11-22-93

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

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NOV 22 1993

MEMORANDUM

7236 SUBJECT: Carcinogenicity Peer Review of Fenbuconazole

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

FROM: SanYvette Williams, D.V.M. S. Williams 11/13/93
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and
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Science Analysis Branch
Health Effects Division (H7509C)

TO: Cynthia Giles-Parker, PM#22
Fungicide-Herbicide Branch
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THROUGH: Penelope A. Fenner-Crisp 11/19/93
Penelope Fenner-Crisp, Ph.D.
Director, Health Effects Division (H7509C)

The Health Effects Division Carcincgenicity Peer Review Committee (CPRC) met on August 11, 1993, to discuss and evaluate the weight-of-the-evidence on Fenbuconazole with particular reference to its carcinogenic potential. The CPRC concluded that Fenbuconazole should be classified as Group C - possible human carcinogen and recommended that for the purpose of risk characterization a low dose extrapolation model applied to the experimental animal tumor data should be used for quantification of human risk (Q_1^*).

This decision was based on the induction of thyroid follicular cell adenomas and/or combined adenomas/carcinomas in male Sprague-Dawley rats in two studies, both by pair-wise comparison with controls and by trend analysis. The studies will be combined for the purposes of deriving the Q_1^*. It was determined by the CPRC that the first rat study, although positive for tumor formation, could have utilized higher dose levels for carcinogenicity testing. The second study utilized adequate doses and extended the carcinogenicity findings of the first study. Fenbuconazole administration in mice resulted in a statistically significant increase in the incidence of hepatocellular carcinomas in male CD-1 mice (trend test only), and in combined hepatocellular adenomas and/or carcinomas (trend and pair-wise comparison) and hepatocellular adenomas (trend test only) in female CD-1 mice in a study which was determined could have had more appropriate, higher dosing of animals. The evidence for genotoxicity was negative; however, the structural correlation with at least seven other related triazole pesticides that are proven liver tumorigens provided sufficient evidence for the carcinogenic potential of Fenbuconazole.

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A. Individuals in Attendance: 010669

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Reto Engler

Marcia Van Gemert

Karl Baetcke

Kerry Dearfield

Elizabeth Doyle

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

SanYvette Williams[1]

Jess Rowland

Lori Brunsman

Bernice Fisher

Lucas Brennecke[2]
(PAI/Clement)

3. Other Attendees:

Diane Mandell (Clement)

[1]Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

[2]Signature indicates concurrence with pathology report.

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B. Material Reviewed:

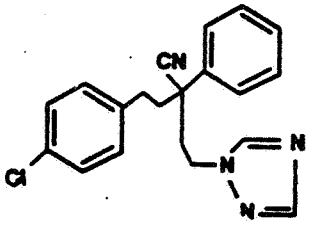
The material available for review consisted of DERs and other data summaries prepared by SanYvette Williams and statistical analyses prepared by Lori Brunsman. The material reviewed is attached to the file copy of this report. All carcinogenicity studies were conducted by Hazleton Washington, Incorporated, Rockville, Maryland, for Rohm and Haas Company, Spring House, Pennsylvania.

C. Background Information

Fenbuconazole [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.

The Caswell (or Tox Chem) Number of Fenbuconazole is 723Q.
The Chemical Abstract Registry Number (CAS No.) is 114369-43-6.

The structure of Fenbuconazole is presented below:



D. Evaluation of Carcinogenicity Data

1. Mouse Carcinogenicity Study

Reference: RH-7592 Technical: 78-Week Dietary Oncogenicity Feeding in Mice. [illegible] MRI Study No. 417-438. Report issued March 20, 1991.

a. Experimental Design

Groups of CD-1 mice (Crl:CD-1(ICR) BR VAF/+) (60/sex/group) were fed diets containing Fenbuconazole (97% purity) at doses of 0, 10, 200 or 650 ppm (males) and 0, 10, 650 or 1300 ppm (females) for 78 weeks. These values correspond to approximately 1.3, 26.3 or 85.3 mg/kg/day, respectively, for males and 1.6, 104.6 and 208.8 mg/kg/day, respectively, for females. Ten animals/sex/group were sacrificed at week 53; survivors were sacrificed at 79 weeks.

