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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Neopynamin (tetramethrin) - Submission of Toxicity
Data to Address Data Gaps Identified in Memorandum
of October 31, 1985 by J. Doherty

EPA Registration No. 10308-1
Caswell No. 844
Project No. 1753
Record No. 173893
Accession Nos. 262776 thru
262783 (except 262779)

FROM: William Dykstra *William Dykstra 7/20/88*
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THRU: Edwin Budd, Section Head
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*Eddy
7/21/88
Meyers
7/22/88*

Requested Action

Review toxicity data submitted in response to data gaps.

Background

Neopynamin[®] (tetramethrin) has been shown to produce a significant increase in interstitial cell adenomas in the testes of male rats. This oncogenic finding has been observed in both Sprague-Dawley and Long-Evans strains of rats. The first study conducted in 1974 with Sprague-Dawley rats (males and females) showed a positive response among the males for increased incidence of testicular adenomas for both dosage level test groups receiving 3000 and 5000 ppm of tetramethrin.

The second study was designed to confirm or otherwise clarify the finding of the first study and consisted of males only of both the Sprague-Dawley and Long-Evans strains of rats. This later study (1981) showed that dosing rats at 5000 ppm resulted in cell adenomas as in the first study. Thus, potential neoplastic effects of tetramethrin were confirmed in independently executed studies.

In the October 31, 1985 memorandum from J. Doherty to T.A. Gardner, TB requested additional toxicity data and studies to fulfill data gaps for tetramethrin.

In the letter of April 28, 1986, from K. Fujimoto to E.J. Gerberg, the registrant (Sumitomo) has responded to the data gaps identified by J. Doherty.

In the May 5, 1986, letter from E.J. Gerberg to A.E. Castillo of EPA, the registrant listed the following attachments (all of which, except for attachment 3, are in EPA Accession No. 262776):

- A. Subchronic toxicity study in dogs, Neopynamin. Addendum to final report. September 1, 1981 (IT-11-0100).
- B. Combined chronic toxicity and oncogenicity study in mice, Neopynamin. Final Report. April 17, 1986 (IT-61-0193). [In EPA Accession Nos. 262773 to 262788, except 262779.]
- C. Three-generation reproduction study - rats. Sumithion and Neopynamin. Final Report. October 16, 1973 (IT-31-0025).
- D. Eye and skin irritation of Neopynamin in rabbits. February 4, 1977 (IT-60-0014).
- E. Acute oral and dermal toxicities of Neopynamin in rats and mice. March 10, 1977 (IT-70-0003).
- F. Six-month oral toxicity study with Neopynamin, or 3,4,5,6-Tetrahydrophthalimidomethyl di-cis, trans chrysanthenate in rats. January 27, 1977 (IT-60-0015).
- G. Subchronic (13-week) inhalation toxicity with Neopynamin in rats. April 1978 (IT-61-0012).
- H. Studies on mutagenicity of Neopynamin with bacterial systems. June 13, 1977 (IT-70-0003).

- I-1. Metabolism of tetramethrin in houseflies and rats in vitro. 1974 (IM-80-0002).
- I-2. Biochemical studies on the mode of action of Pyrethroid insecticides. Part 1., Metabolic fate of Phthaltrin in mammals. 1968 (IM-80-0003).
- I-3. Degradation, metabolism and toxicity of synthetic pyrethroids. April 1976 (JG-50-0003).

Additionally, the registrant stated in the same letter that:

"Sumitomo has no data on the acute dermal LD50 (rabbit) requirement. Therefore a study will be conducted to fulfill this data gap."

"Please note that we submitted a study entitled: 'Chronic toxicity study in rats, Neopynamin technical.' Addendum to final report (HLA Project No. 343-117). January 7, 1986 (IT-61-0191). This was submitted on February 4. The addendum responds to three of four requests for additional information upon the 1974 and 1981 rat chronic studies. The fourth request will be met by a submission to be made by the end of November 1986."

