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

FILE COPY

July 22, 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review Meeting on **FENBUCONAZOLE**

FROM: Esther Rinde, Ph.D. E.R.
Manager, Carcinogenicity Peer Review
Health Effects Division (H7509c)

TO: Addressees

Attached for your review is a package on **FENBUCONAZOLE** prepared by Dr. SanYvette Williams.

A meeting to consider the carcinogenicity classification of this chemical is scheduled for **Wednesday Aug. 11, 1993**, at **10:00 am in Room 817, CM2.**

Addressees

P. Fenner-Crisp
W. Burnam
K. Baetcke
M. Van Gemert
R. Engler
K. Dearfield
H. Pettigrew
B. Fisher
L. Brunsman
E. Doyle
S. Williams
J. Rowland
R. Hill
Y. Woo
D. Mandell (2)

FENBUCONAZOLE PEER REVIEW

DATA PACKAGE

TABLE OF CONTENTS

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **FENBUCONAZOLE:** Peer Review by the Health Effects Division Carcinogenicity Peer Review Committee to Assess the Carcinogenic Potential.

TO: Esther Rinde, PhD.
Manager, HED Carcinogenicity Peer Review Committee
Health Effects Division (H7509C)

FROM: SanYvette Williams, D.V.M. 7/21/93
Toxicology Branch II/Section IV (H7509C)
Health Effects Division

THROUGH: Jess Rowland M.S., Acting Section Head Jess Rowland 7/21/93
Toxicology Branch II/Section IV (H7509C)
Health Effects Division
and
Marcia Van Gemert, Ph.D., Branch Chief
Toxicology Branch II (H7509C) Marcia Van Gemert 7/21/93
Health Effects Division

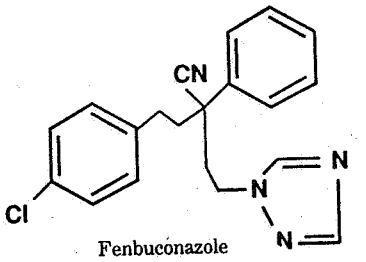
The HED Peer Review Committee is requested to evaluate the carcinogenic potential of fenbuconazole [RH-7592]. A data package consisting of summary of studies submitted to the Office of Pesticide Programs as well as the Data Evaluation Reports of critical studies are attached.

RECEIVED
7/22/93

I. BACKGROUND INFORMATION

Febuconazole [RH-7592], [alpha-(2-(4-chloroophenyl)ethyl)-alpha-phenyl-(1H-1,2,4-triazole)-1-propanenitrile (CA); 4-(4-chlorophenyl)-2-phenyl-2-((1H-1,2,4-triazo-1-yl) methyl)butanenitrile(IUPAC), is an experimental fungicide used to prevent the development of disease incited by many fungi on food and non-food crops.

PC Code: 129011. Tox. Chem. No: 723Q. CAS No: 114369-43-6.



Fenbuconazole

II. EVALUATION OF CARCINOGENICITY EVIDENCE

The registrant conducted a carcinogenicity study in CD-1 mice and two studies with Sprague-Dawley rats. The first rat study was conducted in 1990 at dietary levels of 0, 80 or 800 ppm for 104 weeks. Since the high-dose in the preceding study was not adequate to assess carcinogenicity, a second study was conducted in 1991 with male rats only at dietary levels of 0, 800 or 1600 ppm for 104 weeks the dose levels were recommended by the Agency.

1. Mouse Carcinogenicity Study

Reference: Wolfe, Gary, PhD: RH-7592 Technical: 78-Week Dietary Oncogenicity Toxicity in Mice. MRID No:418933-01; HLA Study No.417-438; Report issued 3/20/91.

a. Experimental Design

Groups of 60 male and 60 female CD-1 (Crl:CD-1(ICR) BR VAF/+) mice were fed diets containing fenbuconazole [97%] at 0, 10, 200 or 650 ppm (males) and 0, 10, 650 or 1300 ppm (females) for 78 weeks. These values correspond to 1.28, 26.28 or 85.26 mg/kg/day, respectively, for males and 1.59, 104.64 and 208.84 mg/kg/day, respectively, for females. Ten animals/sex/group were sacrificed at week 53; survivors were sacrificed at 79 weeks.