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b. Discussion of Tumor Data

Male mice had a significant increasing trend in hepatocellular carcinomas at $p < 0.05$. There were no significant increases in the pair-wise comparisons of the dosed groups with the controls.

Female mice had significant increasing trends in hepatocellular adenomas and combined hepatocellular adenomas and/or carcinomas, both at $p < 0.01$. There was also a significant difference in the pair-wise comparison of the 1300 ppm dose group with the controls for combined hepatocellular adenomas and/or carcinomas at $p < 0.05$.

These statistical analyses were based upon the Exact trend test and Fisher's Exact test for pair-wise comparisons due to the relatively small numbers of tumors observed. See Tables 1 and 2 for tumor analysis results.

Table 1. Fenbuconazole - Charles River CD-1 Mouse Study

Male Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	10	200	650
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 or were 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.

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

Table 2. Fenbuconazole - Charles River CD-1 Mouse Study

Female Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

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

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were 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 10 studies conducted at the [illegible] are tabulated in Table [illegible]. For males, the incidence of carcinomas (5/55, 9%) at the HDT (650 ppm) exceeded both the weighted average of the historical control incidences from all studies (3%) and the upper end of the historical control range (0 to 8.2%). In females, the incidence of adenomas at 1300 ppm (4/47, 9%) also exceeded the weighted average of the historical control incidences (1.4%) and upper end of the range (0 to 6.1%). The increase in carcinomas at this dose (1/47, 2%) exceeded the weighted average of the historical control incidences (0.6%) and was at the high end of the range (0 to 2.1%). Historical control data were not available for combined adenomas/carcinomas.

Table 3. Historical Controls: Incidences of Hepatocellular Adenomas and Carcinomas in Charles River CD-1 Mice[a]

Study Number	Adenomas (%)	Carcinomas (%)
	Males	
5DE	4/51 (7.8)	1/51 (2.0)
6DE	2/49 (4.1)	2/49 (4.1)
1DE	1/49 (2.0)	4/49 (8.2)
2DE	4/49 (8.2)	1/49 (2.0)
10DE	6/55 (11.0)	3/55 (5.5)
7DE	3/47 (6.4)	0/47 (0.0)
11DE	4/50 (8.0)	0/50 (0.0)
8DE	5/50 (10.0)	1/50 (2.0)
4DE	4/50 (8.0)	2/50 (4.0)
26DE	4/49 (8.2)	1/49 (2.0)
Weighted Average	(7.4)	(3.0)
	Females	
5DE	0/49 (0.0)	0/49 (0.0)
6DE	0/48 (0.0)	1/48 (2.1)
1DE	1/48 (2.1)	0/48 (0.0)
2DE	3/49 (6.1)	0/49 (0.0)
10DE	0/55 (0.0)	0/55 (0.0)
7DE	1/49 (2.0)	1/49 (2.0)
11DE	0/50 (0.0)	0/50 (0.0)
8DE	0/49 (0.0)	0/49 (0.0)
4DE	1/50 (2.0)	0/50 (0.0)
26DE	1/48 (2.1)	1/48 (2.1)
Weighted Average	(1.4)	(0.6)

[a] Historical data were obtained from 10 chronic/carcinogenicity studies with Charles River CD-1 mice started at Hazleton between April 1984 and April 1987. All studies were 78 weeks in duration.

c. Non-neoplastic lesions and other findings

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Fenbuconazole in male or female mice. The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Mean body weight gain was significantly decreased compared to control in male mice at the HDT (87% of control) at study termination. Female body weight gain in dosed animals was not different from controls.

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 (HDT) and in females at 650 and 1300 ppm (HDT). It was noted that this study may have been compromised by the use of animals infected with hepatitis which may have potentiated the liver effects of the test compound.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The CPRC agreed that mice in this study were not dosed adequately; testing at higher concentrations may likely result in greater tumor formation, especially in males. This conclusion was based on a relatively small reduction in body weight gain in HDT males only, and alterations in liver histopathology that may have resulted from the animals being infected by hepatitis. Nevertheless, it was agreed that there would be no benefit to repeating the mouse study at this time.