"With this submission, Sumitomo is responding to all the data gaps identified in Dr. Doherty's October 31, 1985 review, with the exception of the acute dermal study and certain data from the 1974 and 1981 rat chronic studies. We therefore look forward to the Agency's review of our submissions."

Conclusions and Recommendations

1. The addendum to the subchronic dog study is acceptable. The study is classified as Core Minimum data.
2. The combined chronic toxicity and oncogenicity study in mice (Attachment B, EPA Accession Nos. 262778 through 262788, except 261779, has been previously reviewed by TB in a separate memorandum by William Dykstra, dated June 6, 1988. The study was classified as Core-Guideline and no oncogenic potential for tetramethrin, under the conditions of this study, was demonstrated. The systemic NOEL was 12 ppm. At the LEL of 60 ppm, there were decreased absolute and relative weights of the thyroid and pituitary in male mice.

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3. With respect to the Neopynamin reproduction study, based on pup body weight, the NOEL of the study is 1000 ppm. However, the study was only an F1a generation study and individual animal data were not reported. The study is classified as Core Supplementary and cannot be upgraded by itself because only an F1a generation was produced.
4. The primary eye and skin irritation studies are acceptable as Core Minimum studies. Technical grade Neopynamin is considered Toxicity Category III for eye effects and Toxicity Category IV for skin effects.
5. The acute oral and dermal toxicity studies on technical grade Neopynamin in mice and rats are both classified as Core Supplementary and are not acceptable. Both studies should be repeated. See detailed review for additional information.
6. The 6-month rat oral toxicity study with Neopynamin is considered an invalid study. No pathology report and no individual animal data were present in the submission.
7. The 13-week inhalation study with Neopynamin is classified as Core Supplementary. Individual animal data were not provided. This study may possibly be upgraded if considerably more detailed information on individual animals were to be provided, including individual necropsy and histopathology sheets.
8. The submitted microbial mutagenicity studies are acceptable and support the registration. In addition to the submitted studies, current guidelines require mammalian assays for all three endpoints, gene mutation, chromosomal aberration, and repair.
9. The submitted metabolism reports are classified as Core Supplementary data since these published articles do not present individual data. The excretory and metabolic fate of tetramethrin in the rat has been partially characterized in these reports.
10. EPA Accession No. 262777 contains "the position of Sumitomo Chemical Company, Ltd., regarding the regulatory significance of benign tumors in male rats noted in two chronic studies of Neopynamin." See the attached cover letter from E.J. Gerberg to A.E. Castillo, dated May 5, 1986, for a listing of the specific contents of this volume. The information submitted in this volume will be considered by

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TB when it assesses the oncogenic potential of tetramethrin. This will be done in a future and separate memorandum(s).

Review

- (1) Subchronic Toxicity Study in Dogs; Neopynamin; Addendum to Final Report; Hazleton Labs America; No. 343-127A; September 1, 1981; Sumitomo No. IT-11-0100.

Note - This submission is a pathology addendum to a 26-week subchronic feeding study in dogs (Hazleton Labs America; No. 343-127; July 17, 1981) that was previously reviewed and classified as Core-reserved--pending submission of this addendum, which was referred to in a letter dated April 26, 1982 from E.J. Gerberg to F.D.R. Gee (of EPA). A copy of the initial review of this study (by J. Doherty, dated April 11, 1983) is appended to this memorandum. The tentative conclusions by J. Doherty are now confirmed and the study is classified as Core-Minimum. The NOEL for the study is 1250 ppm. The LEL is 2500 ppm.

The pathology addendum consisted of additional sectioning and reexamination of the ovaries to further evaluate the compound-related absence of estrus activity in the high-dose females. The findings reported in this addendum replace those for the ovary in the original report.

The results show the absence of corpora lutea in high-dose females indicating that recent ovulation had not occurred.

