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

008296

MAR 20 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Fenethanil(RH-7592 Technical): Confirmation of tumor data for an EUP

CASWELL NO.: 723Q
HED NO.: 0-1965

FROM: SanYvette Williams, D.V.M. SWW 3/6/91
Review Section IV, Tox. Branch II (HFAS)
Health Effects Division (H7509C)

TO: Susan Lewis, PM 21
Registration Division (H7505C)

THRU: Elizabeth Doyle, Ph.D., Acting Section Head E.A. Doyle 3/11/91
Section IV, Tox. Branch II (HFAS)
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D., Chief Marcia van Gemert 3/15/91
Toxicology Branch II (HFAS)
Health Effects Division (H7509C)

Registrant: Rohm and Haas

Action Requested: Evaluate final data provided by the registrant in support of the second year of the subject EUP which included a 24-month chronic toxicity/oncogenicity study in rats and diet analysis, and a special histopathology report from a 78-week oncogenicity study in mice.

Background: One year of a two-year EUP with a temporary tolerance for fenethanil on stone fruit was granted by Registration Division on the basis of evaluation of preliminary data from a rat chronic toxicity study. However, continuation of the temporary tolerance for the second year of the EUP was made contingent upon review of the histopathology report from the study submitted in the Fall, 1990.

Conclusion: The required data was submitted; preliminary results of tumor analysis (Memo by S. Williams, 2/13/91) indicate that the Q_1* for the final data was 0.023 (mg/kg body weight/day)$^{-1}$. This value is not significantly different from the Q_1* derived from the interim data (0.026 (mg/kg body weight/day)$^{-1}$).

1. 3[illegible] Month Dietary Chronic Toxicity-Oncog[illegible]ats (416353-01) and Diet Analysis (41635[illegible]

Male a[illegible] Sprague-Dawley rats exposed for least 100 weeks to [illegible] ppm RH-7592 Technical (the first four weeks dosages ra[illegible]ged between 4 and 600 ppm) exhibited systemic toxicity. Signs of t[illegible]icity were decreased body weights in females, increased liver weights in females and males with centrilobular to midz[illegible]nal hepatocellular enlargement and vacuolization. There was also an increase in thyroid/parathyroid weights in both sexes with slight increases in thyroid focal cystic hyperplasia and follicular cell neop[illegible]asia.

NOEL = 80 ppm in male and female rats
LEL = 800 ppm in male and female rats
MTD = 800 ppm in male and female rats

This study meets most requirements for a chronic toxicity-oncogenicity study according to Guideline (83-5) and is classified Core - Minimum.

2. RH-7592 Technical: 78-Week Dietary Oncogenicity Toxicity Study in Mice (416353-03) Special Histopathology Report.

The administration of RH-7592 to male and female mice over a 78 -week period induced hepatocellular vacuolation and enlargement in both high and mid-dose groups. There was an equivocally small increase in combined liver neoplasms in high-dose females.

NOEL = 10 ppm for both male and female
LEL = 200 ppm for male and 650 ppm for female
MTD = 650 ppm for male and 1300 ppm for female

Classification: (This report is a partial summary of the results of a mouse oncogenicity study and may be upgraded upon the receipt of the entire report.)

This study does not satisfy requirements for an oncogenicity study (83-2) and is classified Core - Supplementary.

008296

Reviewed by: LaYvette Williams, D.V.M. LW 2/5/91
Section IV, Tox. Branch II (HFAS) (H7509C)
Secondary Reviewer: Elizabeth Doyle, Ph.D. EAD 2/5/91
Section IV, Tox. Branch II (HFAS) (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 78-Week Dietary Oncogenicity Toxicity Study in Mice
Special Histopathology Report (83-2)

TOX. CHEM. NO.: 723Q **HED PROJECT NO.:** 0-1965

MRID NO.: 416353-03 **HLA STUDY NO.:** 417-438

TEST MATERIAL: RH-7592 Technical

SPONSOR: Rohm and Haas Company; Toxicology Dept; 727 Norristown Rd.
Spring House, PA 19477

TESTING FACILITY: Hazleton Laboratories America, Inc.
1330-B Piccard Dr.
Rockville, MD 20850-4373

TITLE OF REPORT: RH-7592 Technical: 78-Week Dietary Oncology Toxicity-Oncogenicity Study in Mice

AUTHOR(S): Gary W. Wolfe, Ph.D., D.A.B.T.