2. 1990 (Low-Dose) Rat Carcinogenicity Study

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

a. Experimental Design

Groups of Sprague-Dawley rats (Crl:CD(SD) VAF/+) (70/sex/group) were fed diets containing Fenbuconazole (97% purity) at doses of 0, 4, 40, and 400 ppm for the first two weeks of the study; dose levels of 0, 6, 60, and 600 ppm were given for weeks 3 and 4; and dose levels of 0, 8, 80 or 800 ppm were fed during weeks 4 through 105. An interim sacrifice was conducted (10/sex/group) at week 53; survivors were sacrificed at 105 weeks.

b. Discussion of Tumor Data

Male rats had significant increasing trends in thyroid follicular cell adenomas, and combined thyroid follicular cell adenomas and/or carcinomas ($p < 0.05$). There was also a significant difference in the pair-wise comparison of the 800 ppm dose group with the controls for combined thyroid follicular cell adenomas and/or carcinomas ($p < 0.05$). See Table 4 for tumor analysis results. These statistical analyses were based upon the Exact trend test and Fisher's Exact test for pair-wise comparisons due to the relatively small numbers of tumors observed.

There were no significant compound-related tumors observed in female rats.

Table 4. Fenbuconazole - Charles River Sprague-Dawley Low-Dose (1990) Rat Study

Male Thyroid Follicular Cell Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

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

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were 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 $p < 0.01$.

Historical control data from nine studies conducted at the testing laboratory (Hazleton Labs) are tabulated in Table 5. In male rats, the incidence of thyroid follicular cell adenomas at 800 ppm (6/58, 10%) exceeded the weighted average of the historical control incidences from all studies (4.8%), however the incidence in this group was within the historical control range for this tumor type (0 to 14.8%). Historical control data were not available for combined thyroid follicular cell adenomas and carcinomas.

Table 5. Historical Controls: Incidences of Thyroid Tumor Rates in Male Sprague-Dawley Rats[a]

Study Number	Follicular Cell Adenomas (%)	Follicular Cell Carcinomas (%)
14DE	4/30 (13.3)	0/30 (0.0)
15DE	0/19 (0.0)	0/19 (0.0)
16DE	2/40 (5.0)	2/40 (5.0)
17DE	0/21 (0.0)	1/21 (4.8)
18DE	0/25 (0.0)	0/25 (0.0)
20DE	2/28 (7.1)	2/28 (7.1)
21DE	0/44 (0.0)	2/44 (4.5)
23DE	4/27 (14.8)	2/27 (7.4)
28DE	1/32 (3.1)	2/32 (6.3)
Weighted Average	(4.8)	(3.9)

[a] Historical data were obtained from nine chronic/carcinogenicity studies with Sprague-Dawley rats started at Hazleton between April 1984 and April 1988. All studies were 78 weeks in duration.

c. Non-neoplastic Lesions and Other Findings

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Fenbuconazole in male or female rats or mice. The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Body weight gain was decreased from controls (82% of control) in HDT females at week 78. In contrast, no decrease in body weight gain was found in males at the HDT.

Centrilobular-to-midzonal hepatocellular enlargement and vacuolation and focal cystic hyperplasia were seen in 800 ppm

males and females; these alterations were accompanied by increased organ weight.

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 histopathological lesions of the liver at the HDT. In contrast, it was concluded that the high dose was not adequate to assess the carcinogenic potential of Fenbuconazole in males (despite the formation of thyroid follicular cell tumors) because of the absence of significant alteration in body weight gain or other non-neoplastic effect; a new study conducted in males at a higher dose is described below.

3. 1991 (High-Dose) Male Rat Carcinogenicity Study

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

a. Experimental Design

Groups of Sprague-Dawley rats (Crl:CD(SD) VAF/+) (60 males/group) were fed diets containing Fenbuconazole (97% purity) at 0, 800 or 1600 ppm for 104 weeks. Rats (10/group) were sacrificed at week 53; survivors were sacrificed at 105 weeks.

b. Discussion of Tumor Data

Male rats had a significant increase in the incidence of thyroid follicular cell adenomas at the HDT (1600 ppm) by pair-wise comparison with controls ($p < 0.05$). In addition, there were significant positive trends in thyroid follicular cell adenomas, and combined thyroid follicular cell adenomas and/or carcinomas ($p < 0.05$). These statistical analyses were based upon the Exact trend test and Fisher's Exact test for pair-wise comparisons due to the relatively small numbers of tumors observed. See Table 6 for tumor analysis results.

