FILE COPY

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

NOV 22 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: RfD/Peer Review Report of Resmethrin ([5-(phenylmethyl)-3-furanyl] methyl 2,2-dimethyl-3-(methyl-1-propenyl) cyclopropanecarboxylate)

CASRN. 10453-86-8
EPA Chem. Code: 097801
Caswell No. 083E

FROM: George Z. Ghali, Ph.D.
Manager, RfD/QA Peer Review Committee
Health Effects Division (7509C)

THRU: William Burnam
Co-Chairman, RfD/Peer Review Committee
Health Effects Division (7509C)

Reto Engler, Ph.D.
Co-Chairman, RfD/Peer Review Committee
Health Effects Division (7509C)

TO: Marion Johnson, PM 10
Insecticide-Rodenticide Branch
Registration Division (7505C)

Esther Saito, Chief
Reregistration Branch
Special Review and Re-registration Division (7508W)

The Health Effects Division-RfD/Peer Review Committee met on October 20, 1994 to discuss and evaluate the existing and recently submitted toxicology data in support of Resmethrin re-registration and to re-assess the Reference Dose (RfD) for this chemical in light of the recently-submitted data.

It should be noted that Resmethrin consists of four isomers as follows; 35% d-trans-isomer, 35% l-trans-isomer 15%, d-cis-isomer, and 15% l-cis-isomer. The d-trans isomer is a registered insecticide known as Bioresmethrin. Material available for review consisted of data evaluation records (DERs) for a chronic toxicity/carcinogenicity study in rats **(83-5 or 83-1a and -2a)**, two carcinogenicity studies in mice **(83-2b)**, one-year and six-month feeding studies in dogs **(83-1b)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)** and two multi-generation reproductive toxicity studies in rats **(83-4)**.

A. Chronic and Subchronic Toxicity:

The Committee considered the chronic toxicity phase of the chronic toxicity/carcinogenicity study in rats, (83-1a, MRID No. 00041402, 00085870, 00108828), the one-year and the six-month feeding studies in dogs (83-1b, MRID No. 43062601; 00157961) to be acceptable and the data evaluation records for these studies (HED Doc. No. 001912, 002477, 002478; 010918; 000791, 000000) to be adequate. The Committee questioned the biological significance of a marginal body weight and body weight gain depression (< 10%) observed in males of the mid- and high-dose groups and females of the high-dose group in the chronic toxicity phase of the rat study. However, this was consistent with effects seen in young animals in the rat reproduction studies. Overall, the Committee generally agreed with the reviewer's evaluation and interpretation of the data and recommended no revisions to the data evaluation records.

Since Resmethrin is a member of the pyrethroid class of compounds, many of which are considered to be neurotoxic, the Committee recommended that acute (81-8ss) and subchronic (82-7ss) neurotoxicity studies be performed in rats.

B. Carcinogenicity:

The Committee considered the carcinogenicity phase of the chronic toxicity/carcinogenicity study in rats (83-2a, MRID No. 00041402, 00085870, 00108828) and the carcinogenicity study in mice (83-2b, 1992, MRID No. 43052101 and 1979, MRID No. 00083319) to be acceptable and the data evaluation records (HED Doc. No. 001912, 002477, 002478, 00000; 011067; 001913, 001914, 011067) to be adequate.

The Committee considered the dose levels tested in the rat study to be approaching an adequate dose for carcinogenicity testing based on increased thyroid weights in males and females and increased liver weight in males and females accompanied by non-neoplastic histopathological changes in females. Thyroid follicular cell adenomas in males and females and the combined thyroid follicular cell adenomas and carcinomas in females appeared to be increased in the mid- and high-dose groups. Liver adenomas and the combined adenomas and carcinomas appeared to be increased in females. The Committee noted also that the terminology used in describing and sub-grouping the thyroid histopathological changes, based on prevailing systems before 1980, may be misleading and that if the slides were to be read by an independent pathologist using current terminology, the outcome might have been different. The Committee debated the issue of consulting a pathologist with respect to the terminology/nomenclature used in the study report, but the resolution was not adopted at this time. However, it is obvious that this issue should be resolved prior to submission of the study to the Health Effects Division-Carcinogenicity Peer Review Committee (HED-CPRC). The Committee was informed that the

2

registrant is in the process of completing another chronic toxicity/carcinogenicity study in rats which will be submitted to the Agency in early 1995.

There were two carcinogenicity studies in mice available for review by the Committee dated 1979 and 1992. The Committee considered the 1992 mouse carcinogenicity study (83-2b, MRID No. 43052101) to be acceptable, when viewed together with the 1979 mouse carcinogenicity study, and the data evaluation record to be adequate (HED Doc. No. 011067). The Committee concluded that the chemical was tested at sufficiently high dose level in males based on decreased survival and increased absolute and relative liver and kidney weights. Survival rates in males at week 104 were 24 and 26% for the 600 and 1200 ppm groups, compared to 42 and 40 % in the control and low dose group, respectively. Increased absolute and relative liver and kidney weights were also observed in females. Non-neoplastic histopathological changes, i. e. hypertrophy, were observed in livers of both males and females but not in kidneys of either sex. It should be noted that the Committee, initially, considered the high dose level tested in the 1992 mouse carcinogenicity study to be inadequate, i. e. insufficient, for carcinogenicity testing in females . However, in light of decreased survival rate observed in females of the high dose group in the 1979 mouse carcinogenicity study, the Committee concluded that the high dose tested in the 1992 mouse carcinogenicity study might have approached an adequate dose for carcinogenicity testing in females.

In the 1992 mouse carcinogenicity study, incidences of hepatocellular adenomas were significantly increased in males of the low- ($P < 0.05$), mid- and high-dose levels ($P < 0.01$) when compared to the concurrent control group 1 but not group 2. Incidences of hepatocellular carcinomas were significantly increased in males of the high-dose level ($P < 0.01$) when compared to the concurrent control group 2 but not control group 1. The combined incidences of hepatocellular adenomas and carcinomas were significantly increased at the low- ($P < 0.05$), and mid-dose levels ($P < 0.01$) when compared to concurrent control 1, and at the high-dose level when compared to concurrent control group 1 ($P < 0.01$) and concurrent control group 2 ($P < 0.001$). Incidences of hepatocellular adenomas were 2, 16, 18, 20 and 24% for males of control groups 1 and 2, low-, mid- and high-dose groups, respectively. Incidences of hepatocellular carcinomas were 4, 0, 4, 8 and 12% for males of control groups 1 and 2, low-, mid- and high-dose groups, respectively. Incidences of combined adenomas and carcinomas were 6, 16, 22, 28 and 36% for males of control groups 1 and 2, low-, mid- and high-dose groups, respectively. Variable degrees of statistical significance were attained based on which control group was used in the comparison.

No increase in hepatocellular adenomas and/or carcinomas was observed in females at the dose levels tested in this study.

Historical control data from the testing facilities were limited to one study of 50 animals; incidences of adenomas and carcinomas in males were 8% and 6%, respectively. Supplier historical control data for this strain of mice indicated a range of 0-17% for adenomas and 1-14% for carcinomas in males sacrificed between 21-24 month of age. However, a published report listed the incidence of hepatocellular adenomas up to 31% and carcinomas up to 13% in 24-month old CD-1 mice. Another published report on 84-week old male mice reported 18% adenomas and 2% carcinomas. Mean historical control values for hepatocellular adenomas, carcinomas and the combined incidences of adenomas and carcinomas, though very important in this case, were not provided to the Committee.

The Committee concluded that the carcinogenicity data warrant further discussion by the Health Effects Division-Carcinogenicity Peer Review Committee (HED-CPRC). Therefore, the chemical was referred to the HED-CPRC for weight of the evidence evaluation. However, Committee also indicated that the chemical may not be scheduled for discussion by the Carcinogenicity Peer Review Committee until the new chronic/carcinogenicity study in rats is submitted by the registrant. Under these circumstances, the Committee decided that discussing the older mouse carcinogenicity study (83-2b, 1979, MRID No. 00083319) would not be necessary.

C. Reproductive and Developmental Toxicity:

The Committee considered the reproductive toxicity studies in rats (83-4, two-generation 1994 and three-generation 1979, MRID No. 43189101; 00081276), the developmental toxicity studies in rats (83-3a, MRID No. 00028425) and rabbits (83-3b, MRID No. 00029002) to be acceptable and the data evaluation records for these studies (HED Doc. No. 000000; 001908, 002266, 000000; 001915, 000000; 001911, 000000) to be adequate. It was also proposed to down-grade the three-generation reproduction study from core-minimum to a core-supplementary status based on the lack of a reproductive no-observable effect level (NOEL), but this resolution was not adopted since the lack of a NOEL was not considered to constitute a sufficient reason to down-grade the study. It was recommended to redefine the reproductive and systemic toxicity NOELs for both reproductive toxicity studies as single reproductive/systemic toxicity NOELs. There was no evidence, based on the available data, to suggest that Resmethrin was associated with major developmental or reproductive toxicity under the testing conditions and that the reproductive/developmental toxicity data did not warrant further discussion by the Health Effects Division-Reproductive/Developmental Toxicity Peer Review Committee.

D. Reference Dose (RfD):

The Committee recommended that the existing RfD be revised. This RfD was established by the Health Effects Division-RfD Committee On July 1, 1988 and verified by the Agency RfD Work Group

on July 20, 1988 based on a three-generation reproductive toxicity study in rats with a LOEL of 25.0 mg/kg/day, lowest dose tested (subsequently, in a reevaluation of this study, this LOEL was recalculated based on actual food intake and body weight and found to be 47 mg/kg/day). Decreased pup weight and pup survival were observed at this dose level and higher dose levels. An uncertainty factor (UF) of 100 was applied to account for inter-species extrapolation and intra-species variability. An additional UF of 10 was used to account for the lack of a no-observable effect level. On this basis, the RfD was calculated to be 0.025 mg/kg/day.

Subsequently, a two-generation reproductive toxicity study was submitted to the Agency demonstrating a NOEL of 34.8 mg/kg/day for reproductive/systemic toxicity. Increased mortality in post-weaning F1b males, decreased survival in pups days 0-4, decreased pup birth weight/lactation weight, increased stillborn pups of F1a and F2a and decreased mating index at second F1 mating were observed at the next higher dose level of 70.8 mg/kg/day. An uncertainty factor (UF) of 100 was applied to account for inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.35 mg/kg/day. The Committee recommended using the three-generation reproductive toxicity study with a LOEL of 47.0 mg/kg/day as a co-critical study. It should be noted that this chemical has not been reviewed by the FAO/WHO joint committee on pesticide residue (JMPR).

E. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (Chief, SAB, RfD/Peer Review Committee Co-Chairman), George Ghali (Manager, RfD/Peer Review Committee), Karl Baetcke (Chief, TB I), Marcia Van Gemert (Chief, TB II), Rick Whiting, Henry Spencer, Esther Rinde, William Sette, Susan Makris and Myron Ottley. In attendance also were Kerry Dearfield of SAB, HED and Charles Frick and Barbara Madden of CCB, HED as observers.

Scientific reviewer (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report)

Linnea Hansen _____

Marion Copley _____

Respective branch chief (Committee member; Signature indicates concurrence with the peer review unless otherwise stated)

Karl Baetcke _____

CC: Richard Schmitt
Stephanie Irene
Karl Baetcke
Marion Copley
Linnea Hansen
Debra Edwards
Beth Doyle
Kerry Dearfield
RfD File
Caswell File

F. Material Reviewed:

1. Knickerbocker, M. et al. (1980). A life time evaluation of dietary administration of SBP-1382 to Wistar albino rats. MRID No. 00041402, 00085870, 00108828, HED Doc. No. 00192, 002477, 002478, 000000. Classification: Core-minimum data. This study satisfies data requirement 83-5 or 83-1a and 83-2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

2. Kangas, L. (1992). A dietary oncogenicity study of SBP-1382 in the Albino mouse. MRID No. 43052101, HED Doc. No. 011067. Classification: Core-supplementary data. This study, when viewed together with an older mouse study MRID No. 00083319, satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

3. Cox, G. E. et al. (1979). Evaluation of dietary administration of SBP-1382 in CD-1 outbred Albino mice over 85-week period. MRID No. 00083319, HED Doc. No. 001913, 001914, 011067. Classification: Core-supplementary data. This study, when viewed together with a recent mouse study MRID No. 43052101, satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

4. Daglard D. W. (1993). 52-Week oral toxicity study of SBP-1382 (Resmethrin) technical in dogs. MRID No. 43062601, HED Doc. No. 010918. Classification: Core-minimum data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

5. Gephart, L. et al. (1980). 180-day subchronic oral dosing study with Resmethrin (SBP-1382) in beagle dogs. MRID No. 00157961, HED Doc. No. 000791, 000000. Classification: Core-minimum data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

6. Hoberman, A. M. (1994). Reproductive effects of SBP-1382 (Resmethrin) technical administered orally via the diet to Crl:CD BR VAF/Plus rats for two generations with two litters per generation. MRID No. 43189101, HED Doc. No. 0000000. Classification: Guideline (as upgraded by the RfD/Peer Review Committee). This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

7. Schwartz, C. S. et al. (1979). The evaluation of the effects os SBP-1382 following dietary administration through three generations in Sprague-Dawley rats. MRID No. 00081276, HED Doc. No. 001908. Classification: Core-minimum data. This

1

study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

8. Machi, R. A. et al. (1979). Teratologic evaluation of SBP-1382 technical in the Albino rat. MRID No. 00028453, HEd doc. No. 001915, HED Doc. No. 000000. Classification: Core-minimum data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

9. Knickerbocker, M. et al. (1979). Teratologic evaluation of SBP-1382 technical in Albino rabbits. MRID No. 00029002, HED Doc. No. 001911, 000000. Classification: Core-minimum data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

8

Draft

Dietary Carcinogenicity/Chronic Toxicity Study in Rats/FDRL #5271/1980

The following additional information is provided to supplement the original DERs on this study. A finalized supplemental DER will be prepared following review of this study by the RfD committee.

EPA Reviewer: Linnea J. Hansen, Ph.D. Linnea J. Hansen, Date 10/5/94
Review Section IV, Toxicology Branch I (7509C)
EPA Section Head: Marion P. Copley, D.V.M., D.A.B.T. Date 10/5/94
Review Section IV, Toxicology Branch I (7509C)

DATA EVALUATION RECORD
(Supplemental DER to HED Doc. Nos. 001912, 002477 and 002478)

STUDY TYPE: Chronic Toxicity/Carcinogenicity in Rat (83-1 and 83-2)

TOX. CHEM. NO.: 083E

P.C. CODE: 097801

MRID NOS.: 00041402, 00085870, 00108828

TEST MATERIAL: SBP-1382®, technical

SYNONYMS: Resmethrin; 5-benzyl-furylmethyl (IRS)-cis,trans-chrysanthemate

STUDY NUMBER: 5271

SPONSOR: Roussel Bio Corporation, Lincoln Park, NJ (at time of submission, S.B. Penick, Lyndhurst, NJ)

TESTING FACILITY: Food and Drug Research Laboratories, Inc.

TITLE OF REPORT: A Lifetime Evaluation of the Dietary Administration of SBP-1382® to Wistar Albino Rats.

AUTHOR: Michael Knickerbocker, B.S., Peter J. Becci, Ph.D., George E. Cox, M.D. and Richard A. Parent, Ph.D.

REPORT ISSUED: May 2, 1980

EXECUTIVE SUMMARY: (To be completed following review by RfD Committee. The following summarizes the conclusions of the original DER, except that the ~~NOEL~~ for body

weight depression in males, but not females, is now considered 2500 ppm instead of 500 ppm):

Doses tested: 0, 500, 2500 or 5000 ppm resmethrin in diet (equivalent to 0, 39.5, 193.7 or 400.9 mg/kg/day in males and 0, 47, 232.7 or 450.3 mg/kg/day in females) for 103 weeks (males) or 112 weeks (females).

Systemic toxicity: At 2500 ppm (193.7 mg/kg/day, males, or 232.7 mg/kg/day, females), mean body weight/weight gain was slightly reduced in females during the first year of the study (statistically significantly lower mean body weight during much of the first year). Significantly higher liver weight (33%; 54% at 5000 ppm), along with increased incidence of lesions of the liver (hyperplastic nodules, nuclear hypertrophy) were observed in females.

At 5000 ppm (400.9 mg/kg/day, males or 450.3 mg/kg/day, females), slightly but statistically significantly lower mean body weights were observed in males for the first 18 weeks of the study and in females weights were reduced for much of the first 99 weeks. Mean thyroid weight was increased and increased incidence of thyroid cysts was observed in both sexes. Liver weight in males was increased (31%). (Reduced spleen weights were observed in females at all doses at terminal sacrifice but in the absence of corresponding microscopic effects was not considered a significant toxicologic effect).

No evidence of carcinogenicity was observed in males or females at the doses tested.

NOEL (systemic toxicity): 500 ppm (39.5 mg/kg/day, males or 47 mg/kg/day, females)

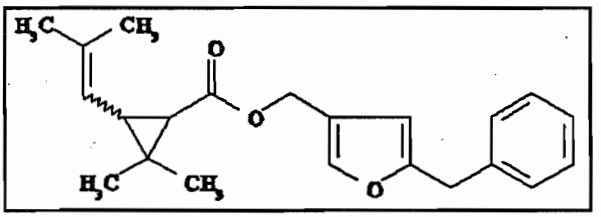
LOEL (systemic toxicity): 2500 ppm (193.7 mg/kg/day, males and 232.7 mg/kg/day, females), based on slightly decreased body weight in females during the first year of the study, increased liver weight and proliferative (non-neoplastic) lesions of the liver in females.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: SBP-1382® (resmethrin), technical
   Description: brown crystalline solid
   Lot/Batch #: 8176-RT
   Purity: 90%
   Stability of compound: Stable at room temperature when stored in dark (information taken from 1-year dog feeding study)
   CAS #: 10453-86-8

Structure



2. Vehicle: Corn oil (unspecified source)

3. Test animals: Species: Rat
Strain: Wistar albino
Age/wt. at receipt of animals: weanling/approx. 50 g.
Source: Charles River Breeding Laboratories, Wilmington, MA
Housing and environmental conditions: Housed individually in wire-mesh cages, ambient temperature 70 ± 3°F, according to standard FDRL procedures and NIH laboratory animal guidelines (NIH-78-23); no further details provided.
Acclimation period: not specified in report

B. STUDY DESIGN AND METHODS

1. Animal assignment: Animals were randomly assigned to the following test groups:

TABLE 1: STUDY DESIGN

Test Group	Dose in diet (ppm)	12-month sacrifice group Males	Female	Lifetime exposure group[1] Males	Females
1 Control	0	10	10	50	50
2 Low (LDT)	500	10	10	50	50
3 Mid (MDT)	2500	10	10	50	50
4 High (HDT)	5000	10	10	50	50

1 Males maintained on diet for 106 weeks and females for 113 weeks

Dose selection rationale: none provided

2. Diet preparation and analysis: Diet was prepared weekly by melting resmethrin at 100°C, mixing with corn oil and combining resmethrin with diet to give a 5% premix, which was used to prepare the three test dietary concentrations. Treated diets were stored at room temperature.

Test compound concentration in the diet was analyzed in samples taken at

11

1 to 3 month intervals during the study. Stability of the test compound in diet under environmental conditions of the animal housing facility was tested at each concentration by removing samples of a test diet preparation from feeders daily for 1 week (duplicate samples tested; taken from top and bottom of cage rack for comparison). Homogeneity was analyzed (triplicate samples) at each concentration from samples of the top, middle and bottom of the mixing bowl.

Results -

Homogeneity Analysis: Test samples showed reasonable homogeneity, with less than 5% variation in mean concentration between samples withdrawn from top, middle and bottom of each diet preparation.

Stability Analysis: After 1 week, slight decreases in concentration, usually less than 10%, were observed. A sample of 5000 ppm diet taken from a feeder on a bottom cage showed almost 20% decrease; however, the sample from the top cage was less than 5% lower.

Concentration Analysis: (see Chemistry Table 5 from study report, attached). Recoveries of test material were 82.8%, 82.4% and 87.3% of target concentration in the 500, 2500 and 5000 ppm diets, respectively. When adjusted for recovery and purity of test material, average dietary concentrations during the study were still relatively low: 77%, 83% and 85% of target concentration. Occasional batches of diet were markedly lower than target (eg., 70% - 57% of target) at all dietary levels.

3. Statistics: Body weight, organ weights, organ to body weight ratios, clinical parameters and food consumption were analyzed using one-way ANOVA. Statistical significance was identified at $p \leq 0.05$. The least significant difference test was used to determine which test groups differed from controls when differences were identified among test groups.

5. Animals received food (Agway Charles River RMH Commercial Laboratory Chow) and water ad libitum.

6. Study was initiated prior to FDA GLP but the final report was reviewed for compliance. Records of instrument maintenance/calibration were not provided, complete written SOPs were not always available and protocol did not provide all data now required.

II. RESULTS

1. Clinical Signs: Individual animal data or summary tables were not provided.

2. Body weight: Animals were weighed weekly for 6 months beginning on the week prior to initiation of dosing and monthly thereafter.

Results - See original DER and selected mean weekly body weights and total weight gain for the 24-month dosing period, shown below in Table 4:

TABLE 4: MEAN BODY WEIGHT GAIN AND TOTAL BODY WEIGHT GAIN (G)[1]

DIETARY DOSE, PPM	0	500	2500	5000
MALES				
Weeks 0 - 15	332.4	335.4	331.9	313.8
Weeks 15 - 30	80.0	75.5	74.5	85.1
Weeks 30 - 58	38.2	30.1	27.0	40.5
Weeks 58 - 78	-24.7	-6.1	-4.3	5.6
Weeks 78 - 103	-45.2	-48.6	-69.5	-64.5
Total Gain	390.7	385.5	359.6	380.2
FEMALES				
Weeks 0 - 15	153.7	153.7	141.9	140.2
Weeks 15 - 30	31.9	34.2	31.0	29.8
Weeks 30 - 58	33.1	32.6	29.2	24.0
Weeks 58 - 78	18.3	28.5	24.1	14.4
Weeks 78 - 103	9.1	15.0	8.9	16.7
Weeks 103 - 113	-12.0	-9.8	-15.6	-13.8
Total Gain	234.2	254.2	219.5	211.3

1 Data taken from Table 1 of study report; gain calculated by reviewer (not analyzed statistically)

Total body weight gain was slightly depressed in females at 2500 (6%) and 5000 ppm (10%). In males at 5000 ppm, body weight gain showed mild depression (5%) in the early weeks of the study. Although overall depression was reported in males at 2500 and 5000 ppm, in contrast to the study report and the original DER, TB-I did not consider the slight decreases at 2500 ppm to represent significant treatment-related toxicity. Statistically significant decreases in mean body weights were observed during the following weeks:

Males at 5000 ppm: Weeks 1 - 18, usually 4% - 7%
Females at 2500 ppm: Weeks 3 - 16, 26 - 50, usually 4% - 5%
Females at 5000 ppm: Weeks 11, 14 - 16, 19, 21 - 99, usually 4% - 5%, increasing to 7% - 9%

3. Blood was collected at 3, 12, 18 and 24 months for hematology and at 12 and 24 months for clinical chemistry analysis from 6 rats/sex/dose group. The study report did not indicate whether animals were fasted prior to bleedings. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*		Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)*		Mean corpusc. volume (MCV)
	Platelet count*		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic and chronic studies

Results - See original DER

b. Clinical Chemistry

X		X	
	Electrolytes:		Other:
	Calcium*		Albumin*
	Chloride*		Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
	Phosphorus*		Cholesterol*
	Potassium*		Globulins
	Sodium*	X	Glucose*
	Enzymes		Total bilirubin
X	Alkaline phosphatase (ALK)		Total serum protein (TP)*
	Cholinesterase (ChE)		Triglycerides
	Creatinine phosphokinase		Serum protein electrophores.
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic and chronic studies

Results - See original DER. The BUN values reported in females at 12 months were (low- to high-dose) 17.5, 22.0, 25.0* and 25.0* mg%, and at 24 months, 19, 20, 30 and 23. TB-I agreed with the original DER that the increase is probably not of toxicologic significance.

4. Urinalysis

Urine was collected from 6 rats/sex/dose at 3, 12, 18 and 24 months. The CHECKED (X) parameters were examined.

X		X	
X	Appearance*	X	Glucose*
	Volume*	X	Ketones*
X	Specific gravity*	X	Bilirubin*
X	pH		Blood*
X	Sediment (microscopic)*		Nitrate
X	Protein*	X	Urobilinogen

* Required for chronic studies

Results - See original DER. The albumin values reported in females at 3 months were (low- to high-dose) 1.00, 1.00, 1.17 and 2.00*; at 12 months were 3.83, 3.00, 2.17* and 2.17* and at 24 months were 5.00, 3.83, 1.67* and 2.33*. TB-I agreed with the original DER that these alterations were not of toxicologic significance.

5. Sacrifice and Pathology

All animals that died or that were sacrificed (by unspecified method) prior to or on schedule were subject to gross pathological examination. The study report did not indicate whether animals were fasted prior to terminal sacrifice. The CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed. The noted tissues were examined from all control and high dose terminal sacrifice animals and from 10/sex at the low and mid doses. Thyroid and liver were later examined from all animals.

X		X		X	
Digestive system		Cardiovasc./Hemat.		Neurologic	
	Tongue		Aorta*	X	Brain*+
	Salivary glands*	XX	Heart*	X	Periph. nerve*
	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*[1]	XX	Spleen	X	Eyes (optic n.)*
X	Jejunum*		Thymus*	Glandular	
X	Ileum*	Urogenital		XX	Adrenal gland*
X	Cecum*	XX	Kidneys*+		Lacrimal gland
X	Colon*	X	Urinary bladder*	X	Mammary gland*
X	Rectum*	XX	Testes*+	X	Parathyroids*++
XX	Liver *+	X	Epididymides	XX	Thyroids*++
	Gall bladder*		Prostate	Other	
X	Pancreas*		Seminal vesicle	X	Bone*
Respiratory		XX	Ovaries*+	X	Skeletal muscle*
	Trachea*	X	Uterus*	X	Skin*
XX	Lung*			X	All gross lesions and masses*
	Nose				
	Pharynx				
	Larynx				

* Required for subchronic and chronic studies.

\+ Organ weight required in subchronic and chronic studies.

\++ Organ weight required for non-rodent studies.

Organ weights: See original DER and table, below:

TABLE 4: MEAN ABSOLUTE AND RELATIVE ORGAN WEIGHT (G AND % OF BODY WT.)[1]

	RESMETHRIN IN DIET, PPM							
	0		500		2500		5000	
ORGAN: Sex/Mo.	ABS	REL	ABS	REL	ABS	REL	ABS	REL
LIVER: 12 mos.								
M	20.40	3.91	20.81	3.92	20.91	4.34	23.82*	4.89*
(%)[2]	--	--	--	--	--	--	(17%)	(25%)
F	11.08	3.92	11.54	4.32	14.82*	5.21*	15.63*	5.79*
(%)	--	--	--	--	(34%)	(33%)	(41%)	(48%)
Termination								
M	18.85	4.07	19.75	4.17	20.56	4.5	24.50*	5.34*
(%)	--	--	--	--	--	--	(32%)	(31%)
F	14.09	4.45	14.89	4.41	17.27*	5.45*	20.34*	6.84*
(%)	--	--	--	--	(23%)	(22%)	(44%)	(54%)
THYROID: 12 mos.								
M	.0242	.0046	.0270	.0051	.0267	.0036	.0308*	.0063*
(%)	--	--	--	--	--	--	(26%)	(37%)
F	.0226	.0081	.0195	.0073	.0227	.0080	.0240	.0089
(%)	--	--	--	--	--	--	--	--
Termination								
M	.0310	.0067	.0330	.0069	.0310	.0068	.0360	.0078
(%)	--	--	--	--	--	--	(16%)	(16%)
F	.0220	.0070	.0250	.0073	.0250	.0079	.0290*	.0088*
(%)	--	--	--	--	--	--	(32%)	(26%)

1 Data taken from Tables 14 and 15 of study report
2 (%) = % less than controls; only shown where >15%
* $p \leq 0.05$

Pathology: See original DER and previous two supplemental DERs. [Note: historical control data for Wistar rat tumor incidence in FDRL studies is not available].

1-912 277

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

00247c

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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

THRU: O. E. Paynter, Chief OEP 9/4/83
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: EPA Reg. No. 432-487. Resmethrin: Review of Thyroid Pathology Data.
TOX Chem No. 83E

Note to PM: This memo concerns data packages sent to TOX Branch as follows:

Dec. 3, 1981 -	S. B. Penick's response to Toxicology Branch's review of the rat chronic feeding/oncogenesis study - revised thyroid pathology report by S. W. Thompson. EPA Acc. No. 246214.
August 25, 1982 -	Reanalysis of thyroid data as prepared by S. B. Penick's consultant Dr. Conrad King.
October 26, 1982 -	Additional information regarding thyroid data in rats as provided by Dr. Conrad King for the S. B. Penick Co. EPA Acc. No. 248547.

Background:

The original review (J. Doherty review dated May 19, 1981, see EPA File No. 432-487) of the rat chronic feeding/oncogenesis study with the synthetic pyrethroid Resmethrin indicated that there was a possible oncogenic effect in the thyroid gland. The following table illustrates the incidence of thyroid adenomas as originally presented to EPA (EPA Acc. No. 242783, Path Table 12).

17

Original Thyroid Data[1]

Dose Level	Males n	Males Adenomas	Males Cysts	Females n	Females Adenomas	Females Cysts
Control	47	2	1	50	1	1
500 ppm	26	4	1	16	1	1
2500 ppm	27	3	2	23	4	0
5000 ppm	47	8	6	48	5	3

n: number of rats examined.

[1] NOTE: Only rats dying after the first year and survivors are included.

The above table also includes the number of incidence of cysts as originally reported. The data as originally presented did not differentiate interstitial adenomas from follicular adenomas.

These data show that there are more incidences of "adenomas" and "cysts" in both the high dose male and female test groups.

The registrant (S. B. Penick Corporation) was asked to reanalyse the thyroid tissue and include those rats from the low and mid dose groups which were not previously examined microscopically. The registrant complied and submitted the revised pathology report by Dr. S. W. Thompson (submission of 12/3/81) and eventually 2 additional submissions, (8/25/82 and 10/26/82). As per the memorandum from Dr. Louis Kasza, DVM, Toxicology Branch (TB) staff pathologist to Edwin Budd, dated 12/7/82, the pathologic effects of Resmethrin in the thyroid (and liver) should be evaluated based on the diagnoses of Dr. Samuel Thompson.

