12-5-91

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

DEC 5 1991

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Fenethanil (RH-7592 Technical)

CASWELL NO.: 723Q
HED NO.: 2-0102
MRID NO.: 420550-01

FROM: SanYvette Williams, D.V.M. 12/4/91
Review Section IV, Tox. Branch II (HFAS)
Health Effects Division (H7509C)

TO: Dolphine Wilson/Cynthia Giles-Parker, PM 22
Registration Division (H7505C)

THRU: Elizabeth Doyle, Ph.D., Section Head E. A. Doyle 12/2/91
Section IV, Tox. Branch II (HFAS)
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D., Chief
Toxicology Branch II (HFAS)
Health Effects Division (H7509C) 12/5/91

[illegible] Rohm and Haas

Action Requested: Evaluate additional data on Fenbuconazole submitted under FIFRA Section 6(a)2.

1. 2 Year dietary chronic/oncogenicity study in male rats. Accession No.: 420550-01
2. Supplement A - RH-7592 Tech.: 104-Week dietary chronic/oncogenicity study in male rats (photomicrographs). Accession No.: 420550-02
3. Rohm and Haas Company's perspective on the carcinogenicity of RH-7592 fungicide. Accession No.: 420219-01

Background: A previous chronic toxicity/oncogenicity study with Fenbuconazole (HWA 417-437; Rhom and Haas Report 88RC-98) did not result in establishing an MTD in male rats according to the Agency. The Agency suggested dosing male rats at the suggested MTD of 1600 ppm RH-7592.

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Conclusion: The additional data has been evaluated and the results of this study indicate that treatment with RH-7592 at levels of 800 and 1600 ppm over 104 weeks does not cause carcinogenesis in male rats. Administration of RH-7592 at 1600 ppm did cause several signs of toxicity in test animals. Adverse effects included increased liver weights with centrilobular to midzonal hepatocellular enlargement and vacuolization (800 and 1600 ppm), decreased body weight gain and increased thyroid/parathyroid weights with a marked increase in follicular cell hypertrophy and a slight increase in follicular cell adenomas (1600). The NOEL for this study is less than 800 ppm, the LOEL is 800 ppm (30.41 mg/kg/day) and the MTD is 1600 ppm (63.94 mg/kg/day).

NOEL = less than 800 ppm/day
LOEL = 800 ppm/day (30.41 mg/kg/day)
MTD = 1600 ppm/day (63.94 mg/kg/day) (systemic toxicity) based on decreased body gain weight, increased liver weight and increased thyroid/parathyroid weight

This study does not conform to guidelines for an oral chronic/oncogenicity study according to guideline #83-1/2 because only males were used. Therefore, it is classified core-supplementary.

This study can be used, however, in conjunction with the previous chronic toxicity/oncogenicity study with RH-7592 in male and female Sprague-Dawley rats (HWA 417-437; Rohm and Haas Report 88RC-98) to fulfill requirements under 707-EUP-121 for use on stone fruits and pecans.

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Primary Review by: SanYvette Williams, D.V.M. 11/26/91
Review Section IV, Tox. Branch II (H7509C)
Secondary Review by: Elizabeth Doyle, Ph.D. E.A. Doyle 11/27/91
Section Head, Review Section IV, Tox. Branch II(H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Dietary Chronic/Oncogenicity (83-1/2)

TOX. CHEM NO: 723Q

ACCESSION NUMBER: 420550-01
HED NO.: 2-0192

TEST MATERIAL: RH-7592 Technical

SYNONYMS: Fenbuconazole

LAB PROJECT ID #: HWA Study No. 417-455

SPONSOR: Rohm and Haas Co.

