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

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SEP 30 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Registration No. 10308-1 - Tetramethrin
Partial Company Response to Toxicology Branch Request for Revised Histopathology Tables and Individual Animal Pathology Data Sheets. Assignment of Core Classification for the 1981 Rat Special Oncogenicity Study (Hazleton No. 343-117).

TOX Chem No. 844
TOX Project No. 1498
Record No. 169601

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Hazard Evaluation Division (TS-769C)

TO: Arturo E. Castillo, PM 17
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THRU: Edwin Budd, Section Head
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In previous memorandums (dated April 11, 1983 and October 31, 1985 for EPA File No. 10308-1) from Toxicology Branch (TB) the Core classification of the two rat oncogenicity studies with the test chemical tetramethrin was stated as being assigned RESERVED pending receipt and review of additional histopathology information. In particular, individual animal pathology sheets reporting both the gross necropsy and the histopathological findings as well as summary tables indicating the exact number of tissues/organs which were actually examined were to be provided.

The registrant has responded by providing information on the second rat study (Hazleton Laboratories 1981 Study No. 343-117 using two strains of male rats) without providing information on the first rat study. TB has been informed by RD (personal communication from Dr. P. Schroeder on August 25, 1986) that the registrant intends to provide the information for the first rat chronic feeding/oncogenicity study by the end of November 1986 (refer to correspondence between the Sumitomo Chemical Company and Dr. Eugene Gerberg dated April 28, 1986).

The information provided by the registrant concerning the 1981 rat study consisted of a summary table of nonneoplastic lesions which included the number of animals for which each tissue was examined and individual animal pathology sheets. This information together with the original submission were reconsidered by TB and CORE assignment for this study was made.

Toxicology Branch Comments:

1. An updated review of the 1981 rat study (Hazleton No. 343-117, dated June 11, 1981) is attached.

2. The CORE classification of this study is SUPPLEMENTARY. This classification results from the design of the study which did not include females and because of the limited number of tissues examined microscopically. Since this study was designed to assess a possible neoplastic effect of tetramethrin in the rat testes inclusion of females and complete microscopic examination of all tissues from all rats were not included. TB, however, considers this study to be useful in assessing potential oncogenicity in the rat testes.

3. Based on the data provided in the original submission and in the addendum, TB maintains that this study demonstrates an association between the presence of tetramethrin in the diet and increased incidences of testicular interstitial adenomas in both strains of rats. The classification of tetramethrin as an oncogen based on the increased incidences of testicular adenomas in this study and in the earlier rat study will be decided upon in the Peer Review meeting for this chemical.

4. In order to assist in preparing the summary package for the Peer Review meeting for tetramethrin, TB requests that the registrant provide the following information:

i. A report on the analyses for confirmation of the dietary concentration of tetramethrin in the test diets.

ii. Historical control data for the spontaneous occurrence of liver tumors (including "neoplastic nodules", adenomas, and hepatocellular carcinomas) in the Long-Evans strain of rat.

The historical control data submitted should include:

a. Data from rats from the same supplier (if possible).

b. Data from all available rat studies with the Long-Evans strain conducted at the testing facility.

c. Data from each individual study should be submitted, results from the different studies should not be pooled and presented in a summary table only, although a pooled summary table may also be presented.

d. For each individual study, the following information should be provided:

- strain and source of the experimental animals
- laboratory performing the study
- dates of initiation and termination of each study
- number of male rats in the control group and the number of animals for which the tissue/organ was actually examined histologically.

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DATA EVALUATION REPORT

Study Type: Oncogenicity - rats (males only - designed to assess potential oncogenicity in the testes).

Accession No.: 247280 (original submission),
261459 (addendum)

MRID No.:

Sponsor: Sumitomo Chemical Company, Osaka, Japan.

Testing Laboratory: Hazleton Labs, America
Study No. 343-117

Date: June 11, 1981 (original study report date);
January 14, 1986 (addendum study date).

The original review of this study (see J. Doherty review dated April 11, 1983 attached) requested that additional information be provided in order to complete the review. The registrant has submitted additional information and the following discussion is an update of the review of this study.

1. Maximum Tolerated Dose

TB considers that the Maximum Tolerated Dose (MTD) was attained in this study. The key criteria reached is the weight loss in the high dose test groups for both strains of rats. For example, the CRCD strain was 13 percent below the control group weight and the Long-Evans strain was 11 percent lower. There were, however, few other signs of toxicity such as obvious behavioral signs, changes in hematology, blood chemistry, or urinalysis. The liver and testes weights (and the brain weight) were elevated in the high dose test groups.

2. Reassessment of the Histopathology Report Based on the Addendum. Individual Organ/Tissue Discussions

a. The testis. This organ was identified as a oncogenic target organ in the original review. The following is a table showing pathological lesion types reported in both strains of rats in their study.