Recommendations and Comments:

1. TB has reviewed the information submitted by the S. B. Penick Corporation regarding the pathology of the thyroid of rats dosed with Resmethrin and has concluded:

   a. The thyroid is affected by the presence of Resmethrin in the diet (either directly or indirectly) and there are statistically significant increases in the frequencies of cysts in the follicules of both males and females in the high dose groups. The female high dose group has a statistically significant increase in thyroid weight. The high dose group males and mid dose group females also have pronounced increases in thyroid weight. A NOEL is set at 2,500 ppm for these effects in the thyroid.

2

18

b. The data (as presented in Dr. Thompson's revised October 29, 1981 thyroid pathology report) do not provide sufficient evidence to conclude that Resmethrin induced thyroid tumors in the rats in this study. The overall magnitude of the response is not sufficient to justify a conclusion that Resmethrin caused an increased incidence of these not uncommon thyroid neoplastic (particularly follicular adenomas) lesions in this study.

Detailed Considerations

Review of Revised Thyroid Pathology Report:

A Lifetime Evaluation of the Dietary Administration of SBP-1382 to Wistar Albino Rats - Supplemental Report (Pathology Report) - Thyroid Pathology.

Food and Drug Research Laboratories, October 29, 1981, Lab No. 5271, (prepared by Samuel W. Thompson, D.V.M.) (EPA Accession No. 246214).

The tissue sections of all specimens of thyroid collected at necropsy for the male and female rats of the control, and high dose groups and the tissues in the low and mid dose that were previously selected for preparation and histology were retrieved from the FDRL. The remaining tissues from the low and mid dose test groups which were not previously selected for histopathology were prepared for examination. In addition, certain specimens of thyroids which may have contained sectioning artifacts were reprepared for histology. All of the tissue samples were reevaluated by Dr. Samuel W. Thompson, then Director of Pathology, FDRL. The criteria which were used to differentiate benign and malignant neoplasms were:

Benign	Malignant
Encapsulated	Non-encapsulated
Non-invasive	Invasive of blood vasculature or capsule of the gland
Little or no anaplasia	Metastases

The statistics used in the report by the sponsor for evaluating the data were the Chi-Square test with Yates correction for 2 x 2 contingency tables. Note: TB used Fisher's Exact test to statistically evaluate some of the data.

Results of the Reanalyses: The following table describes the revised data related to the thyroid tissue.

002478

Comprehensive Table of Data on the Thyroid Glands
from Rats Dosed with SBP-1382[1]

	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
Organ Weight n[2]	15	18	14	19	19	25	16	23
Absolute (mg)	31 ± 6	33 ± 7	31 ± 7	36 ± 7	22 ± 4	25 ± 5	25 ± 9	29 ± 6*
(as % control)				+ 16%		+ 14%	+ 14%	+ 32%
Relative (% B.W.)	.67±.16	.69±.14	.68±.15	.78±.14	.70±.14	.73±.14	.79±.24**	.98±.21**
(as % control)				+ 16%		+ 4%	+13%	+40%
Gross Necropsy n[3]	60	60	60	60	60	60	60	60
other than normal	8	11	12	18	2	5	10	14
as %	13.3	18.3	20.0	30.0	3.3	8.3	16.7	23.3
Histopathology n[3]	59	59	60	60	60	59	58	59
Interstitium or other								
hypertrophy	1	0	0	0	1	0	0	0
Capsule	0	0	0	0	1	0	0	0
Lymphocytic inflam	4	2	2	1	2	2	0	1
Interstitial adenoma	4	3	2	3	2	2	0	1
Lymphocytic leukemia	1	0	0	0	0	0	0	0
Follicles								
cysts	0	4	2	18*	2	3	2	8*
hyperplasia	1	0	0	0	2	4	2	1
squamous metaplasia	0	0	2	2	0	0	0	0
necrosis	0	1	0	0	0	0	0	0
Adenomas (follicular)								
polymorphofollicular	1	3	3	4	0	0	4	3
microfollicular	0	0	0	0	0	0	0	1
papillary	0	0	0	1	0	0	0	0
solid	0	0	0	0	1	1	1	0
Carcinomas (follicular)								
microfollicular	1	0	0	0	0	0	0	0
polymorphofollicular	2	0	0	0	0	0	0	2
Total Follicular Neoplasms (Adenomas & Carcinomas)	4	3	3	5	1	1	5	6

1 These data are from the revised report (S. W. Thompson report, 10/29/81, EPA Acc. No. 264214) except for the organ weight data which is from the original report (EPA Acc. No. 242782).

2 Does not include rats with obvious large sizes (i.e. some rats with thyroid cysts and neoplasms).

3 10-13 of these were sacrificed at 53 weeks or died before 53 weeks.

* Statistically significant by Fishers exact test.

** $P < 0.001$ (t test)

4

20

The above table indicates that the thyroid gland is affected by high levels of Resmethrin in the diet. Statistically significant increases in the weight (absolute and relative) of this organ are attained for the high dose group females. The mid dose group females and high dose group males are also obviously larger in weight (absolute and relative), but statistical significance was not attained.

There were more rats in both the mid and high dose test groups (male and female) which had evidence of a test chemical effect as noted at gross necropsy.

With the exception of the follicles, histopathology did not reveal indications of there being an adverse effect. In particular, several interstitial adenomas were present but their presence was clearly not related to the test material.

The highest level of Resmethrin in the diet affected the follicular cells of the thyroid. In both sexes, the high dose test group had a statistically significant increase in follicular (colloid) cysts. These cysts are considered to be nonneoplastic and a NOEL for this lesion was set at 2500 ppm. A difference between Dr. Thompson's revised report and the original report is that many more cysts were found by Dr. Thompson than were first reported.

When follicular adenomas in males alone are considered, there are 1/59, 3/59, 3/60 and 5/60 rats affected for the control, low, mid and high dose test groups but these data do not show statistical significance (Fisher's one tailed p statistic as determined by J. Doherty and by the test procedure used by the laboratory). There were a total of 3 follicular carcinomas among the male rats, all of which were in the control group. Combining adenomas with carcinomas in the males resulted in a total of 4/59, 3/59, 3/60 and 5/60 incidences of follicular neoplasms for the control, low, mid, and high dose test groups.

Among the females, polymorphofollicular adenomas were found only in the mid (4 incidences) and high (3 incidences) test dose groups. Statistical significance was not $< .05$ for these data. When adenomas plus the two incidences of carcinomas which occurred in the high dose female group are considered, the high dose test group approaches marginal statistical significance ($p = .054$, as determined by J. Doherty using Fisher's one tailed p statistic). The statistical procedure used by the sponsors statistician also did not show that these data were significant.

5

21

002478

The registrant through its consultant, Dr. Conrad D. King, provided a defense that the thyroid tissue was not an oncogenic target for the effects of Resmethrin. The first report by Dr. King (dated 7/7/82) discusses the possibility that thyroid pathology results secondary to damage to the liver resulting from Resmethrin treatment. TB declines from either concurring or disagreeing with this discussion of a possible physiological basis for the thyroid pathology noted in this study. Dr. King's report recognizes that at 5000 ppm there are observable effects in both males and females. Since those effects were determined by Dr. Thompson to be nonneoplastic in nature, a NOEL of 2500 ppm was set for these lesions by TB.

The second report by Dr. King (EPA Acc. No. 248547) provided several published reports which show that the spontaneous rate of occurrencce of thyroid tumors in Wistar rats is 0-30%. Dr. King indicated that the minor increase in incidences for the adenomas in males and females in this study is still well within what can be expected as a spontaneous rate.

Conclusions:

1. Based upon the diagnosis of S. W. Thompson (10/29/81 report), TB has determined that there is insufficient evidence to conclude that Resmethrin induces a positive oncogenic response in the thyroid. The rats dosed with Resmethrin did not develop thyroid neoplasms in a statistically significantly different frequency than did the controls. The slight increases in thyroid neoplasms in the dosed rats can be shown to be within the spontaneous response for the Wistar strain of rat.

2. A NOEL for nonneoplastic effects in the thyroid is set at 2500 ppm. At 5000 ppm there were statistically significant increases in the frequency of cysts in both males and females and female thyroid weights were increased.

John D. Doherty, Ph.D. 2/2/83
Toxicology Branch
Hazard Evaluation Division (TS-769)

2/4/83

OPP:HED:TOX: J.DOHERTY:sb 12/29/82 re/1/31/83 X73713 Rm 814 #ml9

6

22

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

December 7, 1982

002478

TO: Edwin Budd, Section Head
Toxicology Branch, TS-769

OFFICE OF TOXIC SUBSTANCES

FROM: Louis Kasza, Pathologist L.K
Toxicology Branch, TS-769

SUBJECT: Recommendation of Dr. Thompson's Histopathologic Study for the Evaluation of Resmethrin in Chronic Feeding Study

I recommend that the pathologic effects of Resmethrin should be evaluated based on the report of Dr. Thompson.

Reasons:

1) Dr. Thompson used approximately five times as many sections in his examination than the number of sections used in previous studies.

2) Dr. Thompson made all diagnoses without the knowledge of the dose levels administered. Identification of the slides and tabulation of the results took place after completion of the histopathologic descriptions.

3) Dr. Thompson's reevaluation was cosigned by Dr. Becci who was one of the principal coinvestigators in previous studies.

4) Dr. Thompson is well known and is a widely respected pathologist with great experience in rodent pathology. He has published several papers describing the effects of chemicals and lesions in experiments in rodents. His knowledge (published book) in histochemistry makes him one of the most respected scientists in this field.

5) The reevaluation and submission of additional data was requested by the EPA. The submitted data in Dr. Thompson's report were necessary in order to make an evaluation of Resmethrin toxicity in animal experiments.

cc: Dr. O. E. Paynter, TS-769
Branch Chief

Dr. J. Doherty, TS-769
Principal Reviewer

7
23

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

002477

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

To: Franklin D. R. Gee, Product Manager #17
Registration Division (TS-767)

Thru: O. E. Paynter, Branch Chief OEP 7/14/83
Toxicology Branch
Hazard Evaluation Division (TS-769)

Subject: EPA Registration No. 432-487. Review of Rat Liver Pathology Reports Related to the Chronic Feeding/Oncogenesis Study With Resmethrin. Resolution of the Problem of There Being a Possible Oncogenic Response in the Liver of Females. Assignment of a NOEL for Effects in the Liver.

TOX Chem No. 83E

Background:

The S. B. Penick Corp. (Lyndhurst, New Jersey) previously submitted a rat chronic feeding/oncogenesis study with the synthetic pyrethroid Resmethrin. Toxicology Branch review of this study (see J. Doherty review dated May 19, 1981) indicated that the data as presented showed that Resmethrin was associated with higher frequencies of liver neoplasms in the mid (2500 ppm) and high (5000 ppm) dose test groups in females.

The final report as originally presented to EPA (Acc. No. 242782, 242783, 242784, 242785 and 242786) contained the results of 3 microscopic readings of the liver tissue. There were two readings by Dr. Mark K. Walter who was originally responsible for the diagnosis and a reading by Dr. Peter J. Becci and Dr. George Cox. Dr. Walter's original report gave some indications of a neoplastic effect in the liver of females and subsequently Dr. Becci and Dr. Cox prepared additional slides and made their own diagnoses. Dr. Walter was later asked to reevaluate the slides. A summary of the potential neoplastic findings in female rat liver as reported in each of the three readings is as follows:

1811
24

1.) Dr. Walter's original diagnosis: (EPA Acc. No. 242783, Table 9 page 324b and Table 12 page 472-3)

	Control	Low	Mid	High
Nodular hyperplasia	0	0	3	8
Nodule, hyperplastic	1	0	0	1
Adenoma	0	0	0	1
Hepatoma	0	0	0	5

2.) Dr. Becci and Dr. Cox's diagnosis: (EPA Acc. No. 242784, Table 17a)

	Control	Low	Mid	High
Nodule, hyperplastic	1	0	5	13
Adenoma	0	0	5	13
Carcinoma	0	0	0	8

3.) Dr. Walter's revised report: (EPA Acc. No. 242784, Table 17b)

	Control	Low	Mid	High
Hyperplasia, nodular	1	0	6	20
Nodule, hyperplastic	1	0	5	12
Hepatoma	0	0	2	5

Note: There were 46-50 rats examined per group. Some rats have more than one type of suspect neoplasm.

The conclusion in the May 19, 1981 TB review that Resmethrin causes an oncogenic effect in rat liver was based largely on the diagnoses of Drs. Becci and Cox, which show the presence of adenomas and carcinomas. The terms "nodular hyperplasia" and "nodule, hyperplastic" and "hepatoma" are ambiguous and Toxicology Branch advised the Penick Corporation that these lesions would be considered as neoplastic unless they were adequately described differently.

Because of the differences in the terminology used and because not all of the liver tissue in the low and mid dose test groups were reanalyzed and because there were different numbers of slides prepared per rat, the registrant was requested to provide an additional reading. The conditions of this additional reading were that equal numbers of slides for all rats should be read and that the same pathologist read all of the slides. The Penick Corporation complied and Dr. Samuel W. Thompson, then staff pathologist at FDRL, made readings of the slides from all female rats (and selected male rats) and an amendment to the rat chronic feeding/oncogenesis study was submitted. This amendment is reviewed below.

25

As per the memorandum (attached) from Dr. Louis Kasza, DVM, Ph.D., Toxicology Branch staff pathologist to Edwin Budd dated Dec. 7, 1982, the pathologic effects of Resmethrin in the liver (and thyroid) should be evaluated based on the diagnoses of Dr. Samuel Thompson.

Recommendations and Conclusions

1. Oncogenic response in rat liver.

Toxicology Branch (TB) has concluded that there is insufficient evidence to conclude a frank oncogenic response in rat liver.

The revised pathology report as submitted on June 1, 1982 (report prepared and signed by T. G. Hess, S. W. Thompson, and P. J. Becci, dated May 19, 1982 from FDRL) asserts that there is no oncogenic response in the liver of the rats dosed with Resmethrin. This conclusion was made possible because most of the livers previously diagnosed by Drs. Becci and Cox and reported in the original submission as having adenomas or carcinomas were diagnosed by Dr. Thompson as having nonneoplastic lesion types.

As implied by his signature on the May 19, 1982 document, Dr. Becci concurs with the reclassification of these lesions as described by Dr. Thompson in the revised report. There is no indication as to whether Dr. Cox who was also responsible for the original diagnosis also agrees with the reclassification of these lesions.

An important factor leading to the TB conclusion that there is no neoplastic effect of Resmethrin in rat liver was the explicit description of "hyperplastic nodules" as proliferative rather than as a neoplastic lesions by Dr. Thompson. TB recognizes that there is no agreement at this time among pathologists for the classification of "hyperplastic nodules" as being neoplastic or non-neoplastic in nature. TB also recognizes that diagnosis for adenomas (neoplastic tissue) and hyperplastic nodules is difficult.

2. A NOEL for adverse toxic responses.

The liver pathology data (June 1, 1982 submission) clearly indicate a dose response for increased incidences of "hypertrophy of hepatocytes". The low dose test group (females) was statistically significant at the .012 level (Fisher's one tail P statistic). This type of lesion is not,

however, considered by TB to be a definite toxic response but rather a pharmacological response due to the presence of a xenobiotic (i.e., Resmethrin) inducing increased enzyme activity of the liver.

The NOEL for this study is < 500 ppm for any observable effect. The NOEL for toxic responses is 500 ppm. The LEL is 2500 ppm. At 2500 ppm and above there are increases in liver weight and increases in various types of liver lesions.

3. A summary table and discussion of the neoplasms in tissues other than liver and thyroid for the rat chronic feeding/oncogenesis study with Resmethrin is included in this memo.

4. Any other toxicity data requirements which may exist will be addressed when the individual registrations and/or tolerance requests are submitted by Registration Division to Toxicology Branch for review.

Detailed Considerations

Amendment II Supplemental Report (Pathology Report). A Lifetime Evaluation of the Dietary Administration of SBP-1382 to Wistar Albino Rats.

Prepared and signed by Frederick G. Hess, Samuel W. Thompson, DVM, and Peter J. Becci. FDRL, Study No. 5271, May 19, 1982. EPA Acc. No. 247579.

Background:

The original review of this study (see J. Doherty review dated May 19, 1981) concluded that the data as originally presented showed that Resmethrin produced an oncogenic effect in the liver as evidenced by the dose related increases in hyperplastic nodules, adenomas and carcinomas. Hyperplastic nodules were included as neoplastic and the registrant was advised to defend their position that these lesion types should not be classified as such. In a subsequent meeting (Nov. 1981) with the registrant it was decided that the female and certain male liver tissues would have to be reexamined and an equal number of slides from each rat must be examined. All slides must be read by the same pathologist.

Results:

The liver samples were prepared and later examined microscopically by Dr. Samuel W. Thompson, DVM, Diplomate, American College of Veterinary Pathologists. A summary table of the important lesions found in the liver of female rats in this study is shown below.

Lesions: (Nonneoplastic):

1. Showing Possible Dose Response

	Females			
Non-Proliferative:	Control	Low	Mid	High
Number Examined	60	60	60	60
Fibrosis	0	2	1	12
Hemorrhage	1	1	0	11
Hemosiderin Pigment Deposits	1	2	3	10
Bile Pigment Deposits	1	0	3	9
Hypertrophy of Hepatocytes	3	12	25	30
Nuclear Hypertrophy	0	1	6	8
Atrophy of cord cells	0	2	1	10
Necrosis of Indiv. Hepatocytes	1	0	2	9
Necrotic Focus	0	1	0	9
Necrotic Area	0	1	2	5
Acute leukocytic inflam	0	0	1	3
Lymphocytosis	0	2	3	5
Microgranuloma	1	2	2	4
Clear cell area alter	0	0	2	3
Acidophilic cell area alter	0	0	2	2
Basophilic cell area alter	0	0	3	9
Mixed cell area alter	1	0	0	4
Proliferative:				
Hyperplastic focus of hepatocytes	0	0	1	3
Hyperplastic nodules of hepatocytes	1	0	4	8(9)*

2. Not showing Dose Response

Non-Proliferative:				
Subacute lymphatic inflammat.	42	53	37	38
Hematopoiesis, extramedullary	27	32	26	34
Telangiectases	17	15	21	20
Intracytoplasmic microvesicle	52	58	57	54
Intracytoplasmic vacoules	43	51	39	45

5

Lesions: (Nonneoplastic continued):

Proliferative	Females Control	Low	Mid	High
Number Examined	60	60	60	60
Bile duct without connective tissue	42	42	36	38
Bile duct with connective	38	32	29	28
Bile duct with sclerotic	31	37	23	22
3. Gross Necropsy (showing dose response)				
White nodules and other nodules or white areas and/or spots, masses or cyst-like	4	6	15	41
4. Liver Weight (absolute)	14.09	14.89	17.27** 22.6%†	20.34** 44.4%†
(relative)	4.45	4.41	5.45** 22.5%†	6.84** 53.7%†

† As % increase relative to control

* The report indicated that 8 rats were affected with hyperplastic nodules. Toxicology Branch tabulated 9. The rats involved were #425, 428, 433, 444, 455, 456, 461, 462 and 470.

** Statistically significant ($p < 0.05$).

NOTE: Other types of liver pathology were also present but the incidences noted did not reflect a dose response.

As indicated by the above table, the mid and high dose level groups are associated with increased incidences of a variety of lesions both proliferative and non-proliferative. There are also increased incidences of rats with gross necropsy observations. The liver weight of the mid dose group and high dose group females is elevated relative to controls (see original review May 19, 1981).

The data in the table showing the summary of nonneoplastic effects indicates the progression of 3/60, 12/60, 25/60, and 30/60 incidences of "hypertrophy of hepatocytes" among the female controls, low, mid, and high dose test rats. The incidences in the low dose test groups are statistically significant when compared with the control groups ($p = .012$, Fisher's One Tail P statistic). This effect ("hypertrophy of hepatocytes") is not, however, considered by Toxicology Branch to be a definite toxic response but rather an adaptation of the rat to the presence of the xenobiotic.

6

29

The NOEL for non-neoplastic toxic effects in the liver is set at 500 ppm. At 2500 ppm (LEL) there is an increase in liver weight, hyperplastic nodules of hepatocytes, nuclear hypertrophy and possibly also other types of liver pathology. At 5000 ppm the effects noted at 2500 ppm are increased in incidence and other types of lesions appear including fibrosis, hemorrhage, pigment deposit and necrosis are evident.

The oncogenic response (incidences) in liver as described by Dr. Thompson is shown in the following Table.

	Males				Females			
Tumor Type	Control	Low	Mid	High	Control	Low	Mid	High
Number examined	48	49	48	47	60	60	60	60
True liver tumors								
Liver cell adenoma	0	0	0	0	0	0	0	2*
Liver cell carcinoma	0	0	0	0	0	0	0	1*
Hemangioendothelioma	0	0	0	0	0	0	0	1
Total	0	0	0	0	0	0	0	4
Others								
Adenocarcinoma-gastric metastasis to liver	0	0	0	0	1	0	0	0
Leukemia infiltrate	1	0	1	0	0	0	1	0
Reticulum cell Sarcoma	0	0	0	1	0	0	0	0

* The revised pathology report indicates that only two rats were affected with liver cell adenoma or carcinoma. These were females in the high dose test group and one of these had both adenoma and carcinoma. A third female in the high dose test group (# 436) was diagnosed as having hemangioendothelioma. Five other rats (total both sexes) had neoplastic tissue in the liver, but the types of tumors were not considered to be frank liver tumors.

1

30

The above data do not provide sufficient evidence to conclude that Resmethrin induced an oncogenic response in female rat liver. The revised report as shown also shows that there are no frank liver tumors among the males. Thus, the problem (as indicated in the original review of this study) that there may be an oncogenic effect in males is dismissed.

Summary of Neoplasms in the Rat Chronic Feeding/ Oncogenesis Study With Resmethrin.

The following table indicates the frequency of occurrence of selected neoplasms in tissues other than the liver, thyroid gland and ovary as reported in the revised summary table (EPA Accession No. 247579 pages 43-59).

Incidences of Specific Neoplasms

		MALES				FEMALES			
		Control	Low	Mid	High	Control	Low	Mid	High
Pituitary	n	56	33	32	56	54	41	45	55
adenoma		8	7	7	6	16	18	22	12
carcinoma		1	0	0	0	0	0	0	0
Mammary Gland	n	47	26	26	50	60	29	32	59
Fibroadenoma		0	0	0	0	15	7	12	7
Testis	n	60	42	45	60	-	-	-	-
interstitial cell tumor		9	8	14	6	-	-	-	-
Pancreas	n	60	38	35	60	60	33	31	60
adenomas (3 types)		2	1	3	3	3	0	0	3
adenocarcinomas		1	0	0	0	0	0	0	1
Thymus	n	?	?	?	?	?	?	?	?
(total)		1	0	2	0	3	6	2	0
Adrenals	n	59	34	39	60	60	46	52	60
Adenomas		1	0	0	0	3	0	0	2
pheochromocytoma		1	2	1	0	0	0	0	1

n = Number of animals examined.
? = The total number of tissues examined for the thymus was not provided in the report.

8

Other examples of tissues not listed in the above table which had neoplasms were the heart (1 incidence of rhabdomyoma), large and small intestines (one each); mouth (1); salivary gland (2, one adenoma each in the low and high dose female groups); kidneys (1 incidence); lungs (1 adenocarcinoma in the low dose female); two others with systemic tumors); spleen (3 rats with lymphosarcoma, all in the mid dose group, 1 male and 2 females); parathyroid (5 adenomas, 2 in controls (1 male and 1 female), and 3 in the high dose group (2 males, 1 female); brain (7 total, 1 adenoma, control female; 2 astrocytoma, control male; 1 meningioma, low dose group female, 2 glioblastomas both in the high dose group, 1 male and 1 female 1 glioma high dose group male); stomach (3 different types, none in the same group).

Twenty-three incidences (18 males and 5 females) were affected with (various neoplasms in the skin) The neoplasm types included squamous cell carcinoma (1), fibroma (11), lipoma (1), papilloma (3), fibrosarcoma (4), lymphosarcoma (1), hemangiosarcoma (1) and sarcoma (1). None of these showed evidence of being related to Resmethrin in the diet.

There were 11 rats affected with neoplasms in the lymph nodes, these were in the control (5) and in the mid dose group (5) and one high dose test group (1). The neoplastic types were hemangioma, (4) leukemia (1), lymphoma (1) and lymphosarcoma (5).

Pathology of the ovaries: The ovaries are considered separately as below. The following table shows the information related to the ovaries as reported in the original pathology report. (EPA Accession No. 242783)

PATHOLOGY (Ovaries)		FEMALES Control	Low	Mid	High
Gross Necropsy	n	50	49	49	49
Abcessed (nodules, mass, etc.)		4	8	5	8
Color alterations*		1	4	4	6*
Cystic		14	17	16	14
Size alterations		8	10	2	4
Non-neoplastic pathology	n	50	30	23	49
Cystic (various kinds)		12	8	14	12
Interstitial cell hyperplasia		1	0	0	2
Follicular necrosis		2	0	0	0
Abscesses		1	4	3	3
Oophoritis		3	2	3	1
Neoplastic	n	50	30	23	49
Adenoma		0	0	1	0
Granulosa-theca cell tumor*		0	1	0	3*

cont.

Weight	n	16	20	15	22
Absolute	mg	109+35	98+35	118+50	101+22
Relative		.34±.11	.29±.11	.39±.18	.35±.08

* Data are not statistically significant at the .05 level using Fisher's One Tail P Statistic

The rats which developed granulosa-theca cell tumors were a low dose (#343, 113 weeks) and three high dose animals (#443, 100 weeks; #452, 99 weeks; and #473, 113 weeks). All rats affected were aged greater than 99 weeks. None of these rats also had thyroid neoplasms.

Of these four affected rats all but #473 had revealing gross necropsy in the form of abscesses (nodule and/or mass, etc.). There were other rats which had this description at gross necropsy. Many of these were followed up microscopically with diagnoses of oophoritis, abscesses or cysts. There were five rats with gross necropsy indicative of possible neoplasm that were not followed up by a histological description. Three of these were in the control group and one each in the mid and high dose groups.

This apparent increased incidence of neoplasms in the ovary was not considered to be a result of the test chemical because the response in the high dose group was of a low degree of magnitude and because this type of tumor is, although not common, not rare. The increased frequency in the high dose group does not reach statistical significance at the 0.05 level.

John Doherty 2/2/83

John D. Doherty, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769)

RBD 2/4/83

OPP:HED:TOX: J.DOHERTY:sb 1/6/83 X73711 Rm 814 #m21

10

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

December 7, 1982

002417

TO: Edwin Budd, Section Head
Toxicology Branch, TS-769

OFFICE OF TOXIC SUBSTANCES

FROM: Louis Kasza, Pathologist
Toxicology Branch, TS-769 L.K

SUBJECT: Recommendation of Dr. Thompson's Histopathologic Study for the Evaluation of Resmethrin in Chronic Feeding Study

I recommend that the pathologic effects of Resmethrin should be evaluated based on the report of Dr. Thompson.

Reasons:

1) Dr. Thompson used approximately five times as many sections in his examination than the number of sections used in previous studies.

2) Dr. Thompson made all diagnoses without the knowledge of the dose levels administered. Identification of the slides and tabulation of the results took place after completion of the histopathologic descriptions.

3) Dr. Thompson's reevaluation was cosigned by Dr. Becci who was one of the principal coinvestigators in previous studies.

4) Dr. Thompson is well known and is a widely respected pathologist with great experience in rodent pathology. He has published several papers describing the effects of chemicals and lesions in experiments in rodents. His knowledge (published book) in histochemistry makes him one of the most respected scientists in this field.

5) The reevaluation and submission of additional data was requested by the EPA. The submitted data in Dr. Thompson's report were necessary in order to make an evaluation of Resmethrin toxicity in animal experiments.

cc: Dr. O. E. Paynter, TS-769
Branch Chief

Dr. J. Doherty, TS-769
Principal Reviewer

11

34

DATE: 1981

001912

SUBJECT: EPA Registration No. 432-487. 2-year rat chronic feeding/oncogenesis study with resmethrin. Study submitted as 6(a)2 data. Tox. Chem. No. 83E

FROM: John Doherty
TOXICOLOGY BRANCH, HED (TS-769)

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

Background:

The PENICK Corporation has submitted the final report of a 2-year chronic feeding/oncogenesis study with rats for review by TOXICOLOGY BRANCH. The conclusion of this study, according to the testing laboratory, was that resmethrin was associated with increased incidences of proliferative liver lesions and tumors in the high-dose test group.

Conclusions of Toxicology Branch review:

1. TOXICOLOGY BRANCH has concluded that resmethrin is associated with oncogenic effects at both the mid- and high-dose levels in the livers of female rats.

   TOXICOLOGY BRANCH has used the diagnosis of Drs. Becci and Cox (see Pathology Table 17a) to determine that there were both adenoma and nodular hyperplasia in female rats at the mid dose level (2,500 ppm) to justify the conclusion of oncogenic effects at this level. Nodular hyperplasia is considered a primary neoplasm in rats unless proven otherwise (see JNCI 64: 180-190 (1980).

2. The thyroid has also been indicated as being a possible target organ for oncogenic effects of resmethrin. Thyroid tissues for those animals in the low and mid dose groups not yet examined should be prepared and examined.

3. No clear NOEL was established for the effects of resmethrin on spleen weight.

4. The registrant and its consultants are invited to present their case that the thyroid tissue does not show oncogenic effects related to resmethrin and that the effects of resmethrin on spleen weight do not represent a toxic effect.

EPA FORM 1320-6 (REV 3-76)

Review of Study

Title: A Lifetime Evaluation of the Dietary Administration of SBP-1382 to Wistar Albino Rats

Food and Drug Research Laboratories
May 2, 1980, Lab. No. 5271
EPA Accession No. 242782-3-4-5-6 (five volumes)

The one-year interim report of this study was reviewed by J. Doherty. June 26, 1980.

Groups of 60 male and 60 female weanling Wistar albino rats were dosed with 0, 500, 2500, or 5000 ppm of technical resmethrin in their diet. The test chemical was dissolved in corn oil and the controls were fed corn oil in their diet. The male rats were sacrificed during the 106th week, the female rats were sacrificed during the 113th week and this study is considered a lifetime feeding rather than a 2-year feeding study.

RESULTS

1. Mortality (See Pathology Table 1, Volume 2)

	Males	Females
Control	15/30% (23)*	19/38% (13)
Low Dose	18/36% (23)	27/54% (14)
Mid Dose	14/28% (29)	17/34% (14)
High Dose	20/40% (21)	25/50% (13)

* Number of survivors/percentage survival assuming 50 possible survivors; ( ) the number of rats dying spontaneously.

There was no dose-dependent decrease in survivors. Survival in this study is poor (expecially in the male group) because less than 50% of the possible animals survived.

2. Clinical signs - at the highest dose level, a transient increase in rats with tremors and hair loss was noted.

3. Body weight - a NOEL for depression of body weight is 500 ppm for both males and females.

4. Food Consumption - Statistically significant differences were noted but overall food consumption was within 3% of the controls for females and males.

