

CASWELL FILE

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

OCT 20 1987

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Tetramethrin (Neopynamin) - EPA Registration No.  
10308-1 - Mutagenicity Studies and Acute Dermal  
Toxicity Study - MRID Nos. 402757-01, 402758-01,  
402759-01, 402760-01, 402861-01, 402862-01,  
402804-01

Caswell No.: 844  
Project No.: 7-0963  
Record No.: 200979

FROM: William Dykstra  
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*William Dykstra 9/15/87*

TO: Paul H. Schroeder, PM Team 17  
Fungicide-Herbicide Branch  
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THRU: Edwin R. Budd, Section Head  
Review Section II, Toxicology Branch  
Hazard Evaluation Division (TS-769C)

*Budd 10/20/87*  
*10/20/87*

Requested Action

Review submitted mutagenicity studies and acute dermal toxicity study.

Conclusions and Recommendations

1. The results and classifications of the mutagenicity studies are shown in the following table.
2. The acute dermal toxicity study in rabbits is acceptable as Core-Minimum data. The LD<sub>50</sub> was greater than 2000 mg/kg bwt.

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<u>MRID No.</u>	<u>Test</u>	<u>Results</u>	<u>Classification</u>
402757-01	Bacterial Repair	Negative without activation.	Unacceptable; not performed with activation.
402757-01	Ames Test	Negative without activation.	Unacceptable; not performed with activation.
402757-01	Host-Mediated Assay	Negative up to 1/2 LD <sub>50</sub> .	Acceptable; however, tetramethrin was not tested. Allethrin, permethrin, and resmethrin were tested and were negative.
402758-01	UDS in Human Amnion FL Cells	<u>Positive.</u>	Acceptable; however, industrial-grade tetramethrin (72% purity) was used.
402758-01	Ames Test (plate incorporation)	<u>Weakly positive</u> in one strain (TA97) with activation.	Acceptable; however, industrial-grade tetramethrin (72% purity) was used.
402758-01	Ames Test (fluctuation)	<u>Positive</u> in TA97 both with and without activation.	Acceptable; however, industrial-grade tetramethrin (72% purity) was used.
402759-01	Chromosome Damage in Mouse Bone Marrow Cells	Negative at 5000 mg/kg.	Unacceptable. No evidence that compound reached target cells and only males were tested.
402760-01	Ames Test/ <u>E. coli</u> Test	Negative both with and without activation up to 5000 µg/plate.	Acceptable.

Review

1. Mutagenicity of Some Synthetic Pyrethroids in Bacterial Test Systems (MRID No. 402757-01). Sumitomo Research Department Project No. ET-50-0024; September 20, 1975. Test materials: tetramethrin racemic; allethrin racemic (+)-trans, (+)-cis, (+)allethronyl-(+)-trans; phenothrin racemic (+)-trans, (+)-cis; furamethrin racemic; permethrin racemic (+)-trans, (+)-cis; resmethrin racemic (+)-trans, (+)-cis; resmethrin racemic (+)-trans, (+)-cis, (-)-trans, (-)-cis; purities ranged between 93 and 100%.

The positive control compounds were 4-nitroquinolin-N-oxide (4NQO) and N-methyl-N'-nitro-N-nitroso-guanidine (MNNG):

- a. Repair Test: DNA repair-deficient strains (pol<sup>-</sup>, uvr<sup>-</sup>, or rec<sup>-</sup>), and the corresponding wild type strains were used. They were E. coli, W3623 pol<sup>-</sup> and W3623 (wild); B. subtilis, M45 rec<sup>-</sup> and H17 (wild); S. typhimurium, TA1538 uvr<sup>-</sup> and TA1978 (wild). The paper disk method was used. "The diameter of growth inhibition zone of a repair deficient strain produced by a chemical after 24 hrs incubation was measured and compared with that of the corresponding wild type strain." [End of quotation]

Results: All tested pyrethroids and tetramethrin, in particular, gave diameters (mm) of inhibition zones less than 8.0 mm. The result of < 8.0 mm indicates no inhibition on bacterial cell growth (Table I).

In contrast, the positive controls, 4NQO and MNNG, induced significant revertants, which appeared as increased diameter of inhibition zones between 8.2 and 17.8 mm.

Conclusion: The pyrethroids, and in particular tetramethrin, were negative in the bacterial repair assay without activation.

Classification: Unacceptable; not performed with activation.