b. Discussion of Tumor Data

The tumor incidences and statistical analyses are presented in Table 1 and Table 2 for males and females, respectively. In male mice, no increase in hepatocellular tumors were seen in treated animals when compared to controls. However, there was a statistically significant [$p < 0.05$] increasing trend in hepatocellular carcinomas; 5/55 [9%] at 650 ppm compared to 1/57 [2%] at 0 ppm. In female mice, fenbuconazole significantly [$p < 0.05$] increased the incidence of hepatocellular adenomas and carcinomas [combined] at 1300 ppm [5/47, 11%] when compared to controls [0/43, 0%]. Additionally, there was a significant [$p < 0.01$] increasing trends in adenomas and combined adenomas/carcinomas. The HED Reference Dose Committee expressed concerns regarding the MHV titers seen in the sentinal animals at the end of the study which might have potentiated liver toxicity.

Table 1. Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results in **MALE MICE**

Tumor Type	0 ppm	10 ppm	200 ppm	650 ppm
Adenomas	8/57	1/57	8[a]/58	6/55
%	14	2	14	11
p=	0.293	0.016[n*]	0.591	0.416
Carcinomas	1/57	1/57	3/58	5[b]/55
%	2	2	5	9
p=	**0.023***	0.752	0.316	0.095
Combined	9/57	2/57	10/58	10/55
%	16	4	17	18
p=	0.077	0.026[n*]	0.517	0.466

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died/sacrificed before week 53.
[n] Negative change from control.
[a] First adenoma observed at week 53, dose 200 ppm.
[b] First carcinoma observed at week 62, dose 650 ppm.

Table 2. Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results in **FEMALE MICE**

Tumor Type	0 ppm	10 ppm	650 ppm	1300 ppm
Adenomas	0/43	0/46	0/43	4[a]/47
%	0	0	0	9
p=	**0.004****	1.000	1.000	0.070
Carcinomas	0/43	1/46	0/43	1[b]/47
%	0	2	0	2
p=	0.330	0.517	1.000	0.522
Combined	0/43	1/46	0/43	5/47
%	0	2	0	11
p=	**0.004****	0.517	1.000	**0.035***

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died or sacrificed before week 54.
[a] First adenoma observed at week 77, dose 1300 ppm.
[b] First carcinoma observed at week 79, dose 1300 ppm.
Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Historical control data from the testing laboratory [Hazleton Labs] are tabulated in Table 3. The incidence of adenomas in females at 1300 ppm [4/47 (9%)] exceeded both the historical control incidence [7/495 (1.4%)] and range [0 - 6.1%]. The increase in carcinomas at this dose [1/47 (2%)] exceeded the historical control incidence [3/495 (0.6%)] and was at the high end of the range [0 - 2.1%]. Historical control data were not available for the combined adenomas/carcinomas.

Table 3. Historical Control Data for Hepatocellular Tumors in CD-1 Mice[a]

Sex	Tumor Type	Historical Control	
		Incidence	Range
Males	Adenomas	37/499 [7.4%]	2 - 11.0%
	Carcinomas	15/499 [3.0%]	0 - 8.2%
	Combined	Not available [NA]	NA
Females	Adenomas	7/495 [1.4%]	0 - 6.1%
	Carcinomas	3/495 [0.6%]	0 - 2.1%
	Combined	NA	NA

a = SOURCE: Hazleton Laboratories; 10, 78-week studies each comprising 47-55 sex.

c. Non-neoplastic Lesions

Treatment-related non-neoplastic lesions included centrilobular to midzonal diffuse hepatocellular enlargement and a greater incidence and severity of hepatocellular vacuolation observed in males at 200 and 650 ppm and in females at 650 and 1300 ppm. These lesions were also observed in male [800 and 1600 ppm] and female [800 ppm] Sprague-Dawley rats. The incidences are summarized in Table 4.

Table 4. Non-neoplastic Lesions in Mice fed Fenbuconazole

Dose Level [ppm]	0	10	200	650	0	10	650	1300
Sex	Male				Female			
Number Examined	60	59	60	60	58	60	57	60
Hepatocellular enlargement	4	4	22	55	1	1	34	49
Hepatocellular vacuolation	2	1	11	31	4	1	20	31

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The dose levels employed, approved by the Agency, were selected based on the results from a 2-week and 90-day studies [Letter: M.A. Morelli, Rohm-Hass, to L.J. Schnaubelt, RD; 11/18/88].

