UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

APR 15 1996

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review of Fenbuconazole (2nd)

FROM: SanYvette Williams-Foy, D.V.M.
Review Section II
Toxicology Branch II
Health Effects Division (7509C)

and

Esther Rinde, Ph.D.
Manager, Carcinogenicity Peer Review Committee
Science Analysis Branch
Health Effects Division (7509C)

TO: Terri Stowe
Product Manager # 22
Fungicide-Herbicide Branch
Registration Division (7505C)

THROUGH: Stephanie R. Irene Ph.D.
Acting Director, Health Effects Division (7509C)

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on Nov. 08, 1995 to discuss and re-evaluate the weight-of-the-evidence on fenbuconazole with particular reference to its carcinogenic potential. The CPRC concluded that the classification of fenbuconazole should remain as a Group C - possible human carcinogen with a low dose extrapolation model applied to the animal data for the quantification of human risk (Q_1^*). Based on mechanistic data submitted by the registrant for the thyroid tumors, the CPRC agreed that the combined hepatocellular adenoma/carcinoma in the female mice should be used to derive the Q_1^* (instead of the thyroid tumors, as was recommended in the first Peer Review).

SUMMARY

At the first meeting [Memo, dated Nov. 22, 1993], the CPRC classified fenbuconazole as a Group C - possible human carcinogen with a low dose extrapolation model applied to the animal data for the quantification of human risk (Q_1^*). This classification was based on statistically significant increased incidences of thyroid follicular cell tumors (adenomas and combined adenoma/carcinoma) in male Sprague-Dawley rats and hepatocellular tumors (adenomas and/or carcinomas) in both sexes of the CD-1 mouse. The CPRC determined that more appropriate, higher dosing could have been used in the mouse study. Although there was no apparent evidence from genotoxicity, structural correlation with at least seven other related triazole pesticides that are liver tumorigens provided additional support.

Subsequent to the first meeting the registrant submitted additional mechanistic studies for fenbuconazole (details provided in section E). The data from these studies were reviewed by the CPRC at the present meeting. The CPRC agreed that the mechanistic evidence presented for the thyroid tumors appeared to be scientifically plausible and consistent with EPA current policy; however the data provided for the mechanism of liver tumors were suggestive but not convincing, and data gaps remain.

At the present meeting, the CPRC concluded that the classification of fenbuconazole should remain as a Group C - possible human carcinogen with a low dose extrapolation model applied to the animal data for the quantification of human risk (Q_1^*). Based on the mechanistic data submitted by the registrant for the thyroid tumors, the CPRC agreed that the combined hepatocellular adenoma/carcinoma in the female mice should be used to derive the Q_1^* (instead of the thyroid tumors, as was recommended in the first Peer Review).

A. Individuals in Attendance at the meetings:

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

Stephanie Irene

William Burnam

Karl Baetcke

Kerry Dearfield

Yiannakis Ioannou

Hugh Pettigrew

Esther Rinde

Richard Hill

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

SanYvette Williams-Foy[1]

Clark Swentzel

Lori Brunsman

Lucas Brennecke[2]
(PAI/ORNL)

3. Other Attendees:

Bernice Fisher

[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.

B. Material Reviewed

The material available for review consisted of DER's, one-liners, data from the literature and other data summaries prepared and/or supplied by Dr. SanYvette Williams-Foy, and tables and statistical analyses by Lori Brunsman. The material reviewed is attached to the file copy of this report.

C. Background Information

Fenbuconazole [RH-7592], [alpha-(2-(4-chlorophenyl)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 a fungicide used to prevent the development of disease incited by many fungi on food and non-food crops.

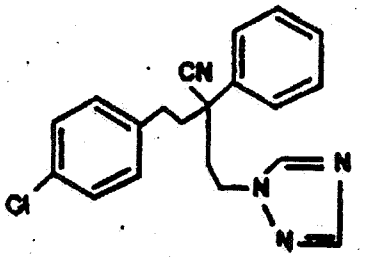
PC Code: 129011. Tox. Chem. No: 723Q. CAS No: 114369-43-6.

