4-11-83

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

002657

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: F.D.R. Gee, Product Manager 17
Registration Divison (TS-767)

THRU: O. E. Paynter Ph.D., Chief
Toxicology Branch, HED (TS-769)

SUBJECT: EPA Registration No. 10308-1. Tetramethrin (Neopynamin(R)). Review of rat chronic feeding/oncogenesis studies (2 studies), mouse range-finding study (13 weeks) and dog subchronic feeding study (26 weeks) with the insecticide Neopynamin. Identification of the testes as on oncogenic target organ for Neopynamin in rats.

Background: Tox Chem. 844

The Sumitomo Chemical Co., New York Office, has submitted several studies in support of registration of their insecticide tetramethrin (or Neopynamin(R)), a synthetic pyrethroid.

Comments:

1. Two separate rat studies indicated that Neopynamin (tetramethrin) is associated with increased incidences of testicular interstitial cell adenomas in rats. The following table illustrates this finding:

Testicular Interstitial Cell Adenomas in Rats

Dose Level	CRCD[a] (1974)	CRCD[b] (1981)	Long-Evans[b] (1981)
Control	2/50 (4%)*	7/50 (14%)	4/50 (8%)
200 ppm		7/50 (14%)	3/50 (6%)
1000 ppm	3/40 (7.5%)	3/50 (6%)	4/50 (8%)
3000 ppm	9/40 (22.5%)		
5000 ppm	14/40 (35%)	16/50 (32%)	22/50 (44%)

* Rats with adenomas/rats scheduled for lifetime feeding (as %).

a. Charles-River CD strain (Sprague-Dawley derived), study by Hazelton Labs (#343-107), dated October 4, 1974.

b. The second study was conducted to determine if the first study was reproducible with respect to production of testicular neoplasms. This study used males only of the Charles River CD strain and the Long-Evans hooded strain. The study was by Hazelton Labs (#343-117, June 11, 1981).

Based on these data using rats as test animals, Neopynamin (tetramethrin) should be regarded as a potential oncogen.

2. Core classification of the two chronic feeding/oncogenesis studies with rats is reserved. The registrant should be asked to provide additional tables which show the date of death for each rat, individual animal pathology sheets which show both gross necropsy observations and microscopic findings for each rat.

For both studies, tables listing each tissue-type examined and the exact number of animals which were examined microscopically should be prepared and submitted.

For the study dated 1981 (the second study) a comprehensive table of nonneoplastic findings should also be prepared and submitted. This table should also include the number of rats examined for each tissue type.

3. A 6-month dog feeding study with Neopynamin was also reviewed. A tentative NOEL of 1250 ppm is assigned for this study. At this level and at higher doses the liver weight is progressively increased. The increase in liver weight at 1250 ppm in the absence of associated liver pathology is considered, however, to be an adaptive rather than a true toxic response.

At 5000 ppm there is noted a failure of the females to show signs of estrus. This effect was also apparent but less evident at 2500 ppm. The albumin level was decreased at 5000 ppm.

Core classification of this study is reserved until TB receives and reviews the addendum to this study referred to in the letter of E. J. Gerberg to F. D. R. Gee dated April 26, 1982.

4. A 13-week mouse feeding study, which was a pilot dose range finding study for the oncogenicity study with mice, was reviewed. This study showed that Neopynamin at 500 ppm, lowest dose tested, and above resulted in the depression of the weights of several endocrine organs and other organs. The effects of Neopynamin in mice will be reevaluated pending receipt of the mouse oncogenesis study (expected in October 1984).

5. T.B. also requests to review other information referred to in a letter from Y. Nishizawa to E. J. Gerberg dated April 2, 1982. This letter refers to a rat reproduction study and fertility studies in rats, teratological studies in rats and rabbits and perinatal and postnatal development in rats. The reproduction study was supposed to have been submitted to EPA on July 1, 1982. This letter also refers to a comprehensive toxicological evaluation of the human health significance of

002657

the toxicity problems associated with tetramethrin. This report, which was supposedly prepared by the Sumitomo Chemical Co., was expected to be sent to EPA by July 1, 1982. TB requests that this overall assessment be submitted to EPA for review.

