

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

TETRAMETHRIN

Chemical Code # 1695, Tolerance # 50174
SB 950 # 327

December 7, 1987

Revised 09/14/89, 07/10/90, 02/20/91, 07/02/91,
03/17/92, 03/24/92, 06/01/93, 12/06/96, 11/17/98, 1/3/01 and 7/28/03

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, possible adverse effect
Teratology, rat:	No data gap, possible adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 167237 & 953973 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T030728

Revised by Stanton Morris, 11/17/98 and by Gee, 1/3/01 and 7/28/03

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

**** 50174-064 052547** "Two Year Dietary Administration in the Rat: Neopynamin Final Report", Hazleton Laboratories, Vienna, VA, Project No. 343-107, 10/4/74. Neopynamin (lot # 14,109B, purity not stated) was administered in the diet to 50 Sprague-Dawley CD rats/sex/group at 0, 1,000, 3,000, or 5,000 ppm for 104 weeks. Treatment-related effects seen at 3,000 and 5,000 ppm were decreased body weights in both sexes and increased absolute liver weights with fine cytoplasmic vacuolation in males (NOEL = 1,000 ppm). A **possible adverse effect** was indicated by an increased incidence of testicular interstitial cell adenomas (oncogenic effect, NOAEL not determined) associated with testicular atrophy (non-oncogenic effect, NOAEL = 1,000 ppm) at 3,000 and 5,000 ppm. Upgraded from unacceptable (M. Silva, 12/7/87) to acceptable by submission of retrospective diet analysis (S. Morris, 7/12/91) and details of the original diet preparation (S. Morris and C. Aldous, 3/17/92).

50174-084; 091543: This document contains a protocol for the retrospective analysis of dietary mixtures of test material prepared in a manner similar to that used in the study at DPR doc. # 50174-064, rec. # 052547. A worksheet was done that resulted in no change in study status (S. Morris, 11/16/90).

50174-085; 096049: This document contains a statement of purity for the test material used in the study at DPR doc. # 50174-064, rec. # 052547. No worksheet was done and there was no change in study status (S. Morris, 02/20/91).

50174-087; 097013: This document contains a retrospective analysis of dietary mixtures of test material prepared in a manner similar to that used in the study at DPR doc. # 50174-064, rec. # 052547. A worksheet was done that resulted in no change in study status (S. Morris, 07/02/91).

50174-092; 098225: This document contains details of the original diet preparation in the study at DPR doc. # 50174-064, rec. # 052547. A worksheet was done that resulted in the study status being changed to acceptable (S. Morris and J. Gee, 1/9/91).

50174-063 052546 "Chronic Toxicity Study in Rats: Neopynamin Technical Final Report," (Hazleton Labs, #343-117, 6/11/81). Neopynamin technical, (purity not stated), was administered in the diet at 0, 200, 1000 or 5000 ppm to 50 male rats/group of each of two strains: Sprague-Dawley CRCD and Long Evans Hooded. These animals were offspring of 30 rats/sex/group, treated with Neopynamin at the above levels from the week prior to breeding through weaning and continued for 104 weeks. NOEL = 1000 ppm for CRCD rats (decreased body weight compared to control). NOEL = 1000 ppm for Long Evans Hooded rats (decreased body weight and increased liver and testes weights compared to control). **Possible adverse effect indicated.** Both strains showed an apparent treatment related increase in incidence of testicular interstitial cell tumors at 5000 ppm. Slight (not statistically significant) increases in tumor incidence were observed in Long Evans rats: malignant mixed cell tumors (1000 and 5000 ppm) and thyroid follicular cell adenomas (5000 ppm). Liver weights were increased over control at 5000 ppm. Supplemental study for #052547. Study design was not for a chronic

study (no interim sacrifice, interim hematology, clinical chemistry and urinalysis, dose analysis or ophthalmology exams were performed). Historical data requested on kidney and thyroid tumor incidence in Long Evans male rats. M. Silva, 12/7/87.

50174-080; 090153: This document contained additional histopathological evaluation data of testicular tumors in the 1974 and 1981 studies (doc. #'s 50174- 064, 063; rec. #'s 052547, 052546) and the historical incidences of testicular tumors in rats in other studies. Evaluation of these data did not result in a change in study status (see DPR Response, 7/10/90). No worksheet was done (Morris, 7/10/90).

