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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review of Tetramethrin

FROM: George Z. Ghali, Ph.D.
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Phil Hutton, PM 17
Insecticide-Rodenticide Branch
Registration Division (H7505C)

The Health Effects Division (HED) Peer Review Committee met on August 30, 1989 to discuss and evaluate the weight of the evidence on tetramethrin, with particular reference to its carcinogenic potential. The Committee concluded that the chemical meets the criteria for Group C, possible human carcinogen, set forth by the Agency's Carcinogen Risk Assessment Guidelines. Quantitative estimation of potential human risk was not recommended.

A. Individuals in Attendance

1. Penelope A. Fenner-Crisp
William L. Burnam
Richard Hill
Karl Baetcke
Marcia van Gemert
Kerry Dearfield
John Quest
Lynnard Slaughter
George Z. Ghali

2. Peer Review Committee in Absentia (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee):

Reto Engler	Reto Engler
Robert Beliles	Robert Beliles
Marion Copley	Marion Copley
Julie Du	Julie Du
Richard Levy	
Esther Rinde	Esther Rinde
William Sette	William Sette
Yin-Tak Woo	Yin tak Woo

3. Reviewers (Non-panel members responsible for data presentation; signatures indicate technical accuracy of panel report):

William Dykstra	William Dykstra
Edwin Budd	Edwin Budd
Bernice Fisher	Bernice Fisher

4. Scientific Observer: Hugh Pettigrew of the Science Support Section, SACB/HED.

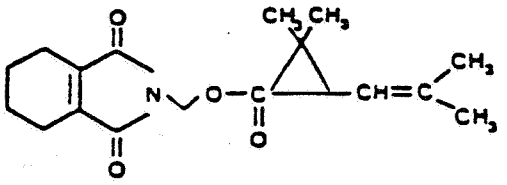
B. <u>Material Reviewed</u>

1. A summary of relevant toxicology information prepared by Dr. W. Dykstra, HED, OPP.

2. Data evaluation records of relevant studies.

3. Other ancillary information including: histologic investigation by Vesselinovich and Ito, historical control data, qualitative risk assessment, addendum to risk assessment, addendum to pathology report, a company response, and a toxicology one-liner.

C. Background



Tetramethrin

Tetramethrin* [3,4,5,6-tetrahydrophthalimidomethyl crysanthemate or 1-cyclohexane-1,2-dicarboximidomethyl-2,2-dimethyl-3(2-methylpropenyl)-cyclopropane carboxylate] is a pyrethroid insecticide developed by Sumitomo Chemical Company. It is registered for nonfood use. It is mainly used for control of mosquitoes, flies, and other flying insects. It is also used in combination with resmethrin or piperonyl butoxide to control household insects and garden pests. The registrant is currently attempting to develop tetramethrin for agricultural use.

D. Evaluation of Oncogenicity Evidence

1. Two-year Oncogenicity Study in the Sprague-Dawley Rat. Report No. 343-107, prepared by Hazleton Laboratories, October 5, 1974, EPA Accession No. 247280.

   Technical tetramethrin was administered in the diet to groups of 50 male and 50 female Charles River, CD-1 Sprague-Dawley rats at levels of 1000, 3000 or 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 or 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.

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* Also called Neo-Pynamin.

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.

Treatment was associated with an increased incidence of "enlarged firm" testes with "subscapular yellow material" in the mid- and high-dose groups in comparison to controls. The treatment also was associated with a statistically significant dose-related increase in the incidence of interstitial cell adenomas in the testes at the mid- and high-dose levels (Table 1).

Table 1. Incidence+ of Interstitial Cell Adenomas in Male Rats: Peto Prevalence Test Results (Memorandum by B. Fisher, October 20, 1988).

Testicular Interstitial Cell Adenoma	Dose (ppm)			
	0	1000	3000	5000
Sprague-Dawley, 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.

*$p < 0.05$

**$p < 0.01$

Historical control data from 1976 to 1980 in which both testes were examined (Raymond H. Cox, Hazleton Laboratory, letter dated August 29, 1989) indicated that the incidence of testicular interstitial cell adenoma ranged from 0.0 to 18.0 percent for studies of 104 weeks' duration and up to 27.1 percent for studies of 130 weeks duration.

