EPA Reviewer: Linnea J. Hansen, Ph.D. _____, Date ____
Review Section IV, Toxicology Branch I (7509C)
EPA Section Head: John Doherty, Ph.D., D.A.B.T. _____, Date 10/30/95
Review Section IV, Toxicology Branch I (7509C)

10/30/95

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: In a dietary chronic toxicity/carcinogenicity study, 50 Wistar rats/sex/dose were fed SB-1382 (resmethrin tech., 90% a.i.) at concentrations of 0, 500, 2500 or 5000 ppm (corresponding to average daily intake of 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). An additional 10 animals/sex/dose were treated and sacrificed at 12 months.

At 2500 ppm (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

1

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). **The LEL for systemic toxicity is 2500 ppm (232.7 mg/kg/day) based on body weight and liver proliferative effects in females. The NOEL is 500 ppm (47 mg/kg/day).**

Carcinogenic effects could not be unequivocally determined in this study due to uncertainty regarding classification of liver hyperplastic nodules and thyroid tumors and lack of historical control data for Wistar rats from the laboratory.

The chronic toxicity phase of the study **(83-1a)** is classified as **Core-minimum** and the carcinogenicity phase of the study **(83-2a)** is classified as **Core-supplementary (not upgradable)**. This study, taken together with a newer rat chronic toxicity/carcinogenicity study (MRID 43601601; reviewed in HED Doc. #011650), satisfy guideline requirements for chronic toxicity/carcinogenicity testing in rat.

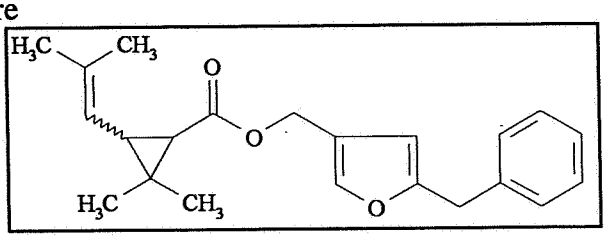
I. MATERIALS AND METHODS

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

Group	Dose in diet (ppm)	12-month sacrifice group Males	12-month sacrifice group Female	Lifetime exposure group[1] Males	Lifetime exposure group[1] 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

Test

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 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:

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.

5

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					20.56	4.5		
M	18.85	4.07	19.75	4.17	--	--	24.50*	5.34*
(%)	--	--	--	--	17.27*	5.45*	(32%)	(31%)
F	14.09	4.45	14.89	4.41	(23%)	(22%)	20.34*	6.84*
(%)	--	--	--	--			(44%)	(54%)
THYROID: 12 mos.					.0267	.0036		
M	.0242	.0046	.0270	.0051	--	--	.0308*	.0063*
(%)	--	--	--	--	.0227	.0080	(26%)	(37%)
F	.0226	.0081	.0195	.0073	--	--	.0240	.0089
(%)	--	--	--	--			--	--
Termination					.0310	.0068		
M	.0310	.0067	.0330	.0069	--	--	.0360	.0078
(%)	--	--	--	--	.0250	.0079	(16%)	(16%)
F	.0220	.0070	.0250	.0073	--	--	.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.

Historical control data for Wistar rat tumor incidence from FDRL is not available. In order to better evaluate the incidence of tumors observed in this study, at the Request of the Agency, the Registrant submitted historical control data for Wistar rats from a study conducted at on rats obtained from Charles River Germany in 1994 (MRID 43271701). A brief summary of the study design and relevant pathology lesions is attached to this review (see Appendix).

DISCUSSION

This study was reviewed by the HED RfD committee (RfD document of 11/22/94).

8

The chronic toxicity phase of this study was determined to be acceptable for regulatory purposes. A NOEL of 500 ppm (39.5 mg/kg/day, males and 47 mg/kg/day, females) and a LEL of 2500 ppm (193.7 mg/kg/day, males and 232.7 mg/kg/day, females), based on decreased body weight/body weight gain during the early portion of the study and proliferative liver effects in females, were determined.

In the carcinogenicity phase of this study, increased incidence of liver "hyperplastic nodules" and "thyroid adenoma" were reported. During the initial review of this study in 1981 and 1982, reevaluation of the slides was conducted (HED doc. #002477 and #002478). It was concluded that the liver lesions were non-neoplastic and that the increased incidence of thyroid tumors (follicular adenomas) was not statistically significantly increased or treatment-related. Because of the age of the study (completed in 1980) and the possibility that classification of neoplastic and hyperplastic lesions in this study was not consistent with current nomenclature, the RfD Committee determined that the lesions identified as liver hyperplastic nodules and thyroid adenomas would need to be to reassessed to evaluate carcinogenicity of resmethrin and that historical control data should be provided. However, FDRL is no longer operating and it is unlikely that microscopic reevaluation of tissues can be performed and historical control data is apparently not available (the Registrant submitted historical control data on Wistar rats from a study conducted in Belgium on rats obtained from Charles River in Germany; see Appendix of this DER). In addition, the quality of the microfiche copies of the study available to the Agency is extremely poor and many pages are illegible, making evaluation of individual animal data impossible.