The table below (presented in the report) shows the type and incidence of ovarian findings:

<u>Findings</u>	<u>Group</u> No. Animals Examined	Sex --- Female ---			
		<u>1</u> 5	<u>2</u> 6	<u>3</u> 6	<u>4</u> 6
Corpora lutea (No. seen in two sections)		4	4	3	0
Ovarian cysts		1	0	0	0
Primordial follicles		5	5	5	5
Primary follicles		5	5	5	5
Secondary follicles		5	5	5	5
Mature follicles (Graffian)		5	5	5	5

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Conclusion

High-dose female dogs did not have corpora lutea in the ovaries, indicating that recent ovulation had not occurred.

Classification

Minimum; the reserved status of the classification is changed to minimum.

Note: New pages 21, 22, and 72 were submitted as correction pages for incorporation into the subject report dated July 17, 1981:

Page 21 - Diet analysis
Page 22 - Incidence of observed toxic signs
Page 72 - Individual clinical signs, distended abdomen in females

- (2) Three-Generation Reproduction Study - Rats; Sumithion and Neopynamin; Final Report; Hazleton Labs America; No. 343-105; October 16, 1973; Sumitomo No. IT-31-0025.

Test Material: Neopynamin; received from Sumitomo Chemical Company, Ltd., on December 30, 1971. The test material was a coarse white powder which, for dosing purposes, was assumed 100% active ingredient.

Note: The reproduction study using sumithion is not being reviewed.

Randomized groups of 15 male and 30 female Sprague-Dawley rats were used in the experiment and received diets of 1000, 3000, and 6000 ppm through weaning of the first filial generation (F_{1a}) only. The control group had 20 males and 40 females.

The parental male and female rats were maintained in individual cages and fed the appropriate diet until they reached maturity (week 9). Mating was between one male and two females within each group for 3 weeks. Following mating, all animals were returned to their individual cages.

Twenty-four hours after birth, the litters were randomly reduced to a maximum of eight pups to be nursed. Pups were weaned, examined for gross abnormality, and discarded.

The reproduction indices were derived as follows: fertility index, number of pregnancies divided by numbers of females mated; gestation index, number of litters born divided by the number of pregnancies observed; live birth index, number of pups born alive divided by the number of pups born;

lactation index, number of pups weaned divided by the number of pups nursed.

Statistical analysis of the data was performed with $p < 0.05$ being significant.

Results

Mean body weight of parental males and females were decreased at 6000 ppm test material at week 9 during the growth phase.

The live birth index for the 3000 and 6000 ppm level pups was significantly higher than the live birth index for control pups.

The lactation index for the 6000 ppm pups (38.4%) was significantly less than the 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 the control group as shown below:

<u>Mean Weight of Pups and Weaning</u>	<u>ppm</u>			
	<u>Control</u>	<u>1000</u>	<u>3000</u>	<u>6000</u>
Males	51.7	50.4	46.1*	33.5*
Females	49.6	47.8	43.7*	36.8*

* $p < 0.05$

Conclusion

Based on pup body weight, the NOEL for this study is 1000 ppm. However, the study was only an F₁ generation study and was very under-reported. For example, individual data were not provided.

Classification

Core-Supplementary. This study cannot be upgraded by itself because only an F₁ generation was produced.

- (3) Eye and Skin Irritation of Neopynamin in Rabbits;
 Institute for Biological Science, Hyogo, Japan;
 February 4, 1977; Sumitomo No. IT-60-0014.

Test Material: Neopynamin, Lot No. 40505; Purity 91.0%.

Eye Irritation: Fifty mg of test material was instilled in the left eye of eight rabbits. The rabbits were divided into two groups.

Group I (five rabbits): 5 minutes after application, the eye was washed with 300 mL of distilled water for 3 minutes. Group II (three rabbits): the eye was washed as above after 24 hours.

The right eye served as a control. Scoring was done at 1, 24, 48, and 72 hours and at 7, 14, and 21 days.

Results

Very slight erythema and edema were observed in the conjunctivae of 2/3 rabbits in group II. This irritation was reversible in 48 hours. No corneal involvement was found.

Toxicity Category: III

Classification: Minimum

Skin Irritation: Test material of 0.5 g was applied to intact and abraded skin under occlusion for 4 hours in six male albino rabbits. Scoring was made at 4, 24, 48, and 72 hours and at 7, 14, and 21 days.