CHRONIC, RAT

See COMBINED, RAT

CHRONIC, DOG

**50174-123 145426 "52-Week Toxicity Study in Dogs with Neo-Pynamin", CHV 343-249; M.D. Walker; Corning Hazleton Incorporated, 9200 Leesburg Pike, Vienna, VA; 3/8/96. Groups of 4 beagle dogs per sex were fed dietary mixtures of tetramethrin (neo-pynamin, lot no. 31006 G, 96.4% stated purity) for 52 weeks at 0, 300, 1200, 5000, or 10000 ppm (analytical dose: male - 0.0, 8.2, 36.1, 147.2 or 286.0 mg/kg/day; female - 0.0, 9.2, 35.5, 157.0, or 324.9 mg/kg/day). One male died at 1200 ppm during week 46. There were no treatment-related clinical signs. Treatment-related effects included: decreased body weight gain and food consumption in females at 10000 ppm; increased liver/gallbladder weights in both sexes at 5000 and 10000 ppm; increased serum phospholipids in males at 1200, 5000, and 10000 ppm and females at 5000 and 10000 ppm; serum cholesterol in males at 1200, 5000, and 10000 ppm and females at 10000 ppm; serum alkaline phosphatase in both sexes at 5000 and 10000 ppm; increased chronic inflammatory renal lesions in males at 10000 ppm; and increased hepatic glycogen in males at 5000 and 10000 ppm and females at 10000 ppm (NOEL = 300 ppm). No adverse effect was indicated. The study was unacceptable (S. Morris and J Gee, 12/02/96) but upgraded with submission of adequate characterization of the purity of the test material (S. Morris and J Gee, 7/20/98).

50174-139; 157779: This document contained analytical data for the test material used in doc. # 50174-123, rec. # 145426. The study was upgraded to acceptable by evaluation of these data (S. Morris and J Gee, 7/20/98)..

50174-113; 133695; "4-Week dietary Toxicity Study in dogs with Neo-Pynamin." (HWA 343-248; M.D. Walker; Hazleton Washington, Inc., Vienna, VA; 10/12/94.) Tetramethrin (Neo-Pynamin T.G., lot No. 31006 G, 96.4% stated purity) was fed in the diets of 2 purebred beagle dogs/sex/dose at 0, 10,000, or 30,000 ppm for 4 weeks. Treatment-related effects were: decreased food consumption and body weight gain in both sexes at 30,000 ppm; increased liver weights in both sexes at 10,000 and 30,000 ppm; and hepatocellular hypertrophy in males at 30,000 ppm and females at 10,000 ppm. This document was submitted as supplemental data to an ongoing, one-year chronic toxicity study in dogs. No worksheet was done (J. kishiyama and S. Morris, 5/9/96).

50174-113; 133696; "Metabolism of tetramethrin in dogs", Study No. 2836; K. Saito; Sumitomo Chemical, Co. Osaka, Japan; 10/14/94. Groups of 3 male beagle dogs were dosed orally for 14 days with tetramethrin by gelatin capsules at 300 mg/kg/day or in the diet at 37.5 mg/kg/day (1250 ppm). On day 15, ¹⁴C-labeled tetramethrin was given at the same levels followed by 2 days of unlabeled material. Pharmacokinetics and metabolism of ¹⁴C-labeled material were measured. The main route of excretion for capsules was feces - for dietary mixtures it was urine. Bioavailability is greater for dietary mixtures than capsules. This document was submitted as supplemental data to an ongoing, one-year chronic toxicity study in dogs. No worksheet was done (J. Kishiyama and S. Morris, 5/9/96).

50174-062; 052544; "Subchronic Toxicity Study in Dogs: Neopynamin Final report," (Hazleton, project #343-127, 6/17/81). Neopynamin technical (lot 00208), 94.6%, was administered in the diet to six beagle dogs/sex/group at 0, 1250, 2500 or 5000 ppm for six months. NOEL <1250 ppm (inhibition of estrus cycle). Increased serum cholesterol at all dose levels and dose-related decrease in Ca⁺, total protein, albumin, and albumin/globulin ratio in both sexes. Increased liver weights in all treated males and in 2500 and 5000 ppm females. **Adverse effect indicated.** Dose related inhibition of estrus activity 2500 and 5000 ppm-treated females. Complete inhibition of estrus at 5000 ppm. Decreased ovary weights at 5000 ppm. Unacceptable. Not upgradeable. Insufficient treatment duration with no NOEL (see addendum, #052545). M. Silva, 12/2/87.

50174-062; 052545; Addendum to Final Report, #052544: Re-examination of ovary slides indicated no corpora lutea in the 5000 ppm group, with fewer corpora lutea in 2500 and 1250 ppm groups relative to controls. M. Silva, 11/25/87.

50174-095; 112093; "Chronic Toxicity in Dogs with Neo-Pynamin"; HWA Study Number 343-235; D.W. Dalgard; Hazleton Washington, Inc., Vienna, VA; 12/19/91. Capsules containing tetramethrin (Neo-Pynamin T.G., lot # 90304, stated purity 95.3%) were given orally by capsule to four beagles/sex/group at 0, 10, 30, 100, or 300 mg/kg/day for 52 weeks. There were no treatment-related effects observed (NOEL \geq 300 mg/kg/day). **No adverse effect** was indicated. The study was unacceptable because there was no analysis of the dosing material (S. Morris and C. Aldous, 3/17/92) and not upgradeable because of an inadequate rationale for the doses used (S. Morris, response dated 2/16/93).

50174-083; 095003: This document contains the protocol for the study in doc. # 50174-095, rec. # 112093 (S. Morris, 02/07/91).