The Registrant recently submitted a new chronic toxicity/carcinogenicity study in rat (MRID 43601601; HED doc no. 011650) which was determined to be acceptable for regulatory purposes. Because adequate data are now available, TB-I will use the new study to evaluate carcinogenicity of resmethrin in rats. In the new study, liver tumors but not thyroid tumors show a treatment-related increase. The effects observed in the liver and thyroid will be considered as additional information but not used as a primary study for evaluation of carcinogenicity of resmethrin.

APPENDIX

Life-Span Data and Historical Data in Carcinogenicity Testing in Wistar Rats Crl:(WI)BR
J. Vandernerghe, D.V.M.
Janssen Research Foundation, Department of Toxicology, Janssen Pharmaceutica N.V., Beerse, Belgium
Reported in 1990 (study initiated in March, 1984)
MRID 43271701

SUMMARY:

In a life-span historical data study, Wistar Crl:(WI)BR rats obtained from Charles River Germany (Sulzfeld facility) a total of 2 groups of 50/sex rats were maintained on basal diet (Huybrechts powdered rat food) for 108 weeks (groups a and b) and 2 groups of 50/sex rats were maintained for 136 weeks (groups c and d) to provide information on survival, body weight (measured every 4 weeks) and incidence of clinical signs and gross/microscopic lesions in control animals. Only information pertinent to the liver and thyroid lesions in the resmethrin 2-year rat study is presented below.

Although this information has been included in the supplemental DER for completeness, in the opinion of TB-I, comparison of this historical control data with those in the rat 2-year study is inappropriate because of uncertainty regarding the nomenclature and because rats were obtained from a different source. However, this does provide some information regarding frequency/variability of the liver and thyroid lesions in Wistar rats. TB-I notes that in the reevaluation in document 002478, a spontaneous rate of 0 - 30% for thyroid adenomas in Wistar rats was reported, but whether this applied to both males and females was not indicated.

Mortality at 104 weeks ranged from 48 to 64% for males and 32 to 54% for females.

The liver and thyroid microscopic lesions observed in males and females in this study are summarized below in Table 1:

TABLE 1: LIVER AND THYROID LESIONS IN CONTROL WISTAR RATS[1]

Lesion/sex	Group a	Group b	Group c	Group d	
NEOPLASTIC LESIONS (N = 50 except where noted)					
MALES:					
- Liver, hepatic neoplastic nodule	2	3	7	6/49	
- Thyroid, adenoma	4	8	7		3/48
adenocarcinoma	4	0	1	2/48	
"light cell" solid adenoma	4	2	3	3/48	
FEMALES:					
- Liver, hepatic neoplastic nodule	9	5	8	12	
- Thyroid, adenoma	1	0	1/49		2/49
"light cell" solid carcinoma	1	7*	2/49		3/49
"light cell" solid adenoma	1	0	0/49	0/49	
NON-NEOPLASTIC LESIONS (N = 50 except where noted)					
MALES:					
- Liver, altered structure	6	10	11	4/49	
ductular proliferation	23	36	21		27/49
focal cellular changes	8	18	14		21/49
clear cell plaques	11	9	7	5/49	
- Thyroid, goiterous	1	0	0		0/48
hyperplasia	0	0	1		0[3]/48
cystic hyperplasia	13	7	8		6/48
light cell hyperplasia	4	4	5		8/48
metaplasia	0	1	0		1/48
FEMALES:					
- Liver, altered structure	3	3	11	3	
ductular proliferation	25	25	11		20
focal cellular changes	15	14	11		22
clear cell plaques	0	1	0/49	0/49	
- Thyroid, cystic hyperplasia	0	1	1/49		0/49
light cell hyperplasia	3	15	9/49		9/49
metaplasia	0	2	2/49		0/49

1 Data taken from Tables 13, 14, 17 and 18 of study report

* $p \leq 0.05$

Liver neoplastic nodules were reported frequently (up to 24% in females; up to 14% in males). In females, thyroid follicular tumors were not common (0 - 4% for adenomas; no adenocarcinomas reported) whereas they were more frequently observed in males (0 - 8% for adenomas and 6 - 16% for adenocarcinomas). The term thyroid "light cell" is presumed to refer to thyroid C-cells.

11

Sign-off date: 10/30/95
DP Barcode: d207002
HED DOC Number: 011716
Toxicology Branch: tb1

12