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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: **RESMETHRIN (SB-1382). ID NO. 097801-062226.** Evaluation of (1) a 4-Week Feeding Study in Mouse (Range-Finding Study for 2-Year Carcinogenicity Study); Supplemental DER for Previously Submitted and Reviewed Wistar Rat 2-Year Chronic Toxicity/Carcinogenicity Study; Historical Control Data on Wistar Rats for Microscopic Liver and Thyroid Pathology.

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From: Linnea J. Hansen, Ph.D. Linnea J. Hansen 9/21/95
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To: Larry Schnaubelt, Manager, PM Team 72
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Special Review and Reregistration Division (7508W)

Through: John Doherty, Ph.D., D.A.B.T., Acting Section Head John Doherty 9/21/95
Section IV, Toxicology Branch I
Health Effects Division (7509C) 10/30/95

I. CONCLUSIONS

A. Mouse 4-week range-finding study: Results are summarized below. In the opinion of TB-I the range-finding study does not support an MTD of 1200 ppm for the mouse carcinogenicity study (MRID 4302101); however, adequate data are available to assess carcinogenicity of resmethrin in mice (see HED doc. no. 011067).

EXECUTIVE SUMMARY: In a 4-week range-finding study for a 2-year carcinogenicity study (MRID 43338601), SB-1382 (resmethrin technical, 88.8% a.i.) was administered in the diet for 4 weeks to 10 male and 10 female Swiss Crl:CD-1(ICR)BR mice/dose group at levels of 0, 625, 1250, 2500 or 5000 ppm (time-

weighted average doses of 0, 105.5, 205.1, 452.3 or 994.5 mg/kg/day for males and 0, 130.8, 298.9, 546.7 or 1195.1 mg/kg/day for females based on theoretical concentration in the diet).

At 1250 ppm, slightly increased absolute and relative liver weights (+32%, males; +23%, females) and fine vacuolization of hepatocytes (9/20 animals) were observed in both sexes. At 2500 ppm, increases in SGOT (females), SGPT, alkaline phosphatase (males) and BUN (males) were observed. A single female had slight spleen atrophy. At 5000 ppm, decreased body weight/body weight gain (males), spleen atrophy, spleen and thymic lymphocytolysis and decreased spleen weight (males) were observed. **The LEL (threshold) for systemic toxicity is 1250 ppm (205.1 mg/kg/day), based on increased incidence of hepatocyte fine vacuolization and mild liver enlargement. The NOEL is 625 ppm (105.5 mg/kg/day).**

This study is classified as **core-supplementary**. It was submitted as additional information (range-finding study for mouse carcinogenicity study) and not to fulfill guideline requirements for resmethrin.

B. Supplemental DER for rat chronic toxicity/carcinogenicity study (FDRL study conducted in 1980; see reviews in HED doc nos. 001912, 002477 and 002478): The following supplemental DER was prepared to provide additional details of the study not in the original reviews (MRID nos. 00041402, 00085870, 00108828) and to review the conclusions, particularly the carcinogenicity evaluation. TB-I notes that the carcinogenicity phase of this study was downgraded by TB-I to Supplementary (not upgradable) but that a new rat carcinogenicity study was recently reviewed and found acceptable for regulatory purposes; see HED doc. no. 011650. Since new data on the rat are available and FDRL is no longer operating, making reexamination of the study difficult if not impossible, reevaluation of the older rat study (re-reading of the histopathology, historical control comparison) will not be performed. Results are summarized below:

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 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. [The NOELs for the two studies are similar (47 vs 42 mg/kg/day in new study) and similar effects were observed at the LOELs (233 mg/kg/day vs. 107 mg/kg/day in new study; decreased body weight in females, hepatotoxicity). Although liver proliferative lesions in females treated at high dose (5000 ppm) in the old study could not be properly evaluated, the new study showed increased hepatocellular adenoma/adenocarcinoma at high dose (2500 ppm) in females. Thyroid effects were not observed in the new study].

C. Historical control data on Wistar Rats: A brief summary of the results pertaining to liver and thyroid microscopic lesions is included in an Appendix to the supplemental DER for the 2-year rat study. The data are of limited use because of uncertainties regarding nomenclature in the two studies and because the data were not collected from the same laboratory or within 2 years of the study.