50174-100; 115982: This document contains a 4-week range-finding study submitted in support of a rationale for the doses used in the study at doc. #50174-095, rec. # 112093. Evaluation of these data resulted in a study status change from "possibly upgradeable" to "not upgradeable" (S. Morris, response dated 2/16/93).

50174-100; 115983: This document contains a 3-week range-finding study submitted in support of a rationale for the doses used in the study at doc. #50174-095, rec. # 112093. Evaluation of these data resulted in a study status change from "possibly upgradeable" to "not upgradeable". No worksheet was done (S. Morris, response dated 2/16/93).

50174-100; 115986: This document contains analysis of the test material used in the

study at doc. #50174-095, rec. # 112093. Evaluation of these data resulted in a study status change from "possibly upgradeable" to "not upgradeable". No worksheet was done (S. Morris, response dated 2/16/93).

ONCOGENICITY, RAT

see COMBINED, RAT

ONCOGENICITY, MOUSE

**** 50174-114 135474** "Dietary Oncogenicity Study in Mice with Neo-Pynamin", HWA 343-242; M. R. Moore; Hazleton Washington, Inc., Vienna, VA; 1/6/95. Tetramethrin (neo-pynamin, lot # 90304, 95.3% stated purity) was fed in the diet to 50 CD-1® mice/sex/group at 0, 150, 3000, or 7000 ppm for at least 78 weeks. There were no treatment-related effects on survival, clinical signs, body weight, food consumption, hematology findings and gross pathology findings. There were treatment-related increases in the incidence of swollen ventral abdominal regions in both sexes, absolute and relative weights for testis/epididymides in males and hepatocellular hypertrophy in females at 7000 ppm and absolute and relative weights for liver/gallbladders in both sexes at 7000 and 3000 ppm (non-oncogenic NOEL = 150 ppm). A **possible adverse effect** was indicated by treatment-related effects seen in male livers: increased incidences of masses at 3000 and 7000 ppm and hepatocellular carcinomas at 7000 ppm. The study was unacceptable (S. Morris and J. Kishiyama, 8/13/96) but upgraded by submission of adequate characterization of the purity of the test material (S. Morris and J. Gee, 9/2/98).

50174-139; 157780: This document contained analytical data for the test material in doc. # 50174-144, rec. # 135474. The study was upgraded to acceptable by evaluation of these data (S. Morris and J Gee, 9/2/98)..

50174 - 145 167237 "Purported evidence for carcinogenicity of tetramethrin in 'Dietary oncogenicity study in mice with Neo-Pynamin'." (D. R. Saunders and A. L. Lawyer, Technology Sciences Group, February 16, 1999). This submission contains documents addressing the adverse effects notation for the study in 50174-114, record 135474. The authors present arguments and supporting documentation why the adverse effects for tumors noted in the liver of male mice are spontaneous in nature rather than treatment-related. The items include: a copy of the April 1996 draft guidelines of US EPA for carcinogen risk assessment [these have been superceded]; a publication by Joseph K. Haseman from *Fundam. Appl. Toxicol.* 3: 334-339 (1983) entitled "A reexamination of false-positive rates for carcinogenic studies"; a copy of the worksheet of 8/13/96; the publication of R. R. Maronpot et al., from *Toxicologic Pathology* 14: 263-273 (1986), "National Toxicology Program nomenclature for hepatoproliferative lesions of rats"; the publication of E. E. McConnell from *JNCI* 76: 283 - 289 (1986), "Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies"; Table 10B from the initial report; pages 47 - 162 from the report; pages 1300 - 1302, 199 - 205, 516 - 812, 814 - 815, 978 - 979 and 179 - 198 of the report. The cover letter states that all data requirements have been fulfilled by studies on file with the Department. The apparent concern is that tetramethrin, given a "low" priority in the initial prioritization, might be re-prioritized by the Department of Pesticide Regulation to a level of greater concern. It should be noted that other studies, for example, in rats, have indicated that the liver is a target organ. Changing the adverse notation for the mouse will not change the adverse effects notation for the rat and the dog. Therefore, no change in status is being made for the mouse at this time. In terms of

statistical analysis, there is a positive trend test for carcinogens but no statistical significance in pair-wise comparisons by Fisher's Exact test. See page 47 of the original report. The risk assessment, when conducted, will address the potential for oncogenicity. The US EPA has listed tetramethrin as "C" for carcinogenicity [possible human carcinogen]. Tetramethrin is not listed under Proposition 65 as "known" to the State to cause cancer. No worksheet. (Gee, 7/28/03).

50174-065 052548 "Combined Chronic Toxicity and Oncogenicity Study in Mice." (Hazleton Laboratories America, Inc. 4/17/86). Neopynamin technical (lot # 00811, 93.3%) was administered at 0, 12, 60, 300 or 1500 ppm in the diet for 104 weeks. NOEL >1500 ppm. No adverse effects indicated. No oncogenic effects or definitive chronic effects observed. A MTD was not reached. No chemical analysis was provided. No ophthalmologic exams were performed. The study status was changed from unacceptable, upgradeable (M. Silva 11/13/87) to unacceptable, not upgradeable (S. Morris, 3/24/92).

