4-29-87

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

FILE COPY

APR 29 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Propiconazole

FROM: Esther Rinde, Ph.D. E. Rinde 3/6/87
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769c)

TO: Lois Rossi
Product Manager 21
Registration Division (TS-767c)

The Toxicology Branch Peer Review Committee met on Jan. 15, 1987 to discuss and evaluate the weight-of-evidence on Propiconazole with particular reference to its oncogenic potential.

A. Individuals in Attendance:

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

Theodore M. Farber	Theodore M. Farber
William L. Burnam	William L Burnam
Reto Engler	Reto Engler.
Donald Barnes	
Louis Kasza	Louis Kasza
Herbert Lacayo	Herbert T Lacayo
Robert Beliles	Robert F Beliles
Judith Hauswirth	Judith A. Hauswirth
Jack Quest	J. Quest
Esther Rinde	Esther Rinde

12201

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

Alan Katz

George Ghali

3. Peer Review Members in Absentia:

Anne Barton

Stephen Johnson

Diane Beal

B. Material Reviewed:

The material available for review consisted of DERs for Chronic/Oncogeniciy studies in CD-1 mice and CD:Crl rats, subchronic studies in the TIF:(RAIF) rat and in Beagle dogs, enzyme induction and promotion studies in the rat and for mutagenicity; "One-Liners"; and historical control data for the Sprague-Dawley rat. A copy of the material reviewed is appended to this report.

C. Background Information:

Propiconazole, also known as Banner/Tilt [1-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-ylmethyl-1H-1,2,4-triazole] is a broad spectrum systemic foliar fungicide. The acute toxicity of propiconazole (technical) is low (Tox Category III for oral, dermal and inhalation routes). Studies reviewed by the Toxicology Branch are attached (one-liners).

D. Evaluation of Oncogenicity Evidence for Propiconazole:

1. Two-Year Feeding Study in CD-1 Mice
Testing Facility: Huntingdon Research Centre

Mice were administered technical propiconazole, in the diet, for 2 years, at levels of 0, 100, 500 or 2500 ppm. Propiconazole was oncogenic for the male mouse liver at 2500 ppm. Tumors occurred with reduced latency; at the 53 week interim kill, 44% of male mice (dosed at 2500 ppm) had liver tumors, compared to 9% of controls. The tumor incidences are given in Table I.

In treated male mice the combined incidence of adenomas/carcinomas was significantly elevated over controls at 2500 ppm ($p<0.001$ - Fisher's one-tail <A.Katz>)). The incidence of non-neoplastic lesions (enlargement, vacuolation/fat deposition at hi-dose) in treated mice of both sexes, and neoplastic lesions in females, were comparable to controls and not treatment-related. There was no treatment-related hepatocytic hyperplasia or necrosis.

The MTD might have been exceeded at the high dose in males, based on increased mortality in the first 52 weeks (which was not sustained throughout the study). There were also statistically significant increases in enzyme levels (SAP, SGOT, SGPT) in high dose males, and increased liver weight in high and mid-dose males at interim and terminal sacrifice. Statistically significant increases in liver weights at interim and terminal sacrifice suggests the MTD was approached in high dose females.

2. Two-Year Feeding Study in Sprague-Dawley CD:crl Rats
Testing Facility: Huntingdon Research Centre

Rats were fed technical Propiconazole in their diets at levels of 0, 100, 500, or 2500 ppm. An increase (not statistically significant) in thyroid follicular adenocarcinoma was noted in females, only at the high dose, which was not considered to be compound related. (The thyroid was not enlarged, and there was no follicular-cell hyperplasia.) There was also an increase in dermal fibromas in males which was not dose-related. The incidences of both thyroid and dermal tumors were within the range reported for historical controls at the same testing facility. These tumor incidences are given in Section 3. (page 5).

A compound-related (but not dose-related) increase in the incidence of total tumors, was also noted by the Committee.

MTD: Apparently achieved at the mid-dose (500 ppm), as evidenced by liver toxicity in males, and exocrine atrophy of the pancreas in females. Body weight gain depression of 13% was also reported for males at the high dose, suggesting the MTD was exceeded at that level in males. The 90-day study results support this finding, although a different strain of rats was used.