REPORT COMPLETED: August 28, 1990

CONCLUSIONS: The administration of RH-7592 to male and female mice over a 78 - week period induced hepatocellular vacuolation and enlargement in both high and mid-dose groups. There was an equivocally small increase in combined liver neoplasms in high-dose females.

NOEL = 10 ppm for both male and female
LEL = 200 ppm for male and 650 ppm for female
MTD = 650 ppm for male and 1300 ppm for female

Classification: (This report is a partial summary of the results of a mouse oncogenicity study and may be upgraded upon the receipt of the entire report.)

This study does not satisfy requirements for an oncogenicity study (83-2) and is classified Core - Supplementary.

A. **STUDY DESIGN:**

This is a special histopathology report in which the liver, testes or ovaries and thyroid were examined from male and female mice. These tissues were collected from all animals on study including unscheduled deaths, interim (52 week) and terminal sacrifices (78 week).

The distribution of dosage groups is listed below:

Text Table 1

Group	Dose (ppm)	Sex	# animals
1	0 (control)	M	60
2	10 (low)	M	60
3	200 (mid)	M	60
4	650 (high)	M	60
1	0 (control)	F	60
2	10 (low)	F	60
3	650 (mid)	F	60
4	1300 (high	F	60

After week 52, 10 male and 10 female mice from each treatment group were sacrificed and necropsied. Those animals sacrificed when moribund and those surviving to the end of the study were also sacrificed and necropsied. Tissues from all were preserved in formalin.

B. **RESULTS:**

The results listed in Table 2 below show alterations in the liver of male and female rats. Centrilobular to midzonal or diffuse hepatocellular enlargement and an increased incidence of vacuolation was presumed to be treatment-related in those test animals receiving high and mid-doses. Hepatocellular enlargement was observed at a rate of 36% (male) and 60% (female) in the mid-dose group. In the hig-dose group the rate was 92% (male) and 82% (female). Vacuolation was observed in 18% (male) and 35% (female) in the mid-dose group. There was an increase to 52% in both male and female in the high-dose group.

The "no effect" level for both parameters was 10 ppm in male and female treated mice.

Table 2

Group	1		2		3		4	
Sex	M	F	M	F	M	F	M	F
# examined[a]	60	58	59	60	60	57	60	60
Liver Finding								
Hepatocellular enlargement	4	1	4	1	22	34	55	49
Hepatocellular vacuolation	2	4	1	1	11	20	31	31

[a] autolytic tissues are deleted from original number

There were some proliferative lesions found in the liver in both sexes. An unadjusted analysis by Cochran-Armitage test for trend and Fisher-Irwin exact test for homogeneity indicated a positive trend in the incidence rate of hepatocellular carcinoma in male mice with 3/60 and 5/60 affected from the mid and high-dose group, respectively.

The only significant difference (at $P \leq .05$) in the incidence of either adenoma or carcinoma between control and treated groups was seen in Group 2 males (Table 3), wherein the incidence of adenomas was significantly lower than those in the control group.

Table 3

Group	1		2					
Sex	M	F	M	F	M	F	M	F
# examined[a]	60	58	59	60	60	57	60	60
Hepatocellular Finding								
Hyperplasia	3	0	0	1	1	0	7	3
Adenoma	8	0	1	0	8[b]	0	6[c]	4
Carcinoma	1	0	1	1	3	0	5	1
Adenoma and Carcinoma combo	9	0	2	1	10	0	9	5

[a] autolytic tissues are deleted from original number
[b] one animal also had carcinoma
[c] two animals also had carcinoma

When looking at combined neoplasms, the female high-dose treatment group displayed a significantly (P = 0.0312) different incidence when compared to controls. There were no hepatocellular neoplasms in the control group, but 5/60 high-dose females had combination neoplasms. It would seem that the presence of these 5/60 (6.7% incidence) neoplasms would indicate a relationship to treatment. In light of the historical control data which shows that the occurrence of tumors is not too far out of the range for adenomas (0%-6.1%) and carcinomas (0% - 2.1%), their presence seem unclear because of the absence of supporting data.

There were many animals from all groups which displayed liver lesions which suggest that a low-grade, chronic disease process was present that was not treatment-related.

The thyroids, testes or ovaries did not exhibit any treatment-related changes.