TESTING FACILITY: Hazleton Washington, Inc.; 133-B Piccard Drive; Rockville, MD 20850-4373

TITLE OF REPORT: RH-7592 Technical: 104-Week Dietary Chronic/Oncogenicity Toxicity Study in Male Rats

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

STUDY COMPLETED: July 15, 1991

CONCLUSION: The results of this study indicate that treatment with RH-7592 at levels of 800 and 1600 ppm over 104 weeks does not appear to cause carcinogenesis in male rats. Administration of RH-7592 at 1600 ppm did cause several signs of toxicity in test animals. Adverse effects included increased liver weights with centrilobular to midzonal hepatocellular enlargement and vacuolization (800 and 1600 ppm), decreased body weight gain and increased thyroid/parathyroid weights with a marked increase in follicular cell hypertrophy and a slight increase in follicular cell adenomas (1600). The NOEL for this study is less than 800 ppm, the LOEL is 800 ppm (30.41 mg/kg/day) and the MTD is 1600 ppm (63.94 mg/kg/day).

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This study does not conform to guidelines for an oral chronic/oncogenicity study according to guideline #83-1/2 because only males were used. This study is classified core-supplementary.

BACKGROUND: A previous chronic toxicity/oncogenicity study with RH-7592 in male and female Sprague-Dawley rats (HWA 417-437; Rohm and Haas Report 88RC-98) was conducted using dose levels up to 800 ppm but did not result in establishing an MTD in the male rats according to the U.S. EPA. The objective of this study was to determine the chronic toxicity and oncogenic potential in male rats at the U.S. EPA suggested MTD of 1600 ppm.

A. MATERIALS:

1. Test compound: RH-7592 Tech., Lot #: BPP-3-1786R; Description: white powder; Purity 96.7%. Acetone was the vehicle.

2. Test animals: Species: male rats; Strain: Sprague-Dawley (Crl:CD BR VAF/+), Age: 46 days, Weight: 214.3 to 266.9 grams; Source: Charles River Labs, Raleigh, NC.

B. STUDY DESIGN:

1. Animal assignment

Test animals were randomly assigned to the following test groups:

Table 1

Test Group	# of animals males	Dietary Levels (ppm) Wks 1,2	3,4	5 to term.
1 Control	60	0	0	0
2 Low	60	400	600	800
3 High	60	800	1200	1600

An additional 15 rats were used as sentinel animals to monitor intercurrent diseases and health status of the population of rats received for this study.

2. Diet :

Test diets were prepared biweekly and dietary concentrations were based on the active ingredient of RH-7592 Tech. Samples of the prepared test and control diets were taken for homogeneity and stability analyses. Test animals were allowed access to food and water ad libitum.

3. Statistics

Appended from pages 22 and 23 of the study.

4. A signed quality assurance statement was included.

5. A signed and dated GLP statement was included.

C. METHODS AND RESULTS:

1. Observations:

Animals were inspected twice a day for signs of mortality and moribundity. Cageside observations were conducted once a day for obvious signs of toxic and pharmacologic effects.

All animals were examined for ophthalmological lesions prior to the initiation of dosing and during Weeks 52 and 104.

Results - There appeared to be no treatment-related effect on survival of test animals. Survival rates were 42%, 40% and 55% for control, low- and high-dose groups, respectively. There appeared to be no clinical signs present that could be attributed to treatment with RH-7592.

There did not appear to be any indications of compound-related ocular abnormalities at either Week 52 or 104.

2. Body weight and food consumption:

Individual body weights and food consumption were recorded prior to treatment and weekly for Weeks 1-14 and once every 2 weeks thereafter. Efficiency of food utilization was calculated weekly for weeks 1-14 and every 2 weeks thereafter through Week 52.

Results - There was a decrease in mean body weights of test animals in the 1600 ppm dose group that was statistically ($p < 0.05$) significant at Weeks 8, 13, 26, 40, 52, 66, 78, 90 and 104.