- b. Ames Test (Reversion Test): "The reversion test was conducted according to the Ames method by using E. coli W3623 trp<sup>-</sup> and W3102 trp<sup>-</sup> and S. typhimurium TA1535 his<sup>-</sup> and TA1538 his<sup>-</sup>. The

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revertant colonies from these nutrient-requiring cells on minimal plates were counted after 2-day incubation." [End of quotation]

Results: At dosages of 0.1, 1.0, and 10.0 mg/plate, none of the pyrethroids, and in particular tetramethrin, produced a significant increase in revertant colonies/plate (Table II). The DMSO control revertants/plate ranged from 5 to 29. The positive controls, MNNG and 4NQO, ranged from 93 to 3000 revertants/plate at a dosage of 0.001 mg/plate which were considered positive results (as expected). The pyrethroids, including tetramethrin, produced between 2 and 40 revertants/plate at the various concentrations tested.

Conclusion: The pyrethroids, and in particular tetramethrin, were not mutagenic in the Ames Test without activation.

Classification: Unacceptable; not performed with activation.

- c. Host-Mediated Assay: In this assay, only allethrin, permethrin, and resmethrin were tested. The pyrethroid of concern, tetramethrin, was not tested in this assay.

The assay was conducted according to the method of Legator and Malling. Approximately 1/2 and 1/4 of the LD<sub>50</sub> values of allethrin, permethrin, and resmethrin were dosed orally to ICR male mice. "Indicator cells (ca. 10<sup>9</sup> cells/host) were injected intraperitoneally. Three hours later, the cells were recovered from the host. Mutation frequency of harvested cells was measured by the plating method. Three mice were used in each group, and replicated tests were done." The positive control used was streptozotocin at 20 mg/kg.

Results: The reversion frequency as reported in Table 3 was  $4.1 \times 10^{-7}$  for the control (corn oil) and  $1.4 \times 10^{-4}$  for streptozotocin. Allethrin, permethrin, and resmethrin produced reversion frequencies ranging from  $1.4 \times 10^{-6}$  to  $5.7 \times 10^{-8}$ .

Conclusion: Allethrin, permethrin, and resmethrin were not mutagenic in the host-mediated assay. However, tetramethrin was not tested in the assay.

Classification: Acceptable.

2. Genotoxicity of Tetramethrin in Mammalian Cells and Salmonella typhimurium (MRID No. 402758-01).

Authors: Chen Ding, Yingnian Yu, Jiao; Iao Zhang, Ahunan Cai, and Xingruo Chen.

Publication Date: 1985; Journal (Chinese) of the Zhejiang University of Medicine, Vol. 14, Issue 1, pages 1-4 (translated).

Materials and Methods: Industrial-grade tetramethrin (72% purity) was used in the experiment.

- a. Unscheduled DNA Synthesis (UDS) Test: "Tetramethrin induced UDS in human amnion FL cells was detected by means of an isotope double-labeling method. Concentrations of tetramethrin ranged from  $5 \times 10^{-3}$  to  $5 \times 10^{-1}$   $\mu\text{g/mL}$ . MNNG was used as a positive control without S9 activation and cyclophosphamide was used as a positive control with S9 activation. Tetramethrin and positive controls were dissolved in DMSO." [End of quotation]

Results: Tetramethrin (72% purity) was positive in the UDS assay both with and without S9. A dose-response relationship was seen in the ranges of  $5 \times 10^{-2}$  to  $5 \times 10^{-0}$   $\mu\text{g/mL}$  both with and without S9. MNNG gave positive results (Table 1).

Conclusion: Tetramethrin was positive in the UDS assay both with and without S9.

Classification: Acceptable: however, industrial-grade tetramethrin (72% purity) was used.

- b. Ames Test (Plate Incorporation): Salmonella typhimurium.

S. typhimurium strains TA100, TA98, and TA97 were used with and without S9. Concentrations of tetramethrin were 5, 50, and 500  $\mu\text{g/plate}$ . At 5000  $\mu\text{g/plate}$ , tetramethrin was toxic. Positive controls were sodium azide ( $\text{NaN}_3$ ), 2,7-AF, 9-AA, and 2-AAF.

Results: The results were negative for tetramethrin without activation in TA97, TA98, and TA100. With S9, tetramethrin is weakly positive (3X more colonies than control group) in TA97. "The number of TA100 revertant colonies also approached three times that of the control group; however, positivity still cannot be assayed." The results

were negative with TA98. Positive controls gave expected positive results (Table 2.)

Conclusion: Tetramethrin was weakly positive in TA97 in plate incorporation method.

Classification: Acceptable; however, industrial-grade tetramethrin (72% purity) was used.

c. Ames Test (Fluctuation Method) Salmonella Typhimurium.

