8-22-95

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Chemical:	**Resmethrin (ANSI)**
PC Code:	**097801**
HED File Code	**13000 Tox Reviews**
Memo Date:	**08/22/95**
File ID:	**TX011650**
Accession Number:	**412-01-0073** /43601601

HED Records Reference Center
12/15/2000

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

8/22/1995

OFFICE OF PESTICIDE PROGRAMS
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM **6(a)(2) Data**

SUBJECT: Resmethrin (SB-1382). ID No. 000432-00487. Review of Chronic Rat Feeding/Carcinogenicity Study Submitted as 6(a)(2) Data.

PC. No.: 097801
Tox. Chem. No.: 083E
Proj. No.: D214512
Submission No.: S485109

FROM: Linnea J. Hansen, Ph.D.
Section IV, Tox. Branch I
Health Effects Division (7509C)
Linnea Hansen 7/26/95

TO: Rick Keigwin, Manager
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Health Effects Division (7509C)
John Doherty 8/2/95

Marion P. Copley, D.V.M., D.A.B.T., Acting Branch Chief
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CONCLUSIONS:

TB-I has evaluated the rat chronic toxicity/carcinogenicity feeding study on resmethrin (see Executive Summary, below, for summary of results). Based on the results of this study (increased incidence of liver and uterine tumors in female rats), resmethrin will be referred to the HED Cancer Peer Review Committee for determination of cancer classification.

EXECUTIVE SUMMARY: In a chronic toxicity/carcinogenicity study (MRID 43601601), 65 Crl:CD BR rats/sex/dose group were fed 0, 250, 1000 or 2500 ppm SB-1382 (resmethrin, 85% a.i.) in their diet for 2 years. Doses correlated to an average daily intake of 10.4, 41.8 or 107.2 mg/kg/day a.i. in males and 12.8, 51.7 or 131.4 mg/kg/day a.i. in females.

At 2500 ppm, mean body weight gain was decreased in females

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EPA Reviewer: Linnea J. Hansen, Date 6/28/95
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: John Doherty, Acting Section Head, Date 8/2/95
Review Section IV, Toxicology Branch I (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Chronic toxicity/carcinogenicity in rodent (83-5)

TOX. CHEM. NO: 083E

P.C.CODE.: 097801

MRID NO.: 43601601

TEST MATERIAL: Resmethrin, technical

SYNONYMS: SB-1382, 5-benzyl-furylmethyl (IRS)-cis,trans-chrysanthemate

STUDY NUMBER: HWA 2623-104

SPONSOR: Roussel UCLAF Corporation, Montvale, NJ

TESTING FACILITY: Hazleton Washington, Vienna, VA

TITLE OF REPORT: Combined Chronic Toxicity and Oncogenicity Study in Rats with SBP-1382 (Resmethrin) Technical

AUTHOR: Janet A. Trutter, M.S., D.A.B.T.

REPORT ISSUED: December 28, 1994

EXECUTIVE SUMMARY: In a chronic toxicity/carcinogenicity study (MRID 43601601), 65 Crl:CD BR rats/sex/dose group were fed 0, 250, 1000 or 2500 ppm SB-1382 (resmethrin, 85% a.i.) in their diet for 2 years. Doses correlated to an average daily intake of 10.4, 41.8 or 107.2 mg/kg/day a.i. in males and 12.8, 51.7 or 131.4 mg/kg/day a.i. in females.

At 2500 ppm, mean body weight gain was decreased in females (up to 20% less than controls) during the last months of the study and a slight increase in the severity of hepatocellular eosinophilic cellular alteration was observed. Anemia (28 - 30% decrease in RBC parameters) was observed in males at week 104. **The threshold LOEL for systemic toxicity is 2500 ppm, based on slight body weight decrease in females and decreased RBC parameters in males, both observed in the last months of the study. The NOEL is 1000 ppm.**

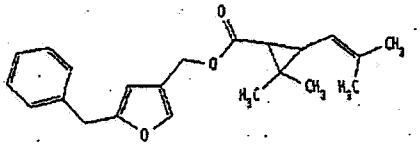
In females, statistically significant increases in the incidence of hepatocellular carcinoma and combined hepatocellular adenoma/carcinoma (16.9% and 21.5%, respectively, vs. 0%, controls) were observed at 2500 ppm. Hepatocellular adenoma was observed in one female at 1000 ppm. The incidence of uterine endometrial stromal polyps was 0% in controls but 1.8%, 5.7% and 7.7% in the low, mid and high dose groups. The HED Cancer Peer Review Committee will determine the carcinogenicity classification of resmethrin.

This study is Core-minimum and satisfies the guideline requirements for a chronic dietary toxicity/carcinogenicity study in rat (83-5). Marginal toxicity was achieved at the HDT and some hematology parameters were lacking.

Special Review Criteria (40 CFR 154.7) None

A. MATERIALS:

1. Test Material: Resmethrin (SB-1382), technical
   Description: brown liquid (solidifying upon exposure to air)
   Lot/Batch #: IN-0837 B3
   Purity: 85% reported by sponsor, impurities not specified
   Stability of compound: Stable at room temperature when stored in dark
   Vehicle: acetone (Mallinckrodt, reagent grade)
   CAS #: 10453-86-8
   Structure:



2. Test animals: Species: rat
   Strain; Crl:CD®BR
   Age and weight at study initiation: 6 weeks old at study start; Males weighed from 179 to 232 g and females between 143 and 193 g
   Source: Charles River Laboratories, Inc., Raleigh, NC
   Housing: individual stainless-steel wire mesh cages
   Environmental conditions: Temperature 62 to 78.6°C. Humidity 19.9% to 78.5%. Light cycle: 12 hr on/12 hr off. Air changes: 15X/hr.
   Acclimation period: 2 weeks
   Diet: Purina Certified Rodent Chow #5002

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B. STUDY DESIGN:

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

TABLE 1: ANIMAL ASSIGNMENT

Test Group	Dose Level		Number Assigned	
	ppm	mg/kg/day[1]	males	females
Control	0	0	65	65
Low Dose	250	10.4♂, 12.8♀	65	65
Mid Dose	1000	41.8♂, 51.7♀	65	65
High Dose	2500	126.1♂, 131.4♀	65	65

1 Average daily compound intake values represent the daily intake of a.i. The compound intake values calculated by study authors (based on food consumption and body weight data) were multiplied by 0.85 to adjust for purity of the a.i. by TB-I.