2. The 1990 Rat Carcinogenicity Study in Males and Females

Reference: Wolfe, Gary, PhD: RH-7592 Technical: 24 Month Dietary Chronic Toxicity/Oncogenicity Study in Rats. MRID Nos: 416353-01 & 416353-02; HLA Study ID#: HLA Study No. 417-437; Report issued August 15, 1990.

a. Experimental Design

Groups of 70 male and 70 female Sprague-Dawley (Crl:CD(SD) VAF/+) rats were fed diets containing fenbuconazole [97%] at 0, 8, 80 or 800 ppm for 104 weeks. An interim sacrifice was conducted in 10 animals/sex/group at week 53; survivors were sacrificed at 105 weeks.

b. Discussion of Tumor Data

The tumor incidence and statistical analyses are presented in Table 5. At 800 ppm, fenbuconazole caused significant [$p < 0.05$] increases in combined thyroid follicular cell adenomas and carcinomas [8/58 (14%)] when compared to controls [1/54 (2%)]. Additionally, there were significant [$p < 0.05$] increasing trends for adenomas and combined adenomas/carcinomas. No such increases were seen in females for this tumor type.

Table 5. Thyroid Follicular Cell Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results in **MALE RATS [1990]**

Tumor Type	0 ppm	8 ppm	80 ppm	800 ppm
Adenomas	1/54	2[a]/58	3/57	6/58
%	2	3	5	10
p=	**0.023***	0.527	0.330	0.069
Carcinomas	0/54	3[b]/58	0/57	4/58
%	0	5	0	7
p=	0.058	0.135	1.000	0.068
Combined	1/54	5/58	3/57	8/58
%	2	9	5	14
p=	**0.022***	0.120	0.330	**0.021***

+ Number of tumor bearing animals/Number of animals examined, excluding those that died/sacrificed before week 54.
[a] First adenoma observed at week 89, dose 8 ppm.
[b] First carcinoma observed at week 75, dose 8 ppm.
Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

c. Non-neoplastic Lesions

Treatment-related non-neoplastic lesions included centrilobular to midzonal hepatocellular enlargement and vacuolation and focal cystic hyperplasia in 800 ppm males and females. Hepatocellular enlargements and vacuolations were also seen in CD-1 mice at 650 ppm [males] and 1300 ppm [females] and in males at 800 and 1600 ppm in the second study. The incidences are summarized in Table 6:

Table 6. Non-neoplastic Lesions in Rats fed Fenbuconazole

Dose Level [ppm]	0	8	80	800	0	8	80	800
Sex	Male				Female			
Number Examined	70	70	70	70	70	70	70	70
Focal cystic hyperplasia	1	4	1	12	2	1	2	0
Hepatocellular enlargement	0	0	1	46	0	0	0	52
Hepatocellular vacuolation	0	0	1	15	0	0	1	30

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The dose levels used in the females were adequate to assess the carcinogenicity as evidenced by significant decreases in body weight gain and the occurrence of life-threatening histopathological lesions. Body weight gain was 18%, 16%, 16%, 26% and 18% lower than controls at weeks 4, 13, 40, 66 and 78, respectively. In contrast, no decreases in body weight gain, alterations in clinical pathology, gross pathology or life-threatening histopathological lesions were seen in males at the high-dose. Consequently, it was concluded that the high dose was not adequate to assess the carcinogenic potential of fenbuconazole in this sex. A new study conducted in males only at a higher dose is described below.

3. The 1991 Rat Carcinogenicity Study in Males Only

Reference: Wolfe, Gary, PhD: RH-7592 Technical: 104-Week Dietary Chronic Toxicity/Oncogenicity Study in Male Rats. MRID Nos: 420550-01; HWA Study No. 417-455; Report issued July 15, 1991.

a. Experimental Design

Groups of 50 male Sprague-Dawley (Crl:CD(SD) VAF/+) rats were fed diets containing fenbuconazole [97%] at 0, 800 or 1600 ppm for 104 weeks. An additional 10 rats/group were sacrificed at week 53; survivors were sacrificed at 105 weeks.

b. Discussion of Tumor Data

The tumor incidence and statistical analyses are presented in Table 7. There was a significant [$p < 0.05$] increase in thyroid follicular cell adenomas at 1600 ppm, [9/55, 16%] when compared to controls [2/59, (3%). Additionally, there was a significant increasing trend for adenomas and combined adenomas/carcinomas.

