 **DP BARCODE:** D292301

TXR#: 0054713

TEST MATERIAL (PURITY): Neopynamin Forte (93.4% a.i.)

SYNONYMS: tetramethrin, neopynamin

CITATION: Pence, D.H. et al. Two-Generation Reproduction Study in Rats with Neopynamin Forte. Hazleton Labs, VA, Lab Report no. HLA 343-147 / IT-61-0201. June 17, 1986. MRIDs 00161842 and 40777801 (duplicate). Unpublished.

Pence, D., Wolfe, G., Kulwich, B. (1986). Two-generation Reproduction Study in Rats: Neopynamin Forte: Final Report. Hazleton Laboratories America, Inc., Lab Report No. 343-147. July 31, 1986. MRID 00161842. Unpublished.

SPONSOR: Sunitomo Chemical Company, Ltd., Osaka, Japan.

EXECUTIVE SUMMARY:

In a 2-generation reproduction study (MRIDs 00161842 and 40777801 (duplicate)), neopynamin forte (93.4% a.i., Lot No. 00402), was administered to parental (P) Sprague Dawley rats 13 males/dose and 26 females/dose in the diet at dose levels of 0, 100, 500, or 3000 ppm (equivalent to 0, 5, 25, or 150mg/kg bw/day). 15 F_1 males and 30 F_1 females were mated to produce the F_2 litters. At 3000 ppm, significantly decreased body weights (↓3-8%) were observed during the growth period of P males and females and F_1 males P and females (↓7-10%). Food consumption was also decreased 7% during the growth phase in P females. Body weights of P and F_1 females were also decreased during gestation and lactation at 3000 ppm. The body weights of P males at 500 and 3000 ppm and F_1 males at 3000 ppm were significantly decreased post mating, while the body weights of 100 ppm F_1 males were significantly increased. During the 30 day post-weaning period, body weights for 3000 ppm F_1 males and females were decreased 6% and 11%, respectively, while weights of 100 ppm F_1 males remained elevated

compared to controls.

For F_2 litters, body weights were significantly decreased for males at Days 7, 14, and 21 and for females at Day 14.

Bile duct hyperplasia was increased in F_1 parental females, with an incidence of 22/25 at 3000 ppm compared to 12/25 in controls.

Clinical observations of the F_1 and F_2 offspring showed an increase in the incidence of small and/or languid pups at 3000 ppm on days 7, 14, and 21 compared to controls.

There were no compound-related effects on male or female fertility rates, gestation length, or offspring survival in any generation.

The parental systemic LOAEL is 150 mg/kg bw/day (3000 ppm) based on decreased body weights in males and females, decreased food consumption in P females, and increased bile duct hyperplasia in F_1 parental females. The parental systemic NOAEL is 25 mg/kg bw/day in males and females (500 ppm).

The offspring LOAEL is 150 mg/kg bw/day (3000 ppm) based on decreased pup body weight in males and females during lactation. The offspring NOAEL is 25 mg/kg bw/day in males and females (500 ppm).

The reproductive LOAEL was not determined. The reproductive NOAEL is 150 mg/kg bw/day in males and females (3000 ppm).

This study is acceptable, guideline and satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800); OECD 416 in rats.

COMMENTS:

1) This DER has been updated with a new Executive Summary and classification information.

2) LOEL and NOEL were changed to LOAEL and NOAEL.

3) The study is listed as MRID 00161842 in the RED for tetramethrin (June 2008).

4) None of the other conclusions of the previous DER were altered.

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 2/27/2009
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/3/09

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0002657, 0003660, 0005899

STUDY TYPE: Chronic Toxicity-rats [feeding] OPPTS 870.4100a [§ 83-1a]; OECD 452.

PC CODE: 069003 **DP BARCODE:** D292301

TXR# :0054713

TEST MATERIAL (PURITY): Neopynamin (purity not provided)

SYNONYMS: tetramethrin

CITATION: Cox, R. (1974). Two-Year Dietary Administration in the Rat, Part A: Final report, NeoPynamin. Hazleton Laboratories, VA. Lab Report No. 343-107. October 4, 1974. MRID 41723301. Unpublished.

Cox, R. (1986). Two-Year Dietary Administration in the Rat: Neo-pynamin: Addendum 1: Final Report. Hazleton Laboratories, VA. Lab Report No. 343-107. (1986). MRID 40009401 Unpublished.

Vessolinovitch, S.D., Ito, N. (1982). Addendum to: Histologic Evaluation and Interpretation of Neo-Pynamin Bioassay Studies Carried Out on Sprague Dawley (1974 and 1981) and Long-Evans (1981) Rats by Hazleton Laboratories, Inc. for Sumitomo Chemical Company, Ltd. September 20, 1982. MRID 00114365. Unpublished.

Vessolinovitch, S.D., Ito, N. (1984). Addendum to: Histologic Evaluation and Interpretation of Neo-Pynamin Bioassay Studies Carried Out on Sprague Dawley (1974 and 1981) and Long-Evans (1981) Rats by Hazleton Laboratories, Inc. for Sumitomo Chemical Company, Ltd. August 24, 1984. MRID 00143555. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a chronic toxicity study (MRIDs 41723301, 40009401, 00114365 and 00143555), Neo-Pynamin (purity and lot number not supplied, 100% purity assumed) was administered to Charles

River CD (CRCD) rats at 0, 1000, 3000, or 6000 ppm in the diet at 60/sex in the control group and 50/sex in the dosing groups (doses were 0, 43, 115, or 210 mg/kg bw/day for males and 0, 50, 140, or 300 mg/kg bw/day for females) for a duration of 2 years. A subset of animals (10/sex/group) was sacrificed at 52 weeks. These animals were the offspring of parental males and females that had received Neo-pynamin at 0, 1000, 3000, or 6000 ppm in the diet for one week prior to mating.

All compound-treated animals had decreased body weights at the beginning of the study. There were not deaths attributed to treatment. There were also no clinical effects (e.g. behavior or appearance of treatment). No effects of treatment on body weight gains or changes were observed at any dose, however, food consumption was lower for all treatment levels. No dose-related effects were observed on hematology, clinical biochemistry, or urinalysis.

Relative liver weights were increased in males and females at 52 weeks at all doses (1000, 3000, and 6000 ppm). At 104 weeks, relative liver weights were increased in males at 3000 and 6000 ppm and in females at 6000 ppm.

In the testis, there was a clear dose-response for the incidence of interstitial adenomas and the incidence of interstitial cell hyperplasia was increased at 3000 and 6000 ppm.

In the kidneys, there was evidence of increased cystic collecting tubules in males and females at 6000 ppm. Also at 6000 ppm, fibrosarcoma was observed in one female cortical adenoma in one male and one female.

Overall, there was no treatment-related increase in the incidence or number of rats with neoplasms. However, receipt and evaluation of data containing the death date, gross necropsy findings, and microscopic findings for each animal are required for risk assessment.

The LOAEL is 43 mg/kg/day (1000 ppm) based on decreased food consumption and increased liver weight in males and females. The NOAEL was not established.

This chronic study in the rat is **Acceptable, Guideline** and satisfies the guideline requirement for a chronic oral study [OPPTS 870.4100, OECD 452] in rats.

CONCLUSIONS:

1) This DER has been updated with a new Executive Summary and classification information.

2) LOEL and NOEL changed to LOAEL and NOAEL.

3) This study was originally classified as Unacceptable, Guideline pending receipt and evaluation of data containing the death date, gross necropsy findings, and microscopic findings for each animal. It was stated in an April 30, 1987 Memorandum (TXR 005899) that the Agency had individual animal data sufficient to conduct survival disparity analyses. Also, sufficient gross and microscopic pathology data were available for detailed pathological analysis with statistical comparisons (MRIDs 40009401, 0014365, and 00143555). Receipt of data that supported statistical analysis of survival and histopathological data supported upgrading this study to

Acceptable, Guideline. This classification is consistent with the RED (June 2008).

4) None of the other conclusions of the previous DER were altered.

DATA EVALUATION RECORD

TETRAMETHRIN (NEO-PYNAMIN)
OPPTS 870.4100b ('83-1b)
STUDY TYPE: CHRONIC TOXICITY - DOG
MRID 44083501

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard
2777 S. Crystal Drive
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 153-2007

Primary Reviewer:
H. Tim Borges, Ph.D., MT(ASCP), DABT — Signature: _____ Date: _____

Secondary Reviewers:
R.A. Young, Ph.D., D.A.B.T. — Signature: _____ Date: _____

Robert H. Ross, M.S., Group Leader — Signature: _____ Date: _____

Quality Assurance:
Lee Ann Wilson, M.A. — Signature: _____ Date: _____

Disclaimer

This review may have been altered subsequent to the contractor=s signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** March 4 2009
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/4/09

DATA EVALUATION RECORD

TXR#: 0054713

STUDY TYPE: Chronic toxicity - dog (feeding)
OPPTS 870.4100b [§83-1b]; OECD 452.

PC CODE: 069003 **DP BARCODE:** D229247

TEST MATERIAL (PURITY): Neo-Pynamin; (Purity = 96.4% a.i.)

SYNONYMS: Tetramethrin

CITATION: Walker, M.D. (1996) 52-Week toxicity study in dogs with neo-pynamin. Corning Hazelton Inc. (CHV), 9200 Leesburg Pike, Vienna, VA 22182-1699. Laboratory report No. CHV 343-249. March 8, 1996. MRID 44083501. Unpublished.

SPONSOR: Sumitomo Chemical Co., Ltd. 1-98, 3-Chome Kasugade-Naka Konohana-ku, Osaka 554, Japan.

EXECUTIVE SUMMARY:

In a chronic toxicity study (MRID 44083501), Tetramethrin (Neo-pynamin, Lot Number 31006 G, 96.4% a.i.) was administered to four purebred beagle dogs/group/sex/dose in the diet at concentrations of 0, 300, 1200, 5000, or 10,000 ppm for 52 weeks (equivalent to 0, 8.2, 36.1, 147.2, and 286.0 mg/kg bw/day for males and 0, 9.2, 35.5, 157.0 and 324.9 mg/kg bw/day for females). Endpoints included mortality and moribunditiy (twice daily), clinical observations (daily), food and test material consumption (weekly), body weight (on arrival, at randomization and weekly), ophthalmological examinations (prior to the start of the study and during Week 52), hematology, clinical chemistry, and urinalysis (Weeks 1, 13, 26, 39, and 52), and clinical pathology.

There were was one unscheduled death at 46 weeks (a 1200 ppm male). Clinical signs preceding death in this animal were changes in feces (yellow, mucoid, and/or soft). This death was not considered treatment-related. Clinical signs in the other animals surviving to terminal kill included discolored or reduced feces, mucoid feces, emesis, and salivation. There were no remarkable ophthalmological findings.

Interpretation of body weight and food consumption data are frustrated by large variations in body weights at the beginning of the study and variability in the food consumption

measurements. Also, palatability had been shown to be an issue in a previous study (CHV Study No. 343-248) at 10,000 ppm. No dose-dependent effects on body weight or body weight gain were observed in males. Body weight for 10,000 ppm females were lower throughout the study, and were significantly decreased (↓25%) compared to controls at Week 52. Body weight gain at Week 52 was also significantly decreased (↓47%) for females. Food consumption was steady over time for males and females. Food consumption for treated males was greater than for male controls, while food consumption for 10,000 ppm females was lower than controls and lower-dose groups. Water consumption was unaffected in both sexes.

There were effects on hematological parameters in males and females that were considered mild effects of treatment. For 10,000 ppm females, significant changes included decreased red blood cell (RBC) count at Week 13, decreased hemoglobin (HGB) at Week 26, and decreased hematocrit (HCT) at Week 13 and Week 26. No hematological effects were observed in male dogs.

Significant and treatment-related effects on clinical chemistry parameters were observed in males and females. Phospholipids were significantly elevated in males dogs at 1200, 5000, and 10,000 ppm, were sustained over Weeks 13, 26, 39, and 52, and were accompanied by increased total cholesterol over Weeks 26, 39, and 52. Phospholipids and total cholesterol were increased in females at Week 13 and Week 52 at 10,000 ppm. Sustained increases in alkaline phosphatase were observed in 10,000 ppm females at Weeks 13, 26, 39, and 52. At 5000 ppm, alkaline phosphatase was significant at Weeks 13, 39 and 52. Sustained decreases in albumin were observed in 10,000 ppm females at Weeks 13, 26, 39, and 52. It was stated that these decreases in albumin in females could be due to malnutrition. There were no treatment-related effects on urinalysis for either sex.

Significant and treatment-related effects on absolute and relative organ weights were observed in males and females. For males, absolute kidney weights were significantly increased at 5000 ppm (44%) and 10,000 ppm (39%). Significant increases in kidney weights were also observed at these doses when expressed relative to body and brain weights at 5000 and 10,000 ppm, and were 33% and 51%, respectively at 10,000 ppm. No effects on kidney weights were observed in females. For both males and females, the absolute and relative (to body and brain weights) liver (with gallbladder) weights were significantly increased. For males, absolute liver/gallbladder weights were significantly increased at 1200 ppm (47%), 5000 ppm (40%) and 10,000 ppm (63%). These increases, expressed relative to body and brain weights, were increased at 1200 ppm (relative to brain only), 5000, and 10,000 ppm and were 54% and 80%, respectively, at 10,000 ppm. For females, absolute liver/gallbladder weights were significantly increased at 5000 ppm (38%). At 10,000 ppm, an absolute increase in liver/gallbladder weight of 24% was observed, but was not significant. However, when expressed relative to body weight or brain weight, significant increases were observed at 5,000 and 10,000 ppm and were 70% and 31%, respectively, at 10,000 ppm.

Microscopic effects observed in the kidneys included minimal to slight chronic inflammatory lesions. These lesions were observed in all groups but were more prevalent in 10,000 ppm males. These were characterized as focal areas of regenerative tubular cells, occasionally accompanied by chronic inflammatory cells and/or fibrosis. The lesions were present mostly within the cortex but according to the report extended into the medulla in severe cases. Foci of

chronic, interstitial inflammation were also observed in all exposure groups, but these were considered to be healed remnants of polynephritis, and so were not related to test chemical exposure. None of these microscopic effects explanation the increased kidney weights found in male dogs.