Dose selection rationale: Doses were selected based on the results of a 90-day feeding study. No further details were provided in the study report but upon request by TB-I the study was provided. Results are briefly summarized in the Appendix of this DER. In the opinion of TB-I, the results of the range-finding study suggest that a high dose greater than 2500 ppm could have been tolerated in the chronic study, particularly in males. This is supported by the earlier chronic study in rats (see Discussion, below).

2. Test material dosing preparation and analysis

Test diets were prepared weekly in Purina Diet #5002 at nominal resmethrin concentrations of 0, 250, 1000 and 2500 ppm. Test material was not adjusted for purity of the active ingredient (100% purity assumed). Test material was heated to 50°C, mixed with acetone vehicle (1% of test diet volume) and premixes prepared. Test diets at the appropriate concentrations were prepared by mixing the premix in a twin-shell mixer with intensifier bar. Homogeneity of 250 and 3000 ppm diets was assessed prior to start of, but not during, the study. The study report stated that at the time of analysis, 3000 ppm was the anticipated high dose for this study but did not indicate why it was changed to 2500 ppm. Stability of the 250 and 3000 ppm dietary preparations was determined from analysis of preparations on Days 0, 7 and 15 stored at room temperature. Duplicate samples from diets at all dose levels were analyzed weekly for concentration during the first 4 weeks of the study and every 4 weeks thereafter. All analyses were conducted by gas chromatography using flame ionization detection.

Results - Concentration: The concentration of test material in the batches of diet prepared for this study were within acceptable range of target concentration. The grand means for each dose group were 94.4%, 96.0% and 97.4% of target (236.1, 960.2 and 2435 ppm, respectively). Individual weekly preparations were within 10%,

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High Dose	2500	126.1♂, 131.4♀	65	65

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usually better, of target concentration with the following exceptions at the 250 ppm level: week 56 (85.9%), week 64 (86.6%) and week 76 (88%).

Homogeneity: The test material was determined to be homogeneously distributed in the diet in the samples tested prior to the study start. The percent relative standard deviations for samples taken from the top, middle and bottom portions of the batches analyzed were 1.51% at 250 ppm and 1.38% at 3000 ppm. Although homogeneity was not tested during the study, the consistency of the duplicate and the weekly samples indicates that acceptable homogeneity was probably achieved during the study.

Stability: Resmethrin was determined to be stable for at least 14 days when stored at room temperature. There were slight decreases in percent of target concentration observed at 250 and 3000 ppm, but values were within 5% of the mean Day 0 recoveries.

3. Animals received food and water ad libitum.

4. Statistics - Cumulative survival was analyzed using life table techniques (Kaplan-Meier product limit estimates, Cox-Tarone binary regression on life tables and Gehan-Breslow methods).

   Body weight, body weight gain, food consumption, clinical pathology and hematology data (except cell morphology and serum hemolysis grading) and organ weight data were analyzed by Levene's test of homogeneity of variances. Homogeneous data were analyzed by ANOVA. Data that were heterogeneous were transformed prior to analysis by ANOVA, followed by Dunnett's test, when significant. When the series of transformations did not achieve variance homogeneity, analyses were performed on rank-transformed data. Clinical observations and gross and nonneoplastic observations were not analyzed statistically.

   For tumors that are not rapidly lethal or palpable, a survival-adjusted incidental tumor method was used for analysis of incidence (logistic regression of tumor prevalences, method of Dinse and Lagakos). Palpable mammary tumors in females were analyzed using life table techniques as described for analysis of survival. Trend was evaluated where monotone responses were observed. Continuity corrected test statistics were used for evaluation of all the incidence tables, where appropriate. Bonferroni's adjustment of significance levels was used for comparison of control and treated groups in the absence of a valid monotone trend. Benign and malignant tumors were analyzed independently and combined where combination was considered appropriate. Analyses were not performed on groups where less than 75% of the tissues were examined microscopically.

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5. A signed and dated quality assurance statement and a GLP statement were present.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected twice daily for signs of toxicity and mortality; a careful cageside exam was performed once daily. A complete physical examination was performed at weighing times.

Results - Selected clinical signs are shown below in Table 2:

TABLE 2: SELECTED CLINICAL SIGNS[1]

Clinical sign/sex	0 ppm	250 ppm	1000 ppm	2500 ppm
MALES:				
Ataxia	9	5	11	15
Hypoactivity	15	16	20	26
Thin	21	20	19	34
Pale body	2	3	5	6
Few feces	8	10	17	19
Pale eyes	3	5	4	12
FEMALES:				
Ataxia	13	17	19	19
Hypoactivity	24	29	33	22
Thin	33	33	36	12
Pale body	5	10	11	2
Few feces	20	26	25	22
Pale eyes	1	8	0	10

1 Data extracted from Table 3 (pp. 97-109) of study report. Data not analyzed statistically.
2 Numbers reflect number of animals affected and not frequency or severity. Severity of signs not indicated in study report.