50174-080 090158 This document contains a 13-week dose range finding study in mice that was submitted in support of a rationale for the doses used in doc. # 50174-065 rec. # 052548. Evaluation of these data did not result in a change in study status (see DPR Response 7/10/90). No worksheet was done (Morris, 7/10/90).

50174-098 113557 This document contains a protocol for a replacement study. A worksheet was done (S. Morris, 3/24/92).

50174-098 113558 This document contains a draft report of a 13-week dose range finding study in mice that was submitted in support of a rationale for the doses used for a replacement study in doc. # 50174-098 rec. # 113557. These data did not adequately support the selection of doses (see DPR Response 3/24/92). No worksheet was done (Morris, 3/24/92).

REPRODUCTION, RAT

50174-002; 953972 "Reproduction study - rats: pyrethrin and Neo-Pynamin (final report)." (Hazleton Laboratories, Inc., 12/02/66) Six male and 12 female rats / group were exposed to dietary mixtures of 0 (10 males, 20 females), 1250, or 5000 ppm of Neopynamin for 2 weeks then through 2 cycles of mating, gestation, weaning, and recovery. **A possible adverse effect** was indicated by decreased weight gains in weanlings at 1250 and 5000 ppm (NOEL < 1250 ppm). The study was unacceptable not upgradeable because the study had too short a pre-mating exposure time, not enough litters, only 1 generation, incomplete necropsy and histopathology data, and a NOEL was not demonstrated (Apostolou, 08/15/85).

50174-061; 051222; "Reproductive Test of Neopynamin Part 1: Fertility Study in Rats," (Hamamatsu Seigiken Research, 6/14/80). Neopynamin technical (lot# 90508, 93.4%) at 0, 100, 300 or 1000 mg/kg/day was administered by gavage (20 animals/sex/group) to females two weeks prior to mating through day 7 of gestation. Males were exposed 9 weeks prior to and through the mating period. At 1000 mg/kg/day, dams demonstrated lower body weight and food consumption in latter stages of pregnancy. Males at 1000 mg/kg/day had increased kidney weights. Dose dependent liver weight increase was observed in males at all doses. Parental NOEL < 100 mg/kg/day, (300 mg/kg/day in females and <100 mg/kg/day in males). Developmental NOEL = 300 mg/kg/day (reduced ossification and fetal weights). **Possible adverse effect indicated**, (fewer corpora lutea, implantations and longer to confirm copulation

than controls.) **Unacceptable**, (inadequate dosing schedule, females sacrificed before littering, 1 generation only). **Not upgradable**. No toxicity was observed with a dose of 1500 mg/kg/day in the pilot study. No analysis of dosing material. M. Silva, 10/22/87.

50174-061 051225 "Reproduction Test of Neopynamin Part 4: Perinatal and Postnatal Study in Rats." (Hamamatsu Seigiken Research, 6/14/80). Neopynamin technical, (lot# 90508, 93.4%) was suspended in 0.5% carboxymethyl cellulose and administered in doses of 0, 100, 300 or 1000 mg/kg/day by gavage to 20 pregnant Sic rats/group (F0). Only F0 were dosed and dosing went from day 17 of pregnancy to day 21 following delivery. Study concluded with sacrifice of F1 animals and examination of F2 20-day fetuses. No adverse effects. Maternal NOAEL = 1000 mg/kg/day (increased liver weight, compared with control.) Developmental NOEL \geq 1000 mg/kg/day (HTD). Data for some F1 animals missing and unaccounted for. Unacceptable. (dosing schedule, no analysis of dosing material). Not upgradeable. Study design precludes evaluation of effects of exposure throughout the life cycle. MTD not reached. M. Silva, 10/27/87.

50174-081 090159 "Three-Generation Reproduction Study - Rats: Sumithion and Neo-Pynamin." (Project No. 343-106, 10/16/73; Hazleton Laboratories, Vienna, VA) Neo-Pynamin, 100% assumed purity, no lot #. Fifteen male and 30 female rats / dose were exposed for an unspecified interval to dietary concentrations of 1000, 3000, or 6000 ppm. A single mating produced an F1A litter. Marginal decreases in parental weight gain and food consumption and weanling weight were seen at 3000 and 6000 ppm. A **possible adverse effect** was indicated by decreased pup survival at weaning (NOEL = 1000 ppm). The study is unacceptable and not upgradeable because only one generation was used. There were many deviations from guidelines including lack of protocol details, male reproductive performance could not be determined, no necropsies, no histopathology, and no individual litter data (Morris, 3/19/90).