A slight dose-related increase in hepatocellular vacuolization suggestive of increased glycogen content was observed in male dogs treated with 5000 and 10,000 ppm and female dogs treated with 10,000 ppm test material. Increased glycogen content was not confirmed with special stains. The results, however, correlate with the increased liver weight found in these treatment groups along with the increased serum cholesterol and phospholipids.

The LOAEL is 36.1/35.5 mg/kg bw/day in males/females (1200 ppm) based on increased absolute and relative (to brain weight) liver/gallbladder weights in males and increased cholesterol and phospholipids in males. The NOAEL is 8.2/9.2 mg/kg/day in males/females (300 ppm).

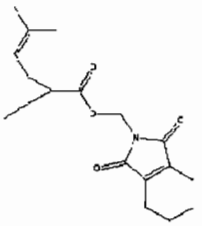
This chronic study in the dog is **Unacceptable, Guideline** and does not satisfy the guideline requirement for a chronic oral study [OPPTS 870.4100, OECD 452] in dogs based on the large variation in pre-study treatment group body weight and the lack of suitable statistical analysis. This study is upgradable to acceptable, guideline pending submission and favorable review of an appropriate statistical analysis and satisfactory demonstration that the variability in pre-study body weights does not unduly hinder study interpretation.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Neo-pynamin

Description:	Yellowish to white granulated solid
Lot/batch #:	31006 G
Purity:	96.4% a.i.
Compound stability:	Duration of study
CAS # of TGAI:	7696-12-0
Structure:	

2. Vehicle and/or positive control: Diet

3. Test animals:

Species:	Dog	
Strain:	Beagle	
Age/weight at study initiation:	Four-five months / Males 5.1-9.2 kg; Females 4.3-7.0 kg	
Source:	HRP, Inc., Cumberland, VA	
Housing:	Individually in elevated stainless-steel cages	
Diet:	PMI® Certified Canine Diet® 5007, *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	16.4-26.7°C (calculated by reviewers)
	Humidity:	19.1-66.1%
	Air changes:	~14.1/hr
	Photoperiod:	12 hours light/dark
Acclimation period:	~ Two weeks	

B. STUDY DESIGN:

1. In life dates: Start – September 23, 1994; End – September 26, 1995

2. Animal assignment: Animals were stratified by weight and assigned to the groups in Table 1 using computer generated random numbers.

TABLE 1: Study design

Test group	Conc. in diet (ppm)	Dose to animal (mg/kg bw/day)	Main study 52 months	
			Male	Female
Control	0	0 ♂/0 ♀	4	4
Low (LDT)	300	8.2 ♂/9.2 ♀	4	4
Mid (MLDT)	1200	36.1 ♂/35.5 ♀	4	4
Mid-High (MHDT)	5000	147.2 ♂/157.0 ♀	4	4
High (HDT)	10,000	286.0 ♂/324.9 ♀	4	4

3. **Dose selection rationale:** The doses were selected based on the results of a previous study (CHV Study No. 343-248) where poor diet palatability resulted in a significant decrease in food consumption at 30,000 ppm test material. In addition, histological changes of centrilobular to midzonal hepatocellular hypertrophy and/or eosinophilic cytoplasmic inclusions were observed at 10,000 and 30,000 ppm.

4. **Diet preparation and analysis:** Diets were prepared weekly and stored at room temperature. The basal and control diet was PMI® Feeds, Inc., Certified Canine Diet® Meal #5007. Before diet preparation, the test material was reduced to a powder in a Waring blender and further reduced by passing through a No. 40 sieve. The required amount of test material for each diet concentration was weighed and mixed in a Waring blender with ~ 200 g of diet to prepare a premix. The premix was added to the required amount of diet for each concentration and mixed at a rate of 1 minute/kg in a Patterson-Kelly twin-shell blender. Diet homogeneity was determined before the start of the study from samples collected from the top, middle, and bottom of prepared 300 ppm and 10,000 ppm diets. Diet stability was tested in a 300 ppm diet after eight days storage at room temperature. Dietary concentration analyses were done on samples collected from the middle of prepared 300, 1200, 5000, and 10,000 ppm diets during weeks 1-4 and during weeks 13, 26, 39, and 52. The stability, homogeneity, and concentration analyses were done by FID/GLC.

Results:

Homogeneity analysis: The relative standard deviations of test material concentration in samples taken from the top, middle, and bottom were 2.51% and 0.82% in the 300 ppm and 1000 ppm diets, respectively. The data indicates that the test material was homogenously distributed.

Stability analysis: The test material concentration of the 300 ppm diet was ~95% of target after storage for eight days at room temperature.

Concentration analysis: Test material concentration as percent of target ranged from 93.7-124% in the 300 ppm diet, 95.2-111% in the 1200 ppm diet, 95.5-105% in the 5000 ppm diet, and 95.7%-106% in the 10,000 ppm diet. The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. **Statistics:** Levene's test for homogeneity of variance was used for all statistically analyzed data. If homogenous, the data were analyzed by ANOVA followed by Dunnett's test to determine differences from control. If heterogeneous, the data underwent rank transformation and if normality reached, analyzed by ANOVA followed by Dunnett's test. If rank transformation was not acceptable, the data were analyzed by Dunnett's test. The statistical methods used were acceptable for homogenous data; however, the analyses used for heterogeneous data are unacceptable. A suitable statistical method for heterogeneous data such as Wilcoxon Rank-Sum or Kruskal-Wallis should have been used had transformations failed.

C. METHODS:

1. **Observations:** Animals were inspected twice daily for mortality and moribundity and once daily for evidence of toxic or pharmacologic effect.

2. **Body weight:** Animals were weighed on arrival, at randomization, and weekly during the study.

3. **Food consumption and compound intake:** Food consumption for each animal was determined at a weekly basis. Food efficiency was not determined. Compound intake (mg/kg bw/day) values were calculated as time-weighted averages from the consumption and body weight gain data.

4. **Ophthalmoscopic examination:** Eyes were examined prior to the start of the study and during week 52. The examination was done using indirect opthalmoscopy with 1% Mydriacy® as the mydriatic agent.

5. **Hematology and clinical chemistry:** Blood was collected from the jugular vein during weeks -1, 13, 26, 39, and 52 with sodium citrate as the anticoagulant for coagulation studies, and EDTA for hematology studies. No anticoagulant was used for clinical chemistry studies. The dogs were fasted overnight before sample collection. Serum samples for estradiol analyses were collected from all females at monthly intervals. The samples were stored at —70°C, but the analyses were not done since histological examination of the female reproductive tract was unremarkable. The CHECKED (X) parameters were examined.

a. Hematology:

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*		Reticulocyte count
	Blood clotting measurements*	X	Red blood cell morphology
X	(Activated partial thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

* Recommended for chronic studies based on Guideline 870.4100.

b. Clinical chemistry:

X	ELECTROLYTES	X	OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphorus*	X	Total Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
X	**ENZYMES** (more than 2 hepatic enzymes eg., *)	X	Total bilirubin*
X	Alkaline phosphatase (ALK)*	X	Total protein (TP)*
	Cholinesterase (ChE)	X	Triglycerides
X	Creatine phosphokinase (CK)		Serum protein electrophoresis
X	Aspartate aminotransferase (AST/SGOT)*	X	Phospholipids
X	Alanine aminotransferase (ALT/ SGPT)*	X	A/G Ratio
	Gamma glutamyl transferase (GGT)*	X	Estradiol
	Glutamate dehydrogenase		
	Sorbitol dehydrogenase*		

* Recommended for chronic studies based on Guideline 870.4100.

6. **Urinalysis:** Urine was collected from overnight in clean containers placed under the drainage opening of each cage. The CHECKED (X) parameters were examined.

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

* Recommended for chronic studies based on Guideline 870.4100.

7. **Sacrifice and pathology:** All animals that died and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. All tissues and organs were examined. The (XX) organs, in addition, were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
	Tongue	X	Aorta, thoracic*	XX	Brain (multiple sections)*+
X	Salivary glands*	X	Heart*+	X	Periph.nerve*
	Esophagus*		Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	XX	Pituitary*
X	Duodenum*	X	Spleen*+	X	Eyes (retina, optic nerve)*
X	Jejunum*	X	Thymus	X	GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*	X	UROGENITAL		Lacrimal gland
X	Colon*	XX	Kidneys*+	XX	Parathyroids*
X	Rectum*	X	Urinary bladder*	XX	Thyroid*
XX	Liver*+	XX	Testes*+	X	OTHER
XX	Gall bladder*	XX	Epididymides*+	X	Bone (sternum)
X	Pancreas*		Prostate*	X	Skeletal muscle
X	RESPIRATORY	XX	Ovaries*+	X	Skin*
X	Trachea*	XX	Uterus*+	X	All gross lesions and masses*
X	Lung*++	X	Mammary gland (females only)*		
	Nose*				
	Pharynx*				
	Larynx*				

* Required for chronic studies based on Guideline 870.4100.
+Organ weight required in chronic studies.
++Organ weight required if inhalation route.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** Sporadic clinical observations noted during the study included discolored feces, emesis, few or no feces, mucoid feces, and salivation.

2. **Mortality:** One male dog in the 1200 ppm group was found dead during week 46. No clinical signs suggestive of toxicity were noted prior to the animal's death. All other animals survived until scheduled termination.

3. **Neurological evaluations:** Neurological studies were not done.

B. BODY WEIGHT AND WEIGHT GAIN:

Because of the large variation in individual animal body weight within and between treatment groups and the low sample size within groups (see study report), interpretation of body weight and body weight gain is impossible (Table 2). The average body weight gain of high-dose male and female dogs was consistently lower throughout the study, suggesting a palatability issue. No other definitive conclusions can be made.

TABLE 2: Mean body weight (kg) and body weight gain (kg)[a]					
	0 ppm	300 ppm	1200 ppm	5000 ppm	10,000 ppm
MALES					
Initial BW	6.7 ± 1.2	7.9 ± 0.19	8.1 ± 0.92	7.6 ± 0.99	8.2 ± 1.04
Final BW	10.5 ± 1.07	12.0 ± 1.06	14.0* ± 1.86	10.8 ± 1.17	10.8 ± 1.64
BWG Wk 1-3 (%C)	0.7	0.7 (0)[b]	0.4 (-43)	0.5 (-29)	0.1 (-86)
BWG Wk 1-13 (%C)	2.6	3.4 (31)	3.1 (19)	2.7 (4)	2.0 (-33)
BWG Wk 13-26 (% C)	0.9	0.8 (-11)	1.4 (56)	0.5 (-44)	0.8 (-11)
BWG Wk 26-53 (% C)	0.3	-0.1	1.4 (466)	0.0	-0.2
Overall BWG Wk -1-53 (%C)	3.8 ± 0.62	4.1 ± 1.21 (10)	5.6+ ± 1.10 (47)	3.2 ± 0.61 (-16)	2.6 ± 0.96 (-32)
FEMALES					
Initial BW	5.6 ± 0.97	5.8 ± 0.83	6.2 ± 0.33	5.8 ± 0.69	4.9 ± 0.42
Final BW	8.7 ± 1.47	8.2 ± 0.71	9.4 ± 1.25	8.9 ± 0.62	6.5* ± 0.71
BWG Wk 1-3 (%C)	0.7	0.2 (-71)	0.4 (57)	0.4 (-43)	0.1 (-86)
BWG Wk 1-13 (%C)	2.1	1.6 (-24)	2.2 (5)	2.0 (-5)	1.0 (-52)
BWG Wk 13-26 (% C)	0.7	0.7 (0)	0.6 (-14)	0.9 (29)	0.6 (-14)
BWG Wk 26-53 (% C)	0.3	0.1	0.4 (133)	0.2 (67)	0.0
Overall BWG Wk -1-53 (%C)	3.0 ± 0.50	2.5 ± 0.69 (-17)	3.2 ± 1.28 (7)	3.0 ± 0.38 (0)	1.6+ ± 0.38 (-47)

% C = Percent of control
[a] Data from pages 60-66 of study report.
[b] Data in parenthesis are percent difference from control
* $p \leq 0.05$.
+ $p \leq 0.05$ calculated by reviewer.

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption:** Total food consumption for the study is shown in Table 3. Because of the large variability in food consumption data, the manner in which the data were presented, and the exclusion of some data without an explanation, interpretation of the results is problematic. However, the decreased food consumption by high-dose female dogs is consistent with the decreased body weight and body weight gain.

TABLE 3: Total food consumption (g) of dogs treated with neo-pynamin for 52 weeks[a]					
	0 ppm	300 ppm	1200 ppm	5000 ppm	10,000 ppm
N	3	4	2	4	4
Males	97,243 ± 5327.4	112,479 ± 16,984.3	124,490 ± 17,302.4	108,964 ± 3240.2	108,036 ± 12,322.8
N	4	4	3	3	2
Females	88,526 ± 10,116.1	85, 407 ± 12,205.3	91,015* ± 4955.1	88,317 ± 4003.1	67,708 ± 9892.2

[a] Data from page 73 of study report.
* $p \leq 0.05$

2. **Compound consumption:** Time-weighted compound consumption is in Table 1.

3. **Food efficiency:** Food efficiency was not calculated.

D. OPHTHALMOSCOPIC EXAMINATION: No treatment-related effects were noted.

E. BLOOD ANALYSES:

1. **Hematology:** As shown in Table 4, the RBC, HGB, and HCT of high-dose female dogs were decreased (occasionally statistically) by Week 13 and Week 26. These effects were generally decreased through the remainder of the study, but were not as severe. The results are consistent with decreased food intake. No effects on red cell parameters were noted in male dogs. Other effects noted were increased platelet counts in mid-high and high-dose male and mid-high dose female dogs, and slightly prolonged APTT times for mid-high and high dose female dogs. These effects were considered random and may reflect a decrement in liver function due to slight hepatic congestion and/or performing laboratory test calibration problems as evidenced by the variation in results between Week 26 and 52 (see study report). The results are not of biological or toxicological importance.

