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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review of Tetramethrin

Caswell No. 844

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Budd 3/1/89

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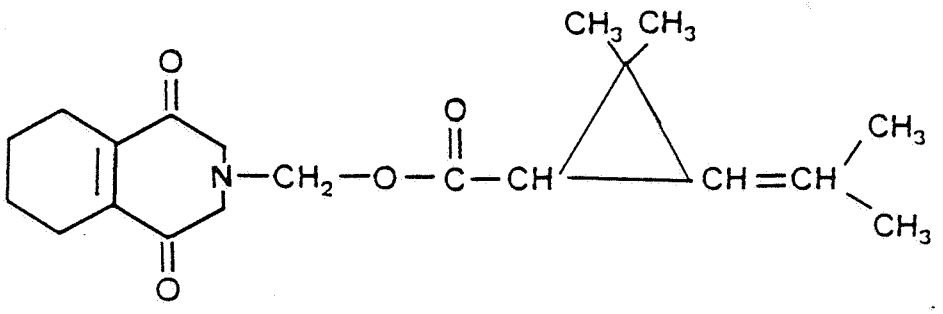
A. Background

Tetramethrin, also called Neo-Pynamin, is a synthetic pyrethroid insecticide. The chemical name is 3,4,5,6-tetrahydrophthalimidomethyl crysanthemate, or (U.S. usage) 1-cyclohexene-1,2-dicarboximidomethyl-2,2-dimethyl-3 (2-methylpropenyl)-cyclopropanecarboxylate.

The chemical has been developed by Sumitomo. It is registered for nonfood use for control of mosquitos, flies, and other flying insects. When used in combination with resmethrin or piperonyl butoxide, it is useful in control of household insects and garden pests.

Sumitomo is attempting to develop tetramethrin for agricultural crops.

The structure is shown below:



B. Evaluation of Oncogenicity Evidence of Tetramethrin

1. 1974 Sprague-Dawley Rat Study

a. Evaluation of Study

Two-year dietary administration in the rat - Neo-Pynamin; conducted by Hazleton Laboratories; Study No. 343-107, October 5, 1974; Accession No. 247280.

The test material, technical tetramethrin, was administered in the diet to randomized groups of 50 male and 50 female Charles River, CD1 Sprague-Dawley rats at levels of 1000, 3000, and 5000 ppm for 104 weeks postweaning.

These treated rats were obtained as F_{1A} weanlings from parental animals which had been dosed with compound at dietary levels of 0, 1000, 3000, and 6000 ppm until sexual maturity, prior to mating, during mating, and throughout the gestation and lactation periods.

The weanlings used were presumably exposed to the test material transplacentally throughout gestation and via maternal milk and the dry diet mixture during lactation.

Dietary exposure of the weanlings then continued throughout their 104-week lifespan. A control group of 60 male and 60 female Sprague-Dawley rats received only a basal laboratory diet. These weanling rats were obtained from concurrent control F_{1A} litters.

Criteria evaluated were physical appearance, behavior, growth, food consumption, survival, clinical pathology analysis, ophthalmological examinations, organ weights, tumor incidence, and gross and microscopic pathology. There was an interim sacrifice at 52 weeks of 10 rats per sex per group. A survival disparity occurred between the low dose male group and controls. However, there were no significant survival trends in either sex.

The overall survival of the rats is shown in the following table.

	Survival Rate at 104 Weeks	
Dose (ppm)	Males	Females
0	33/50	36/50
1000	17/40	26/40
3000	29/40	31/40
5000	22/40	23/40

The weanling rats in the experiment did not have equal body weights at the initiation of the study and consequently there were weight differences throughout the study. The following table illustrates these differences.

Males

Weeks	Control	Low	Mid	High
Start				
0	148	131[1/]	118	98
		89	80	66
26	594	573	530	492
		96	89	83
52	664	636	567	545
76	688	611	589	540
		89	86	78
100	627	571	557	530
		91	89	85

Females

Weeks	Control	Low	Mid	High
Start				
0	128	110[1/]	101	92
		86	79	72
26	332	317	284	262
		95	86	79
52	398	373	336	296
		94	84	74
76	442	392	366	317
		89	83	72
100	463	430	396	398
		93	86	71

1/Top line = weight in grams; lower line = percent of control weight.

Statistical analysis of growth for the first 52 weeks of the study revealed body weight gains which were significantly lower than control for male and female rats at the mid- and high-dose levels.

Statistical analysis of group mean body weights at terminal sacrifice also showed body weights which were significantly lower than control for males and females at the mid- and high-dose levels. Weight differences at the low level, although present, were not statistically significant for either sex.

Food consumption was reported to be lower for all treated groups in comparison to controls.

There were no compound-related effects in hematology, clinical chemistry, and urinalysis.

In the testes, there were higher frequencies of grossly observable lesions described as "enlarged firm" and "subscapular yellow material" for the mid- and high-dose male groups in comparison to controls.

The relative liver weight was significantly increased at all dose levels in comparison to controls for both sexes at 52 weeks and for mid- and high-dose males and high-dose females at 104 weeks.