5. On a mg/kg/day basis females consumed more of the test chemical than did the males across the dosing levels, (39.5, 193.7, 400.9, for males and 47, 232.7 and 450.3 for females).

6. Ocular effects. (Note: the interim report indicated a possible effect). The final report by R. C. Riis, D.V.M. states that ocular abnormalities were variable and not particularly related to systemic effects. The observations of a possible lesion as noted in the interim report were not further substantiated.

7. Hematology and urinalysis (analysis at 3, 12, 18 and 24 months for 6 rats of each sex). No consistent dose-related effects were noted in hematological analyses. At the mid and high dose levels, there were noted alterations in the content of albumin in the urine for females only. For example, at three months the albumin was higher than the control content; at 12, 18 and 24 months both the mid and high dose groups were lower (statistically significant) than the value reported for the control. The physiological and/or toxicological significance of the albumin in the urine and the resmethrin-induced decreases is not known.

8. Biochemistry - assays performed using six rats of each sex at 12 and 24 months. Glucose (mg %), SGPT and SAP were not affected by the presence of the test chemical in the mid- and high-dose groups. BUN was elevated at 12 months in females (see interim report) but no similar effect was noted at 24 months.

9. Organ weights - The interim report indicated differences in absolute and relative weights for liver and spleen for both males and females and possibly for adrenals and thyroids.

   The results of the terminal sacrifices showed that:

   a. Liver weight for both males and females in the high dose and for females in the mid dose test groups were higher.

   b. Thyroid weights for females in the high dose group were higher (32% absolute and 40% relative).

   c. Spleen weights. In males the mid and high dose groups were lower but dose dependence and statistical significance were not obtained. For females the following table has been prepared.

Spleen Weight Data

	12 Months		Terminal	
Dose Level	Abso. Wt.	Rel. Wt.	Abso. Wt.	Rel. Wt.
0	.76	.27	1.15	.36
500	.65	.24	.93	.27*
2500	.63*	.22*	.80*	.25*
5000	.58*	.21*	.81*	.28*

* statistically significant $P < .05$

001912

A statistically significant decrease (25%) in relative spleen weight is noted in the low-dose test group. The consistency of appearance of decreases in spleen weight at both 12 months and at the terminal sacrifice allow the conclusion that this experiment does not demonstrate a NOEL at the lowest dose tested for adverse effects on the spleen.

Pathology

A. Gross Pathology

In particular, the liver exhibited clear indications of proliferative lesions in the female rats in the high dose test group.

B. Histopathology

Histopathology was performed on the rats sacrificed at 1 year and all of the control and high-dose group rats including survivors and spontaneous and moribund deaths. Histopathology was also performed on 10 rats/sex from the low and mid dose groups. For the remainder, only grossly abnormal organs were further examined microscopically. (Note that usually liver was examined histologically for all animals).

The initial reading of the slides was the responsibility of Dr. Mark K. Walter, a resident pathologist at FDRL during the summer of 1979. His report was reviewed by Dr. Peter Becci who noted that livers showed dose-dependent increases in proliferative lesions. Subsequently, Drs. Becci and George F. Cox, staff pathologists at FDRL, recut and reexamined (apparently extensively) slides of the lung and liver tissue. The pathology report (prepared by Drs. Becci and Cox) states that once they reread the slides, the slides were sent to Dr. Walter (who had moved to Iowa) for reexamination. Dr. Walter's diagnosis was different from that of
Drs. Becci and Cox concerning the description of several liver lesions.

TOXICOLOGY BRANCH has accepted the diagnosis of Drs. Becci and Cox for their description of liver lesions. A summary of the tumors produced in the livers of female rats is shown in the following table.

Number of Female Rats Examined 1/		Hepatocellular Adenoma	Hepatocellular Carcinoma	Nodule* Hyperplastic	Total rats* affected
50	Control	0	0	1	1
46	500 ppm	0	0	0	0
49	2,500 ppm	5	0	5	7
49	5,000 ppm	13	8	13	24

* TOXICOLOGY BRANCH considers hyperplastic nodules as a primary neoplasia change in rats. Reference: "Histologic typing of liver tumors of the rat," JNCI 64: 180-190 (1980). See page 185 under primary neoplasms.

** Some rats have more than one lesion.

1/ under at the direction of [illegible]

001912

TOXICOLOGY BRANCH has concluded that on the basis of the data in this table, resmethrin, when administered in the diet at 2,500 and 5,000 ppm, resulted in a dose related increased number of tumors in female rats.

In male rats, there is only a possible oncogenic effect noted. For example, there were 0, 1, 1, and 3 occurrences of hyperplastic nodules in the control, low, mid and high dose groups respectively. There were 2 occurrences of hepatocellular carcinoma in the high-dose male group, whereas there were none reported in the other male test groups. Female rats, but not male rats, in the high-dose test group were also associated with increased incidences of anisokaryosis(

II. The following table shows the incidences of tumors (adenoma) found in the thyroid tissue.

Dose Group	Males	Females
Control	2/47 (4.2%)*	1/50 (2%)
500 ppm	4/26 (15.4%)	1/16 (6.3%)
2,500 ppm	3/27 (11.1%)	4/23 (17.4%)
5,000 ppm	8/47 (17.0%)	5/48 (10.4%)

*Number of adenomas/number animals examined ( ) percentage.

Based on both the percentage and the total number of adenomas obtained, an oncogenic effect is suggested, and can be shown to be statistically significant (personal communication B.Litt December 23, 198X).

The thyroid tissue did not show associated gross pathology other than that the high dose female test group had thyroid weights higher than controls (32% absolute and 40% relative). It is possible that the tumor type is small such that no associated gross observations are evident. The thyroid tissues from the low and mid dose groups that were not processed for histology should be prepared and examined. It is important to note that the thyroid tissue was examined by Dr. Walter only and there is no evidence that Drs. Becci and Cox further reexamined these tissues as they reexamined liver tissues.

III. Mammary and pituitary glands in females. The following table shows the frequency of occurrence of tumors in the mammary and pituitary glands in females.

5

	Mammary* Gland	Pituitary** Gland
Control	15/50 (30%)	15/45 (33.3%)
500 ppm	7/18 (39%)	17/31 (54.8%)
2,500 ppm	12/21 (57%)	22/34 (64.7%)
5,000 ppm	7/49 (14.3%)	12/46 (26.7%)

* benign fibro epithelial tumors: adenoma and fibroadenoma

** adenoma.

For both of these tissues, there is a disturbingly high frequency of occurrence of these commonly occurring tumors in the mid-dose group. However, the high-dose group is less than the control group. Thus, these observations do not support a dose-dependent response for an oncogenic effect. These observations are considered noteworthy but lend no toxicological interpretation at this time.

Conclusions:

1. This study demonstrates that resmethrin is oncogenic and produces liver tumors when fed in the diet at the level of 2,500 and 5,000 ppm for the lifetime of the Wistar female albino rats.

2. The thyroid tissue has also been identified as showing evidence of oncogenic effects.

3. As an oncogenesis evaluation, this study is classified as CORE MINIMUM. All of the tissues in the low- and mid-dose groups should have been prepared and examined histologically. Survival in the male group was poor.

4. As a chronic feeding study, this study is CORE MINIMUM. The laboratory tests were conducted on six and not eight rats of each sex/dose level.

5. This study does not demonstrate a NOEL for systemic effects. Spleen weight (both relative and absolute) were decreased and the spleen relative weight was statistically significantly reduced at the lowest test dose.

Addendum: This addendum is written at the request of Bill Burnam, Deputy Branch Chief, for the purpose of including the statistical methods used in the two year rat chronic feeding/oncogenesis study conducted with resmethrin. (Accession Nos. 242782 thru 242786 inclusive).

All the statistical methodology mentioned here was conducted by Food and Drug Research Labs, Inc.

All parameters from the clinical studies, organ weights, organ to body weight ratios, weekly body weights and food consumptions were evaluated statistically for differences among groups using analysis of variance. Differences among groups were deemed significant when the probability of rejecting the null hypothesis when true was less than 0.05. Any parameters where a difference was found among groups ($P < 0.05$) was then tested using the least significant difference test to determine which test group(s) differed from the control.

Mean body weights were analyzed using a randomized complete block design analysis of variance in which the weeks constituted the blocks.

The incidences of hyperplastic nodules, hepatocellular adenomas and hepatocellular carcinomas that were observed in female rats receiving the compound were found to be statistically significant ($P \leq 0.05$; Fishers Exact Test) when compared to their own controls. Furthermore, a highly significant dose response effect was observed with respect to the hyperplastic nodules and hepatocellular adenomas in female rats ($P \leq 0.01$; ordered chi-square test; reference Fed. Proc. 13:815, 1954).

The data for males showing one or more of the above mentioned responses were apparently analyzed in the same manner.

Note here also that the number of female rats examined with respect to liver lesions (see the data table on page 4 of John Doherty's review and page 10 of accession number 242782) were as follows and is based upon the findings of Drs. Becci and Cox.

Controls	50 animals
Low-dose	46 animals
Mid-dose	49 animals
High-dose	49 animals

91067

[RESMETHRIN, TECH.] Carcinogenicity, Oral Study 83-2

EPA Reviewer: Linnea J. Hansen
Review Section 4, Toxicology Branch I (7509C)
EPA Section Head: Marion P. Copley
Review Section 4, Toxicology Branch I (7509C)

Linnea J. Hansen, Date 6/16/94
Marion Copley, Date 6/21/94

DATA EVALUATION REPORT

STUDY TYPE: Carcinogenicity - Mouse (83-2b)

TOX. CHEM. NO: 083E

P.C.CODE.: 097801

MRID NO.: 430521-01

TEST MATERIAL: SBP-1382

SYNONYMS: Resmethrin; 5-benzyl-3-furylmethyl (IRS)-cis,trans-chrysanthemate

STUDY NUMBER: 83754

SPONSOR: Roussel UCLAF Corporation, Montvale, NJ

TESTING FACILITY: Bio-Research Laboratories Ltd., Senneville, Quebec, Canada

TITLE OF REPORT: A Dietary Oncogenicity Study of SBP-1382 in the Albino Mouse

AUTHOR: L. Kangas, B.A.Sc.

REPORT ISSUED: January 8, 1992

EXECUTIVE SUMMARY: In a 2-year carcinogenicity study, resmethrin (technical, 84.8% a.i.) was administered in the diet for 104 weeks to 50 male and 50 female Swiss Crl:CD-1(ICR)BR mice/dose group at levels of 0, 300, 600 or 1200 ppm. Two control groups of 50 animals/sex each were included. The time-weighted average dose for these dietary levels corresponded to 0, 43.4, 84.3 or 169.3 mg/kg/day for males and 0, 52.9, 105.5 or 208.9 mg/kg/day for females (based on theoretical concentration in diet). An interim sacrifice group was not included.

At 600 ppm, survival in males was decreased during the last months of the study compared to both control groups (43% less than both control groups; difference not statistically significant).

At 1200 ppm, survival in males was also reduced (38% less than controls). No overt treatment-related signs of toxicity were observed in females at any dose. Slightly decreased survival in females at 600 and 1200 ppm (~19% and 14% less than Control group 1, respectively) was not considered toxicologically significant but was considered a possible threshold response based on results of a previously submitted mouse carcinogenicity study. Clinical signs were only observed in preterminal animals and were considered agonal symptoms and not direct effect of treatment (signs included weak condition, distended, blue abdomen, tremors and reduced body temperature). Dose-related increased liver weight was observed at all dose levels but was considered a metabolic adaptive response reflecting induction of hepatic microsomes since it was not accompanied by microscopic lesions other than hypertrophy, and since liver weight was also variable among the 2 male control groups). **The LOEL for systemic toxicity was 600 ppm (84.3 mg/kg/day) in males based on slightly increased mortality and >1200 ppm (208.9 mg/kg/day) in females. The NOEL was 300 ppm (43.4 mg/kg/day in males. A threshold NOEL of ≥1200 ppm (208.9 mg/kg/day was established in females.**

A dose-related increase in combined hepatocellular adenoma/carcinoma was observed in males (at 1200 ppm, 36% vs 16%, Control group 2 and 2%, Control group 1; statistically significant compared to both control groups separately; also significant for trend). Incidence was within historical control range reported from other laboratories. TB-I defers decision to the RfD/Peer Review Committee as to whether the increased incidence of these tumors at 1200 ppm is related to administration of resmethrin.

This study is Core-Supplementary by itself and does not satisfy the guideline requirement for a carcinogenicity study (83-2b) in mice because an MTD was not achieved for females. However, it is Core-Minimum when taken together with a previously submitted mouse oncogenicity study (reviewed in HED Doc. nos. 001913 and 001914) and fulfills the guideline requirements for 83-2b. A new study is not considered necessary at this time.

Special Review Criteria (40 CFR 154.7) None

A. MATERIALS:

1. Test Material: SBP-1382, technical
   Description: waxy yellow solid
   Lot/Batch #: 8N 0731B3
   Purity: 84.8% a.i.
   Stability of compound: stable in dark at room temperature
   CAS #: 10453-86-8

2. Vehicle control: Acetone (BDH Inc.). Lot/Batch # 70627/15148

3. Test animals: Species: Mouse (albino)
Strain: Swiss Crl:CD®-1(ICR)BR
Age/weight at study initiation: About 6 weeks. 15.6 - 32.4 g, males; 16.6 - 25.8g, females
Source: Charles River Canada, St. Constant, Quebec

Housing: individually in mesh-bottomed stainless steel cages (2/cage during acclimatization)
Environmental conditions: Temperature: 22±3°C
Humidity: 50%±20%
Air changes: not indicated
Photoperiod: 12 hr light/12 hr dark
Acclimation period: 2 weeks

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the test groups shown below in Table 1.

TABLE 1: STUDY DESIGN

Test Group	Dose in diet (ppm)	Study duration 24 mos. male	female
1 Control 1	0	50	50
2 Control 2	0	50	50
3 Low (LDT)	300	50	50
4 Mid (MDT)	600	50	50
5 High (HDT)	1200	50	50

Dose selection rational: The study report stated that in a 4-week study by BioResearch Laboratories (Project no. 83753), a maximum tolerated dose of 1200 ppm was established. No further details of the range-finding study were provided.

2. Diet preparation and analysis

Treated diets were prepared weekly by liquefying the test material at 50° C, mixing appropriate amounts with 50 ml acetone vehicle and incorporating into laboratory diet using a Hobart mixer. The amount of test material was not adjusted for

purity, ie was assumed to be 100% for purposes of diet preparation. Diets were stored in the dark at room temperature. Stability of the test compound in diet preparations was analyzed after 15 days storage in room temperature in feeders (not in dark). Homogeneity was tested prior to commencement of treatment by analysis of samples from top, middle and bottom of the mixer at discharge. Concentration of test compound in diet was analyzed weekly for the first four weeks of the study and monthly thereafter using gas chromatographic methods.

Results - Homogeneity Analysis: Analyses conducted pre-study demonstrated reasonable homogeneity of test material in diet preparations. Analytical concentrations at top, middle and bottom of mixer discharge were mostly within 10%, occasionally 15%, of target concentration.

Stability Analysis: Resmethrin was demonstrated to be stable in the diet for at least 15 days, with essentially no loss of material during this time.

Concentration Analysis: Overall the test material concentration in the diet was within acceptable range of target concentration with weekly analytical concentrations showing levels within 15%, usually better, of target. However, the analytical concentrations of resmethrin at one or more dose levels were low (59% - 80% of target) during Weeks 65, 66, 67, 68, 73, 75 and 83. The lower analytical concentrations during this time were considered to be due to lack of mixing of test material prior to removal from the storage container, since analytical values improved when test material was mixed prior to removal.

3. Animals received food (PMI Feeds Certified Rodent Chow 5002) and water ad libitum.

4. Statistics - Bartlett's test was used to analyze body weight, food consumption, feed efficiency and organ weight data for homogeneity of variance. When variance of data was homogeneous; Dunnett's t test was used. When variance of data was heterogeneous, Kruskal-Wallis test was used. Significance of intergroup differences were analyzed using Dunn's test. Tumor and mortality data were analyzed using Fisher's Exact Test. Clinical observation data was not analyzed.

5. A signed and dated quality assurance statement was present.
A signed and dated GLP statement was present.

C. METHODS AND RESULTS

1. Observations:

Animals were inspected twice daily for signs of toxicity and mortality. Detailed clinical examinations were performed daily for the first four days of the study and weekly thereafter.

Results -

Mortality: Survival rates at Weeks 80 and 104 are shown below in Table 1:

TABLE 2: SURVIVAL OF MICE AT 80 AND 104 WEEKS IN 24-MONTH FEEDING STUDY ON RESMETHRIN[1]

Group (ppm)		Males		Females	
		80 Weeks	104 Weeks	80 Weeks	104 Weeks
1	(0)	50 (80)[2]	21 (42)	37 (74)	21 (42)
2	(0)	37 (74)	21 (42)	36 (72)	24 (48)
3	(300)	31 (62)	20 (40)	40 (80)	23 (46)
4	(600)	39 (78)	12 (24)	35 (70)	17 (34)
5	(1200)	31 (62)	13 (26)	43 (86)	18 (36)

1 Data taken from Table 2 of study report. N = 50 for all groups
2 Number of surviving animals (% survival)

Survival curves provided by the study author are appended to this review. In males, survival at Week 104 was decreased compared to controls at 600 and 1200 ppm (43% and 38% lower, respectively). The decreased mortality at these dose levels was not statistically significant and did not show a dose-related effect. However, TB-I agreed with the study authors that it appeared to be a marginal, treatment-related decrease. The cause of the decreased survival was not determined.

In females, survival at Week 104 was 19% and 14% lower than Control group 1 at 600 and 1200 ppm (not statistically significant compared to either control group). Because of the small magnitude of the decrease, TB-I did not agree with the study authors that the decreases were of toxicologic significance because of the small magnitude. However, a previously submitted CD-1 mouse oncogenicity study (MRID 00083319), both males and females showed decreased survival at 1000 ppm, suggesting that the decrease observed in females in this study may represent a threshold response. In that study, decreased survival was attributed to increased amyloidosis; however, in this study survival rate did not correlate with incidence of amyloidosis.

Clinical signs: A summary of selected clinical signs observed in preterminal animals is shown below in Table 3:

TABLE 3: SELECTED CLINICAL SIGNS OBSERVED IN PRETERMINAL[1] ANIMALS[2]

Dietary Dose, PPM:	0 (1)	0 (2)	300	600	1200
MALES: N =	29	29	30	38	37
Blue abdomen	4	3	4	13	14
Distended abdomen	8	13	14	24	19
Reduced body T°	9	5	8	14	14
Swollen prepuce/penis	3	5	7	15	9
Weak condition	9	7	5	10	7
Tremors	5	7	3	7	6
Reduced activity	5	5	5	7	10
FEMALES: N =	29	27	27	34	32
Blue abdomen	3	3	1	5	6
Distended abdomen	6	10	9	16	11
Reduced body T°	9	11	10	11	21
Weak condition	9	10	9	14	17
Tremors	8	6	6	5	13
Reduced activity	9	11	10	9	19

1 Preterminal animals refers to all animals that died or were sacrificed moribund prior to scheduled terminal sacrifice
2 Data taken from Appendix I of study report. (Values reflect only number of animals affected and not number of times during the study that the effect was observed).

Clinical signs in animals athat died or were sacrificed moribund prior to scheduled terminal sacrifice generally reflected deteriorating condition. Increased incidence of distended and/or blue abdomen and swollen urogenital region were observed in males at 600 and 1200 ppm. Decreased body temperature was observed in males and females. The incidence of tremors and reduced activity was increased in females at 1200 ppm. These observations were considered agonal and not due to treatment, since no treatment-related clinical signs were reported in males or females surviving to study termination.

2. Body weight

Animals were weighed weekly beginning on the week prior to initiation of dosing.

Results - Selected mean weekly body weights and total weight gain for the 24-month dosing period are shown below in Table 4:

47

TABLE 4: SELECTED MEAN BODY WEIGHT AND TOTAL BODY WEIGHT GAIN (G)[1]

DOSE, PPM	0 (1)	0 (2)	300	600	1200
MALES					
Week 0	28.83	27.90	28.44	28.41	28.51
Week 13	36.98	37.18	36.83	37.05	37.57
Week 52	40.65	40.70	40.62	41.98	41.90
Week 75	40.88	41.13	40.30	42.17	42.26
Week 104	39.87	39.62	38.48	40.11	42.651*1,2
Total Gain	11.04	11.72	10.04	11.7	14.14
FEMALES					
Week 0	21.34	20.91	21.21	21.38	21.16
Week 13	28.59	27.72	28.48	29.29**2	28.94*1
Week 52	33.57	32.34	34.09	34.11	32.93
Week 75	34.42	34.14	34.66	34.31	33.90
Week 104	35.11	33.52	34.73	35.74	33.75
Total Gain	13.77	12.61	13.52	14.36	12.59

1 Data taken from Table 3 of study report
* $p < 0.05$; ** $p < 0.01$
Note: Treatment groups were compared to each control group separately for statistical analyses. Numbers after p values refers to control group (*1* or *2*) at which the indicated level of statistical significance was observed.

No significant treatment-related differences in mean body weight were observed in treated groups compared to either control group. Sporadic statistically significant differences, both increases and decreases, were observed but were of small magnitude and not dose-related. At Week 104, body weight gain in females was reduced by less than 9% compared to control group 1 but was the same as Control group 2.

3. Food consumption and compound intake:

Food consumption for each animal was measured weekly and mean consumption was calculated as g food/animal/week. Mean food efficiency [(body weight gain, kg ÷ food consumption, kg per unit time) X 100] and mean compound intake (mg/kg/day) values were calculated by the study authors as time-weighted averages from the food consumption and body weight gain data.

Results - Food consumption: No treatment-related effects on mean weekly food consumption were observed. Sporadic, statistically significant decreases occurred occasionally among all groups.

- Compound consumption (time-weighted average; calculated by study authors using

the theoretical concentrations): Average compound consumption during the study was 43.3, 84.3 and 169.3 mg/kg/day for males and 52.9, 105.5 and 208.9 mg/kg/day for females in the 300, 600 and 900 ppm groups, respectively.

- Food efficiency: There were no treatment-related effects on food efficiency. Weekly efficiency values varied considerably among all groups, including the two control groups. Sporadic statistically significant differences from the control groups were observed among all treated groups.

4. Ophthalmoscopic examination

Eyes of all surviving animals were examined by indirect ophthalmoscopy and biomicroscopy at pretreatment, Week 80 (18 mos.) and at Week 103 prior to termination.

Results - No treatment-related effects were observed at Weeks 80 or 103 of the study. Sporadic incidence of cataracts, central corneal opacities and retinal degenerative lesions were observed among all groups, including both control groups.

5. Hematology

Blood was collected at 12 and 24 months for hematology analysis (blood smears) from all surviving animals. At 12 months, blood was obtained from the lateral tail vein and at 24 months, from the abdominal aorta at terminal sacrifice. Smears were examined for differential white blood cell count and red/white blood cell morphology.

Results - No treatment-related effects on white blood cell count or morphology were observed.

6. Sacrifice and Pathology

All animals that died or that were sacrificed (by exsanguination under ether anesthesia) prior to or on schedule were subject to gross pathological examination. Animals were fasted overnight prior to terminal sacrifice. The CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X		X		X	
Digestive system		Cardiovasc./Hemat.		Neurologic	
X	Tongue	X	Aorta*	XX	Brain*
X	Salivary glands*	XX	Heart*	X	Periph. nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen	X	Eyes (optic n.)*
X	Jejunum*	X	Thymus*	Glandular	
X	Ileum*	Urogenital		XX	Adrenal gland*
X	Cecum*	XX	Kidneys*+		Lacrimal gland
X	Colon*	X	Urinary bladder*	X	Mammary gland*
X	Rectum*	XX	Testes*+	X	Parathyroids*++
XX	Liver *+	X	Epididymides	X	Thyroids*++
X	Gall bladder*	X	Prostate	Other	
X	Pancreas*	X	Seminal vesicle	X	Bone*
Respiratory		XX	Ovaries*+	X	Skeletal muscle*
X	Trachea*	X	Uterus*	X	Skin*
XX	Lung*			X	All gross lesions and masses*
	Nose				
	Pharynx				
	Larynx				

* Required for subchronic and chronic studies.
\+ Organ weight required in subchronic and chronic studies.
++ Organ weight required for non-rodent studies.

Results -

a. Organ weight - Absolute and relative mean organ weights that were significantly different in treated groups when compared to one or both control groups are shown below in Table 5:

TABLE 5: SELECTED ABSOLUTE AND RELATIVE ORGAN WEIGHT DATA[1]

PPM IN DIET		0 (1)	0 (2)	300	600	1200
MALES:						
Liver	abs	1.449	1.896	2.089**1*	2.156***1*	2.723****1*
	rel	4.237	5.587	6.410***1*	6.296***1*	7.695****1*
Kidney	abs	0.719	0.715	0.741	0.759	0.89***2*
	rel	2.127	2.144	2.304	2.222	2.557***1/*2*
FEMALES:						
Liver	abs	1.424	1.310	1.547	1.829***2*	2.023****1/***2*
	rel	4.824	4.546	5.430**2*	6.248**1/****2*	7.378****1,2*
Kidney	abs	0.531	0.490	0.515	0.571**2*	0.594***1,2*
	rel	1.821	1.729	1.826	1.944**2*	2.166***1,2*

1 Data taken from Tables 8-11 of Study Report
* p < 0.05 ** p < 0.01 *** p < 0.001 Note: Treated groups were compared to each control group separately. Numbers after p values indicate the control group (*1* or *2*) at which indicated level of statistical significance was observed.

50

Statistically significant, dose-related increases in mean absolute and/or relative liver weights were observed at all dose levels in males and females (compared to one or both control groups). At 1200 ppm relative liver weights compared to control groups 1 and 2 were increased by 82% and 38% in males and 55% and 62% in females, respectively. TB-I considered these effects to be due to metabolic adaptation and microsomal induction and not of clear toxicologic significance since no lesions other than hypertrophy were observed microscopically, and since there was also considerable variation between male control groups (32%).

Relative kidney weights were statistically significantly increased in males and females at 1200 ppm (20% in males and 19 - 25% in females), and in females at 600 ppm (7%). In the absence of corresponding gross or microscopic pathology, this effect was not considered to be of toxicological significance.

b. Gross pathology - No treatment-related gross lesions were observed. Grossly visible masses in liver correlated with the microscopic observation of tumors identified at each dose level (see neoplastic microscopic pathology, below).

c. Microscopic pathology -

1) Non-neoplastic - Table 6 shows the incidence of selected microscopic lesions observed in this study (preterminal and terminal animals combined):

TABLE 6: INCIDENCE OF SELECTED NONNEOPLASTIC MICROSCOPIC LESIONS[1]

	DOSE IN DIET, PPM				
OBSERVATION	0 (1)	0 (2)	300	600	1200
MALES					
ADRENAL GLAND, Cystic degen.	6	7	12	5	7
HEART, Fibrosis	11	12	11	19	16
LIVER:					
Diffuse hypertrophy	3	0	6	5	19
Focal hypertrophy	1	0	1	3	0
Centrilobular hypertrophy	0	0	6	9	18
Focal hepatoc. hyperplasia	0	2	2	2	1
Centrilobular degeneration	1	1	0	1	2
FEMALES					
ADRENAL GLAND, cystic degen.	24	25	30	26	38
HEART, Fibrosis	6	5	9	9[2]	6
LIVER:					
Diffuse hypertrophy	2	0	1	5	8
Focal hypertrophy	1	0	0	0	2
Centrilobular hypertrophy	0	0	0	0	0
Focal hepatoc. hyperplasia	1	2	2	3	0
Centrilobular degeneration	0	0	0	2	1
Focal hepatocell. vacuoliz.	1	1	1	0	3

1 Data taken from Table 8 of study report. For all groups N = 50 except where noted.
2 N = 49

51

No treatment-related non-neoplastic microscopic lesions of toxicologic significance were observed in males or females. Dose-related increased incidence of hepatocellular centrilobular hypertrophy (males) and diffuse hepatocellular hypertrophy (males and females) were observed but were considered by TB-I to be an adaptive metabolic response to treatment. The hypertrophy correlated with increased liver weight observed in treated animals. The study authors reported a slight increase in cardiac fibrosis among preterminal males; however, this was only seen at 600 ppm and TB-I agreed that this was not a direct effect of treatment. Increased incidence of adrenal cortical cysts in females at 1200 ppm occurred at high background incidence and was not considered treatment-related. Amyloidosis in several organs was observed frequently among all groups and showed no treatment-related increase in incidence or severity; slight increases in some tissues were observed in females at 600 ppm, but was considered a background lesion.

2) Neoplastic - Table 7 shows incidence of microscopic neoplastic lesions observed in the liver. Statistical significance was calculated by comparing treatment groups to each other and comparing treatment groups to each control group separately:

TABLE 7: INCIDENCE (%) OF MICROSCOPIC NEOPLASTIC LESIONS IN LIVER[1]

	DOSE IN DIET, PPM				
OBSERVATION	0 (1)	0 (2)	300	600	1200
MALES					
LIVER:					
Hepatocellular adenoma	1 (2)	8 (16)*1	9 (18)**1	10 (20)**1	12 (24)**1
Hepatocellular carcinoma	2 (4)	0	2 (4)	4 (8)	6(12)**2
Combined adeno/carcino	3 (6)	8 (16)	11 (22)*1	14 (28)**1	18 (36)**1***2
FEMALES					
LIVER:					
Hepatocellular adenoma	2 (4)	0	1 (2)	2 (4)	3 (6)
Hepatocellular carcinoma	0	0	0	2 (4)	0
Combined adeno/carcino	2 (4)	0	1 (2)	4 (8)	3 (6)

1 Data taken from Table 8 of study report. For all groups, N = 50
* p < 0.01; ** p < 0.001; *** p < 0.001. (Statistical analyses performed by reviewer; Fisher's exact test; no adjustments for mortality).
Note: Treated groups were compared to each control group separately. Number after p notation indicates the control group that was significant at the indicated level.

Slight increases in tumor incidence for hepatocellular adenoma and carcinoma were observed in treated males, but statistically significant increases were observed in each case compared to one but not the other control group. However, combined incidence of hepatocellular adenoma/carcinoma was increased at 1200 ppm (36% vs. 16% in control group 2 and 2% in group 1) and the increase was statistically significant compared to both controls. The study authors also determined that the incidence of adenoma and carcinoma were significantly different from only one control group, but did not analyze the combined tumor

52

incidence. They considered the increased incidence of proliferative liver lesions to be due to the metabolic effects of resmethrin.

The tumors did not affect mortality in treated animals; most preterminal animals died or were sacrificed during the last few months of the study. Examination of the individual animal data indicated that time to tumor onset was not affected by treatment for either adenoma or carcinoma. The first adenoma was observed in preterminal animals at Week 50 (1 Control; 1, 1200 ppm); the rest were observed between Weeks 81 to 104.

