10/05/1994 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.

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Review Section IV, Toxicology Branch I (7509C)

Linnea P. Hansen, Date 10/5/94
Marion Copley, Date 10/5/94

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)

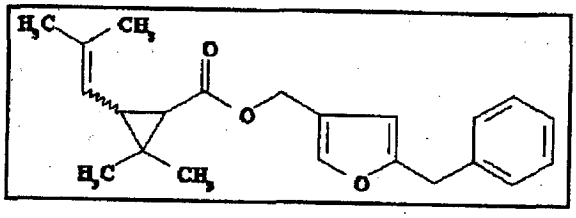
LOEL (systemic toxicity): 2500 ppm (193.7 mg/kg/day, males and 232.7 mg/kg/day, females), based on slightly decreased body weight in females during the first year of the study, increased liver weight and proliferative (non-neoplastic) lesions of the liver in females.

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		Lifetime exposure group[1]	
		Males	Female	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

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.

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	Appearance*
	Volume*
X	Specific gravity*
X	pH
X	Sediment (microscopic)*
X	Protein*

* Required for chronic studies

X	
X	Glucose*
X	Ketones*
X	Bilirubin*
	Blood*
	Nitrate
X	Urobilinogen

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	Digestive system
	Tongue
	Salivary glands*
	Esophagus*
X	Stomach*
X	Duodenum*[1]
X	Jejunum*
X	Ileum*
X	Cecum*
X	Colon*
X	Rectum*
XX	Liver *+
	Gall bladder*
X	Pancreas*
	Respiratory
	Trachea*
XX	Lung*
	Nose
	Pharynx
	Larynx

X	Cardiovasc./Hemat.
	Aorta*
XX	Heart*
X	Bone marrow*
X	Lymph nodes*
XX	Spleen
	Thymus*
	Urogenital
XX	Kidneys*+
X	Urinary bladder*
XX	Testes*+
X	Epididymides
	Prostate
	Seminal vesicle
XX	Ovaries*+
X	Uterus*

X	Neurologic
X	Brain*+
X	Periph. nerve*
X	Spinal cord (3 levels)*
X	Pituitary*
X	Eyes (optic n.)*
	Glandular
XX	Adrenal gland*
	Lacrimal gland
X	Mammary gland*
X	Parathyroids*++
XX	Thyroids*++
	Other
X	Bone*
X	Skeletal muscle*
X	Skin*
X	All gross lesions and masses*

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

7

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].

8