The following table of relative liver weights shows these changes:

Relative Liver Weight

Males

	Control	Low	Mid	High
52 Weeks	2.65	3.09[1/]	3.57[1/]	3.86[1/]
		+17%[2/]	+35%	+46%
104 Weeks	2.99	3.31	3.76[1/]	4.16[1/]
		+11%	+26%	+39%

Females

	Control	Low	Mid	High
52 Weeks	2.51	2.77[1/]	3.18[1/]	3.32[1/]
		+10%	+27%	+32%
104 Weeks	3.08	3.33	3.20	4.06[1/]
		+8%	+4%	+32%

1/Statistically significant at the 0.05 level.
2/Percent increase in relative weight.

Statistical analysis of the incidence of interstitial cell adenomas in the testes showed increases at the mid- and high-dose levels. The

following table (memorandum of B. Fisher, October 20, 1988) details these results:

Tetramethrin - Rat Study, Charles River CD (1974) - Male Interstitial Cell Adenoma Rates† and Peto Prevalence Test Results (p Values)

Testicular Interstitial Cell Adenoma	Dose (ppm) 0	1000	3000	5000
Charles River CD - 1974	2/42	3/30	9/36	14/35
(percent)	(5)	(10)	(25)	(40)[a]
p =	0.0000**	0.1313	0.0034**	0.0000**

†Number of tumor-bearing animals/Number of animals at risk, excluding those that died before observation of the first tumor.
[a]First adenoma at week 83.
Note: Significance of trend denoted at control. Significance of pairwise comparison with control denoted at Dose level.
*$p < 0.05$ and **$p < 0.01$

Pairwise comparison of treated males to controls showed a statistically significant increase in interstitial cell adenomas in the mid- and high-dose groups. Additionally, there was a statistically significant trend in interstitial cell adenomas with increasing dose.

b. MTD Considerations

The decreased body weight of mid- and high-dose males and females indicates that an MTD was employed.

2. 1981 Sprague-Dawley and Long-Evans Rat Studies

a. Evaluation of Studies

Chronic toxicity studies in rats (Sprague-Dawley and Long-Evans); Hazleton Project No. 343-117; June 11, 1981.

Technical tetramethrin was evaluated for chronic toxic effects and oncogenic potential in Sprague-Dawley CRCD® and Long-Evans Hooded rat strains.

This study was composed of two phases: The in utero exposure phase and the 104-week chronic exposure phase.

At start of the in utero phase, the rats of each strain were divided into four groups (30 animals/sex/group). Technical tetramethrin was administered in the diet at 0, 200, 1000, and 5000 ppm, beginning 1 week prior to breeding, continuing through weaning and selection of offspring for the chronic feeding phase.

Following weaning, randomized groups of 50 male offspring of each strain were selected to continue on the chronic part of this study for 104 weeks. Criteria evaluated included physical appearance, behavior, growth, food consumption, survival, clinical pathology data, organ weights, tumor incidence, and gross and microscopic pathology.

The following table shows that there were no compound-related effects of the test chemical on survival for both strains.

	Strain	
	CRCD	Long-Evans
Control	30/50 (60%)*	37/50 (74%)
Low	26/50 (52%)	37/50 (74%)
Mid	26/50 (52%)	34/50 (68%)
High	30/50 (60%)	34/50 (68%)

*Number of survivors/Number of starters (as percent).

At termination of the study, the high-dose test groups of both strains were significantly lower in body weight than controls.

The CRCD strain was 13 percent lower and the Long-Evans strain was 11 percent lower at the high-dose level than their respective controls. Decreased body weight gain was evident in the high-dose test groups in the first year of the study. Food consumption was lower in the high-dose groups of both strains at the initial weeks of the study.

There were no compound-related effects in hematology, clinical chemistry, and urinalysis.

There were significant increases in the absolute and relative liver weights for the high-dose groups of both strains at 104 weeks. The CRCD strain had a 12 percent increase in absolute and 31 percent increase in relative liver weights. The Long-Evans strain had an 18.4 percent increase in absolute and 33.5 percent increase in relative liver weight.

Histopathological examination revealed a compound-related significantly increased incidence of interstitial cell tumors in the testes of the high-dose rats of both strains.

The following table (memorandum of B. Fisher, October 20, 1988) shows the statistical analysis of the incidence of interstitial cell adenomas.

Tetramethrin - Rat Studies, Charles River CD and Long-Evans (1981) Male Interstitial Cell Adenoma Rates† and Cochran-Armitage Trend Test and Fisher's Exact Results (p Values)

Testicular Interstitial Cell Adenoma	Dose (ppm) 0	200	1000	5000
Charles River CD - 1981	7/39	7/40	3/40	16/39
(percent)	(18)	(17)	(7)	(41)[a]
p =	0.0006**	0.5951	0.1451	0.0229*
Long-Evans 1981	4/42	3/44	4/39	22/43
(percent)	(10)	(7)	(10)	(51)[b]
p =	0.0000**	0.4736	0.6011	0.0000**

†Number of tumor-bearing animals/Number of animals at risk, excluding those that died before observation of the first tumor.
[a]First adenoma at week 88.
[b]First adenoma at week 89
Note: Significance of trend denoted at control. Significance of pairwise comparison with control denoted at Dose level.
*$p < 0.05$ and **$p < 0.01$

Pairwise comparison of treated males to controls shows a statistically significant increase in high-dose testicular adenomas in both Sprague-Dawley and Long-Evans rats in comparison to controls.