In-laboratory historical control data were limited to one study of 50 animals; incidence of adenoma was 8% and carcinoma was 6% in males. Supplier historical control data for this strain of mice gave a range of 0 - 17% for adenoma and 1 - 14% for carcinoma in males sacrificed between 21 - 24 months of age. However, a published report listed the incidence of hepatocellular adenomas up to 31% and carcinomas up to 13% in 24-month old CD-1 male mice. Another published report on 84-week old male mice reported 18% adenomas and 2% carcinomas. The incidence for each tumor type observed in this study therefore fall within ranges for control males of this strain reported by other laboratories. TB-I defers determination of the relationship of the tumors incidence to resmethrin treatment to the RfD/Peer Review Committee.

No increases in the incidence of liver tumors or other neoplastic lesions were observed in females.

E. DISCUSSION:

Adequate toxicity to evaluate carcinogenic potential was marginally achieved in males based on slightly decreased survival (not statistically significant) at 600 and 1200 ppm. Liver effects included enlargement and hypertrophy in both males and females; however, in the absence of microscopic pathology other than hypertrophy, they were considered to be metabolic adaptive responses indicating induction of hepatic microsomes (it is noted, however, that liver is usually a target organ for pyrethroid compounds). Animals that died or were sacrificed prior to study termination at 104 weeks showed increased incidence of some clinical signs: blue and/or distended abdomen, weak condition, tremors in females. Since these symptoms were not observed in animals surviving to termination, TB-I agreed with the study authors that these symptoms appeared to be agonal and not a direct effect of treatment. A NOEL of 300 ppm (43.4 mg/kg/day) and LOEL of 600 ppm (84.3 mg/kg/day) was established for males based on decreased survival.

There were no overt treatment-related effects observed in females. TB-I does not agree with the study author that the slightly decreased survival in females at 600 and 1200 ppm was adequate to establish a toxic dose level. Although an MTD may not have been achieved in

females in this study, in a previously submitted mouse oncogenicity study (MRID 00083319; reviewed in HED doc. nos. 1913, 1914; supplemental DER contained in same HED document as this DER), survival in both sexes at termination was significantly reduced at 1000 ppm (40% less than controls). The slight decreases in the newer study may therefore represent a threshold response. A threshold NOEL of $\geq$1200 ppm (208.9 mg/kg/day) was therefore established for females. Although dietary doses in this study were about 20% higher than the earlier mouse study, actual doses administered may be closer to each other because purity of the test material in this study was slightly lower (about 5%) and analyses of the test diets indicated occasional low values.

A slight dose-related increase in the incidence of combined hepatocellular adenoma/carcinoma was observed in males. Inadequate in-laboratory historical control data is available to assess whether the incidence is within their range (incidence in one available study was considerably lower than observed here). Published reports from other laboratories indicate highly variable incidence of these tumors in male CD-I mice and the incidence observed in this study was within the range of at least one other report. No increases in any tumor incidence were reported in the previously submitted mouse carcinogenicity study at similar (slightly lower) doses. TB-I defers determination of the relationship of these tumors to treatment with resmethrin to the RfD/Peer Review Committee since the increased incidence was marginal and limited historical control data was available.

F. STUDY DEFICIENCIES are as follows:

- MTD not achieved in females,
- dietary concentration deviated significantly from target on several occasions
- summary tables not prepared for gross lesions,
- individual animal clinical observation data not included in report.

Although this study by itself does not satisfy guideline requirements for 83-2b based on inadequate dose levels in females, a new study is not required. When this study is taken together with the previously submitted mouse oncogenicity study (reviewed in HED Doc. nos. 001913 and 001914), it provides adequate information to assess the carcinogenicity of resmethrin in mice. The NOEL/LOEL for systemic toxicity based on increased mortality are similar in the two studies.

RESMETHRIN

Page_____ is not included in this copy.

Pages 55 through 56 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

0011067

[RESMETHRIN, TECH.] Carcinogenicity, Oral Study 83-2

EPA Reviewer: Linnea J. Hansen
Review Section 4, Toxicology Branch I (7509C)
EPA Section Head: Marion P. Copley
Review Section 4, Toxicology Branch I (7509C)

Linnea J. Hansen, Date 6/15/94
Marion Copley, Date 6/22/94

SUPPLEMENTAL DATA EVALUATION REPORT
(Supplemental to original DER, HED Doc. nos. 001913, 001914)

STUDY TYPE: Carcinogenicity - Mouse (83-2b)

TOX. CHEM. NO: 083E

P.C.CODE.: 097801

MRID NO.: 00083319

TEST MATERIAL: SBP-1382

SYNONYMS: Resmethrin; 5-benzyl-3-furylmethyl (IRS)-cis,trans-chrysanthemate

STUDY NUMBER: 5270

SPONSOR: At time of study, S.B. Penick. Lyndhurst, NJ. Current Registrant is Roussel UCLAF Corporation, Montvale, NJ

TESTING FACILITY: Food and Drug Research Laboratories, Inc., Waverly, NJ

TITLE OF REPORT: Evaluation of Dietary Administration of SBP-1382 in CD-1 Outbred Albino Mice Over an 85-Week Period

AUTHOR: G.E. Cox, M.D., M. Knickerbocker and R. Parent, Ph.D.

REPORT ISSUED: June 6, 1979

EXECUTIVE SUMMARY: In an 85-week carcinogenicity study, resmethrin (technical, 90% a.i.) was administered to 75 male and 75 female albino outbred CD-1 mice/dose group at dietary concentrations of 0, 250, 500 or 1000 ppm. The time-weighted average dose for these dietary levels corresponded to 0, 36.3, 71.3 or 137.9 mg/kg/day for males and 0, 41.6, 82.9 or 165.8 mg/kg/day for females (based on theoretical concentration). An interim sacrifice group was not included.

At 1000 ppm, survival was reduced (about 40% less than controls, both males and females).

57

Incidence of amyloidosis as measured by increased organ involvement was slightly increased and was considered to be the primary cause of increased mortality. **The LOEL for systemic toxicity is 1000 ppm in males (137.9 mg/kg/day) and females (165.8 mg/kg/day) based on decreased survival related to increased incidence of amyloidosis. The NOEL is 500 ppm (71.3 mg/kg/day in males; 82.9 mg/kg/day in females).**

No treatment-related increases in tumor incidence were observed at any of the dose levels tested.

This study is Core-Supplementary and by itself does not satisfy the guideline requirement for a carcinogenicity study (83-2b) in mice due to several study deficiencies (individual body weight and food consumption data not provided, analysis of test diets not provided, some tissues not examined microscopically). However, together with a second mouse oncogenicity study submitted by Roussel UCLAF (MRID 430521-01; review in same HED Document as this DER), there is adequate information available to evaluate the carcinogenic potential of resmethrin. The two mouse carcinogenicity studies taken together therefore fulfill the guideline requirements for 83-2b.

Special Review Criteria (40 CFR 154.7) None

Note: This DER is intended to provide an Executive Summary and to supplement the original DER where information was not provided that might be necessary for evaluation of the study. The conclusions in this DER supersede those of the original DER, where different.

A. MATERIALS:

1. Test Material: SBP-1382, technical
   Description: waxy amber solid
   Lot/Batch #: 8176-RT
   Purity: 90% a.i.
   Stability of compound: stable in dark at room temperature
   CAS #: 10453-86-8

2. Vehicle and/or positive control: corn oil (unspecified source).

3. Test animals: Species: Mouse
   Strain: CD®-1 outbred albino
   Age/weight at study initiation: About 4 weeks. Mean body wt. about 29.5 g, males; 23.9 g, females (individual body weight data was not included in the study report).
   Source: Charles River Breeding Laboratories, Wilmington, MA

58

Housing: 5/cage, in wire mesh-bottomed stainless steel cages.

Environmental conditions:	Temperature:	70±3°F
	Humidity:	not indicated
	Air changes:	not indicated
	Photoperiod:	12 hr light/12 hr dark
Acclimation period:	not indicated	

B. STUDY DESIGN:

1. Animal assignment: See original DER. The study report did not indicate whether animals were assigned randomly to treatment groups.

   Dose selection rational: The study report stated that doses of 500, 2500 and 5000 ppm were initially chosen based on the results of a subchronic feeding study. However, the Registrant requested that testing be conducted at lower dose levels. No additional information was provided.

2. Diet preparation and analysis

   Treated diets were prepared biweekly by liquefying the test material at 100° C, and dissolving or suspending the test material in corn oil (volume not indicated). The test material/corn oil mix was combined with a small amount of laboratory diet to make a premix in a Hobart mixer and then with more diet to achieve the appropriate concentration. It was not stated in the report whether the test material was adjusted for purity. Diets were stored at room temperature. Although it was stated in the protocol for diet preparation that samples of the diet were removed after preparation for analysis, the analytical data were not included in this report.

3. Animals received food (Charles River Rat/Mouse/Hamster Formula-Agway) and water ad libitum.

4. Statistics - One-way ANOVA for fixed effects (completely randomized classification) was used to analyze body weight, food consumption, hematology and absolute/relative organ weight data. Differences from controls were considered statistically significant when $p < 0.05$. The least significant difference test was then used to determine which test groups showed differences from controls.

5. A signed and dated quality assurance statement was present.
   A signed GLP statement was present; the study was conducted under FDA GLP but was conducted prior to EPA GLP guidelines.

C. METHODS AND RESULTS

1. Observations: Animals were inspected daily for signs of toxicity and mortality. More detailed clinical exams including palpation were performed weekly.

Results -

Mortality: See original DER and the attached mortality table taken from the study pathology report. TB-I considers the decreased survival in males and females (about 40% lower than controls) at 1000 ppm to be treatment-related. Survival in high dose males was comparable to controls until about week 81, whereas survival in high dose females began to decrease by about week 62. Increased mortality appeared to have been related to increased incidence of amyloidosis at 1000 ppm (see attached tables from study report and Microscopic Pathology, p. 8).

Clinical signs: No treatment-related effects were reportedly observed. However, data on daily observations was not included in this report.

2. Body weight

Animals were weighed weekly for the first 6 months of the study, and monthly thereafter.

Results - Mean body weight data from selected times during the study are attached to this DER (tables copied from the study report) and total mean body weight gain during the study is shown below in Table 1.

TABLE 1: MEAN TOTAL BODY WEIGHT GAIN, GRAMS (PERCENT OF CONTROL GAIN)[1]

DOSE, PPM	0	250	500	1000
Gain in Males, g (% of Control)	12.0	11.5 (100%)[2]	14.1 (123%)	13.8 (126%)
Gain in Females, g (% of Control)	11.2	11.1 (105%)	12.4 (123%)	15.3 (150%)

1 Values calculated from data in Table 1 of study report; statistical analysis not performed.

2 Mean percent body weight gain compared to controls expressed by calculating the percent weight gain per dose group [(g mean weight gain ÷ g initial mean body weight) X 100], then dividing the treatment group by control group values.

No treatment-related effects on body weight or body weight gain were observed in males or females. Although the mean body weight of high dose males was statistically significantly lower than controls (up to about 9% lower), it was not considered a treatment-related effect because the initial mean body weight of males at high dose was also about 9% less than controls. Body weight gain expressed as percent of initial body weight was actually greater in high dose males and females when compared to controls.

3. Food consumption and compound intake:

Food consumption for each animal was measured weekly and mean consumption was calculated as g food/cage/week. Food efficiency was not calculated. Mean compound intake (mg/kg/day) values were calculated by the study authors as time-weighted averages using the food consumption and body weight gain data.

Results - Food consumption: No treatment-related effects on mean weekly food consumption were observed in males or females. The overall mean weekly food consumption in males was 38.2, 38.4, 38.8 and 36.4 g* ($p<0.05$) at 0, 250, 500 and 1000 ppm, respectively. High dose males showed slightly reduced mean food consumption throughout the study which were occasionally statistically significant. However, because the decreases were small (<10%; overall mean <5% less than controls), they were not considered of toxicologic significance.

In females, sporadic, statistically significant decreases occurred occasionally and overall mean weekly food consumption was slightly reduced in all groups: 38.0, 36.4*, 35.8* and 37.0 g* at 0, 250, 500 or 1000 ppm, respectively. However, no dose-response was observed and the decrease was small at high dose (<3% less than controls).

- Compound consumption (time-weighted averages): Average compound consumption during the study was 36.3, 71.3 and 137.9 mg/kg/day for males and 41.6, 82.9 and 165.8 mg/kg/day for females in the 250, 500 and 1000 ppm groups, respectively. Calculations were based on theoretical concentrations of test material in the diet.

4. Ophthalmoscopic examination: Not conducted.

5. Hematology: Blood was collected for total white blood cell counts at study initiation, 12 months and prior to termination from 25 animals/sex/dose group. At termination a differential count was also performed. The method of bleeding was not described. It was not stated whether animals were fasted prior to bleeding. Red blood cells were not examined.

Results - No treatment-related effects on white blood cells were observed. Statistically significant decreases in total WBC counts in females at high dose at 12 months (-24% compared to controls) were also seen at study initiation and were not observed at termination.

6. Sacrifice and Pathology

All animals that died or that were sacrificed (by chloroform anesthesia) prior to or on schedule were subject to gross pathological examination. Animals were fasted overnight prior to terminal sacrifice. The CHECKED (X) tissues were collected for histological examination from all control and high dose animals and from 20 animals/sex in the low and mid dose groups. The (XX) organs, in addition, were weighed.

X		X		X	
Digestive system		Cardiovasc./Hemat.		Neurologic	
|	Tongue	|	Aorta*	| XX |	Brain*+
|	Salivary glands*	| XX |	Heart*	| X |	Periph. nerve*
|	Esophagus*	| X |	Bone marrow*	| X |	Spinal cord (3 levels)*
| X |	Stomach*	| X |	Lymph nodes*	| XX |	Pituitary*
| X |	Duodenum*	| XX |	Spleen	| X |	Eyes (optic n.)*
| X |	Jejunum*	|	Thymus*	Glandular	
| X |	Ileum*	Urogenital		| XX |	Adrenal gland*
| X |	Cecum*	| XX |	Kidneys*+	|	Lacrimal gland
| X |	Colon*	| X |	Urinary bladder*	| X |	Mammary gland*
| X |	Rectum*	| XX |	Testes*+	|	Parathyroids*++
| XX |	Liver *+	| X |	Epididymides	| XX |	Thyroids*++
|	Gall bladder*	|	Prostate	Other	
| X |	Pancreas*	|	Seminal vesicle	| X |	Bone*
Respiratory		| XX |	Ovaries*+	| X |	Skeletal muscle*
|	Trachea*	| X |	Uterus*	| X |	Skin*
| X |	Lung*			| X |	All gross lesions and masses*
|	Nose				
|	Pharynx				
|	Larynx				

* Required for subchronic and chronic studies.
\+ Organ weight required in subchronic and chronic studies.
++ Organ weight required for non-rodent studies.

Results -

a. Organ weight - Absolute and relative mean organ weights that were significantly different in treated groups compared to controls are shown below in Table 2:

62

TABLE 2: SELECTED ABSOLUTE (G) AND RELATIVE (% BODY WT) ORGAN WEIGHT DATA[1]

PPM IN DIET	0		250		500		1000	
	ABS	REL	ABS	REL	ABS	REL	ABS	REL
MALES:								
Adrenals	0.008	0.22	0.008	0.24	0.010*	0.27*	0.011*	0.33*
Brain	0.47	1.29	0.47	1.34	0.48	1.38	0.46	1.45*
Liver	2.29	6.20	2.03*	5.80	2.44	6.95*	2.31	7.15*
Kidney	0.78	2.14	0.77	2.19	0.86*	2.44*	0.78	2.43*
FEMALES:								
Adrenals	0.013	0.41	0.012	0.39	0.011*	0.38	0.012	0.39
Brain	0.49	1.58	0.47*	1.58	0.47*	1.58	0.49	1.59
Liver	2.11	6.71	1.98	6.54	2.07	6.87	2.35	7.61
Kidney	0.60	1.91	0.57	1.88	0.58	1.92	0.64	2.07

1 Data taken from Table 7 of Study Report
* $p < 0.05$

Small but statistically significant increases in relative weights of the liver, kidneys, spleen and adrenal gland were observed in males at 500 and 1000 ppm. With the exception of the adrenal gland, which showed increases of 23% and 50% compared to controls at 500 and 1000 ppm, respectively, the increases were small (less than 15%). In the absence of correlating microscopic lesions, these increases are not considered of toxicologic significance.

No statistically significant, treatment-related increases in organ weights were observed in females, although slight liver enlargement (25%) was observed at 1000 ppm.

b. Gross pathology - No treatment-related gross lesions were observed. Some commonly observed gross lesions included subcutaneous edema, distended bladder, blood or dark fluid in the gastrointestinal tract, prostate and/or seminal vesicle enlargement in males and mottling or discoloration of various organs.

c. Microscopic pathology -

1) Non-neoplastic - See original DER. Table 3 below shows the incidence of selected microscopic lesions observed in this study (unscheduled and terminal

sacrifice animals combined):

TABLE 3: INCIDENCE OF SELECTED NONNEOPLASTIC MICROSCOPIC LESIONS[1]

OBSERVATION	DOSE IN DIET, PPM 0	250	500	1000
MALES:				
Intestine, lge: N =	(72)	(20)	(20)	(74)
Amyloidosis	4	2	2	10
% incidence	6	10	10	14
Pancreas: N =	(74)	(20)	(20)	(72)
Amyloidosis	8	1	1	17
% incidence	11	5	5	24
Spleen: N =	(74)	(20)	(20)	(73)
Amyloidosis	15	3	7	34
% incidence	20	15	35	47
Stomach, N =	(73)	(20)	(20)	(74)
Amyloidosis	15	2	4	41
% incidence	21	10	20	55
Testes: N =	(74)	(20)	(20)	(74)
Amyloidosis	7	2	0	20
% incidence	9	10	0	27
Atrophy	14	5	3	23
% incidence	19	25	15	31
FEMALES				
Intestine, lge: N =	(71)	(20)	(20)	(75)
Amyloidosis	5	2	5	30
% incidence	7	10	25	40
Pancreas: N =	(72)	(20)	(19)	(71)
Amyloidosis	7	4	5	17
% incidence	10	20	26	24
Spleen: N =	(73)	(20)	(20)	(72)
Amyloidosis	40	9	12	53
% incidence	55	45	60	74
Stomach, N =	(74)	(20)	(19)	(75)
Amyloidosis	35	11	14	57
% incidence	47	55	74	76
Uterus: N =	(71)	(20)	(20)	(74)
Amyloidosis	12	1	3	23
% incidence	17	5	15	31

1 Data taken from Tables 6 and 7 of study pathology report.

Slightly increased incidence of amyloidosis in some organs was reported. No statistical significance was determined by the study authors; however, the increases were sufficient to

suggest a possible treatment-related effect. Although amyloid was a common microscopic finding among all animals, the number of organs affected/animal was increased at 1000 ppm (see HED Doc. no. 001914). Amyloid was also found frequently in other organs not listed in Table 3, including thyroid, adrenals, mesentery, kidney and liver. The comparative severity of the amyloidosis was not quantitated in this study. Elevated incidence was observed in some organs relative to controls at low and/or mid dose. Other frequently observed lesions that did not appear to be treatment-related included chronic pneumonitis, renal calcification, focal lymphocytic aggregates, atrial thrombosis and adrenal cortical hyperplasia or atrophy.

2) Neoplastic - Table 4 shows incidence of liver microscopic neoplastic lesions observed this study. These data are provided for comparison with tumor incidence in these organs in the second mouse carcinogenicity study submitted for resmethrin:

TABLE 4: INCIDENCE OF MICROSCOPIC NEOPLASTIC LESIONS IN LIVER AND LUNG[1]

	DOSE IN DIET, PPM			
OBSERVATION	0	250	500	1000
MALES				
LIVER - NO. EXAMINED	(74)	(20)	(20)	(74)
Hepatocellular adenoma	6	3	1	7
Hepatocellular carcinoma	2	0	2	0
FEMALES				
LIVER - NO. EXAMINED	(73)	(20)	(20)	(75)
Hepatocellular adenoma	0	0	0	0
Hepatocellular carcinoma	0	0	0	0

1 Data taken from Table 8 of study pathology report.

No treatment-related increases were observed for incidence of any neoplastic lesion. The most frequently observed tumor type was hemangioma, which occurred in lymph nodes, spleen, liver, uterus and ovaries and showed no treatment-related increase (data not shown in Table 4). Alveologenic carcinomas of the lung were also observed in several animals among all dose groups and with no association with treatment.

E. DISCUSSION:

TB-I agrees with the conclusions of the study authors and the Addendum to the original DER (HED Doc. no. 001913) that a NOEL for systemic toxicity of 500 ppm and a LOEL of 1000 ppm were determined for mice in this study, based on decreased survival in both males and females. The decreased survival in high dose animals occurred during the second year of the study but was observed earlier in females (about week 62) than in males (about week 81). Decreased survival appeared to be related to the increased

incidence and organ involvement of amyloidosis. Mortality resulting from amyloidosis was also high among control animals but appeared to be exacerbated by treatment, particularly at high dose. Comparative severity of the lesions within each organ was not determined in this study report. Although the incidence of amyloidosis in any given organ was not statistically significantly increased according to the study authors, the frequency of the observation per animal showed a treatment-associated increase (see original DER) and was particularly evident at 1000 ppm in males. The increase was less pronounced in females but was likely to account for their increased mortality as well. The increased incidence of amyloidosis at high dose may have been secondary to stress or other effect of the test material. Similar but less pronounced effects on mortality were observed in a second mouse carcinogenicity study on resmethrin.

No increases in any tumor incidence were observed in mice treated with resmethrin at dietary doses up to 1000 ppm.

F. STUDY DEFICIENCIES are as follows:
- analyses of dietary concentrations, homogeneity and stability not included in the study report,
- some tissues required by Guideline 83-2 were not reported to have been examined microscopically,
- individual animal body weight data not included in report,
- individual food consumption data not included in report,
- summary of clinical signs not included in report.

Although this study does not satisfy guideline requirements for 83-2b based on numerous study deficiencies, no additional information is required at this time because this study, taken together with a second mouse carcinogenicity study, provides adequate information to evaluate the carcinogenic potential of resmethrin in mice. The NOEL and LOEL in this study are supported by the results of the second study (NOEL = 600 mg/kg/day). The decreased survival after chronic treatment is consistent with the effects observed at similar doses in the second mouse study, although effects were marginal in females in the second study. Although dose levels were reported to be slightly higher in the second study (1200 vs 1000 ppm, HDT; doses about 20% greater using theoretical dietary levels), actual doses in the 2 studies may have been closer to each other because of slightly lower purity (5% less) of technical resmethrin and occasional periods of low dietary concentrations in the second study.

RESMETHRIN

Page_____ is not included in this copy.

Pages 67 through 70 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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

001913

MEMORANDUM

DATE: DEC 15 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Reg. No. 432-487. Company Response to the Problem of Amyloidosis Increase in the Mouse Oncogenesis Study with Resmethrin.

TOX Chem. No. 83C

FROM: John Doherty 12/1/81
Toxicology Branch/HED (TS-769)

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

Background:

The Penick Corporation previously submitted a mouse oncogenesis study with the insecticide resmethrin and review of this study (see J. Doherty review, dated December 11, 1979) indicated that the test chemical may be associated with increased incidences of amyloidosis at all dose levels including the low dose level. The registrant was asked to reexamine tissues in the low and mid dose groups and to provide a demonstration that amyloidosis in the low and mid dose groups was not related to ingestion of resmethrin. NOTE: The testing laboratory already had conceded that the high dose groups (male and female) develcped higher frequencies of amyloidosis probably as a non-specific result of the test chemical and that this was related to early deaths of the mice.

Registrants Response:

1. The registrant replied that amyloidosis occurs frequently in mice and its occurrence in this study is not conclusively related to ingestion of resmethrin. They request that a NOEL of 500 ppm be assigned for this lesion.

2. EPA's request to reanalyze certain slides and grade the amyloidosis (i.e. as 1-4 depending on severity) as well as to analyze unread slides was not carried out by the registrant.

3. The registrant provided "Addendum Statement on Amyloidosis" prepared by George E. Cox, M.D., Director of Pathology, at Food and Drug Research Laboratories, Inc. where the study was originally conducted. In this statement Dr. Cox asserted that "although the high level of mortality was real and the amyloidosis (regarded as causative) was a marked finding, it (amyloidosis) is of trivial importance as an indicator of test material toxicity". Dr. Cox indicated that the amyloidosis commonly occurs in this strain of mice, and its predisposition is idiopathic and determined genetically. One of a number of factors which

Table 1

Percent Incidence Amyloid Found per Tissue Examined*

	Control		250		500		1000	
	M	F	M	F	M	F	M	F
Adrenals	63.4 (45/71)	83.8 (62/74)	85.0 (17/20)	73.7 (14/19)	95.0 (19/20)	75.0 (15/20)	86.3 (63/73)	90.5 (67/74)
Epididymides	0 (0/73)	-	0 (0/20)	-	0 (0/20)	-	2.7 (2/73)	-
Heart	55.4 (41/74)	84.9 (62/73)	80.0 (16/20)	65.0 (13/20)	85.0 (17/20)	75.0 (15/20)	89.2 (66/74)	90.7 (68/75)
Lrg. Intestines	5.6 (4/72)	7.0 (5/71)	10.0 (2/20)	10.0 (2/20)	10.0 (2/20)	25.0 (5/20)	13.5 (10/74)	40.0 (30/75)
Sml. Intestines	81.1 (60/74)	95.9 (71/74)	80.0 (16/20)	85.0 (17/20)	95.0 (19/20)	100 (20/20)	94.5 (69/73)	91.9 (68/74)
Kidneys	68.5 (50/73)	87.8 (65/74)	100 (20/20)	85.0 (17/20)	100 (21/21)	100 (21/21)	90.4 (66/73)	94.7 (71/75)
Liver	54.1 (40/74)	69.9 (51/73)	70.0 (14/20)	60.0 (12/20)	55.0 (11/20)	85.0 (17/20)	79.7 (59/74)	92.0 (69/75)
Lungs	6.8 (5/73)	0 (0/74)	20.0 (4/20)	5.0 (1/20)	20.0 (4/20)	0 (0/20)	10.8 (8/74)	1.3 (1/75)
Lymph Nodes	17.7 (11/62)	35.4 (22/62)	26.3 (5/19)	30.0 (6/20)	37.5 (6/16)	33.3 (6/18)	20.3 (13/64)	47.1 (33/70)
Mamm. Gld.	-	4.3 (3/70)	-	5.3 (1/19)	-	0 (0/20)	-	2.9 (2/68)
Mesentery	14.0 (6/43)	74.5 (35/47)	35.7 (5/14)	75.0 (12/16)	46.2 (6/13)	100 (15/15)	32.5 (13/40)	90.2 (46/51)
Ovaries	-	91.5 (65/71)	-	80.0 (16/20)	-	89.5 (17/19)	-	90.7 (68/75)
Pancreas	10.8 (8/74)	9.7 (7/72)	5.0 (1/20)	20.0 (4/20)	5.0 (1/20)	26.3 (5/19)	23.6 (17/72)	56.3 (40/71)
Saliv. Gld.	100 (1/1)	87.5 (7/8)	50.0 (3/6)	100 (5/5)	50.0 (1/2)	100 (2/2)	66.7 (4/6)	71.4 (5/7)
Skin	1.4 (1/74)	1.4 (1/74)	10.0 (2/20)	5.0 (1/20)	0 (0/20)	0 (0/20)	1.4 (1/74)	0 (0/75)
Spleen	20.3 (15/74)	64.8 (40/73)	15.0 (3/20)	45.0 (9/20)	35.0 (7/20)	60.0 (12/20)	46.6 (34/73)	75.6 (53/72
Stomach	20.5 (15/73)	47.3 (35/74)	10.0 (2/20)	55.0 (11/20)	20.0 (4/20)	73.7 (14/19)	55.4 (41/74)	76.0 (57/75
Testes	9.5 (7/74)	-	10.0 (2/20)	-	0 (0/20)	-	27.0 (20/74)	-
Thyroid	34.3 (24/70)	77.8 (56/72)	55.0 (11/20)	65.0 (13/20)	50.0 (10/20)	78.9 (15/19)	75.0 (54/72)	86.3 (63/73
Uterus	-	15.9 (12/71)	-	5.0 (1/20)	-	15.0 (3/20)	-	31.1 (23/74

* (No. of animals with amyloidosis per number of animals examined)
From FDRL Study No. 5270, Path Table 6

might accentuate an already extensive ongoing activity, Dr. Cox indicated was a high concentration of various nonspecific test materials in the diet. Thus, the increased incidences of amyloidosis are nonspecific.

4. The registrant consulted Conrad King, DVM, Ph.D. for his "third party" opinion. Dr. King's opinion was that the amyloid findings already presented demonstrate an equivocal effect which would remain equivocal even if a dose related increase in amyloid was found on reexamination. The rationale for his opinion was that the high spontaneous incidence of amyloidosis found in test animals in this study could have been exacerbated by either physiological stress or other nonspecific factors.

Conclusions:

Additional work to quantitate amyloid is not required in light of the explanations provided by Drs. Cox and King above. The increased incidences of amyloid which occur in the low dose groups for some tissues are not considered to be of toxicological concern.

NOTE: A table showing the rates of amyloidosis in all groups is appended.

Attachment

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.

1 of 3

EPA FORM 1320-6 (REV. 3-76)

74

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.

001914

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.

EPA:OPP:HED:TOX:RD JDOHERTY:sb 11/30/79 X73710 TS-769 Rm. 816 CM #2

3 16

010918

[RESMETHRIN]

Chronic Oral Study 83-1

EPA Reviewer: Linnea J. Hansen
Review Section IV, Toxicology Branch I (7509C)
EPA Section Head: Marion P. Copley
Review Section IV, Toxicology Branch I (7509C)

Linnea J. Hansen, Date 4/5/94

Marion Copley, Date 4/6/94

DATA EVALUATION REPORT

STUDY TYPE: Chronic Oral - Dog (83-1b)

TOX. CHEM. NO: 083E

P.C.CODE.: 097801

MRID NO.: 430626-01

TEST MATERIAL: SBP-1382

SYNONYMS: Resmethrin; 5-benzyl-3-furylmethyl (IRS)-cis,trans-chrysanthemate

STUDY NUMBER: HWA 2623-105

SPONSOR: Roussel Bio Corporation, Lincoln Park, New Jersey

TESTING FACILITY: Hazleton Washington, Inc., Vienna, VA

TITLE OF REPORT: 52-Week Oral Toxicity Study of SBP-1382 (Resmethrin) Technical in Dogs

AUTHOR: Dan W. Dalgard, D.V.M.