Results

No erythema or edema was observed at any time in the intact and abraded skin.

Toxicity Category: IV

Classification: Minimum

(4) Acute Oral and Dermal Toxicities of Neopynamin in Rats and Mice; Institute for Biological Science, Hyogo, Japan; March 10, 1977; Sumitomo No. IT-70-0003.

Test Material: Neopynamin technical; Lot No. 40505; purity 91.3%.

a. Mice, Oral LD₅₀

Groups of 10 male and 10 female mice received oral dosages of 770, 1000, 1400, 2000, and 2500 mg/kg of test material dissolved in corn oil. The volume was 10 mL/kg. Observation was for 14 days.

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Results: LD₅₀ = 1920 mg/kg (males)
LD₅₀ = 2000 mg/kg (females)

Toxic signs: Hypersensitivity, muscular fibrillation, tremors, and clonic convulsion at 1000 mg/kg and above. The onset of symptoms developed within 30 minutes posttreatment. Death of animals was observed 1 to 2 hours after dosing and the toxic signs of surviving animals disappeared in 4 to 6 hours.

Necropsy: No gross lesions were observed.

Toxicity Category: (III)

Classification: Supplementary (The mice were not fasted prior to dosing.)

b. Rats, Oral LD₅₀

Groups of 10 male and 10 female Sprague-Dawley rats received oral dosages of 1000, 2500, and 5000 mg/kg of test material in corn oil. The volume was 10 mL/kg. Observations were for 14 days.

Results: No deaths.
LD₅₀ > 5000 mg/kg.

Toxic Signs: No toxic signs.

Necropsy: No gross lesions were observed.

Toxicity Category: (IV)

Classification: Supplementary. (The rats were not fasted prior to dosing.)

c. Mice and Rats, Dermal LD₅₀

Groups of 10 males and 10 female dd mice and Sprague-Dawley rats received dosages of 1000, 2500, and 5000 mg/kg of test material dissolved in corn oil on the shaved skin under occlusion for an unknown duration of exposure. Observation was for 14 days.

Results: No deaths.
Dermal LD₅₀ > 5000 mg/kg mice
Dermal LD₅₀ > 5000 mg/kg rats

Toxic Signs: No toxic signs.

Necropsy: No gross lesions were observed.

Toxicity Category: (IV)

Classification: Supplementary. (The test material should not have been dissolved in corn oil and the duration of exposure was not reported.)

- (5) Six-month oral toxicity study with Neopynamin or 3,4,5,6-tetrahydrophthalimidomethyl dl-cis, trans chrysanthemate in rats; Institute for Biological Science, Hyogo, Japan; January 27, 1977; Sumitomo No. IT-60-0015.

Test Material: Neopynamin, purity 91.3%, Lot No. 40505.

Randomized groups of 16 male and 16 female Sprague-Dawley rats were fed with the diet containing 0, 500, 1500, and 5000 ppm of test material on an ad libitum basis for 6 months. (Two female rats in the 500 ppm group were lost by accident immediately after initiation of the study.) Rats were housed four to a cage.

Criteria evaluated included clinical signs, body weight, food consumption, and water consumption.

Urinalysis was performed on nine male and nine female rats from the control and highest dose at weeks 4 and 26. Measurements included glucose, occult blood, ketones, protein, bilirubin, and urobilinogen.

At termination of the 6-month feeding, the rats were fasted for 24 hours and anesthetized with diethyl ether. The following hematologic and blood biochemical data were obtained individually.

Hematologic Examination: Erythrocyte count, leucocyte count (including differential, by giemsa staining method), hemoglobin, thrombocyte, and hematocrit.

Blood Biochemical Examination: Sodium, potassium, calcium, albumin, glucose, BUN, total protein, uric acid, bilirubin, SGOT, SGPT, SAP, cholesterol, creatinine, α -lucine aminopeptidase, and cholinesterase.