Table I

Incidence (%) of Liver Cell Tumors in Male Mice fed Propiconazole

Tumor Type*	Dose 0	100 ppm	500 ppm	2500 ppm
0-52 wk.				
Deaths[1]*	2	5	4	10
Adenoma[2]	0	0	2(50)	0
Carcinoma[3]	0	0	0	1(10)
Combined[4]	0	0	2(50)	1(10)
53 wk.Kill[1]	11	11	11	9
Adenoma[2]	1(9)	0	2(18)	1(11)
Carcinoma[3]	0	0	1(9)	3(33)
Combined[4]	1(9)	0	3(27)	4(44)
54-78 wk.				
Deaths[1]	10	11	10	15
Adenoma[2]	4(40)	1(9)	0	4(27)
Carcinoma[3]	2(20)	218)	1(10)	10(67)
Combined[4]	6(60)	3(27)	1(10)	14(93)
79-92 wk.				
Deaths[1]	9	9	6	11
Adenoma[2]	0	0	0	5(45)
Carcinoma[3]	3(33)	1(11)	3(50)	6(55)
Combined[4]	3(33)	1(11)	3(50)	11(100)
93-104 wk.				
Deaths[1]	7	7	9	5
Adenoma[2]	3(43)	1(14)	1(11)	1(20)
Carcinoma[3]	3(43)	2(29)	3(33)	3(60)
Combined[4]	6(86)	3(43)	4(44)	4(80)
105 wk.				
Final Kill[1]	24	20	21	14
Adenoma[2]	5(21)	5(25)	5(24)	11(79)
Carcinoma[3]	7(29)	2(10)	7(33)	3(21)
Combined[4]	12(50)	7(35)	12(57)	14(100)
Total[1]	63	63	61	64
" Adenoma[2]	13(21)	7(11)	10(16)	22(34)
" Carcinoma[3]	15(24)	7(11)	15(25)	26(41)
" Combined[4]	28(44)	14(22)	25(41)	48(75)

1 = No. of animals examined
2 = Does not include animals having both adenomas and carcinomas
3 = Includes animals having both adenomas and carcinomas
4 = Total tumor bearing animals

* Overall Peto Trend Test, based on these time intervals indicated a statistically significant ($p \leq 0.0001$) dose-trend relationship for combined tumors (R. Levy).

D.

3. Historical Control Information:

Huntingdon Research Centre, Sprague-Dawley Rats:

1. Dermal Fibromas in Males

Historical Control
Overall Incidence (No. with Lesion/No. Examined) = 29/662 (4%)
Range: 0-10 %

Lifetime Study in Rats with CGA-64250 Technical:
Males

Dose	Incidence	Percentage
Control	0/59	0
100 ppm	3/61	5
500 ppm	1/58	2
2500 ppm	5/61	8

2. Thyroid Follicular Adenoma and Adenocarcinoma in Females

	Adenocarcinoma	Adenoma
Historical Control Overall Incidence:	7/609 = 1%	2/609 = 0.3%
Range:	0-4 %	0-4%

Lifetime Study in Female Rats with CGA-64250 Technical

	Adenocarcinoma		Adenoma	
Dose	Incidence	Percentage	Incidence	Percentage
Control	0/64	0	1/64	2
100 ppm	0/66	0	0/66	0
500 ppm	0/65	0	0/65	0
2500 ppm	2/67	3	1/67	1

E. Additional Toxicology Data on Propiconazole:

1. Metabolism:

Metabolism studies were recently submitted and have not yet been completely reviewed by TOX Branch. It appears that the primary metabolite in urine for male mice is a glucuronide with the dioxilane ring cleaved; for female mice: alpha OH carboxylic acid, conjugate of intact dioxilane ring. In rats (both sexes), there is oxidation of the propyl side-chain. Cleavage of the dioxilane ring yields a metabolite with closer resemblance to Baytan, which has produced liver tumors (preliminary review) in female mice (CF_1/W74 SPF). Bayleton, which metabolizes to Baytan, did not produce liver tumors in the mouse. Triazole alanine has been identified as the major metabolite of propiconazole in plants.

2. Non-Oncogenic Toxicological Effects:

Subchronic Studies

90-day feeding study in TIF (RAIF) SPF rats (Ciba-Geigy Ltd.)