The HED Carcinogenicity 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. It was concluded that a Group C - possible human carcinogen classification be placed on this chemical. It was also recommended that for risk characterization a low dose extrapolation model applied to the experimental animal (thyroid) tumor data should be used for quantification of human risk (Q_1^*) (CPRC memo dated November 22, 1993). 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 (Qualitative Risk Assessment memo from L. Brunsman, 11/19/93). The studies were combined for the purpose of deriving the Q_1^* (1.65×10^{-2} Quantitative Risk Assessment memo from B. Fisher dated 2/7/94). The committee determined that the first rat study, although positive for tumor formation, could have utilized higher dose levels for carcinogenicity testing. The second study utilized adequate dosages and extended the carcinogenicity findings of the first study.

Fenbuconazole administration 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 that fenbuconazole could have been given at higher doses in test 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.

At a March 14, 1995 meeting with Rohm and Haas, representatives from RD and HED agreed that the fenbuconazole unit risk, Q_1^*, should be

recalculated based upon the new 3/4's power scaling factor instead of the previous 2/3's power. The revised unit risk (Memo from B. Fisher dated March 15, 1995), Q_1^*(mg/kg/day)$^{-1}$ of fenbuconazole, based upon male rat thyroid follicular cell (adenomas and/or carcinomas) tumor rates is 1.06×10^{-2} in human equivalents.



STRUCTURE OF FENBUCONAZOLE

D. Evaluation of Carcinogenicity Evidence

Thyroid Function Test

Reference: Hazleton, G.A., DiDonato, L.J., Quinn, D.L., Shade, W.D., and Frantz, J.D., "RH-7592: Thyroid Function and Hepatic Clearance of Thyroxine in Male Rats" MRID#: 41875020; Report #: 90R-071; Report Finalized: March 5, 1991.

a. Experimental Design

Thyroid function and hepatic clearance of L-thyroxine were investigated in Crl:CD®BR male rats fed fenbuconazole (RH-7592). The study design allocated groups of 20 male rats to dose levels of 0, 1600 ppm (116 mg/kg/day), or 3200 ppm (231 mg/kg/day), and groups of 10 male rats to dose levels of 8 ppm (1 mg/kg/day) or 800 ppm (57 mg/kg/day) of fenbuconazole for 4 or 13 weeks. Only 10 animals per dose group received histopathological evaluations of the thyroid. An additional 20 male rats were designated for the recovery group in which animals were dosed at 1600 or 3200 ppm for the first 4 weeks of the study, followed by 9 weeks of normal diet. After this time they were sacrificed.

b. Results

Thyroid weights (absolute and relative) were increased in test animals at 4 and 13 weeks. Absolute thyroid weights were increased at Week 4 by 8, 36, or 8% at doses of 800, 1600, or 3200 ppm, respectively. Relative thyroid weights at Week 4 were increased by 34% at 1600 ppm and by 47% at 3200 ppm. Absolute thyroid weights

were increased at Week 13 by 31, 41, or 34% at doses of 800, 1600 or 3200 ppm, respectively. Relative thyroid weights were increased by 30, 47, or 67% at doses of 800, 1600, or 3200 ppm, respectively. Treatment-related histopathological changes at these doses consisted of diffuse follicular cell hypertrophy/hyperplasia. A low incidence of focal hyperplasia of the follicular epithelium was observed at 1600 and 3200 ppm. Serum TSH levels were increased at Week 4 by 79, 83, or 106% and at Week 13 by 13, 59, or 64% at doses of 800, 1600 or 3200, respectively. Serum T_4 levels were decreased at Week 4 by 21, 14, or 53% and at Week 13 by 8, 34, or 51% at doses of 800, 1600 or 3200 ppm, respectively.