Table 7. Thyroid Follicular Cell Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results in **MALE RATS [1991]**

Tumor Type	0 ppm	800 ppm	1600 ppm
Adenomas	2/59	5[a]/58	9/55
%	3	9	16
p=	**0.013***	0.212	**0.020***
Carcinomas	2/59	0/58	2[b]/55
%	3	0	4
p=	0.596	0.252[n]	0.664
Combined	4/59	5/58	10/55
%	7	9	18
p=	**0.038***	0.489	0.058

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died/sacrificed before week 54.
[n] Negative change from control.
[a] First adenoma observed at week 51, dose 800 ppm.
[b] First carcinoma observed at week 67, dose 1600 ppm.
Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Historical control data from the testing laboratory [Hazleton] are tabulated in Table 8. The incidence of follicular cell adenomas in males at 800 ppm [6/58 (10%)] in the 1990 study and at 1600 ppm [9/55 (16%)] in the 1991 study exceeded the historical control incidence [13/265 (4.9%)], was within the range [0 - 14.8%] in the first study, and exceed the range in the second study. Follicular cell carcinomas at 800 ppm [4/58, 7%] exceeded the historical control incidence [11/265 (4.2%)] and was at the high end of the range [0 - 7.4%] in the first study; a similar trend was not seen with the second study. Historical control data were not available for the combined adenomas/carcinomas.

Table 8. Historical Control Data for Follicular Cell Adenomas & Carcinomas in Sprague-Dawley Rats[a].

Sex	Tumor Type	Historical Control	
		Incidence	Range
Males	Adenomas	13/265 [4.9%]	0 - 14.8%
	Carcinomas	11/265 [4.2%]	0 - 7.4%
	Combined	NA	NA

a= SOURCE: Hazleton Laboratories; nine studies each comprising of 50 mice/sex.

c. Non-neoplastic Lesions

Treatment-related non-neoplastic lesions included centrilobular to midzonal hepatocellular enlargement and vacuolation and follicular cell hypertrophy at 1600 ppm. The incidences are summarized in Table 9.

Table 9. Non-neoplastic Lesions in Male Rats fed Fenbuconazole

Dose Level [ppm]	0	800	1600
Number Examined	50	50	50
Follicular cell hypertrophy	1	0	21
Hepatocellular enlargement	0	38	42
Hepatocellular vacuolation	0	11	16

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The high dose used in this study was adequate to assess the carcinogenicity as evidenced by significant decreases in body weight gain and by the induction of thyroid tumors similar to those seen in females in the 1990 study at 800 ppm.

III. ADDITIONAL TOXICOLOGY DATA

1. Metabolism

Following oral administration ^{14}C-fenbuconazole was rapidly and extensively absorbed from the gastrointestinal tract and eliminated primarily in the feces. Metabolism was extensive since the unmetabolized parent compound accounted for 9-15% of the recovered radio-activity in the feces and 0-3% in the urine. Thirteen metabolites of fenbuconazole and its conjugates were identified. Following intravenous administration, biliary excretion appears to be a major excretion route as indicated by high radioactivity in the feces. This was supported by the high amount of metabolites detected in the feces rather than unabsorbed parent compound [MRID No 418750-17 and 418750-18; HED Doc. No 930063].

2. Mutagenicity

Fenbuconazole was shown to be a nonmutagen for gene mutation, structural chromosomal aberration and other genotoxic effects. It was nonmutagenic both in the presence and absence of metabolic activation in the Ames assay; however, these studies were classified as unacceptable; postive controls were not included in the assays. Fenbuconazole was nonmutagenic in the HGPRT locus Chinese hamster overy cells both with and without activation. In an *in vivo* cytogenetic assay, fenbuconazole did not elicit chromosomal aberrations in the bone marrow of rats. The compound was negative in an unscheduled DNA assay using cultured rat primary heatocytes [MRID No. 410312-16; 17; 18; 19 and 20; HED Doc.No.00767].

3. Reproductive Toxicity

In a two-Generation reproduction study, Sprague-Dawley rats were fed diets containing fenbuconazole at 0, 8, 80 or 800 ppm. Reproductive effects seen among females treated at 800 ppm in the P1 and P2 generations included increases in maternal death during delivery, increases in the number of dams not delivering viable or delivering nonviable offspring, decreases in body weight and food consumption. Based on these findings, the parental & reproductive NOEL was 80 ppm [4 mg/kg/day] and the LOEL was 800 ppm [40 mg/kg/day] [MRID No. 418750-15; HED Doc.No. 010109].