II. ACTION REQUESTED

On June 8, 1994, Roussel UCLAF submitted the following studies for review by the Agency: (1) MRID 43271701, Life-Span Data and Historical Data in Carcinogenicity Testing in Wistar Rats and (2) MRID 43338601, A 4-Week Dietary Toxicity Study of SBP-1382 in the Albino Mouse. This was in response to a request for this information by TB-I. The historical control data were requested from the study lab (FDRL) that conducted a 2-year rat study completed in 1980 (see summary, above) but since none was apparently available, data on Wistar rat from another lab was sent instead. The range-finding study was requested to provide justification for the dose selection in the mouse carcinogenicity study.

In addition, TB-I prepared a supplemental DER for the previously reviewed rat chronic toxicity/carcinogenicity study (see above). This supplement was prepared prior to the RfD meeting on resmethrin (see RfD report dated 11-22-94) to provide additional study details not in the original reviews. The Committee agreed with the conclusions of the review for the chronic toxicity phase of the study but deferred consideration of the carcinogenicity phase pending evaluation of the new rat chronic toxicity/carcinogenicity study on resmethrin. As of this writing, the Committee has not met to evaluate the new study.

[RESMETHRIN, TECH.] 4 Week Dietary Study, Mouse (Range-Finding) 111716

EPA Reviewer: Linnea J. Hansen
Review Section 4, Toxicology Branch I (7509C)
EPA Section Head (Acting): John Doherty
Review Section 4, Toxicology Branch I (7509C)

Linnea J. Hansen Date 9/3/95
John Doherty, Date 9/5/95

DATA EVALUATION REPORT

STUDY TYPE: 4-Week Toxicity/Range-finding (non-guideline)

TOX. CHEM. NO: 083E

P.C.CODE.: 097801

MRID NO.: 433386-01

TEST MATERIAL: SBP-1382

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

STUDY NUMBER: Laboratory Project ID 83753 (RBC-RSM-2)

SPONSOR: Roussel UCLAF Corporation, Montvale, NJ

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

TITLE OF REPORT: A 4-Week Dietary Toxicity Study of SBP-1382 in the Albino Mouse

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

REPORT ISSUED: November 27, 1989

EXECUTIVE SUMMARY: In a 4-week range-finding study for a 2-year carcinogenicity study, SB-1382 (resmethrin technical, 88.8% a.i.) was administered in the diet for 4 weeks to 10 male and 10 female Swiss Crl:CD-1(ICR)BR mice/dose group at levels of 0, 625, 1250, 2500 or 5000 ppm (time-weighted average doses of 0, 105.5, 205.1, 452.3 or 994.5 mg/kg/day for males and 0, 130.8, 298.9, 546.7 or 1195.1 mg/kg/day for females based on theoretical concentration in the diet).

At 1250 ppm, slightly increased absolute and relative liver weights (+32%, males; +23%, females) and fine vacuolization of hepatocytes (9/20 animals) were observed in both sexes. At 2500 ppm, increases in SGOT (females), SGPT, alkaline phosphatase (males) and BUN (males) were observed. A single female had slight spleen atrophy. At 5000 ppm, decreased body weight/body weight gain (males), spleen atrophy, spleen and thymic lymphocytolysis and

decreased spleen weight (males) were observed. **The LEL (threshold) for systemic toxicity is 1250 ppm (205.1 mg/kg/day), based on increased incidence of hepatocyte fine vacuolization and mild liver enlargement. The NOEL is 625 ppm (105.5 mg/kg/day).**

This study is classified as **core-supplementary**. It was submitted as additional information (range-finding study for mouse carcinogenicity study) and not to fulfill guideline requirements for resmethrin.

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: 88.8% a.i.
   Stability of compound: stable in dark at room temperature
   CAS #: 10453-86-8

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

3. Test animals: Species: Mouse (albino)
   Strain: Swiss Crl:CD®-1(ICR)BR
   Age/weight at study initiation: About 6 weeks. 25.0 - 29.1 g, males; 20.6 - 24.5g, females
   Source: Charles River Canada, St. Constant, Quebec

   Housing: individually in mesh-bottomed stainless steel cages (2/cage during acclimatization)
   Environmental conditions: Temperature: 22±3°C
   (Target ranges) Humidity: 50±20%
   [Report stated that only minor deviations were occasionally observed which did not affect study results.]
   Air changes: not indicated
   Photoperiod: 12 hr light/12 hr dark
   Acclimation period: 1 week

B. STUDY DESIGN:

1. Animal assignment

This study was conducted as a range-finding study for a 2-year carcinogenicity study in CD-1 mice (MRID 43052101; reviewed in HED doc. no. 011067). Animals were assigned randomly to the test groups shown below in Table 1.