Additionally, there are statistically significant trends in interstitial cell adenomas in both strains with increasing dose.

b. MTD Considerations

The significant decreases in body weight in the high-dose groups of Sprague-Dawley and Long-Evans rats indicates that an MTD was employed.

C. Historical Control Data

There were no historical control data available from Hazleton Labs for Long-Evans rats.

The following historical control data from Hazleton Labs on Sprague-Dawley rats were submitted by the registrant.

Table 1. Hazleton Laboratories Historical Control Data
Interstitial Cell Tumors in Sprague-Dawley Rats

Study	Year	Weeks	Finding	Terminal	Unsched	Total	Percent
A/1	1976	104	Interstitial Cell Tumor	4/34	N/A	N/A	11.8
A/2	1976	104	Interstitial Cell Tumor	5/33	N/A	N/A	15.2
B	1976	104	Interstitial Cell Tumor	1/33	1/17	2/50	4.0
C	1977	118	Interstitial Cell Tumor	1/14	1/36	2/50	4.0
D	1977	104	Interstitial Cell Tumor	0/10[a]	N/A	N/A	0.0
E	1977	104	Interstitial Cell Tumor	3/31	0/15	3/46	6.5
			- Unilateral	2/31	0/15	2/46	4.3
			- Bilateral	1/31	0/15	1/46	2.2
F	1977	104	Interstitial Cell Tumor	2/20[b]	N/A	N/A	10.0
G	1978	104	Interstitial Cell Tumor	6/35	0/15	6/50	12.0
H	1978	104	Interstitial Cell Tumor	2/35	1/15	3/50	6.0
I	1978	104	Interstitial Cell Tumor	9/33	0/17	9/50	18.0
J	1978	120	Interstitial Cell Tumor	5/20	0/21[c]	5/41	12.2
K	1979	104	Interstitial Cell Tumor	1/23	1/26	2/49	4.1
L	1979	104	Interstitial Cell Tumor	7/31	1/18	8/49	16.3
M	1979	104	Interstitial Cell Tumor	2/28	1/22	3/50	6.0

N/A = Not Available
[a]Only 10/sex/group required for microscopic evaluation of tissues.
[b]Only 20/sex/group required for microscopic evaluation of tissues.
[c]Microscopic evaluation not conducted on 9 males.

Table 1. Hazleton Laboratories Historical Control Data
Interstitial Cell Tumors in Sprague-Dawley Rats
(cont'd)

Study	Year	Weeks	Finding	Terminal	Unsched	Total	Percent
N	1980	104	Interstitial Cell Tumor	2/22	0/3[d]	2/25	8.0
O/1	1980	130	Interstitial Cell Tumor	6/13	8/45	14/58	24.1
			- Unilateral	4/13	4/45	8/58	13.8
			- Bilateral	2/13	4/45	6/58	10.3
O/2	1980	130	Interstitial Cell Tumor	8/23	8/36	16/59	27.1
			- Unilateral	6/23	4/36	10/59	16.9
			- Bilateral	2/23	4/36	6/59	10.2
P/1	1980	130	Interstitial Cell Tumor	5/19	2/41	7/60	11.7
P/2	1980	130	Interstitial Cell Tumor	3/16	4/33	6/60	10.0

[d]Only tissues with gross lesions examined for animals dying on test.

Table 2. Hazleton Laboratories Historical Control Data

Study	Finding	Duration (Weeks)	Terminal Sacrifice	Unscheduled Sacrifice	Terminal & Unscheduled Sacrifice	Percent
Studies Terminated in 1983-1986			Males	Males	Males	
A	Interstitial Cell Tumor - Unilateral	104	3/24	0/6	3/30	10.0
B	Interstitial Cell Tumor - Unilateral	104	7/66	3/34	10/100	10.0
	Interstitial Cell Tumor - Bilateral		2/66	0/34	2/100	2.0
	Mesothelioma		0/66	1/34	1/100	1.0
C	Interstitial Cell Tumor - Unilateral	104	5/48	2/52	7/100	7.0
	Interstitial Cell Tumor - Bilateral		4/48	0/52	4/100	4.0
	Mesothelioma of Tunica Vaginalis - Bilateral		1/48	1/52	2/100	2.0
	Mesothelioma of Tunica Vaginalis - Unilateral		0/48	1/52	1/100	1.0

Table 2. Hazleton Laboratories Historical Control Data (cont'd)