6. Note to PM. The rat studies, mouse range-finding study and protocol for the mouse oncogenesis study and the dog subchronic feeding study have been retained by TB for future reference.

Recommendations:

1. Neopynamin was clearly shown to be oncogenic in two strains of rats. Toxicology Branch recommends against the registration of any new uses for this chemical.

2. With respect to existing uses for this chemical, a risk assessment should be performed as soon as possible. Toward this end, Registration Division is requested to ask Exposure Assessment Branch (EAB/HED) to prepare exposure estimates for all existing uses of tetramethrin and submit these estimates to Toxicology Branch.

3. Registration Division is also requested to ask the registrant (Sumitomo) for all the information described above under comments.

4. Toxicology Branch will prepare a risk assessment for this chemical as soon as possible.

John Doherty, Ph.D. 4/7/83
Toxicology Branch
Hazard Evaluation Division (TS-769)

4/11/83

A. Two-Year Dietary Administration in the Rat - Neopynamin - Final Report 002657

Hazleton Labs, October 4, 1974, #343-107
EPA Accession No. 247280

B. Substance Tested. The substance tested was Neopynamin - described as a coarse white powder or coarse white granular material, unpleasant odor. The precise purity or lot numbers of the test material were not given. For the purposes of determining the dosage levels, 100% purity was assumed by the testing laboratory.

C. The test rats used were Charles River CD. They were obtained from parental rats which were dosed with Neopynamin. For example, the testing laboratory was conducting a multigeneration reproduction study with Neopynamin and the rats bred for the F_1A generation (Hazelton project number 343-106) were selected for the two year chronic feeding study. The parental rats were dosed with 0, 1000, 3000, or 6000 ppm of Neopynamin. There was noted a decrease in body weights for the rats at the initiation of the experiment as indicated in the table in Part E below for all dose groups.

The experiment was initiated with 60 rats of each sex in the control groups and 50 rats of each sex for the dosed groups. The protocol called for an interim sacrifice at 52 weeks of 10 rats per sex per group. Thus, there were 50 control rats and 40 treated rats per sex per group scheduled for dosing for the 2-year period. At sacrifice, the rats were exsanguinated under pentobarbital anesthesia.

D. Fresh diets were prepared weekly. On a mg/kg/day basis the test rats received 43, 115 and 210 mg/kg/day for males and 50, 140 and 300 mg/kg/day for females.

E. Survival and reactions to the chemical in the diet. The overall survival of the rats is shown in the following table.

	Males	Females
Control	33/50 (66%)	36/50 (72%)
Low	17/40 (43%)	26/40 (65%)
Mid	29/40 (73%)	31/40 (78%)
High	22/40 (55%)	23/40 (58%)

This information shows that overall survival is good. The ideal of having 50% survival or 25 rats being dosed for 2 years was nearly attained. There is no indication that the presence of the Neopynamin in the diet was related to increased deaths.

The rats were reported as being observed every day and there were no effects of the test chemical in the overall appearance or behavior of the rats.

F. The rats in this experiment did not have equal body weights at the initiation of the study and consequently there were weight differences throughout the study as indicated in the following table.

Weeks Start	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
0	148	131 1/ 89	118 80	98 66	128	110 4 86	101 79	92 72
26	594	573 96	530 89	492 83	332	317 95	284 86	262 79
52	664	636 96	567 85	545 82	398	373 94	336 84	296 74
76	688	611 89	589 86	540 78	442	392 89	366 83	317 72
100	627	571 91	557 89	530 85	463	430 93	396 86	398 71

1/ Top line weight in grams, lower line as % of control weight.

Assignment of a NOEL for decrease in body weight gain is complicated by the differences in body weight at the initiation of the experiment for both sexes. However, because no progressive decline in body weight was noted over the 2-year course of dosing, it is apparent that Neopynamin does not cause serious depressions in body weight in mature rats.

Food consumption was reported to be lower for all treatment levels.

G. Hematology - Determinations were made at weeks 13, 26 (groups 1 and 4 only), 52 and 104 for all groups. The parameters measured were hematocrit, Hb, erythrocyte counts, total and differential leukocyte counts and prothrombin time. Five rats of each sex per group were assayed.