Several clinical signs (shown above in Table 2) were observed in more of the 2500 ppm males than the controls and ataxia occurred among more treated females than controls. However, TB-I examined the individual animal data and agreed with the study author that these were probably not treatment-related effects. In the majority of cases, onset of these signs shortly preceded unscheduled death/moribund sacrifice, or occurrences were sporadic. Among all animals including those that survived to termination, signs did not appear until very late in the study, were generally sporadic and were not consistent for males and females. Ataxia and other signs were often observed among animals that died or were sacrificed moribund and had pituitary tumors, which were not increased by treatment with resmethrin. Thinness, pallor and

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hypoactivity may be observed in old animals.

Other frequently observed clinical signs among all animal groups included sores especially on the feet of males, urine stains, periorbital and perinasal staining, alopecia, chromodaccryorrhea, dyspnea, soft feces, anorexia, malocclusion and swelling in various regions of the body.

Survival at selected times during the study is shown below in Table 3:

TABLE 3: SURVIVAL AT SELECTED INTERVALS DURING THE STUDY[1]

		0 ppm	250 ppm	1000 ppm	2500 ppm
MALES:	Week 26	64 (98)[2]	64 (98)	64 (98)	65 (100)
	52	64 (98)	63 (97)	63 (97)	65 (100)
	78	56 (86)	48 (75)	48 (75)	58 (89)
	104	27 (43)	29 (45)	29 (45)	31 (48)
	Termination	26 (41)	29 (45)	29 (45)	31 (48)
FEMALES:	Week 26	65 (100)	65 (100)	65 (100)	65 (100)
	52	64 (98)	62 (95)	64 (98)	64 (98)
	78	56 (86)	53 (82)	55 (85)	54 (83)
	104	31 (48)	18 (28)	17 (27)	29 (45)
	Termination	31 (48)	18 (28)*	17 (27)*	28 (43)

1 Data extracted from Table 2A (pp. 81 - 87) of study report
2 Number of survivors (percent survival)
* $p \leq 0.05$ (only cumulative survival was analyzed statistically)

No treatment-related effects on survival were observed. A statistically significant decrease in survival of low and mid-dose females was observed at termination. Survival in these groups began to decrease relative to controls during the last 18-20 weeks of the study. TB-I agreed with the study author that this was not treatment-related since no dose-response was observed. The reason for reduced survival at these doses was unclear. The major causes of mortality noted by the study author were neoplasms of the pituitary gland, mammary gland (females) and hematopoietic system.

2. Body weight

Animals were weighed prior to initiation of treatment, weekly from Weeks 1 to 17 and every 4 weeks for the duration of the study.

Results - Mean body weights at selected intervals and cumulative body weight gain for males and females are shown below in Table 4:

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TABLE 4: SELECTED MEAN BODY WEIGHT VALUES AND CUMULATIVE GAIN (GRAMS)[1]

DOSE, PPM:	0	250	1000	2500
Males:				
Initial wt.	204	202	204	200
Week 26	661	664	668	657
Week 52	737	741	763	744
Week 78	745	751	758	735
Week 101	685	708	698	674
Week 105	659	685	665	627
CUMULATIVE GAIN, 1 YR	533	540	560	544
2 YR	461	485	462	430
Females:				
Initial wt.	164	164	165	165
Week 26	370	374	367	368
Week 52	431	439	443	419
Week 78	475	487	494	468
Week 101	504	511	504	453*
Week 105	491	501	484	427*
CUMULATIVE GAIN, 1 YR	266	275	279	254
2 YR	327	340	317	263*

1 Data taken from Table 4a (PP. 111 - 115) of study report
* $P \leq 0.05$

Results - For most of the study, no treatment-related differences in body weight/weight gain were observed in either sex. Statistically significant reductions in body weight were observed on three occasions in high-dose males and a single occasion in high-dose females, but were not considered treatment-related due to the small magnitude ($\leq$3%) and sporadic occurrence. However, body weight/weight gain decreased during the last months of the study in females at 2500 ppm. At weeks 101 and 105, statistically significantly decreased body weight (-9% and -13% of controls, respectively) and weight gain (-20% of controls, week 105) were observed in high dose females. This correlated with a slight decrease in food efficiency during the last weeks (see below).

Males showed a slight decrease in body weight/weight gain only during the last few weeks of the study, but the decrease was small (at week 105, less than 5%, body weight and 10%, body weight gain) and not statistically significant. The study authors considered the decreases in both males and females to be age-related and unrelated to treatment and noted that the body weights were within historical control range. TB-I agrees with this conclusion for males, but considers the decrease in females to be treatment-related. No treatment-related effects were observed at lower doses in either sex.

3. Food consumption

Food consumption was recorded weekly pretest, between Weeks 1 to 17 and every 4

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weeks thereafter. Food efficiency was calculated by the study authors based on body weight gain (grams) and food consumption (grams) during a given interval.

Results - No treatment-related decreases in mean food consumption were seen during the study. Sporadic statistically significant differences from controls were observed among treated animals, but a consistent, dose-related effect was not observed.

There were no consistent effects on food efficiency during the study that appeared to be treatment-related, although a slight decrease in high-dose females compared to other dose groups occurred during the last few weeks of the study. This may have been related to the decline in body weight of high-dose females during that time.

4. Ophthalmoscopic examination

A complete indirect ophthalmologic examination was performed on all animals at pretest and on survivors at 104 weeks.

Results - No treatment-related ocular effects were observed. An increased incidence of corneal opacities was observed at 104 weeks in surviving males at 2500 ppm (5/31, vs. 1/31, 1/35 and 1/29 at 0, 250 and 1000 ppm, respectively). A similar increase was not observed in females. The corneal opacities observed in surviving males at high dose varied in character (eg., diffuse vs. focal, neovascularization). TB-I agreed with the study ophthalmologist that the opacities were probably related to age, trauma or environmental conditions, rather than treatment. There was no accompanying increase in the incidence of microscopic lesions of the eye in high dose males.