Study	Finding	Duration (Weeks)	Terminal Sacrifice Males	Unscheduled Sacrifice Males	Terminal & Unscheduled Sacrifice Males	Percent
Studies Terminated in 1983-1986						
D	Interstitial Cell Tumors	104	4/43	1/16	5/59	8.5
	Mesothelioma, Tunica Vaginalis		0/43	1/16	1/59	1.7
E	Interstitial Cell Tumor	104	1/23	0/26	1/49	2.0
	Mesothelioma		0/23	1/26	1/49	2.0
F	Interstitial Cell Tumor	104	2/32	0/18	2/50	4.0
G	Interstitial Cell Tumor	104	6/44	0/23	6/67	9.0

Studies Terminated in 1981-1982		Duration (Weeks)	Terminal Sacrifice	Percent
A	Interstitial Cell Tumor	104	6/49	12.2
B	Interstitial Cell Tumor	104	1/43	2.3
C	Interstitial Cell Tumor	104	5/60	8.3
	Mesothelioma		4/60	6.7

It can be seen that the incidence of interstitial cell adenomas in the historical controls range from 0.0 to 18.0 percent for studies of 104-week duration and up to 27.1 percent for studies of 130-week duration.

The incidence of interstitial cell adenomas in the 1974 study was 25 percent at the mid dose and 40 percent at the high dose.

In the 1981 studies, the incidences were 41 and 51 percent for the high-dose groups in the Sprague-Dawley and Long-Evans strains, respectively.

The incidences of interstitial cell adenomas in the mid- and high-dose groups in the 1974 study exceed the range of historical controls for the 104-week duration.

Similarly, the incidence of interstitial cell adenomas at the high dose with the Sprague-Dawley and Long-Evans strains in 1981 exceeds the range of historical controls.

3. 1986 $B_6C_3F_1$ Mouse Study

a. Evaluation of Study

Combined chronic feeding/oncogenicity study in mice with tetramethrin. Cox, R.H.; Dudeck, L.E.; Alsaker, R.D., et al. Study Number 343-136. Conducted by Hazleton Laboratories, April 17, 1986; Amendment May 29, 1987; Accession Nos. 262778-262788; 402763-01; and 402804-00 and -01.

Randomized groups of 90 male and 90 female $B_6C_3F_1$ mice were dosed with dietary levels of 0, 12, 60, 300, and 1500 ppm of technical tetramethrin for 2 years.

There were no significant dose-related trends in survival; mortality was significantly lower in males receiving 300 ppm than in controls.

There were no compound-related effects on toxic signs, body weight, food consumption, hematology, clinical chemistry, urinalysis, and gross pathology.

The absolute and relative weights of the thyroid and pituitary (at termination) were significantly ($p < 0.05$) decreased in males receiving 60, 300, and 1500 ppm when compared to controls but there were no underlying histopathological findings in these organs. Spleen weights were decreased for the 300 and 1500 ppm male groups.

There was a significant increase ($p < 0.05$) in the incidence of hemangiosarcoma of the spleen in mid-dose males (300 ppm), but when hemangiosarcomas at all sites were analyzed there was no significant increase. It was noted that all of the hamangiosarcomas in the spleens of males were in animals that survived to final sacrifice. The following table shows the results in both sexes.

Organ/Neoplasm	Males Dose Level (ppm)				
	0	12	60	300	1500
All Sites	68	67	69	70	68
Hemangioma	1	1	1	2	0
Hemangiosarcoma	4	6	5	9	0
percent	7	10	9	16	0
Organ/Neoplasm	**Females Dose Level (ppm)**				
	0	12	60	300	1500
All Sites	70	69	67	70	70
Hemangioma	0	3	1	3	1
Hemangiosarcoma	2	3	2	3	1
percent	3	9	4	9	3

Statistical analysis of adenomas of the Harderian gland of males (but not females) receiving 1500 ppm indicated a significant increase ($p < 0.05$) when compared to controls. There was no significant dose-related trend, however. The following table shows the results in both sexes.

Organ/Neoplasm	Males Dose Level (ppm)				
	0	12	60	300	1500
Harderian gland	(68)	(69)	(69)	(68)	(69)
Adenoma	1	5	5	3	7
percent	1.4	7.2	7.2	4.4	10.1
Organ/Neoplasm	**Females Dose Level (ppm)**				
	0	12	60	300	1500
Harderian gland	(67)	(68)	(69)	(69)	(70)
Adenoma	2	5	4	4	2
percent	2.9	7.3	5.7	5.7	1.4

The laboratory historical incidence of adenoma of the Harderian gland based on two studies (120 male, 119 females) was 7.2 percent (range 0 to 16%) and 4.6 percent (range 0 to 10%) in untreated males and females, respectively. In the NTP data base, the

range for males (36 studies) was 0 to 12 percent and the mean was 2.7 percent. Since the incidence of Harderian adenomas in the high dose in the tetramethrin study (10%) was within historical range, the increase in the high dose over concurrent controls was not considered biologically significant.

Based on a decrease in absolute and relative weight of thyroid and pituitary in males receiving 60, 300, and 1500 ppm, the NOEL is 12 ppm and the LEL is 60 ppm.

b. MTD Considerations

The selection of doses for the chronic study was based on the results of the 13-week pilot study in mice.