The highest dose tested was considered adequate for carcinogenicity testing based on a statistically significant decrease in body weight gains (>15%) in both males and females of the mid- and high-dose groups at terminal sacrifice. Food consumption was reported to be lower for all treated groups in comparison to controls.

2. Two-Year Oncogenicity Study in Sprague-Dawley and Long-Evans Rats. Report No. 343-117, prepared by Hazleton Laboratories, June 11, 1981.

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

At the 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 or 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.

Treatment did not have any effect on survival of either strain. The highest dose tested was considered adequate based upon significant decreases in body weight gain in the high-dose groups of both strains (13% in Sprague-Dawley and 11% in Long-Evans) at termination of the study.

Treatment caused a statistically significant increase in the incidence of interstitial cell adenomas of the testis in male Sprague-Dawley ($p < 0.05$) and Long-Evans ($p < 0.01$) rats of the high-dose groups, with a statistically

significant ($p < 0.01$) positive dose-response trend. The first adenoma was observed at week 88 and 89, respectively, for the Sprague-Dawley and Long Evans rats.

The findings of the two studies are presented in Table 2 below (taken from memorandum by B. Fisher, dated October 20, 1988).

Table 2. Incidence+ of Testicular Interstitial Cell Adenomas in Male Sprague-Dawley and Long-Evans Rats: Fisher's Exact and Cochran-Armitage Trend Test.

Testicular Interstitial Cell Adenoma	Dose (ppm)			
	0	200	1000	5000
Sprague-Dawley, 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)	(7)	(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.

*$p < 0.05$

**$p < 0.01$

Historical control data from Hazleton Laboratories for Sprague-Dawley rats in which both testes were examined (Raymond H. Cox, Hazleton Laboratories, letter dated August 29, 1989) indicated that the incidence of interstitial cell adenomas compiled from 1981 to 1982 ranged from 2.3 to 12.2 percent, and from 1983 to 1986 ranged from 2.0 to 9.0 percent for studies of 104 weeks' duration. There were no historical control data available on this type of tumor in the Long-Evans strain.

According to Hazleton Laboratories letter (Raymond H. Cox, August 29, 1989) "the Hazelton SOP [Standard Operating Procedure] Number 11,011 - Tissue Trimming General Procedures, was first issued 10/01/82 and required histologic preparation of both testes and epididymides. Prior to 1982, project protocols were the sole source of which tissues to process, but to the best of my knowledge almost always required both testes and epididymides."

3. Two-Year Oncogenicity Study in $B_6C_3F_1$ Mice. Report No. 343-136, dated April 17, 1986 by Hazleton Laboratories, and Amendment dated May 29, 1987. Accession Nos. 262778-88; 402763-01; 402804-00; and 402804-01.

   Groups of 90 male and 90 female $B_6C_3F_1$ mice were administered tetramethrin in the diet at dosage levels of 0, 12, 60, 300 or 1500 ppm for 2 years.

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

   The highest dose tested was considered adequate for carcinogenicity testing based upon decreased relative weights in the thyroid, adrenal, and pituitary in both sexes at 1500 and 5000 ppm in a pilot study. Additionally, there were body weight gain decreases in males (9%) and females (7.5%) associated with <u>higher</u> food consumption at the high dose of 5000 ppm in the pilot study. In the chronic study, the absolute and relative weight of the thyroid and pituitary were also significantly decreased at 60, 300 and 1500 ppm.

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 (taken from a summary prepared by Dr. W. Dykstra, HED, OPP) shows the results in both sexes.

Table 4: Incidence of Harderian Gland Adenomas in Male and Female $B_6C_3F_1$ Mice.

Organ/Neoplasm	Males				
	Dose Level (ppm)				
	0	12	60	300	1500
No. Harderian Glands Examined	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
No. Harderian Glands Examined	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 males, 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.

E. 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 the first five 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 by hydrolysis of the ester linkage to chrysanthemumic acid and the respective primary alcohol.

2. Subchronic Toxicity - In beagle dogs, dietary administration of tetramethrin at concentrations of 0, 1250, 2500 or 5000 ppm for 6 months resulted in decreased absolute and relative ovarian weight in high-dose females. High-dose female dogs did not have corpora lutea, indicating that recent ovulation had not occurred. Additionally, there was no evidence of endometrial hypertrophy in the uterus of the high-dose female dogs.