TABLE 1: STUDY DESIGN

Test Group	Dose in diet (ppm)	Dose in diet (mg/kg/day)	Study duration 4 wks. male	female
1 Control	0	0	10	10
2 Low dose (LDT)	625	105.5♂/130.8♀	10	10
3 Mid (MDT1)	1250	205.1♂/298.9♀	10	10
4 Mid (MDT2)	2500	452.3♂/546.7♀	10	10
5 High (HDT)	5000	994.5♂/1195.1♀	10	10

2. Diet preparation and analysis

Treated diets were prepared weekly by liquefying the test material at 50° C, mixing with acetone vehicle and mixing appropriate amounts into laboratory diet. The test material was assumed to be 100% for purposes of diet preparation. Diets were stored in the dark at room temperature. Stability and homogeneity of the test compound in diet preparations (control, 625 ppm and 5000 ppm) were analyzed using the same samples prior to initiation of the study: stability after 0, 4, 8 and 14 days storage in room temperature in feeders (top and bottom of jars) and homogeneity by analysis of samples from top, middle and bottom of the mixer at discharge. Concentration of test compound in diet was analyzed at Weeks 1 and 4 using gas chromatographic methods.

Results - Stability Analysis: Resmethrin was demonstrated to be stable in the diet for at least 14 days. One sample taken on day 8 showed variation in measurements: 85.1% for top of jar and 57.1% for the bottom. Reanalysis of the bottom sample gave a mean of 72.4±2.7% and analysis of a second sample taken from the bottom gave 88.8%. The study authors attributed the variation to inhomogeneity and as a result also analyzed homogeneity of the Week 1 sample at 625 ppm to ensure homogeneity.

Homogeneity Analysis: Analyses demonstrated acceptable homogeneity of test material in diet preparations. Analytical concentrations at top, middle and bottom of the mixer discharge were within 3% of their mean concentration. Analysis of the 625 ppm group

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for Week 1 also showed acceptable homogeneity (within 3% of their mean concentration).

Concentration Analysis: Overall, the test material concentration in the diet samples taken from Weeks 1 and 4 was within acceptable range of target concentration. Individual measurements for each dose level were within 13% of target concentration and mean concentration measurements for each dietary concentration were within 10% of target concentration with the following exceptions: at week 1, 2500 ppm (12% less) and at week 4, 625 and 1250 ppm (11% less than target). TB-I does not consider this variation to affect the study.

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 and organ weight data for homogeneity of variance. When variance of data was homogeneous, ANOVA and Dunnett's t test were used. When variance of data was heterogeneous, Kruskal-Wallis test was used and significance of intergroup differences was analyzed using Dunn's test. Clinical observation and gross/microscopic pathology data were apparently not analyzed for statistical significance.

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

C. METHODS AND RESULTS

1. Clinical Observations/Mortality:

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: One male (#5009) in the 5000 ppm dose group died on day 5. There was no mortality among females.

Clinical signs: One male (#5005) at 5000 ppm had reduced activity and hyperreflexivity during the ophthalmologic examination following administration of atropine. The study author noted that this animal had also shown significant weight loss (6.5g) during the fourth treatment week. A second male (#5006) was reported to appear thin and produce few feces during week 4, when a 0.1 g weight loss was

observed. No clinical signs of toxicity were observed in females.

2. Body weight

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

Results - Mean weekly body weights and total weight gain for the 4-week dosing period are shown below in Table 2:

TABLE 2: MEAN WEEKLY BODY WEIGHT AND TOTAL BODY WEIGHT GAIN (G)[1]

DOSE, PPM	0	625	1250	2500	5000
MALES					
Week 1	28.47±1.63	28.47	28.66	28.71	26.89±2.13
Week 2	29.50±1.86	29.32	30.02	29.79	27.88±2.75
Week 3	30.43±1.90	30.43	31.10	30.65	29.23±2.51
Week 4	31.74±1.96	31.21	32.17	31.59	28.89±3.54**
Total Gain	4.69	4.10	5.31	4.79	1.81
FEMALES					
Week 1	23.32±0.99	23.71	22.87	23.87	23.72±1.23
Week 2	23.92±0.90	24.21	23.39	24.83	23.41±1.30
Week 3	24.58±1.31	25.39	23.64	25.89	24.25±1.36
Week 4	25.61±1.51	26.05	24.81	26.04	25.12±1.36
Total Gain	2.90	3.25	2.81	3.82	2.41