S. typhimurium strain TA97 was used both with and without S9. Tetramethrin concentrations were 5, 50, and 500 µg/mL. The positive controls were 2-AAF and 9-AA. DMSO was the negative control.

Results: Tetramethrin was positive for mutagenicity in TA97 both with and without S9 at 50 and 500 µg/mL. Positive controls also gave positive results (Table 3).

Conclusion: Tetramethrin was positive for mutagenicity in TA97 with and without S9.

Classification: Acceptable; however, industrial-grade tetramethrin (72% purity) was used.

3. In vivo chromosomal Aberration Test of Neopynamin (tetramethrin) in Mouse Bone Marrow Cells (Sumitomo Research Laboratory Project No. IT-60-0197; March 26, 1986). MRID No. 402759-01. Test material tetramethrin; Lot No. 90508; purity 93.4%.

Groups of six male ICR strain mice received single, intraperitoneally, doses of 1200, 2400, or 5000 mg/kg of test material and were sacrificed at 6, 24, and 48 hours after treatment. The vehicle was corn oil (10 mL/kg). The positive control was Mitomycin C (4 mg/kg) and was administered at 6, 24, and 48 hours prior to sacrifice.

Following sacrifice, bone marrow cells in both femurs of each mouse were used to make chromosomal slide preparations.

Results: Tetramethrin was not mutagenic under the conditions of the assay (Table 1). The percent cells with aberrations for tetramethrin ranged between 0.3 and 2.3%, corn oil controls ranged between 0.7 and 2.0%,

and the percent aberrations of the positive control assays ranged from 9.0 to 60.0%.

Conclusion: Tetramethrin was not mutagenic in the bone marrow chromosome aberration assay.

Classification: Unacceptable, because no evidence that the compound (tetramethrin) reached target cells and only males were tested.

4. Reverse Mutation Test of Neopynamin (tetramethrin) in Salmonella typhimurium and Escherichia coli (Sumitomo Research Lab Project No. IT-70-0205; December 25, 1986). MRID No. 402760-01; test material tetramethrin; Lot No. 60210; purity 94.0%).

S. typhimurium strains TA100, TA98, TA1535, TA1537, and TA97 and E. coli WP2uvrA were used. Concentrations of tetramethrin were 100, 200, 500, 1000, 2000, and 5000  $\mu$ g/plate both with and without S9 activation. Positive controls were as follows:

Without S9 Mix

TA100	methyl methanesulfonate	200 $\mu$ g/plate
TA98	2-nitrofluorene	1 $\mu$ g/plate
TA1535	sodium azide	0.5 $\mu$ g/plate
TA1537	ICR-191	1 $\mu$ g/plate
TA97	ICR-191	1 $\mu$ g/plate
WP2uvrA	N-ethyl-N'-nitro-N-nitroso-guanidine	2 $\mu$ g/plate

With S9 Mix

TA100	benzo(a)pyrene	5 $\mu$ g/plate
TA98	benzo(a)pyrene	5 $\mu$ g/plate
TA1535	2-aminoanthracene	2 $\mu$ g/plate
TA1537	benzo(a)pyrene	5 $\mu$ g/plate
TA97	benzo(a)pyrene	5 $\mu$ g/plate
WP2uvrA	2-aminoanthracene	80 $\mu$ g/plate

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Results: Precipitation of tetramethrin was observed at doses of more than 2000 µg/plate without S9 and 5000 µg/plate with S9.

The number of revertant colonies per plate with and without S9 ranged from 8 to 133 for DMSO (solvent control) and from 6 to 197 for all concentrations of tetramethrin in all bacterial systems. There were no doublings of the numbers of revertants/plate for the tetramethrin concentrations in comparison with solvent controls for any bacterial strain of S. typhimurium or E. coli.

Tetrametrin was negative for mutagenicity in this assay. The positive controls gave the expected positive results.

Conclusion: Tetramethrin was negative for mutagenicity in this assay.

Classification: Acceptable.

5. Acute Dermal Toxicity of Neopynamin (tetramethrin) in Rabbits (Sumitomo Lab of Biochemistry and Toxicology; Lab Project No. IT-70-0207; March 19, 1987); test material tetramethrin; Lot No. 50408; 94.6% purity).

One group of five male and five female NZW rabbits received 2000 mg/kg of test material on shaved skin of the trunk under occlusion for 24 hours. Observation was for 14 days.

Results: No deaths. LD<sub>50</sub> > 2000 mg/kg (both sexes).

Toxic Signs: No toxic signs and no skin erythema observed.

Body Weight: All animals gained weight.

Necropsy: No compound-related lesions.

Toxicity Category: III - Caution

Classification: Minimum

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