REPORT ISSUED: November 23, 1993

EXECUTIVE SUMMARY: In a 52-week oral toxicity study, groups of 4/dose/sex beagle dogs were administered resmethrin (technical, 86.3% a.i.; doses not adjusted for purity) at 0, 12.5, 125, 500 or 2000 mg/kg/day in gelatin capsules (administered 2-4 times daily). When adjusted for purity of active ingredient, doses were 8.1, 108, 430 or 1720 mg/kg/day.

At 430 mg/kg/day, males had reduced body weight gain and food consumption during the first few weeks of the study (-33% during Weeks 1-13), resulting in slightly lower total mean body weight gain (-18%; not statistically significant). One male had bilateral diffuse posterior capsule cataracts. Females also showed reduced mean body weight gain and food consumption during Weeks 1-13 (-41%; not statistically significant); however, body weight gain during the entire study was comparable to controls. At 1720 mg/kg/day, males and females had further decreases in mean body weight gain and pronounced liver enlargement (~60%). Slightly increased

77

severity (slight or moderate vs. minimal in controls) of vacuolization of the gall bladder mucosa epithelium were observed in males and possibly females, and 2 males had midzonal-centrilobular hypertrophy of liver. Diffuse posterior capsule cataracts were observed in two males. **The LOEL of 430 mg/kg/day is based on cataract formation in males and slightly decreased body weight gain in males and females during the early weeks of the study. The NOEL is 108 mg/kg/day.** (Actual doses received at 430 and 1762 mg/kg/day are somewhat lower than administered dose due to excretion of pieces of unabsorbed test material in the feces).

This study is Core-minimum and satisfied the guideline requirements for 83-1b, chronic toxicity study in the dog.

Special Review Criteria (40 CFR 154.7) None

A. MATERIALS:

1. Test Material: Resmethrin, technical
   Description: Light brown solid
   Lot/Batch #: IN-0198-B3
   Purity: 86.3% a.i.
   Stability of compound: Stable at room temperature when stored in dark
   CAS #: 10453-86-8
   Structure

2. Vehicle: Gelatin Capsules (no liquid vehicle used)

3. Test animals: Species: Dog
   Strain: Beagle
   Age and weight at study initiation: about 5 mos; males weighed between 6.6 - 8.5 kg; females weighed between 6.2 - 8.3 kg.
   Source: Hazleton Research Products, Cumberland, VA
   Housing: Individual stainless steel cages
   Environmental conditions: Temperature: 62 - 83°F
   Humidity: not stated in report
   Air changes: 10 - 17 changes/hr
   Photoperiod: 12 hr light/12 hr dark
   Acclimation period: 3-1/2 weeks

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the test groups in Table 1:

TABLE 1: STUDY DESIGN[1]

Test Group	Dose, oral in gelatin capsule: Target dose (mg/kg/day)	Actual dose[1] (mg/kg/day)	No. animals assigned: Sacrifice: 12 months male	female
1 Control	0	0	4	4
2 Low (LDT)	12.5	8.1	4	4
3 Mid (MDT1)	125	108	4	4
4 High (MDT2)	500	430	4	4
4 High (HDT)	2000	1720	4	4

1 Dose adjusted for purity of active ingredient (~86%)

Dose selection rationale: None provided. However, test material was administered up to the limit dose of 2000 mg/kg/day. The study author also did not indicate the rationale for using capsules instead of admixture in diet.

2. Test material dosing preparation and analysis

Test material was administered orally once daily in gelatin capsules, 7 days a week, for 52 weeks. The test material was liquified in a water bath at 50°C and appropriate amounts were added to gelatin capsules by syringe. Capsules were prepared weekly for each dog based on its weight at the start of that week. Amount of test material per capsule was adjusted so that control and high dose dogs received 4 capsules/day during Weeks 1-2, 3 capsules/day during Weeks 2-4, 2 capsules/day during Weeks 5-8 and 3 capsules/day for the duration of the study. All other dose groups received 2 capsules/day throughout the study. The study report did not indicate the reason for changing the frequency of dosing. Dosages were not adjusted for purity of the active ingredient (100% purity assumed). The adjusted doses are used in this DER.

Prepared capsules were stored in the dark at room temperature. A stability study verifying that test material was stable in capsules for at least 7 days was conducted for a previous study (HWA 2623-102) but data was not included with this study report. Homogeneity and concentration analyses were not performed since resmethrin was not diluted in vehicle.

3. Animals received food (Purina Certified Canine Diet #5007) and water ad libitum.

4. Statistics - Statistical analyses were performed on mean body weight change, total food consumption, clinical pathology (except cell morphology, reticulocyte count and urinalysis) and organ weight. A diagram showing analyses used is attached (Appendix I). Where data showed heterogeneity of variance, various transformations were performed to achieve homogeneity as diagrammed. When the entire series of transformations did not achieve

homogeneity of variance, analyses were performed on rank-transformed data. Statistical significance was identified at 5% two-tailed probability level.

5. A signed and dated quality assurance statement was present.
A signed and dated GLP statement was present.

C. METHODS AND RESULTS:

1. Observations:

Animals were inspected daily for signs of toxicity and mortality. A thorough clinical examination was performed once each week.

Results - There was no mortality during the study.

At 1720 mg/kg/day, feces discolored by the test material and containing pieces of the unabsorbed resmethrin were frequently observed in both males and females. Weekly clinical effect data for individual animals indicated that feces containing pieces of test material were observed in 1/3 - 1/2 of the weeks of the study but daily incidence was not indicated). To a lesser extent this was also seen at 430 mg/kg/day.

One high-dose female developed tremors classified as slight during Week 18. Bloody feces and partial closure of eyes were also seen in this animal at Week 18. Due to the isolated incidence, it was not considered a treatment-related effect.

2. Body weight

Animals were weighed prior to initiation of treatment and weekly throughout the study.

Results - Mean body weight gain for males and females during 13-week intervals is shown below in Table 2:

TABLE 2: MEAN BODY WEIGHT GAIN AT 13-WEEK INTERVALS[1]

DOSE, MG/KG/DAY:	0	8.1	108	430	1720
MALES: Weeks 1-13	3.7	2.9	2.6	2.48*	1.5*
1-26	4.2	3.2	3.6	3.1	2.2
1-39	4.0	3.0	3.3	3.3	2.5
1-52	4.4	3.2	3.8	3.6	2.3
FEMALES: Weeks 1-13	1.7	2.5	2.2	1.0	1.0
1-26	2.0	2.9*	2.5	1.4	1.4
1-39	2.0	2.8	2.4	1.8	1.4
1-52	2.3	3.3	3.3	2.3	1.5

1 Data taken from Table 2B of study report * $p < 0.05$

Males at 430 and 1720 mg/kg/day showed statistically significant decreases in mean body weight gain during the first 13 weeks of treatment (33% and 59% less than controls, respectively). Females at 430 and 1720 mg/kg/day also had decreased mean body weight gain during this time period (41% less than controls at each dose) but the reduction was not statistically significant. At 52 weeks total mean body weight gains were not statistically significant (for males, 18% and 48% less than controls at 430 and 1720 mg/kg/day, respectively; for females, 35% less than controls at 1720 mg/kg/day). Mean body weights at 1720 mg/kg/day groups were 13% and 8% less than controls for males and females, respectively and were not statistically significant. The decreased weight gain at the two highest doses during the early portion of the study appeared to be related to decreased food consumption which occurred during the first weeks of the study (see below) and at high dose corresponded to the 4 capsule/day dosing regimen.

3. Food consumption

Food consumption for each animal was recorded weekly up to Week 16 and monthly thereafter. Food efficiency was not calculated.

Results - Representative mean weekly food consumption is shown in Table 3:

TABLE 3: REPRESENTATIVE MEAN WEEKLY FOOD CONSUMPTION (KG/ANIMAL/WEEK)[1]

SEX/WEEK	0	8.1	108	430	1720
MALES /1	2.2	2.1	1.8	1.6	1.2
2	2.3	2.3	1.9	2.0	1.2
3	2.4	2.4	2.1	2.1	1.7
4	2.2	2.2	1.8	1.8	2.1
13	2.0	2.2	1.8	2.0	1.9
28	2.2	2.4	2.1	2.4	2.3
40	2.2	2.3	1.9	2.1	2.2
52	2.2	2.2	1.9	2.0	2.1
1-52[2]	53.7	52.5	48.8	50.6	49.3
FEMALES/1	1.8	2.0	1.8	1.3	1.2
2	1.8	1.9	1.9	1.8	1.4
3	1.9	2.2	2.1	1.8	1.9
4	2.2	2.1	1.9	1.5	1.9
13	1.9	1.8	1.9	1.4	1.9
28	2.2	2.0	1.9	2.1	1.5
40	2.0	2.0	2.0	1.9	1.7
52	1.8	1.7	2.0	1.8	1.4
1-52	49.2	50.2	49.6	40.3	42.2

1 Data taken from Table 3 of study report
2 52-week total represents sum of measured consumption only

81

No statistically significant decreases in mean food consumption were seen during the study; however, food consumption of treated animals tended to be lower, particularly during the first few weeks of the study. During that time high dose dogs ate about 33 - 50% less than controls. Food consumption of high dose animals appeared to increase when dosing was changed from 4 to 3 capsules daily. The decreased food consumption during the first weeks of the study correlated with decreased body weight gain among these animals. TB-I considered these decreases to be treatment-related and possibly related to greater bioavailability of smaller doses administered more frequently.

4. Ophthalmoscopic examination

Eyes were examined by indirect ophthalmoscopy following administration of a mydriatic agent prior to initiation of treatment and during Week 51.

Results - Bilateral posterior subcapsular cataracts were observed in 1 male at 430 mg/kg/day and 2 males at 1720 mg/kg/day. No treatment-related lesions were seen among females. The dogs were examined by a veterinary ophthalmologist and the lesions were determined to be a possible effect of treatment.

5. Blood was collected at 2 weeks pretest and at Weeks 13, 26, 39 and 52 for hematology and clinical analysis from all animals (fasted overnight). The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*		Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)*		Mean corpusc. volume (MCV)
X	Platelet count*		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic and chronic studies

Results - Mean values for hematologic parameters showing statistically significant differences from controls are attached (Appendix II; Table 4 from study report). Hematocrit, hemoglobin and erythrocyte count were slightly reduced in high dose males at 52 weeks (13-17% less than controls). RBC means were slightly reduced throughout the study. At 430 mg/kg/day, all 3 parameters were also reduced at Week 52 to a similar extent. TB-I agreed with the study author that this was probably a treatment-related effect but that the magnitude of the decreases were not biologically significant. The study authors stated that the values

were within normal biological variation. Females showed sporadic reductions of comparable magnitude in RBC, hemoglobin and hematocrit at mid and high doses.

b. Clinical Chemistry

X	Electrolytes:	X	Other:
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*		Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	Enzymes	X	Total bilirubin
	Alkaline phosphatase (ALK)	X	Total serum protein (TP)*
	Cholinesterase (ChE)		Triglycerides
	Creatinine phosphokinase		Serum protein electrophores.
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic and chronic studies

Results - No biologically significant differences were observed among treated animals when compared to controls. Sporadic incidences of statistically significant differences from controls observed among each dose group were not considered of biological significance. Cholesterol and alkaline phosphatase were not determined.

6. Urinalysis

Urine was collected from fasted animals at 2 weeks pretest and Weeks 13, 26, 39 and 52. The CHECKED (X) parameters were examined.

X		X	
X	Appearance*	X	Glucose*
	Volume*	X	Ketones*
X	Specific gravity*	X	Bilirubin*
X	pH	X	Blood*
X	Sediment (microscopic)*		Nitrate
X	Protein*	X	Urobilinogen

* Required for chronic studies

Results - No treatment-related effects were observed on the urinalysis parameters examined.

83

7. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X	X	X
Digestive system	Cardiovasc./Hemat.	Neurologic
| | Tongue	| X | Aorta*	| XX | Brain*
| X | Salivary glands*	| XX | Heart*	| X | Periph. nerve*
| X | Esophagus*	| X | Bone marrow*	| X | Spinal cord (3 levels)*
| X | Stomach*	| X | Lymph nodes*	| XX | Pituitary*
| X | Duodenum*	| XX | Spleen	| X | Eyes (optic n.)*
| X | Jejunum*	| X | Thymus*	Glandular
| X | Ileum*	Urogenital	| XX | Adrenal gland*
| X | Cecum*	| XX | Kidneys*+	| X | Lacrimal gland
| X | Colon*	| X | Urinary bladder*	| X | Mammary gland*
| X | Rectum*	| XX | Testes*+	| XX | Parathyroids*++
| X | Liver *+	| XX | Epididymides	| XX | Thyroids*++
| X | Gall bladder*	| X | Prostate	Other
| X | Pancreas*	| X | Seminal vesicle	| X | Bone*
Respiratory	| XX | Ovaries*+	| X | Skeletal muscle*
| X | Trachea*	| X | Uterus*	| X | Skin*
| X | Lung*		| | All gross lesions and masses*
| | Nose		
| | Pharynx		
| | Larynx		

* Required for subchronic and chronic studies.
\+ Organ weight required in subchronic and chronic studies.
++ Organ weight required for non-rodent studies.

Results -

a. Organ weight - Mean absolute and relative liver (+gall bladder) weights are shown below in Table 4:

TABLE 4: MEAN ABSOLUTE AND RELATIVE ORGAN WEIGHT (G AND % OF BODY WT.)[1]

	RESMETHRIN, MG/KG/DAY									
	0		8.1		108		430		1720	
ORGAN: Sex	ABS	REL	ABS	REL	ABS	REL	ABS	REL	ABS	REL
LIVER[2] M	298	2.5	290	2.7	261	2.4	295	2.7	400	3.9*
F	225	2.5	272	2.6	268	2.7	232	2.6	333	4.0*

1 Data taken from Table 7 of study report
2 Liver weight includes gall bladder weight
* $p \leq 0.05$

84

At 1720 mg/kg/day significant elevations in mean absolute and relative liver weights were observed in both males and females (56 and 60%, respectively). TB-I agreed with the study author that this was a treatment-related effect, although the toxicologic significance is unclear in the absence of histopathological and clinical chemistry effects.

b. Gross pathology - No treatment-related gross lesions were observed.

c. Microscopic pathology -

1) Non-neoplastic - Lesions observed in the liver and gallbladder in males and females are summarized below in Table 5:

TABLE 5: INCIDENCE OF MICROSCOPIC LESIONS IN LIVER AND GALL BLADDER[1]

	DOSE, MG/KG/DAY				
OBSERVATION	0	8.1	108	430	1720
MALES					
LIVER:					
Midzonal-centrilobular hypertrophy, minimal	0	0	0	0	2
GALL BLADDER:					
Vacuolization of mucosa,					
minimal	2	1	1	2	1
slight	0	0	0	0	3
ALL GRADES	2	1	1	2	4
FEMALES					
LIVER:					
Bile duct, hyperplasia, minimal	0	0	0	1	1
GALL BLADDER:					
Vacuolization of mucosa,					
minimal	2	0	1	3	1
slight	1	0	0	0	0
moderate	0	0	0	0	1
ALL GRADES	3	0	1	3	2

1 Data taken from Table 8 of study report. For all groups, N = 4.

Midzonal to centrilobular hepatocellular hypertrophy (minimal) of the liver was observed in 2 males at 1720 mg/kg/day but was not accompanied by other microscopic lesions or increased hepatocellular proliferation. The observed hypertrophy was consistent with the increased liver weights in males, although females also showed significantly increased liver weight. Bile duct hyperplasia (minimal) was observed in one female at 430 and one at 1720 mg/kg/day; this lesion was not considered treatment-related because the severity was

minimal. Vacuolization of gall bladder mucosa was observed in males and females at all dose levels but severity and incidence of lesions increased in males at high dose (2 minimal; controls vs 3 slight and 1 minimal at high dose) and possibly severity increased at high dose in females (1, moderate). The study author only considered the lesions in males to be treatment-related. TB-I considered the increased severity of gall bladder mucosa vacuolization in one female at high dose to be a possible treatment-related effect. No other treatment-related lesions were observed.

2) Neoplastic - No neoplastic lesions were observed.

E. DISCUSSION:

Minimal effects were observed in beagles treated with resmethrin at 430 mg/kg/day. Males and females showed weight loss and decreased food consumption during the first 1-2 weeks of the study and a bilateral posterior capsular cataract was observed in one male. At 1720 mg/kg/day, two males developed cataracts. In males and females at 1720 mg/kg/day, more pronounced decreases in mean body weight gain were observed during Weeks 1-13 which corresponded to decreased food consumption. Weight loss occurred during Weeks 1 and 2. Livers of males and females were enlarged by about 50-60% but hepatocytes did not show histopathological effects and no liver-related clinical chemistry parameters were affected by treatment. In females, minimal bile duct hyperplasia was observed in one animal at 430 and one at 1720 mg/kg/day. Males and possibly females showed a slight increase in severity of gall bladder mucosa vacuolization at 1720 mg/kg/day. Although the observed effects on liver and gall bladder were limited, TB-I considers them indicative of minimal liver toxicity based on the magnitude of liver enlargement and the apparent effects on the biliary system.

NOEL: 108 mg/kg/day
LOEL: 430 mg/kg/day, based on decreased body weight gain in males and females during the early portion of the study and on occurrence of bilateral posterior subcapsular cataract in one male.

Actual doses of resmethrin were less than target doses, particularly at 430 and 1720 mg/kg/day, since pieces of the test compound were frequently excreted in the feces and therefore not well absorbed. In addition, the doses were not adjusted for purity of the test material (86%); NOEL and LOEL for this study were therefore based on doses adjusted for purity. The rationale for administration of resmethrin in capsules, as opposed to admixed with diet, was not provided in the study report. This may account for the relatively low level of toxicity observed at high doses.

F. STUDY DEFICIENCIES are as follows:

- Some clinical chemistry parameters not examined,

- Route of administration may have significantly reduced bioavailability of test material as compared to administration in diet.

The above deficiencies would not be expected to significantly alter the conclusions of the study.

Core-classification: Minimum. This study is considered acceptable for regulatory purposes.

RESMETHRIN

Page_____ is not included in this copy.

Pages 88 through 90 are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

[RESMETHRIN] DRAFT Chronic Oral Study 83-1

EPA Reviewer: Linnea J. Hansen
Review Section IV, Toxicology Branch I (7509C)
EPA Section Head: Marion P. Copley
Review Section IV, Toxicology Branch I (7509C)

Linnea J. Hansen, Date 6/2/94
Marion Copley, Date 6/10/94

DATA EVALUATION REPORT
(Supplemental DER to Original Review, HED Doc. No. 000791)

STUDY TYPE: Chronic Oral - Dog (83-1b)

TOX. CHEM. NO: 083E

P.C.CODE.: 097801

MRID NO.: 00157961

TEST MATERIAL: SBP-1382

SYNONYMS: Resmethrin; 5-benzyl-3-furylmethyl (IRS)-cis,trans-chrysanthemate

STUDY NUMBER: 6289

SPONSOR: At time of study, S.B. Penick Corporation, Lyndhurst, NJ. Registrant is now Roussel Bio Corporation, Lincoln Park, New Jersey

TESTING FACILITY: Food and Drug Research Lab, Waverly, NJ

TITLE OF REPORT: 180-Day Subchronic Oral Dosing Study with Resmethrin (SBP-1382) in Beagle Dogs

AUTHOR: L. Gephart, M.P.H., W. Johnson, Ph.D., Becci, Ph.D. and R. Parent, Ph.D.

REPORT ISSUED: December 18, 1980

EXECUTIVE SUMMARY: In a 180-day oral toxicity study, groups of 6 beagle dogs/dose/sex were administered resmethrin (technical,) in gelatin capsules admixed with silicate filler as vehicle. Controls received capsules containing 100 mg/kg filler only; doses not adjusted for purity) at 0, 10, 30 or 100/300 mg/kg/day in the diet. The high dose was changed from 100 mg/kg/day to 300 mg/kg/day on Day 57 of the study.

No significant treatment-related effects were observed at any dose tested. Mild liver enlargement occurred in males (+15% of controls at 300 mg/kg/day) and in females

(+27%; 16% at 30 mg/kg/day) but no microscopic lesions or changes in liver-related clinical chemistry parameters were observed. The increased liver weight is therefore considered an adaptive metabolic response to administration of the test material. Slightly increased incidence of salivation at 300 mg/kg/day was also not considered of toxicologic significance in the absence of other effects. **The LOEL is >300 mg/kg/day based lack of significant toxicologic effects at the highest dose tested. The NOEL is ≥ 300 mg/kg/day.**

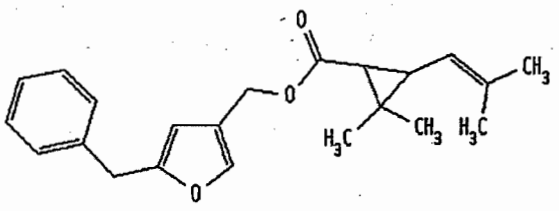
This study is Core-minimum and satisfied the guideline requirements for 83-1b, chronic toxicity study in the dog. Although no treatment-related toxicity was observed in this study, a LOEL for systemic toxicity (430 mg/kg/day) was established in a more recent 1-year dog oral toxicity study submitted (MRID 430626-01).

Special Review Criteria (40 CFR 154.7) None

Note: This DER supplement is intended to provide an Executive Summary and details of the study that were not included in the original DER. The conclusions of this supplemental DER supercede those of the original DER, where different.

A. MATERIALS:

1. Test Material: Resmethrin, technical
   Description: Light tan powder
   Lot/Batch #: 8147-LCO-1/FDRL ID No. 79-1149; 8176-RT/FDRL ID No. 80-0265; 8147-LCO-1/FDRL ID No. 80-0386
   Purity: For the 8147 lots, reported at 48.89% ai; analytical value (supplied in silicate filler)
   For the 8176 lot, 90% a.i. (technical grade, supplied neat for admixture with silicate filler).
   Stability of compound: Stable at room temperature when stored in dark
   CAS #: 10453-86-8
   Structure



2. Vehicle: Gelatin Capsules with Microcel E silicate filler (Lot no. 9199-RB, FDRL ID

92

no. 79-1170).

3. Test animals: Species: Dog
Strain: Beagle
Age and weight at study initiation: 5-6 mos; males weighed between 6.6 - 13.1 kg; females weighed between 6.4 - 10.2 kg.
Source: Laboratory Research Enterprises, Kalamazoo, MI
Housing: Individual pens (cage type not described)
Environmental conditions: It was stated in the study report that animals were housed in a controlled environment; however, actual conditions were not reported. A 12 hr on/off photoperiod was used.
Acclimation period: not indicated

B. STUDY DESIGN:

1. Animal assignment: See original DER. Assignment to test groups was random.

Dose selection rationale: None provided. The study authors also did not indicate the rationale for using capsules instead of admixture in diet.

2. Test material dosing preparation and analysis

Test material was administered orally in gelatin capsules as a 50% w/w mixture of test material in Microcel E silicate filler, 7 days a week, for 26 weeks. Frequency of capsule administration varied with dose group: 3-5 capsules/day, controls; 1, 10 mg/kg/day; 2-3, 30 mg/kg/day; 5-10, 100 mg/kg/day or 14-34, 300 mg/kg/day. It was stated in the study protocol that dosage would be determined based on the most recent body weight measurement for each animal. Dosages were not adjusted for purity of the active ingredient (100% purity assumed).

Test material was stored frozen (reported $<0°C$). Concentration of test material in silicate filler was verified analytically as 48.89% a.i. Homogeneity of bulk test material (SBP-1382 in silicate filler), stability and concentration analyses of the prepared capsules were determined periodically throughout the study.

Results - Homogeneity: Measurements of the concentration of test material in Microcel E silicate filler (50% w/w) taken from top, middle and bottom layers of the material were homogeneous within 1% of each other.

Stability: Test material in silicate filler was stable for at least 7 days (only interval tested). Measurements at 7 days were within 7% of original analytical concentration.

Concentration: Samples of dosing preparations at each dose level were taken for analysis at week 1, 2, 3, 5, 8, 9, 17 and 26. Average dietary concentration was within 5% of target concentration. Occasional variations outside acceptable range (±15%) of target concentration at mid-dose at week 1, low dose at week 5 and high dose at week 26 were not considered to have significantly affected the course of the study.

3. Animals received food (Purina Certified Canine Diet #5007) and water ad libitum.

4. Statistics - Statistical analyses of body weight, food consumption, clinical chemistries and organ weight data were analyzed using one-way analysis of variance (ANOVA). Differences among groups were identified using the Least Significant Difference test. Differences were judged to be statistically significant where $p < 0.05$.

5. A signed and dated quality assurance statement and GLP statement were present; however, this study was conducted prior to EPA GLP guidelines, and was conducted under FDA GLP guidelines. A Quality Insurance Unit inspected the study on several occasions.

C. METHODS AND RESULTS:

1. Observations:

Animals were inspected daily for signs of toxicity and mortality. A thorough clinical examination was performed once each week.

Results - See original DER. There was no mortality during the study. Incidence of tremors is shown below in Table 1:

TABLE 1: CLINICAL OBSERVATIONS[1]

	0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	300 mg/kg/day
Males:				
Tremors	1 (1)[2]	0	2 (1,14)	5 (1,1,1,2,3)
Avg. time to occurrence	17	-	91	131
Salivation	2 (1,2)	1 (1)	3 (2,3,3)	6 (1,1,1,3,4,6)
Avg. time to occurrence (days)	80	71	107	88
Females:				
Tremors	0	0	1 (1)	1 (1)
Avg. time to occurrence (days)	-	-	95	142
Salivation	1 (2)	1 (2)	0	4 (5,7,8,50)
Avg. time to occurrence (days)	59	48	-	62

1 Data taken from Table 1 and Appendix III of study report
2 Number of dogs affected (total number of days effect was observed in each animal affected)

Although the number of males with tremors (classified as slight to mild) at 300 mg/kg/day was increased compared to controls (5 vs. 1), TB-I agrees with the original DER that this was not a treatment-related effect since frequency of observation was low (total 1-2 days/animal) at high dose. Similarly, salivation showed increased incidence and frequency among some animals at 300 mg/kg/day but with one exception (50 days for one female), frequency was low and probably not of toxicologic significance in the absence of other effects. Excess salivation may have been related to the large number of capsules administered daily to the high dose animals. Lacrimation was observed frequently among animals in all four groups.

2. Body weight

Animals were weighed prior to initiation of treatment and weekly throughout the study.

Results - Mean body weight gain for males and females at selected intervals is shown below in Table 2:

TABLE 2: MEAN BODY WEIGHT GAIN (KG) AT 13-WEEK INTERVALS[1]

DOSE, MG/KG/DAY:	0	10	30	300
MALES: Weeks 1-5	0.7	1.1	0.9	0.9
5-10	0.2	0.5	0.7	0.6
10-15	0.4	0.7	0.1	0.0
15-20	0.4	0.2	0.7	0.4
20-23	0.3	0.4	0.3	0.4
23-25	0.0	0.3	0.1	-0.1
25-26	0.0	-0.2	0.0	0.0
1-26	1.7	2.8	2.5	2.0
FEMALES: Weeks 1-5	0.5	0.5	0.6	0.7
5-10	0.3	0.4	0.4	0.2
10-15	0.1	0.0	0.0	0.0
15-20	0.5	0.5	0.5	0.2
20-23	0.4	0.2	0.4	0.4
23-25	0.3	0.0	0.0	0.2
25-26	-0.1	0.1	0.0	-0.4
1-26	2.0	1.7	1.9	1.3

1 . Data taken from Table 2B of study report

Results - No treatment-related effects on body weight or body weight gain were observed. Sporadic, statistically significant differences in the mean body weight, both increases and decreases, were observed among all treated groups compared to the controls. At termination, mean body weights at 0, 10, 30 or 300 mg/kg/day were 11.6, 13.3, 12.7 or 12.1 for males and 9.8, 9.8, 9.9 or 9.3 for females, respectively. In general, the variable body weights appeared to correlate with variations in food

95

consumption that occurred in all groups. The decrease in mean body weight observed at 26 weeks in high dose females was not considered treatment-related since it was only observed during the last weeks of the study and was not statistically significant.

3. Food consumption

Food consumption for each animal was recorded weekly. Food efficiency was not calculated.

Results - Representative mean weekly food consumption is shown in Table 3:

TABLE 3: SELECTED MEAN DAILY FOOD CONSUMPTION (G/ANIMAL/DAY)[1]

SEX/WEEK	0 MG/KG/DAY	10 MG/KG/DAY	30 MG/KG/DAY	300 MG/KG/DAY[2]
MALES/ 1	398.3	352.5	378.3	425.0
5	525.0	512.5	437.5	582.5
10	505.8	432.8	495.8	522.2
15	473.7	618.5	469.7	563.5
20	448.0	384.2	559.2	518.3
23	539.2	452.3	550.0	549.2
26	522.7	572.2	511.8	537.3
FEMALES/1	263.3	416.7*	395.8*	365*
5	329.8	361.2	443.3	376.2
10	398.2	390.2	474.8	485.8
15	381.2	496.0	508.2	498.3
20	448.0	467.2*	288.2 —	273.7
23	456.7	465.0	418.3	419.2
26	397.0	496.5	368.0	257.3*

1 Data taken from Table 3 of study report
* $p < 0.05$

No treatment-related decreases in mean food consumption were seen during the study. Variable food consumption was observed among all groups. Sporadic statistically significant increases and decreases in food consumption were observed in treated animals compared to controls.

4. Ophthalmoscopic examination

Eyes were examined by indirect ophthalmoscopy following administration of a mydriatic agent prior to initiation of treatment and during Week 25.

Results - No treatment-related ocular effects were observed.

5. Blood was collected at Weeks 4, 8, 12, 16, 20 and 26 for hematology and clinical

analysis from all animals (fasted 14 - 16 hrs). The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*		Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)*		Mean corpusc. volume (MCV)
X	Platelet count*		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic and chronic studies

Results - No treatment-related effects on blood cell parameters were observed.

b. Clinical Chemistry

X		X	
	Electrolytes:		Other:
X	Calcium*	X	Albumin*
X	Chloride*		Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*	X	Cholesterol*
	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	Enzymes	X	Total bilirubin
X	Alkaline phosphatase (ALK)	X	Total serum protein (TP)*
	Cholinesterase (ChE)		Triglycerides
	Creatinine phosphokinase		Serum protein electrophores.
X	Lactic acid dehydrogenase (LDH)		
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic and chronic studies

Results - No biologically significant differences were observed among treated animals when compared to controls.

6. Urinalysis

Urine was collected from fasted animals at Weeks 4, 8, 12, 16, 20 and 26. The

CHECKED (X) parameters were examined.

X		X	
X	Appearance*	X	Glucose*
	Volume*	X	Ketones*
X	Specific gravity*	X	Bilirubin*
X	pH		Blood*
X	Sediment (microscopic)*		Nitrate
X	Protein*	X	Urobilinogen

* Required for chronic studies

Results - No treatment-related effects were observed on the urinalysis parameters examined.