No consistent dose related effects were noted.

NOEL > 5000 ppm.

H. Clinical Biochemistry - Determinations were made at weeks 13, 26 (groups 1 and 4), 52 and 104 weeks for all groups. The parameters determined were fasting blood sugar, BUN, total serum protein, bilirubin, serum alkaline phosphatase, serum glutamic-pyruvic transaminase, serum glutamic oxaloacetic transaminase, and serum protein electrophoresis. At weeks 52 and 104, serum Na^+, K^+, Cl^-, CO_2, Ca^{++} and albumin were determined. Five rats per sex from each group were assayed.

No consistent dose-related effects were noted.
NOEL > 5000 ppm.

I. Urinalysis - Determinations made at same frequencies as above. Determinations were made on specific gravity, pH, glucose, ketones, protein, bilirubin, and microscopic examination of the sediment.

No consistent dose related effects were noted.
NOEL > 5000 ppm.

J. Gross pathology - The summary table indicates that most of the organs/tissues were examined. The following organs/tissues are specifically discussed.

J.1. The liver - Included because this organ is recognized as being a target organ for the metabolism and in some cases toxicity of pyrethroids. (A page is apparently missing which lists the gross necropsy of the rats dying during the study including lung and liver data.) The gross necropsy for the survivors revealed that there were higher incidences of "enlarged lobes" among the high dose group males (but not females) whereas the females had higher incidences of cystic appearance. There was otherwise no evidence of a neoplastic response as evidenced by the frequency of masses or nodules being increased with the level of Neopynamin in the diet.

J.2. The testes - There were higher frequencies of grossly observable lesions described as "enlarged firm" and "subcapsular yellow material" for the mid- and high-dose test groups. (Refer to oncogenic findings in this organ below.)

J.3. The kidney - Several types of rather general changes in appearance were noted in this organ at slightly higher frequency for the dosed rats than for the controls, but clear dose responses were not noted.

The gross appearance of other organs did not provide indications that they were target organs for Neopynamin. Autolysis was not serious for this study. Only a single rat was considered by the laboratory as being too damaged for use.

K. Organ weights - The thyroid, heart, liver, spleen, kidneys, adrenals, testes (not ovaries) were weighed for the 1-year interim sacrifice groups and the survivors.

k.1. The liver showed signs of increased weight at all dose levels as follows.

002657

Relative Liver Weight

	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
52 Weeks	2.65	3.09 1/ +17% 2/	3.57 1/ +35%	3.86 1/ +46%	2.51	2.77 1/ +10%	3.18 1/ +27%	3.32 1/ +32%
104 Weeks	2.99	3.31 +11	3.76 1/ +26%	4.16 1/ +39%	3.08	3.33 + 8%	3.20 + 4%	4.06 1/ +32%

1/ Stat. sig. at the 0.05 level.
2/ % increase in relative weight.

K.2. The testes. Effects on absolute or relative weight were noted for the high-dose group males at both the interim and terminal sacrifices. These were of the order of -11% at 52 weeks (absolute weight) and +16% at terminal sacrifice. See oncogenic discussion of testes below.

The other organs did not show differences in weight in consistency or magnitude to be of obvious toxicological concern.

NOEL < 1000 ppm (LDT), effects on liver weight are noted but these may be a pharmacological response related to detoxification rather than a true toxicological response.

L. Histopathology - Microscopic examinations of a series of 26 typical organs were scheduled for routine examination for the control and high dose test groups. Sections of liver and kidney as well as any unusual lesions were examined for the low and mid dose test groups.

Individual animal pathology reports were not presented. Thus, it is difficult to tell if gross necropsy observations were adequately followed up microscopically. Pathology data are presented as tables of incidences with information on the number of tissues examined. Additional tables indicate the animal's number and degree (as graded 1-4) of lesions observed. Considerable effort is required on the part of the reviewer to evaluate the pathology of a given tissue for all the rats in this study because there are separate tables for early deaths and survivors.