Liver weights (absolute and relative) were increased in test animals at 4 and 13 weeks. Absolute liver weights were increased at Week 4 by 21, 33, or 36% and at Week 13 by 21, 53, or 53% at doses of 800, 1600, or 3200 ppm, respectively. Relative liver weights at Week 4 were increased by 16, 33 or 85% and at Week 13 by 21, 51, or 92% at doses of 800, 1600, or 3200 ppm, respectively. Biliary excretion of ^{125}I-L-thyroxine, primarily as the glucuronide, was increased 2-times at 4 and 13 weeks in treated rats at 3200 ppm when compared to the controls. The <u>in vitro</u> activity of hepatic microsomal UDP-glucuronosyltransferase, with L-thyroxine as the substrate, was increased in treated rats at 3200 ppm (54% at Week 4 and 25% at Week 13 per unit weight of microsomal protein; 337% at Week 4 and 300% at Week 13 per whole liver basis).

Reversibility was demonstrated in the recovery rats which received 1600 or 3200 ppm fenbuconazole for 4 weeks followed by a control diet for 9 weeks. Thyroid weight, pathology and serum hormones, as well as the biliary excretion and glucuronidation of L-thyroxine were comparable to control animals.

The qualitative risk assessment (Memo: L. Brunsman dated September 26, 1995) indicates that after 4 weeks (Table 1), male rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 1600 and 3200 ppm dose groups with the controls, for thyroid diffuse hypertrophy/hyperplasia at 4 weeks, all at $p < 0.01$.

After 13 weeks (Table 2), there was a significant trend in thyroid diffuse hypertrophy/hyperplasia ($p < 0.01$). There were significant differences in the pair-wise comparisons of the 1600 and 3200 ppm dose groups with the controls for thyroid diffuse hypertrophy/hyperplasia at 13 weeks, all at $p < 0.05$. [Note: The thyroid lesions that were of a diffuse distribution were not separated (hypertrophy/hyperplasia). Hypertrophy and hyperplasia are not interchangeable and no explanation was given for their being categorized together.]

Table 1. Male Thyroid Lesion Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values) at the 4-Week Sacrifice

Description	0 ppm	8 ppm	800 ppm	1600 ppm	3200 ppm
Focal Hyperplasia (%) p =	0/10 (0) 0.118	0/10 (0) 1.000	0/10 (0) 1.000	1[a]/10 (10) 0.500	1/10 (10) 0.500
Diffuse Hypertrophy/Hyperplasia (%) p =	1[b]/10 (10) 0.000**	2/10 (20) 0.500	4/10 (40) 0.512	9/10 (90) 0.001**	10/10 (100) 0.000**

[+]Number of lesion bearing animals/Number of animals examined.
[a]First focal hyperplasia observed at week 4, dose 1600 ppm.
[b]First diffuse hypertrophy/hyperplasia observed at week 4, 0 ppm.

Table 2. Male Thyroid Lesion Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values) at the 13-Week Sacrifice

Description	0 ppm	8 ppm	800 ppm	1600 ppm	3200 ppm
Focal Hyperplasia (%) p =	0/10 (0) 0.200	0/10 (0) 1.000	0/10 (0) 1.000	1/10 (10) 1.000	1[a]/10 (10) 0.500
Diffuse Hypertrophy/Hyperplasia (%) p =	6[b]/10 (60) 0.000**	5/10 (50) 0.500[a]	9/10 (90) 0.152	10/10 (100) 0.043*	10/10 (100) 0.043*

[+]Number of lesion bearing animals/Number of animals examined.
[a]First focal hyperplasia observed at week 13, dose 3200 ppm.
[b]First diffuse hypertrophy/hyperplasia observed at week 13, 0 ppm.

Conclusions drawn from this study were that high doses of fenbuconazole lead to increases in hepatic metabolism and biliary excretion of L-thyroxine, primarily as the glucuronide. In response to more rapid removal of thyroid hormone, blood concentrations of the pituitary-derived hormone, TSH, were increased. Therefore, increased levels of TSH led to over-stimulation of the thyroid gland, producing follicular cell hypertrophy/hyperplasia. [The registrant hypothesized that chronic follicular hypertrophy/hyperplasia due to a secondary or indirect mechanism, such as prolonged stimulation of the thyroid by TSH, may progress to follicular neoplasia of the thyroid.]