4. Developmental Toxicity

In CRL:CD rats given oral administration of fenbuconazole at 0, 30, 75 or 150 mg/kg/day during gestation days 6 through 15, maternal toxicity was manifested as decreases in mean body weight and body weight gain at 75 and 150 mg/kg/day and a substantial increase in resorption sites at 150 mg/kg/day which may have contributed to a decrease in live fetuses per dam in both the mid and the high doses. Mean fetal weight was reduced at 150 mg/kg/day. There was an increase in the incidence of skeletal variants, predominantly fetuses with a 14th rudimentary rib at 150 mg/kg/day [DER did not present incidence for this skeletal variation]. Based on these findings, the maternal and developmental toxicity NOELs and LOELs established were 30 mg/kg/day and 75 mg/kg/day, respectively [MRID Nos. 410735-05 & 410312-14; HED Doc.No. 007677].

In rabbits given oral administration of fenbuconazole at dose levels of 10, 30 and 60 mg/kg/day during gestation days 7-19, no maternal toxicity was evidenced at any dose level. However, at 60 mg/kg/day, only 1/11 viable litters survived indicating this to be a fetotoxic dose. No developmental toxicity was seen in fetuses born to does given 10 or 30 mg/kg/day; fetal evaluations were not meaningful in the 60 mg/kg group because only 1 of the pregnant does produced a viable fetus. The NOEL for maternal toxicity can be established at $\leq$30 mg/kg/day; neither a NOEL nor a LOEL can be established for developmental toxicity [MRID No. 41875014; HED Doc.No. 010109].

5. Acute, Subchronic, and Chronic Toxicity Studies

Acute: Fenbuconazole is classified in Toxicity Category III for acute oral and inhalation toxicity, and in Toxicity Category IV for acute dermal irritation, primary eye irritation and primary dermal irritation. Fenbuconazole is not a skin sensitizer.

Subchronic: In CD-1 mice fed diets containing fenbuconazole at 0, 20, 60, 180 or 540 ppm for three months, liver toxicity was manifested as increases in transaminase activities, liver weights, and histopathology [hypertrophy of hepatocytes] in both sexes at 60, 180 and/or 540 ppm. The NOEL was 20 ppm and the LOEL, based on heptatotoxicity was, 60 ppm [MRID No. 410735-03; HED Doc. No. 007677].

In Sprague-Dawley rats fed diets containing fenbuconazole at 0, 20, 80, 400 or 1600 ppm for three months, liver and thyroid glands were identified as the target organs. Hepatotoxicity was manifested as decreases in triglycerides, increases in cholesterol and GGT, increase in liver size, and histopathological changes such as hepatocellular hypertrophy and vacuolation of hepatocytes at doses >80 mg/kg/day. The effect on thyroid glands was an increase in thyroid follicle cell size at 400 and 1600 ppm in males and at 1600 ppm in females. The NOEL was 20 ppm and the LOEL, based on hepatotoxicity, was 80 ppm [MRID No. 410735-02; HED Doc.No. 007677].

In Beagle dogs fed diets containing fenbuconazole at 0, 30, 100, 400 or 1600 ppm for three months, primary effects seen in the liver included decreases in serum protein, increases in triglygerides, increases in liver weights and histopathological lesions characterized as diffuse hepatocellular hypertrophy and multifocal vacuolation at dose >400 ppm. The NOEL was 100 ppm and the LOEL, based on hepatocellular hypertrophy, was 400 ppm [MRID No.410735-04; HED Doc.No.007677].

CHRONIC: Groups of 4 male and 4 female dogs were fed diets containing fenbuconazole at 0, 15, 150 or 1200 ppm for 52 weeks; these dose levels correspond to 0, 0.38, 3.75 or 30 mg/kg/day, respectively. No treatment-related effects were observed in males at 15 or 150 ppm. In females, fenbuconazole at 1200 ppm decreased body weight gain and induced adaptive changes in the liver which were reflected by increased metabolic activity. The NOEL was 150 mg/kg/day [3.75 mg/kg/day] the LOEL, based on decreases in body weight gain and increased liver weight, was 1200 ppm [30 mg/kg/day][MRID No.418750-49; HED Doc. No. 010109].