Following necropsy, selected organs were weighed. These organs included brain, lung, heart, spleen, liver, kidney, testis or ovary, thyroid, adrenal, and pituitary.

All organs and the following tissues were examined histologically: brain, eyeball, spinal cord, trachea, lung, heart, spleen, bone marrow, mesenteric lymph node, thymus, esophagus, stomach, small and large intestine, salivary gland, liver, pancreas, kidney, urinary bladder, testis, prostate, ovary, uterus, pituitary, thyroid, adrenal, and skin.

Statistical Analysis: Body weight, hematologic and blood biochemical values, organ weight and ratio of organ weight to body weight were statistically analyzed; mean values of each test group were compared with those of the control group by using the Student t-test.

Results

There were no compound-related toxic signs during the study. There was no compound-related mortality. One male rat at 500 ppm died in week 23 of apparent pneumonia.

Body weight gains of males and females at the 5000 ppm level were significantly decreased in comparison to controls during the study. Food and water consumption were comparable between control and treated groups during the study.

Urinalysis results showed no significant effects. Hematologic data did not reveal any compound-related findings, although the hemoglobin values were significantly decreased in males at 5000 and 1500 ppm.

Biochemical data showed significant decreases in bilirubin at all dosages in both males and females. Cholesterol values were significantly decreased in both sexes at 5000 ppm.

The toxicological significance of these and other biochemical findings remains uncertain.

The absolute liver weight of males in the low- and high-dose groups were significantly increased and the mid-dose liver weight was also increased in males.

The relative liver weight of male rats showed a dose-related, significantly increased effect. Female rats showed significantly increased relative liver weight at the high dose.

The absolute and relative liver weight values are shown below:

Absolute and Relative Liver Weight

<u>Sex</u>	<u>Dietary Level (ppm)</u>	<u>Liver (g)</u>	<u>Liver (%)</u>
M	0	13.60	2.30
M	500	15.17*	2.58**
M	1500	15.10	2.63*
M	5000	17.57**	3.41**
F	0	6.40	2.20
F	500	6.61	2.17
F	1500	6.52	2.37
F	5000	6.74	2.65**

* p < 0.05.

** p < 0.01.

The significant increase in absolute and relative liver weight is considered compound-related in both sexes. Other organ weight changes were not considered related to treatment.

Conclusion: No NOEL was established based on increased absolute and relative liver weight in male rats. A pathology report was not included with the submission. Additionally individual animal data were not provided.

Classification: Invalid

- a. Invalid animal data not submitted.
- b. No pathology report submitted.
- c. No table for clinical signs submitted.

- (6) Subchronic (13-week) inhalation toxicity study with Neopdynamin in rats; Central Institute for Nutrition and Food Research; Report No. R4882; April 1978; Sumitomo No. 17-51-3012.

Neopdynamin was used and the vehicle was chloroethane (1,1,1-trichloroethane).

Randomized groups of 10 male and 10 female SPF Wistar derived rats were exposed for 9 hours/day, 5 days/week during a period of 13 weeks to aerosolized test substance.

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The test groups were as follows:

<u>Group No.</u>	<u>Neopynamin mg/m³ of Air</u>	<u>Chlorothane g/m³ of Air</u>
1	0	0
2	0	5.12
3	1.30	5.50
4	5.03	5.32

Impaction samples of the test atmospheres revealed that the maximum particle diameter was less than 1 micron.

The rats were housed individually during the exposures. After each exposure the animals were kept five to a cage and provided ad libitum with food and water. Individual body weight and average food consumption per group were recorded weekly. At week 13, hematological studies on each animal included hemoglobin, packed cell volume, erythrocytes, and total and differential leucocytes. At the same time, urinalysis examinations were made in pooled urine samples of each of the groups and included pH, appearance, glucose, protein, occult blood, ketones, and microscopy of the sediment.

At terminal sacrifice, blood chemistries were performed on all the rats of each group using blood from the abdominal aorta and included glucose, BUN, serum protein, albumin, SGOT, SGPT, and SAP.