TABLE 4. RBC, HGB, and HCT of female dogs fed neo-pynamin for 52 weeks.

Group (ppm)	Week				
	-1	13	26	39	52
Females – RBC (millions/µL)					
0	5.80 ± 0.203	6.72 ± 0.429	6.69 ± 0.511	5.76 ± 0.456	6.87 ± 0.562
300	5.76 ± 0.293	6.11 ± 0.361	6.02 ± 0.394	5.91 ± 0.250	6.39 ± 0.144
1200	5.88 ± 0.357	6.77 ± 0.795	6.94 ± 0.584	6.14 ± 0.292	7.34 ± 0.495
5000	5.84 ± 0.551	6.14 ± 0.329	6.27 ± 0.782	5.51 ± 0.733	6.81 ± 0.360
10,000	6.06 ± 0.501	5.82* ± 0.183	5.93 ± 0.303	5.81 ± 0.409	6.63 ± 0.487
Females – HGB (g/dL)					
0	13.0 ± 0.86	14.8 ± 0.44	15.4 ± 0.97	13.8 ± 1.11	16.3 ± 1.07
300	12.8 ± 0.75	14.0 ± 0.89	13.9 ± 0.86	14.3 ± 0.75	15.2 ± 0.31
1200	13.2 ± 0.74	15.4 ± 1.99	16.0 ± 1.57	14.6 ± 1.15	17.3 ± 0.88
5000	12.9 ± 0.88	14.2 ± 0.68	14.3 ± 1.37	13.1 ± 1.93	15.7 ± 0.85
10,000	13.1 ± 1.16	13.0 ± 0.47	13.1* ± 0.51	13.1 ± 0.88	15.1 ± 0.91
Females – HCT (%)					
0	37.9 ± 2.12	42.3 ± 1.23	43.9 ± 2.71	37.9 ± 2.88	45.6 ± 3.51
300	37.6 ± 2.28	40.2 ± 2.40	39.8 ± 2.19	39.5 ± 1.57	42.5 ± 1.16
1200	38.5 ± 1.90	44.1 ± 4.96	45.9 ± 4.14	40.5 ± 2.68	48.3 ± 2.44
5000	37.8 ± 2.19	40.3 ± 1.76	41.3 ± 4.07	36.3 ± 4.46	44.0 ± 1.77
10,000	38.3 ± 3.24	37.1* ± 1.29	37.5* ± 1.33	36.8 ± 2.27	42.3 ± 2.64

Data from Table 7, pages 87-89 of MRID 44083501
* $p \leq 0.05$

2. **Clinical chemistry:** The cholesterol and phospholipid concentrations of male dogs treated with ≥1200 ppm test material were statistically increased from week 13 through the remainder of the study (Table 5). These same parameters were increased in 5000 and 10,000 ppm female dogs, though not always statistically due to the low number of animals used. In addition, ALK activity was increased in male and female dogs receiving ≥5000 ppm from week 13 for females and week 26 for males. These results are consistent with extra- or intra-hepatic congestion. In addition, the albumin concentration of female dogs receiving 10,000 ppm test material was statistically decreased from week 13 through the remainder of the study. This result is consistent with malnutrition. Other statistically significant events were noted but were considered unrelated to treatment and not biologically or toxicologically significant.

TABLE 5. Selected clinical chemistry parameters of dogs fed neo-pynamin for 52 weeks.

Group (ppm)	Week				
	-1	13	26	39	52
Males – Cholesterol (mg/dL)					
0	158 ± 28.1	132 ± 17.4	125 ± 22.2	125 ± 16.1	120 ± 13.2
300	176 ± 27.8	157 ± 19.8	145 ± 10.6	137 ± 9.3	128 ± 13.2
1200	164 ± 8.8	186* ± 2.2	173* ± 16.0	188* ± 24.0	183* ± 17.8
5000	191 ± 31.5	195# ± 38.6	172* ± 27.4	184* ± 25.4	169* ± 26.6
10,000	174 ± 25.5	202# ± 33.5	188* ± 29.2	186* ± 23.2	170* ± 27.0
Males – Phospholipid (mg/dL)					
0	283 ± 26.0	295 ± 16.2	243 ± 21.9	248 ± 17.9	299 ± 19.6
300	299 ± 21.9	321 ± 24.1	265 ± 4.3	267 ± 6.4	314 ± 24.9
1200	289 ± 14.3	348* ± 7.3	286* ± 10.5	303* ± 17.2	402* ± 45.4
5000	316 ± 29.0	357* ± 34.9	287* ± 24.7	307* ± 23.0	388* ± 41.7
10,000	306 ± 25.7	375* ± 34.6	310* ± 26.4	329* ± 27.4	418* ± 62.8
Males - ALK (U/L)					
0	149 ± 20.4	91 ± 14.3	53 ± 10.5	49 ± 19.0	41 ± 11.3
300	155 ± 35.6	94 ± 20.5	66 ± 20.4	60 ± 26.0	61 ± 22.6
1200	129 ± 16.4	85 ± 13.3	68 ± 16.9	60 ± 15.4	59 ± 16.3
5000	158 ± 13.7	111 ± 19.1	92# ± 28.9	87# ± 29.6	95* ± 38.8
10,000	154 ± 36.9	121 ± 33.9	104* ± 32.8	102# ± 32.7	103* ± 28.3
Females – Cholesterol (mg/dL)					
0	149 ± 10.8	131 ± 22.2	131 ± 14.8	171 ± 27.3	122 ± 22.8
300	148 ± 20.7	128 ± 14.7	160 ± 28.0	126 ± 17.3	138 ± 26.2
1200	133 ± 27.1	136 ± 15.6	136 ± 31.7	164 ± 42.3	141 ± 27.7
5000	162 ± 21.3	173 ± 19.1	184# ± 21.5	197 ± 48.9	167 ± 24.3
10,000	150 ± 32.4	193* ± 59.0	182# ± 49.1	201 ± 51.3	193* ± 47.8
Females – Phospholipid (mg/dL)					
0	278 ± 8.4	292 ± 31.2	254 ± 20.2	295 ± 15.6	302 ± 48.4
300	275 ± 17.2	295 ± 19.8	275 ± 18.5	255 ± 16.4	333 ± 56.8
1200	260 ± 34.2	298 ± 20.4	250 ± 34.8	284 ± 38.8	336 ± 53.9
5000	295 ± 18.3	354* ± 18.5	300* ± 17.5	314 ± 31.9	396# ± 39.7
10,000	278 ± 33.1	366* ± 42.4	295# ± 23.7	325 ± 26.6	450* ± 79.5
Females – ALK (U/L)					
0	141 ± 11.5	78 ± 3.3	52 ± 8.4	42 ± 5.1	48 ± 5.5
300	137 ± 26.1	79 ± 18.6	54 ± 14.6	49 ± 10.1	47 ± 9.0
1200	140 ± 6.5	86 ± 3.3	69 ± 12.5	59 ± 11.6	54 ± 32.8
5000	152 ± 9.3	110* ± 26.1	92# ± 37.4	93* ± 41.3	114*33.7
10,000	154 ± 18.9	151* ± 28.9	123* ± 21.1	111* ± 23.4	128* ± 17.3
Females – Albumin (g/dL)					
0	3.7 ± 0.10	3.6 ± 0.22	3.8 ± 0.29	3.5 ± 0.21	3.6 ± 0.15
300	3.8 ± 0.17	3.6 ± 0.17	3.8 ± 0.13	3.6 ± 0.17	3.7 ± 0.16
1200	3.5 ± 0.17	3.6 ± 0.22	3.8 ± 0.18	3.5 ± 0.08	3.8 ± 0.17
5000	3.8 ± 0.17	3.4 ± 0.13	3.6 ± 0.20	3.4 ± 0.15	3.5 ± 0.17
10,000	3.7 ± 0.10	3.0* ± 0.10	3.2* ± 0.15	3.0* ± 0.16	3.1* ± 0.15

Data from Table 8, pages 110-129 of MRID 44083501

* $p \leq 0.05$ as calculated by study author

$p \leq 0.05$ as calculated by study reviewer using Kruskal Wallis or ANOVA following Bartlett's test for homogeneity

F. URINALYSIS:

No treatment-related effects were noted.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** Shown in Table 6 are selected organ weights of dogs treated with neo-pynamin for 52 weeks. The absolute and relative to body and brain kidney weights of male dogs treated with ≥5000 ppm test material were statistically increased 33-51% by the end of the treatment period. A similar effect in treated female dogs was not observed. The absolute and relative liver weights of both male and female dogs were increased with treatment. For males, the absolute liver weight of male dogs treated with ≥1200 ppm test material was statistically increased 40 – 63% above control while the liver weight relative to brain weight was increased in these animals 47 – 80% above control. For female dogs, the absolute and relative to body and/or brain weight of the liver was statistically increased 31 – 70% relative to control at diet concentrations ≥5000 ppm. Additionally, the absolute and relative to brain weight of the liver from female dogs treated with 1200 ppm test material was increased ~20% above control, although the results were not statistically significant.

   Although other statistically significant effects were found on organ weight, none were considered related to treatment.

TABLE 6. Selected absolute and relative organ weight of dogs fed diets containing neo-pynamin for 52 weeks

Dose (ppm)	Organ	Male			Female		
		Absolute Weight (g)	Relative to Body (%)	Organ to Brain Ratio	Absolute Weight (g)	Relative to Body (%)	Organ to Brain Ratio
0	Kidney	43.2 ± 4.2	0.42 ± 0.05	0.53 ± 0.05	41.6 ± 8.0	0.50 ± 0.04	0.56 ± 0.10
300		56.7 ± 2.9 (31)[a]	0.49 ± 0.06 (17)	0.71 ± 0.03 (34)	38.0 ± 4.1 (-9)	0.48 ± 0.07 (-4)	0.51 ± 0.04 (-9)
1200		57.2 ± 7.8 (32)	0.42 ± 0.01 (0)	0.73 ± 0.14 (38)	42.0 ± 6.1 (1)	0.46 ± 0.04 (-8)	0.57 ± 0.07 (2)
5000		62.1* ± 8.0 (44)	0.60* ± 0.11 (43)	0.80* ± 0.11 (51)	47.3 ± 4.4 (14)	0.56 ± 0.02 (12)	0.64 ± 0.07 (14)
10,000		59.9* ± 11.4 (39)	0.56# ± 0.10 (33)	0.80* ± 0.13 (51)	35.0 ± 2.8 (-16)	0.56 ± 0.02 (12)	0.49 ± 0.02 (-12)
0	Liver/Gall Bladder	246 ± 40	2.4 ± 0.2	3.0 ± 0.5	196 ± 0.40	2.3 ± 0.2	2.6 ± 0.05
300		287 ± 28 (16)	2.5 ± 0.1 (4)	3.6 ± 0.5 (20)	186 ± 21 (-5)	2.4 ± 0.2 (4)	2.5 ± 0.2 (-4)
1200		362* ± 28 (47)	2.7 ± 0.3 (13)	4.6* ± 0.5 (53)	234 ± 50 (19)	2.5 ± 0.3 (9)	3.2 ± 0.6 (23)
5000		344* ± 40 (40)	3.3* ± 0.3 (38)	4.4* ± 0.4 (47)	270* ± 22 (38)	3.2* ± 0.1 (39)	3.7* ± 0.4 (42)
10,000		401* ± 74 (63)	3.7* ± 0.5 (54)	5.4* ± 0.8 (80)	243 ± 34 (24)	3.9# ± 0.3 (70)	3.4# ± 0.5 (31)

Data from pages 147-155 of MRID 44083501

[a] Results in parentheses are percent difference from control

* $p \leq 0.05$ as calculated by study author

$p \leq 0.05$ as calculated by study reviewer using ANOVA following Bartlett's test for homogeneity

2. **Gross pathology:** No treatment-related effects were noted at necropsy.

3. **Microscopic pathology:** Minimal to slight chronic renal inflammatory lesions were observed in all groups but were more prevalent in 10,000 ppm males. These were characterized as focal areas of regenerative tubular cells, occasionally accompanied by chronic inflammatory cells and/or fibrosis. The lesions were present mostly within the cortex but extended in severe cases down into the medulla. Chronic interstitial foci of inflammation were also present in some animals in the absence of tubular alterations or fibrosis. The lesions did not appear active and were seen to some extent in all exposure groups. Microcaliculi were present within the renal medulla of most dogs and were considered unrelated to treatment. Incidence and severity of microscopic renal lesions could not be reconstructed from the data provided.

   A slight but noticeable dose-related increase in hepatocellular vacuolization suggestive of increased glycogen content was observed in male dogs treated with 5000 and 10,000 ppm and female dogs treated with 10,000 ppm test material. Special stains for glycogen content were not used. These results correlated with the increased liver weight found in these treatment groups and the increased serum cholesterol and phospholipids. Incidence and severity of microscopic liver findings could not be reconstructed from the data provided.

   All other histologically observed lesions were considered sporadic and unrelated to treatment.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS= CONCLUSIONS:

Based on the results, the study author concluded that treatment of male and female dogs with neo-pynamin for 52 weeks increased the liver weight, increased hepatocellular vacuolization (presumed to represent glycogen), and induced a significant increase in total serum cholesterol and phospholipid. These effects were present in varying degrees in males and females treated with ≥1200 ppm test material. The study author considered these effects to be mild, but related to exposure and established a NOEL of 300 ppm for male and female dogs treated with neo-pynamin in the diet for 52 weeks.

B. REVIEWER COMMENTS:

In this study, male and female beagle dogs were fed diets containing 300, 1200, 5000, or 10,000 neo-pynamin for 52 weeks. Because of the large variation in the initial body weight of dogs utilized in the study, interpretations of body weight and body weight gain of the animals is impossible. As reported in the study, the body weight gain of high-dose female dogs was statistically decreased ~47% compared to control by study end. This is commensurate with the decreased food consumption of high-dose female dogs. The average body weight gain of high-dose male and female dogs was consistently lower throughout the study, strongly suggesting a palatability issue.