50174-081; 090160; "Two - Generation Reproduction Study in Rats: Neopynamin Forte." (HLA 343-147; Sumitomo Chemical Co., Ltd., Osaka, Japan; Hazleton Laboratories, Inc., Vienna, VA; 6/17/86) Neopynamin Forte, lot # 00402, 93.4% stated purity. Thirteen (F0) or 15 (F1) male and 26 (F0) or 30 (F1) female adult Sprague-Dawley rats / dose were exposed to dietary concentrations of 0, 100, 500, or 3000 ppm for the entire study. Each male was mated with 2 females. There was one litter / generation. No adverse effect indicated because there were no significant toxicological effects on parents, reproductive parameters, or pups except for decreases in adult and pup weight gain at 3000 ppm (15-week adult weights \geq 90% control, weanling \geq 82%). The study is unacceptable and not upgradeable because of inadequate dosing (S. Morris; 3/20/90, 2/13/91).

50174-083; 095001: This document contains a missing page from 50174-081, 090160. Evaluation of these data did not result in a study status change (S. Morris, 2/13/91).

SUMMARY: The collective data from the 1973 (50174-081, 090159) and 1986 (50174-081, 090160) studies are sufficient to fill the data gap. A **possible adverse effect** is indicated by decreased weanling weights in both studies at 3000 ppm and decreased pup survival in the 1973 study at 6000 ppm with a NOAEL = 1000 ppm (S. Morris, 2/13/91).

TERATOLOGY, RAT

50174-061 051223 "Reproduction Test of Neopynamin Part 2: Teratology Study in Rats,"

(Hamamatsu Seigiken Research, 6/14/80). Neopynamin (technical lot# 90508, 93.4%) at 0, 100, 300 or 1000 mg/kg/day was administered by gavage to 30 pregnant rats/group. Dosing was day 7-17 of pregnancy (presence of vaginal plug = day 0 of pregnancy). 20 were sacrificed on day 20 of pregnancy and 10 delivered naturally. The study was for two generations beginning with pregnant females (F0) and continuing through examination of F2 fetuses at the 20th day of gestation. Only the F0 animals received Neopynamin. No adverse effect. Maternal NOEL = 300 mg/kg/day (Transient decrease in weight gain, food consumption and increase in water consumption). Transient liver and kidney weight increase at 1000 mg/kg/day when compared to controls. Developmental NOEL \geq 1000 mg/kg/day. Not acceptable. Upgradable. No analysis of dosing material. M. Silva 12/3/87.

50174-084; 091544: This document contains a protocol for the retrospective analysis of dietary mixtures of test material prepared in a manner similar to that used in the study at DPR doc. # 50174-061, rec. # 051223. A worksheet was done that resulted in no change in study status (S. Morris, 11/16/90).

** 50174-096; 112094; "An oral teratology study of Neo-Pynamin in the rat." (K. Robinson, G. Washer and J.W. Noveroske; Bio-Research Laboratories Ltd., Senneville, Quebec, Canada; Project No. , 12/16/91) Groups of gravid female rats were treated by oral gavage with tetramethrin suspensions (Neo-Pynamin T.G., lot no. 90304, Z 95% purity, 0.5% carboxymethylcellulose vehicle) at 0, 150, 500, or 1000 mg/kg/day on gestation days 6 through 15 and sacrificed on day 20. All adults were given complete gross pathology and detailed reproductive track examinations. All fetuses were weighed and given detailed external examinations. Approximately 1/2 of the fetuses in each litter were given detailed, internal, microscopic examinations and their heads were examined by the Wilson technique. All fetal skeletons were examined by the Dawson technique. There were no treatment-related maternal or developmental effects. The high dose met the EPA limit test. No adverse effect was indicated but a possible adverse effect was indicated by a pilot study (see below 50174-097, 112095). The study is acceptable (S. Morris and C. Aldous, 3/17/92).

50174-097; 112095; "An oral range-finding study of Neo-Pynamin in the rat"; K. Robinson, G. Washer and J.W. Noveroske; Bio-Research Laboratories Ltd., Senneville, Quebec, Canada, 12/11/91. Groups of 6 gravid female Sprague-Dawley rats were treated by oral gavage with tetramethrin (Neo-Pynamin T.G., lot no. 90304, Z 95% purity, 0.5% carboxymethylcellulose vehicle) on gestation days 6 through 15 at 0, 500, 750, 1000, or 1500 mg/kg/day. On gestation day 20, the female rats were sacrificed and given complete gross pathology examinations and detailed examinations of the reproductive organs. The fetuses were weighed and given detailed external examinations. There were no treatment-related maternal signs of toxicity (maternal NOEL \geq 1500 mg/kg/day). There were no major or minor fetal external abnormalities. A possible adverse effect was indicated by treatment-related increased resorptions and pre- and post-implantation losses and decreased live litter size at 1500 mg/kg/day (NOAEL = developmental NOEL = 1000 mg/kg/day). The statistical significance of the effects seen in the pilot study and the high dose at which they occurred may be considered in subsequent hazard identification and risk assessment. Evaluation of this study was included on the worksheet for the main study (50174-096, 112094; 3/17/92, S. Morris and C. Aldous).