E. ADDITIONAL TOXICITY DATA ON FENBUCONAZOLE

Mechanistic Studies

The registrant has performed additional mechanistic toxicology studies for fenbuconazole as they relate to the hypothesis (Figure 1) that thresholds exist for hepatic biochemical and physiological effects relating to the pathogenesis of the observed liver tumors in mice and thyroid tumors in rats. A summary of results from each study is given below:

a. Summary of Key Results of Fenbuconazole Dose-Response Study in Female Mice
(RH-7592: Cell Proliferation and Enzyme Induction in the Liver of Mice. Report #: 95R-035)

Study Design

Groups of female mice (10/dose) were fed diets containing 0, 20, 60, 180 or 1300 ppm RH-7592. A sixth treatment group was fed with a diet containing 1000 ppm phenobarbital for 1 and 4 weeks. Actual compound intake for each group was 0, 5.2, 13.6, 47.4 and 32.36 mg/kg/day RH-7592 and 230 mg/kg/day phenobarbital. Histopathological examinations were performed at necropsy in addition to enzyme evaluations.

Results

-Fenbuconazole produced increases in absolute (45-50%) and relative (50-55%) liver weight at a dose of 1300 ppm at 1 and 4 weeks. No effects were observed on liver weight at doses up to and including 180 ppm.

-Fenbuconazole produced changes in liver histopathology (centrilobular to midzonal hepatocellular hypertrophy with increased eosinophilia) at a dose of 1300 ppm at 1 and 4 weeks. No effects were observed on liver histopathology at doses up to and including 180 ppm.

-Fenbuconazole produced a marked increase in liver cell proliferation (852%) at a dose of 1300 ppm at 1 week, but not at 4 weeks. No effects were observed on liver cell proliferation at doses up to and including 180 ppm.

-Fenbuconazole produced increases in Cytochrome P_{450} (77% at 180 ppm and 180% at 1300 ppm) and Cytochrome P_{450} enzyme activity (PROD, 148% at 180 ppm and 258% at 1300 ppm) and in Cytochrome b_5 (106%) at a dose of 1300 ppm at 4 weeks. No effects on the Cytochrome P_{450} system were observed at doses up to and including 60 ppm.

-The effects of fenbuconazole on liver weight, histopathology, cell proliferation, Cytochrome P_{450}, Cytochrome P_{450} enzyme activity (PROD), and Cytochrome b_5 at 4 weeks (1300 ppm) were completely reversible after a 6-week recovery period.

-The effects produced by fenbuconazole on mouse liver were similar to those produced by phenobarbital at a dose of 1000 ppm for 1 and 4 weeks including: increases in liver weight, cell proliferation, Cytochrome P_{450}, Cytochrome P_{450} enzyme activity (PROD), Cytochrome b_5 and changes in the histopathological appearance of the liver. Similarly, the effects of phenobarbital on the liver were completely reversible after a 6-week recovery period.

b. Summary of Key Results of a Study on Fenbuconazole in Male Rats

Study Design

Groups of male rats (10/dose) were fed diets containing 0 or 1600 ppm (130 mg/kg/day) RH-7592 for 1 and 4 weeks. A third group was fed the diet containing 1000 ppm (86.9 mg/kg/day) phenobarbital. At necropsy (Week 4 or 10), livers were removed and weighed and liver microsomal enzymes were measured.

Results

-Fenbuconazole produced increases in absolute (37%) and relative (45%) liver weight and changes in liver histopathology (centrilobular to midzonal hepatocellular hypertrophy with increased eosinophilia) at a dose of 1600 ppm for 4 weeks.

-Fenbuconazole produced increases in Cytochrome P_{450} (171%), Cytochrome b_5(157%) and Cytochrome P_{450} enzyme activity (PROD, 933%) at a dose of 1600 ppm for 4 weeks or 10 weeks.