In the pilot study, there were decreased relative weights in the thyroid, adrenal, and pituitary in both sexes at 1500 and 5000 ppm.

In the chronic study, the absolute and relative weights of the thyroid and pituitary were also significantly decreased at 60, 300, and 1500 ppm. In both the pilot study and the chronic study, there were no histopathological lesions associated with organ weight decreases.

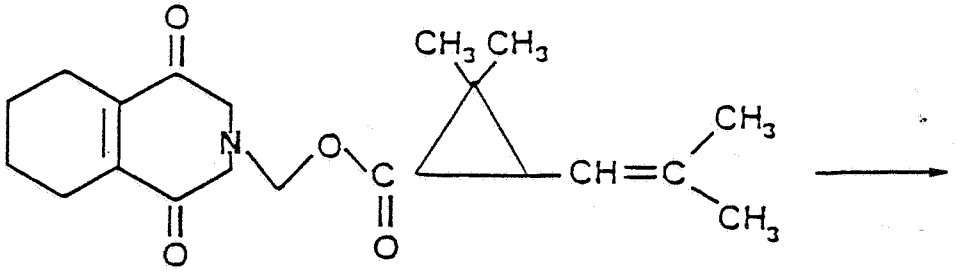
Additionally, in the pilot study, there were body weight decreases in males (-9%) and females (-7.5%) associated with higher food consumption at the high dose of 5000 ppm. These body weight decreases in the pilot study support an MTD of 1500 ppm in the chronic study. Tetramethrin can be regarded as having adverse effects on the endocrine organs of mice.

D. Additional Toxicology Data on Tetramethrin

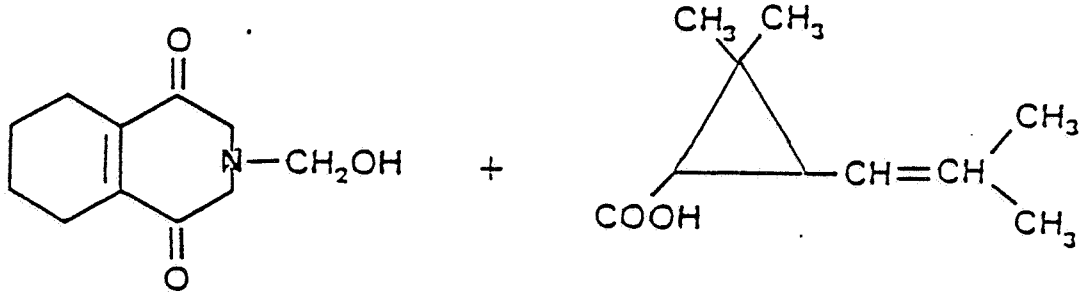
1. Metabolism

Tetramethrin-C^{14} was orally administered to male Wistar rats. Approximately 95 percent of the radioactivity was recovered in the excreta (urine, 47%; feces, 42%) during 5 days after treatment. The content of tetramethrin in the tissues was less than 1 percent and in the expired $C^{14}O_2$ was less than 0.2 percent. About half of the tetramethrin was found to be excreted into the feces unabsorbed and approximately 40 percent of the excreta was unchanged tetramethrin.

The major route of metabolism is hydrolysis of the ester linkage:



Tetramethrin



MTI + Chrysanthemumic Acid

Tetramethrin, once absorbed into rats, is metabolized rapidly to MTI and is ultimately converted to water-soluble metabolites.

2. Nononcogenic Toxicological Effects

a. 6-Month Dog Study

Four groups of 6 male and 6 female beagle dogs were fed 0, 1250, 2500, and 5000 ppm technical tetramethrin in their diet for 26 weeks.

There were no deaths or effects in hematology, clinical chemistry, urinalysis, or ophthalmology. Liver weight was elevated in high-dose males and females. The absolute and relative ovarian weight

was decreased in high-dose females. High-dose female dogs did not have ovaries, indicating that recent ovulation had not occurred. Additionally, there was no evidence of endrometrial hypertrophy in the uterus of the high-dose female dogs.

Classification: Minimum

b. Rat and Rabbit Teratology Studies

Teratology, Rat - Randomized groups of 30 pregnant Slc:SD(SPF) rats were dosed during days 7 to 17 of gestation with 0, 100, 300, and 1000 mg/kg of technical tetramethrin. High-dose dams exhibited body weight loss and increased liver, kidney, and ovarian weight. There was no evidence of developmental toxicity.

Classification: Guideline

Teratology, Rabbit - Randomized groups of 10 "Japanese White Rabbits" were dosed during days 6 to 18 of gestation with 0, 50, 150, or 500 mg/kg of technical tetramethrin. High-dose dams exhibited body weight loss. High-dose pups showed decreased body weight. There was no evidence of terata. Developmental NOEL is 150 mg/kg. LEL is 500 mg/kg and effect is decreased pup weight.