Group(ppm)	CRCD 0	CRCD 200	CRCD 1000	CRCD 5000	Long Evans 0	Long Evans 200	Long Evans 1000	Long Evans 5000
Mineralized Seminiferous tubules	8	2	6	4	0	2	3	4
Testicular degeneration	13	14	10	18	13	10	13	19
Aspermatogenesis	8	9	7	12	6	8	8	15
Hypospermatogenesis	3	5	5	7	7	6	3	14
Interstitial cell hyperplasia	1	0	2	0	0	1	4	1
Interstitial cell tumor (unilateral and bilateral)[1]	7	7	3	16	4	3	4	22
Number examined[2]	48	48	48	48	49	50	49	49

[1]Note: The number of tumors was not reported in the revised submission in the table of nonneoplastic findings. Information on the number of tumors can be found in the original study report (EPA Accession No. 247280). The original study report did not include the number of rats for which testis tissues were examined.

[2]Note: The denominator (number examined) was provided by the study report. Since several of the testis slides were "autolysed" or "missing", TB may use a lower number for statistical evaluation of the data for the Peer Review of this chemcial.

In addition to the interstitial cell tumors as indicated above there was evidence of other tumor types in this organ but their incidence frequency or their type did not suggest a test chemical dependence. These tumors included mesotheliomas (5 in the Long-Evans strain, two each in the control and high dose test groups and one in the low dose group; and 1 in the CRCD strain), single incidences of seminoma, prostatic carcinoma (metastatic) and acinar cell carcinoma (metastatic). There were also several other types of nonneoplastic lesions present in the testes which were of occasional (1-4) incidences only and did not show evidence of test chemical related effects.

In conclusion the, data presented indicate an association between the highest test dose level of tetramethrin and increased incidences of testicular tumors. The classification of tetramethrin as an oncogen will be decided upon at a future Peer Review meeting for this chemical.

b. The liver. In the original review a question of possible oncogenicity in the liver was raised based mainly on the presence of apparently increased incidences of "neoplastic nodules" and "hepatocellular carcinoma" in the Long-Evans strain of rat. The following table shows the frequency of occurrence of these lesion types.

Dose Group (ppm)	CRCD n	CRCD Neoplastic nodules	CRCD Hepatocellular carcinoma	CRCD Total*	Long-Evans n	Long-Evans Neoplastic nodules	Long-Evans Hepatocellular carcinoma	Long-Evans Total*
Control 0	33	2	4	6	26	1	0	1
Low 200	34	0	1	1	29	5	6	10
Mid 1000	36	2	2	4	26	2	2	4
High 5000	33	3	6	8	35	2	5	6

*Total rats affected; some have both neoplastic nodule and carcinoma but were counted only once to obtain the total.

Inspection of the table of the nonneoplastic liver findings did not reveal indications of test chemical related nonneoplastic lesions in the liver. In particular, there were no incidences of hyperplasias or hypertrophies. The only evidence of test chemical effects on the liver were increased weights noted in both strains.

There was no indication of a test chemical related increase in liver tumors in the first rat study using CRCD strain rats (EPA Accession No. 247280, p. 31 of the report for this study). For example, among the males there were four incidences of hepatocellular adenomas, one each in the control and mid-dose group and two each in the low-dose group. Among the females there were two incidences reported, one each in the mid- and high-dose test groups. (Note, there were 50 controls and 40 of each test dose rats reported as having been examined.)

In conclusion, TB does not consider at this time that the available data indicate that the liver is a definite target organ for an oncogenic effect of tetramethrin. Although the data on the Long-Evans strain when the low dose group is compared with the control group is somewhat disturbing, the balance of the other data do not support evidence for a neoplastic effect. In particular there is no dose response for the next two higher doses and the two other sets of test data with the CRCD strain do not show indications of a possible effect.

A final conclusion with regard to a possible neoplastic effect in the liver of the Long-Evans strain of rat will be made by the Peer Review committee. In order to assist in this decision, the registrant should provide historical control data for the spontaneous occurrence of liver tumors including neoplastic nodules, adenomas and hepatocellular carcinomas.

c. In the original review of this study, TB noted that there were tumors described as "tissue masses-no specific organ" all of which had slightly higher incidences in the high dose group when compared to the control group. These tissue masses included fibromas, lipomas, keratoacanthomas, squamous cell carcinoma, sarcoma, fibrosarcomas and basal cell adenomas. This distribution of nonspecific tumor types partially accounts for there being a higher number of net tumors (74) in the high dose test group than in the control (41) males*. Comparision of the data from the 1981 study with the 1974 study does not demonstrate a consistancy for a test chemical related increase in these nonspecific organ types of neoplasms.