Rats (20/sex/group) fed propiconazole technical (CGA 64250, 88% a.i.) in their diet at 0, 240, 1200 or 6000 ppm, showed no overt signs of toxicity, however body weight gains of high dose males and mid- and high dose females were significantly reduced. Hemoglobin, hematocrit and red cell count were also depressed in high dose females at termination. Serum alkaline phosphatase was increased in high dose females, and serum gamma glutamyl transpeptidase was increased in both sexes at the high dose. The LEL was determined to be 1200 ppm and the NOEL, 240 ppm, based on reduced body weight gain in mid-dose females. (The study was classified as "Core-Minimum".)

90 day feeding study in Beagle dogs (Ciba-Geigy, Ltd.)

Beagle dogs (4/sex/group) fed propiconazole technical (CGA 64250, 88% a.i.) in their diet at 0, 50, 250 or 1250 ppm, had increases in lymphoid follicles of the mucous membrane of the pyloric stomach in 3 high dose males and 1 high dose female. The NOEL and LEL were determined to be 50 ppm and 250 ppm, respectively based on the above findings (only one considered to be compound-related). (The study was classified as "Core-Minimum".)

Special Studies

1) Enzyme Induction in Rat/RAI, Mouse/Mag - Propiconazole was administered via gavage at 0, 20, 80, 160 Or 320 mg/kg.

Enzymes induced in the liver: ethoxycoumarin O-deethylase, epoxide hydrolase, gamma glutamyl transpeptidase, glutathione S-transferase and UDP-glucuranosyltransferase (similar to those induced by phenobarbital). Significant, dose related increases in liver weights were found at all dose levels in both species and hepatic DNA content was increased in both species. The significance of this finding was not immediately apparent.

2) Promotion in Rats/Tif:RAIf - Technical propiconazole (89.7% a.i.) was fed to rats for 2,4 or 8 weeks at 2000 ppm.

Propiconazole enhanced the formation of GGT-positive foci (focal proliferative changes); this effect was initiated by pre-treatment with N-nitrosodiethylamines. Thus, under these study conditions propiconazole showed promoting activity.

3. Mutagenicity:

The results of mutagenicity assays on technical propiconazole (all acceptable) are summarized below:

Test	Material	Results
Ames (TA98,100,1535,1537)	CGA 64250 (88% a.i.)	Negative ± Activation
Dominant Lethal (mouse)	" "	Negative
Chinese hamster Nucleus anomaly	" "	Negative
DNA repair (human fibroblasts)	" (90.7% a.i.)	Negative
DNA repair (rat hepatocytes)	" "	Negative
Mammalian microsome (S. cerevisiae D7)	" "	Negative ± Activation
Cell transformation (BALB/3T3)	" "	Negative

4. Structure-Activity Correlations:

Propiconazole is structuraly related to the following 1,2,4-triazole fungigides: Bitertanol (Baycor ™), Triadimefon (Bayleton ™), Triadimenol (Baytan ™), and Etaconazole. (Structures are shown in Figure 1.)

Triadimefon is metabolized to triadimenol [Tox Document #004695]. Mutagenicity studies (all acceptable) reviewed by Tox Branch have been negative for all 4 compounds.

Bitertanol and Triadimefon were negative in 2-year feeding studies in both the rat and the mouse; Triadimenol was negative in the rat, and positive in the mouse; Etaconozole was positive in both the rat and the mouse. None of these chemicals has been evaluated in Peer Review.

	Oncogenicity 2-yr. Feeding		Teratogenicity	
	Rat	Mouse	Rat	Rabbit
Propiconazole	-	+[1]	-	-
Bitertanol	-	-	+[3]	?
Triadimefon	-	-	+	-
Triadimenol	-	+[2]	-	?
Etaconazole	+[4]	+[5]	-	-

[1]Hepatocellular adenomas and carcinomas
[2]Hepatocellular adenomas and hyperplastic nodules
[3]Cleft palate

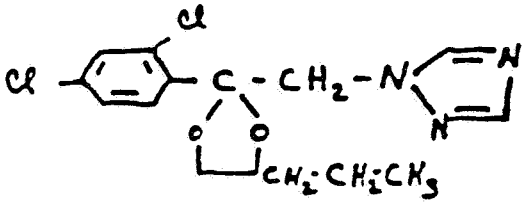
+ = positive study
- = negative
? = supplementary

[4]Formal DER not prepared by TOX Br.; appears positive based on cursory examination of summary data tables and conclusions drawn by Registrant.