-The effects of fenbuconazole on liver weight, histopathology, and Cytochrome P_{450} enzyme system at 4 weeks (1600 ppm) were completely reversible after a 6-week recovery period.

-The effects produced by fenbuconazole on rat liver were similar to those produced by phenobarbital at a dose of 1000 ppm for 4 weeks including: increases in liver weight and the Cytochrome P_{450} enzyme system as well as changes in the histopathological appearance of the liver. Similarly, the effects of phenobarbital on the liver were completely reversible after a 6-week recovery period.

-Fenbuconazole induced a similar type of liver Cytochrome P_{450} (i.e., CYP2B) in the rat that was previously shown in the mouse, when analyzed by Western immunoblotting (Appendix 1).

2. Human Data

The registrant supplied the following additional supporting data from information from human studies which relate to liver tumor pathogenesis in animals: 1) There is no convincing evidence that humans treated with drugs or exposed to chemicals that induce hepatic microsomal enzymes are at increased risk for the development of thyroid cancer (Curran and DeGroot, 1991). 2) There was no effect on serum T_3, T_4, or TSH levels in normal healthy adults after administration of phenobarbital (100 mg/day for 14 days) (Ohnhaus et al., 1981). 3) Human studies indicate that microsomal enzyme inducers do not alter thyroid function until a certain degree of enzyme induction occurs (i.e. alteration of antipyrine clearance is more than 60% above baseline levels) (McClain, 1989). 4) Based on the results of many epidemiologic studies, the primary response in man to marked disturbance in thyroid function has occurred in the formation of goiter rather than neoplasia (Hill, 1988). 5) Similarly, many epidemiological studies examining long-term phenobarbital use among patients for convulsive disorders indicate no increase in the frequency for thyroid or liver tumors (Clemmesen et al., 1974, Clemmesen and Hjalgrim-Jensen, 1977, 1978, 1981, White et al., 1979, Friedman 1981, Olsen et al., 1989).

3. Structure-Activity Relationships

Fenbuconazole is structurally related to Bayleton, Baytan, Baycor, Propiconazole, Etaconazole, Azaconazole, Hexaconazole, Cyproconazole, Uniconazole and Tebuconazole, seven of which are liver tumorigens. These were discussed at the first Peer Review and were considered to provide additional support for the carcinogenic potential of fenbuconazole. A summary of the tumor types and cancer classification for these compounds 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.

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 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.

Table 1. Related conazole compounds.

Compound	Non-Carcinogenic Effects	Carcinogenic Effects	Peer Review Results
Bayleton PC 109901	**NMRI mouse**, 1800 ppm: Hepatocellular hypertrophy, altered cell foci, single cell necrosis, hyperplastic nodules, all $p<0.01$ in ♂ & ♀. Only hepatocellular hypertrophy at 300 ppm in ♂ ($p<0.01$), single cell necrosis, & Kupfer cell accumulation in ♀ at 300 ppm. **Wistar rat**, 50-1800 ppm. At HDT: cystic hyperplasia. Enz. inducer.	Only hepatocellular adenoma, at 1800 in (22%)♂ & (18%)♀ $p<0.05$ for trend and paired comps. Hist. Conts.: 18.4% ♂, and 2.0% ♀. Dose-rel. trend in TFC adenomas in ♂ & comb. w. cystic hyperplasia in ♂ & ♀; Pairwise comparisons not significant.	**C NQ** (7/31/90)
Baytan PC 127201	**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. **Rat**, 125-2000 ppm, increases in thyroid adenoma.		**Weak C** SAP 12/23/87
Baycor PC 112403		**Mouse:** up to 500 ppm: (-) **Rat:** up to 500 ppm : (-)	
Uniconazole PC 128976	**Crl:CD-1(ICR)BR mouse**, 10-1500 ppm. 1500 ppm: Incr. abs. & rel. liver wt., focal chr. inflammat. & necrosis. **Crl:CD-1(ICR)SD rat**, 10-1000 ppm. 1000 ppm: rd. body wt. gain, centrilob. hepatocell. enlargement & vacuolization in ♂ & ♀.	Incr. incidence of hepatocell. adenomas and carcinomas in HDT males only. No increase in neoplastic findings	**C NQ**