C. **CONCLUSIONS:**

The administration of RH-7592 to male and female mice over a 78 - week period induced hepatocellular vacuolation and enlargement in both high and mid-dose groups. There was an equivocally small increase in combined liver neoplasms in high-dose females.

NOEL = 10 ppm for both male and female
LEL = 200 ppm for male and 650 ppm for female
MTD = 650 ppm for male and 1300 ppm for female

(This report is a partial summary of the results of a mouse oncogenicity study and may be upgraded upon the receipt of the entire report.)

This study does not satisfy requirements for an oncogenicity study (83-2) and is classified Core - Supplementary.

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Reviewed by: SanYvette Williams, D.V.M. SW 3/6/91
Section IV, Tox. Branch II (HFAS) (H7509C)
Secondary Reviewer: Elizabeth Doyle, Ph.D. EAD 3/11/91
Section IV, Tox. Branch II (HFAS) (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 24 Month Feeding/Oncogenicity - Rat and Diet Analysis (83-5)

TOX. CHEM. NO.: 723Q **HED PROJECT NO.:** 0-1965

MRID NO.: 416353-01 and 416353-02

HLA STUDY NO.: 417-437

TEST MATERIAL: RH-7592 Technical

SPONSOR: Rohm and Haas Company; Toxicology Dept; 727 Norristown Rd. Spring House, PA 19477

TESTING FACILITY: Hazleton Laboratories America, Inc.
1330-B Piccard Dr.
Rockville, MD 20850-4373

TITLE OF REPORT: RH-7592 Technical: 24-Month Dietary Chronic Toxicity-Oncogenicity Study in Rats

AUTHOR(S): Gary W. Wolfe, Ph.D., D.A.B.T.

REPORT COMPLETED: August 15, 1990

CONCLUSIONS: Male and female Sprague-Dawley rats exposed for least [illegible] weeks to 800 ppm RH-7592 Technical exhibited systemic toxicity. Signs of toxicity were decreased body weights in females, increased liver weights in females and males with centrilobular to midzonal hepatocellular enlargement and vacuolization. There was also an increase in thyroid/parathyroid weights in both sexes with slight increases in thyroid focal cystic hyperplasia and follicular cell neoplasia.

NOEL = 80 ppm in male and female rats
LEL = 800 ppm in male and female rats
MTD = 800 ppm in male and female rats

This study meets most requirements for a chronic toxicity-oncogenicity study according to Guideline (83-5) and is classified Core - Minimum.

Classification: core - Minimum

I. **MATERIALS:**

1. Test compound: RH-7592 Technical Description: white solid

(powder) Lot #BPP3-1786R, Purity: 96.7% (the concentration was adjusted to 100% for dosing purposes) contaminants: not submitted

2. Test animals: Species: Rat, Strain: Sprague-Dawley (Crl:CD (SD)VAF/+), Age: 52 days, Weight: Males - 162-328 g; Females - 156-227 g ;Source: Charles River Laboratories, Raleigh, NC.

B. **STUDY DESIGN:**

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

Test Group	# animals Male / Female	Dietary Levels (ppm) Wks 1,2	3,4	5 to term
1 Cont.	70 / 70	0	0	0
2 Low (LDT)	70 / 70	4	6	8
3 Mid (MDT)	70 / 70	40	60	80
4 High (HDT)	70 / 70	400	600	800

According to the registrant (p. 13), Dose levels (ppm) were adjusted during Week 1 - 4 to accommodate the increasing body weights and food consumption and produce similar mg/kg/dose levels.

2. Diet preparation - Diet was prepared biweekly and stored at ambient temperature. Samples of treated food were analyzed for stability and concentration at preparation. Diets were established to be maximally stable for at least 17 days.

Results - The analysis for homogeneity in all dose samples was run to fulfill 2 criteria: a) adequate mixing with a coefficient of variation ≤ 10% and b) the average % of target within 10% of the nominal target value. Both these criteria were met when samples were taken from the top, middle and bottom stratum of all samples with the exception of the 40 and 60 ppm sample taken from the bottom stratum at each concentration. Both were 80% of the target assay and as such, the mixing process was deemed satisfactory by the registrant.