5. Blood was collected from the orbital sinus of the first 10 animals/sex/dose group (fasted overnight) at Weeks 26, 52, 72 and 104 for clinical analysis and hematology (no pretest samples were collected). The CHECKED (X) parameters were examined.

a. Hematology

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

* Required for subchronic and chronic studies

** Control, high dose and moribund animals only

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Results - Selected hematology parameters are shown below in Table 5:

TABLE 5: SELECTED HEMATOLOGY PARAMETERS[1]

		0 ppm	250 ppm	1000 ppm	2500 ppm
MALES:					
RBC count (MI/µl)	Week 26	8.79	8.56	8.39	8.48
	52	8.07	7.74	7.90	7.67
	78	7.91	7.22	7.89	7.44
	104	7.76	7.00	7.22	5.63*[2] (27.5)
Hemoglobin (g/dl)	Week 26	16.1	16.0	15.3*	15.3*
	52	15.5	15.3	15.1	14.5
	78	14.8	13.6	14.4	13.5
	104	14.3	13.1	12.9	9.9* (30.7)
Hematocrit (%)	Week 26	45.4	45.2	42.7*	42.9*
	52	41.8	41.2	40.6	38.7
	78	42.0	38.8	40.5	38.2
	104	41.2	37.3	37.0	29.3* (28.9)
FEMALES:					
RBC count (MI/µl)	Week 26	8.00	8.20	7.95	8.17
	52	7.53	7.69	7.41	7.36
	78	7.22	7.15	6.88	7.55
	104	6.22	6.44	6.35	6.36
Hemoglobin (g/dl)	Week 26	15.8	15.8	15.4	15.4
	52	15.5	15.6	15.1	14.8*
	78	14.5	14.0	13.5	14.4
	104	12.4	12.2	12.5	12.2
Hematocrit (%)	Week 26	43.4	42.7	42.7	43.7
	52	41.3	40.1	40.1	39.4
	78	39.8	37.8	37.8	40.6
	104	35.3	35.6	35.6	34.5

1 Data taken from Table 7A (p. 154) of study report
2 Numbers in parentheses indicate percent increase compared to controls; only shown where increase is greater than 10%.
* $p \leq 0.05$

Males at 2500 ppm showed statistically significantly decreased RBC count, hemoglobin and hematocrit at 104 weeks (decreased by approximately 30% compared to controls). Three of the males showed pronounced depression in these values. The study report provided historical control data for hematology values only for sampling times up to 80 weeks; these values were at the lower limit of the 80 week historical control data. Hemoglobin and hematocrit were also statistically significantly reduced in the 1000 and 2500 ppm males at week 26, but only by 5 to 6%. Hemoglobin and hematocrit were reduced by about 9% at week 78 at 2500 ppm, but not significantly. TB-I agreed with the study author that the decreases in high dose males at week 104 appeared to be

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treatment-related. There were no treatment-related effects on the RBC parameters of females; a single small but significant reduction in hemoglobin (less than 5% below controls) at week 52 was observed at 2500 ppm. No treatment-related effects on leukocyte counts or cellular morphology were observed in either sex.

b. Clinical Chemistry

X	Electrolytes:
X	Calcium*
X	Chloride*
	Magnesium
X	Phosphorus*
X	Potassium*
X	Sodium*
	Enzymes
X	Alkaline phosphatase (ALK)
	Cholinesterase (ChE)
X	Creatinine phosphokinase
	Lactic acid dehydrogenase (LDH)
X	Serum alanine aminotransferase (also SGPT)*
X	Serum aspartate aminotransferase (also SGOT)*
	Gamma glutamyl transferase (GGT)
	Glutamate dehydrogenase

X	Other:
X	Albumin*
X	Blood creatinine*
X	Blood urea nitrogen*
X	Cholesterol*
X	Globulins
X	Glucose*
X	Total bilirubin
X	Total serum protein (TP)*
X	Triglycerides
	Serum protein electrophores.

* Required for subchronic and chronic studies

Results - Selected clinical chemistry parameters are shown below in Table 6:

TABLE 6: SELECTED CLINICAL CHEMISTRY PARAMETERS[1]

SEX/PARAMETER/WEEK		0 ppm	250 ppm	1000 ppm	2500 ppm
Males:					
BUN	26	14	14	14	18*
(mg/dl)	52	12	11	12	12
	78	15	15	14	15
	104	16	16	16	20
Cholesterol	26	79	76	68	71
(mg/dl)	52	90	93	89	75
	78	109	99	109	88
	104	139	125	117	99
Triglyceride	26	136	138	124	130
(mg/dl)	52	116	138	98	85*
	78	138	111	97	89*
	104	122	158	93	84
Albumin	26	4.5	4.6	4.5	4.8*
(g/dl)	52	4.3	4.4	4.2	4.4
	78	4.0	3.8	3.9	4.1
	104	3.9	3.7	3.8	3.5
Globulin	26	2.3	2.3	2.2	2.1
(g/dl)	52	2.5	2.5	2.5	2.2
	78	2.8	2.8	2.6	2.6
	104	3.2	2.9	2.9	2.9
Females:					
BUN	26	13	15	15	18*
(mg/dl)	52	12	12	12	15*
	78	14	17	12	15
	104	18	17	17	16
Cholesterol	26	93	89	70	62*
(mg/dl)	52	112	98	73*	63*
	78	113	110	85*	63*
	104	102	123	90	76
Triglyceride	26	122	135	95	92
(mg/dl)	52	109	98	81	80
	78	149	129	76*	90
	104	88	146	75	46
Albumin	26	5.8	5.8	6.0	5.9
(g/dl)	52	5.6	5.5	5.9	5.3
	78	5.2	4.9	5.0	5.3
	104	4.4	4.3	4.5	4.8
Globulin	26	2.2	2.0	2.0	1.9
(g/dl)	52	2.4	2.3	2.2	2.0*
	78	2.6	2.5	2.4	2.3
	104	2.9	2.8	2.7	2.8

1 Data taken from Table 8A (pp. 168-173) of study report
* $p \leq 0.05$

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Statistically significant decreases in serum cholesterol (-33% to -44% lower than controls) were observed in females at 2500 ppm at 26, 52 and 78 weeks. Mean values in the 2500 ppm group were at or below historical control range for female rats for the appropriate sampling time. At 1000 ppm, statistically significant reductions (-25 to -34%) were also observed but values were within historical control range. No significant effects on cholesterol were observed in males. Triglyceride levels showed statistically significant reductions (-27 to -36%) in males at weeks 52 and 78 at 2500 ppm but values were within historical control range, which varied considerably. No significant reductions were observed in females. TB-I considered the reduction in serum cholesterol to be related to treatment (possibly a mild hypolipidemic effect) but it was not used in determination of the LEL because the biological significance is unclear.

