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

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MEMORANDUM NOV 5 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Franklin Gee, Product Manager #17
Registration Division (TS-767)

SUBJECT: FAP 9H5210 and EPA Reg. No. 432-487. Company Response to Toxicology Branch Review of 3-Generation Rat Reproduction Study with Resmethrin.

TOX Chem. ~~No. 83E~~

Background:

The Penick Corporation previously submitted a 3-generation rat reproduction study with the synthetic pyrethroid resmethrin and this study was reviewed by Toxicology Branch (see J. Doherty review dated November 28, 1979). This review indicated that the lowest dose level (500 ppm) demonstrated increases in the number of pups cast dead and that pup weight at 21 days was decreased. The mid and high dose test groups also showed these effects and a NOEL could not be established. The company has submitted a response to this review. They have also submitted the results of an additional (preliminary) 1-generation rat reproduction study with Resmethrin.

Toxicology Branch Comments:

1. A NOEL for pups cast dead and reduced pup weight at 21 days is set at < 500 ppm (lowest dose tested in both studies).

Although the revised statistical analysis on the 3-generation study indicated that there were no statistically significant differences in the number of pups cast dead or pups dead at 4 days when the low dose groups are compared with the controls, the results presented in the 1-generation rat reproduction study (see review as follows) confirmed that at 500 ppm there is an increase in the number of pups cast dead. Thus, the potential for resmethrin to cause pups to be cast dead is evident at 500 ppm.

The revised statistical report also shows that two matings (F_1B and F_3A) in the 3-generation study had lower body weights at 21 days in the low dose groups (500 ppm) and these differences were statistically significant.

2. The extent of effects at 500 ppm, although evident, are not considered of sufficient magnitude or consistency to warrant requiring an additional reproduction study.

3. It should be noted that 500 ppm is also the lowest dose level used in the rat 2-year chronic feeding/oncogenesis study which is currently under review. This chronic feeding study has shown that there are liver lesions in the low dose group. Thus, failure of both the 3-generation rat reproduction study and the rat chronic feeding/oncogenesis studies to show true NOELs will necessitate that a safety factor of greater than the conventional 100 fold be used for setting the ADI for resmethrin. Selection of the appropriate safety factor for resmethrin will be discussed further in the review of the rat chronic feeding/oncogenesis study.

4. In response to the registrant's request to assign a NOEL of 275 ppm for the 3-generation reproduction study, Toxicology Branch replies that it is not current policy to extrapolate to a NOEL when there are effects evident at the lowest dose level tested.

Summary of Company's Defense:

Documents Submitted

1. A statistical analysis of the effects of dietary SBP-1382 on three generations of Sprague-Dawley rats by Dr. Thomas E. Norwood, consultant in statistics, dated 5/4/81.

2. The evaluation of the effects of SBP-1382 following dietary administration through one generation in Sprague-Dawley rats (7/10/78). FDRL #5458.

These reports are in EPA Accession Nos. 245845, -6, -7, -8, -9, -50, -51, -52.

A. Review of Revised Statistical Analysis:

1. Pups cast dead.

In the revised statistical analysis (performed by Dr. Norwood), an alternative to the binomial formula (which was originally used) was employed to assess the data. The alternative method takes the litter to litter variability into account using a formula employed for population surveys. A key difference in the two statistical approaches is that the binomial formula yields standard errors which are much lower than the alternative approach with the result being that the binomial method would cause differences to be declared statistically significant without taking into account the litter to litter variability.

By the alternative method, no statistically significant differences in the number of pups cast dead or pups dead at 4 days were found between controls and 500 ppm. At the higher doses (800 and 1250 ppm) significant differences were noted.

A statistical NOEL (by extrapolation) for the effect of resmethrin to cause increases in the number of pups cast dead was determined to be 486 ppm.

2. Mean body weight at weaning (21 days).

The revised report indicated that only the F_1B and F_3A generations were statistically significantly ($p < 0.05$) lower in weight for the 500 ppm group. The F_1A generation was originally reported as being statistically significantly lower also but the reanalysis reported finding errors in the original analysis. The mid and high dose test groups were lower in all generations.

A statistical NOEL (by extrapolation) for the effect of reduced body weight at weaning was determined to be 275 ppm.

3. The statistical procedures used by Dr. Norwood to determine statistical significance were reviewed and accepted by the Toxicology Branch statistician B. Litt. B. Litt did not, however, accept the statistical calculations of the NOELs (by extrapolation). See B. Litt's memo dated October 21, 1982, attached.

B. Review of One-Generation Reproduction Study:

Four groups of 20 male and 20 female Sprague-Dawley rats were dosed with 0, 500, 2500 or 5000 ppm of resmethrin (90% pure) and allowed to mate and produce F_1A and F_1B generations (19 weeks). The F_1B generation was special in that for the mid dose level, test feed was removed at days 6, 15, 18 or 21 of gestation or was continued through lactation. Pups in this generation were also cross fostered.

Results:

Ninty-five to one-hundred percent of the dams became pregnant. One hundred percent of the control and 500 ppm dose group had a 100% gestation index. As the dose level increased

to 2500 and 5000 ppm the index fell to 70% and 57.9% respectively. The litter size (number of pups per litter) was decreased in the 5000 ppm group only. The number of live births per litter was 11.8, 11.8, 7.0 and 4.8 for the control, low, mid and high dose groups. The number of pups cast dead was 1, 6, 63, and 95 for the control, low, mid and high dose groups. The low dose group was statistically significantly increased for number of pups cast dead. The birth weights of the pups (as mean litter weight) were affected in both the mid (-6.7%) and high (-17%) dose test groups. The viability index (survival to day 4) was the same for the control and 500 ppm dose group. Only one pup in the mid and high dose groups survived to day 4. There was no significant difference in the lactation index for the control and low dose test group.

Cross fostering was attempted by placing pups from the mid and high dose test groups with control pups. Although the dams received the pups, the pups died after one day. (Note the results of the F_1B generation were not reported in complete form but effects of the chemical in the diet even when the test chemical was stopped at day 15 resulted in adverse effects on the viability of the pups.) These data indicate a transplacental toxicity for resmethrin.

Conclusion: Core Supplementary (for 1-generation study).

This study confirms that resmethrin causes stillbirths (pups cast dead) and decreased pup weight. There is a small effect on the number of stillbirths at the low dose of 500 ppm but the pups in this generation were reported as being otherwise healthy.

John Doherty 11/4/82.

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Toxicology Branch
Hazard Evaluation Division (TS-769)

Rec'd 11/4/82 W2B

Attachment

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