Classification: Guideline

c. Reproduction Studies

1) Fertility Study in Rats

Randomized groups of 20 Slc:SD strain rats were dosed with 0, 100, 300, and 1000 mg/kg/day with technical tetramethrin by stomach tube from premating through day 7 of gestation. Results showed that the average number of days required from start of mating until copulation was 7 days for the high-dose group and only 3 to 4 days for other groups. High-dose pups had decreased body weight, decreased body length, and increased delayed ossification. NOEL = 300 mg/kg; LEL = 1000 mg/kg and effects include increased latency of copulation and decreased pup weight and length.

Classification: Supplementary

2) One-Generation Rat Reproduction Study

Randomized groups of 15 male and 30 female Sprague-Dawley rats were dosed with 0, 1000, 3000, and 6000 ppm of technical tetramethrin through weaning of first filial generation (F_1a). Mean body weight of parental animals was decreased at 6000 ppm during week 9 of growth phase. The live birth index was significantly higher for the 3000 and 6000 ppm pups than in controls. The lactation index for 6000 ppm pups (88.4%) was significantly less than for controls (96.0%). The mean body weight of male and female pups at weaning was significantly less in the 3000 and 6000 ppm groups than in controls. NOEL = 1000 ppm. LEL = 3000 ppm and effect is decreased pup weight.

Classification: Supplementary

3) Two-Generation Rat Reproduction Study

Randomized groups of 13 male and 26 female Sprague-Dawley rats received 0, 100, 500, and 3000 ppm of technical neopynamin forte in their diet for two generations with one litter per generation. The NOEL for the study was 500 ppm. At the LEL of 3000 ppm, there were decreased body weights of males and females during growth of each parental generation, decreased food consumption for females during growth of the first generation, decreased body weights of females during gestation and lactation of each generation, decreased pup body weight for each litter of both generations, and increased incidence of bile duct hyperplasia in the liver of females of the second parental generation.

Classification: Guideline

Although the study was conducted with neopynamin forte, the study fulfills the data requirement for a two-generation rat reproduction study with tetramethrin.

3. Mutagenicity

Tetramethrin has been tested in 10 mutagenicity studies which are summarized in the following table. These studies include gene mutation, chromosomal aberration, and DNA repair. Technical tetramethirn was negative in all assays. It was negative in the Ames Assay (three studies), rec-assay (B. subtilis), DNA repair test without activation (not acceptable since not performed with activation), host-mediated assay in ICR male mice, and chromosome damage in ICR male mice (not acceptable).

However, industrial grade tetramethrin (72% purity) was positive in the Ames Assay, and in UDS in human aminon FL cells.

Mutagenicity Assays

Test	Test Material	Results	Classification
E. coli WP2 uvrA; S. typhimurium TA97, TA98, TA100, TA1535, TA1537	94.0% Technical	Negative up to 5000 ug/plate (precipitation) both with and without activation.	Acceptable
E. coli W3623 trp$^-$ and W3102 trp$^-$; S. typhimurium TA1535 his$^-$; TA1538 his$^-$	93 to 100%	Negative up to 10 mg/plate without activation	Unacceptable; not performed with activation
S. typhimurium TA97, TA98, TA100	72% purity industrial grade	Weakly positive in TA97 with activation	Acceptable; however, industrial grade tetramethrin (72% purity) was used
S. typhimurium TA97(fluctuation method)	72% purity industrial grade	Positive in TA97 both with and without activation	Acceptable; however, industrial grade tetramethrin (72% purity) was used

Mutagenicity Assays (cont'd)

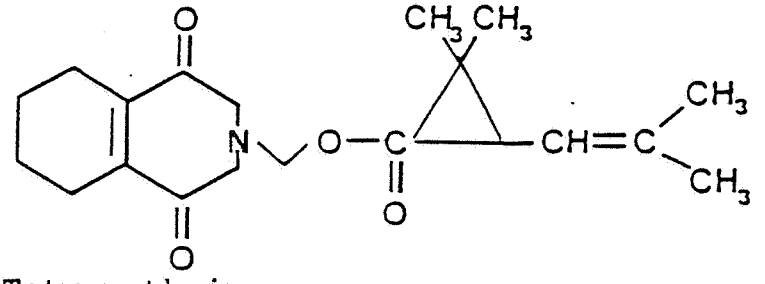
Test	Test Material	Results	Classification
S. typhimurium TA98, TA100, TA1535, TA1538	Technical	Negative up to 10,000 ug/plate both with and without activation	Acceptable
Rec-Assay			
B. subtilis M45, H17 wild type strain	Technical	Negative up to 10,000 ug/paper disk	Acceptable
Repair Test			
DNA repair - deficient strains (pol^-, uvr^- or rec^-), E. coli W3623, B. subtilis M45, S. typhimurium TA1538	Technical, 93 to 100% purity used	Negative without activation	Unacceptable; not performed with activation
Host Mediated Assay			
ICR male mice	Technical allethrin, permethrin, and resmethrin	Negative up to 1/2 LD_{50}	Acceptable; however, tetramethrin was not tested. Allethrin, permethrin, and resmethrin were tested
Host Mediated Assay			
ICR male mice S. typhimurium G46	Technical tetramethrin	Negative up to 1000 mg/kg	Acceptable;