TB-I agreed with the study author that the other statistically significant changes in clinical chemistry parameters shown above in Table 6 were not treatment-related. The variations observed were within historical control range, not biologically significant and were not sustained.

6. Urinalysis

Urine was collected from fasted animals at Weeks 26, 52, 78 and 104 (no pretest samples were collected). The CHECKED (X) urine parameters were examined.

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

* Required for chronic studies

Results - No treatment-related effects were observed on the urinalysis parameters examined. A summary table of the urinalysis results was not included in the study report; examination of individual animal data and calculation of parameter mean values by the TB-I indicated no effects of treatment.

7. Sacrifice and Pathology

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

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

* Required for subchronic and chronic studies.

+ Organ weight required in subchronic and chronic studies.

Results -

a. Organ weight - Selected absolute and relative organ weights are shown below in Table 7:

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TABLE 7: SELECTED ABSOLUTE (G) AND RELATIVE (%) MEAN ORGAN WEIGHT DATA[1,2]

		0 ppm	250 ppm	1000 ppm	2500 ppm
Males:					
Liver	abs	19.64±2.38	19.71±4.41	20.54±2.92	22.49±4.28
	()[3]	--	--	--	(+15)
	rel	2.877±0.536	2.746±0.657	3.091±0.704	3.748±0.975*
	()	--	--	--	(+30)
Spleen	abs	1.32±0.27	1.69±0.79	1.50±0.67	1.77±0.81
	()	--	(+28)	(+14)	(+34)
	rel	0.199±0.051	0.235±0.112	0.223±0.104	0.299±0.169
	()	--	(+18)	(+12)	(+50)
Pituitary	abs	0.026±0.014	0.033±0.024	0.056±0.050	0.116±0.174
	()	--	(+27)	(+115)	(+346)
	rel	0.0038±0.0018	0.0046±0.0034	0.0094±0.0115	0.0228±0.0372
	()	--	(+21)	(+147)	(+500)
Females:					
Liver	abs	16.71±4.78	17.41±2.92	17.25±4.16	15.97±3.81
	()	--	--	--	--
	rel	3.400±0.696	3.413±0.901	3.701±0.704	3.790±0.826
	()	--	--	--	(+12)
Spleen	abs	1.13±0.51	0.91±0.44	0.87±0.87	0.78±0.24
	()	--	(-19)	(-21)	(-31)
	rel	0.233±0.106	0.179±0.084	0.185±0.185	0.187±0.071
	()	--	(-23)	(-25)	(-25)
Pituitary	abs	0.206±0.199	0.126±0.110	0.156±0.127	0.171±0.24
	()	--	(-39)	(-24)	(-17)
	rel	0.0504±0.0542	0.0246±0.0207	0.0357±0.0337	0.0452±0.0400
	()	--	(-51)	(-29)	(-10)

1 Data taken from Table 10 (pp. 213 - 222) of study report.
2 N = 10 for all groups except control male livers, where N = 9 due to exclusion of 1 animal with large liver mass.
3 Numbers in parentheses show % change from control values; only values ≥10% are given.
* $p \leq 0.05$

A statistically significant increase in the relative liver weight of males at 2500 ppm was observed (30.3% greater than controls). Absolute liver weight was also increased but the increase (14.5% greater than controls) was not statistically significant. The relative liver weight was increased because at termination, body weights of males at 2500 ppm were lower than controls (680, 720, 682 and 617 g, controls to high dose, respectively). TB-I considers the increase to be treatment-related but not toxicologically significant and not used to determine the LEL.

The pituitary gland and spleen showed variable changes (not statistically significant) in males and females and were not considered to be related to treatment. The large increase in mean pituitary gland weight in high-dose males appeared to be due to large

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pituitary neoplasms in several animals.

b. Gross pathology - Grossly observable lesions related to treatment were observed only in the liver. Table 8 below shows liver-related findings:

TABLE 8: SELECTED LIVER GROSS LESIONS[1]

Sex:Observation	0 ppm	250 ppm	1000 ppm	2500 ppm
MALES: (N = 65)				
Liver				
mass	4	1	1	2
pale	1	1	6	9
enlarged	18	16	18	20
FEMALES: (N = 65)				
Liver				
mass	3	1	1	11
pale	5	3	4	3
enlarged	7	9	10	7

1 Data taken from Tables 9A and 9B (pp. 185 and 201) of study report.

An increase in the incidence of liver masses was observed in females at 2500 ppm. The increase corresponded to the increased incidence of liver neoplasms (see Neoplastic lesions, below). A higher incidence of enlarged liver was observed in males at 2500 ppm among terminal sacrifice animals (1, 1, 4 and 11, low to high dose, respectively) but not total animals on the study. Dark areas were increased among high dose females. There was no consistent correlation with microscopic effects for the two findings.

c. Microscopic pathology - Selected nonneoplastic microscopic lesions are shown in Table 9 below:

TABLE 9: SELECTED NON-NEOPLASTIC MICROSCOPIC LESIONS[1]