3. Animals received food (Purina Lab Rodent Chow, control or treated) and water ad libitum.

4. Statistics - Cumulative survival through termination (Week 105), was analyzed using the National Cancer Institute Package which incorporates both adjusted and unadjusted analyses of incidence. The Unadjusted Analyses include: the Exact one-tailed permutation test, Cochran-Armitage 2-tailed test for trend and Fisher-Irwin exact test. The Kaplan-Meier produce limit estimation of adjusted incidence, Cox's logistic score tests for trends and homogeneity

and Modified Kruskal-Wallis nonparametric test for trend and homogeneity were used in performing the adjusted analyses.

5. Quality assurance was documented with signed and dated GLP and quality assurance statements.

C. **METHODS AND RESULTS:**

1. Observations - Animals were inspected twice a day for signs of toxicity and mortality.

   Results - Toxicity - No unusual or treatment related clinical observations were reported.

   Mortality (survival) - (See attached Study Figure 2.) No treatment related effects in survival were reported in either sex. The adjusted survival rate in males was comparable to controls. The adjusted survival rate in females was 10% less than and 14% greater than controls in the mid and high-dose animals, respectively.

2. Body weight - Animals were weighed prior to treatment, weekly for 14 weeks, then once every two weeks for the remainder of the study.

   Results - Mean body weight change and growth from initiation of treatment through week 78 was significantly decreased in the Group 4 females when compared to the controls. Mean body weight as a percent of control was decreased in high dose male and more obviously in high dose females.

   Decreased mean body weight gain as a percent of control along with a significant decrease in mean absolute body weight at intervals during Week 4 through Week 78 indicate that Group 4 females were undergoing a depression of body weight. At Weeks 4, 13, 40, 66 and 78, body weight gain was 18%, 15.6%, 16.1% 26.1% and 18.4% less than controls, respectively. These females also had lowered body weights during Week 92 and 104 which appeared lower, yet not significantly lower because of high standard deviations at some intervals.
   Group 4 males had a statistically significant change in body weight through Week 78 which appears spurious.

   Mean weekly body weights, body weight change and growth were comparable to controls.

   There were no effects on body weight gain observed in animals on the 8 or 80 ppm diets in males or females. Therefore, the NOEL for RH-7592 was 80 ppm.

COMPARISON OF BODY WEIGHT GAIN (g)

Period Weeks	Dietary Concentration of RH-7592 (ppm) 0	8	80	800
Males				
Initial Weight	290.5	298.6*	295.9	292.4
4	432.7	460.0	457.3	460.7
8	524.7	525.2	514.8	520.3
13	596.2	593.8	589.5	592.2
26	687.4	694.2	695.8	684.5
40	748.1	748.0	744.2	739.2
52	794.3	803.7	798.0	770.6
66	857.4	844.7	841.6	809.2
78	861.0	820.6	838.5	793.1*
92	830.5	781.2	796.9	779.3
Final Weight	828.8	774.4	779.9	750.1
Females				
Initial Weight	189.6	192.3	195.1	190.8
4	267.6	269.7	271.1	255.4*
8	306.4	306.6	307.2	283.5*
13	328.9	332.9	334.9	308.3*
26	374.2	378.2	381.6	343.7*
40	404.5	401.9	413.3	371.1*
52	440.4	455.6	463.1	396.7*
66	488.1	503.6	493.9	411.3*
78	493.8	522.1	526.5	438.9*
92	530.8	513.9	536.3	446.8
Final Weight	512.4	559.5	527.4	462.7

3. Food consumption and compound intake - Consumption was determined and mean daily diet consumption was calculated. Efficiency and compound intake were calculated from the consumption and body weight gain data.

Results - Food consumption - Mean total food consumption was significantly lower than controls in Group 3 (mid-dose) males at intervals 1-78, 1-90 and 1-104. It was also significantly lower in Group 4 (high dose) females at intervals 1-4, 1-13 and 1-26. Weekly food consumption values were significantly increased relative to controls for Group 3 males at 13 weeks, Group 2 and

3 females at 13 weeks, Group 3 females at 78 and 90 weeks, Group 2 males at 40 weeks and Group 4 females at 78 weeks.

Food efficiency - There was considerable variation, but no treatment-related effects were reported.

Compound intake - (See attached Text Table 2)
Female rats on all treated diets consistently received more test material than males on the same diet from Week 7 until the termination of the study. All animals received the greatest doses early in the study when food consumption was highest due to rapid growth. Intake of test material decreased until about Week 92 in males and Week 68 in females.