Following necropsy, the following organs were weighed: heart, kidneys, liver, spleen, brain, testes, ovaries, thymus, adrenals, and lungs with trachea and larynx. Tissue samples of these organs and of salivary glands, pituitary, eyes, spinal cord, head (after removal of the skin, eyes, brain, and lower jaw), stomach, pancreas, small and large intestine, mesenteric lymph nodes, urinary bladder, epididymis, prostate, uterus, skin, bone marrow (sternum) and sciatic nerve were fixed in 10% neutral formalin. Microscopic examination was conducted upon all male and female rats of the control group, the solvent group, and the high-dose group. Kidneys were examined from all rats.

Statistical analyses of body weight, hematological, and biochemical values were carried out using the Wilcoxon test. Organ-to-body weight ratios were evaluated by means of the Student t-test.

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Results

There were no compound-related toxic signs or mortalities during the study. Body weight, food consumption, and food efficiency were not affected by treatment.

Hematological findings were unremarkable. Biochemical values were comparable between control and treated groups. Increases in mean SGPT values in both control and treated males were considered due to an accidental overdose of barbiturate just prior to exsanguination. No liver effects were indicated by the high SGPT values. Urinalysis measurements were unremarkable.

Relative organ weights showed no compound-related effects. However, group four females had significantly increased brain-to-body weight ratio; group two females had significantly decreased relative ovary weight; and group four males had an increase in relative adrenal weight.

Gross and histopathological examination did not show any compound-related effects. However, the incidence of male rats showing a moderate or high number of proteinaceous droplets in the cytoplasm of tubular epithelial cells in the kidneys was increased, but not dose-related, in the solvent control and Neopynamin-treated groups than in the controls.

Conclusion: The NOEL for the study is the high-dose group, 5.03 mg/m³, for Neopynamin.

Classification: Supplementary. Individual animal data were not provided. This study may possibly be upgraded if considerably more detailed information on individual animals were provided, including individual necropsy and histopathology sheets.

(7) Studies on Mutagenicity of Neopynamin with Bacterial Systems; Institute for Biological Science, Hyogo, Japan; June 13, 1977; Sumitomo No. IT-70-0023.

A. Rec-Assay-Method of T. Kada and Y. Sadaie; Mutation Res. 16:165 (1972).

DNA-damaging (radiometric) capacity of Neopynamin at dosages of 1, 10, 100, and 10,000 μ g/paper disk was determined by using the rec-assay method in Bacillus subtilis M45 recand H17 wild-type strain. The negative control was DMSO (10,000 μ g/paper disk) and the positive control was MNNG (1, 10, and 100 μ g/paper disk).

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The bacterial cells were inoculated on broth plate with soft agar, to which each chemical dissolved in DMSO (10 mL) was applied with paper disk.

The diameter of growth inhibition zone was measured after 24-hour incubation at 37 °C.

Results: Neopynamin was not inhibitory on the growth of both M45 and H17 strains. MNNG inhibited both strains of B. subtilis.

Conclusion: Neopynamin was not mutagenic in this rec-assay.

Classification: Acceptable

- B. Ames Test-methods of B.N. Ames, F.D. Lee, and W.E. Durston; Proc. Nat. Acad. Sci. USA 70:782 (1973) and B.N. Ames, W.E. Durston, E. Yamasaki, and F.D. Lee; Proc. Nat. Acad. Sci. USA 70:2281 (1973).

Salmonella typhimurium TA100, TA98, TA1535, and TA1538 were used to detect the increase of his + revertant colonies on minimal plates with or without S9 mixture obtained from PCB-treated Sprague-Dawley rats.

Neopynamin was tested at dosages of 1, 10, 100, 1000, and 10,000 ug/plate. The positive controls were MNNG and AAF and were tested at 10 and 100 ug/plate both with and without S9. DMSO was the negative control.

The bacterial cells (ca. 2×10^8) mixed with S9 mixture of phosphate buffer (0.2 mL) were poured onto minimal plate and incubated for 48 hours at 37 °C.