Specific organ discussion:

1. The testes showed a positive oncogenic response as follows:

Group	n	Rats With Interstitial Cell Adenoma		Rats With Interstitial Cell Hyperplasia[1/]	
Control	50	2	(4%)[2/]	10	(20%)
Low	40	3	(7.5%)	8	(20%)
Mid	40	9	(22.5%)	14	(35%)
High	40	14	(35%)	15	(38%)

[1/] Not neoplastic. [2/] as percent rats available

2. The kidney showed some evidence of differences in gross necropsy (although not definite). There were increased incidences of "cystic" collecting tubules as follows: There were 12/50 (24%), 14/40 (35%), 12/40 (30%) and 20/40 (50%) among the males; there were 6/50 (12%), 5/40 (12.5%), 0/40 (0%) and 8/40 (20%) among the females. Both sexes appear to be affected in the high dose test group. However, a definite test chemical effect is not established for induction of cysts in the kidney. However, a single male and a single female (both high dose groups) had cortical adenoma. A single female (high dose group) had fibrosarcoma.

3. The liver - relative liver weights were increased at all doses (at one year). The liver is a known target organ for the effects of pyrethroids because other studies with these agents usually show increases in hypertrophy or hyperplasia.

   There were no unusual lesions in the liver to suggest that this organ was affected by the chemical. Increases in hyperplasia were not reported. Focal bile duct dilation was increased in the high-dose group, but the increase is not considered of sufficient magnitude or consistency to be conclusively related to the test chemical.

   Only six rats had hepatocellular adenoma: 4 males (a control, two low dose, and a mid dose test rat) and 2 females (a mid- and high-dose test rat.) There was a single incident of cholangiocarcinoma in the high-dose group females.

4. The lung. There were no lung tumors reported. Nonneoplastic pathology of the lungs was not remarkable.

5. The thyroid - in several longterm studies with pyrethroids the thyroid has shown some evidence of dose-related pathology. There were a total of 6 rats which were reported as having follicular adenoma. (Three among the males, one in the low-dose group and 2 in the high dose group, three among the females, one in the controls and two in the high-dose test group.) Nonneoplastic pathology of the thyroid was unremarkable.

6. Tables I and II below discuss other oncogenic aspects of this study.

002657

Table I. Total Neoplasms

	Males			Females	
	n*	Rats Affected with Neoplasms	Incidences	Rats Affected with Neoplasms	Incidences
Control	50	30	36/34**	42	65
Low	40	18	19/16	30	48
Mid	40	19	26/17	27	56
High	40	22	33/19	30	45

*n = rats in each group

** Total incidences/not including rats with interstitial cell adenoma in the testes.

Table II. Distribution of Incidences of Neoplasms*

	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
Pituitary (adenoma)	15	8	7	6	22	11	19	22
Mammary gland fibroadenoma, cyst adenoma adenocarcinoma	1	0	0	0	38	30	29	12
Skin (sub cutis, fibroma, papilloma hemangiosarcoma aquamous cell carcinoma, keratocanthana	5	3	5	1	2	0	2	2
Pancreas - islet cell adenoma	6	0	0	2	0	0	0	1
Thyroid	0	1	0	2	1	0	0	2
Adrenals	3	0	1	2	1	2	1	1

* The actual number of individual rats examined for each tissue was not provided.

Other neoplasms were distributed among all dose groups in a nondose dependent manner.

Conclusion: Core Classification of this study is reserved. The registrant must provide individual animal pathology sheets which show the date of death of each rat, all gross necropsy findings and all microscopic findings. These data are necessary for EPA to do a risk assessment. In addition, the registrant must provide a table listing each tissue examined and number of animals for which actual tissue analysis was made for that tissue.

This study provides sufficient data to conclude that there is a dose-related increase in rats with interstitial cell adenomas in the testes.

002657

The NOEL is tentatively set at <1000 ppm (the lowest dose level tested). At this level there is noted an increase in liver weight. At the higher dose levels there was a progressive increase in liver weight. There were no increases in pathological lesions in the liver which were associated with this weight gain. The level of 1000 ppm may be used in ADI determinations because this increase in liver weight is considered by Toxicology BRANCH to be adaptive rather than a true toxicological response to the test chemical.

002657

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

Hazleton, June 1?, 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 follow-up 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	-	2	3	-	3	2	-
Hepatocellular carcinoma	4	1	2	6	1	2	2	1
total	6	1	4	9	1	11	4	1

(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.