The RBC, HGB, and HCT concentrations of high-dose female dogs were decreased (occasionally statistically) by Week 13 and Week 26. These values were generally decreased through the remainder of the study, but were not as severe. The results are consistent with

decreased food intake. No effects on red cell parameters were noted in male dogs. Based on historical data provided by the laboratory, the results were generally within established ranges and not considered of biological importance. The cholesterol and phospholipid concentrations of male dogs treated with ≥1200 ppm test material were statistically increased from week 13 through the remainder of the study. These same parameters were increased in 5000 and 10,000 ppm female dogs, though not always statistically. In addition, ALK activity was increased in male and female dogs receiving ≥5000 ppm from week 13 for females and week 26 for males. These results are consistent with extra- or intra-hepatic congestion. In addition, the albumin concentration of female dogs receiving 10,000 ppm test material was statistically decreased from week 13 through the remainder of the study; consistent with malnutrition. These results were generally within established historical ranges provided by the laboratory, but are considered toxicologically relevant. No treatment-related effects were noted for urinalysis or opthalmoscopic parameters.

The absolute and relative to body and brain kidney weights of male dogs treated with ≥5000 ppm test material were statistically increased 33-51% by the end of treatment. A similar effect in treated female dogs was not observed. The absolute and relative liver weights of both male and female dogs were increased with treatment. For males, the absolute liver weight of male dogs treated with ≥1200 ppm test material was statistically increased 40 – 63% relative to control while the liver weight relative to brain weight was increased in these animals 47 – 80%. For female dogs, the absolute and relative to body and/or brain weight of the liver was statistically increased 20 – 70% relative to control at diet concentrations ≥1200 ppm.

Microscopically, minimal to slight chronic renal inflammatory lesions were observed in all groups but were more prevalent in 10,000 ppm males. These were characterized as focal areas of regenerative tubular cells, occasionally accompanied by chronic inflammatory cells and/or fibrosis. The lesions were present mostly within the cortex but extended in severe cases down into the medulla. Chronic interstitial foci of inflammation were present in some animals in the absence of tubular alterations or fibrosis. According to the study report, the lesions did not appear active and were seen in to some extent in all exposure groups. Microcaliculi were present within the renal medulla of most dogs and were considered unrelated to treatment. An explanation should be provided why these were considered unrelated to treatment.

A slight dose-related increase in hepatocellular vacuolization suggestive of increased glycogen content was observed in male dogs treated with 5000 and 10,000 ppm and female dogs treated with 10,000 ppm test material; but special stains for glycogen (such as Congo Red or Periodic Acid-Schiff) were not used. Therefore, these results are considered presumptive and not confirmed. The results, however, correlate with the increased liver weight found in these treatment groups along with the increased serum cholesterol and phospholipids. No explanation was provided for the increased kidney weight found in male dogs.

Based on the lack of suitable statistical analyses, the large variation in pre-study treatment group body weights, the lack of studies to confirm presumptive microscopic correlates for the increased liver and kidney weights observed, and an inadequately described pathological report, this study is considered **Unacceptable/Guideline**. It can be upgraded with suitable analyses describing the microscopic effects relative to total and relative organ weights for the

kidney and liver weights of male and female dogs found in this study, and a suitable explanation for the clinical effects found.

Based on the data provided in the study report, a LOAEL or NOAEL can not be established.

C. STUDY DEFICIENCIES:

Statistical analyses were not adequate for the study or for proper interpretation.

Selection of body weight range prior to the study for male and female dogs was not adequate.

Microscopic data provided for the study were not suitable for second party (EPA) interpretation based on the pathological reports provided. Studies on observed microscopic evidence were not adequate. No suitable explanation for the increased kidney weights for male dogs was provided. There were only presumptive (but not confirmatory) correlates for the increased liver weight found in male and female dogs. Special stains for hepatic glycogen content and a properly written pathological report should have been provided.

The study report was poorly written and not conducive to second party (EPA) interpretation.

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** March 4, 2009
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/4/09

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0009836

STUDY TYPE: Chronic toxicity - dog –capsule; OPPTS 870.4100b [[§ 83-1b]; OECD 452.

PC CODE: 069003 **DP BARCODE:** D292301

TXR#:0054713

TEST MATERIAL (PURITY): Neo-pyanmin, technical (95.3% a.i.)

SYNONYMS: tetramethrin

CITATION: Dalgard, D.W. (1991). Chronic Toxicity Study in Dogs with Neo-Pynamin. Hazleton Washington, Inc., VA. Lab Report No. HWA 343-235 / IT-11-0242. December 19, 1991. MRID 42189301. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a chronic toxicity study (MRID 42189301), Neo-pynamin (95.3% a.i., Lot No. 90304) was administered to beagle dogs 4 sex/dose in capsules at dose levels of 0, 10, 30, 100, or 300 mg/kg/day for 1 year.

The following findings were attributed to estrus and pregnancy in females and so were not compound related. Gross necropsy findings at 100 mg/kg/day in females consisted of ovaries of unequal size and thickened uterine wall, increased absolute ovarian and uterine weight (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 the uterus. Also at 100 mg/kg/day, one female dog was found to be pregnant. At 300 mg/kg/day in females, there was also an increased histological incidence of stromal hypertrophy/edema of the vagina, and gross vaginal necropsy findings consisting of a thickened wall and increased relative (to body weight) ovarian (60%) and uterine (198%) weight.

At 300 mg/kg/day, there was a 22% decrease in body weight gain in males, which was not statistically significant and not considered biologically related.
There were no compound-related systemic effects.

The LOAEL was not established. The NOAEL is 300 mg/kg/day.

This chronic study in the dog is acceptable, guideline and satisfies the guideline requirement for a chronic oral study [OPPTS 870.4100, OECD 452] in dogs.

COMMENTS:

1) This DER has been updated with a new Executive Summary.

2) LOEL and NOEL were changed to LOAEL and NOAEL.

3) The original DER (TXR 0009836) classified this study as core minimum (old classification system) because estrus in 3 females and pregnancy in one female was not considered to change the conclusions of the study. The RED for tetramethrin (June 2008) classified this study as acceptable, non-guideline. This is due to an error in the RED. The correct classification, using the current system is Acceptable/guideline.

4) None of the other conclusions of the previous DER were altered.

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** March 4, 2009
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/4/09

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXRs: 0005533, 069003, 0003660, 0005899

STUDY TYPE: Carcinogenicity [feeding] - rat; OPPTS 870.4200a [§ 83-2a]; OECD 451.

PC CODE: 069003 **DP BARCODE:** D292301

TXR#: 0054713

TEST MATERIAL (PURITY): Neopynamin (90.0% a.i., Lot 72875; 93.6% a.i., Lot 90112).

SYNONYMS: Tetramethrin

CITATION: Pence, H., Serotam, D., Alsaker, R., et al. (1981). Chronic Toxicity Study in Rats: NeoPynamin Technical. Hazleton Laboratories, VA. Lab Report No. 343-117. June 11, 1981. MRID 41723302. Unpublished.

Cox, R. (1986). Chronic Toxicity Study in Rats, Neopynamin Technical: Addendum III to Final Report. Hazleton Laboratories, VA. Lab Report No. 343-117. January 14, 1986. MRID 40007501. Unpublished.

Vessolinovitch, S.D., Ito, N. (1982). Addendum to: Histologic Evaluation and Interpretation of Neo-Pynamin Bioassay Studies Carried Out on Sprague Dawley (1974 and 1981) and Long-Evans (1981) Rats by Hazleton Laboratories, Inc. for Sumitomo Chemical Company, Ltd. September 20, 1982. MRID 00114365. Unpublished.

Vessolinovitch, S.D., Ito, N. (1984). Addendum to: Histologic Evaluation and Interpretation of Neo-Pynamin Bioassay Studies Carried Out on Sprague Dawley (1974 and 1981) and Long-Evans (1981) Rats by Hazleton Laboratories, Inc. for Sumitomo Chemical Company, Ltd. August 24, 1984. MRID 00143555. Unpublished.

Pence, D. (1986). Chronic Toxicity Study in rats: Neopynamin Technical: Addendum to Final Report. Hazleton Laboratories, VA. Lab Report No. 343-117. 1986. MRID 00156488. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a carcinogenicity study (MRIDs 41723302, 40007501, 00114365, 00143555, 00156488), Neopynamin (90.0% a.i., Lot 72875; 93.6% a.i., Lot 90112) was administered to Charles River CD (CRCD) and Long-Evans rats 30/sex/dose in the diet at dose levels of 0, 200, 1000 or 5000 ppm (10, 50, or 250 mg/kg bw/day) for one week prior to breeding. After weaning, male pups were chronically fed 0, 200, 1000, or 5000 ppm (10, 50, or 250 mg/kg bw/day) Neopynamin for 104 weeks.

There were no treatment-related deaths. There were no compound-related changes in clinical signs, hematology, clinical chemistry, or urinalysis. There was a decrease in body weight for 5000 ppm animals compared to controls (↓13% for CRCD, ↓11% Long-Evans) at termination and were also evident in the first year of the study. Food consumption was initially decreased, but not sustained, for the high dose test groups.

There were increases in both absolute and relative liver weights for 5000 ppm animals (CRCD 12% and 27.2%, Long-Evans 18.4% and 33.5%, respectively). Euplastic nodules and hepatocellualr carcinomas were observed in the livers of CRCD and Long-Evans rats, but no dose-related effects of the test compound were observed.

In the testis at 5000 ppm, absolute and relative weights were increased 11% and 27.2%, respectively in Long-Evans rats. In CRCD rats, relative weights were increased 15.1%, but absolute weights were decreased 2%. Interstitial cell tumors in the testis were increased from 3/50 unilateral and 4/50 bilateral at 0 ppm to 5/50 unilateral and 11/50 bilateral at 5000 ppm in CRCD rats. In Long-Evans Rats, interstitial cell tumors were increased from 4/10 unilateral and 0/50 bilateral at 0 ppm to 10/50 unilateral and 12/50 bilateral at 5000 ppm. 10 other incidences of other neoplasms were also reported in the testis at 1000 and 5000 ppm. In CRCD rats, 1 seminoma, 1 mesothelioma, and 1 metastatic prostatic carcinoma were observed at 1000 ppm and 1 metastatic acinar carcinoma at 5000 ppm. In Long-Evans rats, 2 mesotheliomas and 2 metastatic neurofibrosarcoma was observed in controls, 1 mesothelioma was present at 1000 ppm, and 2 meotheliomas were present at 5000 ppm.

Relative, but not absolute brain weights were higher (16% CRCD, 10% Long-Evans), but may have been a secondary consequence of decreased body weight.

The LOAEL is 250 mg/kg/day (5000 ppm) in males based on decreased body weight, increased absolute and relative liver weights, and increased incidence of interstitial cell tumors in the testis. The NOAEL is 50 mg/kg/day (1000 ppm).

At the doses tested, there was a treatment related increase in interstitial cell tumor incidence when compared to controls. Dosing was considered adequate based on decreased body weight in the 5000 ppm dose groups in both strains of rats (e.g. a maximum tolerated dose/MTD was attained).

This carcinogenicity study in the rat is **Acceptable, Guideline** and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451].

COMMENTS:

1) This DER has been updated with a new Executive Summary and classification information.

2) LOEL and NOEL changed to LOAEL and NOAEL.

3) The original classification for this study was unacceptable, guideline because no females were included in the F1 generation and because pathological examination in some tissues was considered incomplete. This study was upgradable to acceptable, guideline because this study was designed primarily to investigate the effects of the test compound on the testes, which is not relevant to females. Also, gross and microscopic pathology data were provided for other organ systems detailed analysis of histopathology in both rat strains was provided (00143555). Together, this supported classification of this study as acceptable, guideline, which is consistent with the RED (June 1998).

4) None of the other conclusions of the previous DER were altered.

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** February 3, 2009
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/3/09

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0006950

STUDY TYPE: Combined chronic toxicity/carcinogenicity in the diet-; OPPTS 870.4300 [§ 83-5]; OECD 453.

PC CODE: 069003 **DP BARCODE:** D292301

TXR#: 0054713

TEST MATERIAL (PURITY): Neo-pynamin (93.3% a.i.)

SYNONYMS: Tetramethrin

CITATION: Cox, R.H., Dudeck, L.E., Alsaker, R.D., et al. (1986). Combined Chronic Toxicity and Oncogenicity Study. Hazleton Laboratories America, Inc., VA. Lab Report No. 343-136. April 17, 1986. MRID 00158951. Unpublished.

Cox, R. (1987). Combined chronic Toxicity and Oncogenicity Study in Mice: Neopynamin Technical: Amendment to Final Report (IT-71-0210). Hazleton Laboratories America, Inc., VA. Lab Report No. 343-136. May 29, 1987. MRID 40276301. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a combined chronic/carcinogenicity study (MRIDs 00158951, 40276301) neo-pynamin (93.3% a.i., Lot No. 00811) was administered to B6C3F1 mice 50/sex/dose (main group) in the diet at dose levels of 0, 12, 60, 300, or 1500 ppm (actual intake was 0, 2.27 ± 0.54, 11.90 ± 4.47, 57.82 ± 14.76, or 289.4 ± 73.3 in males and 0, 2.64 ± 0.64, 13.81 ± 3.47, 68.20 ± 15.87, or 391.1 ± 78.5 mg/kg bw/day in females) for 24 months. Two satellite groups (10/sex/dose) were similarly administered neo-pynamin for 12 months and 24 months for blood and tissue histopathology (Satellite 1) and 10/sex/group for 6 months and 18 months for blood (Satellite 2).

There were no significant, dose-related trends in survival. There were no effects of dosing on body weights, food consumption, or clinical laboratory findings. The absolute and relative thyroid and pituitary weights (at 105 week termination) were significantly decreased in males receiving 60, 300, and 1500 ppm neo-pynamin compared to controls. In females, absolute and

relative adrenal weights were significantly decreased at 1500 ppm at termination. However, there were no correlating histologic changes in the endocrine organs.