1 Data taken from Table 3 of study report
* $p < 0.05$; ** $p < 0.01$

Statistically significant decreases in mean body weight were observed in males at 5000 ppm compared to controls (-8.4%). The study report noted that gain was also significantly decreased but did not provide a "p" value. Males at 5000 ppm gained 61% less weight than controls. No statistically significant decreases in mean body weight were observed in females; gain at 5000 ppm was lower than controls but represented only a 2% decrease in mean body weight.

3. Food consumption and compound intake:

Food consumption for each animal was measured weekly and mean consumption was calculated as g food/animal/week. Spillage was assessed twice weekly for correction of food consumption values.

Results - No treatment-related effects on mean weekly food consumption were observed. Food consumption was variable among dose groups but did not show a treatment-related effect. Total food consumption by males at 625 and 1250 ppm was

about 10% less than controls or males at 2500 and 5000 ppm; total consumption by females at 1250 and 5000 ppm was 7 - 9% more than the other treated or control groups. During the study, males consumed a total of 151.3, 138.3, 136.4, 149.6 and 155.9 g (low to high dose, respectively) and females consumed 146.7, 143.1, 156.1, 150.0 and 159.5 g (low to high dose).

- Compound consumption: The study author provided mean minimum achieved intake values of SBP-1382 for males of 105.5, 205.1, 452.3 and 994.5 mg/kg/day, low-to high dose, respectively, and for females of 130.8, 298.9, 546.7 or 1195.1, low to high dose.

4. Ophthalmoscopic examination

Eyes of all surviving animals were examined by indirect ophthalmoscopy and biomicroscopy slit microscopy pretreatment and during Week 5.

Results - No treatment-related effects were observed.

5. Hematology

Blood was collected from the orbital sinus at 4 weeks for clinical chemistry and hematology analyses from 5 males and females/dose group. Animals were fasted overnight prior to collection of blood.

a. Hematology

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

* Required for subchronic studies

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

b. Clinical Chemistry

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

* Required for subchronic studies

Results - Selected clinical chemistry parameters are shown below in Table 3:

TABLE 3: SELECTED CLINICAL CHEMISTRY PARAMETERS AT 4 WEEKS[1]

		Dietary concentration, ppm				
Clinical Parameter/Sex		0	625	1250	2500	5000
Blood urea nitrogen (mg/dl)	♂	24.0 (2)[2]	25.4 (4)	25.0 (3)	40.4 (3)	38.1 (2)
	♀	22.2 (1)	--	26.8 (2)	20.6 (3)	32.3 (2)
SGOT (U/L)	♂	99.0 (4)	111.2 (5)	111.0 (4)	127.2 (5)	317.0** (2)
	♀	135.0 (3)	140.3 (4)	161.6 (5)	211.0 (5)	164.8 (5)
SGPT (U/L)	♂	37.3 (4)	30.6 (5)	53.0 (4)	73.0 (4)	112.0* (3)
	♀	36.0 (3)	47.7 (3)	42.8 (4)	79.8 (4)	52.3 (4)
Alk. Phosphatase (U/L)	♂	122.7 (4)	106.3 (5)	108.5 (4)	214.5 (4)	203.0 (3)
	♀	125.0 (2)	141.3 (3)	186.3 (3)	156.3 (3)	228.3** (3)

1 Data taken from Tables 7 and 8 of study report
2 Number in parentheses is N or number of animals sampled
* $p < 0.05$ ** $p < 0.01$

Statistically significant increases in SGOT and SGPT (males) and alkaline phosphatase (females) were observed at 5000 ppm. BUN was increased in females at 2500 ppm and both sexes at 5000 ppm. At 2500 ppm, SGOT (females), SGPT (both sexes) and alkaline phosphatase (males) were

increased compared to controls due to elevation in one or two animals. Interpretation of the clinical chemistry data was complicated by the small and variable sample size. Clinical chemistry evaluations were limited by lack of adequate blood samples for analysis of all of the parameters. Females were not examined for blood ions, total protein, albumin or A/G ratio and males were not evaluated for Na, K or Cl. Many other parameters only were evaluated in 1 - 3 animals.