Sex:Lesion	0 ppm	250 ppm	1000 ppm	2500 ppm
MALES:				
LIVER (# examined)	(65)	(65)	(65)	(65)
Eosinoph. cell. alt., min. to sl.	6 (9.2)	3 (4.6)	9 (12.3)	12
moderate	3 (4.6)	1 (1.6)	1 (1.6)	4 (6.2)
moderately severe	0	1 (1.6)	0	0
total incidence	9 (13.9)[2]	5 (7.7)	10 (15.4)	16 (24.6)
Hepatocell. enlarg., min. to sl.	0	2 (3.1)	1 (1.6)	1 (1.6)
Focal necrosis, min. to sl.	2 (4.6)	2 (3.1)	2 (3.1)	4 (6.2)
moderate	1 (1.6)	0	0	0
total incidence	3	2	2	4
Centrilob. degen./necr., min. to sl.	0	0	3 (4.6)	3 (4.6)
moderate	0	0	1 (1.6)	1 (1.6)
moderately severe	0	1 (1.6)	1 (1.6)	0
total incidence	0	1 (1.6)	5 (7.7)	4 (6.2)
Pigment, min. to sl.	0	0	4 (6.2)	4 (6.2)
moderate	0	0	1 (1.6)	0
total incidence	0	0	5 (7.7)	4 (6.2)
Thyroid (# examined)	(64)	(36)	(36)	(65)
C-cell hyperplasia, min. to sl.	1 (1.6)	1 (2.7)	7 (19.4)	9 (13.8)
Lymph node, mesenteric (# examined)	(57)	(34)	(32)	(55)
Reticuloendothelial hyperplasia	6 (10.5)	3 (8.8)	1 (3.1)	6 (10.9)
Increased pigment	0	1 (2.9)	2 (6.2)	2 (3.6)
FEMALES:				
Liver (# examined)	(65)	(65)	(65)	(65)
Eosinoph. cell. alter., min. to sl.	8 (12.3)	7 (10.8)	7 (10.8)	5 (7.7)
moderate	1 (1.6)	0	0	3 (4.6)
moderately severe	0	0	1 (1.6)	3 (4.6)
total incidence	9 (13.9)	7 (10.8)	8 (12.3)	11 (16.9)
Hepatocel. enlarg., min. to sl.	8 (12.3)	7 (10.8)	5 (7.7)	13 (20)
Focal necrosis, min. to sl.	1 (1.6)	2 (3.1)	2 (3.1)	5 (7.7)
moderate	0	1 (1.6)	1 (1.6)	1 (1.6)
total incidence	1 (1.6)	3 (4.6)	3 (4.6)	6 (9.2)
Centrilob. degen./necr., min. to sl.	4 (6.2)	0	2 (3.1)	2 (3.1)
moderate	0	3 (4.6)	3 (4.6)	2 (3.1)
moderately severe	0	1 (1.6)	1 (1.6)	1 (1.6)
total incidence	4 (6.2)	4 (6.2)	6 (9.2)	5 (7.7)
Pigment, sl. to min.	1 (1.6)	2 (3.1)	2 (3.1)	3 (4.6)
Thyroid (# examined)	(63)	(46)	(46)	(61)
C-cell hyperplasia, min. to sl.	3 (4.8)	7 (15.2)	3 (6.5)	8 (13.1)
Lymph node (# examined)	(57)	(41)	(37)	(50)
Reticuloendothelial hyperplasia	4 (7.0)	2 (4.9)	4 (10.8)	8 (16.0)
Increased pigment	0	1 (2.4)	3 (8.1)	5 (10.0)

1 Data taken from Table 11C (pp. 261 - 282) and Appendix 10 (pp. 1113 to 2484) of study report. Data not analyzed statistically.
2 Numbers in parentheses following no. animals affected represent percent incidence.

The incidence of some microscopic lesions in the liver, thyroid and lymph nodes was slightly increased in treated animals at 2500 ppm and sometimes 1000 ppm (see above table). Thyroid: In the thyroid, the incidence of c-cell hyperplasia (minimal to slight) in males was higher at 1000 and 2500 ppm than controls. This increase was not considered toxicologically significant because of the minimal degree of severity, the frequency of this lesion in old rats and the variable dose-reponse observed in females. There was also no increase in the incidence of c-cell adenoma or carcinoma. Dr. Lucas Brennecke, consulting veterinary pathologist to HED, concurred with this assessment (personal communication). Liver: In males, an increased incidence of centrilobular degeneration/necrosis and pigment deposition at 1000 and 2500 ppm, and eosinophilic cellular alteration at 2500 ppm, were observed. Focal necrosis was observed at a higher incidence in females at 2500 ppm. In most instances lesions were classified as minimal to slight, although moderate to severe centrilobular degeneration/necrosis was observed in females in a non dose-related incidence. Although the incidence of eosinophilic cellular alteration did not increase in females at 2500 ppm, a slight increase in severity was observed. TB-I agreed with the study pathologist that these lesions were of questionable toxicologic significance with the exception of the increased severity of the eosinophilic cellular alteration in females, which may have been a marginal treatment-related effect. (Dr. Brennecke also did not consider the liver lesions of minimal to slight severity to be treatment-related). Lymph nodes: Slight increases in the incidence of pigment deposition and reticuloendothelial hyperplasia in females were at 2500 ppm not considered treatment-related since they were increased in the unscheduled sacrifice animals and similar effects were not observed in mandibular or other lymph nodes examined.