Table 6. Fenbuconazole - Charles River Sprague-Dawley High-Dose Rat Study

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Male Thyroid Follicular Cell Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)		
	0	800	1600
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 or were sacrificed before week 51.

[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 pairwise comparison with control denoted at [illegible]
If *, then $p < 0.05$. If **, then $p < 0.01$.

Historical control data for thyroid follicular cell adenomas and carcinomas from the testing laboratory (Hazleton Labs) were previously shown in Table 5. In rats of this (high dose) study, the incidence of thyroid follicular cell adenomas at 1600 ppm (9/55, 16%) exceeded both the weighted average of the historical control incidences from all studies (4.8%) and the historical control range for this tumor type (0 to 14.8%). Historical control data were not available for combined thyroid follicular cell adenomas and carcinomas.

c. Non-neoplastic Lesions and Other Findings

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Fenbuconazole in male rats. The statistical evaluation of

mortality was based upon the Thomas, Breslow and Gart computer program.

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Mean body weight gain was significantly decreased (76% of control) in HDT rats after 104 weeks of treatment.

Treatment-related non-neoplastic lesions included centrilobular to midzonal hepatocellular enlargement and vacuolation and follicular cell hypertrophy at 1600 ppm.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The HDT in this study was determined to be adequate for assessing the carcinogenicity as evidenced by significant decreases in body weight gain and by the induction of liver histopathology at the HDT (1600 ppm).

E. Additional Toxicological Data on Fenbuconazole.

1. Metabolism

Reference: MRID No 418750-17 and 418750-18; HED Doc. No. 930063.

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.

2. Genotoxicity

Reference: MRID Nos. 410312-16, -17, -18, -19 and -20; HED Doc. No. 00767.

Fenbuconazole was shown to be not active in assays 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 due to the absence of positive controls in the assays. Fenbuconazole was nonmutagenic in the HGPRT locus Chinese hamster ovary 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 hepatocytes.

3. Subchronic and Chronic Toxicity

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Reference: MRID No. 410735-03; HED Doc. No. 007677.

In CD-1 mice fed diets containing Fenbuconazole at dose levels of 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 hepatotoxicity was, 60 ppm.

Reference: MRID No. 410735-02; HED Doc.No. 007677.

In Sprague-Dawley rats fed diets containing Fenbuconazole at dose levels of 0, 20, 80, 400 or 1600 ppm for three months, the 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 ppm. Increased thyroid follicle cell size occurred 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.

Reference: MRID No.410735-04; HED Doc.No.007677.

In Beagle dogs fed diets containing Fenbuconazole at dose levels of 0, 30, 100, 400 or 1600 ppm for three months, primary effects seen in the liver included decreases in serum protein, increases in triglycerides, 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.

Reference: MRID No. 410735-01; HED Doc. No. 010109.

Groups of 4 dogs/sex/group were fed diets containing Fenbuconazole at dose levels of 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) and the LOEL, based on decreases in body weight gain and increased liver weight, was 1200 ppm (30 mg/kg/day).

Reference: MRID No. 416353-01 and 416353-02; HED Doc.No.008296.

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In a chronic toxicity study with Sprague-Dawley rats (discussed in the carcinogenicity section), dietary administration of Fenbuconazole at dose levels of 0, 10, 80, or 800 ppm for 104 weeks caused significant decreases in body weight gain and increased liver weight in females at 800 ppm and increases in thyroid weights in males. Treatment had no effect on survival, food consumption, clinical signs, or hematology, clinical chemistry or urinalysis 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 decreases in body weight gain and hepatotoxicity, was 800 ppm in females; a LOEL was not established in males.

Reference: MRID No. 420550-01; HED Doc. No. 009977.

In another chronic toxicity study with male Sprague-Dawley rats (discussed under carcinogenicity), dietary administration of Fenbuconazole at dose levels of 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.