Propiconazole PC 122101	**CD-1 mouse**, 100,500,2500 ppm. At 500 ppm: decr. b.w. gain, incr. liver lesions ♂. At 2500 ppm: incr. mortality ♂, incr. food consumption ♂, increased SGPT and SGOT in ♂ & ♀, hepatocyte enlargement, vacuolation and fat deposition.	Statistically significant trend and pairwise comparisons in liver adenomas and combined. For carcinomas 2 pathologists were significant, the third was not.	C NQ
Etaconazole PC	**Registration vouluntarily withdrawn**	Increased incidence of liver adenomas and carcinomas in Swiss mice	
Azaconazole PC 128882	**Mouse**, 25,100 &400 ppm. There is the question of whether the MTD was reached.	No oncogenicity effect.	
HexaconazolPC 128925	**CD-1/Alpk mouse**, 5, 40 & 200 ppm. In the HDT males bw. gains were 11% lower, not for ♀. HDT showed centrilobular fatty infilt. and hepatic hypertroph. for ♂ & ♀. MTD not reached. **ALpk:APfSD (Wistar derived) rats**, 10, 100, 1000 ppm. SGOT, SGPT and hepatic aminopyrine-N-demethylase increased at MDT and HDT. Abs. and rel. liver wts. increased in HDT males. Fatty infiltration of the liver, increased cortical vacuolation of the adrenals and tubular atrophy of the testes at MDT and HDT.	No oncogenicity effect. Should be seen with caution because MTD was not reached. 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
Cyproconazole PC 128993	**CD-1 mouse**, 5,15, 100 & 200 ppm. Focal hepatocytic inflammation, single-cell necrosis & diffuse hepatocytic hypertrophy in ♂ & ♀. Hepatic lytic necrosis	Significant incidence of adenomas & carcinomas at the MDT and HDT in males and at the HDT in females.	C Q
Tebuconazole	At 1500 ppm, an increase in the incidence of focal hepatocyte hyperplasia and histiocytic sarcomas. Other findings were decreased body weight and food efficiency; also clinical pathological changes.	Statistically significant increase in the incidence of hepatocellular adenomas, carcinomas, and combined adenomas/carcinomas in both sexes by positive trend and pairwise comparison at the 1500 ppm.	C NQ

F. WEIGHT OF THE EVIDENCE CONSIDERATIONS:

1. In male rats, thyroid tumors appear to be due to a secondary mechanism linked to liver hypertrophy and enzyme induction, both of which are reversible. These effects are similar to those produced by phenobarbital. Conclusions drawn from this study were that high doses of fenbuconazole lead to increases in hepatic metabolism and biliary excretion of L-thyroxine, primarily as the glucuronide. In response to more rapid removal of thyroid hormone, blood concentrations of the pituitary-derived hormone, TSH, were increased. Therefore, increased levels of TSH led to over-stimulation of the thyroid gland, producing follicular cell hypertrophy/hyperplasia. [The Registrant hypothesized that chronic follicular hypertrophy/hyperplasia due to a secondary or indirect mechanism, such as prolonged stimulation of the thyroid by TSH, may progress to follicular neoplasia of the thyroid.]

The CPRC agreed that the mechanistic evidence presented for the thyroid tumors appeared to be scientifically plausible and consistent with EPA current policy.

2. In female mice, liver tumors induced by fenbuconazole may occur by promotional activity through a mode of action similar to phenobarbital (details are presented in section E.).

The studies submitted by the registrant to show a mechanistic basis for the liver tumors were considered by the CPRC to be suggestive, but not convincing.