002657

Subchronic Toxicity in Dogs - Neopynamin - Final Report (26 weeks)

Hazleton (America) July 17, 1981, #343-127
EPA Acc. No. 247280

Four groups of 6 male and 6 female beagle dogs were dosed with 0, 1250, 2500 or 5000 ppm of Neopynamin (technical, lot #00208, 94.6% purity) in their diets. The dosing period was for 26 weeks. Blood analysis (hematology and clinical chemistry) and urinalysis were conducted at weeks 0, 4, 8, 13, 17, 21 and 26.

Results:

1. There were no deaths. There were some signs of nervous system stimulation noted in the mid- and high-dose groups. These signs would be expected for a pyrethin administered at high dosage. However, the report states that these signs were of low frequency (and apparently also of low intensity). The effects of the test chemical on the estrus cycle are discussed below.

2. Pronounced effects on body weight gain and food consumption were not reported.

3. No effects were noted on any of the hematology parameters investigated (hematocrit, hemoglobin, erythrocyte count, platelet count and total and differential white blood cell counts). No effects were noted in any of the urinalysis parameters investigated (appearance, specific gravity, protein, pH, glucose, bilirubin, ketones, urobilinogen, reducing substances and microscopic examination of the sediment.

4. The clinical chemistry parameters investigated included: total cholesterol, BUN, SGPT, SGOT, lactate dehydrogenase, alkaline phosphatase, total protein, albumin, albumin/globulin ratio, fasting glucose, Na^+, K^+, Ca^{2+}, Cl^-, direct bilirubin, total bilirubin and globulin.

   Of these several parameters there were possible dose-related deviations noted in BUN, glucose, Ca^{++}, total protein, albumin, albumin/globulin ratio, Cl^- and bilirubin. Consistency in these deviations was not evident for bilirubin, Cl^- glucose, BUN, Ca^{++} (down 4% to as much as 13%) and total protein.

   The albumin content was decreased for the high dose males at weeks 4-26 (~22%) and for high dose females at weeks 8-21 (~17%). The cholesterol content for all dosed dogs was higher than for the controls, but dose response relationships were not evident and statistical significance was only occasionally attained.

   It is concluded that a NOEL for changes in clinical chemistry is 2500 ppm. At 5000 ppm (LEL) there is consistancy in depression of albumin levels in both males and females. The toxicological significance of this depression is uncertain.

5. Ophthalmologic examination (performed after 26 weeks using an indirect ophthalmoscope). No treatment-related changes noted.

002657

6. Organ weights - At termination, the absolute and relative weight of the brain, heart, liver, thyroid, kidneys, testes with epididymides, ovaries, adrenals and pituitary were determined. Of these there were indications of adverse effects on liver and ovary weights as shown in the following table.

		Liver		Ovaries
		Males	Females	Females
Control	ab.	232.17	229.17	1.440
	rel.	2.498	2.629	0.0164
Low	ab.	299.17 (29%)	233.67 (2%)	1.575
	rel.	2.9[illegible] (17%)	2.583	0.074
Mid	ab.	351.17 *(51%)	272.333 (19%)	1.3833
	rel.	3.009 (20%)	3.188 (21%)	0.0155
High	ab.	370.53 *(60%)	266.000* (16%)	0.7383* (-49%)
	rel.	3.453 *(30%)	3.286 (25%)	0.0091* (-45%)

n = 6 for all determinations
(% difference)
* statistically significant

7. Gross Necropsy - There were no dose-related increased incidences of lesions that were observable at gross necropsy. In particular, there were no unusual findings in either the livers or the ovaries.

8. Histopathology - A comprehensive list of tissues were examined from all dogs on the study. The following comments relate to the histopathological findings.

   1. Ovaries. There were 4, 4, 2, 0 (of 6 dogs) which had evidence of corpora lutea present. Note that ovary weight was decreased and the females in the high dose group did not show signs of estrus.

   2. Uterus. There were 4, 4, 3, 0 dogs (of 6 dogs) which showed "endometrial hypertrophy." This provides some additional evidence of an effect on the female reproductive tract.