4. Structure-Activity Relationships

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 compounds are shown in Figure 1. A summary is provided below:

Bayleton has been classified as a Group C carcinogen with no Q_1^* (nq); 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 is a Group C carcinogen (nq) 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 is a Group C (nq) carcinogen; based on hepatocellular adenomas, carcinomas, and/or adenomas and carcinomas combined in male CD-1 mice. Propiconazole was non-carcinogenic in Sprague-Dawley rats.

Etaconazole increased the incidence of liver adenomas and carcinomas in Swiss mice; registration voluntarily withdrawn. If classified, Etaconazole would most likely be classified as a Group B2. No

information was available on the carcinogenicity of this chemical in rats.

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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. Azaconazole was non-carcinogenic in Wistar rats.

Hexaconazole was classified a Group C with Q_1^* 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 was classified a Group B2 carcinogen; based on hepatocellular adenomas and carcinomas in male and female CD-1 mice. Cyproconazole was non-carcinogenic in Wistar rats; however, dose levels were determined to be inadequate to assess the carcinogenicity in this study.

Uniconazole was classified a 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 Sprague-Dawley rats.

Tebuconazole was classified a Group C (nq) carcinogen; based on hepatocellular adenomas and carcinomas in Winkelmann Bor:NMRI(SPF-Han) mice. Non-carcinogenic in male or female CD rats.

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Figure 1. Structures of Related Triazole Pesticides.

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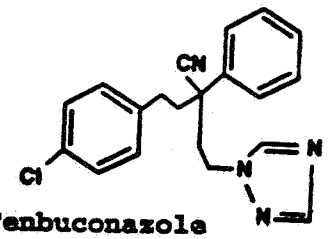
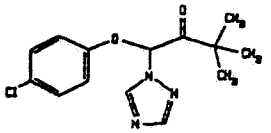
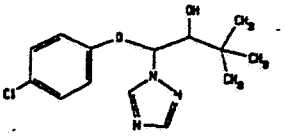


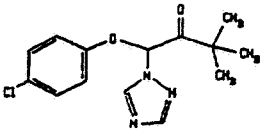
Fenbuconazole



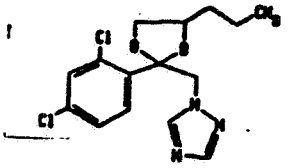
Bayleton



Baytan



Baycor



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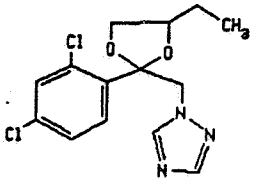

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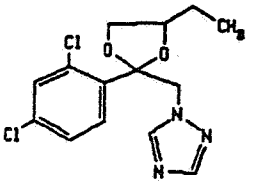

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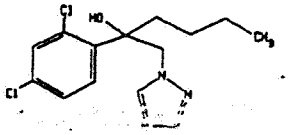

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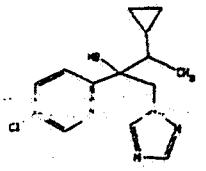

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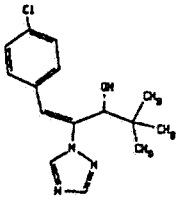

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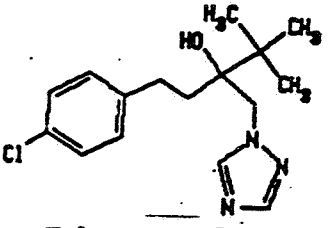

Tebuconazole

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F. Weight of the Evidence Considerations

The Committee considered the following observations regarding the toxicology of Fenbuconazole for a weight-of-the-evidence determination of its carcinogenic potential:

1. In CD-1 mice, Fenbuconazole administration in the feed resulted in an increased incidence of hepatocellular adenomas, carcinomas, and/or combined adenomas/carcinomas. Male mice had a statistically significant increasing trend in hepatocellular carcinomas. In females at the HDT, there was a statistically significant increase in combined hepatocellular adenomas and/or carcinomas by pair-wise comparison with concurrent controls, and a statistically significant increasing trend in both the incidences of adenomas, and combined adenomas/carcinomas.