TERATOLOGY, RABBIT

50174-002; 953971; "Reproduction study - rabbits: Neo-Pynamin and pyrethrins (final report)." (Hazleton Laboratories, Inc.; 08/03/66) Nine does / group were mated and exposed to Neopynamin at 0, 30, or 90 mg/kg on gestation days 8 through 16. On gestation days 29 or 30, 4 dams / dose were sacrificed and their pups were harvested by Caesarian Section. The other 5 dams / dose and their fetuses were sacrificed at term. All uteri and fetuses were grossly examined. Two fetuses / litter were examined for skeletal abnormalities. No adverse effects were indicated. The study was unacceptable and not upgradeable because of too few pregnancies, no justification of doses, exposure interval too short, test material not characterized, too few fetuses examined, and missing data (Apostolou, 08/15/85).

50174-061; 051224; "Reproduction Test of Neopynamin Part 3: Teratology Study in Rabbits," (Hamamatsu Seigiken Research 6/14/80). Neopynamin technical, lot# 90508, 93.4% suspended in 0.5% carboxymethyl cellulose (CMC), was administered at 0, 100, 300 or 500 mg/kg/day by gavage to ten pregnant animals/group from day 6 through 18 of gestation. The day of mating = day 0 of pregnancy. No adverse effect. Maternal NOEL > 500 mg/kg/day. Developmental NOEL \geq 500 mg/kg/day. In a pilot study of similar duration, where non-pregnant animals were used, 1500 mg/kg/day gave minimum toxicity (decreased weight gain when compared to controls). Unacceptable. Not upgradeable. Too few animals. No MTD reached. M. Silva, 10/22/87.

** 50174-091; 093030; "An Oral Teratology Study of Neo-Pynamin in the Rabbit." (K. Robinson, G. Washer and J.W. Noveroske; Bi-Research Laboratories Ltd., Senneville, Quebec, Canada; Project I.D. 95088, 7/18/91.) Groups of 20 or 21 artificially-inseminated female New Zealand white rabbits were dosed with suspensions of tetramethrin (Neo-Pynamin T.G., lot # 90304, 95.3% stated purity, 0.5% carboxymethylcellulose vehicle) by oral gavage at 0, 30, 100, or 500 mg/kg/day on gestation days 7 through 19 and sacrificed on day 29. All adults were given complete gross pathology and detailed reproductive track examinations. All fetuses were given detailed, internal, microscopic examination. One third of the fetal heads were examined by the Wilson technique. All fetal skeletons were examined by the Dawson technique. There were no treatment-related maternal or developmental effects. Dosing adequacy and NOEL's were established by a range-finding study (see below 50174-091, 093031). No adverse effect was indicated. Maternal and developmental NOEL's were 440 mg/kg/day based on decreased maternal weight gain and passage of feces and increased abortions and maternal lethality seen in the pilot study at 500 mg/kg/day and adjusted for analytical values in main study. The study was acceptable (S. Morris and C. Aldous, 3/17/92).

50174-091; 093031; "An Oral Range-Finding Teratology Study of Neo-Pynamin in the Rabbit"; K. Robinson, G. Washer and J.W. Noveroske; Bi-Research Laboratories Ltd., Senneville, Quebec, Canada; Project I.D. 95088; 7/18/91. Groups of five artificially-inseminated female New Zealand white rabbits were dosed with suspensions of tetramethrin (Neo-Pynamin, lot # 90304, 95.3% stated purity, 0.5% carboxymethylcellulose vehicle) by oral gavage at 0, 250, 500, 1,000, or 1,500 mg/kg/day on gestation days 7 through 19 and sacrificed on day 29. All adults were given complete gross pathology and detailed reproductive track examinations. All fetuses were given a detailed external examination and weighed. Treatment-related decreased maternal weight gain and passage of feces and increased abortions and maternal lethality were seen at 500, 1,000, and 1,500 mg/kg/day. These results established the adequacy of dosing and NOEL's in the main teratology study (see above 50174-091; 093030). Details of the pilot study are discussed in the worksheet for the main study (S. Morris and C. Aldous, 1/14/92).

50174-083; 095002: This document contains the protocol for the study at DPR doc. # 50174-091, rec. # 093030. No worksheet was done (S. Morris, 02/07/91).

GENE MUTATION

50174-060 051219 "Studies on Mutagenicity of Neopynamin with Bacterial Systems." (Institute for Biological Science, Hyogo, Japan; Ref. #70-0023, 6/13/77). *Salmonella typhimurium*, strains TA100, TA98, TA1535, and TA1538 were used in gene mutation assays with and without metabolic activation at 1, 10, 100, 1000 and 10,000 ug/plate in three replicated trials. No adverse effect. No increase in revertant colonies reported. Unacceptable. Upgradeable. No cytotoxicity data provided. No information on purity of test material was provided. No list of components in the bacterial growth media or details of protocol used to prepare metabolic activation for the assay. Should list individual plate counts. M. Silva, 11/13/87.