3. Reproductive and Developmental Toxicity - There was no evidence of developmental toxicity in either rats or rabbits up to the highest dose tested (1000 and 500 mg/kg/day, respectively).

   In a fertility study in rats, treatment of parental animals (both sexes) resulted in an increase in the average number of days required from start of mating until copulation, decreased body length and weight, and increased delayed ossification in the offspring of the high-dose group (1000 mg/kg/day).

   In a two-generation reproduction study in Sprague-Dawley rats, mean body weight gain of parental animals was decreased at 6000 ppm during week 9 of the 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 control (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.

In a two-generation study with neopynamin forte (which is not exactly identical to tetramethrin) at 3000 ppm, there were decreased body weight gain 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.

4. Mutagenicity - Technical tetramethrin was not mutagenic when tested in several bioassay systems including assays for gene mutation, chromosomal aberration, and DNA repair. However, industrial grade tetramethrin (72% purity) was positive in the Salmonella assay and for unscheduled DNA synthesis (UDS) in human amnion FL cells. No positive response was obtained when the UDS assay was repeated with technical tetramethrin.

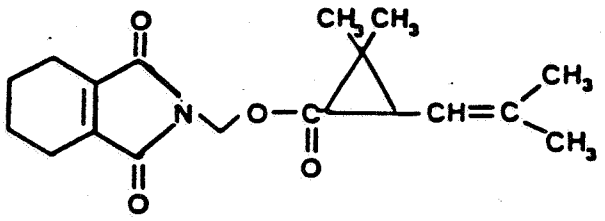
5. Structure-Activity Considerations - Tetramethrin is structurally similar to other pyrethroids such as cypermethrin, permethrin, bifenthrin, and PP993, in that they are all esters of specific acids and alcohols. However, it should be emphasized that in all these analogues, the alcohol portions of these esters differ significantly from each other. Furthermore, the acid portion of all these ester analogues has a halogenated vinyl or vinylidene moiety, while tetramethrin does not.

   Permethrin induced hepatocellular and bronchioalveolar tumors in female mice and was negative in the rat and was classified as a Group C carcinogen by the HED Peer Review Committee (4/7/1989).

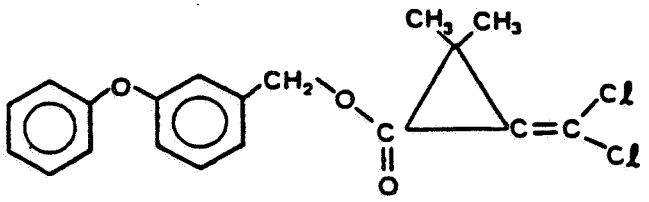
   Cypermethrin induced lung tumors in female mice and was classified as a Group C carcinogen by the HED Peer Review Committee (2/17/1988).

   Bifenthrin produced urinary bladder leiomyo sarcomas in male mice and was classified as a Group C carcinogen by the HED Peer Review Committee (6/2/1987).

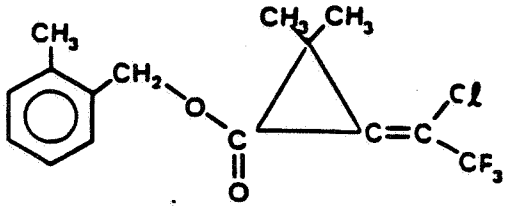
   PP993 was negative in the rat for carcinogenicity and has not been tested in the mouse. PP993 has not been evaluated by the HED Peer Review Committee for classification of carcinogenic potential.