The LOAEL is 11.90 mg/kg bw/day (60 ppm), based on decreased absolute and relative thyroid and pituitary weight in male mice. The NOAEL is 2.27 mg/kg bw/day (12 ppm).

At the doses tested, there was no clear evidence of an oncogenic response. There was a significant increase ($p \leq 0.05$) in the incidence of hemangiosarcoma of the spleen in males at 300 ppm, however, when hemangiosarcomas at all sites were analyzed, this difference was not significant. Adenomas of the Harderian gland were significantly increased in males receiving 1500 ppm when compared to controls, but there was no dose-related trend. Dosing was considered adequate based on decreased absolute and relative thyroid and pituitary weights.

This chronic/carcinogenicity study in the rat is acceptable, guideline and satisfies the guideline requirement for a chronic/carcinogenicity study OPPTS 870.4300); OECD 453] in rats.

COMMENTS:

1) This DER has been updated with a new Executive Summary.

2) LOEL and NOEL have been changed to LOAEL and NOAEL.

3) Mean compound intake instead of estimated compound intake was used for the doses, and so the LOAEL and NOAEL are slightly higher than in the RED for tetramethrin (June 2008) (e.g. 11.90 mg/kg LOAEL vs. 9 mg/kg; 2.27 mg/kg NOAEL vs. 1.8 mg/kg).

3) None of the conclusions of the previous DER were altered.

EPA Reviewer: Jessica P. Ryman **Signature:**
Reregistration Branch 4, Health Effects Division (7509P) **Date:** 03/11/2009
EPA Secondary Reviewer: Marquea D. King **Signature:**
Reregistration Branch 4, Health Effects Division (7509P) **Date:** 3/11/09

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0054412

STUDY TYPE: Combined chronic toxicity/carcinogenicity-diet-mouse; OPPTS 870.4300 [§ 83-5]; OECD 453.

PC CODE: 069003 **DP BARCODE:** D229511

TXR#: 0054713

TEST MATERIAL (PURITY): Neo-Pynamin (93.5% a.i.)

SYNONYMS: Tetramethrin

CITATION: Moore, M.R. Dietary Oncogenicity Study in Mice with Neo-Pynamin. Hazleton Laboratories, Inc., VA. Lab Report No. 343-242-. January 6, 1995. MRID 44096001. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a combined chronic / carcinogenicity study (MRID 44096001) Neo-Pynamin (93.5% a.i., Lot No. 90304) was administered to Crl: CD-1 (ICR) BR mice 50/sex/dose in the diet at dose levels of 0, 150, 3000, 7000 ppm (equivalent to 0, 23/28, 484/566, or 1134/1326 mg/kg bw/day in males/females) for 78 weeks. The 7000 ppm dose was in excess of the 1000 mg/kg bw/day limit dose in both males and females.

There were no adverse, compound-related effects on survival, and there were no statistically significant differences in survival between any treatment groups. There were no clinical signs of toxicity. Weekly mean body weights were significantly lower for 7000 ppm females versus controls, and body weight gain over the duration of the study (Weeks 1-78) was 8% lower in 7000 ppm females than controls, but this difference was not statistically significant. There were no compound-related effects on food consumption.

There were no treatment-related effects on hematology or gross pathology. Dose-related increases in absolute and relative (to body and brain) liver weights were observed in the 3000 and 7000 ppm males and females. These increases were significant (compared to controls) at 7000 ppm. For absolute liver weights, the values were 2.58 ± 0.84 g at 7000 ppm vs. 1.81 ± 0.36 g in control males and 2.00 ± 0.22 g at 7000 ppm vs. 1.71 ± 0.39 g in control females. Also,

significant increases in the mean and absolute testes/epididymis were observed in males at 7000 ppm (0.45 ± 0.06 g vs. 0.39 ± 0.04 g in controls).

In the kidney, liver, glandular stomach, and small intestine, the incidence and severity of amyloidosis were generally increased in 7000 ppm animals compared to controls. Supporting this is the finding that amyloidosis as a cause of death for unscheduled-death animals was greater in 7000 ppm animals than controls (11/16 (69%) versus 6/13 (46%) for males and 11/16 (69%) versus 3/13 (23%) for females).

Histomorphological alteration in the liver at 7000 ppm was considered an effect of treatment Hepatocellular carcinoma was increased in 7000 ppm males compared to controls (9/60 or 15% versus 4/50 or 8%), although the biological significance is questionable because there was no information regarding relative times of onset. In females, the incidence of centrilobular hypertrophy increased with dose and was considered a treatment-related effect.

The LOAEL was not established. The NOAEL (M/F) is 1134/1326 mg/kg bw/day.

At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. There was trend ($p<0.02$) toward an increase in hepatocellular carcinomas in male mice at 7000 ppm, but no pairwise significant differences were observed. Dosing was considered adequate, as it exceeded the limit dose.

This chronic/carcinogenicity study in the mouse is acceptable, guideline and satisfies the guideline requirement for a chronic/ carcinogenicity study OPPTS 870.4300); OECD 453] in mice.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

COMMENTS:

1) This is a new DER.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: Neo-pynamin

Description: white/light-yellow granular powder

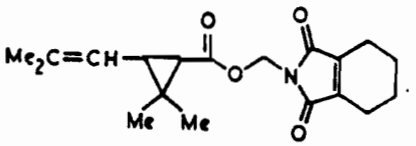
Lot/Batch #: # 90304

Purity: Purity: 95.3% a.i.

Compound Stability: not reported; on file with the sponsor

CAS # for TGAI: 7696-12-0

Structure::



2. Vehicle and/or positive control: The test material was administered in rodent chow (Purina® Certified Rodent Chow® #5002); no positive control was used in this study.

3. Test animals:

Species: Species: mouse

Strain: Strain: Crl:CD-1® (ICR)BR

Age/weight at study initiation: 44 days of age; males: 24.0 - 32.0 g; females: 19.0 - 26.0 g

Source: Charles River Laboratories, Inc., Raleigh, NC

Housing: Individually housed in stainless-steel, hanging, wire-mesh cages

Diet: Purina® Certified Rodent Chow® #5002 was available *ad libitum*

Water: Water: tap water was available *ad libitum*

Environmental conditions:

Temperature:	18.4-27.8°C (calculated by reviewers)
Humidity:	21.6-71.2%
Air changes:	10/hr
Photoperiod:	12 hrs dark/ 12 hrs light

Acclimation period: 15 days

B. STUDY DESIGN:

1. **In life dates:** Start: June 25, 1992; end: December 30, 1993

2. **Animal assignment/dose levels:** Animals were assigned randomly using a computerized body weight randomization program. Animals were assigned to groups so as to attain homogeneity of variance and means by Bartlett's test and One Way Analysis of Variance (ANOVA). The variation in weights did not exceed "2 standard deviations and the mean weights of each group of each sex did not differ statistically. The test groups are presented in Table 1.

TABLE 1: STUDY DESIGN

Test group	Conc. in diet (ppm)	Dose to animal (mg/kg/day) Male/Female	Main study 18 months		Interim sac. months	
			Male	Female	Male	Female
Control	0	0/0	50	50	NA	NA
Low (LDT)	150	23.3/28.5	50	50	NA	NA
Mid (MDT)	3000	483.8/566.5	50	50	NA	NA
High (HDT)	7000	1134.2/1326.2	50	50	NA	NA

3. **Dose selection:** Dose selection was based on a 13-week study (species not reported) (HWA Project No. 343-240). These results were not reported by the study author. In another study dated August 27, 1981, groups of 20 male and 20 female B6C3F$_1$ mice were fed 0, 500, 1500, or 5000 ppm of Neo-Pynamin for 13 weeks. Body weight gain was reduced by 9 and 7.5% for males and females, respectively, receiving the high dose. Relative liver weights were elevated by 21 and 14% in males and females. respectively, at the high dose and by 6% at the mid dose for males. Relative weights of the thyroid, adrenal glands, and ovaries were reduced at all three doses or at the mid and high doses; relative pituitary and spleen weights were reduced at the high dose. No gross lesions occurred, and microscopic observations were not made.

4. **Diet preparation and analysis:** The test diets were prepared once a week by first reducing the material to a fine powder in a Waring blender, mixing appropriate amounts of test material with 200 g of basal diet (Purina® Certified Rodent Chow® #5002) for about 2 minutes in a Waring blender. Basal diet was added to the premix to achieve the desired concentration, and this preparation was mixed in a Hobart mixer for 15 minutes. Purity was assumed to be 100% for test diet preparation. The test diet was stored at room temperature. Samples for homogeneity tests were taken from the top, middle, and bottom of prestudy mixes of 150- and 7000-ppm dietary preparations before study initiation, week 1, and week 3. Samples for stability analysis also were taken from 150- and 7000-ppm prestudy mixes and stored at room temperature for 8 and 11 days. Concentrations were verified on all diets prepared during weeks 1, 4, 8, 12, 24, 36, 48, 60, 72, and 78.

Results:

Homogeneity analysis: 150-ppm dietary preparation: Considerable variations occurred in measurements of test material at this concentration due to interference by the feed; duplicate samples showed as much variation as was observed among the top, middle, and bottom samples. Samples taken from week 1 and 3 preparation showed considerably less variation (<10%) at the three levels. 7000-ppm

dietary preparation: All samples taken from the three levels in the mixer were within 10% of each other.

Stability analysis: After storage for 8 or 11 days at room temperature the concentrations were within 8% of the concentration at day 0 for the 150- and 7000-ppm samples.

Concentration analysis: All samples were within 11% of the target concentrations. The analytical data showed that the mixing procedure was adequate, the test material was stable in the feed, and the concentrations were acceptable.

5. **Statistics:** Body weights, body weight gain, food consumption, hematology (except grading of cell morphology), fasted terminal body weights, and organ weight data: treatment groups were compared with controls using analysis of variance (ANOVA) and other methods shown by the flowchart in the appendix of this Data Evaluation Report (DER).

Survival data were analyzed using the National Cancer Institute Package. Incidences of liver tumors were analyzed by unadjusted and survival adjusted methods. The unadjusted method consisted of the Cochran-Armitage trend test and Fisher-Irwin exact test for pairwise comparison of treated groups with controls. The survival adjusted method used the logistic prevalence technique. Both methods use one-sided probabilities.

Statistical significance level: 5%, one-tailed for survival and incidence data and two-tailed for data analyzed by ANOVA.

C. METHODS:

1. Observations: Animals were inspected for signs of toxicity and mortality twice daily with about 6 hours separating each inspection.

1a. Cageside observations: Careful cage-side observations were conducted once daily for obvious toxic signs.

1b. Clinical examinations: Detailed physical examinations were performed weekly.

1c. Neurological evaluations: Neurological observations were not performed.

2. Body weight: Animals were weighed on day 1 of treatment, once weekly for the first 13 weeks and every four weeks thereafter up to week 74 and the first day of week 79.

3. Food consumption and compound intake: Food consumption for each animal was measured weekly for the first 13 weeks, every four weeks through week 73, and at week 78. Mean daily diet consumption was calculated as g food/animal/week. Food efficiency (body weight gain in kg/food consumption in kg per unit time H 100) was calculated by the reviewer, and mean compound intake (mg/kg/day) values were calculated from the consumption and body weight data.

4. Ophthalmoscopic examination: Eyes were not examined. Ophthalmoscopic examinations are not required based on Subdivision F Guidelines.

5. **Hematology and clinical chemistry:** Blood was collected from ten fasted animals of each sex per group during week 53 and from all surviving animals at study termination for evaluation of hematology parameters. The animals were anesthetized with CO_2/O_2 and bled from the orbital venous

sinus. The CHECKED (X) parameters were examined.

a. Hematology:

	Hematocrit (HCT)*		Leukocyte differential count*
	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)*
	Leukocyte count (WBC)*		Mean corpusc. HGB conc.(MCHC)*
	Erythrocyte count (RBC)*		Mean corpusc. volume (MCV)*
	Platelet count*		Reticulocyte count
	Blood clotting measurements*		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Recommended for combined chronic/carcinogenicity studies based on Guideline 870.4300.

b. Clinical chemistry: Clinical chemistry is not required for rodent oncogenicity studies based on Subdivision F Guidelines

6. Urinalysis: Urinalysis is not required for rodent oncogenicity studies based on Subdivision F Guidelines

7. Sacrifice and pathology: All animals that died, sacrificed *in extremis*, or sacrificed on schedule at termination were subjected to gross pathological examination. The animals were killed by exsanguination after anesthetizing with sodium pentobarbital. The CHECKED (X) tissues were collected for histological examination. All tissues collected from controls and high-dose animals, animals dying early, or sacrificed *in extremis* were examined microscopically. In addition, all gross lesions, lungs, livers and kidneys from low- and mid-dose groups were examined microscopically. The [XX] organs were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
x	Tongue	x	Aorta*	xx	Brain*+
x	Salivary glands*	x	Heart*	x	Periph. nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	x	Spleen*	x	Eyes (optic n.)*
x	Jejunum*	x	Thymus*		
x	Ileum*				GLANDULAR
x	Cecum*		UROGENITAL	x	Adrenal gland*
x	Colon*	xx	Kidneys*+		Lacrimal gland
x	Rectum*	x	Urinary bladder*	x	Mammary gland
xx	Liver*+	xx	Testes*+	x	Parathyroids*
xx	Gall bladder*	xx	Epididymides	x	Thyroids*
x	Pancreas*	x	Prostate		
		x	Seminal vesicle		OTHER
	RESPIRATORY	x	Ovaries*	x	Bone*
x	Trachea*	x	Uterus*	x	Skeletal muscle*
x	Bronchi	x	Cervix	x	Skin*
x	Lung*	x	Vagina	x	All gross lesions and masses*
	Nose				
	Pharynx				
	Larynx				

*Required for rodent oncogenicity studies based on Subdivision F Guidelines.
+Organ weight required in rodent oncogenicity studies.