In a chronic toxicity study with Sprague-Dawley rats [discussed under carcingoencity], dietary admininstration of fenbuconazole at 0, 10, 80, or 800 ppm for 104 weeks caused significant decreases in body weight gain and increased liver weight in female at 800 ppm and increases in thryroid weights in males. Treatment had no effect on survival, food consumption, clinical signs, or hematology, clinical chemistry or urinanalyses paramters in either sex. At 800 ppm, treatment caused alterations in organ weights, gross pathology and induced non-neoplastic and neoplastic lesions in the liver and/or thyroids of females. No treatment-related effects were observed in males at any dose levels. For chronic toxicity, the NOEL was 800 ppm for males and 80 ppm for females. The LOEL, based on decreses in body weight gain and hepatotoxicity, was 800 ppm in females; a LOEL was not established in males [MRID No. 416353-01 & 416353-02; HED Doc.No.008296].

In another chronic toxicity study with males Sprague-Dawley rats [discussed under carcinogencity], dietary administration of fenbuconazole at 0, 800 or 1600 ppm caused no effects on survival, clinical signs, or clinical pathology. Treatment-related effects at 1600 ppm were decreases in body weight gain, increases in liver and thyroid weights, non-neoplastic and neoplastic lesions. For chronic toxicity, a NOEL of 800 ppm and a LOEL of 1600 ppm were established [MRID No. 420550-01; HED Doc. No. 009977].

IV. STRUCTURE-ACTIVITY CORRELATIONS

Fenbuconazole is structurally related to Bayleton, Baytan, Baycor, Propiconazole, Etaconazole, Azaconazole, Hexaconazole, Cyproconazole, Uniconazole and Tebuconazole. The structural formulas, tumor type, and cancer classification of these compound are shown in Figure 1. A summary is provided below:

Bayleton: Group "C(nq)" carcinogen; based on hepatocellular adenomas in male and female NMRI mice and a dose-related trend for thyroid follicular cell adenomas in males and cystic hyperplasia in both sexes.

Baytan: "Weak C" carcinogen; based on hepatocellular adenomas and hyperplastic nodules in female CF1-W74 mice.

Baycor: was non carcinogenic in male and female mice and male and female rats doses up to and including 500 ppm.

Propiconazole: Group C (nq) carcinogen; based on hepatocellular adenomas, carcinomas, and/or adenomas and carcinomas combined in CD-1 mice.

Etaconazole: increased the incidence of liver adenomas and carcinomas; registration voluntarily withdrawn.

Azaconazole: was non carcinogenic in male and female mice [strain not specified]; the doses used may not have been adequate to assess the carcinogenic potential of this compound.

Hexaconazole: Group C (Q) carcinogen; based on benign Leydig cell testicular tumors in ALpk:APfSD (Wistar derived) rats. Doses used in the CD-1/Alpk mouse study were not adequate to assess carcinogenicity.

Cyproconazole: Group C (nq) carcinogen; based on hepatocellular adenomas and carcinomas in male and female CD-1 mice.

Uniconazole: Group C (nq) carcinogen; based on hepatocellular adenomas and carcinomas in male Crl:CD-1(ICR)BR in male mice. Non carcinogenic in male or female rats.

Tebuconazole: Recently reviewed by HRC, classification pending; induced hepatocellular tumors in mice.

IV. WEIGHT OF EVIDENCE CONSIDERATIONS:

The weight-of-the-evidence for the determination of the carcinogenic potential of fenbuconazole is presented below:

1. In CD- mice, fenbuconazole appears to induce hepatocellular adenomas and/or adenomas/carcinomas combined. In males, there was no significant increase in the pair-wise comparisons of the dosed groups with the controls. However, there was a significant [p=0.023] trend for hepatocellular carcinomas. In females, there was a significant [P=0.035] increase in pair-wise comparison at the 1300 ppm [11%] group compared to controls [0%] for combined adenomas/carcinomas as well as increasing trends for adenomas [p=0.004] and adenomas/carcinomas combined [p=0.004].