Table 2**

Mean body weight (g)

Dose Level (ppm)	Week:	Start	4	8	13	
0		240.1	405.1	500.5	571.6	
800		244.3	415.3*	504.4	575.7	
1600		240.8	403.4	483.1*	550.0*	
	Week:	16	22	26	34	40
0		604.0	650.9	683.2	703.8	723.4
800		602.6	643.3	668.6	689.6	704.3
1600		579.4	616.9	637.6*	656.0	665.6*
	Week:	52	66	78	90	104
0		770.4	841.1	850.4	833.7	792.1
800		742.1	796.7	825.6	786.6	747.0
1600		694.9*	752.3*	762.7*	747.9*	664.5*

* Significantly different from control value, P≤0.05
** Excerpted from pages 117-122 of the study.

Table 3**

Mean Body Weight Change (G)

Dose Level (ppm)	Week 0-13	0-26	0-40	0-52	0-66	0-78	0-90	0-104
0	331.5	443.1	483.3	530.6	600.0	609.9	593.5	553.0
800	331.3	424.5	460.3	498.2	552.4	581.2	545.1	506.5
1600	309.2*	397.1*	425.0*	454.2*	510.6*	520.5*	506.3*	421.5*

**Excerpted from page 122.

A statistically ($p < 0.05$) significant decrease in mean body weight change was observed from initiation to Week 104 in the 1600 ppm dose group males.

Table 4**

Growth Analyses+

Dose Level (ppm)	Weeks 0 - 13	0 - 26	0 - 40	0 - 52
0	3.93	6.71	7.68	8.96
800	3.95	6.41	7.33	8.41
1600	3.70*	5.99*	6.78*	7.66*

**Excerpted from page 124.
*Significantly different from control, $P \leq 0.05$
+ Rao's growth analysis parameters derived from Rao's growth analysis.

There was no data for Week 52 through Week 104 present. Growth analysis data show a statistically ($p<0.05$) significant decrease at 1600 ppm of RH-7592 at 13 week intervals up to WeeK 52 of the study. Growth parameters were not calculated for Week 52 through Week 104.

Food and compound consumption - There were no statistically significant differences in total food consumption observed throughout the treatment period in either dose group when compared to controls. At Week 90, the 800 ppm dose group showed a significant decrease in food consumption when compared to controls. Food efficiency values were comparable to controls. There were no significant differences in the amount of RH-7592 consumed by males at 800 (30.42 mg/kg/day) or 1600 (63.94 mg/kg/day) ppm when compared to controls.

3. Clinical Pathology.

Blood was collected from 10 randomly selected rats/group at Weeks 14, 27, 53, 79 and 105. Cell morphology and differential counts were performed on Group 1 and 3 animals only and all moribund-sacrificed animals except as noted in the study. The CHECKED (X) parameters were examined:

a. Hematology

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Erythrocyte count*
X Leukocyte count*
X Platelet*
X Leukocyte differential count*
X Coagulation: thromboplastin time (PT)*

X Reticulocyte count (RETIC)
X Red cell morphology
X Mean corpuscular HGB concentration (MCHC)
X Mean corpuscular volume (MCV)
X myeloid/erythroid ratio (M/E ratio)

* Required for subchronic and chronic studies

Results - The mean hematocrit (HCT) value was significantly decreased for the high-dose group when compared to the control at Weeks 14 and 53, while hemoglobin (Hg) in the same dose group was significantly decreased at Week 53. In addition, the mean leukocyte (WBC), corrected leukocyte and lymphocyte counts were significantly decreased when compared to the control at Week 79. This reviewer agrees with the author that those few parameters (Hgb, HCT, WBC, corrected WBC, and Lymphocyte) that were statistically different from controls do not appear to be related to treatment with RH-7592.

b. Clinical Chemistry

Electrolytes

X Calcium*
X Phosphorus*
X Chloride*
X Sodium*
X Potassium*

Enzymes

X Serum alanine aminotransferase (SGPT)*
X Serum aspartate aminotransferase (SGOT)*
X Alkaline phosphatase (ALP)
X Gamma glutamyltransferase (GGT)

Thyroid Function Tests (Blood collected at Weeks 85 and 103 for these tests).