Recommendations from the second cancer peer review of fenbuconazole:

It is the Committee's opinion that the registrant has taken important steps toward demonstrating a mode of action of mouse liver tumor formation. However, studies to date have been conducted over short periods of time (4 weeks), and there is no linkage of precursor events with ultimate tumor formation. It is important that further work be conducted that better establish the events in the carcinogenic process. Repeat dosing studies that include elements of dose response and time action could be designed that would specifically address the various critical events that are part of the process. Such things might include but are not necessarily limited to such effects as liver enlargement, induction of particular microsomal enzymes, development of foci of alteration, growth of foci, development and progression of hepatocellular hyperplasia, with linkage to benign and malignant tumor formation. Stop studies could demonstrate the reversibility of various events.

The registrant claims that fenbuconazole and phenobarbital are working through the same types of microsomal enzyme induction. Data to date show that there are similarities and differences in the spectrum of P450 enzyme isoforms that are induced by the two chemicals. It is important to determine which of these forms are relevant to the the proposed carcinogenic mode of action of the compounds, which are the ones that are not, and why. A qualitative and quantitative comparison should also be made between the murine and human P450 subtypes so that the implications of the the rodent findings to humans can be made.

It is recognized that compounds closely related to fenbuconazole are used as pharmaceuticals. The information bearing on these compounds should be summarized and relevant publications referenced. It is our understanding that at least some of the compounds have also induced liver tumors in rodents and that the liver is a target organ in humans. The implications of these findings to the assessment of fenbuconazole's carcinogenicity should be developed.

G. Classification of Carcinogenic Potential:

The Peer Review Committee considered the criteria contained in the EPA's "Guidelines for Carcinogen Risk Assessment" [FR51: 33992-34003, 1986] for classifying the weight of evidence for carcinogenicity.

At the first meeting [Memo, dated Nov. 22, 1993], the CPRC classified fenbuconazole as a Group C - possible human carcinogen with a low dose extrapolation model applied to the animal data for the quantification of human risk (Q_1^*). This classification was based on statistically significant increased incidences of thyroid follicular cell tumors (adenomas and combined adenoma/carcinoma) in male Sprague-Dawley rats and hepatocellular tumors (adenomas and/or carcinomas) in both sexes of the CD-1 mouse (in which higher dosing could have been used). Although there was no apparent genotoxicity evidence, structural correlation with other related triazole pesticides that are liver tumorigens provided additional support.