4. Ophthalmological examinations were performed on all animals prior to the first dose, on control, and high dose animals at Week 52 and 104.

Results - No treatment-related effects were observed.

5. Blood was collected before treatment and at weeks 14, 27, 32 (males for hematology only), 53, 79 and 104 on 10 animals/sex/group. The CHECKED (X) parameters were examined:

a. Hematology:

X		X	
x	Hematocrit (HCT)		Total plasma protein (TP)
x	Hemoglobin (HGB)	x	Leukocyte differential count
x	Leukocyte count (WBC)	x	Mean corpuscular HGB (MCH)
x	Erythrocyte count (RBC)	x	Mean corpuscular HGB conc. (MCHC)
x	Platelet count	x	Mean corpuscular volume (MCV)

Results -

At week 27, the males in group 3 and 4 revealed a slight but significant ($p \leq 0.05$) decrease in hemoglobin and packed cell volume. These appear to be transient effects that became comparable to controls by week 32 (males) and 52 (females). Group 4 females exhibited a significant increase in platelets at week 105. At week 27, there was a significantly decreased white blood cell count and corrected white blood cell count in males in Groups 2-4 considered to be incidental. At week 32 the significantly increased leukocyte count, corrected leukocyte count, and absolute lymphocyte count was considered to be spurious.

b. Clinical Chemistry

X		X	
	Electrolytes:		Other:

x	Calcium	x	Albumin
x	Chloride	x	Blood creatinine
	Magnesium	x	Blood urea nitrogen
x	Phosphorous	x	Cholesterol
x	Potassium	x	Globulins
x	Sodium	x	Glucose
	Enzymes:	x	Total Bilirubin
x	Alkaline phosphatase	x	Total Protein
	Cholinesterase		Triglycerides
x	Creatinine phosphokinase		
x	Lactic acid dehydrogenase		
x	Serum alanine aminotransferase (also SGPT)		
	Serum aspartate aminotransferase (also SGOT)		

Results -

A significant increase in total cholesterol was observed in Group 4 females at Week 27, 79 and 105 that appears to be treatment-related. There were no other significant changes that could be considered treatment-related.

6. Urinalysis - Urine was collected from fasted animals at 14,27,53,79 and 105 weeks. The CHECKED (X) 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)		Nitrate
X	Protein		Urobilinogen

Results -

Males in Group 2-4 exhibited a general increase in severity grading for total urine protein at Week 27, but because there was no dose-response, and inconsistent occurrences across intervals, this [illegible] not considered to be significant.

7. Sacrifice and Pathology -

All animals that died and that were sacrificed on schedule were subject to gross pathological examination. The CHECKED (X) tissues were collected for histological examination. The (XX) organs were also weighed.

X		X		X	
	Digestive system		Cardiovas./Hematol.		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 nerve)
X	Jejunum		Thymus		Glandular
X	Ileum		Urogenital	XX	Adrenals
X	Cecum	XX	Kidneys		Lacrimal gland
X	Colon	X	Urinary bladder	X	Mammary gland
X	Rectum	XX	Testes	XX	Parathyroids
		XX	Epididymides	XX	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	XX	Liver		All gross lesions and masses

Results -

a. Organ weight - (See attached excerpts from Tables 9A, 9B, 10A, 10B, 11A and 11B, respectively.)

There was an absolute and relative increase in liver weight at the interim (Week 52) and terminal sacrifice in both sexes of Group 4 (high dose). A statistically significant increase ($p \leq 0.05$) was noted in the absolute weights at Week 52 in Group 4 males and at termination in Group 4 females. Both males and females in Group 4 had elevated organ to body weight ratios at interim and terminal necropsy. In addition, the liver to brain weight ratio in Group 4 males at Week 52, and both sexes at terminal sacrifice were significantly increased.

Statistically significant increases ($p \leq 0.05$) in the absolute body weight of the thyroid/parathyroid were noted in Group 4 males. The organ to body weight ratio of both male and females in Group 4 and the organ to brain weight ratio of Group 4 males were also significantly increased.

Other changes in organ weights include decreased relative thyroid/parathyroid body weight in Group 2 males at interim sacrifice, increased heart and epididymis to body weight ratio in males and females at terminal sacrifice, respectively. These changes were not considered by the registrant to be treatment-related due to lack of pathological correlation and/or low magnitude of difference.

b. Gross pathology - There were no rats which exhibited any treatment-related gross pathological changes .

c. Microscopic pathology

Group 4 rats, those dying when moribund and those scheduled for

interim and terminal sacrifice, exhibited slight centrilobular to midzonal hepatocellular enlargement and vacuolization in 4/10 males and 7/10 females. These effects indicate the RH-7592 did have a dose-effect on the liver.

