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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANC

MEMORANDUM

DATE: July 14, 1981

SUBJECT: EPA Reg. No. 432-487. 180-Day Subchronic Feeding Study with Resmethrin in Dogs
Tox Chem No. 83E

FROM: John Doherty
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for WB

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Background:

The Penick Corporation has submitted a 180-day subchronic feeding study with dogs as a partial fulfillment of the requirement for the registration of and setting tolerances for the synthetic pyrethrin resmethrin.

Conclusion:

1. The study has been reviewed and found to be acceptable (Core-Guideline) for meeting the requirement for a non rodent subchronic (6 month or longer) feeding study.

2. The NOEL for this study is 10 mg/kg/day. At higher levels there are statistically significant increases in liver weights.

Review of Study

180-Day Subchronic Oral Dosing Study with Resmethrin (SBP-1382) in Beagle Dogs.

Food and Drug Research Laboratories, Inc. December 18, 1980.

Four groups of 6 male and 6 female beagle dogs aged 5-6 months were dosed with 0, 10, 30, 100 or 300 mg/kg/day of SBP-1382 for 180 days. The test chemical was administered via gelatin capsules as a mixture with silicate filler. The control group received the silicate filler only. After 57 days on the test the original high dose group (100 mg/kg) was changed to 300 mg/kg of resmethrin and the control group was changed from 100 mg/kg to 300 mg/kg of silicate filler.

NOTE: During the first two weeks of the study some of the control dogs inadvertantly received SBP-1382 because of a contaminated subsample of the silicate filler. As indicated by analysis of the samples used for dosing, during the first week some control dogs (but not all) may have received as much as 30 mg/day and during the second week some dogs may have received as much as 1.6 mg/day of SBP-1382.

Results:

1. All dogs survived the 180 day dosing period.

2. Daily observations - the report concludes that no adverse reactions attributable to the test chemical developed. The high dose group (especially when dosed with 300 mg/kg) was reported as developing salivation and tremors, but these were of short duration and not consistant observations. There were no behavior or motor function tests conducted to appraise either the heart or reflexes of these dogs.

3. There were no trends for adverse effects on body weight or food consumption noted.

4. Hematology (determinations were made at pretest, 4, 8, 12, 16, 20, and 26 weeks on fasted dogs). There were no consistant dose related effects noted on total and differential leucocyte counts, erythrocyte counts, hemoglobin, hematocrit, or platelet counts.

5. Clinical Chemistry (determined at pretest, 4, 8, 12, 16, 20 and 26 weeks on fasted dogs). There were no consistant dose related effects noted on alkaline phosphatase, urea nitrogen, glutamate pyruvate transaminase, glutamate oxaloacetate transaminase, lactate dehydrogenase, glucose, total and direct bilirubin, total cholesterol, albumin, globin, protein, serum, Na^+, K^+, Ca^{++}, or Cl^-.

6. Urinalysis (determined at pretest, 4, 8, 12, 16, 20 and 26 weeks on fasted dogs). There were no consistant dose related adverse effects noted on pH, sediment, specific gravity, urobilinogen, appearance, color, protein, bilirubin, ketones or glucose.

7. Organ Weights. Absolute and relative weights of the following organs were determined: adrenals, brain, epididymides, heart, kidneys, liver, pituitary gland, spleen, testes, thyroid and parathyroid, uterus and ovaries.

   The liver showed signs of a response to the test chemical.

	Male		Female	
	Absolute (gm)	Relative (%)	Absolute (gm)	Relative (%)
Control	332.8 ± 12.5	2.92 ± .09	262.8 ± 13.6	2.75 ± .08
Low	385.2 ± 29.5	2.97 ± .16	287.5 ± 27.4	2.97 ± .14
Mid	351.8 ± 28.2	2.89 ± .21	306.3 ± 22.5	3.19 ± .18[a]
High	395.5 ± 33.1	3.36 ± .12[b]	315.5 ± 13.7	3.50 ± .10[a]

a.) significantly different from control, $p \leq 0.05$ and 16% and 27% higher than control

b.) 15% higher than control but not statistically significan

Among the males, the spleen was higher in weight for the high dose group (17% absolute and relative). The kidneys were higher for the mid and high dose groups (22% absolute and 16% relative and 24% absolute and 20% relative).

The thyroids and parathyroids were higher for the mid and high dose groups (37% absolute and 25% relative and 31% absolute and 23% relative).

The pituitary was higher in the all dosed groups as shown in the following tabl

Male Pituitary Weight

	Absolute (gm)	Relative (%)
Control	56 ± 6	4.9 ± 0.5
Low	68 ± 8 (21%)	5.3 ± 0.5 (8%)
Mid	74 ± 10 (32%)	6.0 ± 0.7 (13%)
High	71 ± 8 (27%)	6.3 ± 0.8 (29%)

The increases in the weights of the male spleen, kidneys, thyroids and parathyroids and pituitaries are noted but are not statistically significant or considered by Toxicology Branch to be related to ingestion of the test chemical.

8. Gross Necropsy - The principle gross necropsy findings were mostly color alterations and other minor changes which are common in beagle dogs.

   The liver did not show dose related changes. There were incidences of color alterations and "swollen" appearance.

9. Histology - No dose related changes were reported. There were no neoplasms reported. The liver was not associated with unusual findings. The only microscopic finding in the liver was one occasion of vacuolation in a low dose group female.

   The lungs were shown to have higher incidences of pneumonia in the mid and high dose group but this is not considered to be related to the test chemical.

Conclusion:

This study is CORE GUIDELINES. A NOEL of 10 mg/kg/day is supported. At higher levels the liver weight (relative to body weight) is increased. The high dose group and possibly the mid dose group shows some signs of reaction to the chemical (watery eyes, salivation) that were of short duration.

TS-769:th:TOX/HED:JDoherty:7-14-81:card #2