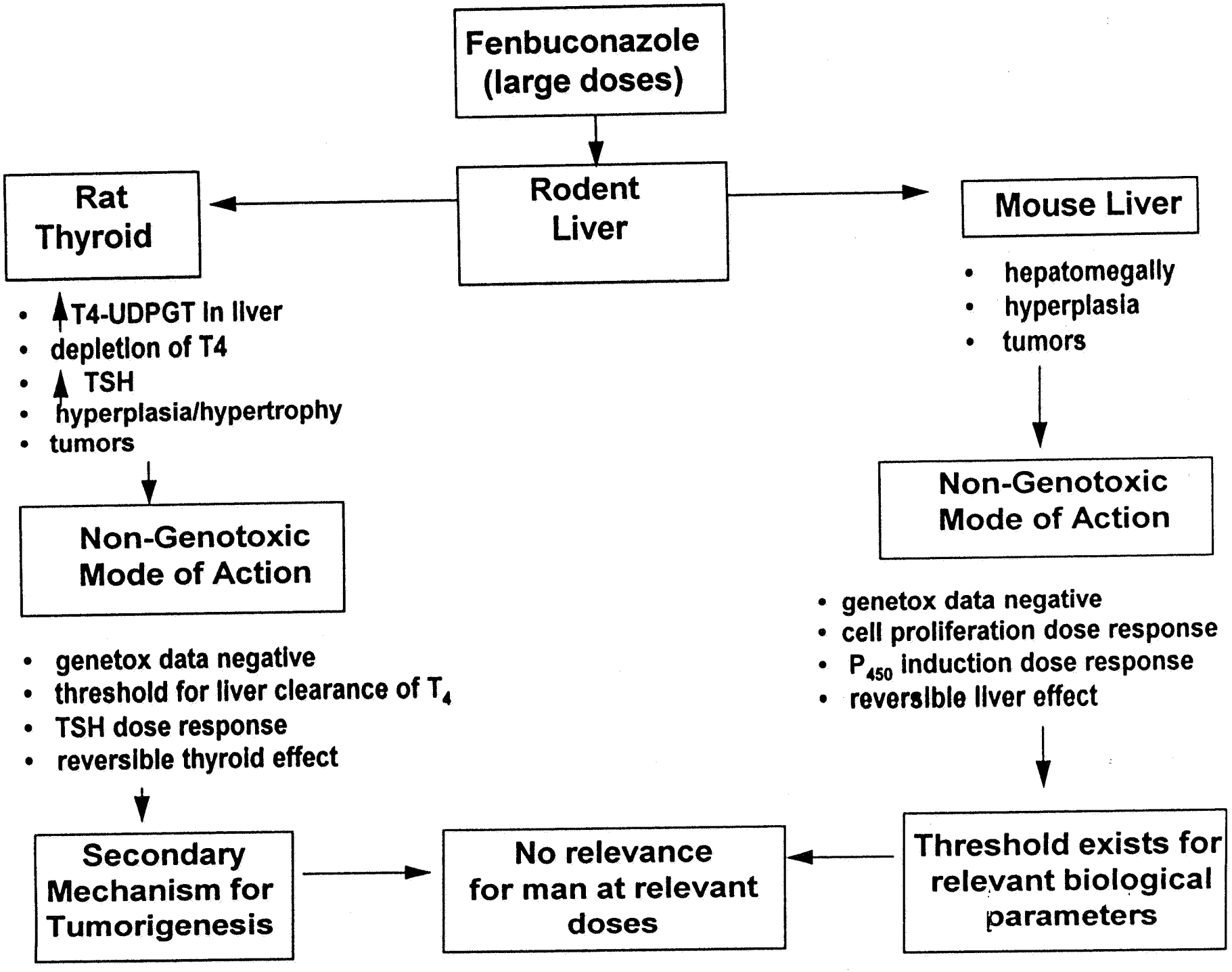
At the present meeting, the CPRC concluded that the classification of fenbuconazole should remain as a Group C - possible human carcinogen with a low dose extrapolation model applied to the animal data for the quantification of human risk (Q_1^*). Based on mechanistic data submitted by the registrant for the thyroid tumors, the CPRC agreed that the combined hepatocellular adenoma/carcinoma in the female mice should be used to derive the Q_1^* (instead of the thyroid tumors, as was recommended in the first Peer Review).

H. Induces Cancer Call -- Fenbuconazole

After a full evaluation of all of the data and supporting information regarding animal carcinogenicity, the Committee concludes that exposure to fenbuconazole resulted in an increased incidence of thyroid follicular cell tumors (benign and malignant) in male Sprague-Dawley rats and hepatocellular tumors (benign and/or malignant) in both sexes of the CD-1 mice. Although there does not appear to be evidence of genotoxicity there was structural correlation with other related triazole pesticides which are also liver tumorigens.

The Committee agrees that fenbuconazole induces cancer in animals.

Figure 1


Fenbuconazole (large doses)
Rodent Liver
Rat Thyroid
Mouse Liver
• ↑T4-UDPGT in liver
• depletion of T4
• ↑ TSH
• hyperplasia/hypertrophy
• tumors
• hepatomegally
• hyperplasia
• tumors
Non-Genotoxic Mode of Action
Non-Genotoxic Mode of Action
• genetox data negative
• threshold for liver clearance of T_4
• TSH dose response
• reversible thyroid effect
• genetox data negative
• cell proliferation dose response
• P_{450} induction dose response
• reversible liver effect
Secondary Mechanism for Tumorigenesis
No relevance for man at relevant doses
Threshold exists for relevant biological parameters