Mutagenicity Assays (cont'd)

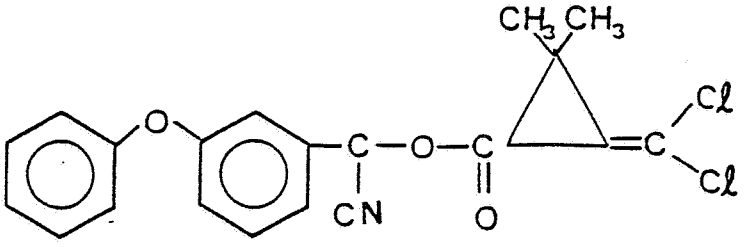
Test	Test Material	Results	Classification
Chromosome damage in mouse bone marrow cells, ICR male mice	Technical, 93.4% purity	Negative at 5000 mg/kg	Unacceptable; no evidence that compound reached target cells and only males were tested
UDS in human amnion FL cells	72% purity, industrial grade	Positive both with and without activation	Acceptable; however, industrial grade tetramethrin (72% purity) was used

4. Structure-Activity Correlations

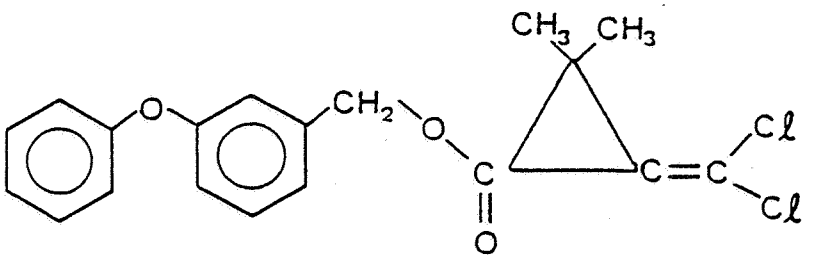
Tetramethrin is structurally related to the following four synthetic pyrethroids:



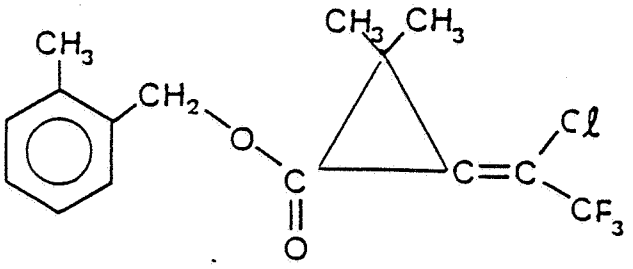
Tetramethrin



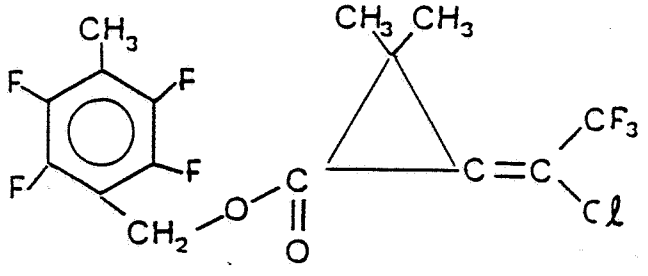
Cypermethrin



Permethrin



Bifenthrin



PP993

Permethrin induced hepatocellular and bronchioalveolar tumors in female mice and was negative in the rat. Permethrin has not been evaluated by the Peer Review Committee.

Cypermethrin induced lung tumors in female mice and was classified as a Category C oncogen by the Peer Review Committee.

Bifenthrin produced urinary bladder leiomysarcomas in male mice and was classified as a Class C oncogen by the Peer Review Committee.

PP993 was negative in the rat for oncogenicity and has not been tested in the mouse. PP993 has not been evaluated by the Peer Review Committee.

E. Sumitomo Consultants' Evaluation

In 1982, Sumitomo requested a reevaluation of histologic diagnoses of all rats in both experiments and an assessment of the biologic significance of these studies.

The histologic investigation was conducted by Drs. S.D. Vesselinovitch and N. Ito.

The testicular interstitial lesions were classified into one of three categories: 1) intersitial, Leydig cell, diffuse hyperplasia; 2) nodular hyperplasia; and 3) adenoma.

The results of their analyses are shown below in tabular form.

Experimental Results of Feeding Neo-Pynamin to Rats in Three Different Studies (1982) (Evaluted by Drs. Vesselinovitch and Ito)

Dose	Sprague-Dawley (1974)		Sprague-Dawley (1981)		Long-Evans (1981)		Pooled	
(ppm)	Ratio	Percent	Ratio	Percent	Ratio	Percent	Ratio	Percent
0	1/44	2.27	5/41	12.19	1/43	2.32	7/128	5.47
200	....	....	7/45	15.55	2/44	4.54	9/89	10.11
1000	3/30	10.10	2/41	4.87	3/43	6.97	8/114	7.02
3000	8/36	22.22	....	....	....	....	8/36	22.22
5000	12/37	32.43	14/40	35.00	15/47	31.91	41/124	33.06

*Number of rats bearing interstitial tumor(s)/Number of rats at risk after 80 weeks.