50174-020 034777 This document contains an exact duplicate of doc. # 50174-060, rec. # 051219. No worksheet was done (Silva, 11/24/87).

50174-060; 051220; "Studies on Mutagenicity of Neopynamin with Bacterial Systems." (Institute for Biological Science, Hyogo, Japan; Ref #70-0023, 6/13/77). Male ICR mice were used as hosts and Neopynamin was administered orally at 200 and 1000 mg/kg. *Salmonella typhimurium* (G-46) was injected one hour after dosing and harvested two hours later. No adverse effect. Unacceptable. Not upgradeable. The summary and results table was very brief with no data presented on individual replicates. No evidence was presented that the indicator was actually exposed to the test substance. No toxicity data were given. No justification was made for the sample timing. No list of bacterial growth media, or details of protocol used to treat the animals and obtain cells for the assay was provided. M. Silva, 11/17/87.

50174-020; 953973 This document contains an exact duplicate of doc. # 50174-060, rec. # 051220. No worksheet was done (Silva, 11/24/87).

** 50174-071 068106 "Reverse Mutation Test of Neopynamin in *Salmonella typhimurium* and *Escherichia coli*" (Laboratory Project ID: IT-70-0205; Takarazuka Research Center, Japan, 12/25/86) Neopynamin, lot No. 60210, 94% purity. The plate incorporation method was used with *Salmonella typhimurium* strains TA100, TA98, TA1535, TA1537, and TA97 and *Escherichia coli* strain WP2uvrA at 5000, 2000, 1000, 500, 200, 100, 0 ug/plate, with and without metabolic activation. No adverse effect was indicated. The study was acceptable (Morris/Shimer, 06/16/89).

CHROMOSOME EFFECTS

** 50174-060; 051221; "In Vivo Chromosomal Aberration Test of Neopynamin in Bone Marrow Cells." (Doc. Code IT-60, Ref. No. -0197; Takarazuka Research Center, Japan; 03/28/86) Neopynamin, lot # 90508, 93.4% stated purity, corn oil suspensions; Single, i.p. doses of 1200, 2400, or 5000 mg/kg were given to 6 male ICR mice / group. Two hours before sacrifice, colchicine was administered i.p. at 4 mg/kg. The mice were sacrificed 6, 24, or 48 hours after exposure to the test material and 50 metaphase, bone marrow cells / mouse were scored for chromosome abnormalities. No adverse effect was indicated. The study was acceptable.

(Silva, 11/16/87; Morris, 08/21/89, 03/23/90).

50174-060; 068107; This document contained individual data for the study at doc. #

50174-060 rec. # 051221. Evaluation of these data did not result in a change of study status (Shimer/Morris, 08/21/89).

50174-080; 090156; "Metabolism of Tetramethrin Isomers in Rats." (Kaneko, H et al., Journal of Pesticide Science, 6:425-435 (1981)) The study found no remarkable, sex-related differences in the excretion, distribution, and nature and amounts of metabolites of tetramethrin in Sprague-Dawley rats. The study provided adequate rationale for using only one sex in the study at doc. # 50174-060 rec. # 051221. Evaluation of these data resulted in a change of study status (Morris, 03/23/90).

DNA DAMAGE

50174-060; 051218; "Studies on Mutagenicity of Neopynamin with Bacterial Systems," (Institute for Biological Science, Hyogo, Japan; Ref.# 70-0023, 6/13/77). *Bacillus subtilis*, H-17 wild and M45 rec- strains, were used in a DNA repair assay at 1, 10, 100, 1000, and 10,000 ug/paper disk. No adverse effect. Unacceptable. Not upgradeable. No positive control for other than DNA effects. No solubility or cell toxicity data were given, therefore it is a no test. Guidelines call for a list of bacterial growth media composition. Individual plate counts should be provided. M. Silva, 12/3/87.

50174-020; 034777; This volume contains an exact duplicate of doc. # 50174-060, rec. # 051218. No worksheet was done (Silva, 11/24/87).

** 50174-054; 075771 "In vitro unscheduled DNA synthesis (UDS) assay of Neopynamin in rat hepatocytes." (Ref. No. IT-80-0213, Study No. 1280; Takarazuka Research Center, Osaka, Japan; 06/30/88) Neopynamin, Z 94% stated purity; Unscheduled DNA synthesis (UDS) was determined by autoradiographic analysis of 3H incorporation in the nuclei of primary rat hepatocytes treated with Neopynamin at 0.2, 1, 5, 25, 50, or 100 ug/ml for 20 hours in the presence of 3H-thymidine. No adverse effect was demonstrated. The study was acceptable (Morris, 08/26/89).

NEUROTOXICITY

Not required at this time.

SUPPLEMENTAL

50174-103; 125687 This document contains a risk assessment evaluation conducted by the registrant. No worksheet was done (S. Morris, 5/6/96).