7. Sacrifice and Pathology

All animals were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X		X		X	
Digestive system		Cardiovasc./Hemat.		Neurologic	
	Tongue	X	Aorta*	XX	Brain*+
X	Salivary glands*	XX	Heart*	X	Periph. nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	XX	Pituitary*
X	Duodenum*	XX	Spleen	X	Eyes (optic n.)*
X	Jejunum*	X	Thymus*	Glandular	
X	Ileum*	Urogenital		XX	Adrenal gland*
X	Cecum*	XX	Kidneys*+		Lacrimal gland
X	Colon*	X	Urinary bladder*	X	Mammary gland*
X	Rectum*	XX	Testes*++	XX	Parathyroids*++
XX	Liver *+	XX	Epididymides	XX	Thyroids*++
X	Gall bladder*	X	Prostate	Other	
X	Pancreas*		Seminal vesicle	X	Bone*
Respiratory		XX	Ovaries*+	X	Skeletal muscle*
X	Trachea*	XX	Uterus*	X	Skin*
X	Lung*				All gross lesions and masses*
	Nose				
	Pharynx				
	Larynx				

* Required for subchronic and chronic studies.
+ Organ weight required in subchronic and chronic studies.
++ Organ weight required for non-rodent studies.

Results -

a. Organ weight - See original DER. In contrast to the original review, TB-I does not

98

consider the increased liver weights sufficient for establishing a NOEL in the absence of microscopic lesions or altered clinical chemistry profiles.

b. Gross pathology - No treatment-related gross lesions were observed.

c. Microscopic pathology - No treatment-related microscopic lesions were observed.

E. DISCUSSION: TB-I does not currently agree with the conclusions of original DER that a NOEL of 10 mg/kg/day and LOEL of 30 mg/kg/day were observed, based only on liver enlargement (+17% in males). This effect is considered, as noted by the study author, a result of increased hepatic metabolism of the test compound. TB-I agrees that the reported increase in salivation and mild tremors at 300 mg/kg/day were not of toxicologic significance. They were also not seen in the 1-year dog study at doses up to about 1400 mg/kg/day.

NOEL: $\geq$300 mg/kg/day
LOEL: >300 mg/kg/day

STUDY DEFICIENCIES are as follows:

- LOEL not achieved,
- Purity of technical SBP-1382 not stated,
- Some clinical chemistry parameters not examined,
- Some details on study methods and results not included in report,
- Study conducted for 6 months; at time of conduct this was accepted by Agency
- Study not conducted under EPA GLP

Core-classification: Minimum. This study is considered acceptable for regulatory purposes, despite the deficiencies listed above, which are not expected to significantly alter the conclusions of the study. In addition, a second study in dogs (1 yr exposure) determined a similar LOEL. Although the study report did not include the % a.i. in the technical resmethrin that was not 50% in silicate filler, based on the analytical report, the concentrations of a.i. in the dosing preparations were adequate and indicated that in general the appropriate amount of test material was administered.

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

000741

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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
Toxicology Branch, HED (TS-769)

R. R. Loche 7/22/81
for CJB

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

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.

154

100

000741

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^-.

2

000741

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 significant

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 table.

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.

3

102

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

[Resmethrin] DRAFT Reproduction Study (83-4)

EPA Reviewer: Linnea J. Hansen, Ph.D. Linnea J. Hansen, Date 9/22/94
Review Section IV, Toxicology Branch I (7509C)
EPA Section Head: Marion P. Copley, D.V.M., D.A.B.T. Marion Copley, Date 9/24/94
Review Section IV, Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Multigeneration Reproduction - 2-Generation Study in Rat (83-4)

TOX. CHEM. NO.: 083E

P.C. CODE: 097801

MRID NO.: 431891-01

TEST MATERIAL: SBP-1382®, technical

SYNONYMS: Resmethrin; 5-benzyl-furylmethyl (IRS)-cis,trans-chrysanthemate

STUDY NUMBER: 718-004 (Laboratory Protocol No.); RBT-92-102 (Sponsor ID)

SPONSOR: Roussel Bio Corporation, Lincoln Park, NJ

TESTING FACILITY: Argus Research Laboratories, Inc., Horsham, PA

TITLE OF REPORT: Reproductive Effects of SBP-1382® (Resmethrin) Technical Administered Orally via the Diet to Crl:CD®BR VAF/Plus® Rats for Two Generations with Two Litters per Generation.

AUTHOR: Alan M. Hoberman, Ph.D., D.A.B.T.

REPORT ISSUED: February 1, 1994

EXECUTIVE SUMMARY: In a 2-generation reproduction study, resmethrin (SBP-1382® technical, 86.3% a.i.) was administered continuously in the diet to Crl:CD®BR VAF/Plus® rats (30/sex/dose) at concentrations of 0, 250, 500 or 1000 ppm (0, 17.4, 34.8 or 70.8 mg/kg/day, respectively, based on body weight and food consumption during premating periods). P_1 and F_1 males and females were mated 1:1 for up to 21 days after at least 80 days on test diet before the first mating period, and after a 26 day (P_1) or 17 day (F_1) postweaning rest period.

Parental (systemic) toxicity: At 1000 ppm, P_1 females showed slightly decreased body weight/weight gain during gestation (5.4% less than controls) and no weight gain during the first

4 days of lactation, probably due to reduced litter weights. F_{1b} males and females showed decreased body weight (5% to 7% less than controls) early in postweaning, due largely to reduced weight during lactation. Deaths of 2 F_{1b} males (days 37 and 44 post-weaning) were possible effects of treatment. **The LEL for parental (systemic) toxicity is 1000 ppm (70.8 mg/kg/day), based on slight decreases in body weight gain in P_1 females during gestation and lactation, decreased body weight in F_{1b} males and females, and possible treatment-related mortality in postweanling F_{1b} males. The NOEL is 500 ppm (34.8 mg/kg/day).**

Reproductive/offspring toxicity: At 1000 mg/kg/day, significantly decreased viability indices were observed in all generations, with more pronounced decreases in the F_{1a} and F_{2a} generations (33% and 45% less than controls) than the F_{1b} and F_{2b} generations (15% and 9% less than controls). Mean pup birth weight was also significantly decreased in the F_{1a} and F_{2a} generations (8% less than controls), and to a lesser extent in the F_{1b} and F_{2b} generations (5 to 7% less than controls). Pup weight and weight gain were significantly decreased at day 21 of lactation (8% to 15%). A slight increase in stillborn pups was observed in the "a" generations (1.8% and 3.4%, vs. 0.5% - 0.7%, controls). Significantly decreased mating index (30% and 18% less than controls, males and females, respectively) was observed during the F_1 second cohabitation. **The LEL for reproductive and offspring toxicity is 1000 ppm (70.8 mg/kg/day), based on decreased mating index in males and females during the second F_1 mating, decreased viability index and decreased pup weight in all generations at birth and during lactation, and possible slight increase in stillborn pups in the F_{1a} and F_{2a} generations. The NOEL is 500 ppm (34.8 mg/kg/day).**

This study is Core-minimum and satisfies the guideline requirement for a reproduction study (83-4) in the rat.

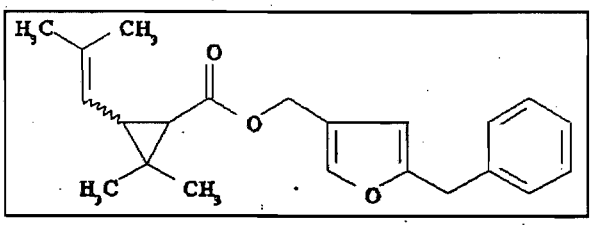
Special Review Criteria (40 CFR 154.7) None

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: SBP-1382® (resmethrin), technical
   Description: waxy, tan solid
   Lot/Batch #: IN-0198-B3
   Purity: 86.3% (% a.i. not stated in study report; information taken from 1-year dog feeding study, MRID 430626-01)
   Stability of compound: Stable at room temperature when stored in dark (not stated in study report; information taken from 1-year dog feeding study)
   CAS #: 10453-86-8

Structure



2. Vehicle: None (mixed directly in diet)

3. Test animals: Species: Rat
   Strain: Crl:CD®BR VAF/Plus®
   Age/weight at study initiation: 48 days/60 to 101 g, males and 59 to 97 g, females
   Source: Charles River Laboratories, Portage, MI
   Housing: Mating: one male and one female in male wire-bottom stainless steel cage
   Post-partum: individual dams in nesting boxes no later than day 20 of gestation and for 21 days post-partum
   All other times: individually, wire-bottom stainless steel cage
   Environmental conditions:
   Temperature: 70 - 78°C, except for 7 occasions when the temperature reached up to 81°C for ½ - 8 hrs
   Humidity: 40 - 80%, except for 3 occasions when the humidity was 34 - 38% for ½ hr.
   Air changes: ≥10/hr (filtered air)
   Photoperiod: 12 hr light/12 hr dark
   Acclimation period: about 16 days

4. Diet preparation and analysis: Diet was prepared at least weekly by mixing appropriate amounts of test substance with resmethrin and was stored in the dark at room temperature in airtight containers. Test material was assumed to be 100% for dosage calculations. Homogeneity and stability were tested during the range-finding study at concentrations up to 900 ppm. During the study, samples of treated food were analyzed at study start and at monthly intervals for concentration.

   Results -

   Homogeneity Analysis: Most preparations of diet with resmethrin were relatively homogeneous, with relative standard deviations of 3% - 6%. The greatest variation was observed in the 600 ppm diet, where the concentration of the top portion was ±2% of target concentration, compared to -7% to -12% in the middle and bottom samplings.

Stability Analysis: Resmethrin was demonstrated to be stable for at least 7 days in diet under the conditions of storage used in this study.

Concentration Analysis: Most batches of diet tested were within acceptable range of target concentration (±10%). However, analytical concentrations were lower than expected (-11% to -15%) on several occasions at all dose levels). These variations are noted but are not considered to significantly affect the results of the study.

5. Animals received food (Purina Certified Rodent Chow #5002) and water ad libitum.

B. STUDY DESIGN AND MATING PROCEDURES

1. Animal assignment: P_1 animals were randomly assigned to test groups shown below:

TABLE 1 **Animal Assignment: P1 Generation**

Test groups		Dose	Animals per group [2]	
No.	Designation	(ppm)[1]	Males	Females
1	Control	0	30	30
2	Low (LDT)	250	30	30
3	Mid	500	30	30
4	High (HDT)	1000	30	30

1 Diets were administered from the beginning of the study until the animals were sacrificed.
2 The same number of animals were picked from the F_1 litters as parents for the F_2 generation.

2. Mating procedure: One male and one female were placed (random assignment) in the male's cage for a period of up to 21 days. Females were examined daily for evidence of mating and those females with copulatory plugs and/or spermatozoa in vaginal smears were removed to their individual cage. The day on which evidence of mating was observed was designated Day 0 of gestation. Any female showing no evidence of mating after 14 days was placed with another male for up to 7 days.

3. Mating schedule: Matings were conducted with males and females from the P_1 parental generation and from animals culled from the F_{1b} generation. All P_1 and F_{1b} parental females were examined for estrous cycling by vaginal cytology for 7 days prior to the start of the cohabitation periods. For the P_1 generation matings, males and females were cohabited starting after at least 80 days' administration of test diet at the appropriate dietary dose levels. The second mating of P_1 animals was conducted following a 26-day post-weaning rest period and the 7-day estrous cycle examination.

For the F_1 matings, cohabitation was initiated after at least 80 days post-weaning (including estrous cycle examination). The second mating period was initiated after

a post-weaning rest period of 17 days (including the 7-day estrous cycling tests). The same pairs of males and females were cohabited for the second generation matings, whenever possible. All cohabitations were conducted for no more than 21 days. Where no evidence of mating was observed after 14 days, the male was replaced with a proven fertile male for up to 7 days.

4. Culling of litters and selection of F_1 parental animals: All litters larger than 8 pups were culled to 8 on Day 4 postpartum. Whenever possible, equal numbers of males and females were retained in a litter. From the remaining F_{1b} pups, 30 males and 30 females/dose level were randomly selected on Day 21 postpartum and used for the second-generation matings.

5. Dose selection rational: Doses were selected based on results of a one-generation range-finding study, described in Appendix I of the study report. Eight Crl:CD®BR VAF/Plus® rats/sex/dose were administered 125, 250, 500 or 1000 ppm resmethrin in the diet (equivalent to average dose of 0, 5.8, 11.0, 22.7 or 44.2 mg/kg/day, premating males and 0, 7.1, 13.4, 28.9 or 56.7 mg/kg/day, premating females). All animals were administered test diet for 14 days prior to cohabitation and during a 7-day cohabitation. Males were administered test diet after cohabitation for a total of 55 days on test diet; females were administered test diet until scheduled sacrifice on day 21 postpartum (total of 57 - 63 days on test diet) or until day 25 of presumed gestation for females that did not deliver or were not pregnant (40 - 46 days on test diet).

   No mortality or overt clinical signs of toxicity were observed and body weights, weight gain and food consumption were comparable among all groups during premating, gestation and lactation. At 1000 ppm, in utero deaths were increased, and gestation index and viability index were decreased (50% less than controls). In addition, the study author reported difficulties with delivery (perivaginal bleeding often associated with stillbirths or resorptions, pale appearance, delivery of additional pup 2 days postpartum) among all treatment groups but not controls: 3/5, 2/4 and 2/4 dams at 250, 500 and 1000 ppm, respectively. The relationship of this to treatment is unclear since there was no dose response and the number of dams/dose group was small.

C. METHODS

1. Observation Schedule

   a. Parental animals: Observations and the schedule for those observations are summarized below in Table 2.

TABLE 2: Observation Schedule

Viability:	2X/day
Clinical signs:	1X/day
Body weight and food consumption	
Premating:	Weekly (parental P_1 and F_{1b} males and females)
Gestation:	Days 0, 6, 10, 15 and 20; body weight only on day 25
Lactation:	Days 1, 4, 7, 10 and 14; body weight only on days 16, 18 and 21

b. Reproductive performance: Parental reproductive performance was assessed from breeding and parturition records of animals in the study. Length of gestation was noted. The following indices were calculated:

$$\text{Male (female) mating index} = \frac{\text{No. males (females) that mated}}{\text{No. males (females) cohabited}} \times 100$$

$$\text{Male fertility index} = \frac{\text{No. females pregnant}}{\text{No. males mated}} \times 100$$

$$\text{Female fertility index} = \frac{\text{No. females presumed pregnant}}{\text{Total no. females mated}} \times 100$$

$$\text{Gestation index} = \frac{\text{No. live litters born}}{\text{No. confirmed pregnancies}} \times 100$$

c. Litter observations: The following litter observations were made (see Table 3).

TABLE 3 F1/F2 Litter Observation Schedule

Number of live pups:	Daily
Pup weight:	Lactation Days 1,4,7,14,21
External alterations:	Daily
Number of dead pups:	Daily
Sex of each pup (m/f):	Lactation Days 1,4,7,14,21

Dead pups were examined grossly for external and internal abnormalities and a possible cause of death was determined for pups born or found dead. Lungs of pups found dead on Day 1 were placed in water to determine if the animal was stillborn (lungs

sink) or died postpartum (lungs float). The following F_1 indices were calculated:

$$\text{Live born index} = \frac{\text{No. live pups born}}{\text{No. live + dead pups born}} \times 100$$

$$\text{Viability index} = \frac{\text{No. live pups at day 4}}{\text{No. pups born alive}} \times 100$$

$$\text{Lactation index} = \frac{\text{No. live pups at day 22}}{\text{No. pups born alive}} \times 100$$

d. Necropsy

1) Parental animals: All surviving parental P_1 and F_1 males were sacrificed as soon as possible after the second litters were produced in that generation. Maternal animals were sacrificed on Day 25 postpartum after the last litter of each generation was weaned. Females that did not bear young were sacrificed on Day 25 of presumed gestation. All animals were sacrificed by carbon dioxide asphyxiation. In addition, animals that died during the study were subjected to post mortem examinations as described below.

Necropsy observations: Gross examination consisted of external and internal examination of all body surfaces and the cervical, thoracic and abdominal viscera.

The following tissues (X) from all male and female P_1 and F_{1b} parental animals were prepared in 10% buffered formalin for microscopic examination and weighed (XX):

Reproductive organs:

XX Ovaries	XX Epididymides
XX Uterus	XX Prostate
XX Vagina/cervix	XX Seminal vesicles/coagulating gland
	XX Testes

Other organs/tissues:

XX Brain[1]	XX Pituitary gland
XX Liver[2]	X Gross lesions

1 Weighed but not examined microscopically
2 Weighed but only F_{1b} parental animals examined microscopically

Microscopic examination of the above tissues (except brain and P_1 livers) was conducted on all control and high-dose animals from both parental generations. All

tissues were collected from one control animal and preserved for possible microscopic examination.

2) Offspring: Culled offspring from each litter generation were sacrificed on Day 4 postpartum. The F_1 and F_2 offspring maintained through lactation and not selected as parental animals were sacrificed at 21 days of age. All sacrifices were by carbon dioxide asphyxiation. These animals were necropsied and subjected to complete post mortem gross examinations.

D. STATISTICAL ANALYSIS: Paternal, maternal and pup incidence data were analyzed by the Variance Test for Homogeneity of the Binomial Distribution. Body weight, food consumption, litter averages for pup body weights, percent male pups and percent pup mortality were analyzed by Bartlett's test of homogeneity of variances and ANOVA, followed by Dunnett's test when ANOVA was significant. When Bartlett's test was significant, Kruskal-Wallis test or Fisher's Exact test was used, as appropriate. Dunn's Method of Multiple Comparisons was used to identify significance of individual groups when the Kruskal-Wallis test was significant. The Kruskal-Wallis test was also used to analyze all other natural delivery data. Statistical significance was identified where $P \leq 0.05$.

E. COMPLIANCE Signed and dated GLP and Quality Assurance statements were provided.

II. RESULTS

A. SYSTEMIC (PARENTAL) TOXICITY

1. Mortality and clinical signs:

Mortality - In the P_1 generation, one male at 250 and one at 500 ppm were found dead during the premating period (days 106 and 120, respectively). The deaths did not appear to be treatment-related since a dose-response was not observed. There was no mortality among P_1 females.

In the F_{1b} generation, two males at 1000 ppm were found dead on days 37 and 44 postweaning. Cause of death in these animals was not determined, but they were considered possibly treatment-related since they occurred only at the high dose and since postweaning pup mortality was also increased at that dose. One F_{1b} female died on day 23 of presumed F_{2b} gestation, apparently from complications during delivery. The relationship of this death to treatment is unclear.

Clinical signs - No treatment-related clinical signs were observed among P_1 or F_{1b} parental males or females. Sporadically effects observed among all treatment and

control groups included alopecia, chromorhinorrhea and chromodacryorrhea.

2. Body weight:

P_1 males - No treatment-related effects were observed. Sporadic statistically significant decreases in mean body weight observed at 500 ppm during days 8-15 and an increase at 1000 ppm during days 162-165 were not considered effects of treatment.

P_1 females - During the F_{1a} gestation period, females at 1000 ppm showed slight decreases in mean body weight gain during gestation (5.4% less than controls, Days 1 - 20) and lack of weight gain during days 1-4 of lactation (see Appendix 1). Body weight and weight gain were comparable by the end of lactation. The study authors considered the decreases secondary to reduced litter size and weight at this dose.

F_1 males - At 1000 ppm, statistically significantly lower mean body weight (4% to 7% less than controls) for the first 36 days post-weaning was observed (see Appendix 2 of DER). However, this decrease was due to reduced birth/lactation weight, resulting in lower body weight at Day 1 post-weaning. Mean body weight gain was comparable to controls during this time except during Days 8 - 15 (10% less than controls). Mean body weight was comparable to controls by the end of premating.

F_1 females - At 1000 ppm, significantly decreased mean body weight (6.5% less than controls) was observed on Day 8 postweaning and significantly decreased body weight gain during Days 1 - 8 (7% less than controls). This appeared to be related to reduced pup weight during lactation (Appendix 2). The decrease did not persist throughout premating and body weight gain during premating was comparable to controls. There were no treatment-related effects observed during either F_{2a} or F_{2b} gestation or lactation, except for an initial body weight decrement on Days 1-4 of F_{2a} lactation in the 1000 ppm group (see Appendix 3).

3. Food consumption:

P_1 males - No treatment-related effects on food consumption were observed. A statistically significant increase in the 500 ppm group between days 64 - 71 was not considered toxicologically significant.

P_1 females - No treatment-related effects were observed during premating or gestation. Throughout F_{2a} lactation at 1000 ppm, food consumption was statistically significantly decreased (13 to 17% less than controls; see Appendix 4). During F_{2b} lactation, slight decreases were also observed at 1000 ppm but were not significant ($< 10\%$ less than controls; data not shown). Decreases in food consumption during lactation in this and

subsequent litters were probably related to reduced nutritional demands from smaller litter size.

F_{1b} males - No treatment-related effects on food consumption were observed. Slight but statistically significant increases (less than 10%) were observed at 1000 ppm during the first several weeks of post-weaning, which the study authors considered secondary to decreased body weight at the start of premating (data not shown). Small, statistically significant increases were also seen at 500 ppm but were not considered effects of treatment.

F_{1b} females - No treatment-related effects on food consumption were observed during F_{2a} or F_{2b} premating or gestation. A slight but statistically significant increase (7% above controls) between days 8 - 22 of premating at 1000 ppm was not considered of toxicological significance. A slight but statistically significant decrease in food consumption during F_{2a} lactation (< 10%) was observed at 1000 ppm (see Appendix 3) and was probably due to reduced nutritional demands of the smaller litters.

4. Test Substance Intake: Based on food consumption, body weight and dietary analyses results, average doses expressed as mg test substance/kg body weight were calculated by the study author. Average compound intake during the pre-mating period is shown below in Table 4:

TABLE 4: AVERAGE TEST COMPOUND INTAKE (MG/KG/DAY) DURING PREMATINGS[1]

	CONCENTRATION OF RESMETHRIN IN DIET			
Premating period:	0 ppm	250 ppm	500 ppm	1000 ppm
P_1 males Days 1-80	0	16.6	33.5	67.0
Days 106-165	0	11.6	23.5	47.0
P_1 females Days 1-80	0	20.2	40.1	81.1
P_1 Premating Average	0	17.2	34.3	69.1
F_1 males Days 1-99	0	15.6	31.8	64.2
Days 127-176	0	11.4	22.8	46.3
F_1 females Days 1-99	0	21.5	43.3	89.7
P_1 Premating Average	0	17.5	35.3	72.5
P_1/F_1 COMB. TIME-WEIGHTED AVG.	0	17.4	34.8	70.8

1 Data taken from Tables B1, C1, D1, E1 of study report

Mean test compound intake was higher in females than males by about 30% during the premating intervals, and also greater for males in the first premating period compared to the second period (age-related decrease). Test compound intake of females during the interval between first and second matings was not determined.

Average test compound consumption during gestation and lactation is shown below in Table 5:

TABLE 5: AVERAGE COMPOUND CONSUMPTION (MG/KG/DAY), GESTATION AND LACTATION[1]

	CONCENTRATION OF RESMETHRIN IN DIET			
	0 PPM	250 PPM	500 PPM	1000 PPM
Gestation F_{1a} (Days 1-20)	0	18.2	36.2	73.9
F_{1b}	0	15.4	31.4	63.5
F_{2a}	0	15.9	32.0	67.9
F_{2b}	0	15.8	30.2	62.4
COMBINED GESTATION AVG.	0	16.3	32.5	66.9
Lactation F_{1a} (Days 1-14)	0	33.6	66.9	117.1
F_{1b}	0	30.8	58.0	109.4
F_{2a}	0	31.3	61.4	116.5
F_{2b}	0	29.6	53.6	122.9
COMBINED LACTATION AVG.	0	31.3	60.0	116.5

1 Data taken from Tables C2, C3, E2, E3 of study report

Test compound intake was similar among all generations during gestation. During the F_{1a} gestation period, dams at 1000 ppm consumed slightly more test compound (~16%) than during the F_{1b} gestation period, particularly during the first several days. At 1000 ppm, F_{1a} gestation compound consumption was slightly greater than F_{2b} gestation, but only by about 8%. Average daily intake was greatest during the lactation periods due to the increased nutritional demands of nursing. Lactation values were also comparable for all generations at 1000 ppm, although the F_{1a} and F_{2b} generations showed overall slight increases (5 to 8%). Average daily intake at each dose was proportional to the increment (2X) in the dietary concentration.

5. Necropsy results

a) Organ weights: No treatment-related effects on organ weights (reproductive organs, brain, pituitary, liver) were reported. The study authors noted a statistically significant increase in mean absolute brain weight of the high-dose P_1 males (mean brain weights, 2.17, 2.23, 2.21 and 2.25 g at 0, 250, 500 and 1000 ppm, respectively). However, TB-I agreed with their conclusion that this was not treatment-related due to the small magnitude of the difference (3.7%), lack of significant relative organ weight increase and absence of this finding in P_1 females or in F_{1b} males or females.

b) Pathology

1) Macroscopic examination: The report noted no observations that were related to the administration of the test substance in any of the parental animal groups.

2) Microscopic examination: The report noted no microscopic observations that were related to the administration of the test substance in the reproductive organs, liver (F_{1b} only examined) or pituitary gland of any of the parental (P_1 or F_{1b}) animal groups. Non-treatment related lesions observed in both control and high dose adult animals of both the P_1 and F_{1b} generations included chronic interstitial prostatitis, testicular atrophy, pigmented macrophage in uterus, cystic endometrial glands, hepatocellular vacuolization or focal necrosis of the liver (F_{1b} males) and vacuolization of pars distalis of the pituitary in F1b males.

B. REPRODUCTIVE AND OFFSPRING TOXICITY

1. Mating and fertility performance of P_1 and F_1 parental animals: Mating and fertility parameters of the F_1 generation parental animals are shown below in Table 6 for both litter groups:

Table 6: P_1 Male and Female Mating and Fertility Indices[1]

Observation	Dose group: Control	Low	Mid	High
P_1 Parents, first cohabitation				
Males				
Number cohabited	30	30	30	30
Precoital interval (days)	3.4	3.0	3.7	3.4
Mating index	100.0	100.0	93.3	96.7
Fertility index	96.7	96.7	100.0	93.1
Females				
Number cohabited	30	30	30	30
Precoital interval (days)	3.4	3.0	3.9	3.5
Mating index	100.0	100.0	100.0	100.0
Fertility index	96.7	96.7	93.3	90.0
P_1 Parents, second cohabitation				
Males				
Number cohabited	30	29[2]	29[2]	30
Precoital interval (days)	3.8	3.6	2.9	4.2
Mating index	90.0	100.0	100.0	86.7
Fertility index	81.5	75.9	75.9	76.9
Females				
Number cohabited	30	30	30	30
Precoital interval (days)	4.0	3.6	3.0	5.0
Mating index	100.0	100.0	100.0	93.3
Fertility index	80.0	76.7	73.3	78.6
F_1 Parents, first cohabitation				
Males				
Number cohabited	30	30	30	28[2]
Precoital interval (days)	6.1	4.0	4.2	4.0
Mating index	86.7	93.3	100.0	89.3
Fertility index	76.9	92.8	76.7	92.0
Females				
Number cohabited	30	30	30	30
Precoital interval (days)	6.1	3.9	4.2	5.4
Mating index	96.7	96.7	100.0	90.0
Fertility index	79.3	93.1	76.7	92.6
F_1 Parents, second cohabitation				
Males				
Number cohabited	30	30	30	28[2]
Precoital interval (days)	3.8	3.1	4.9	6.3
Mating index	93.3	93.3	86.7	64.3**
Fertility index	85.7	85.7	92.3	77.8
Females				
Number cohabited	30	30	30	30
Precoital interval (days)	4.3	3.6	5.3	8.0
Mating index	93.3	93.3	100.0	76.7**
Fertility index	85.7	85.7	86.7	78.3

1 Data from Tables B11, B12, C19, C20, D11, D12, E19 and E20 of study report
2 Excludes animals found dead during premating or postweaning periods
** $p < 0.01$

During the second F_1 cohabitation, both sexes showed slightly increased time to mating and significantly decreased mating index at 1000 ppm. Mating was not affected during any other cohabitation period. Fertility was unaffected by treatment.

2. Gestation observations: Gestation/litter observations are summarized below in Table 7:

TABLE 7 Reproductive Performance: Gestation and Litter Parameters[1]

Observation	Dose group: Control	Low	Mid	High
	F_{1a} Generation			
Gestation length, days	22.8	22.6	22.7	22.7
Gestation index	100.0	100.0	100.0	100.0
Number of litters, Day 1	29	29	28	27
Mean litter size, Day 1	13.8	13.7	14.6	13.1
Liveborn pups/litter	13.7	13.6	14.2	12.7
Total stillborn pups (%)	2 (0.5)	3 (0.8)	9 (2.2)	12 (3.4)
Stillborn pups/litter	0.1	0.1	0.3	0.4
Litters with stillborn pups (%)	2 (6.9)	3 (10.3)	4 (14.3)	5 (18.5)
Total litter losses at birth	0	0	0	0
Total litter losses by Day 21 (%)	0	0	0	2 (7.4)
Total liveborn pups, Day 1	398	394	399	343
Total live pups, Day 4 pre-cull	392	385	386	228
Total live pups, Day 21	230	229	224	168**
Total pup deaths, Day 1	2	3	3	13**
Days 2-4	4	6	10	102**
Days 5-7	0	0	0	0
Days 8-14	0	0	0	1
Days 15-21	1	0	0	1
Days 1-21	7	9	13	116**
Liveborn index	99.5	99.2	97.9	96.6
Viability index	98.5	97.7	96.7	66.5**
Lactation index	99.6	100.0	100.0	99.4
Mean pup weight (g), Day 1	6.1	5.9	5.8	5.6**
Mean pup weight (g), Day 21	43.3	42.0	40.3**	37.3**
Mean wt. gain (g) - Day 1-21[2]	37.2	36.1	34.5	31.7
Male:female ratio	48.6	53.3	54.1	48.6

1 Data taken from Tables C19, C21 and C23 of study report
2 Body weight gain calculated by reviewer; not analyzed statistically
* $p<0.05$. ** $p<0.01$.

TABLE 10 Reproductive Performance: Gestation and Litter Parameters (cont.)