TB-I considers the increased values of the above liver-related clinical chemistry parameters at 2500 and 5000 ppm to be probable effects of treatment, due to increases in one or more individual animals and because liver is a target organ for resmethrin, based on the other liver parameters (weight, microscopic pathology) that were affected in this study. However, TB-I did not agree with the study author that the marginal increases in enzymes at 1250 ppm were treatment-related.

6. Sacrifice and Pathology

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

X		X		X	
Digestive system		Cardiovasc./Hemat.		Neurologic	
X	Tongue	X	Aorta*	XX	Brain*
X	Salivary glands*	XX	Heart*	X	Periph. nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	XX	Pituitary*
X	Duodenum*	XX	Spleen	X	Eyes (optic n.)*
X	Jejunum*	X	Thymus*	Glandular	
X	Ileum*	Urogenital		XX	Adrenal gland*
X	Cecum*	XX	Kidneys*+		Lacrimal gland
X	Colon*	X	Urinary bladder*	X	Mammary gland*
X	Rectum*	XX	Testes*+	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*
X	Lung*	X	Vagina	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 kidney weights are shown below in Table 4:

TABLE 4: SELECTED ABSOLUTE (G) AND RELATIVE (% BODY WEIGHT) ORGAN WEIGHT DATA[1]

PPM IN DIET		0	625	1250	2500	5000
MALES:						
Liver	abs	1.12±.076	1.20	1.48*	1.86**	2.49±.396**
	rel	4.13±.188	4.56	5.36*	7.18**	10.43±1.66**
Spleen	abs	0.072±.013	0.063	0.083	0.063	0.049±.018*
	rel	0.264±.039	0.241	0.298	0.244	0.200±.058**
Kidney	abs	0.426±.021	0.412	0.421	0.447	0.423±.036
	rel	1.58±.180	1.57	1.53	1.73	1.77±.143
FEMALES:						
Liver	abs	0.904±.075	1.11**	1.15**	1.71**	2.05±.134**
	rel	4.30±.273	5.207	5.62	7.80**	10.20±1.49**
Spleen	abs	0.067±.004	0.079	0.064	0.075	0.060±.013
	rel	0.317±.046	0.370	0.314	0.343	0.295±.045
Kidney	abs	0.286±.024	0.311	0.421	0.343**	0.317±.027
	rel	1.37±.119	1.46	1.52	1.57	1.584±.265

1 Data taken from Tables 9-11 of Study Report.
* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

Absolute and relative liver weights had statistically significant increases at 2500 and 5000 ppm in both sexes. At 2500 ppm, increases of approximately 50% above controls were seen which increased to 2-fold or greater at 5000 ppm. Significantly enlarged livers were also seen at 1250 ppm in both sexes but the increase was smaller ($\leq$30%) and the decrease in relative weight was significant only in males. Although a significant increase in absolute liver weight was observed at 625 ppm in females (+23%), TB-I did not consider this increase adequate for determination of an LEL due to lack of other liver effects at that dose. Absolute/relative spleen weights were reduced in males (-32%/-24%). Spleen weight in females was slightly lower than controls (-10%) but was not significant. Unlike the 2-year study, kidney weights were not significantly increased; a significant increase in absolute kidney weight at 2500 ppm in females was not considered treatment-related due to lack of dose-response.

b. Gross pathology - Two males at 5000 ppm had enlarged livers and discoloration and two females at 2500 ppm and one at 5000 ppm had discoloration of the liver. No other

treatment-related gross lesions were observed.

c. Microscopic pathology -

1) Non-neoplastic - Table 5 shows the incidence of selected microscopic lesions observed in this study (preterminal and terminal animals combined):

TABLE 5: INCIDENCE OF SELECTED NONNEOPLASTIC MICROSCOPIC LESIONS[1]

OBSERVATION	DOSE IN DIET, PPM 0 (1)	625	1250	2500	5000
MALES					
LIVER:					
Fine vacuolization	0	0	4	10	10
Hypertrophy	1	0	1	9	1
SPLEEN: Atrophy	0	0	0	0	6
THYMUS:					
Lymphocytolysis	0	0	0	0	4
Atrophy	0	0	0	0	1
Cortical necrosis	0	0	0	0	2
FEMALES					
LIVER:					
Fine vacuolization	0	0	5	10	9
Hypertrophy	1	0	0	4	10
SPLEEN:					
Atrophy	0	0	0	1	1
Lymphocytolysis	0	0	0	0	3
THYMUS: Lymphocytolysis	1	1	1	4	4

