MICROFICHE

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

D11067

JUN 22 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RESMETHRIN. ID #00432-00487. Evaluation of New Mouse Dietary Carcinogenicity Study and Reevaluation of Previously Submitted Mouse Carcinogenicity Study on Resmethrin (SBP 1382).

Tox. Chem. No.: 083E
PC No.: 097801
Submission No.: S455645
Barcode No.: D198236

FROM: Linnea J. Hansen, Ph.D. Linnea J Hansen 6/17/94
Section IV, Tox. Branch I
Health Effects Division (H7509C)

TO: Robert Brennis, Manager, PM Team 10
Joseph Tavano, Reviewer, PM Team 10
Reregistration Division (7505C)

THRU: Marion P. Copley, D.V.M., D.A.B.T., Section Head
Section IV, Tox. Branch I
Health Effects Division (H7509C) Marion Copley 6/21/94

CONCLUSIONS:

TB-I has reviewed the new mouse carcinogenicity study on resmethrin and the previously submitted mouse carcinogenicity study on resmethrin was reevaluated (see attached DER and supplemental DER, respectively). Although neither study by itself satisfies the guideline requirement for 83-2b (see summaries, below), when taken together they provide adequate information to define a NOEL and LOEL for systemic toxicity and to assess the carcinogenic potential of resmethrin in mice. A slight increase in the incidence of hepatocellular carcinomas and combined adenomas/carcinomas was observed in males in MRID 430521-01 at 1200 ppm; TB-I defers determination of carcinogenic potential of resmethrin to the HED RfD/Peer Review Committee.

MRID 430521-01 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

1 of 32

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 (weak condition, distended, blue abdomen, tremors and reduced body temperature) were only observed in preterminal animals and were considered agonal symptoms and not direct effect of treatment. 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.

MRID 00081319 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). 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.

ACTION REQUESTED:

On June 29, 1993, Roussel UCLAF submitted for review a mouse dietary carcinogenicity study on SBP-1382 (Registration No. 432-487, technical resmethrin with antioxidant; MRID 430521-01). The previously submitted mouse dietary carcinogenicity study (MRID 00083319), which had been classified as Core-Minimum, was also reevaluated by TB-I.

CC: Richard King, PM Team 72, SRRD

[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).

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

5

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 [illegible] 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 (-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:

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	1.28	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	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]

	DOSE IN DIET, PPM			
OBSERVATION	0	250	500	1000
MALES:				
Intestine, lge: N =	(72)	(20)	(20)	(74)
Amyloidosis	4		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	5*	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	4	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.

Page_____ is not included in this copy.

Pages 14 through 17 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.

✓ 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.

011067

[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).

18

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

5. 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 (3/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, 73, 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.

21

011067

[RESMETHRIN, TECH.]

Carcinogenicity, Oral Study 83-2

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.

32

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	3	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	2	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:

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	37.01	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	42.65*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	29.48	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 .. 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 ups.

- 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 (12 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 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.

25

Ex 1067

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	1.496	2.088**1	2.156**1	2.723***1
	rel	4.237	5.587	6.410**1	7.296**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.

2/0

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. vacuolia.	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

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

28

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

29

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-1 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-1 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.

Page_____ is not included in this copy.

Pages 31 through 32 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.

✓ 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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DATE: DEC 15 1981

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

TOX Chem. No. 83E

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) developed 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

34

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)	54.8 (40/73)	15.0 (3/20)	45.0 (9/20)	35.0 (7/20)	60.0 (12/20)	46.6 (34/73)	73.6 (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	-	16.9 (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

END

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)

38

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

40

END