II. RESULTS:

A. OBSERVATIONS:

1. Clinical signs of toxicity: The incidence of swollen ventral abdomen showed a marginally significant (p=0.1) increase in high-dose male (24%) and female mice (16%) compared with corresponding controls (12 and 6%, respectively). Other common clinical signs such as skin sores, rough hair coat, alopecia, and urine stain were observed at similar frequencies in all groups.

2. Mortality: There were no treatment-related effects on survival in either male or female mice administered the test material. At study termination, 39 (78%), 36 (72%), 37 (74%), and 34 (68%) males and 38 (76%), 38 (76%), 38 (76%), and 34 (69%) females in the control, 150, 3000, and 7000 ppm dose groups, respectively, were still alive.

3. Neurological evaluations: Not applicable.

B. BODY WEIGHT:

Selected mean body weights and body weight gain values are summarized in Table 2. Body weights in male mice fed 150 ppm of the test material were slightly greater (up to 107%) than the control values throughout the study; statistical significance was achieved at some weighing intervals between 9 and 66 weeks. Body weights of the other male groups receiving the test material were similar to control weights. In females receiving 7000 ppm, body weights were significantly lower (up to 6%) than the control values sporadically during the first 26 weeks, from weeks 38 to 54, and sporadically until study termination. Mean body weights of the other dose groups were similar to control weights. Male mice receiving 150 ppm gained more weight than controls during the first year (116%) and over the entire study period (122%, $p<0.05$). High-dose females gained less than controls during the first year (-15%; N.S. (not significant)) and over the entire study (-8%, N.S.). Neither body weight nor body weight gain showed clear dose-related changes in either sex.

Table 2. Selected mean body weights and weight gain in male and female mice fed Neo-Pynamin for 79 weeks

Week	Male				Female			
	Control	150 ppm	3000 ppm	7000 ppm	Control	150 ppm	3000 ppm	7000 ppm
Body weight (g)								
1	28.2	28.2	28.4	28.0	22.1	22.1	23.0*	21.8
4	30.9	32.0	31.5	31.1	25.1	24.9	25.7	24.2
8	33.7	34.7	34.0	33.8	27.6	27.7	27.9	27.3
13	35.1	36.1	35.0	35.1	29.4	29.3	29.4	29.2
26	37.6	39.2*	37.2	36.7	32.0	32.1	31.3	30.2*
50	39.1	40.8*	38.5	38.7	34.7	34.1	34.2	32.5*
62	38.4	40.0	38.2	38.0	35.2	34.7	34.5	33.1*
70	38.9	40.1	38.7	38.6	36.2	35.8	34.9	34.2*
79	37.9	39.9	38.1	38.3	34.8	35.0	36.1	33.7
Body weight gain (g)								
1-50[a]	10.9	12.6 (116)	10.1 (93)	10.7 (98)	12.6	12.0 (95)	11.2 (89)	10.7 (85)
1-78	9.6	11.7* (122)	9.8 (102)	10.2 (106)	12.7	12.9 (102)	13 (102)	11.7 (92)

Data taken from Table 4A and 4B, pages 74-77 and page 82, MRID 44096001.
[a]Calculated by the reviewer using mean body weights; numbers in parentheses are percent of controls weight gain calculated by the reviewer.
*$p<0.05$, treated group compared with control.

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption:** Food consumption data are summarized in Table 3. Food consumption was significantly increased (up to 113%; $p<0.05$ compared with controls) in male mice of all dose group at sporadic intervals during the study. Food consumption by high-dose female mice was significantly decreased (up to -7%; $p<0.05$ compared with controls) at sporadic intervals during the study. No clear dose-related trend was observed for either sex. Overall food consumption was similar for all groups of male and female mice.

Table 3. Mean weekly food consumption in male and female mice fed Neo-Pynamin for 79 weeks

Week	Male				Female			
	Control	150 ppm	3000 ppm	7000 ppm	Control	150 ppm	3000 ppm	7000 ppm
Weekly consumption (g)								
1	39.8	41.1	41.6*	39.3	37.0	37.5	38.4	36.3
8	41.2	43.2	43.7*	43.5*	42.9	41.1	41.6	40.3*
25	34.1	34.2	34.8	34.4	36.0	36.7	35.5	33.4*
49	41.6	43.5	42.2	42.7	45.0	45.4	43.6	42.0*
61	40.3	40.3	41.2	41.8	42.9	43.1	42.1	43.3
78	34.8	37.1*	36.1	37.0*	37.3	38.1	39.1	37.3
Total food consumption (g)								
1-78	1091.9	1115.6	1138.4	1121.1	1127.2	1112.0	1114.9	1098.1
Food efficiency[a]	0.879	1.049	0.861	0.910	1.127	1.160	1.166	1.065

Data taken from Table 5, pages 84-87, MRID 44096001.
[a]Calculated by the reviewer using total body weight gain and total food consumption data.

2. **Compound consumption (time-weighted average):** Mean daily consumption of test material over the duration of the study is presented in Table 1.

3. **Food efficiency:** Food efficiency values for male and female mice are presented in Table 3. Food efficiency in females receiving the high-dose was slight less than that of the controls. In male mice receiving the high-dose, food efficiency was slightly greater than of controls. No dose-related trend effect was observed for either sex; the slight differences between treatment groups and controls are not considered to be treatment related.

D. OPHTHALMOSCOPIC EXAMINATION: The eyes were not examined; ophthalmoscopic examinations were not required for rodent oncogenicity studies at the time this study was conducted.

E. BLOOD ANALYSES:

1. **Hematology:** No treatment-related hematologic effects were observed in male or female mice receiving Neo-Pynamin in the diet for 53 or 79 weeks.

2. **Clinical Chemistry:** Clinical chemistry tests were not conducted; these tests were not required for rodent oncogenicity studies at the time this study was conducted.

F. URINALYSIS: The urine was not examined; these tests were not required for rodent oncogenicity studies at the time this study was conducted.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** Mean absolute liver/gall bladder weights were significantly elevated ($p<0.05$) in male (143%) and female mice (117%) compared with corresponding controls. The liver-to-brain weight was increased in males (142%, $p<0.05$) and in females (114%, N.S.) and the liver-to-body weight also was significantly increased in both sexes (145% for males and 124% for females; $p<0.05$ compared with controls). Absolute liver weights showed dose-related increases in males at all doses and in females at the two highest doses. The mean absolute testes/epididymides weight as well as the testes-to-brain and testes-to-body weights were increased in males receiving the high dose (115, 117, and 118%, respectively). The study authors excluded the testes weight of one high-dose animal (No. A41168) from the analysis; the testes weighed 4.62 g, about 10 times greater than the testes weight in other animals of the same dose group. No gross or microscopic lesions were observed suggesting that the recorded weight may have been an error.

Table 4. Mean organ weights in male and female mice fed Neo-Pynamin for 79 weeks

Organ	Concentration (ppm)			
	0	150	3000	7000
Males				
Liver/gall bladder (g)	1.81	1.83	2.06	2.58*
Relative to brain wt. (%)	3.391	3.411	3.882	4.831*
Relative to body wt. (%)	5.290	4.939	6.145	7.651*
Testes/epididymides (g)	0.39	0.37	0.37	0.45*
Relative to brain wt. (%)	0.725	0.696	0.701	0.845*
Relative to body wt. (%)	1.133	1.007	1.130	1.332*
Females				
Liver/gall bladder (g)	1.71	1.62	1.86	2.00*
Relative to brain wt. (%)	3.125	2.809	3.333	3.564
Relative to body wt. (%)	5.410	5.214	5.871	6.711*

Data taken from Table 9, pages 143 and 144, MRID 44096001.
*$p<0.05$, treated group compared with control.

2. **Gross pathology:** The incidences of selected gross lesions are summarized in Table 5. The only gross lesions showing significantly increased incidences were granular, pitted, or rough kidney in females receiving 7000 ppm and enlarged mesenteric lymph nodes in females receiving 3000 or 7000 ppm. All the kidney lesions and most of the enlarged lymph nodes occurred in animals dying before study termination. Enlarged livers occurred at similar incidences in all groups of male mice, and the incidence of liver masses was slightly increased, but not significantly, in males receiving 3000 or 7000 ppm. Most of the enlarged livers occurred in mice that died before study termination; whereas liver masses occurred more often in animals surviving to study termination. In addition to the lesions listed in Table 5, ovarian cysts, uterine cysts, and thickened wall uteri occurred at high incidences in all dose groups including controls; the incidences were particularly high in females surviving to study termination. In male mice, alopecia occurred at high incidences in all groups, with the incidence being slightly higher in controls (22%) and low-dose animals (26%) than in mid-dose (16%) or high-dose animals (12%).

Table 5. Selected gross lesions in male and female mice fed Neo-Pynamin for 79 weeks – scheduled and unscheduled deaths

Organ/Lesion	Concentration (ppm)							
	0	150	3000	7000	0	150	3000	7000
	Males				Females			
Unscheduled Deaths								
No. animals/group	13	14	13	16	13	13	13	17
Liver,								
Enlarged	8[a]	3	35	9	3	3	3	5
Mass	1	1		0	1	0	0	0
Kidney, granular, pitted, rough	2	1	1	2*	0	1	0	5*
Mesenteric lymph node, enlarged	0	0	3	2	2	1	5	6
Unscheduled + Scheduled Deaths								
No. animals/group	50	50	50	50	50	50	50	50
Liver,								
Enlarged	8	5	3	9	3	4	3	5
Mass	8	5	12	11	2	0	0	1
Kidney, granular, pitted, rough	2	2	1	2*	0	1	0	5*
Mesenteric lymph node, enlarged	1	2	4	3*	2	2	8*	8*

Data taken from Table 8A (pages 100-113) and Table 8C (page 127-139), MRID 44096001.
[a]Number of animals having a lesion.
*$p<0.05$ treated group compared with controls using Fisher Exact Test or trend test using Cochran-Armitage Trend Test in the control column, calculated by the reviewer.

3. Microscopic pathology:

a. Non-neoplastic: Non-neoplastic – The incidences of selected nonneoplastic lesions are summarized in Table 6. Amyloidosis and centrilobular hypertrophy of the liver were the most prominent findings in mice fed Neo-Pynamin. In animals dying before study termination, the incidence of centrilobular hypertrophy was higher in 7000-ppm group males (25%) than in controls (8%); two females in the 7000-ppm group developed centrilobular hypertrophy, but none of the controls developed this lesion. Amyloidosis was seen in multiple organs including the liver, kidney, adrenal cortex, thyroid, heart, spleen, and glandular stomach. The incidence of amyloidosis in the liver of high-dose males dying before study termination was 69% compared with 62% in controls; the incidence was 59% ($p<0.05$) in high-dose females compared with only 8% in controls. Amyloidosis in the kidney occurred in 81% of the high-dose males compared with 69% of the controls and in 71% of the high-dose females compared with 46% of the controls.

Additionally, amyloidosis was the cause of death in 6/13 (46%), 7/14 (50%), 5/13 (38%), and 11/16 (69%) male mice in the control, low-, mid-, and high-dose groups, respectively; and in 3/13 (23%), 5/13 (38%), 3/13 (23%), and 11/16 (69%, $p<0.05$

compared with controls) female mice, respectively. The severity of amyloidosis in the kidney was slightly increased in treated animals of both sexes compared with the controls.

For the combined unscheduled and scheduled deaths, the incidences of centrilobular hypertrophy and amyloidosis were significantly ($p<0.05$) increased in high-dose females compared with controls. Centrilobular hypertrophy was observed in 18% of high-dose females compared with only 4% of the controls; amyloidosis of the liver occurred in 26% of high-dose females compared with only 4% of controls. There were no treatment-related effects on centrilobular hypertrophy or amyloidosis of the liver in male mice as the incidences were similar in control and treated groups and showed no dose-related increases. No treatment-related effects were noted for average severity of these lesions in either sex. The incidences of amyloidosis in the kidney were high for all treatment and control groups of both sexes. Amyloidosis occurred more often in the kidneys than in other organs and it appeared to develop first in the kidneys before it was seen in other organs. The average severity of amyloidosis in the kidney could not be calculated, because the study authors did not provide the data.

Table 6. Selected nonneoplastic histopathologic lesions in male and female mice fed Neo-Pynamin – unscheduled and scheduled deaths

Organ/Lesion	Concentration (ppm)							
	0	150	3000	7000	0	150	3000	7000
	Males				Females			
Unscheduled deaths								
No. animals/group	13	14	12	16	13	13	13	17
Liver								
Centrilobular hypertrophy	1	3	2	4	0	1	1	2
Amyloidosis	8(3.5)[a]	7(3.0)	3(3.0)	11(2.8)	1(2.0)	2(1.5)	3(2.0)	10*(2.1)
Kidney								
Amyloidosis	9(3.6)	8(3.8)	5(4.2)	13(4.0)	6(3.2)	5(4.2)	5(3.6)	12 (3.9)
Unscheduled + Scheduled Deaths								
No. animals/group	50	50	49	50	50	50	50	50
Liver								
Centrilobular hypertrophy	13(2.4)	10(2.3)	11(2.1)	13(2.5)	2*(2.0)	4(2.3)	4(1.3)	9* (2.3)
Amyloidosis	8(3.5)	9(3.3)	4(2.5)	12(2.8)	2*(2.0)	2(1.5)	6(1.7)	13*(2.1)
Kidney								
Amyloidosis	13	14	9[b]	16	15	11	12	16

Data taken from Tables 10A (pages 147-162), 10C (pages 181-198), MRID 44096001.
[a]Number of animals having a lesion; numbers in parentheses are the average severity grade; grades ranged from 1 to 5.
[b]This site was examined in 50 animals at this dose level.
*$p<0.05$ treated group compared with controls using Fisher Exact Test or trend test using Cochran-Armitage Trend Test in the control column, calculated by the reviewer.

b. Neoplastic: Neoplastic – The incidences of hepatocellular adenomas and carcinomas developing in mice fed Neo-Pynamin are summarized in Table 7. There were no statistically significant increases in the incidences of neoplastic lesions in male or female mice. However, a statistically significant ($p<0.05$) dose-related trend (Cochran-Armitage trend test) was noted for hepatocellular carcinomas in male mice and a marginally significant trend ($p=0.071$) for adenomas/carcinomas combined in female mice. The incidences of hepatocellular carcinomas (18%) in high-dose male mice and hepatocellular adenomas/carcinomas combined in female mice (4%) exceeded the range of historical controls (see Table 7).