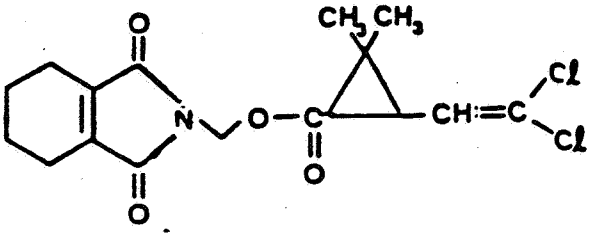
Tetramethrin



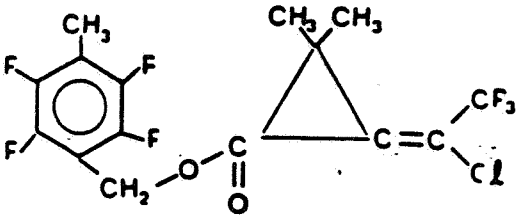
Permethrin



Bifenthrin



Cypermethrin



PP993

F. Other Considerations; Sumitomo Consultants' Evaluation

In 1982, Sumitomo requested a reevaluation of histologic diagnoses of all rats in both experiments and an assessment of the biological 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) interstitial, Leydig cell, diffuse hyperplasia; 2) nodular hyperplasia; and 3) adenoma.

Their overall evaluation of the carcinogenic 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."

G. Weight-of-the-Evidence

The HED Peer Review Committee considered the following facts to be of significance in the weight-of-the-evidence determination of tetramethrin:

1. Tetramethrin administration to F_1A weanling Sprague-Dawley rats in the 1974 study (from parental animals which had been dosed with this chemical until sexual maturity) was associated with a statistically significant increase in interstitial cell adenomas in the testes in the mid- and high-dose males which was also dose-related. The increase was outside the historical control range. The MTD was considered to be reached based upon statistically significant decreases in body weight gains in both males and females

of the mid- and high-dose groups at terminal sacrifice.

2. Tetramethrin administration to Sprague-Dawley and Long-Evans rats in the 1981 study (from parental animals which has been dosed with this chemical) was associated with a statistically significant increase of testicular interstitial cell adenomas in male Sprague-Dawley ($p < 0.05$) and Long-Evans ($p < 0.01$) rats of the high-dose groups, with a statistically significant ($p < 0.05$) dose-response trend. The increase in the Sprague-Dawley rats was outside the historical control range for that strain. No historical control data were available on the Long-Evans strain.

   The highest dose tested was considered adequate based upon a significant decrease in body weight gain in the high-dose groups of both rat strains.

3. In $B_6C_3F_1$ mice, the most frequently observed tumors were hemangioma, hemangiosarcoma, and Harderian gland adenomas in both sexes. These tumors were not considered as treatment-related because of the lack of statistical significance and for being within the historical control range.

   The highest dose tested was considered adequate based upon decreased absolute and relative weights in the thyroid and pituitary in both sexes in the main study, and decreased relative weight of thyroid, adrenal and pituitary in both sexes in a pilot study at a concentration equivalent to the high dose in the main study.

4. Although industrial grade tetramethrin (72% purity) was positive in some microbial and mammalian *in vitro* bioassays, technical tetramethrin was not mutagenic when tested in several bioassay systems including gene mutation, chromosomal aberration, and DNA repair assays.

5. Although tetramethrin belongs to the pyrethroid group, its ester components differ significantly from those pyrethroid analogues. Therefore, any attempt to correlate the structure of tetramethrin to other pyrethroids may be misleading and could be misinterpreted.

F. Conclusions

The Committee agreed, based upon the available information, to classify tetramethrin as a Group C, possible human carcinogen. The Group C classification is supported by the following:

1. Tetramethrin administration to Sprague-Dawley rats was associated with a statistically significant dose-related increase in the incidence of interstitial cell adenomas in the testes in mid- and high-dose males. These results were reproducible in a second study in Sprague-Dawley rats and a new study in Long-Evans rats. This increase was outside the historical control range for Sprague-Dawley rats. No historical control data were available on Long-Evans rats.

2. Tetramethrin administration to $B_6C_3F_1$ mice did not alter the spontaneous tumor profile for this strain of mice.

Quantitative estimation of potential human risk was not recommended. The Committee based its decision on the fact that this type of tumor, i.e., interstitial cell adenomas of the testes, is confined to a benign tumor and does not progress to a malignant tumor in rats (however, this tumor can progress to a malignant tumor in man); occurred at a later stage of the study; the exposure started in utero (animals may be more sensitive at this stage of development) and the treatment did not cause reduction in latency. Furthermore, technical tetramethrin is not mutagenic and structurally does not relate to known chemical mutagens and/or carcinogens.

Parts of this report were taken directly from a summary dated November 3, 1988 prepared by Dr. W. Dykstra, HED, OPP.