The thyroid gland was also examined at interim sacrifice. The low and mid-dose evaluation revealed a low incidence of parafollicular ("C"-cell hyperplasia in 5/20 low-dose rats (3 male, 2 female) and 4/20 mid-dose rats (1 male, 3 female) that appears to be comparable to controls.

At terminal sacrifice, alterations in the liver of both high-dose male and female also consisted of centrilobular to hepatocellular enlargement and vacuolization which appears treatment-related. An increase in the incidence of focal cystic hyperplasia and follicular cell neoplasia was noted in 12/70 and 8/70 Group 4 males as noted in Text Table 3.

Text Table 3
Focal Cell Neoplasia/Hyperplasia

	Male Rats			
Group	1	2	3	4
# examined	70	70	70	70
Focal cystic hyperplasia	1	4	1	12
Follicular cell adenoma	1	2	3	6
Follicular cell carcinoma	0	3	0	4
Total rats with follicular cell neoplasia	1	5	3	8[a]

[a] Two rats had both adenoma and carcinoma

D. **DISCUSSION:**

There were no treatment related effects observed with regard to survival which ranged between 32% and 48% for the males and 35% and 59% for the females. Also a compound-related depression of bodyweight was evident throughout the study for high-dose females. Yet, no differences were noted in the mean body weights among the male groups.

The only treatment-related finding in hematology, clinical chemistry, or urinalysis parameters was an increase in total cholesterol in the Group 4 females.

There were no gross findings which could be considered treatment-related at Week 52 or terminal necropsy. There were, however, several significant treatment-related effects observed at the highest dose level. Liver weights (absolute and/or relative) were increased in both sexes exposed to 800 ppm RH-7592 Technical for 52 and 104 weeks. Both absolute and relative thyroid/parathyroid weight and relative

absolute and relative thyroid/parathyroid weight and relative (organ/body) epididymis weight were increased in high-dose males at terminal sacrifice. In high-dose females, relative (organ/body) thyroid/parathyroid and relative (organ/body) heart weights were increased at terminal sacrifice. Heart and epididymis weights were not considered to be different due to treatment, however.

There were treatment-related effects observed in the liver and thyroid/parathyroid of high-dose rats at interim and terminal sacrifice. Findings on histopathology correlated with changes in liver and thyroid/parathyroid weights. With the enlargement and vacuolization of hepatocytes, a relation to treatment can be assumed.

An MTD appears to be reached on the basis of decreased body weight gain.

Increased occurrence in the thyroid/parathyroid of cystic hyperplasia and follicular cell neoplasia in males is also treatment-related. A statistically significant increase in combined incidence of adenomas and carcinomas in this organ using Fisher's Exact Test ($p = .01658$) and with Cochran-Armitage for Trend ($p = .0150$) can be shown when compared to controls. Yet, according to reference ranges supplied by the registrant, these results are comparable to controls.

It should be noted that there was a dosage adjustment during the first four weeks of study ranging from 4 ppm to 600 ppm. The 8, 80 and 800 ppm dosages were used from Week 5 to termination of the study. This might have a bearing on the validity of actual results in the study.

E. CONCLUSIONS:

Male and female Sprague-Dawley rats exposed for at least 104 weeks to up to 800 ppm RH-7592 Technical produced systemic toxicity. Signs of toxicity were evidenced by decreased body weights in females, increased liver weights in females and males along with centrilobular to midzonal hepatocellular enlargement and vacuolization. There was also an increase in thyroid/parathyroid weights in both sexes with slight increases in thyroid focal cystic hyperplasia and follicular cell neoplasia. Those rats exposed to 8 or 80 ppm of RH-7592 Technical exhibited no remarkable treatment-related effects throughout the study. Thus, 80 ppm would be considered the no effect level (NOEL).

NOEL = 80 ppm in male and female rats
LEL = 800 ppm in male and female rats
MTD = 800 ppm in male and female rats

This study meets most requirements for a chronic toxicity-oncogenicity study according to Guideline (83-5) and is classified Core - minimum.

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