   In male mice, the incidence of carcinomas at the HDT exceeded both the weighted average of the historical control incidences from all studies and the incidences in all 10 of these studies. In females, the incidence of adenomas at the HDT also exceeded both the weighted average of the historical control incidences and the incidences in all 10 studies. The increase in carcinomas at this dose exceeded the weighted average of the historical control incidences and was equal to or greater than the incidences in 8/10 of these studies. Historical control data were not available for combined adenomas/carcinomas. It was agreed by the CPRC that dosing in this study was not appropriately high enough, and that the carcinogenic effect (particularly the induction of malignant tumors) in mice may have been greater if dosing had been higher.

2. In male Sprague-Dawley rats, Fenbuconazole induced thyroid follicular cell adenomas and carcinomas. Female rats did not develop tumors. In the lower-dose study reported in 1990, there was a statistically significant increase in combined thyroid follicular cell adenomas/carcinomas by pair-wise comparison with control at the HDT, and a statistically significant increasing trend in both adenomas and combined adenomas/carcinomas.

   Historical control data from the testing laboratory for male rats indicate that the incidence of thyroid follicular cell adenomas at the HDT exceeded the weighted average of the historical control incidences from all studies and exceeded the incidences in 7/8 of these studies. Historical control data were not available for combined thyroid follicular cell adenomas and carcinomas. The CPRC agreed that dosing of female rats was adequate, based on decreased body weight gain and liver histopathological effects. However, males were determined to be inadequately dosed (despite the formation of thyroid follicular cell tumors) because of the absence of significant alteration in body weight gain or

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other non-neoplastic effect. A new study conducted in males at a higher dose is described below.

In the second higher-dose study in males reported in 1991, there was a statistically significant increase in the incidence of thyroid follicular cell adenomas at the HDT (1600 ppm) by pair-wise comparison with controls. In addition, there were significant positive trends in thyroid follicular cell adenomas, and combined thyroid follicular cell adenomas and/or carcinomas.

In rats of this study, the incidence of thyroid follicular cell adenomas at the HDT exceeded both the weighted average of the historical control incidences from all studies and the incidences in all 9 studies. Historical control data were not available for combined thyroid follicular cell adenomas and carcinomas. Dosing in this study was determined to be adequate on the basis of significant decreases in body weight gain and by the induction of liver histopathology at the HDT.

3. In subchronic and chronic studies, 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 of the thyroid in male rats at 800 ppm and thyroid follicular cell hypertrophy at 1600 ppm indicating the thyroid to be the second target organ in male rats only.

4. There was no evidence for genotoxicity both <u>in vivo</u> and <u>in vitro</u>.

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

G. Classification of Carcinogenic Potential:

The CPRC considered the criteria contained in the EPA's "Guidelines for Carcinogenic Risk Assessment" (FR51: 33992-34003, 1986) for classifying the weight of evidence for carcinogenicity.

The CPRC agreed that the classification for Fenbuconazole should be Group C - possible human carcinogen - and recommended that for the purpose of risk characterization a low dose extrapolation model applied to the experimental animal tumor data should be used for quantification of human risk (Q_1^*).

This decision was based on the induction of thyroid follicular cell adenomas and/or combined adenomas/carcinomas in male Sprague-Dawley rats in two studies, both by pair-wise comparison with controls and by trend analysis. The studies will be combined for the purposes of deriving the Q_1^*. The first rat study, although positive for tumor formation, was determined by the CPRC that higher dose levels for carcinogenicity testing could have been utilized. The second study utilized adequate doses and extended the carcinogenicity findings of the first study. Fenbuconazole administration in mice resulted in a statistically significant increase in the incidence of hepatocellular carcinomas in male CD-1 mice (trend test only), and in combined hepatocellular adenomas and/or carcinomas (trend and pair-wise comparison) and hepatocellular adenomas (trend test only) in female CD-1 mice in a study which was determined could have more appropriate, higher dosing of animals. The evidence for genotoxicity was negative; however, the structural correlation with at least seven other related triazole pesticides that are proven liver tumorigens provided sufficient evidence for the carcinogenic potential of Fenbuconazole.