Results: Neopynamin did not increase the number of revertant colonies in comparison to negative controls. The positive controls increased the number of revertant colonies.

Conclusion: Neopynamin was not mutagenic in the Ames Assay.

Classification: Acceptable

- C. Host-mediated Assay-Method of M.S. Legator and H.V. Malling; in Chemical Mutagen, A. Hollaender, ed., 596 (1971) Plenum Press.

The mutagenic potential of Neopynamin was tested in vivo by the host-mediated assay. Male ICR mice

received Neopynamin at 200 and 1000 mg/kg; the positive control DMNA at 50 and 100 mg/kg; and the negative control corn oil at 3000 mg/kg orally and after 1 hour ca. 5×10^8 cells of Salmonella typhimurium G46 were injected intraperitoneally.

Two hours thereafter, 1.0 mL of saline was injected and the indicator cells were harvested. The number of mutant cells and survival were measured by plate technique.

Results:

Neopynamin did not increase the mutation frequency in comparison to negative controls. The positive control DMNA increased the mutation frequency.

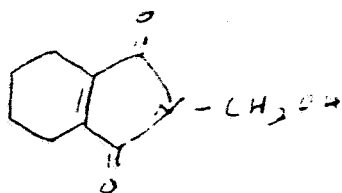
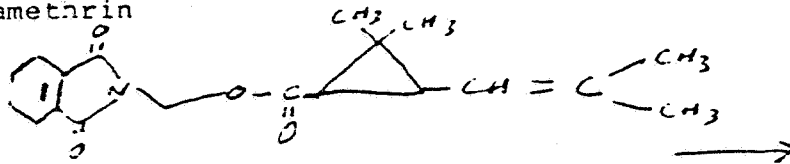
Conclusion: Neopynamin was not mutagenic in the host-mediated assay.

Classification: Acceptable

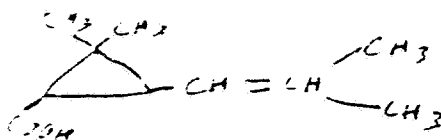
- (8) Metabolism of Tetramethrin in Houseflies and Rats in vitro (T. Suzuki and J. Miyamoto); Pesticide Biochemistry and Physiology, 4:86-97 (1974); Sumitomo No. IM-80-0002.

This published article dealt with the effects of various chemicals on the metabolism of tetramethrin by homogenates of housefly abdomens and rat liver. The enzyme activity was localized mainly in the microsomal fraction.

Tetramethrin



MTE



Chrysanthemic Acid

The reaction indicates that cleavage is catalized either by a carboxyesterase or a hydrolase and that some pyrethroids are metabolised in insects primarily through hydrolytic pathways. Metabolites from oxidative pathways (as in mammals) are formed in minor quantities.

Classification: Supplementary

- In vitro data only.
- Individual data not provided.

- (9) Biochemical studies on the Mode of Action of Pyrethroidal Insecticides Part I. Metabolic Fate of Phthalthrin in Mammals. J. Miyamoto et al., Agriculture and Biological Chemistry, 32(5):628-640 (1968); Sumitomo No. IM-80-J003.

This published article elucidated the major metabolic pathways of phthalthrin (neopynamin, tetramethrin) in vivo in rats. Tetramethrin-C¹⁴ 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 very low (less than 1%). The expired C¹⁴ was less than 0.2 percent.

About half of the tetramethrin was found to be excreted into feces unabsorbed and approximately 40 percent of the excreta was tetramethrin unchanged.

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

From the results, absorption of tetramethrin is slow from the intestinal tract and rapid degradation of the compound in animal tissues is presumed.

Classification: Supplementary

- Individual data not provided.

- (10) Degradation, Metabolism, and Toxicity of Synthetic Pyrethroids. (J. Miyamoto; Environmental Health Perspectives, Vol. 14, pp. 15-23, 1976; Sumitomo No. JG-50-0023.)