X Triiodothyroxine (T_3)
X Thyroxine (T_4)
X Thyroid Stimulating Hormone (TSH)

Other

X Albumin*
X Blood creatinine*
X Blood urea nitrogen*
X Glucose*
X Total bilirubin*
X Total protein*
X Cholesterol
X Albumin/globulin ratio
X Globulins
X Triglycerides

* Required for subchronic and chronic studies

Results - The mean aspartate and alanine aminotransferase values were statistically ($p < 0.05$) significantly decreased for the low-dose (800 ppm) males when compared to the control value at Week 14. Mean calcium, albumin, and total protein values were statistically ($p < 0.05$) significantly increased for the high-dose males when compared to controls. Mean triglyceride values were significantly decreased in the high-dose males at Week 14 and the low- and high-dose males at Week 53 when compared to controls. Mean total bilirubin values were statistically ($p < 0.05$) significantly decreased compared to the control at Week 79.

The mean T_4 value for high-dose males was significantly decreased compared to the control value at Week 103. The mean TSH values for the same treatment group were increased compared to controls at Weeks 85 and 103.

4. Urinalysis

Urine was collected from randomly selected fasted animals at Weeks 14, 27, 53, 79 and 105 months. The CHECKED (X) parameters were examined:

X Appearance*
X Volume*
X Specific gravity*
X pH
X Sediment (microscopic)*
X Protein*
X Glucose*
X Ketones*
X Bilirubin*
X Occult Blood*
X Protein - SSA

* Required for chronic studies

Results - There were no treatment-related findings.

5. Sacrifice and Pathology

Necropsies were performed on all found dead and moribund-sacrificed animals, accidental deaths, on 10 animals/group randomly selected at Week 53 for the interim sacrifice and on all remaining animals following at least 104 weeks of RH-7592 administration. Terminal body weights were recorded before necropsy. The necropsies included examination of the following: external surfaces, all orifices, carcass, external surface of the brain, nasal cavity and paranasal sinus, thoracic, abdominal, and pelvic cavities and their viscera, cervical tissues and their organs and the cranial cavity. The following tissues from each animal were preserved for histopathological examination:

Digestive System	Cardiovasc./Hemat.	Neurologic
X Tongue	X Aorta	X Brain
X Salivary glands	X Heart	X Periph. nerve
X Esophagus	X Bone marrow	X Spinal cord
X Stomach	X Lymph nodes	X Pituitary
X Rectum	X Spleen	X Eyes (optic nerve)
X Colon	X Thymus	
X Cecum		
X Ileum		
X Jejunum	Urogenital	Glandular
X Duodenum	X Kidney*	X Adrenals
X Liver*	X Urinary bladder	X Lacrimal gland
X Gallbladder	X Testes	X Mammary gland
X Pancreas	X Epididymis	X Thyroids
	X Prostate	X Parathyroids
	Seminal vesicle	X Harderian glands
Respiratory	X Ovaries	
X Trachea	X Uterus	
X Lung	X Vagina	Other
		X Bone (sternum & femur)
		X Skeletal muscle
		X Skin (treated & untreated)*
		X All gross lesions & masses*

* Recommended by Subdivision F (October 1982) Guidelines

(Livers, thyroids and testes from all rats, and all tissues from 5 rats from the control and high-dose groups at the terminal sacrifice and 2 rats from the high-dose group which were unscheduled deaths were submitted for peer review to Pathology Associates, Inc. in Frederick, MD.)

a. Gross pathology:

There were no apparent macroscopic abnormalities attributed to treatment with RH-7592.

b. Organ weight - At interim sacrifice, there was a decreasing trend in body weight in test animals treated at the 800 and 1600 ppm doses. An increasing trend that became statistically significant ($p < 0.05$) at 1600 ppm in absolute liver and thyroid weight was noted. Thyroid weight was also significantly increased in the low (800 ppm) dose males. A statistically significant ($p < 0.05$) decreasing trend in absolute kidney and testicular weight was present at terminal sacrifice in the high-dose group. (*Note: Data on relative organ weights were not listed in this study.)