50174-104; 125692 "Three-Month Inhalation Toxicity Study of Neo-Pynamin in Rats." (Study ID 2189; S. Kawaguchi; Environmental Health Science Laboratory, Osaka, Japan; 8/9/91.) Groups of 10 Sprague-Dawley rats/sex were exposed to aerosols of tetramethrin (neo-pynamin, 95.3% stated purity, corn oil carrier) at 0 (corn oil), 0 (air only), 20.3, 134, or 824 mg/m³, 6 hours/day, 5 days/week for 13 consecutive weeks. Group mean body weight gain was reduced

for males at 134 and 824 mg/m³ and for females at 824 mg/m³. Treatment-related clinical signs were seen in both sexes: bradypnea at 134 and 824 mg/m³ and hair loss, reduced activity, nasal discharge, dark red substance around snout, red tears, salivation, and urinary incontinence at 134 and 824 mg/m³. Bilirubin and urobilinogen levels were increased in females at 134 mg/m³ and both sexes at 824 mg/m³. There were treatment-related hematology changes: decreased monocyte counts in males at 134 and 824 mg/m³; decreased mean corpuscular volume and hemoglobin in females at 824 mg/m³; decreased mean corpuscular hemoglobin concentration in both sexes at 824 mg/m³; prolonged prothrombin and activated partial thromboplastin times in both sexes at 824 mg/m³. Treatment-related changes in blood chemistry were: increased total serum protein in males at 20.3, 134, and 824 mg/m³ and females at 824 mg/m³; increased globulin levels, total cholesterol, phospholipid, and gamma-glutamyl transpeptidase in males at 134 and 824 mg/m³ and females at 824 mg/m³; increased inorganic phosphorous in males at 824 mg/m³; decreased albumin-globulin ratio in both sexes at 824 mg/m³; decreased glucose in females at 134 and 824 mg/m³; glutamic-oxaloacetic transaminase and alkaline phosphatase in males at 824 mg/m³; and decreased leucine aminopeptidase in males at 134 and 824 mg/m³. Treatment-related organ weight increases were: liver in both sexes at 20.3, 134, and 824 mg/m³ and kidney in males at 134 and 824 mg/m³ and females at 20.3, 134, and 824 mg/m³. Liver discoloration and enlargement were seen in both sexes at 134 and 824 mg/m³ and soft livers in males at 134 mg/m³ and both sexes at 824 mg/m³. Treatment-related histopathology findings were: hepatocellular hypertrophy in both sexes at 134 and 824 mg/m³; focal liver necrosis in males at 824 mg/m³; hyaline droplets in renal tubules of males at 134 and 824 mg/m³; hyaline casts in renal tubules and basophilic renal tubules in males at 824 mg/m³. No worksheet was done (J. Kishiyama and S. Morris, 8/13/96).

50174-105; 125695; "Three-Month Inhalation Toxicity Study of Neo-Pynamin in Rats (Determination of the No Observed Effect Level)." (Study ID 2189; S. Kawaguchi; Environmental Health Science Laboratory, Osaka, Japan; 8/9/91.) Groups of 10 Sprague-Dawley rats/sex were exposed to aerosols of tetramethrin (neo-pynamin, 95.3% stated purity, corn oil carrier) at 0 (corn oil), 0 (air only), 1.9, 4.4, or 19.8 mg/m³, 6 hours/day, 5 days/week for 13 consecutive weeks. The only treatment-related observation was increased relative liver weight in females at 19.8 mg/m³. No worksheet was done (J. Kishiyama and S. Morris, 8/13/96).

50174-138 153691 "Tetramethrin: Motor activity measurements in male and female mice postnatally exposed to tetramethrin by inhalation (including measurement of muscarinic acetylcholine receptors in the brain)." (I. Ivens, J. Pauluhn and G. Schmuck, Bayer AG, Wuppertal, study no. T3059027, 12/17/96) NMRI female mice and their litters of 8 pups (4 males and 4 females) were exposed to tetramethrin (96.2% in polyethylene glycol 400) by whole body inhalation for 6.3 hours per day for 7 consecutive days. Nominal doses were 0, 1.5, 8 or 40 mg/m³ (analytical doses of 1.78, 7.94 and 37.8 mg/m³). Pups were tested for spontaneous motor activity on day 17 of age (day following last exposure) and at 4 months ("adults"). Eight parameters were recorded: Horizontal time (HA), number of movements (NM), number of stereotypy (NS), total distance (TD), vertical activity (VA), vertical time (VT), movement time (MT) and stereotypy time (ST). Different animals were tested each time as the first groups were sacrificed after motor activity measurement and the brains removed for muscarinic receptor determination. Although dams were exposed, they were not evaluated. There was no treatment-related effect on clinical signs or body weight. A statistically significant reduction in horizontal activity was found in male mice at the high dose and could not be excluded as due to exposure. There were no differences in spontaneous motor activity at 4 months. There was a

dose-dependent increase in muscarinic acetylcholine receptor (mAChR) density in male mice (only sex reported) at 17 days but not at 4 months. Acetyl cholinesterase and choline acetyltransferase were measured but no significant changes were found at either time. Study is supplemental. (Gee, 1/3/01)