Neoplastic - Selected neoplastic lesions are shown below in Table 10:

TABLE 10: SELECTED NEOPLASTIC MICROSCOPIC LESIONS[1]

Sex:Lesion	0 ppm	250 ppm	1000 ppm	2500 ppm
MALES:				
Liver (N = 65)				
hepatocellular adenoma	2	0	0	1
hepatocellular carcinoma	2	1	1	0
combined adenoma/carcinoma	4	1	1	1
FEMALES:				
Liver (N = 65)				
hepatocellular adenoma	0	0	1 (1.5)[2]	3 (4.6)
hepatocellular carcinoma	0	0	0	11** (16.9)
combined adenoma/carcinoma	0	0	1 (1.5)	14** (21.5)
Uterus, N =	(65)	(55)	(53)	(65)
endometrial stromal polyp	0	1 (1.8)	3 (5.7)	5** (7.7)

1 Data taken from text Tables 2A and 2B (pp. 63, 64) of study report.
2 Number in parentheses following no. animals affected indicates percent incidence)
** $p \leq 0.01$

The study author noted an increase in the incidence of hepatocellular neoplasms in females at 2500 ppm. Hepatocellular carcinoma was observed at an incidence of 17% (statistically significant) and hepatocellular adenoma at 4.6%. The combined incidence of these tumors (21.6%) was also significant. Significant positive trends were also observed for adenoma, carcinoma and combined incidence. The study author provided historical control data for their laboratory for this strain of rat conducted between 1989 and 1992, but not at later times[1]. The incidence of hepatocellular carcinomas in females at 2500 ppm was outside the range of the historical controls, indicating a treatment-related increase at the high dose. The tumor did not appear to affect survival. Among the unscheduled deaths/sacrifices for females, hepatocellular carcinomas were identified in females that died during weeks 83 and 93, and two hepatocellular adenomas were identified in females that died during weeks 75 and 98. No increase in the incidence of liver tumors was observed in males.

A statistically significant increase in the incidence of endometrial stromal polyps of the uterus was also observed in females at 2500 ppm, with a significant positive trend also observed. The study pathologist considered this tumor to be unrelated to treatment because the incidence (7.7%) was within historical control range for this laboratory (data from studies conducted between 1989 and 1992 were provided)[2].

No other types of tumors showed a treatment-related incidence. Frequently observed tumors among all test groups included pituitary adenoma in both sexes and mammary gland fibroadenoma and carcinoma in females.

The carcinogenicity classification of resmethrin will be determined by the HED Cancer Peer Review Committee.

E. DISCUSSION:

TB-I considers the highest dose tested, 2500 ppm, to be a threshold LEL. Systemic toxicity at this dose level was only observed towards the last weeks or months of the study in males and females. In males, significant depression of RBC parameters was observed at week 104. The mean values reported in this study were outside the range of

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[1]For females, range of incidence of hepatocellular carcinoma in historical controls was 0 - 4.0% (mean 0.5%) in 12 studies of 626 animals. Range of incidence of hepatocellular adenoma was 0 - 2.2% (mean 0.5%). For males, range of incidence of hepatocellular carcinoma was 0 - 8.0% (mean 3.1%) in 12 studies of 678 animals. Range of incidence of hepatocellular adenoma was 0 - 4.1% (1.0%).

[2]The historical control incidence for uterine endometrial stromal polyp ranged from 0 to 13.3% with a mean incidence of 4.9%; data from a total of 15 studies and 693 animals.

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historical control values from the supplier (Charles River); in-house values for 2 year-old rats were not included in this study report. In females, body weight and body weight gain were depressed during the last months of the study. The results of the study suggest that higher doses could have been tested since these effects were not observed until very late in the study. The subchronic range-finding study that was used to determine the doses in this study was provided upon request of TB-I (see Appendix for summary of results). Mild toxicity to the liver (hepatocyte vacuolization showing a dose-related increase in severity, with mild clinical chemistry effects at higher doses) was observed at 2500 ppm in both sexes, with females showing more pronounced effects. At 5000 ppm, overt toxicity was observed in both sexes, including reduced body weight gain and clinical signs. The range-finding study also demonstrated that thyroid is a target organ, with dose-related increased follicular cell vacuolization observed in females. The results of the range-finding study suggest that an intermediate dose between 2500 and 5000 ppm might have been more appropriate in the chronic study, particularly for males. In the chronic toxicity study, the HDT of 2500 ppm appears to represents a threshold LEL. Furthermore, the results are consistent with an earlier study on resmethrin in rats (MRIDs 00041402, 00085870, 00108828; see HED Doc. nos. 002477, 002478, 001912 and RfD/Peer Review of 11-22-94; draft supplementary DER is forthcoming with NOEL = 500 ppm and LEL = 2500 ppm following RfD recommendations). In the earlier study, rats were tested up to 5000 ppm and minimal toxicity was observed in females at 2500 ppm. An increase in the incidence of liver hyperplastic nodules and liver tumors was observed. However, there are questions regarding the classification of hyperplastic nodules and it was uncertain whether the lesions were hyperplastic or neoplastic. The current study suggests that the lesions may have been tumors. The earlier study also demonstrated increased thyroid cysts at 5000 ppm and a possible increase in follicular neoplasms at 2500 and 5000 ppm.

Increased incidence of thyroid tumors is sometimes associated with compounds, including some pyrethrins, that also cause liver tumors. In the current study, no evidence was provided to support a relationship of increased liver tumors with thyroid effects. There was no indication of compound related increases in thyroid tumors (combined follicular cell adenoma/carcinoma incidence was 2/64, 1/36, 2/36 and 2/60 in males and 0/63, 0/46, 1/46 and 1/61 in females, control to high dose, respectively). TB-I does not consider the single incidences in females to be treatment-related. C-cell hyperplasia was observed at higher incidence in low- and high dose females compared to controls (see Table 9, p. 16 of DER), but a dose-response was not observed. Combined C-cell adenoma/carcinoma incidence was 10/63, 7/46, 1/46 and 7/61 in females, control to high dose, respectively.

A new study testing resmethrin at higher doses is not required because resmethrin appeared to be carcinogenic in females at the highest dose tested and because no carcinogenic effects were observed in males at 5000 ppm in the previous chronic study in rats. The tumor incidence observed in rodents fed resmethrin will be considered by the

HED Cancer Peer Review Committee.