3. Overall Conclusion

CORE classification of this study is assigned as SUPPLEMENTARY. The study was designed to assess for possible oncogenic effects of tetramethrin in the rat testes. In this regard the study provides useful information. The SUPPLEMENTARY classification results from the fact that the study did not include females and because pathological examination of many of the other tissues/organs types was incomplete. A higher classification would imply a more complete study.

The study demonstrated that the MTD was achieved based on body weight loss in the high dose test groups. The study also demonstrated increased incidences of testicular interstitial adenomas in the high dose test groups for both strains of rats.

*Note: Since the study was positive for testicular interstitial tumors, the balance of the difference between the high dose group is mostly accounted for by this tumor type.

Original Review
April 11, 1983

A. Chronic Toxicity Study in Rats (Sprague-Dawley and Long-Evans) - Neopynamin Technical - Final Report [Note: males only]

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Hazleton, June 11, 1981, No. 343-117
EPA Accession No. 247280.

B. Substance Tested. Neopynamin was from lots 72875 (90.0% purity) and lot 90112 (93.6% purity). Dosages were adjusted to 100% purity for preparation of the test diets.

C. Two strains of rats were used for this study. The Charles River CD strain (CRCD) and the Long-Evans hooded strain. The first phase of this study consisted of exposing 30 males and 30 females per dose level of each strain to Neopynamin at dose levels of 0, 200, 1000 or 5000 ppm. After 1 week of exposure, the rats within a given dosing group were bred to produce a generation which had in utero exposure. After lactation and at weaning (21 days) and allowing time for the selection process, the male pups were selected for the chronic feeding aspect of this study. Thus, four groups of 50 rats from each strain were dosed at 0, 200, 1000 or 5000 ppm of Neopynamin. The duration of the feeding period was for 104 weeks.

D. Diet analysis: Beginning with week 55 samples of the test diets were saved, but there are no data which show that actual analysis was made.

E. Survival: The following table shows that survival was good for both strains of rats tested and that there was no effect of the test chemical on survival.

	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 %)

There were no compound-related changes in behavior of the test rats reported. The appearance of the rats (palpable nodules, tissue masses, and wart-like lesions) was reported as being evenly distributed among the test groups for both strains of rats.

F. Body weight and food consumption. Both of the high-dose test groups were lower in body weight at termination. The CRCD strain was 13% lower and the Long-Evans strain was 11% lower than their respective controls. Changes in body weight gain were evident in the high-dose test groups in the first year of the study. There was noted an initial but not sustained lower consumption of food in the high dose test groups.

Note for parts G, H, and I below: analysis was made on 10 rats/strain/test dose level.

G. Hematology - There were no consistent dose-related changes noted in hematocrit, Hb, RBC count, total leukocyte count (WBC), differential leukocyte count, MCV, MCHb, and MCHbC.

H. Clinical chemistry - There were no consistent dose-related changes noted in alkaline phosphatase, total bilirubin, BUN, glucose, SGPT, total protein, albumin, globulin, and albumin/globulin ratio.

I. Urinalysis - There were no consistent dose-related changes noted in the appearance, pH, specific gravity, glucose, ketones, protein, bilirubin, occult blood, or microscopic observations of the spun deposit.

J. Gross pathology: Individual gross pathology findings are presented in a comprehensive table which includes some 126 pages. Animals with a specific type of grossly observable lesion are scored with a P, a scale of 1-5 was sometimes used to indicate the degree of the lesion.

The liver and testis for both strains of rats were noted to have compound-related lesions. See discussion of these organs below under microscopic findings.

K. Organ weights: The brain, heart, liver, spleen, kidneys, and testes with epididymides, pituitary, thyroid and adrenals were weighted.

There were increases noted in the absolute and relative liver weight for the high-dose test group of both strains (the CRCD strain was 12% absolute and 31% relative higher; the Long-Evans strain was 18.4% absolute and 33.5% relative higher). Liver weight increases would be expected to occur in rats dosed with these levels of a synthetic pyrethroid.

The testis weights were elevated for the Long-Evans strain (11% absolute and 27.2% relative). Relative weight of the testis for the CRCD strain was also elevated (15.1%) but absolute weight was slightly lower (2%).

The brain relative weight was also higher (16% for the CRCD strain and 10% for the Long-Evans strain). This may be a secondary effect due to overall weight loss in this group.

A NOEL for changes in organ weights is set at 1000 ppm.

L. Histopathology. Evidence was presented that the following tissues were examined: brain, pituitary, thyroid, parathyroids, adrenals, heart, lungs, spleen, liver, kidneys, stomach, small intestine, pancreas, mesenteric lymph nodes, abdominal adipose tissue, peritoneal wall, mesentery, testes, prostate, seminal vesicles, salivary glands, thymus, mediastinum, mammary gland, urinary bladder, other lymph nodes, skin, the aorta, eyes, tongue, muscle, nasal turbinates, preputial glands, colon, cecum, ureters. It must be noted that this list of tissues was not examined for all rats. The only tissues routinely examined were pituitary, thyroid, adrenals, testis with epididymides, prostate, seminal vesicles, mammary gland and unusual lesions.