In comparison to Vesselinovitch and Ito, the Hazleton findings are shown below:

Experimental Results of Feeding Neo-Pynamin to Rats in Three Different Studies (1982) (Evaluted by Hazleton Pathologists)

Dose	Sprague-Dawley (1974)		Sprague-Dawley (1981)		Long-Evans (1981)		Pooled	
(ppm)	Ratio	Percent	Ratio	Percent	Ratio	Percent	Ratio	Percent
0	2/44	4.54	7/41	17.07	4/43	9.30	13/128	10.15
200	....	....	7/45	15.55	3/44	6.82	10/89	11.23
1000	3/30	10.10	3/41	7.31	4/43	9.30	10/114	8.77
3000	9/36	25.00	....	....	....	....	9/36	25.00
5000	14/37	37.84	16/40	40.00	22/47	46.80	52/124	41.93

*Number of rats bearing interstitial tumor(s)/Number of rats at risk after 80 weeks.

*Animals dying prior to 80 weeks are not included because the first tumors were noted after 80 weeks and only "at risk" rats are included.

Table 3. Vesselinovitch and Ito (1982) Historical Control Data from Hazleton Laboratories Chronic Rodent Studies with Sprague-Dawley Rats from Charles River Breeding Laboratories, Inc.

				Number of Interstitial Cell Tumors Noted			
				One Testis		Both Testes	
Group	Project No.	Year	Duration (Weeks)	Ratio	Percent	Ratio	Percent
1	417-351 Group 1-Control	1976	104	0/27	0.0	4/7	57.1
2	417-351 Group 2-Control	1976	104	0/25	0.0	5/8	62.5
3	610-119	1976	104	0/30	0.0	1/3	33.3
4	785-300	1976	104	....	...	0/3	0.0
5	165-149	1977	104	0/10	0.0	1/4	25.0
6	174-123	1977	104	0/8	0.0	0/2	0.0
7	174-122	1977	104	...	...	3/31	9.6
8	141-263	1977	104	...	...	2/20	10.0
9	132-134	1978	104	6/35	17.1	0/6	0.0
10	132-132	1978	104	0/29	0.0	2/6	33.3
11	132-137	1978	104	2/17	11.8	7/16	43.7
12	958-102	1978	104	0/12	0.0	5/8	62.5
13	798-177	1979	104	....	....	1/23	4.3
14	947-103	1979	104	....	....	7/31	22.6
15	798-181	1979	104	....	....	2/28	27.1
16	417-383	1980	104	....	....	2/22	9.1
17	444-215 Group 1-Control	1980	130	....	....	8/13	61.5

Table 3. Vesselinovitch and Ito (1982) Historical Control Data from Hazleton Laboratories Chronic Rodent Studies with Sprague-Dawley Rats from Charles River Breeding Laboratories, Inc. (cont'd)

Group	Project No.	Year	Duration (Weeks)	Number of Interstitial Cell Tumors Noted: One Testis Ratio	One Testis Percent	Both Testes Ratio	Both Testes Percent
18	444-215 Group 2- Control	1980	130	....	....	10/23	47.5
19	444-215 Group 4- Control	1980	130	....	....	5/19	26.3
20	444-214 Group 1- Control	1980	130	....	....	3/16	18.7

Based on their analyses, Vesselinovitch and Ito conclude that there is a statistically significant increase in interstitial cell (Leydig cell) adenomas in males exposed to the highest dose level. This incidence, however, did not exceed the maximal incidence of 62.5 percent observed in the historical controls presented by Vesselinovitch. The historical control data presented by Vesselinovitch in Table 3 is the same historical control data as presented in Table 1 by Hazleton. Based on Dr. Vesselinovitch's letter of August 26, 1988, the incidence of interstitial cell tumors in the historical controls ranges from 0 to 62.5 percent when two testes are examined and 0 to 17.1 percent when only one testis was examined. It can be seen by comparing Tables 3 and 1 that Dr. Vesselinovitch has an almost threefold increase in range observed in Table 3 in comparison to Table 1.

Dr. Vesselinovitch states in his August 26, 1988 letter that:

> In the Neo-Pynamin studies both testes in treated groups always were examined histologically. Consequently, for proper comparison with the treated groups in the Neo-Pynamin studies, it was necessary to

> determine the incidence in historic control animals in those Hazleton studies in which both testes were sampled and examined microscopically.

Their overall evaluation of the oncogenic effect of tetramethrin is as follows:

> The statistical indication of Neo-Pynamin tumorigenicity is biologically questionable because the tumor involved is hormonally dependent, occurred only at a single site, in a single sex, in a single species, and because the response to the highest dose was within the incidence range observed in the historic controls. Since the treatment with Neo-Pynamin did not influence the development of malignant tumors at any site and because the interstitial (Leydig cell) adenomas represent a morphologic endpoint which is not associated with the malignancy, it has been concluded that the conducted bioassays did not show carcinogenic potential of Neo-Pynamin.