UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

001914

DATE: December 11, 1979

SUBJECT: EPA Reg. No. 432-487, Evaluation of Mouse Oncogenic Study with Resmethrin.

Caswell #83E

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

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

Action Requested:

Review and evaluate a mouse oncogenic study for purposes of supporting registration and petitions for Resmethrin.

Conclusion:

Toxicology Branch was not able to determine if a No-Effect-Level (NOEL) for the lesion described as amyloidosis was established for Resmethrin in this study. Insufficient data are presented to determine if there is an increase in this lesion in the low and mid dose levels and if the severity of this lesion is dose dependent.

Therefore Toxicology Branch requests that the slides showing the presence of amyloidosis be reexamined and the lesion be graded 1-4. The tissues from the mice in the low and mid dose groups that have not yet been examined should be included in the reassessment. The report should clearly demonstrate to EPA's satisfaction that amyloidosis is not related to the test material at the low and mid dose.

Review of the Study: (In EPA accession #238953-7)

Evaluation of Dietary Administration of SBP-1382 in CD-1 Outbred Albino Mice Over an 85 Week Period.

Food and Drug Research Laboratories; June 6, 1979; Laboratory No. 5270

75 male and 75 female CD-1 albino mice were grouped into 4 groups and fed diets containing 0, 250, 500 or 1000 ppm. The duration of feeding was for 85 weeks.

Results:

1. Survival

Dose	% Survival Males	Females
0	51	52%
250	57	57%
500	43	60%
1000	31	32%*

*Chemically related (Statistically significant).

2. Body weight data:

All three test groups for the males were lower in body weight (significantly). For females, low and mid levels, but not the high dose was lower.

Graphical analysis of the data by Toxicology Branch (J. D. D.) failed to demonstrate that the weight loss in males at the low dose is a chemical or dose effect. The mice in this group were significantly lower in weight at the initiation of this experiment.

3. Food consumption:

Males at the highest dose and females at all doses were lower. The low dose females were 4% lower overall. This is not considered a toxicological effect because the high dose group was 3% lower (i.e. no dose response).

4. Leukocyte counts (25 mice/sex/group) initially, 12 months and at termination. No dose related hematological changes were noted.

5. The following organ weight differences when compared to the control group in males were noted:

i) Absolute and relative adrenal weights increased at 500 ppm (20% and 23%) and 1000 ppm (31% and 50%). These increases were statistically significant. At 250 ppm there was a 5% and 10% increase that was not statistically significant.

ii) Liver weight relative increase at 500 ppm (12%) and 1000 ppm (15%).

iii) Kidney weight relative increase at 500 ppm (14%) and 1000 ppm (14%).

iv) Brain weight at 1000 ppm (12%) increase.

Other variations did not demonstrate a dose response dependence.

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6. Pathological examinations were conducted by three pathologists; Drs. D. R. Weaver, J. T. King and W. C. Tuft of the Robert Packer Hospital, Sayre, Pa.

A. Pathology. Amyloidosis was observed in a greater number of mice fed the high dose level than in the control group. The laboratory report does not comment on the occurrence of this lesion in the mid and low dose groups. This reviewer has determined that there might also be a chemically related increase in amyloidosis at the low and mid doses. For example:

	Amyloid Frequency*	
Dose	Males	Females
0 (control)	4.69	8.10
250	6.15 (30%)**	8.16
500	6.40 (36%)	9.10 (12%)
1000	7.40 (58%)	10.32 (27%)

*Incidences of amyloid per animal.
**(% higher than control).

One of the pathologists asserted that the occurrence of amyloidosis at the highest dose was probably related to the increase death rate at this dose.

B. Oncogenic Evaluation: No evidence of neoplastic or preneoplastic effects were reported.

Discussion:

Toxicology Branch is unable to conclude if a NOEL for the lesion of amyloidosis was demonstrated in this study.

As an oncogenic evaluation, this study is CORE GUIDELINES, and adequately demonstrates that in this strain of mice resmethrin does not produce neoplastic lesions.

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