The non-neoplastic lesions are presented in a table of individual animal responses (this table covers 126 pages). The presence of a lesion is indicated by a P and other indicators (see Tables 9A and 9B). No summary table was included which tabulated the findings. There were no individual animal pathology sheets presented so that it could be determined if there was an adequate followup of gross necropsy observations by microscopy.

Oncogenic Findings

The total number of incidences reported for each strain per dose group (not including the testis which are discussed separately below) is as follows:

	Strain	
	CRCD	Long-Evans
Control	41/50	75/50
Low	60/50	80/50
Mid	60/50	60/50
High	74/50	81/50

*total incidences of neoplams of any kind (except testicular adenomas)/number of rats per groups.

For the CRCD strain, the difference between 41 for the controls and 74 for the high dose test group suggests that there may be an oncogenic target other than the testis. All dose groups for the Long-Evans strain are essentially equivalent in frequency to the control.

Individual Organ Discussion

1. The testis was indicated in the report discussion as being a target organ for the oncogenic effects of Neopynamin. The following table shows the response for interstitial cell tumors.

		Strain					
		CRCD			Long-Evans		
	n	Unilateral	Bilateral	Total	Unilateral	Bilateral	Total
Control	50	3*	4	7	4	0	4
Low	50	5	2	7	3	0	3
Mid	50	1	2	3	2	2	4
High	50	5	11	16	10	12	22

* Numbers of rats affected.

In addition to the above, 10 other incidences of various types of neoplasms were reported in the testis: 1 seminoma, 1 mesothelioma, and 1 prostatic carcinoma (metastatic), all in the mid-dose CRCD strain; 1 acinar carcinoma, metastatic (CRCD strain high-dose), 2 mesothelioma and 1 neurofibrosarcoma (metastatic) in the Long-Evans control, and 1 mesothelioma in the mid-dose and 2 in high-dose Long-Evans strain.

2. The liver. The liver showed increased weight, increased frequencies of gross lesions and has also been indicated as a possible oncogenic target in other studies with other synthetic pyrethroids. The neoplastic findings for Neopynamin in liver from this study are shown in the following table. (Only frank liver tumors are included.)

	← CRCD*				Long-Evans →			
	Control	Low	Mid	High	Control	Low	Mid	High
Neoplastic Nodules	2	0	2	3	1	5	2	2
Hepatocellular carcinoma	4	1	2	6	0	6	2	5
total	6	1	4	9	1	11	4	7

(The exact number of livers examined from each group is not known to TB at this time).

The response of the Long-Evans strain with respect to production of hepatocellular carcinomas and total of nodules plus carcinomas is disturbing. However, considering the dose levels involved (0, 500, 1000, 5000) there is no relationship between response and the test dose level. Thus, the response in the Long-Evans strain, although disturbing, is considered to be most likely spontaneous in origin. This problem will be reconsidered when the exact number of tissues examined is provided.

3. The lung. The lung has been implicated as a possible target organ for the neoplastic effects of other pyrethroids. In this study, there were no incidences of frank lung tumors in the CRCD strain. There were 3 incidences in the Long-Evans strain of bronchiolar alveolar adenoma, low-dose test group only.

4. Tissue masses. Among the CRCD rats, a large part (14 incidences) of the difference between the controls (41 instances) and the high-dose groups (74 incidences) were found to be in the group described as tissue masses-no specific organ. For example, there were 4 fibromas in the high-dose group, only one in the controls; 4 lipomas in the high-dose group, none in the controls. Similarly there were 2 keratoacanthomas, 1 squamous cell carcinoma, 1 sarcoma, 2 fibrosarcomas and 2 basal cell adenomas in the high-dose test group and none of these in the control. The pituitary had 5 more adenomas in the high dose test group than in the controls. Similarly some 14 other tissue types had 1, 2, or 3 incidences of a neoplasm type which was not present in the control. Thus, the difference between 41 and 74 (or 33 incidences) is not accounted for by a specific organ or tumor type.

Conclusion: CORE Classification of this study is reserved. This study has provided confirmatory data that the testis is a target organ for an oncogenic effect of tetramethrin.

The registrant is requested to provide the following so that review of the study may be completed and a risk assessment be conducted.

1. Tables summarizing (tabulating) the non-neoplastic findings. These tables must include the exact number of tissues and rats examined.

2. Individual animal pathology sheets which show both the gross and microscopic findings and the date of death of each rat.