STUDY DEFICIENCIES: (1) Only marginal toxicity achieved at the HDT;
(2) Some hematologic parameters were not included in the study report (MCH, MCHC, MCV).

These deficiencies do no alter the conclusions of the study.

Text Table 1
SBP-1382 (Resmethrin) Technical Induced
Changes in Rat Liver and Thyroid

Group	1	2	3	4	5	6	1	2	3	4	5	6
Sex	Male						Female					
Number Examined:	20	20	20	20	20	20	20	20	20	20	20	20
Liver												
Vacuolization, increased, hepatocyte, periportal to diffuse	8	17	20	19	20	7	8	17	20	19	17	3
Mean Severity:	0.6	1.5	2.8	3.1	3.1	0.9	0.7	1.9	2.8	2.9	2.3	0.4
Hypertrophy, hepatocyte, periportal to diffuse	0	0	19	19	20	20	0	1	18	19	20	19
Mean Severity:	0.0	0.0	2.3	3.0	3.6	4.0	0.0	0.1	2.2	2.2	3.0	3.1
Number Examined:	20	0	0	0	0	20	20	20	20	20	20	14
Thyroid												
Vacuolization, increased, follicular cell	0	-	-	-	-	0	2	3	9	18	20	11
Mean Severity:	0.0	-	-	-	-	0.0	0.1	0.2	0.7	1.8	1.9	2.0

Table taken from study report (MRID 43601601), p. 33

APPENDIX

SUMMARY OF RANGE-FINDING STUDY (13-MONTH FEEDING STUDY) FOR CHRONIC TOXICITY/CARCINOGENICITY STUDY IN RAT

MRID: to be assigned
Study Title: Subchronic Toxicity Study in Rats with SBP-1382 (Resmethrin) Technical
Study No.: HWA 2623-101 (RBT-91-125)
Performing Laboratory: Hazleton Washington, Inc.
Study Author: Mercedes A. Sarabian; M.S., D.A.B.T.
Completed January 11, 1993

20 Crl:CD BR rats/sex/dose were administered resmethrin (SB-1382 tech., 86.3% a.i.) in the diet at concentrations of 0, 500, 1250, 2500, 5000 or 10,000 ppm for a total of 13 weeks. Mean compound consumption of a.i. corresponded to 0, 30.0, 75.8, 154.1, 315.9 or 769.5 mg/kg/day in males and 0, 34.3, 86.1, 169.5, 355.6 or 798.2 mg/kg/day, females. The study was conducted according to standard Guideline procedures for a subchronic feeding study in rodent (82-1a).

The following findings were observed. Effects on body weight, organ weight, hematology and clinical chemistry parameters shown below represent statistically significant changes. A summary table of histopathology results taken from the study report is attached and provides incidence and mean severity data on the observed liver and thyroid lesions.

500 PPM

Males: increased hepatocyte vacuolization, periportal to diffuse (minimal to slight)

Females: increased mean liver weight (+12%)
increased hepatocyte vacuolization, periportal to diffuse (minimal to slight)

1250 PPM

Males: increased hepatocyte vacuolization (slight to moderate)
increased hepatocyte hypertrophy, periportal to diffuse (slight to moderate)

Females: increased BUN (+27%)
increased mean liver weight (+24%)
increased hepatocyte vacuolization, periportal to diffuse (slight to moderate)
increased hepatocyte hypertrophy (slight to moderate)
increased thyroid follicular cell vacuolization (minimal)

2500 PPM

Males: increased BUN (+29%)
increased mean liver weight (+22%)
increased hepatocyte hypertrophy (moderate)
increased hepatocyte vacuolization (moderate)

[redacted]

[Resmethrin/1994]

Females: increased BUN (+53%)
increased mean liver weight (+44%)
increased mean thyroid weight (+23%)
increased hepatocyte hypertrophy comparable to 1250 ppm females
increased hepatocyte vacuolization comparable to 1250 ppm females
increased thyroid follicular cell vacuolization (minimal to slight)

5000 PPM
Males: clinical signs (tremors, hypersensitivity to touch/sound, hunched posture)
decreased mean body weight gain (-13%)
increased liver weight (+29%)
increased BUN (+59%), ALT (+44%), Alb (+11%)
increased hepatocyte vacuolization comparable to 2500 ppm males
increased hepatocyte hypertrophy, moderate to marked

Females: clinical signs (tremors, hypersensitivity to touch/sound, hunched posture, poor appetite/thinness)
decreased mean body weight gain (-30%)
decreased RBC parameters (-6%)
increased BUN (+67%)
increased mean liver weight (+48%)
increased mean thyroid weight (+19%)
increased hepatocyte vacuolization (slight to moderate)
increased hepatocyte hypertrophy (moderate)
increased thyroid follicular cell hypertrophy (slight)

[redacted]

10,000 PPM
Males: clinical signs (as in the 5000 ppm group and also hyperactivity, nasal/eye crust
decreased mean body weight gain (-51%)
increased BUN (+41%), ALT (+35%), ALT (+56%), Alb (+11%)
increased mean liver weight (+18%)
increased hepatocyte hypertrophy (marked)

Females: mortality (45%);
clinical signs (as in the 5000 ppm group and also hypoactivity, nasal/ey
decreased mean body weight gain (-55%)
decreased RBC parameters (-8 to -9%)
increased BUN (+53%)
increased mean liver weight (+58%)
increased hepatocyte hypertrophy comparable to 5000 ppm female
increased thyroid vacuolization (slight)

At 5000 ppm, clinical signs did not begin to appear until afte
later. At 10,000 ppm, some clinical signs appeared within days o
including tremors and urine stains. Mortality in females at 10,0
the first 6 weeks of the study. The exact cause of death