Table 7. Neoplastic lesions in male and female mice fed Neo-Pynamin – unscheduled and scheduled deaths combined

Organ/Lesion	Concentration (ppm)							
	0	150	3000	7000	0	150	3000	7000
	Males				Females			
No. animals/group	50	50	49	50	50	50	50	50
Hepatocellular adenoma	6 (12%)	2 (4%)	5 (10%)	4 (8%)	0 (0%)	0 (0%)	2 (4%)	1 (2%)
Hepatocellular carcinoma	4 (8%)	3 (6%)	5 (10%)	9 (18%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Hepatocellular adenoma/carcinoma	10 (20%)	5 (10%)	10 (20%)	13 (26%)	0 (0%)	0 (0%)	2 (4%)	2 (4%)
Historical Control Data								
Hepatocellular adenoma	range = 4.3-16.2%; avg. = 10.3%				range = 0-2.0%; avg. = 0.6%			
Hepatocellular carcinoma	range = 1.7-10.6%; avg. = 4.8%				range = 0-2.0%; avg. = 0.4%			
Hepatocellular adenoma/carcinoma	range = 8.0-25.5%; avg. = 14.3%				range = 0-2.0%; avg. = 1.0%			

Data taken from Tables 10c (page 181), 11a (page 201), and pages 1301 and 1302, MRID 44096001.

III. DISCUSSION AND CONCLUSIONS:

A. DISCUSSION:

Groups of male and female mice were administered the test material, Neo-Pynamin, in the diet at concentrations of 0, 150, 3000, or 7000 ppm for up to 79 weeks. There were no treatment-related effects on the survival of either sex. Generally, body weights, body weight gain, and food consumption were similar in all groups of male mice, with one exception, the 150-ppm group males gained significantly more weight over the entire study than did the controls. This observation is not considered to be treatment-related. In females, body

weights were similar for the control, 150-, and 3000-ppm groups; however, at 7000 ppm, body weights were significantly less than controls at some time points between 9 and 66 weeks. Body weight gain in 7000-ppm group females was 15% lower during the first year of treatment, but was only 8% lower over the entire study. Although the decrease in body weights of 7000-ppm group females was statistically significant compared with controls and probably treatment related, the magnitude of the difference and the sporadic nature of the effects suggest that it is not biologically significant. Decreases in food consumption were more sporadic than the decreases in body weights. Food efficiency was similar for all groups.

There were no treatment-related effects on hematologic parameters evaluated in this study.

The liver appears to be the target organ in mice administered Neo-Pynamin in the diet. At 7000 ppm marginally significant ($p=0.1$) increases were noted in the incidence of swollen ventral abdomen in male and female mice; statistically significant increases in absolute liver weights in both sexes, significant increases in the incidence of centrilobular hypertrophy and amyloidosis in females were observed at the same dose. The swollen ventral abdomen could be associated with enlarged livers or liver masses. Increased liver weights in males were associated grossly with liver masses and microscopically with neoplasms (discussed below). Therefore, the increased liver weight in male rats is not considered to be a nonneoplastic effect. The increased liver weight in 7000-ppm females may be associated with histopathologic liver lesions (centrilobular hypertrophy, amyloidosis, and neoplasms). Centrilobular hypertrophy generally occurred in animals that had amyloidosis in the liver, suggesting a correlation between these two liver lesions. No other pathological effect was associated with centrilobular hypertrophy. The study authors consider centrilobular hypertrophy to be of minimal toxicologic significance. However, this lesion appears to be related to treatment with Neo-Pynamin in female mice. The incidence was significantly increased at the high-dose, and the dose-related trend was statistically significant. Enlarged livers were associated with moderate to severe amyloidosis in the liver particularly in male mice, but the incidences were not significantly increased in treated males. In addition, enlarged livers and amyloidosis occurred most often in animals that died before study termination than in those surviving to study termination.

Amyloidosis in the kidney occurred at a higher incidence in the high-dose male and female groups, the average severity was slightly higher than that of the controls, and amyloidosis also occurred more often in the kidney than in the liver or other organs. Amyloidosis in the kidney probably accounted for the increased incidence of granular, pitted, and rough kidneys; it may have accounted for the increase in mortality due to amyloidosis seen in both sexes at the high dose. The increase in the percentage of high-dose females dying from amyloidosis achieved statistical significance, but the increase in the percentage of high-dose males dying from amyloidosis did not achieve statistical significance. In cases where amyloidosis was the cause of death, the kidney lesions was graded as moderate to severe, more often severe.

Increased mean absolute and relative testes weights were observed in male mice fed 7000 ppm of the test material. The increased weight was not associated with increased incidences of gross or microscopic lesions in the testes. Therefore, the increased mean testes weight is considered to be a chance observation unrelated to treatment with the test material. The testes weight in one male was not included in the calculation of the mean weight. It appeared from the individual animal data that the recorded weight, which was about tenfold higher than that of other animals, may have been in error, because this pronounced increase in weight was not accompanied by either gross or microscopic findings.

The mesenteric lymph nodes were significantly enlarged in females fed 3000 and 7000 ppm of the test material. However, no single microscopic finding was associated with the enlarged nodes; therefore, they are not considered to be treatment related.

In conclusion, the lowest-observed-effect level (LOEL) is 7000 ppm (1326.2 mg/kg/day) based on liver toxicity in female mice (amyloidosis and centrilobular hypertrophy); no treatment-related toxicity was observed in male mice. The corresponding no-observed-effect level (NOEL) is 3000 ppm (566.5 mg/kg/day) for females and >7000 ppm for males.

The increased liver weights and liver masses seen upon gross examination were due to liver neoplasms. Five of the ten high-dose males chosen for organ weight measurements had hepatocellular neoplasms, whereas only three controls had neoplasms. Further, the hepatocellular neoplasms in high-dose males were generally larger than those seen in controls. The incidence of hepatocellular carcinomas showed a marginally significant ($p=0.071$) increase in male mice fed 7000 ppm of the test material, but the incidence of adenomas or adenomas/carcinomas combined were not significantly increased. The incidence of hepatocellular carcinomas at 7000 ppm (18%) also was outside the upper range of historical controls (10.6%). The higher incidence of hepatocellular carcinomas in 7000-ppm males compared with that of controls suggests that administration of the Neo-Pynamin may have accelerated the progression of adenomas to carcinomas, but had no effects on the overall incidence of hepatocellular neoplasms. No statistically significant increases in the incidences of neoplastic lesions were observed in female mice administered Neo-Pynamin. In females fed 3000 and 7000 ppm of the test material, the incidences of hepatocellular adenomas and carcinomas combined exceeded that of historical controls. However, the incidence was too low (4%) to attribute to administration of the test material. Therefore, this study showed no evidence of carcinogenic activity in male or female mice fed the test material for up to 79 weeks. Dosing was adequate for evaluating carcinogenicity as the limit dose (1000 mg/kg/day) was exceeded in both sexes.

C. STUDY DEFICIENCIES

There were no deficiencies in this study. The doses failed to establish a NOEL for male mice, but the limit dose (1000 mg/kg/day) was administered to both sexes.

EPA Reviewer: Jessica P. Ryman, Ph.D. **Signature:** Jessica P. Ryman, Ph.D.
Reregistration Branch 4, Health Effects Division (7509P) **Date:** December 10, 2008
EPA Secondary Reviewer: Abdallah Khasawinah, Ph.D. **Signature:** A. Khasawinah
Reregistration Branch 4, Health Effects Division (7509P) **Date:** Dec. 10, 2008

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0006386

TXR#: 0054713

STUDY TYPE: ***In vitro* Geneotoxicity (*E. coli* and Salmonella)-** OPPTS 870.5265 [§ 84-2]; OECD 471

PC CODE: 069003 **DP BARCODE:** D292301

TEST MATERIAL (PURITY): Tetramethrin (94% a.i.)

SYNONYMS: Neopynamin

CITATION: Kogiso, S., Yamada, F., Hara, M. *et al.* (1987). Reverse Mutation Test of Neopynamin in *Salmonella typhimurium* and *Escherichia coli*. Sunitomo Research Laboratory, Japan. December 25, 1986. Lab Report No. IL-70-0205. MRID 40276001. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In an *in vitro* geneotoxicity assay (MRID 40276001), *S. typhimurim* (strains TA100, TA98, TA 1535, TA 1537, and TA97) and *E. coli* (strain WP2uvrA) were exposed to tetramethrin (94.0%, Lot No. 60210) in a DMSO vehicle at concentrations of 100,200,500,1000, 2000, and 5000 µg per plate (precipitating concentrations) in the presence or absence of S9 activation. Appropriate positive controls in the absence/presence of S9 were as follows: TA100 (methyl methanesulfonate, 200 µg/plate / benzo(a)pyrene, 5 µg/plate), TA98 (2-nitrofluorene, 1 µg/plate / benzo(a)pyrene, 5 µg/plate), TA1535 (sodium azide, 0.5 µg/plate / 2-aminoanthracene, 2 µg/plate), TA1537 and TA97 (ICR-191, 1 µg/plate / benzo(a)pyrene, 5 µg/plate), and Wp2 uvrA (N-ethyl, N'-nitro-N-nitroso-guanidine, 2 µg/plate / 2-aminoanthracene, 80 µg/plate).

The number of revertant colonies in the presence or absence of S9 ranged from 8 to 133 for DMSO (vehicle control) and from 6 to 197 for all concentrations of tetramethrin in all bacterial systems. There were no doublings in the numbers of revertants/plate for the tetramethrin concentrations in comparison with solvent controls from any bacterial strain of S. typhimurium or *E. coli.*

There was no evidence of mutagenicity in the presence or absence of S9 activation in *S. typhimurium* or *E. coli* bacterial strains.

These studies are classified as **Acceptable/Guideline** and meet the guideline requirement for an ***In vitro*** **Geneotoxicity** study [OPPTS 870.5265 [§ 84-2]; OECD 471].

COMMENTS:

1) This DER has been updated with a new Executive Summary.

2) None of the other conclusions of the previous DER were altered.

EPA Reviewer: Jessica P. Ryman, Ph.D. **Signature:** Jessica P. Ryman, Ph.D.
Reregistration Branch 4, Health Effects Division (7509P) **Date:** December 10, 2008
EPA Secondary Reviewer: Abdallah Khasawinah, Ph.D. **Signature:** A. Khasawinah
Reregistration Branch 4, Health Effects Division (7509P) **Date:** Dec. 10, 2008

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0010277, 0054562

TXR#: 0054713

STUDY TYPE: ***In vitro* Mammalian Cytogenetics**-mammalian bone marrow chromosomal aberration OPPTS 870.5385; OECD 475

PC CODE: 069003 **DP BARCODE:** D292301

TEST MATERIAL (PURITY): Neo-pynamin, T.G. (95.3%)

SYNONYMS: Tetramethrin

CITATION: Murli, H. (1992). Mutagenicity Test on Neo-Pynamin Measuring Chromocomal Aberrations In Vivo in Mouse Bone Marrow Cells (1992). Hazleton, Washington (HWA), VA. Lab Reprot No. HWA-12 400-0-0451IP/IT-21-0254. May 29, 1992. MRID 42414403. Unpublished.

Murli, H. (1992). Bone Marrow Toxicity Study for In Vivo Murine Bone Marrow Cytogenetics Assay with Neo-Pynamin: Final Report. Hazleton, Washington (HWA), VA. Lab Report No. 12400-1-459IP. July 24, 1992. MRID 42414402. Unpublished.

Murli, H. (1992). Single Acute Exposure Dose Selection Study on Neo-Pynamin: Final Report. Hazleton, Washington (HWA), VA. Lab Report No.12400-0-59IP. July 24, 1992. MRID 42414401. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In a mammalian cell cytogenetics assay for chromosome aberration (MRID 42414403, 42414402, 42414401), adult ICR mice 5/sex/dose were exposed to neo-pynamin (95.3%, Lot No. 90304) by i.p. injection (10 ml/kg in a corn oil vehicle) at doses of 0, 500, 1000, or 2000 mg/kg for 6, 18, or 30 hours. An additional 10/sex were dosed at 2000 mg/kg in the event that any high-dose animals died on study. Positive controls (5/sex) were administered cyclophosphamide i.p. at 60 mg/kg and sacrificed at 18 hours. One and one half to 2.5 hours prior to sacrifice, all animals were injected with

2 mg/kg colchicine to arrest cell division in metaphase. Bone marrow cells were isolated at sacrifice, fixed on glass slides, and analyzed for chromosomal aberrations and mitotic index.

Clinical signs of hyperactivity, tremors, and diarrhea were observed in 1000 and 2000 mg/kg animals. There were two deaths (1/sex at 2000 mg/kg) that occurred after demonstration of severe clinical signs. Positive controls did induce the appropriate response. **There was no evidence of chromosomal aberration induced over background levels or changes in mitotic index for males or females at any dose.**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement *OPPTS 870.5375; OECD 473* for cytogenetic mutagenicity assay.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided.

COMMENTS:

1) This DER has been updated with a new Executive Summary and classification information.

2) This classification is consistent with the RED for tetramethrin (June 18, 2008). Upgrading to acceptable, guideline was granted in a March 8, 1994 Memo (TXR: 0054562).

2) None of the other conclusions of the previous DER were altered.

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** February 3, 2009
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/3/09

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0007306

STUDY TYPE: Other Genotoxicity: Unscheduled DNA Synthesis in Primary Rat Hepatocytes/Mammalian Cell Cultures; OPPTS 870.5550 (*in vitro)*[§ 84-2]; OECD 482 (*in vitro*)

TXR: 0054713

PC CODE: 069003 **DP BARCODE:** D292301

TEST MATERIAL (PURITY): Neopynamin (94.0% a.i.)