1 Data taken from Table 14 of study report. For all groups N = 10.

No treatment related effects were observed at 625 ppm. At 1250 ppm, incidence of fine vacuolization of hepatocytes (mostly grade 2 or mild severity) was observed in about half of the males and females. Incidence of this lesion showed a dose-dependent increase and severity was slightly increased (increased frequency of grade 3 or moderate severity at 2500 and 5000 ppm). The study author noted that vacuolization was primarily periportal and was associated with granular appearance of liver cytoplasm and often liver enlargement. Hypertrophy was observed in males and females at 2500 and 5000 ppm, although the reason for the decrease in males at 5000 ppm compared to 2500 ppm (1 animal vs. 9) is unclear.

In addition, lymphocytolysis of the spleen and thymus was observed at 2500 and 5000 ppm. Atrophy of the spleen was observed primarily in males at 5000 ppm but one female at 2500 and at 5000 ppm also were affected. Thymic atrophy and cortical necrosis were observed in males at 5000 ppm (1 and 2, respectively). Because these effects were not seen in control animals except for thymic lymphocytolysis in one female, and given the young age of these animals, TB-I agreed with the study author that lymphocyte effects

were related to treatment. The splenic atrophy observed in 6/10 males correlated with the reduced spleen weight at 5000 ppm. A single female with spleen atrophy also had a lower spleen weight.

E. DISCUSSION:

In this 4-week mouse feeding study, liver and spleen/thymic lymphocytes were the main target organs for resmethrin. At 2500 and 5000 ppm, liver enlargement and fine vacuolization and hypertrophy were observed in both sexes. At 5000 ppm, several liver-related clinical chemistry parameters were observed. Effects were less pronounced at 1250 ppm: 9/20 animals had fine vacuolization and liver weights were only marginally increased. Interpretation of clinical chemistry data was complicated by the small sample size for some dose groups. Atrophy and/or lymphocytolysis of the spleen and thymus at 5000 ppm in males and at 2500 and 5000 ppm in females were also observed.

Based on the results of this 4-week feeding study, the study author selected 1250 as a maximum tolerated dose (MTD) for a subsequent mouse carcinogenicity study. TB-I considers the toxicity observed at this dose to be marginal and the MTD to be greater than 1250 ppm.

F. STUDY DEFICIENCIES: blood from inadequate numbers of animals assayed for numerous clinical chemistry parameters.

This study was conducted as a range-finding study for the mouse carcinogenicity study and was submitted as additional information on resmethrin. The study is Core-supplementary since it was not conducted as a guideline study, but does provide useful information for effects from short-term repeated dietary exposure to resmethrin.

EPA Reviewer: Linnea J. Hansen, Ph.D.
Review Section IV, Toxicology Branch I (7509C)
EPA Section Head: John Doherty, Ph.D., D.A.B.T.
Review Section IV, Toxicology Branch I (7509C)

Linnea J. Hansen Date 9/21/95
John Doherty, Date 9/20/95

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 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.

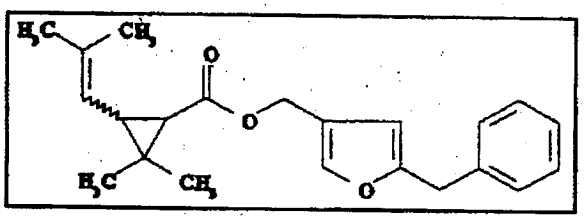
The chronic toxicity phase of the study **(83-1a)** is classified as **Core-minimum** and the carcinogenicity phase of the study **(83-2a)** is classified as **Core-supplementary (not upgradable)**. This study, taken together with a newer rat chronic toxicity/carcinogenicity study (MRID 43601601; reviewed 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

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.

a. Hematology

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

* Required for subchronic and chronic studies

Results - See original DER

b. Clinical Chemistry

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

* Required for subchronic and chronic studies

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

4. Urinalysis

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

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

* Required for chronic studies

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

5. Sacrifice and Pathology

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

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

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

Organ weights: See original DER and table, below:

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

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

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

Pathology: See original DER and previous two supplemental DERs.

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 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). 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 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.