This published literature review article summarizes the metabolism and toxicity of pyrethroids. No method or individual data are submitted. The author's summary is presented below:

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"Synthetic pyrethroidal compounds undergo biodegradation in mammals both oxidatively and hydrolytically, and depending on the type of compound, either of the pathways may predominate. Thus, (+) - or (+)-trans isomers of the chrysanthemumate ester of primary alcohols such as fenothrin, furamethrin, proparthrin, resmethrin, and tetramethrin (and possibly permethrin, too) are metabolized mainly through hydrolysis of the ester linkage, with subsequent oxidation and/or conjugation of the component alcohol and acid moieties. On the other hand, the corresponding (+)-cis enantiomers and chrysanthemumate of secondary alcohols like allethrin are resistant to hydrolytic attack, and biodegraded via oxidation at various sites of the molecule. These rapid metabolic degradations, together with the presumable incomplete absorption from the gastrointestinal tract, would generally contribute to the low acute toxicity of synthetic pyrethroids.

"These compounds are neither skin irritants nor skin sensitizers, and inhalation toxicity as well as dermal toxicity are fairly low. Neither is teratogenic in rats, mice, and/or rabbits or mutagenic on various bacterial strains. Subacute and chronic feeding of higher amounts of the compounds to rats invariably causes some histopathological changes in liver; however, these are neither indicative nor suggestive of tumorigenicity.

"Based on existing toxicological information, the present recommended use patterns might afford sufficient safety margin on human population.

"However, in extending usage to agricultural pest control, much more extensive investigations should be forthcoming from both chemical and biological aspects, since there is scant information on the fate of these pyrethroids in the environment. Also several of the compounds may be very toxic to certain kinds of fish and arthropods."

Classification: Supplementary

2 Attachments

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Please reply to:
1330 Dillon Heights Ave.
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5 May 1986

Attachment 1

(From EPA accession
no. 262777)

Mr. Arturo E. Castillo, PM 17
U. S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Subject: Neopynamin^R (tetramethrin).
EPA Reg. No. 10308-1.
Risk Assessment.

Dear Mr. Castillo,

Please find enclosed a letter from Dr. K. Fujimoto, plus three attachments, setting forth the position of Sumitomo Chemical Company, Ltd., regarding the regulatory significance of benign tumors in male rats noted in two chronic studies of Neopynamin. Dr. Fujimoto gives the background to this matter before going on to discuss the evaluation of Neopynamin under EPA's cancer risk assessment guidelines. Following this, he discusses the evidence and notes the biological irrelevance of these tumors to humans. Finally, he covers the risk assessment itself and concludes that Neopynamin does not present a carcinogenic hazard to man.

The three attachments are:

- A. letter from Dr. Y. Nishizawa to Dr. E. J. Gerberg
September 9, 1982.
- B. letter from Dr. M. Ueda to Dr. E. J. Gerberg
August 13, 1984.
- C. Cancer Risk Assessment for Neopynamin. Frank W. Carlborg.
February 13, 1986

We would appreciate receiving an accession number for Attachment C.

Please feel free to contact us if there are any questions arising from Dr. Fujimoto's letter.

Yours sincerely,

SUMITOMO CHEMICAL COMPANY, LTD.

Eugene J. Gerberg, Ph.D., R.P.E.
Technical Advisor

Enclosures (3)

By J. DeKerly, 4/11/83

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

00679 b
Attachment 2

Hazleton (America) July 17, 1981, #143-127
EPA Acc. No. 247280

Four groups of 5 male and 6 female beagle dogs were dosed with 0, 1250, 2500 or 5000 ppm of Neopynamin (technical, lot #G0208, 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 pyrethrin 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⁺, Ca²⁺, 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 3-21 (~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 1250 ppm. At 5000 ppm (L2L) there is consistency 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.

by J. Doherty, 4/11/83
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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.

		<u>Liver</u>		<u>Ovaries</u>
		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.	2.928 (17%)	2.583	0.074
Mid	ab.	351.17 *(51%)	272.333 (19%)	1.3833
	rel.	3.009 (20%)	3.138 (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 on 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 (~13%), which was not reported as being

by J. Doherty, 4/11/83
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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. (cc [unclear])