Observation	Dose group Control	Low	Mid	High
	F_{1b} Generation			
Gestation length, days	22.9	22.8	23.0	23.0
Gestation index	100.0	100.0	100.0	100.0
Number of litters, Day 1	24	23	22	22
Mean litter size, Day 1	13.5	14.2	12.2	12.8
Liveborn pups/litter	13.3	14.1	12.0	12.5
Total stillborn pups (%)	4 (1.2)	3 (0.9)	1 (0.4)	5 (1.8)
Stillborn pups/litter	0.2	0.1	0.0	0.2
Litters with stillborn pups (%)	3 (12.5)	1 (4.3)	1 (4.5)	4 (18.2)
Total litter losses at birth	0	0	0	0
Total litter losses by Day 21 (%)	0	0	1 (4.5)	2 (9.1)
Total liveborn pups, Day 1	320	324	265	275
Total live pups, Day 4 preculling	309	318	260	225
Total live pups, Day 21	186	182	160	144
Total pup deaths, Day 1	4	2	2	13**
Days 2-4	7	4	3	37**
Days 5-7	0	0	0	2
Days 8-14	0	0	0	1
Days 15-21	0	0	0	1
Days 1-21	11	6	5	54**
Liveborn index	98.8	99.1	98.9	97.5
Viability index	96.6	98.1	98.1	81.8**
Lactation index	100.0	100.0	100.0	97.3**
Mean pup weight (g), Day 1	6.1	6.0	6.2	5.7
Mean pup weight (g), Day 21	47.8	49.0	48.0	43.8
Mean wt. gain (g) - Day 1-21[2]	41.7	43.0	41.8	38.1
Percent male pups, Day 1	48.6	53.3	54.1	48.6

1 Data taken from Tables C20, C22 and C24 of study report
2 Body weight gain calculated by reviewer; data not analyzed statistically
* $p<0.05$. ** $p<0.01$.

TABLE 7 Reproductive Performance: Gestation and Litter Parameters (cont.)[1]

Observation	Dose group Control	Low	Mid	High
	F_{2a} Generation			
Gestation length, days	22.9	22.8	23.0	22.9
Gestation index	100.0	100.0	100.0	100.0
Number of litters, Day 1	23	27	23	25
Mean litter size, Day 1	12.9	13.4	13.1	13.7
Liveborn pups/litter	12.8	13.2	13.0	13.3
Total stillborn pups (%)	2 (0.7)	5 (1.4)	1 (0.3)	6 (1.8)
Stillborn pups/litter	0.1	0.2	0.0	0.2
Litters with stillborn pups (%)	2 (8.7)	2 (7.4)	1 (4.3)	5 (20.0)
Total litter losses at birth	0	0	0	0
Total litter losses by Day 21 (%)	1 (4.3)	1 (3.7)	0	2 (8.0)
Total liveborn pups, Day 1	294	358	300	333
Total live pups, Day 4 preculling	291	337	286	181**
Total live pups, Day 21	166	200	180	131
Total pup deaths, Day 1	0	9*	4	15**
Days 2-4	3	12	10	137**
Days 5-7	9	5*	0	1**
Days 8-14	0	0	0	2**
Days 15-21	0	1	2	2
Days 1-21	12	27	16	157**
Liveborn index	99.0	98.6	99.3	97.4
Viability index	99.0	94.1	95.3	54.4**
Lactation index	94.8	97.1	98.9	96.3
Mean pup weight (g), Day 1	6.0	6.0	5.8	5.5**
Mean pup weight (g), Day 21	46.0	42.3*	44.0	41.6**
Mean Wt. gain (g) - Day 1-21[2]	40.0	36.3	38.2	36.1
Percent male fetuses, Day 1	48.2	51.8	50.2	47.5

1 Data taken from Tables E19, E21 and E23 of study report

2 Body weight gain calculated by reviewer; data not analyzed statistically

* $p<0.05$ ** $p<0.01$

TABLE 7 Reproductive Performance: Gestation and Litter Parameters (cont.)[1]

Observation	Dose group: Control	Low	Mid	High
	F_{2b} Generation			
Gestation length, days	23.0	23.0	23.2	23.0
Gestation index	100.0	95.8	100.0	94.4
Number of litters, Day 1	23	27	23	25
Mean litter size, Day 1	14.2	12.7	11.8	13.8
Liveborn pups/litter	14.0	12.5*	11.3*	13.7
Total stillborn pups (%)	3 (0.9)	4 (1.4)	12 (3.9)**	2 (0.8)
Stillborn pups/litter	0.1	0.2	0.5**	0.1
Litters with stillborn pups (%)	1 (4.2)	2 (8.7)	6 (23.1)	2 (11.8)
Total litter losses at birth	0	0	0	0
Total litter losses by Day 21 (%)	2 (8.3)	0	1 (3.8)	0
Total liveborn pups, Day 1	337	287	295**	233
Total live pups, Day 4 preculling	312	284	279	196**
Total live pups, Day 21	174	180	183	135
Total pup deaths, Day 1	1	0	2	5**
Days 2-4	24	3*	14	32**
Days 5-7	0	0	2	1
Days 8-14	0	0	0	0
Days 15-21	0	0	1	0
Days 1-21	25	3*	19	38**
Liveborn index	99.1	98.0	96.1**	99.1
Viability index	92.6	99.0*	94.6	84.1**
Lactation index	100.0	100.0	98.6	99.3
Mean pup weight (g), Day 1	5.9	6.1	6.2	5.6
Mean pup weight (g), Day 21	49.1	47.9	49.1	44.1**
Wt. gain (g) - Day 1-21[2]	43.2	41.8	42.9	38.5
Percent male pups, Day 1	52.6	52.3	54.4	50.5

1 Data taken from Tables E20, E22 and E24 of study report
2 Body weight gain calculated by reviewer; not analyzed statistically
* $p<0.05$ ** $p<0.01$

Gestation and birth parameters: Gestation index, gestation length and number of litters produced were not affected by resmethrin up to 1000 ppm. The number of stillborn pups and litters containing stillborn pups showed slight, non-statistically significant

increases at 1000 ppm in the F_{1a} and F_{2a} litter generations, resulting in very slightly decreased liveborn indices. TB-I considered this a possible effect of treatment, since the decrease in viability index was pronounced in these generations (including deaths on Day 1 postpartum) and since birth weights were also decreased (decreased live births were also reported in the range-finding study at 1000 ppm). In the F_{2b} generation, a statistically significant increases in the number of stillborn pups was observed at 500 ppm. TB-I agreed with the study author that the increase was probably not related to treatment since no dose response was observed (pup weights were also not affected at that dose).

3. Offspring toxicity

a. Viability and clinical signs:

Viability during lactation was significantly reduced among pups in the 1000 ppm groups of all four offspring groups. Decreased viability was more pronounced in the first (a) litters of both the F_1 and F_2 generations (decreased by 33 - 45% compared to controls) than in the second (b) litters (decreased by 9 - 15%). This effect may have been related to slightly greater compound consumption among the dams during gestation and lactation of the "a" generations. Lactation index was unaffected by treatment.

Clinical signs - No treatment-related clinical signs were observed among offspring of the F_1 and F_2 generations.

b. Body weight: Statistically significant reductions of about 8% in mean pup birth weight were observed in the F_{1a} and F_{1a} offspring groups at 1000 ppm. Smaller, non-significant effects (5 to 7% decrease) were also observed in the "b" offspring groups and were probably a marginal effect of treatment. The decrease may have been greater in the "a" offspring because of slightly greater compound intake of the dams during gestation.

Mean body weight and weight gain were also decreased at 1000 ppm on day 21 postpartum (end of lactation) in the F_{1a}, F_{1b}, F_{2a} and F_{2b} offspring by 15%, 8%, 10% and 10%, respectively. Decreases were statistically significant for all but the F_{1b} offspring; body weight gain data were not analyzed statistically.

c. Necropsy results: No treatment-related macroscopic lesions or abnormalities were reported. Skull sections did not show any effect of treatment on the incidence of hydrocephalus.

III. DISCUSSION

A. SYSTEMIC TOXICITY: In general, TB-I agreed with the conclusions of the study author. The results of this study suggest that nursing and young rats may be more sensitive to resmethrin than mature adult rats. The effects on body weight appeared to be either the result of toxicity in the young (nursing) animals, or in gestating/lactating dams, secondary to effects on litter size/weight. No toxicity was observed among P_1 males or females during either premating interval, and the small decreases in maternal body weight at 1000 ppm during late gestation and Days 1 - 4 of gestation were probably related to the reduced size of the litters at that dose. In the F_{1b} rats used for mating, the reduction in body weight during the first week(s) postweaning was primarily related to the reduced body weights at birth and during lactation. The two males that died during the study also died shortly after weaning (Days 37 and 44). The slight decreases in maternal food consumption relative to controls during several of the lactation periods were probably due to reduced milk production burden from reduced litter size. The minimal toxicity observed in adult rats at the doses tested in this study is consistent with results of other studies on rats which tested at similar dose levels (developmental, chronic).

B. REPRODUCTIVE AND LITTER TOXICITY: Resmethrin at 1000 ppm in the diet caused a pronounced decrease in pup survival (decreased viability index) and pup body weight in all litter generations, and possibly a slight increase in stillborn pups in the first litters of each generation. Toxicity was slightly greater in the first (a) litter of each generation, possibly due to slightly increased compound intake by the dams during the first gestation periods. The toxicity observed in pups from the 1000 ppm group suggests that the offspring may be affected both in utero, as evidenced by reduced birth weight and possible increases in stillbirths, as well during lactation, suggested by the decreased body weights of surviving pups on Day 21 postpartum. TB-I notes that a metabolite of resmethrin is found in the milk of goats given resmethrin. The mating index, but not fertility or gestation indices, of F_{1b} rats was reduced during the second cohabitation period.

C. STUDY DEFICIENCIES: No significant deficiencies were identified.

D. CORE CLASSIFICATION: Core-Guideline
Maternal NOEL = 500 ppm (34.8 mg/kg/day, premating average)
Maternal LOEL = 1000 ppm (70.8 mg/kg/day, premating average), based on marginal decreases in body weight or weight gain of P_1 females during gestation and lactation and of F_{1b} males and females during early postweaning and possible mortality of postweaning F_{1b} males.
Reproduction/Offspring Toxicity NOEL = 500 ppm (34.8 mg/kg/day)
Reproduction/Offspring Toxicity LOEL = 1000 ppm (70.8 mg/kg/day), based on decreased viability index and pup weight in all generations, decreased mating index during the F_{2b} cohabitation and possible increase in stillborn pups in the F_{1a} and P_{1a} offspring.

RESMETHRIN

Page_____ is not included in this copy.

Pages 123 through 129 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Draft

3-GENERATION REPRODUCTION STUDY IN RATS/FDRL #5739; 1979 - The following information is supplied as supplemental information for the original DER for this study. A finalized supplemental DER will be prepared following review by the RfD.

EPA Reviewer: Linnea J. Hansen, Ph.D. Date 10/5/94
Review Section IV, Toxicology Branch I (7509C)
EPA Section Head: Marion P. Copley, D.V.M., D.A.B.T. Date 10/5/94
Review Section IV, Toxicology Branch I (7509C)

DATA EVALUATION RECORD
Supplemental DER to HED Doc. Nos. 001908 and 002266)
#2

STUDY TYPE: Multigeneration Reproduction - 3-Generation Study in Rat (83-4)

TOX. CHEM. NO.: 083E

P.C. CODE: 097801

MRID NO.: 00081276

TEST MATERIAL: SBP-1382®, technical

SYNONYMS: Resmethrin; 5-benzyl-furylmethyl (IRS)-cis,trans-chrysanthemate

STUDY NUMBER: 5739

SPONSOR: Roussel Bio Corporation, Lincoln Park, NJ (at time of submission, S.B. Penick, Lyndhurst, NJ)

TESTING FACILITY: Food and Drug Research Laboratories, Inc.

TITLE OF REPORT: The Evaluation of the Effects of SBP-1382® Following Dietary Administration Through Three Generations in Sprague-Dawley Rats.

AUTHOR: Charles S. Schwartz, B.S., Larry Gephart, M.P.H., Peter J. Becci, Ph.D. and Richard A. Parent, Ph.D.

REPORT ISSUED: July 13, 1979

EXECUTIVE SUMMARY: (To be completed following review by RfD Committee; summary below reflects the conclusions of the original DER):

Doses tested: 0, 500, 800 or 1250 ppm resmethrin in diet (approximately 0, 25, 40 or 62.5 mg/kg/day), continuously to male and female Wistar rats during a 3-generation

reproduction study.

Maternal (systemic) toxicity NOEL: 500 ppm
Maternal (systemic) toxicity LOEL: 800 ppm, based on depression of mean body weight in F_0 and F_1 males and females during pre- and/or intermating periods. At 1250 ppm, depression of body weight was also observed in pregnant dams during the F_{2a} and F_{3b} gestation periods.

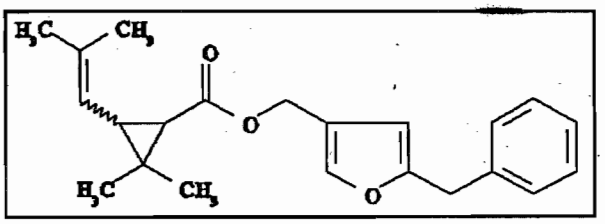
Reproductive/offspring toxicity NOEL: Less than 500 ppm (lowest dose tested).
Reproductive/ offspring toxicity LOEL: 500 ppm, based on slight decreases in mean pup weight by Day 21 of lactation (F_{1a}, F_{1b}, F_{3a} generation litters) and possible increase in stillborn pups in the F_{3b} generation litter at all doses. At 800 and 1250 ppm, dose-dependent decreased viability index, decreased pup birth weight and increased stillborn pups were also observed in most or all generation litters.

Classification: Core-Minimum

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: SBP-1382® (resmethrin), technical
   Description: brown crystalline solid
   Lot/Batch #: 8176-RT
   Purity: 90%
   Stability of compound: Stable at room temperature when stored in dark (information taken from 1-year dog feeding study)
   CAS #: 10453-86-8
   Structure



2. Vehicle: Mazola® corn oil

3. Test animals: Species: Rat
   Strain: Sprague-Dawley BLU (SD)
   Age/wt. at receipt: Weanling/approx. 50 g
   Source: Blue Spruce Farms Inc., Altamont, NY

131

Housing and Environmental conditions: Housed individually (except during mating) according to standard FDRL procedures and NIH laboratory animal guidance (NIH-78-23); no further details provided.

Acclimation period: about 8 days

4. Diet preparation and analysis: Diet was prepared weekly by melting the test substance at 100°C, mixing with Mazola® corn oil and combining appropriate amounts of test substance with diet to give a 10% premix, which was used to prepare the three test dietary concentrations. Treated diets were stored at room temperature in plastic bags.

   Test compound concentration in the diet was analyzed in samples taken at 3-month intervals. Stability of the test compound in diet under environmental conditions was tested at each concentration by removing samples of a test diet preparation from feeders daily for 1 week. Duplicate samples were analyzed using gas chromatography methods.

   Results - Homogeneity Analysis: Not conducted.

   Stability Analysis: After 1 week, slight decreases in the concentration of test compound in diet were observed at 500, 800 and 1250 ppm ($\leq 10\%$).

   Concentration Analysis: When adjusted for recovery, analytically determined dietary concentrations were within 10% of target concentration except for the initial sampling of the 500 and 800 ppm diets, where concentrations were 78% and 86%.

5. Animals received food (Agway Charles River RMH Commercial Laboratory Chow) and water ad libitum.

B. STUDY DESIGN AND MATING PROCEDURES

1. Animal assignment: P_1 animals were randomly assigned to test groups shown below:

TABLE 1 **Animal Assignment: P1 Generation**

Test No.	groups Designation	Dose (ppm)[1]	Animals per group[2] Males	Females
1	Control	0	20	20
2	Low (LDT)	500	20	20
3	Mid	800	20	20
4	High (HDT)	1250	20	20

1 Diets were administered from the beginning of the study until the animals were sacrificed.

2 The same number of animals were picked from the F_{1a} litters as parents for the F_2 generation.

132

2. Mating procedure: One male and one female were placed (random assignment) in the male's cage for up to 7 days. Females were examined daily for evidence of mating and those females with copulatory plugs were removed to their individual cage. The day on which evidence of mating was observed was designated Day 0 of gestation. Any female showing no evidence of mating after 7 days was placed with another male for up to 7 days. Females that did not mate after cohabitation with 3 males were not included in the study. Dams with vaginal plugs that did not show large weight gain indicative of pregnancy on Day 8 of presumed gestation were remated and recording of gestation weights continued according to both mating dates until determination of actual successful mating date was made (eg. second vaginal plug, body weight gain).

3. Mating schedule: Matings were conducted with males and females from the F_0 parental generation and with animals culled from the F_{1a} and F_{2a} generations (at least 1/sex/litter), avoiding sibling matings. For the F_0 generation matings, males and females were cohabited after 10 weeks' administration of test diet at the appropriate dietary dose levels. The second mating of F_0 animals was conducted following a 2-week rest period after weaning of F_{1a} pups.

   For the F_{1a} and F_{2a} parental animals, cohabitation was initiated after 8 weeks post-weaning. The second mating period was initiated after a rest period of 2 weeks after weaning of the F_{2a} or F_{3a} generation pups.

4. Culling of litters and selection of F_1 parental animals: All litters larger than 8 pups were culled to 8 on Day 4 postpartum. Whenever possible, equal numbers of males and females were retained in a litter. From the remaining F_{1a} and F_{2a} pups, 20 males and 20 females/dose level were randomly selected on Day 21 postpartum and used for the second- and third-generation matings.

5. Dose selection rational: No information provided.

C. METHODS

1. Observation Schedule

   a. Parental animals: Observations and the schedule for those observations are summarized below in Table 2.

TABLE 2: Observation Schedule

Viability and clinical signs:	1X/day
Body weight and food consumption	
F_0 Premating:	Weekly, first 10 weeks of study
F_0 Mating Interval:	Weekly, 2 week interval between F_{1a} weaning and second mating
F_{1a} and F_{2a} Premating:	Weekly, 8 week interval between weaning and mating
F_{1a} and F_{2b} Mating Interval:	Weekly, 2 week interval between F_{2a}/F_{3a} weanings and second matings
Mating:	not recorded
Gestation:	Days 0, 8, 15 and 19; body weight only on day 25
Lactation:	Days 28, 35 and 42 after presumed Day 0 of gestation

b. Reproductive performance: Parental reproductive performance was assessed from breeding and parturition records of animals in the study. The following indices were calculated:

$$\text{Male fertility index} = \frac{\text{No. females pregnant}}{\text{No. males mated}} \times 100$$

$$\text{Female fertility index} = \frac{\text{No. females presumed pregnant}}{\text{Total no. females mated}} \times 100$$

$$\text{Gestation index} = \frac{\text{No. live litters born}}{\text{No. confirmed pregnancies}} \times 100$$

c. Litter observations: The following litter observations were made:

TABLE 3 F1/F2 Litter Observation Schedule

Number of live pups:	At Birth and Lactation Days 1,4,21
Pup weight:	At Birth and Lactation Days 1,4,21
External alterations:	At Birth and Lactation Days 1,4,21
Number of dead pups:	At Birth and Lactation Days 1,4,21
Sex of each pup (m/f):	At Birth and Lactation Days 1,4,21

The following litter indices were calculated:

$$\text{Stillborn index} = \frac{\text{No. stillborn pups}}{\text{No. live + dead pups born}} \times 100$$

$$\text{Viability index} = \frac{\text{No. live pups at day 4}}{\text{No. pups born alive}} \times 100$$

$$\text{Lactation index} = \frac{\text{No. live pups at day 21}}{\text{No. pups born alive}} \times 100$$

d. Necropsy

1) Parental animals: All surviving parental P_1 and F_1 males were sacrificed as soon as possible after the second litters were produced in that generation. Maternal animals were sacrificed on Day 21 postpartum after the last litter of each generation was weaned. Females that did not bear young were sacrificed on Day 21 of presumed gestation. All animals were sacrificed by chloroform anesthesia.

Necropsy observations: The only animals given post-mortem gross or microscopic examinations were the F_{2a} males and females. Gross examinations were performed. The following tissues (X) were preserved in 10% buffered formalin (but not examined microscopically):

Reproductive organs:

X Ovaries	X Epididymides
X Uterus	X Prostate
X Vagina/cervix	X Seminal vesicles/coagulating gland
	X Testes

Other organs/tissues:

X Brain	X Eyes
X Liver	X Pituitary gland
X Stomach	X Spleen
X Pancreas	X Thyroid
X Large intestine	X Parathyroids
X Small intestine	X Adrenals
X Heart	X Gross lesions
X Kidneys	X Lungs
X Urinary bladder	

2) Offspring: Culled offspring from each litter generation were sacrificed on Day 4 postpartum. The offspring maintained through lactation and not selected as parental animals were sacrificed at 21 days of age. All sacrifices were by chloroform anesthesia. All pups were discarded after sacrifice.

D. STATISTICAL ANALYSIS: Body weight, food consumption and continuous reproductive data were evaluated by ANOVA (one-way). Discrete data were evaluated by binomial expansion methods. When dose responses were evident, they were evaluated by partitioning the treatment variance to yield variance due to linear regression as described by Remington and Schork. Significance was identified where $p \leq 0.05$.

II. RESULTS See original DER

Attached tables The following tables taken from the study report provide information not included in the original DER:

- Selected mean parental body weights, pre- or intermating (statistically significant decreases);
- Dam mean body weight, F_{2a} and F_{3b} gestations (statistically significant decreases);
- Dam mean body weight gain, all generations;
- Litter observations, all generations;
- Pups cast dead, all generations;
- Viability index, all generations

RESMETHRIN

Page_____ is not included in this copy.

Pages 137 through 153 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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

002266

MEMORANDUM NOV 5 1982

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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.

154

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

156

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.

11/4/82

John Doherty, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769)

11/4/82

Attachment

OPP:HED:TOX: J.DOHERTY:sb 12/7/81 rew:10/29/82 X73711 #m7

157

Caswell 00E

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

002266

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: October 21, 1982

TO: Edwin R. Budd and John Doherty
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: FAP 9H5210 and EPA Reg. No. 432-487
Statistical Review of Thomas E. Norwood Re-analysis
3-Generation Rat Reproduction Study with Resmethrin

The techniques currently used to analayze multigeneration reproductive studies are inadequate in that they fail to consider the study as a unified entity that is to say that the design of the study is not used as the basis for statistical analysis. For each measure of success, say mortality by the end of day 4, the statistic used should include results from each generation. This review is not the place to make new policy, and therefore Dr. Norwood's use of mathematical extrapolation of study data to zero-respond levels is not admissable. Even if the policy were acceptable, no evidence is furnished to establish that the log-probit is an appropriate model for any of the study responses.

The technique used by Dr. Norwood to estimate standard errors is reasonable, at least for proportion of pups cast dead or dead by end of day 4 and here we agree that the suggested method seems appropriate. It is less clear that this applies equally well to continuous data. The use of 'T tests' in this sort of experiment is less than optimal. TOX Branch accepts the use here as prevailing state-of-the-art. On that basis any single $p = .05$ might be a chance occurrence as we expect approximately 5 false positives out of 100 independent tests. But 2 tests on the same parameter would be $.05 \times .05 = .0025$ or a very rare event indeed. In this experiment Dr. Norwood shows in Table V that the mean body weight for pups at weaning, or 21 days, was statistically significantly lower in the 500 ppm Resmethrin fed animals in the F1B (52.9 ± 1.3) and the F3A (49.3 ± 1.3) generations compared to the control animals (56.5 ± 1.2 and 53.9 ± 0.8 respectively).

158

No other findings at the 500 ppm dose level are reported to be statistically significant. In so far as it is possible to verify what was done I concur with the results of Dr. Norwood's individual statistical tests for the data from this Resmethrin 3-generation study in rats.

Bertram Litt, Statistician
Toxicology Branch
Hazard Evaluation Division

BLitt/ccw 10/21/82 #8

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: November 28, 1979

001908

SUBJECT: EPA Reg. No. 432-487, Three-Generation Reproduction Study (Rats) with Resmethrin (SBP-1382 Technical). Caswell #83E

FROM: John Doherty 11/29/79
Toxicology Branch/HED (TS-769)

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

Action Requested:

Review three-generation reproduction study with resmethrin (technical) and determine if study meets EPA standards to support the safety of resmethrin. This study is in EPA accession #240984.

Conclusion:

1. The study has been reviewed and classified as CORE GUIDELINES.

2. The data in the study do not support a NOEL of 500 ppm (the lowest dose level tested). Statistically significant increases in percent of F3B pups cast dead and decreases in the mean body weights of the pups at weaning were observed at the 500 ppm dose level.

3. EPA regulations require that a NOEL be established for a reproduction study. Therefore, a second study will have to be submitted in order to establish a NOEL.

Detailed Review of Study:

The Evaluation of the Effects of SBP-1382 Following Dietary Administration Through Three-Generations in Sprague-Dawley Rats.

Food and Drug Research Laboratories; July 13, 1979. (Laboratory No. 5739).

Protocol:

Four groups of 20 male and 20 female rats each were given diets containing 0, 500, 800 or 1250 ppm of resmethrin (technical contained 90% active ingredient). These groups were labelled the F0 generation and were mated to produce first an F1A generation and were subsequently remated to produce a F1B generation. Twenty rats per sex were selected from the F1A group to be mated to produce F2A and F2B generations. Twenty rats per sex from the F2A generation were mated to produce F3A and F3B generations.

43

160

Results:

1. Fertility indexes and gestation indexes did not show compound related effects at any dose.

2. Viability indexes (pups that survived to 4 days) were adversely affected at 800 ppm and 1250 ppm - being more serious at 1250 ppm.

3. Lactation indexes, as indicated by both pup survival to 21 days and by dam efficiency, were not affected at any test dose.

4. Mean litter size at birth (number of pups per litter) was not affected at 500 ppm. At 800 ppm, the F1B litter was depressed. At 1250 ppm, F1B, F2A and F3A litters were depressed.

5. Pups cast dead. The 500 ppm group had a single incidence of a statistically significant increased parameter for the F3B generation. This was in a progression of 1.2% (3/244 for 0 ppm), 4.3% (12/282 for 500 ppm), 4.5% (11/246 for 800 ppm) and 7.7% (19/246 for 1250 ppm). At 800 and 1250 ppm all generations except F3A for 800 ppm were statistically increased over the controls. This significant difference and obvious trend does not support a NOEL of 500 ppm. See attached table.

6. Mean litter weights at birth and at 4 days were adversely (lower weights) affected at 1250 ppm and possibly lower ~~in weight~~ at 800 ppm.

7. Mean pup weights at weaning. All litters of the 500 ppm group had lower mean pup weights at weaning than the controls (except F3B). F1A, F1B and F3A litters were statistically significantly lower. All generations in the 800 and 1250 ppm groups were also statistically significantly lower in weight. A progressive dose response decrease is supported. See attached table.

8. Mean weekly body weights and food consumption were tabulated for F0, F1A and F2A adult groups. Adverse effects (depression) were noted at 800 and 1250 ppm.

9. Mean dam body weight during lactation. Highest dose level dams only were adversely affected.

10. General observations. None are reported that do not also appear in the controls.

11. Gross pathology (on 80 males and 80 females of the F2A generation as adults). Did not reveal tumors or other gross morphologic evidence that was considered by the pathologist (George E. Cox) to be compound related.

Conclusions:

A CORE GUIDELINES study. The occurrence of statistically significant deviations related to an increase in pups cast dead and lower mean pup weights at weaning in the 500 ppm group prevent Toxicology Branch concurrence with the laboratory's assertion that the NOEL is 500 ppm. The NOEL is < 500 ppm.

Attachment:

EPA:OPP:HED:TOX:RD BUDD:sb 11/26/79 X77395

3

162

[RESMETHRIN, TECH.] DRAFT Developmental Study (83-3)

EPA Reviewer: Linnea J. Hansen, Ph.D.
Review Section 4, Toxicology Branch I (7509C)
EPA Section Head: Marion P. Copley, D.V.M., D.A.B.T.
Review Section 4, Toxicology Branch I (7509C)

Linnea J. Hansen, Date 6/2/94

Marion Copley, Date 6/10/94

DATA EVALUATION RECORD
(Supplement to Original Review, HED Doc. no. 001915)

STUDY TYPE:	Developmental Study - Rat (83-3a)
TOX. CHEM. NO.:	083E
P.C. CODE:	097801
MRID No.:	00028453
TEST MATERIAL:	SBP-1382, technical
SYNONYMS:	Resmethrin; 5-benzyl-3-furylmethyl (IRS)-cis,trans chrysanthemate
STUDY NUMBER:	2054-066
SPONSOR:	(at time of study) S.B. Penick Co., Orange Research Laboratory, Orange, NJ. Registrant is now Roussel Uclaf Corporation, Montvale, NJ
TESTING FACILITY:	Booz, Allen and Hamilton, Inc., Foster D. Snell Division, Florham Park, NJ
TITLE OF REPORT:	Teratologic Evaluation of SBP-1382 Technical in the Albino Rat
AUTHORS:	Richard A. Machi, B.S., Claudine Kam, M.S., Michael A. Gallo, Ph.D. and Kent R. Stevens, Ph.D.
REPORT ISSUED:	November 26, 1979

EXECUTIVE SUMMARY: In a developmental toxicity study, 25 pregnant Blu (SD) BR strain rats per dose group received 0, 20, 40 or 80 mg SBP 1382/kg/day (technical, 86.5% a.i.; dose not adjusted for purity of test material or increase in maternal body weight during treatment) in corn oil by gavage from gestation Day 6 through 15, inclusive. In addition, a group of 25 rats received 250 mg/kg/day aspirin (salicylic acid) as a positive control for developmental toxicity. Animals were received time-pregnant from the vendor, usually on Day 2 of gestation.

Maternal toxicity occurred at the highest dose tested (80 mg/kg/day) as statistically significant

decreases in mean body weight gain at Day 20 of gestation (-33% of vehicle controls) and in food consumption between Days 11-20 of gestation (-26% of vehicle controls). (Positive control group showed no significant maternal toxicity; decreased body weights were due to the sharply reduced litter size). **The maternal toxicity LOEL is 80 mg/kg/day, based on reduced body weight and body weight gain, and reduced food consumption. The maternal toxicity NOEL is 40 mg/kg/day.**

Developmental toxicity was noted in the high dose groups (80 mg/kg/day) as marginally decreased mean fetal weight (-11% of vehicle controls; not statistically significant) and an increased incidence in delayed ossification of the metacarpals and metatarsals (18% litter incidence vs. 0%, controls) and partial skull (24% litter incidence, vs 13% in controls). A marginal increase in the incidence of distal metacarpals (fetal incidence 19% vs. 7%, controls) and metatarsals (fetal incidence 34% vs. 20%, controls) was also seen. **The developmental toxicity LOEL = 80 mg/kg/day, based on increased incidence of skeletal variations and delayed ossification, and on marginally decreased fetal body weight.**

This study is classified Core-Minimum and satisfies the Guideline requirement (83-3a) for a developmental toxicity (teratology) study in rats, despite several study deficiencies (see Discussion, below).