   3. The only pathology reported in the liver was "focal lymphohistocytic infiltration, focal neutrophil infiltration, hepatocyte vacuolar change and centrilobular vacuolar change." Most dogs were affected with the first listed lesion. The other lesion types were reported as isolated occasions only.

Conclusion: CORE Classification of this study is reserved. A NOEL of 1250 ppm is assigned. At 5000 ppm there is noted a definite effect in the females as evident by failure to show signs of estrus (no dogs in the high-dose group showed signs of estrus). This effect was less evident at 2500 ppm. This was also evidenced by a decrease in ovary weight and differences in the pathology of ovaries and the uterus.

At 2500 ppm, there is noted an increase in liver weight (~50%). The increase noted at 1250 ppm (~29%), which was not reported as being

statistically significant for the low-dose group males is likely a result of the test chemical (pyrethroids are known to increase liver weight). Since there was no associated pathology in the liver, this liver increase in weight is considered to be due to adaptation of the dog to the test chemical.

There was also noted a decrease in the blood level of albumin at 5000 ppm.

TB requests that the addendum to this study mentioned in the letter dated April 26, 1982, from E. J. Gerberg to F. D. R. Gee be submitted to this branch for review.

002657

13-Week Dose Range Finding Study in Mice - Neopynamin - Final Report Hazleton, August 27, 1981, #343-135

4 groups of 20 male and 20 female B6C3F1 mice were dosed with 0, 500, 1500 or 5000 ppm of Neopynamin (lot number not stated but the purity was stated as being 93.3%) for 13 weeks. The purpose of this study was to determine dose levels for a chronic toxicity/oncogenesis study.

Results:

1. There were no deaths or obvious clinical signs of intoxication noted that were attributed to the test chemical.

2. The high-dose groups (male and female) showed reduced weight gain but higher level of food consumption. At termination, the males (-9%) and females (-7.5%) were statistically significantly lower in body weight.

3. Organ weights (the brain, thyroid, adrenals, pituitary, heart, liver, spleen, kidneys, testes or ovaries were weighted at termination). Several organs are discussed as follows:

   Liver: The high-dose group males (+21%) and females (+14%) were elevated in relative weight. This observation is consistent with known effects of pyrethroids. The mid-dose group males were also slightly elevated (+6% relative weight).

   Other organs having deviations in relative weight are shown in the following table:

	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
Brain	-	-	-	+12.4%	-	-	-	-
Thyroid	-	-16%	-16%	-57%		-24%	-36%	-42%
Adrenals	-	-20%	-13%	-32%	-	-	-20%	-25%
Pituitary	-	-	-	-45%	-	-	-18%	-43%
Testes	-			+10%				
Ovaries					-	-17%	-35%	-55%
Spleen	-	-	-	-	-	-	-	-15%
Kidneys					-	-	-	+7%

Toxicology Branch notes in particular the changes in organ weights in the endocrine glands (thyroid, adrenals, pituitary). These occur in both sexes, and in several cases, also in the low dose groups as well as being in a clear dose-response manner. This chemical must be a regarded as having adverse effects on the endocrine organs in mice. The effects on the ovaries are consistent with effects noted in dogs.

The effects of Neopynamin on these organs must be reevaluated when the long-term mouse study is submitted.

4. Gross necropsy - There were no dose related gross necropsy observations noted. No histopathology or microscopic observations were made.

Conclusion: This study is Core Supplementary. Several organs appear to be affected by dietary administration of Neopynamin. The low dose test group (500 ppm) may be causing decreases in the thyroid, adrenals and ovary weight. The pituitary and also the brain, kidneys and spleen may be affected by dietary administration of Neopynamin. The effects on these organs must be reevaluated when the mouse lifetime feeding study is submitted.

Note: The mouse oncogenicity study was initiated at Hazleton Laboratories, Vienna, Va., on January 11, 1982, and the final report is expected to be completed by October 1984. (See letter from D. H. Pence to Y. Nishizawa February 11, 1982). The dietary levels selected for this study (presumably based on the results of the 13-week mouse study, above) are 0, 12, 60, 300 and 1500 ppm. A copy of the study protocol (dated (February 3, 1981) was included with the 13-week range finding study.