When compared to historical controls, the incidence of adenomas [9%] in females at the high dose exceeded both the historical control incidence [1.4%] and range [0-2.7%] of the testing laboratory. Carcinomas at this dose [2%] exceeded the historical control incidence [0.6%] and were at the high end of the range [0-2.1%]; however, there was no pair-wise significance nor there was a trend for this tumor type. Historical control data were not available for the combined tumors.

2. In Sprague-Dawley rats, fenbuconazole appears to induce thyroid follicular cell adenomas and/or adenomas/carcinomas combined in males only at high doses. In one study, there was a significant [0.021] increase in pair-wise comparison at 800 ppm [14%] for combined adenomas/carcinomas when compared to controls [2%]. Also, there was a significant [0.022] trend for this tumor type. Additionally, there were significant increasing trends for adenomas [p=0.023] and combined adenomas/carcinomas [p=0.022]. In the other study, there was a significant [p=0.020] increase in adenomas [16%] at 1600 ppm when compared to controls [3%]. Additionally, there were significant trends for adenomas [p=0.013] and combined adenomas/carcinomas [p=0.038].

When compared to historical controls, the incidence of follicular cell adenomas in males in both studies [10% at 800 ppm in the first study and 16% at 1600 ppm in the second study] exceeded the historical control incidence [4.9%] but was within the range [0 - 14.8%] in the first study and exceeded range in the second study. In the first study, follicular cell carcinomas at 800 ppm [7%] exceeded the historical control incidence [4.2%] and was at the high end of the range [0 - 7.4%]. A a similar trend was not seen with the second study. Historical control data were not available for the combined adenomas/carcinomas.

3. Fenbuconazole induced non-neoplastic lesions included centrilobular to midzonal hepatocellular enlargement and hepatocellular vacuolation in both sexes of mice and rats at the high doses indicating the liver to be target organ in both sexes/species. Treatment also induced focal cystic hyperplasia in males at 800 ppm and follicular cell hypertrophy at 1600 ppm indicating the thyroid to be the second target organ in male rats only.

4. Fenbuconazole was nonmutagenic both *in vivo* and *in vitro*.

5. Several structural analogues of fenbuconazole induced hepatocellular adenomas and/or carcinomas in different strains of mice. One analog, Bayleton also induced in thyroid follicular cell adenomas in males and cystic hyperplasia in both sexes, while another analog, Hexaconazole, induced benign Leydig cell testicular tumors in rats.

Fig. 1 Structurally related to fenbuconazole

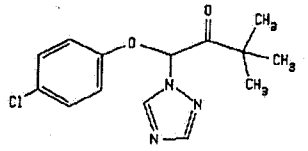
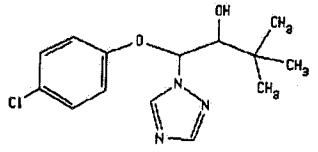
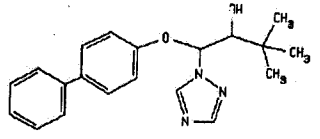
Compound	Structure	Carcinogenic Effect	Carcinogen Class
Bayleton PC 109901 Tx.# 862AA		**NMRI Mouse**, 50, 300, & 1800 ppm. Only hepatocellular adenoma, at 1800 ppm in (22%)♂ & (18%)♀, $p<0.05$ for trend and paired comparisons Hist. Conts.: 18.4% ♂, and 2.0% ♀. **Wistar rat**, 50, 500 & 5000 ppm. Dose related trend in TFC adenomas in ♂ & comb. w. cystic hyperplasia in ♂ & ♀; pairwise comparisons not significant.	**C NQ**
Baytan PC 127201 T.# 074A		**CF1-W74 mouse**, 2000 ppm: Hepatocellular adenomas and hyperplastic nodules ($p<0.01$) in ♀. No increase in ♂. Adrenal adenomas noted in ♀ LDT and HDT but not in hist. conts. No elevation in carcinomas.	**Weak C SAP 12/23/87.**
Baycor PC 112403 T.# 087AA		**Mouse:** up to 500 ppm: (-) **Rat:** up to 500 ppm : (-)	