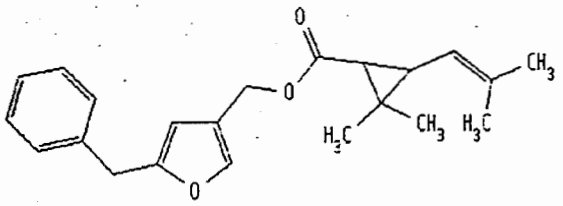
Special Review Criteria (40 CFR 154.7) None

Note: This DER supplement is intended to provide an Executive Summary and details of the study that were not included in the original DER. The conclusions of this supplemental DER supersede those of the original DER, where different.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: SBP-1382 (resmethrin)
   Description: not provided in study report
   Lot/Batch #: 9037-RB/LS#4549 (all LS lot #s assigned by laboratory)
   Purity: 85.6% a.i.
   Stability of compound: stable under storage conditions
   CAS #: 10453-86-6
   Structure



2. Vehicle and/or positive control: Corn Oil, Lot #LS4551, Supplier: Mazola. Positive control - salicylic acid, Lot #LS 4552 (supplier not indicated in study report).

3. Test animals: Species: Rat
Strain: BLU: (SD) BR
Age and weight at study initiation: about 13 weeks/197-300 g (females)
Source: Blue Spruce Farms, Altamont, NY
Housing: individually in suspended wire-mesh bottom cages
Environmental conditions: Temperature: 70±3°F
No other information provided

Acclimation period: none (matings were done at the supplier in 3 stages and pregnant dams were supplied 2-3 days after mating; total of 125 pregnant dams supplied).

B. PROCEDURES AND STUDY DESIGN:

1. Mating: Mating was conducted at the supplier's facility in 3 groups that were each mated 2 days apart. Females were mated 3:1 with fertile male albino rats of the same strain. Day 0 of gestation was designated as the day on which a vaginal sperm plug was observed. The number of male rats used for the matings was not indicated. About 40 pregnant females were produced in each mating group.

2. Animal Assignment and dose selection are described in the original DER. Assignment was random. Animals from each mating group were included in all the dose groups.

3. Dose selection rationale: No rationale was provided in the study report

4. Dosing: Test material and positive control were administered in corn oil in a volume of 10 ml/kg body weight/day prepared daily during the dosing period. The test material was kept in a 60°C incubator in an amber bottle during the treatment period to keep it in a molten state for dosing. The dosing solutions were not reported to have been analyzed for concentration. Solutions were prepared by adding 0.20, 0.40 or 0.80 g of molten test substance and diluted to 100 ml with corn oil to obtain the 3 dosing concentrations. Dosing was based on individual animal body weight on gestation day 6. Negative controls received corn oil only.

C. OBSERVATIONS:

1. Maternal Observations and Evaluations - The animals were checked daily for mortality or clinical signs. Dams were sacrificed by CO_2 asphyxiation on day 20 of gestation. Examinations at sacrifice consisted of examination of body and organ surfaces for grossly visible abnormalities and detailed examination of the urogenital tract. Uteri

were removed, weighed and cesarean section performed. The contents of each uterus were examined to determine number of corpora lutea, implantation sites, early/late resorptions, live/dead fetuses, sex of fetuses and body weight of all live fetuses. The above information was also collected from dams that died or were sacrificed moribund during the study, but these dams were excluded from statistical evaluation of the data.

2. Fetal Evaluations - The fetuses were examined in the following manner: All fetuses were examined grossly for visible external abnormalities. One-third of the fetuses per litter were randomly selected (and any fetus showing external abnormality) for examination of viscera, and were preserved in Bouin's fluid. Visceral examinations were conducted using the Wilson free-hand slicing technique. The remaining fetuses were fixed overnight in 70% isopropyl alcohol, macerated in 2% KOH, washed, stained with Alizarine red S dye, cleared and examined under low power magnification for variations and malformations of the skeleton.

3. Historical control data were not provided to allow comparison with concurrent controls.

D. STATISTICAL ANALYSIS: The study protocol included in the study report stated that control and test groups would be analyzed statistically using 95% confidence intervals for all percentages and proportions. Where appropriate, analysis by ANOVA using an 0.05 level of significance was employed. No further details were provided.

E. COMPLIANCE: Signed and dated GLP and Quality Assurance statements were not provided. The study was conducted prior to initiation of EPA Good Laboratory Practices. The report stated that the study was conducted according to the Booz, Allen and Hamilton Good Laboratory Procedures guidelines and that the Quality Assurance Unit reviewed the protocol and final reports.

II. RESULTS

A. MATERNAL TOXICITY: (Daily examinations conducted as described above under methods).

1. Mortality - The 18 deaths during the study described in the original DER occurred as 0, 9, 3, 2 and 4 among the vehicle control, positive control, low, mid- and high dose groups, respectively. Examination at necropsy indicated that at least 14 of these deaths were due to gavage error as indicated by fluid in lungs/thoracic cavity or red/distended stomach. No relationship of mortality to treatment with the test material was observed.

2. Clinical Observations - No treatment-related clinical observations were reported. Incidence of rales and red nasal discharge were reported among all dose groups.

3. Body Weight - Mean body weights during treatment and non-treatment portions of gestation are given in the attached table taken from the study report. Mean body weight gain data is presented below in Table 1:

TABLE 1 Body Weight Gain (grams)[a]

Group:	Prior to Dosing Period	Dosing Period	Post Dosing Period	Entire Gestation Period	Corrected Body Weight Gains Dosing P.[1]	Entire[2]
Control	25.03	30.75	68.48	124.26	-1.25	54.53
Aspirin	25.44	-19.83	33.99	39.60	-32.10	27.33
LDT	22.23	16.83	85.93	124.99	49.34	58.82
MDT	26.41	35.14	63.72	110.99	-29.44	46.41
HDT	24.58	15.43	85.93	83.55	-45.88	22.24

a = Data calculated from body weight data in Table 3 of study report. Body weight gain data not analyzed statistically

[1] Corrected body weight gain for dosing period = body weight gain for dosing period minus gravid uterus weight.

[2] Corrected body weight gain for entire gestation period = body weight gain for entire gestation period minus gravid uterus weight.

Mean maternal body weight gain was decreased at 80 mg/kg/day (-33% of controls; statistically significant). The decrease was partially due to slight reduction in mean pup weight and to decreased food consumption during the latter half of gestation. However, corrected body weight gain at 80 mg/kg/day was less than half the vehicle control, low or mid-dose gain, suggesting that the decrease was also related to toxicity of resmethrin.

Positive controls: Corrected body weight gain was also significantly reduced in the aspirin-treated dams and is considered a treatment-related effect.

4. Food Consumption

The summary table of mean food consumption during gestation from the study report is attached to this DER.

Results - Treatment-related effects on food consumption were observed at 80 mg/kg/day and, to a lesser extent, at 40 mg/kg/day. Mean food consumption between Day of receipt (approximately Day 2 of gestation) and Day 20 for dams treated with

resmethrin at 20, 40 and 80 mg/kg were 9%, 17% and 24% less, respectively, than vehicle controls. At 80 mg/kg/day, consumption was statistically significantly lower during gestation Days 6 - 21. Food efficiency calculations [using (total food consumption ÷ uncorrected total gestational body weight gain)x100] indicate that there was a slight decrease among the high dose group (41% vs. 47%, controls and 50%, 20 and 40 mg/kg/day). In the absence of other signs of maternal toxicity, TB-I does not consider the decreases in food consumption at low and mid dose to be of toxicologic significance.

Positive controls: Food consumption was 19% lower than vehicle controls.

5. Gross Pathology - No treatment-related gross pathology was observed at necropsy.

6. Cesarean Section Data - The summary table from the study report is attached. TB-I considers the slight decrease in mean fetal body weight (-11% of controls; not statistically significant) at 80 mg/kg/day to represent a marginal treatment-related effect, possibly secondary to decreased food consumption and body weight in females at this dose.

Positive controls: Fetuses in the aspirin-treated group showed sharply reduced number of live fetuses/dam, increased resorptions/dam and decreased average fetal weight. Mean gravid uterine weight was also markedly decreased due to increased fetal death.

B. DEVELOPMENTAL TOXICITY:

1. External Examination - No treatment-related effects were observed (see original DER and attached table from study report).

2. Visceral Examination - No treatment-related effects were observed (table from study report attached; also see original DER).

Positive controls: an increased incidence of auricle engorged with blood clot and enlarged liver blood vessel were observed; however, the small number of animals (9) available for evaluation makes interpretation of variations difficult.

3. Skeletal Examination - Skeletal effects are described in the original DER; table from study report is also attached. TB-I agrees with the conclusions of the original DER. Incidence of partial skull and incompletely ossified metacarpals and metarsals showed increased litter incidence (skull, 24% vs 13%, controls; metacarpals/tarsals, 18% vs 0%, controls) the incidence of distal metacarpals and metatarsals showed increased fetal incidence only (19% vs. 7%, controls and 34% vs. 20%, controls, respectively), since it was already observed frequently on a litter basis in controls.

Positive controls: An increased incidence of partial skull or skull with wide cranial suture, partially ossified ilium, ischium and pubis, partially ossified leg bones, distal metacarpals and metatarsals was observed.

III. DISCUSSION

A. MATERNAL TOXICITY: Maternal toxicity was observed at the highest dose tested (80 mg/kg/day) based on a statistically significant decrease in mean body weight on Day 20 and decreased body weight gain during gestation, corrected and total, compared to the vehicle control group. The decrease was only partially accounted for by decreased gravid uterus weight (due to slight reduction in mean fetal weight) or to decreased food consumption, which was statistically significantly lower than vehicle controls between Days 11 - 20 of gestation.

B. DEVELOPMENTAL TOXICITY:

1. Deaths/Resorptions: No treatment-related effects on fetal death or resorptions were observed at any dose level of resmethrin tested.

2. Altered Growth: A marginal decrease in mean fetal weight (-11% compared to vehicle controls) was observed at 80 mg/kg/day. Although this decrease was not statistically significant, TB-I considers it to be a marginal treatment-related effect, probably related to the decreased food consumption and body weights in dams at this dose.

3. Developmental Variations: Slightly increased incidence of skeletal variations were observed in fetuses from the 80 mg/kg/day group. These included distal metatarsals, partial skull and delayed ossification of metacarpals and metacarpals. The effects are consistent with slight delays in development and were probably secondary to maternal toxicity observed at the high dose.

4. Malformations: No treatment-related malformations were observed in this study at any dose level tested.

C. STUDY DEFICIENCIES:

- analyses of dosing solutions not conducted,
- methods used for statistical analysis not indicated,
- relatively high incidence of gavage error mortality,
- not conducted under EPA GLP (old study)

D. CORE CLASSIFICATION: Core-minimum. Although there were several deficiencies in this study, TB-I considers the study to have been adequate for assessing the developmental toxicity of resmethrin in rats. The study was conducted prior to FIFRA 1988 GLP guidelines,

or development of Guidelines for 83-3.

TB-I is concerned about the high incidence of gavage errors in this study, but adequate numbers of surviving dams and litters were available for examination. Although there was no analysis of the dosing solutions themselves, the method of dose preparation was adequately described and the concentration analysis of the test material provided information on concentration and stability under the conditions of storage during this study. Actual dose concentration of resmethrin is lower than nominal, based on the purity (86.5%) and lack of correction during the dosing period for maternal body weight gain.

Maternal NOEL = 40 mg/kg/day
Maternal LOEL = 80 mg/kg/day, based on decreased maternal body weight/body weight gain and food consumption.
Developmental Toxicity NOEL = 40 mg/kg/day
Developmental Toxicity LOEL = 80 mg/kg/day, based on increased incidence of skeletal variations and marginally decreased fetal body weight.

RESMETHRIN

Page_____ is not included in this copy.

Pages 171 through 177 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE JUN 26 1980

SUBJECT EPA Reg. No. 432-407, Technical Resmethrin (SBP-1382), Rat Teratology Study.

001915

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

TOX Chon. #83E

TO I. D. R. Geo, PM #17
Registration Division (TS-767)

Action Requested:

Review rat teratology study to support registrations/tolerances with resmethrin.

Conclusion:

Accept the study as a valid demonstration that resmethrin is not a teratogen in this strain of rat at doses up to and including 80 mg/kg. The NOEL for fetotoxicity is 40 mg/kg.

Detailed Review of Study

Identification of Study

Teratologic Evaluation of SBP-1382 Technical in the Albino Rat:

Booz, Allen and Hamilton, Inc., Foster D. Snell Division; Florham Park, NJ; (Project #2054-066); Nov. 26, 1979; EPA Accession No. 241765, -66, -68, -69, and -70.

5 groups of BDJ:(SD) BR female rats approximately 13 weeks of age were mated (3:1) with males of the same strain. Each group consisted of 25 females and were administered the following doses in Mazola corn oil: 0, 20, 40, 80 mg/kg of resmethrin, or 250 mg/kg of aspirin. Dosing was by gavage on days 6 through 15 of gestation. The rats were sacrificed on day 20 of gestation and the dams and pups examined.

Results:

A. Dam Data

1. Mortality. No dose related deaths although across the groups 19 of 125 died. 14 deaths were attributed to dosing mechanical artifacts. All animals were reported as being thrifty throughout the study.

2. Body weight and food consumption. The study shows that food consumption during treatment for all resmethrin treated groups was generally lower than controls. For the 11-15 day interval, food consumption for all groups dosed with resmethrin was statistically significantly lower. Only the high dose group demonstrated a significantly lower body weight.

EPA Form 1320-6 (Rev. 3-76)

178

3. Litter reproduction data. No statistically significant differences were noted with respect to number of live litters, fetuses/dam, fetus weight, resorptions/dam or weights of gravid uteri. Necropsy of the resmethrin treated dams at sacrifice was not remarkable.

B. Pup Data

1. Gross and soft tissue abnormalities. No resmethrin related abnormalities were noted.

2. Skeletal findings (2/3 of fetuses). No significant differences were reported. This reviewer notes that there were higher frequencies of missing sternebrae for the mid and high dose resmethrin treated groups. For example:

Dose	Frequency*
0	0.66
20 mg/kg	0.48
40 mg/kg	0.95
80 mg/kg	1.22

*Frequency = total incidences of missing sternebrae (including manubrium, second, third, fourth, and fifth, and xiphisternum) divided by the number of pups examined.

Other skeletal differences noted by this reviewer were (for the highest dose group only):

Skeletal Fault	% of Pups with Skeletal Fault	
	Control	High Dose
Partial skull	1.6%	8.1%
Distal metacarpels	7.5%	19.1%
Incompletely ossified metacarpels	0	6.6%
Incompletely ossified metatarsals	0	3.4%

For these parameters, the low and mid dose were essentially equivalent to the control.

These skeletal findings indicate a slight fetotoxic effect.

C. Treatment with the positive control (aspirin) resulted in a variety of teratogenic effects as noted in both the soft tissue and skeletal data tables.

Discussion:

This test is Core-Guidelines. Resmethrin did not exhibit a teratogenic effect. A slight fetotoxic effect, as evident by the aberrations in the skeletal findings, was noted in 80 mg/kg test group pups.

OPP:HED:TOX: J.ECHERTY:sb 5/13/30 X73710 TS-769 Rm. 814 CM 2 #8

[RESMETHRIN, TECH.] DRAFT

Developmental Study (83-3)

EPA Reviewer: Linnea J. Hansen, Ph.D.
Review Section 4, Toxicology Branch I (7509C)
Linnea J. Hansen, Date 6/2/94
EPA Section Head: Marion P. Copley, D.V.M., D.A.B.T.
Review Section 4, Toxicology Branch I (7509C)
Marion Copley, Date 6/6/94

DATA EVALUATION RECORD
(Supplement to Original Review, HED Doc. no. 001911)

STUDY TYPE:	Developmental Study - Rabbit (83-3b)
TOX. CHEM. NO.:	083E
P.C. CODE:	097801
MRID No.:	00029002
TEST MATERIAL:	SBP-1382, technical
SYNONYMS:	Resmethrin; 5-benzyl-3-furylmethyl (IRS)-cis,trans chrysanthemate
STUDY NUMBER:	6288
SPONSOR:	(at time of study) S.B. Penick Co., Orange Research Laboratory, Orange, NJ. Registrant is now Roussel Uclaf Corporation, Montvale, NJ
TESTING FACILITY:	Food and Drug Research Laboratories, Inc., Waverly, NY
TITLE OF REPORT:	Teratologic Evaluation of SBP-1382 Technical in Albino Rabbits
AUTHORS:	M. Knickerbocker, P. Becci, Ph.D. and R. Parent, Ph.D.
REPORT ISSUED:	October 31, 1979

EXECUTIVE SUMMARY: In a developmental toxicity study, 20 pregnant New Zealand White Minnikin rabbits per dose group received 0, 10, 30 or 100 mg SBP 1382/kg/day (technical resmethrin, 90% a.i.; doses not adjusted for purity of test material or for body weight gain during gestation) in corn oil by gavage (1 ml/kg body wt.) from gestation Days 6 through 18, inclusive. In addition, a group of 20 rabbits received 2.5 mg/kg aqueous 2-aminonicotinamide on Day 9 of gestation as a positive control for developmental toxicity.

No maternal toxicity was observed at any dose tested (up to 100 mg/kg/day). **The maternal toxicity LOEL > 100 mg/kg/day. The maternal toxicity NOEL $\geq$ is 100 mg/kg/day.**

Developmental toxicity was noted in the high dose group (100 mg/kg/day) as statistically significantly increased litter incidence of fused sternebrae (38% vs. 0%, controls) and extra sternebrae (38% vs. 15%, controls). **The developmental toxicity LOEL = 100 mg/kg/day, based on increased incidence of skeletal variations, and a possible marginal increase in resorbed litters.**

No teratogenic effects were observed at the doses tested.

This study is classified as Core-minimum and satisfies the requirement (83-3b) for a developmental toxicity (teratology) study in rabbits, despite study deficiencies (see Discussion, below).

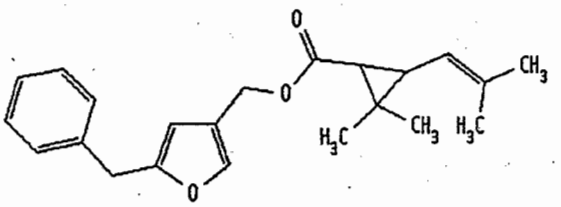
Special Review Criteria (40 CFR 154.7) None

Note: This DER supplement is intended to provide an Executive Summary and details of the study that were not included in the original DER. The conclusions of this supplemental DER supercede those of the original DER, where different.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: SBP-1382 (resmethrin)
   Description: tan crystalline solid
   Lot/Batch #: 8176-RT
   Purity: 90% a.i.
   Stability of compound: not indicated in study report
   CAS #: 10453-86-6
   Structure



2. Vehicle and/or positive control: Corn Oil, Lot and supplier not indicated.
   Positive control - 6-aminonicotinamide, Lot and supplier not indicated.

182

3. Test animals: Species: Rabbit
   Strain: New Zealand White Minnikin
   Age and weight at study initiation: about 5 months/1.45-2.52 kg (females)
   Source: Dutchland Laboratory Animals, Denver, PA
   Housing: individually in wire-mesh bottom cages
   Environmental conditions: It was stated that the animals were housed in temperature controlled quarters; however, data on actual conditions during the study were not provided. Animals were administered Charles River Rodent Chow (Agway) and tap water ad libitum.

   Acclimation period: not indicated

B. PROCEDURES AND STUDY DESIGN:

1. Mating: Female rabbits were injected with 200 IU human chorionic gonadotropin (marginal ear vein), then placed in the male's cages to mate. Copulation was taken as positive evidence of pregnancy. It was stated in the study report that mating was performed according to the laboratory standard operating procedure, but details were not provided. No further details were provided.

2. Animal Assignment and dose selection were described in the original DER. Assignment was random. Enough females were mated (20/dose group) to allow extra females in each dose group so that in the event of excessive mortality or reduced fertility there would still be at least 12 pregnant females.

3. Dose selection rationale: No rationale was provided in the study report

4. Dosing: Test material and positive control were administered in corn oil in a volume of 1 ml/kg body weight/day prepared daily during the dosing period. The dosing solutions were not reported to have been analyzed for concentration, homogeneity and stability. Dosing was based on individual animal body weight on gestation day 6. Negative controls received corn oil only.

   Positive control animals were administered 2.5 mg/kg aminonicotanimide in a total volume of 2 ml water/kg on Day 9 of gestation only.

C. OBSERVATIONS:

1. Maternal Observations and Evaluations - The animals were checked daily for mortality or clinical signs. Maternal body weights were determined on Days 0, 6, 12, 18, 19 and 29. Dams were sacrificed by intracardiac injection of a lethal dose of sodium pentobarbital on day 29 of gestation. The report did not state whether females were

examined sacrifice for grossly visible abnormalities. Uteri were removed, weighed and cesarean section performed. The contents of each uterus were examined to determine number of corpora lutea, implantation sites, early/late resorptions, live/dead fetuses, sex of fetuses and body weight of all live fetuses. The above information was also collected from dams that died or were sacrificed moribund during the study, but these dams were excluded from statistical evaluation of the data.

2. Fetal Evaluations - The fetuses were examined in the following manner: All fetuses were examined grossly for visible external abnormalities. Fetuses were then placed in an incubator (exact temperature illegible in copy of study report) for 24 hrs to determine neonatal viability. Survivors were sacrificed by exposure chloroform vapor. All fetuses were then examined for visceral/soft tissue abnormalities. Eviscerated and skinned fetuses were processed for skeletal examination by fixation in 70% isopropyl alcohol, maceration in 3% KOH, washing, staining with Alizarin-red S dye and clearing with glycerine. Skeletons were examined under low power magnification for variations and malformations.

3. Historical control data were provided for a limited number of parameters from Dutch belted but not New Zealand Minnikin rabbits for comparison with concurrent controls (attached).

D. STATISTICAL ANALYSIS: Control and test groups were compared using 95% confidence intervals for proportions or by computation of exact probabilities. Continueous data were analyzed by one-way completely ramdon classification ANOVA for fixed effects. Statistical significance was assumed where $p < 0.05$. The least significant difference test was employed to determine which test groups differed from the control. All comparisons used the dam or litter as unit of observation.

E. COMPLIANCE: Signed and dated GLP and Quality Assurance statements were not provided. The study was conducted prior to initiation of EPA Good Laboratory Practices. The report stated that the study was conducted according to FDA Good Laboratory Procedures guidelines and that a Quality Assurance Unit reviewed the protocol and final reports.

II. RESULTS

A. MATERNAL TOXICITY: (Daily examinations conducted as described above under methods).

1. Mortality - No treatment-related mortality was observed. At 0, 10, 30 or 100 mg/kg/day, 1, 3, 0, 2 and 0 does died or were sacrificed. Three does died in the positive control group (2.5 mg/kg aminonicotinamide). The study report did not

indicate whether mortality resulted from gavage error or other cause; no gross examination was performed at necropsy to determine cause of death.

2. Clinical Observations - No treatment-related clinical observations were reported.

3. Body Weight - There were no treatment-related effects on mean maternal body weight or body weight gain. Corrected mean body weights were also similar among all groups (data not shown).

4. Food Consumption - Not measured in this study.

5. Gross Pathology - Not indicated in report if gross examinations were conducted at sacrifice.

6. Cesarean Section Data - The summary table from the study report is attached. A non-statistically significant increase in completely resorbed litters was observed at high dose: 3/16 litters (19%), vs 0% in vehicle controls and low- and mid-dose. Statistically significant increases in the number of dams with one or more resorption was increased at all dose levels but since there was no dose-related increase, TB-I considers it to be sporadic and not a treatment-related effect.

   Also attached to this DER are additional calculations of cesarean parameters on fetal survival from a letter (Dr. Ralph Fogleman to Dr. Maarten deVries, 1-14-80) that were included with the study report. No significant treatment-related effects were observed following treatment with resmethrin.

   Positive controls showed pronounced reduction of the number of fetuses/dam, average fetal weight, viability and total litter resorption (60%).

B. DEVELOPMENTAL TOXICITY:

1. External Examination - No treatment-related effects were observed (see attached table from study report).

   Positive controls showed statistically significant increases in the incidence of clubbed feet, crossed hindlegs, underdeveloped eyes, harelip, short tail and small size.

2. Visceral Examination - No treatment-related effects were observed (table from study report attached). TB-I does not currently agree with the original DER that the occurrence of "dark liver" at all dose levels in treated fetuses only was related to treatment since the incidence did not show a dose-response.

3. Skeletal Examination - Skeletal effects are described in the original DER; table from study report is attached. TB-I agrees with the conclusions of the original DER that the sternebral effects (fused and extra) were treatment-related effects.

Positive controls showed statistically significant increases in the incidence of fused and extra sternebrae, scrambled vertebrae, tail defects and scoliosis. Incomplete ossification of the sternebrae (not statistically significant) was also observed in 5/6 litters.

III. DISCUSSION

A. MATERNAL TOXICITY: There was no evidence of maternal toxicity observed in this study.

B. DEVELOPMENTAL TOXICITY:

1. Deaths/Resorptions: A slight increase in totally resorbed litters was observed at 100 mg/kg/day; 3 litters (19%) were affected compared to 0 at all doses (except for the positive control, which had 60% litters affected. This increase was not statistically significant, and litter resorption is not uncommon among rabbits. TB-I considers the increase a possible marginal effect of treatment. Statistically significant increases at low and mid dose in the number of does with one or more resorption were considered a sporadic occurence.

2. Altered Growth: No treatment-related effects on fetal growth were observed.

3. Developmental Variations: Statistically significant increases in the incidence of skeletal variations (fused sternebrae and extra sternebrae) were observed in fetuses at 100 mg/kg/day. Historical control data was not available for comparison. TB-I considers this to be a treatment-related effect. Although incidence of dark livers were reported in all treatment groups (liver incidence about 25%), it is not considered a clear treatment-related effect since neither fetal nor litter incidence showed a dose-response.

4. Malformations: No treatment-related malformations were observed in this study at any dose level tested.

C. STUDY DEFICIENCIES:

- analyses of dosing solutions not included (stated to have been summarized in Volume V, not in the study report available to the reviewer,
- method used for statistical analysis not indicated,
- not conducted under EPA GLP (old study),
- incubation of fetuses for 24 hrs after cesarean section, which would interfere with

detection of delayed ossification,
- numerous details of the study procedure (eg mating procedure, enviromental conditions) were omitted from the study report,
- pre- and postimplantation loss not determined,
- complete gross examinations of dams at sacrifice not performed.

D. CORE CLASSIFICATION: Core-Minimum. The study is considered adequate for regulatory purposes despite the above deficiencies, since adequate numbers of litters were available for analysis and a NOEL/LOEL for developmental toxicity was established. Although the ability to detect delayed ossification may have been compromised by the study design, there was no maternal toxicity and no effect on fetal growth which might have caused increased incidence of this effect. The study was conducted under FDA GLP guidelines and with quality assurance, and for the most part was conducted according to standard procedures for developmental toxicity studies.

Maternal NOEL $\geq$ 100 mg/kg/day
Maternal LOEL > 100 mg/kg/day.
Developmental Toxicity NOEL = 30 mg/kg/day
Developmental Toxicity LOEL = 100 mg/kg/day, based on increased incidence of skeletal variations and possibly slightly increased total litter resorption.

RESMETHRIN

Page_____ is not included in this copy.

Pages 188 through 194 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X___ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE JUL 07 1980

SUBJECT EPA Reg. No. 432-487; Technical Resmethrin (SBP-1382); Review of Rabbit Teratology Study

TOX. Chem. No. 83E

FROM John Doherty 6/26/80
Toxicology Branch/HED (TS-769)

Budd 6/27/80

001911

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

Action Requested:

Review rabbit teratology study to support registrations/tolerances with resmethrin.

Conclusion:

This study has been classified as Core Minimum and demonstrates that resmethrin does not induce teratogenic effects in rabbits at dose levels up to and including 100 mg/kg.

Remarks:

Resmethrin treated dams at all doses are reported as having pups with "dark livers". The testing laboratory describes this as a possible fetotoxic effect-despite the fact that there was no dose dependence relationship observed. Toxicology Branch accepts this interpretation of a possible fetotoxic effect at the lowest dose tested (10 mg/kg). It is apparently a species related effect because a teratology study in rats with the same test material did not demonstrate a similar lesion (see review by John Doherty, EPA Reg. No. 432-487, dated 6/26/80).

Detailed Review of Study

Identification of Study:

"Teratologic Evaluation of SBP-1382 Technical in Albino Rabbits"

Food and Drug Research Laboratories, Inc.; Report No. 6288; October 31, 1979; EPA Accession No. 241800.

Protocol:

5 groups of 20 pregnant female New Zealand White Minnikin rabbits (a hybrid strain resulting from the cross of New Zealand White and Dutch-Belted rabbits) were dosed orally with either 0, 10, 30, or 100 mg/kg of technical resmethrin [(5-Benzyl-3-furyl) methyl 2,2-dimethyl-3-(2-methylpropenyl)cyclopropanecarboxylate, 90%], or 2.5 mg/kg of 6-aminonicotinamide (6-AN) in corn oil. Resmethrin was administered on days 6 through 18 of gestation. The positive control (6-AN) was administered only on day 9 of gestation. On day 29 of gestation, all females were sacrificed and their fetuses subjected to examination.

Results:

A. Maternal and Reproductive Effects.

1. The lowest % pregnancy was in the control group (70%). The % pregnancy in the test group dams was 75-90%.

2. There was no apparent effect of resmethrin on body weights of the test dams.

3. No overt toxic effects (general appearance or behavior) were noted.

4. At all doses of resmethrin treated dams, there was a decreased percentage of implants resulting in live fetuses and an increased percentage of resorption sites. Although these parameters were different from the control, they did not show a change with increasing dose.

5. The average number of live fetuses per test dam was comparable to controls. Neonatal survival was not adversely affected.

There is apparently a discrepancy between the summary table and the discussion related to dam reproduction data. The summary table states that 15 of 18 positive control dams and 16 of 16 high dose group dams had pregnancies that went to term. However, the same table states that 9 of 18 positive control and 3 of 16 high dose group dams had litters completely resorbed. This discrepancy should be clarified.

B. Effects on the Fetuses.

1. Soft tissues - The only remarkable finding was an increase in "dark livers" for all doses of rabbits treated with resmethrin. This anomaly did not demonstrate a dose dependent effect. It is considered, however, to be a possible fetotoxic effect.

	% of Fetuses with "Dark Liver"	Incidences/Litters Effected
Negative Control	0%	0/0
10 mg/kg	23%	13/4
30 mg/kg	17%	14/4
100 mg/kg	14%	8/3

2. Skeletal findings - The high dose group exhibited an increase in fused and extra sternebrae that was statistically significant. This finding is a frequent observation in teratology studies and is considered to be an effect due to stress rather than a teratogenic effect.

C. The Positive Control.

1. 6-amimonicotinamide induced a variety of expected abnormalities in the fetuses.

Discussion:

This study is Core Minimum.

This study could be upgraded if an explanation for the discrepancy in dam reproduction data (described above) is provided by the registrant or testing laboratory.