At interim sacrifice, statistically significant ($p < 0.05$) increases in liver/body and thyroid/body ratios were presented in data of males treated at both the low- and high-dose of RH-7592. An increasing trend that became significant at 1600 ppm was observed in the spleen/body and testes/body weight ratios when compared to controls. At terminal sacrifice, an increasing trend that became statistically significant at 1600 ppm RH-7592 was noted after assessment of the liver/body weight and brain/body weight ratios.

At interim sacrifice, statistically significant ($p < 0.05$) increases in liver/brain weight ratio (1600 ppm) and thyroid/brain weight ratios (both 800 and 1600 ppm groups) were observed when compared to the control. At terminal sacrifice, the liver/brain weight ratio (9.392) was significantly ($p < 0.05$) increased in the high-dose group when compared to controls (7.999).

c. Histopathology:

At interim sacrifice, the liver and thyroid glands appeared to be the only two organs expressing compound related histopathological changes. Slight (6/10; 60%) or moderate (4/10; 40%) centrilobular to midzonal hepatocellular enlargement was present in the livers of low-dose rats, with hepatocellular vacuolization in 7/10 (70%) rats. Hepatocellular enlargement was moderate (5/10; 50%) to moderately severe (5/10; 50%) and hepatocellular vacuolization was present in 100% of the rats. Follicular cell hypertrophy of minimal or slight severity occurred in 8/10 (80%) of those treated with 1600 ppm RH-7592.

There appears to be evidence of toxicity in test animals that died or were sacrificed prematurely. As seen in the table below, an increased incidence of centrilobular to midzonal hepatocellular enlargement was noted in both low- and high-dose groups.

Table 5*
Compound-Related Liver Changes in Unscheduled Deaths

Dose (ppm)	0	800	1600
# Examined	29	30	23
Centrilobular to midzonal Hepatocell. Enlargement	0	18	15
minimal	-	4	1
slight	-	12	5
moderate	-	2	9
Centrilobular to midzonal Hepatocell. vacuolization	0	3	3
minimal	-	2	0
slight	-	1	3

*Appended from Text Table 2, page 48.

At terminal sacrifice, the livers (Table 6) of rats in the low- and high-dose group, along with the thyroid glands (Table 7) of rats in the high-dose group, exhibited compound-related histopathological changes. As shown in the table below, hepatocellular enlargement was generally of slight to moderate severity in low-dose rats and was moderate to moderately severe in high-dose rats. These data also indicate adverse response to treatment with RH-7592.

Table 6*
Compound-Related Liver Changes at Terminal Sacrifice

Dose (ppm)	0	800	1600
Number examined	21	20	27
Centrilobular to Midzonal Hepatocellular Enlargement	0	0	27
minimal	-	1	0
slight	-	6	0
moderate	-	13	12
moderately severe	-	0	15
Centrilobular to Midzonal Hepatocellular Vacuolization	0	8	13
minimal	-	4	7
slight	-	4	5
moderate	-	0	1

*Excerpted from Text Table 3 page 49.

In the thyroid gland (Table 7), there was minimal to slight follicular cell hypertrophy in 12/27 (44%) of high-dose males. The incidence of follicular cell adenoma was slightly increased in high-dose animals. Overall, the incidence of follicular cell adenomas was 2/60 (3.3% in the control group, 5/60 (8.3%) in the 800 ppm dose group, and 9/60 (15%) in the high-dose group.

Table 7*
Incidence of Thyroid Follicular Cell Hypertrophy and Neoplasia

Dose Level (ppm)	0	800	1600
Number Examined	60	60	60
Follicular cell hypertrophy	1	0	21
Follicular cell adenoma	2	5	9[a]
Follicular cell carcinoma	2	0	2[a]

[a] Animal number B07287 had both adenoma and carcinoma
*Excerpted from page 51 of the study.

