UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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DATE: APR 29 1980

SUBJECT: EPA File No. 432-487, Resmethrin, Review of Special Neurotoxicity Studies. Caswell #83E

FROM: John Doherty
Toxicology Branch/HED (TS-769)

TO: F. D. R. Gee, PM #17
Registration Division (TS-767)

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Action Requested:

Review and evaluate special neurotoxicity study in rats with synthetic pyrethrin resmethrin.

Studies Submitted:

1. Evaluation of the Neurotoxic Effects of SBP-1382 in Albino Rats - Phase I

2. Supplementary Report to Phase I

3. Evaluation of the Neurotoxic Effects of SBP-1382 in Albino Rats - Phase II

EPA Accession Nos. 241501, 241502, 241503.

Background:

Natural and some synthetic pyrethrins have been reported to have the property of causing characteristic nerve damage that is described (in part) by axonal swelling, degeneration and disintegration. A description of this lesion can be found in PP 7F2013, accession No. 096384, tabs 104, 110, 111, 115, 117, 118. This petition and associated data are the property of Shell Oil Company. In tab 104, reference is made to the results of a study with resmethrin that demonstrated that this chemical caused the lesions to a minimal degree at doses of 5 gm/kg/day applied dermally.

Dr. R. Engler (EPA) subsequently asked the Penick Corporation to conduct studies to determine a NOEL for the ability of resmethrin to cause this lesion (see letter from Dr. M. L. de Vries, addressed to Dr. Engler and dated October 17, 1978). The studies submitted here are in response to Dr. Engler's request.

Conclusion:

1. These studies fail to demonstrate that resmethrin, when given orally at these near lethal doses causes a neuropathy that is sometimes associated with synthetic pyrethrins.

2. If review of the rat chronic feeding/oncogenesis, mouse oncogenesis, or dog chronic feeding studies with resmethrin indicate a neuropathy or neurotoxic response, then Toxicology Branch (TB) may request additional studies related to the effects of resmethrin on the nervous system.

3. The marginal positive response obtained with resmethrin applied dermally at 5 gm/kg for 5 days is not considered at this point in time, to be of toxicological significance or to represent a hazard.

Review of Studies Submitted

1. Evaluation of the Neurotoxic Effects of SBP-1382 in Albino Rats - Phase I.
Food and Drug Research Laboratories, Inc.; July 5, 1979, Study No. 6067.

The purpose of this study was to establish the dosage levels of SBP-1382 which produces signs of neurologic damage associated with peripheral axonal breaks, swelling and vacuolization of the myelin and any other morphologic changes in rats.

4 groups of 20 rats (all male Sprague-Dawley) were dosed with either 5,800, 8,600, 12,640, or 16,660 ppm of SBP-1382. Note, no control group was included. The rats were fed these diets for 7 days. After the 7 day feeding period, the rats were returned to untreated diet for an additional 7 days and then sacrificed and necropsied.

At necropsy the entire spinal cord and both sciatic nerves with surrounding muscle were excised and preserved in 10% neutral buffered formalin.

Results:

1. Toxic symptoms were noted in the low dose groups (tremors, nasal discharge, blanching of the feet and lacrimation). Deaths occured at the higher doses as did increases in the intensity of other symptoms. All rats in the highest test group died during testing.

The 8,600 and 12,640 ppm dose levels groups showed decreases in weight gain relative to the 5,800 ppm test group.

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2. Gross Necropsy - a dose dependent response was obtained with respect to the number and severity of a variety of lesions. At the lowest dose 10 of 20 rats were considered within normal limits. A variety of lesions related to poisoning developed in the other rats, these included enlarged lymph nodes and thymus.

3. Microscopic Findings. This study reports that SBP-1382 induced neuronal cytoplasmic vacuolation in the spinal cords at all test dose levels investigated. For example:

Level	Mean No. of neurons affected per cross section of spinal cord.
5,800	5.24
8,600	5.43
12,640	6.70
16,660	15.97

Appendix IV. Pathologists report (George E. Cox, M.D. and Peter J. Becci, Ph.D.) elaborates further on the type and frequency of this lesion. They conclude that this lesion was confined to the spinal cord and did not occur in the sciatic nerve.

At the highest dose level, there was slight to moderate nuclear proliferation in the muscle of 5 animals. In a single 12,640 ppm dosed animal, there was slight myocytolysis and this lesion was present in greater frequency and intensity in the high dose group.

Conclusion:

Since there was no suitable control for comparision, it is not possible to determine if at the lower doses SBP-1382 induces histopathological changes. Or if these lesions were related to the test chemical or were artifacts of tissue preparation.

2. Supplementary Report for Evaluation of the Neurotoxic Effects of SBP-1382 in Albino Rats - Phase I.

Food and Drug Research Laboratories, October 10, 1979.

(This study was conducted to supplement the preceding study which did not run appropriate controls.)

SBP-1382 (resmethrin) was fed in the diet to a single group of 6 rats at a dose level of 12,640 ppm for 7 consecutive days. A control group of 6 rats was also maintained on vehicle only. 7 days after the test diet was discontinued, the rats were sacrificed. Their spinal cords were necropsied and examined histopathologically.

This study differs from the previous study in that in this study the tissues were fixed by whole body perfusion with 4% formaldehyde - 1% glutaraldehyde in a 176 mOsM phosphate buffer.

Results:

No lesions were noted in the controls or SBP-1382 treated rats. The observations in the previous study giving some evidence for lesions in the spinal cord were not reproduced.

3. Evaluation of the Neurotoxic Effects of SBP-1382 in Albino Rats - Phase II.

   Food and Drug Research Laboratories, Inc.; July 20, 1979.

   Four groups of 20 rats of each sex were started on this experiment. These rats were dosed with 0, 500, 800, or 1,250 ppm of resmethrin for 32 weeks. (Except for the last 30 days, the high dose group was split so that 10 of each sex continued on 1,250 ppm and 10 were dosed with 5,000 ppm.) During the 32 week feeding period, the rats were bred twice to produce F_2A and F_2B generations.

   After 32 weeks all rats were sacrificed, subject to necropsy and the entire spinal cord and both sciatic nerves were excised and preserved in 10% buffered formalin.

Results:

1. The 0, 500, 800, 1,250 ppm test animals were reported as normal. The 5000 ppm group exhibited slight tremors. There were some deviations in body weight in both males and females, but the labortory asserts that these were not significant. In turn, the increases in food consumption were considered incidental.

2. No significant gross or histopathological lesions were reported. The pathologist report (Appendix IV) indicates that no lesions (in particular in the spinal cord, sciatic nerve or skeletal muscle) were noted.

   A NOEL of 1250 ppm for 32 weeks of feeding is noted for the lesion of neuropathy.

A NOEL of 5000 ppm is acceptable for 30 days of feeding. The dose level (if any) which will produce the suspected lesion is not established. It is important to indicate that a NOEL for pydrin for the lesions in the sciatic nerve is 1500 ppm (PP 9F2031, Acc No. 096384, Tab. 117) for 8 days of feeding. Definite effects were noted at 3000 ppm. Ideally, this study should have included pydrin as a positive control.

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