SYNONYMS: Tetramethrin

CITATION: Kogiso, S. In vitro Unscheduled DNA Synthesis (UDS) Assay of Neopynaim in Rat Hepatocytes. Takarazuka Research Center, Osaka, Japan. Lab Report No. 1280/IL-80-0213. June 30, 1988. MRID 40778401. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In an unscheduled DNA synthesis assay (MRID 40778401), primary rat hepatocyte cultures were exposed to neopynamin (94.0% a.i., Lot No. 60210) in dimethyl sulfoxide at concentrations of 0, 0.2, 1, 5, 25, 50, or 100 µg/mL for 20 h.

Prior to the unscheduled DNA synthesis assay, neopynamin was tested up to 100 µg/mL, which was both cytotoxic and precipitating (precipitation started at ≥30 µg/mL) . The positive control induced the appropriate response. **There was no evidence that unscheduled DNA synthesis, as determined by nuclear silver grain counts, was induced.**

This study is classified as acceptable, guideline and satisfies the guideline requirement for Test Guideline OPPTS 870.5550; OECD 482/486 for other genotoxic mutagenicity data.

COMMENTS:

1) This DER has been updated with a new Executive Summary and classification information.

2) None of the other conclusions of the previous DER were altered.

EPA Reviewer: Jessica P. Ryman **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** February 3, 2009
EPA Secondary Reviewer: Marquea D. King **Signature:**
Risk Assessment Branch 4, Health Effects Division (7509P) **Date:** 3/3/09

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0011167

STUDY TYPE: Acute Neurotoxicity - Rats OPPTS 870.6200a [§ 81-8]; OECD 424.

PC CODE: 069003 **DP BARCODE:** D292301

TXR#:0054713

TEST MATERIAL (PURITY): Tetramethrin, technical grade (95.1% a.i.)

SYNONYMS: Neo-pynamin

CITATION: Robinson, et. Al. An Acute Study of the Potential Effects of Orally Administered Neo-Pynamin on Behavior and Neuromorphology in Rats (1992). Bio-Research Laboratories, Quebec, Canada. December 1, 1992. Lab Report NO. 97137 (Sunitomo No. IL-21-0258). MRID 42601501. Unpublished.

Robinson, K., Benjamin, W., Noveroske, J.W. An Acute Study of the Potential Effects of Orally Administered Neo-Pynamin on Behavior and Neuromorphology in Rats-Supplemental Volume (1993). Bio-Research Laboratories, Quebec, Canada. December 3, 1993. Lab Report NO. 97137 (Sunitomo No. IT-21-0258). MRID 43152701. Unpublished.

Robinson, K., Benjamin, W., Noveroske, J.W. A Time of Peak Behavioral Effects Study on a Single Oral Administration of Neo-Pynamin in Rats (1992). Bio-Research Laboratories, Quebec, Canada. 1992. Lab Report NO. 97139. MRID 42601502. Unpublished.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

In an acute neurotoxicity study (MRIDs 42601501, 43152701, 42601502) groups of fasted 46-49 day old Sprague-Dawley rats (Crl: CD (SD) BR) 12 /sex/dose) were given a single oral dose (gavage) of tetramethrin (95.1% a.i., Lot No. 90304) in 0.5% aqueous carboxymethylcellulose at doses of 0, 500, 1000, or 2000 mg/kg bw and observed for 14 days. Neurobehavioral assessment (functional observational battery for both qualitative and quantitative measurements and motor activity) was performed in 12 animals/sex/group at 1.5 hours after dosing (day 0) and on days 7

and 14. Body weight was measure for each animal weekly and clinical signs were recorded daily. After 14 days, 6/sex/dose were euthanized and perfused for neuropathological examination. The remaining 6/sex/dose were killed by rapid decapitation, followed by free-hand dissection of brain structures (cerebellum, cerebral cortex with some striatum and all of the hippocampus, dorsolateral thalamus with the lateral genticulate nucleus, some striatum and some cerebral cortex, and remaining brain (midbrain, hindbrain) with a slight amount of cerebral cortex as described in MRID 43152701) immunohistochemical GFAP quantification and a complete necropsy with fixation and histopathological analysis of any abnormal tissues.

There were no treatment related effects on mortality, clinical signs, body weight, brain weight or gross and histologic pathology or neuropathology in males or females. FOB and motor activity testing revealed no treatment-related effects in males. In females, there were statistically significant increases at day 0 at both the 1000 and 2000 mg/kg dose in normal arousal and moderate movement of locomotor activity level. However, these findings were not observed at Day 7 and Day 14 and so were not considered to be indicative of neurotoxicity.
Based on the effects seen in this study, a LOAEL was not established. The NOAEL was 2000 mg/kg/day (single dose) in males and females.

This neurotoxicity study is classified as unacceptable, guideline and does not satisfy the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424). This study is upgradable to acceptable, guideline pending receipt and evaluation of positive control data.

COMMENTS:

1) This DER has been updated with a new Executive Summary and classification information.

2) LOEL and NOEL changed to LOAEL and NOAEL.

3) The classification information is consistent with the previous DER. The RED (June 2008) has no classification information for this study.

4) None of the other conclusions of the previous DER were altered.

EPA Reviewer: Jessica P. Ryman, Ph.D. **Signature:**
Reregistration Branch 4, Health Effects Division (7509P) **Date:** December 12, 2006
EPA Secondary Reviewer: Abdallah Khasawinah, Ph.D. **Signature:**
Reregistration Branch 4, Health Effects Division (7509P) **Date:** Dec. 12, 2006

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0010235

TXR#: 0054713

STUDY TYPE: Metabolism - rat; OPPTS 870.7485 [§ 85-1)]; OECD 417.

PC CODE: 069003 **BARCODE:** D292301

TEST MATERIAL (PURITY): 3,4,5,6-tetrahydropthalimidomethyl (1 RS, trans)-chrysanthemate, trans-tetramethrin (t-NPY) (98.1% a.i., >99% radiochemical purity)

SYNONYMS: t-tetramethrin, t-NPY

CITATION: Shiba, K. 1992. Metabolism of (1RS, trans)-Tetramethrin in rats. Environmental Health Science Laboratory, Sunitomo Chemical Co., Ltd., Osaka, Japan. Lab. Report No. 2556. August 5, 1992. MRID 42448901.

Shiba, K. 1992. Metabolism of (1RS, cis)-Tetramethrin in rats. Environmental Health Science Laboratory, Sunitomo Chemical Co., Ltd., Osaka, Japan. Lab. Report No. 2556. August 6, 1992. MRID 42448902.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

The metabolism of *trans-* and *cis-* tetramethrin were investigated in separate studies (MRIDs 42448901 and 42448902). In the present study (MRID 42448901), [^{14}C] *trans-* tetramethrin (specific activity 49.5 mCi/mmole, >99% radiochemical purity, Lot No. C-91-005A), labeled at two internal carbons on the aromatic ring was administered to Sprague-Dawley rats 5/sex/dose by gavage (in a corn oil vehicle) at dose levels of 2 or 250 mg/kg. Repeated dose animals (5/sex) were administered 2 mg/kg/day of unlabeled *trans-* tetramethrin (98.1% a.i., Lot T-9101) for 14 days followed by a single administration of 2 mg/kg/day [^{14}C] *trans-* tetramethrin on day 15. A control group was treated concurrently with corn oil only for 14 days (5/sex) and then 3/sex were given a singly oral dose of 2 mg/kg [^{14}C] *trans-* tetramethrin.

[^{14}C] *trans-* tetramethrin was rapidly and almost completely eliminated (95-101%) within 7 days of dosing. The excretion and radioactivity in the urine was 42-71% and was 29-58% in the feces. The highest radiolabeled residue levels were observed in blood cells. The total residues in all

tissues at day 7 post exposure accounted for <0.04% of the administered dose.

Thirty-four metabolites were detected in the feces. The major metabolite was identified as TPI-SA (1-sulfo, 1,2-cyclohexanedicarboximide). Twenty-two urinary metabolites were detected as mostly alcohol and dicarboxylic acid derivatives. The major metabolites were identified as 3-OH-HPI-1 (3-hydroxy-1,2,-cyclohexanedicarboximide).

The biotransformation reactions of t-tetramethrin were as follows:
(1) cleavage of the ester linkage, (2) cleavage of the imide linkage, (3) hydroxylation of the cyclohexene or cyclohexane ring, (4) oxidation of the methyl group of the isobutenyl moiety, (5) reduction at the 1,2-double bond of the tetrhydropthalimide moiety and (6) incorporation of the sulfonic acid group to the 1,2-double bond of the tetryhydropthalimide moiety.

This metabolism study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats.

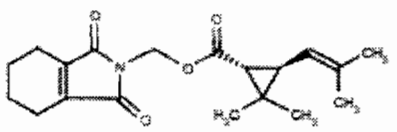
COMMENTS:

1) This DER has been updated with a new Executive Summary.

2) The companion study to this is MRID 42448902, which investigates the metabolism of cis-tetramethrin, which was also rapidly eliminated and had the same proposed biotransformation reactions. However, no *cis*-tetramethrin was observed in red blood cells.

3) None of the other conclusions of the previous DER were altered.

4) *trans*- tetramethrin Structure



EPA Reviewer: Jessica P. Ryman, PhD. **Signature:**
Reregistration Branch 4, Health Effects Division (7509P) **Date:** December 10, 2008
EPA Secondary Reviewer: Abdallah Khasawinah, Ph.D. **Signature:**
Reregistration Branch 4, Health Effects Division (7509P) **Date:** Dec. 10, 2008

Template version 02/06

DATA EVALUATION RECORD-SUPPLEMENT
Previous TXR: 0010235

TXR#: 0054713

STUDY TYPE: Metabolism - rat; OPPTS 870.7485 [§ 85-1)]; OECD 417.

PC CODE: 069003 **BARCODE:** D292301

TEST MATERIAL (PURITY): (1 RS, cis)-tetramethrin {3,4,5,6-tetrahydropthalimidomethyl (1RS, trans)- chrysanthemate}, (98.1% a.i., >99% radiochemical purity)

SYNONYMS: cis-tetramethrin; (c-NPY); c-neopynamin

CITATION: Shiba, K. 1992. Metabolism of (1RS, cis)-Tetramethrin in rats. Environmental Health Science Laboratory, Sunitomo Chemical Co., Ltd., Osaka, Japan. Lab. Report No. 2556. August 6, 1992. MRID 42448902.

Shiba, K. 1992. Metabolism of (1RS, trans)-Tetramethrin in rats. Environmental Health Science Laboratory, Sunitomo Chemical Co., Ltd., Osaka, Japan. Lab. Report No. 2556. August 5, 1992. MRID 42448901.

SPONSOR: Sumitomo Chemical Company, Limited, Osaka, Japan.

EXECUTIVE SUMMARY:

The metabolism of *trans-* and *cis*-tetramethrin were investigated in separate studies (MRIDs 42448901 and 42448902). In the present study (MRID 42448902), [^{14}C] *cis-* tetramethrin (specific activity 49.5 mCi/mmol, >99% radiochemical purity, Lot No. C-91-015A), labeled at the 1,2-double bond of the tetrahydropthalimide ring was administered to Sprague-Dawley rats 5/sex/dose by gavage (in a corn oil vehicle) at dose levels of 2 or 250 mg/kg. Repeated dose animals (2/sex) were administered 2 mg/kg/day of unlabeled cis-tetramethrin (98.8% a.i., Lot T-9102) for 14 days followed by a single administration of 2 mg/kg [^{14}C] *cis-* tetramethrin on day 15. A control group was treated concurrently with corn oil only for 14 days (2/sex) and then given a singly oral dose of 2 mg/kg [^{14}C] *cis-* tetramethrin.

[^{14}C] *cis-* tetramethrin was rapidly and almost completely eliminated (>96%) within 7 days of administration. [^{14}C]-labeled urinary excretion was higher in the females than in the males, whereas [^{14}C]-labeled fecal excretion was higher in males. Total residues in all tissues accounted for 0.5% of the administered dose.

Thirty-three metabolites were detected in the feces. The main metabolites were Unknown 34, TPA-SA, and Unknown 39. Twenty-three urinary metabolites were detected. The major metabolite was identified as 3-OH-HPI-1.

No dose-related differences in metabolic fate were observed among all groups. Fecal excretion of the parent compound was greater in the low- and high-dose groups (single oral dose groups) than in the repeated dose and control groups. No parent compound was detected in the urine. The biotransformation reactions of *cis*- tetramethrin were proposed by the sponsor as (1) cleavage of the ester linkage, (2), cleavage of the imide linkage, (3) hydroxylation of the cyclohexene or cyclohexane ring of the 3,4,5,6-tetrahydropthalimide moiety, (4) oxidation at the methyl group of the isobutenyl moiety, (5) reduction at the 1,2-double bond of the tetrahydropthalimide moiety and (6) incorporation of the sulfonic acid group tot the 1,2-double bound of the tetrhydropthalimide moiety.

This metabolism study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats.

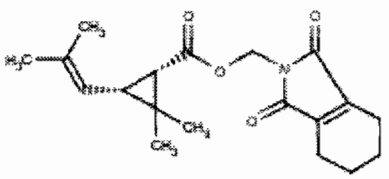
COMMENTS:

1) This DER has been updated with a new Executive Summary.

2) The companion study to this is MRID 42448901, which investigates the metabolism of *trans*-tetramethrin. which was also rapidly eliminated and had the same proposed biotransformation reactions. However, the largest fraction of *trans*-tetramethrin was observed in red blood cells.

3) None of the other conclusions of the previous DER were altered.

4) *cis*-Tetramethrin Structure:



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R168564

Chemical Name: Tetramethrin

PC Code: 069003
HED File Code:
Memo Date: 3/3/2009
File ID: 00000000
Accession #: 000-00-0130

HED Records Reference Center
3/31/2009