D. DISCUSSION/CONCLUSIONS:

-No treatment-related effects were observed with respect to survival which ranged between 40 to 55%.

-There were no clinical signs, tissue masses or ophthalmological findings related to treatment since they were observed sporadically at a low frequency or were similar to those commonly noted in animals of this age and strain.

-For Weeks 8, 13, 26, 40, 52, 66, 78, 90 and 104 at 1600 ppm, mean body weight was statistically significantly decreased when compared to the control. The low-dose (800 ppm) group appeared to be expressing a decreasing trend in body weight around Week 26 through Week 104. A significant decrease in mean body weight change and growth seemed evident at the intervals evaluated. Analyses performed using growth intervals based on absolute mean body weight data (Table 4) were significantly decreased compared to controls. The findings for the test animals appears to be treatment-related.

-[illegible] weekly food consumption was similar between control and treatment groups. Mean compound consumption at 800 and 1600 ppm was 30.41 and 63.94 mg/kg/day, respectively.

-This reviewer tends to agree with the author that those few parameters (Hg, HCT, WBC, corrected WBC, and Lymphocyte) that were statistically different from controls, along with clinical chemistry findings, do not appear to be related to treatment with RH-7592. There were no treatment-related changes seen after urinalysis.

-There were no treatment-related findings noted upon gross examination in any test animals.

-An increasing trend in absolute (no relative organ weight data was included for evaluation) liver weights was noted at interim and terminal sacrifices. Statistically significant increases at 1600 ppm were observed in absolute liver/body and brain weight ratios at the 12-month

interim necropsy. In addition, The 800 ppm males displayed significant increases in the liver/body weight ratios.

-At terminal necropsy, liver/body and brain weight ratios were statistically significantly elevated also possibly due to treatment with RH-7592. In addition, the absolute thyroid/parathyroid/body weight ratios were increased in the low- and high-dose males at interim necropsy. Terminal-sacrifice and absolute brain, kidney, and testes weights were significantly decreased for high-dose males compared to controls.

-The increases in liver and thyroid weights correlate with histopathological changes in the liver and thyroid of high-dose males. Centrilobular to midzonal hepatocellular enlargement (48/60; 80% and 52/60; 87%) and vacuolization (18/60; 30% and 26/60; 43%) were noted in the low- and high-dose group males, respectively compared to 0/60 for hepatocellular enlargement and vacuolization in the concurrent control group.

-There was a marked increase in the thyroid gland follicular cell hypertrophy and a slight increase in follicular cell adenoma in the high-dose group compared to controls. The incidence of thyroid follicular cell adenomas at 1600 ppm (9/60=15%) was significantly elevated. However, the author indicates that this finding was within the historical control range.

-There was no increase in the incidence of follicular cell carcinomas or combined adenomas plus carcinomas in the high-dose group when compared to controls. This reviewer agrees with the author that insufficient evidence was presented to warrant a conclusion indicating that RH-7592 is carcinogenic to rats.

The results of this study indicate that treatment with RH-7592 at levels of 800 and 1600 ppm over 104 weeks does not appear to be carcinogenic in male rats. Administration of RH-7592 at 1600 ppm did cause several signs of toxicity in test animals. Adverse effects included increased liver weights with centrilobular to midzonal hepatocellular enlargement and vacuolization (800 and 1600 ppm) and decreased body weight gain and increased thyroid/parathyroid weights with a marked increase in follicular cell hypertrophy and a slight increase in follicular cell adenomas (1600 ppm). The NOEL for this study is less than 800 ppm, the LOEL is 800 ppm (30.41 mg/kg/day) and the MTD is 1600 ppm (63.94 mg/kg/day).

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males were used. However, this study can be used in conjunction with the previous chronic toxicity/oncogenicity study with RH-7592 in male and female Sprague-Dawley rats (HWA 417-437; Rohm and Haas Report 88RC-98) to fulfill this guideline. This study is classified core-supplementary.

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Page_____ is not included in this copy.

Pages 17 through 18 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

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____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

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