Fig. 1 cont'd Structurally related to fenbuconazole

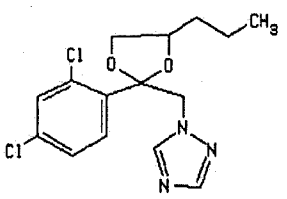
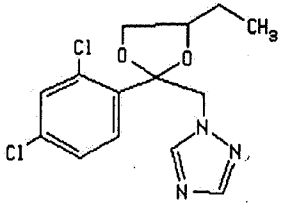
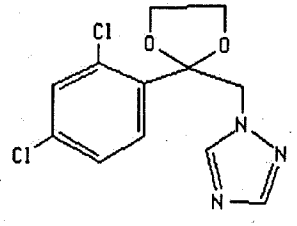
Propiconazole **PC 122101** **T# 323EE**		**CD-1 mouse**, 100, 500 & 2500 ppm. Statistically significant trend and pairwise comparisons in liver adenomas and combined at 2500 ppm. For carcinomas only there were statistically significant trend and pairwise comparisons at the HDT for data from 2 of 3 pathologists; for the data from the third pathologist only the trend was significant (p = 0.028), the pairwise comparison HDT vs. control had a p = 0.050.	**C NQ**
Etaconazole **PC**		**Swiss mouse** increased incidence of liver adenomas and carcinomas in both males and females. Registration voluntarily withdrawn.	
Azaconazole **PC 128882** **T# 321A**		**Mouse**, 25,100 &400 ppm. There is the question of whether the MTD was reached. No carcinogenicity effect.	

Fig. 1 cont'd Structurally related to fenbuconazole

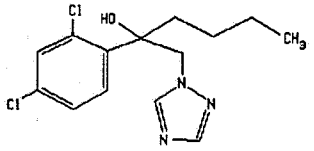
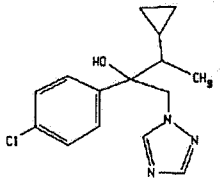
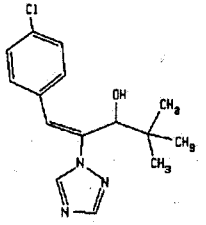
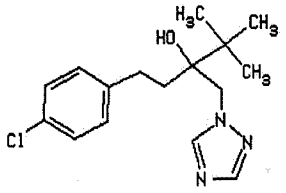
Compound	Structure	Carcinogenic Effect	Carcinogen Class
Hexaconazole PC 128925 T# 480G		**CD-1/Alpk mouse**, 5, 40 & 200 ppm. No carcinogenicity effect. Should be evaluated with caution because the MTD was not reached. **ALpk:APfSD (Wistar derived) rats**, 10, 100, 1000 ppm. There was a significant ($p<0.01$) dose-related trend and a significant pair-wise comparison with controls at the HDT for benign Leydig cell tumors in the testes. The incidence at the HDT (16%) exceeded historical control values of up to 6.0%	**C Q** (Based on rat Study)
Cyproconazole PC 128993 T# 272E		**CD-1 mouse**, 5,15, 100 & 200 ppm. Significant incidence of adenomas & carcinomas at the MDT and HDT in males and at the HDT in females.	**B2**
Uniconazole PC 128976 T.# 207H		**Crl:CD-1(ICR)BR mouse**, 10, 40, 200 & 1500 ppm. Increased incidence of hepatocell. adenomas and carcinomas in 1500 ppm males only. **Crl:CD-1(ICR)SD rat**, 10, 40 200 & 1000 ppm. No increase in neoplastic findings.	**C NQ**

Table 12. Structurally related triazole pesticides (Continued).

Compound	Structure	Carcinogenic Effect	Carcinogen Class
Tebuconazole PC 128997 T# 463P		**Bor:NMRI(SPF Han) mouse**, 0, 20, 60 & 180 ppm for 21 months. No carcinogenicity effect. The MTD was not reached. **Bor:NMRI(SPF Han) mouse**, 0, 500 & 1500 ppm for 91 weeks. For males: statistically significant dose-related trend and pairwise comparisons vs controls at the HDT for hepatocellular adenomas, hepatocellular carcinomas and combined adenomas/carcinomas. For females: statistically significant dose-related trend and pairwise comparisons vs controls at the HDT for hepatocellular carcinomas and combined adenomas/carcinomas. **Bor:WISW (SPF-Cpb) rats**, 100, 300 & 1000 ppm for 104 weeks. There was a significant dose-related trend in thyroid follicular tumors in males, but it could be due to increased survival at the HDT. There were no significant differences in the pair-wise comparisons vs controls. No significant compound-related tumor effects were observed for females.	Underwent Peer Review. Final Report in preparation