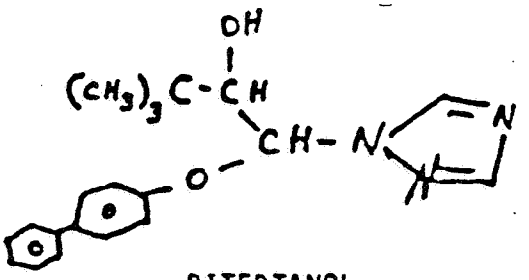
[5]Hepatic parenchymal cell nodules, based on a supplementary study; a more recent study, not formally evaluated, indicates increases in the incidences of hepatocellular carcinomas/adenomas in both sexes of mice, based on conclusions drawn by Registrant.

7

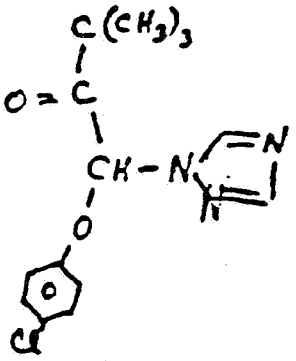
FIGURE 1



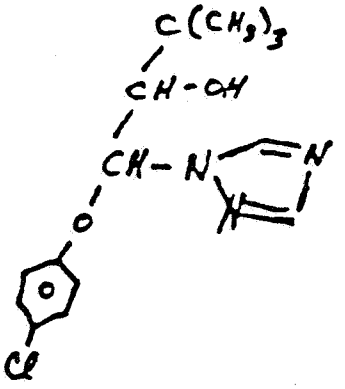
PROPICONAZOLE
(Tilt®)



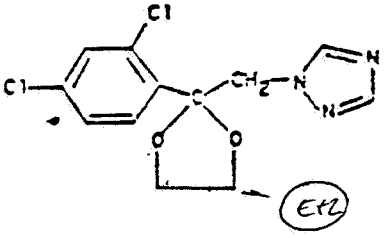
BITERTANOL
(Baycor®)



TRIADIMEFON
(Bayleton®)



TRIADIMENOL
(Baytan®)



ETACONAZOLE

F. Weight of Evidence Considerations:

The Committee considered the following toxicology data on propiconazole to be of importance in a weight of evidence determination of oncogenic potential:

Oral administration of propiconazole to CD-1 mice resulted in a statistically significant increase in combined adenomas and carcinomas of the liver in male mice at 2500 ppm. Tumors occurred with reduced latency (44% in treated animals versus 9% in controls at 53 weeks).

Oral administration of propiconazole to Sprague Dawley CD:crl rats:
While a compound-related (but not dose related) increase in incidence of total tumors, was noted by the Committee, it was agreed that the overall evidence for propiconazole in the rat was negative for oncogenicity.

Enzyme induction in the rat was also noted, as was propiconizole's ability to act as a promotor in the rat.

Evidence from structure-activity relationships is mixed: Etaconazole, which was the closest analog, was positive in both the rat and mouse; Bitertanol and Triadimifon were negative in both the rat and mouse; Triadimenol was negative in the rat, and positive in the mouse. None of these chemicals has been evaluated in Peer Review.

Evidence from short-term tests suggests that propiconazole is not a mutagen, however it should be noted that all of its analogs (even those which tested positive as oncogens) were also negative for mutagenicity.

G. Classification of Oncogenic Potential:

Criteria contained in the EPA Guidelines [1986 FR51:33992-34003] for classifying a carcinogen were considered.

Based on evidence of carcinogenicity in a single species, in a single sex, the Committee classified propiconazole as a Group C - Possible Human Carcinogen.

A classification of Category B2 was also discussed based on promotor activity in the rat (suggestive of activity in that species, as well) but it was generally agreed that this evidence was no more than suggestive. Furthermore, testing for promoting activity at this time has not undergone sufficient scientific validation to make unequivocal predictions about a chemical. It was also noted that Etaconazole, the closest analog, is apparently a postive oncogen in both the rat and mouse; however, the Committee agreed that in the absence of other supporting evidence, eg: from short-term tests, dose-response effects, or a positive finding in a second species, the data could not support a B2 classification.

The Committee also recommended that a risk assessment should be performed on propiconazole, based on the early onset of tumors in the mouse, the suggestion of promotor activity in the rat and some SAR. The Q1* is 7.87×10^{-2} $(mg/kg/day)^{-1}$, based on the Weibull time to tumor model (Lacayo memo, 2/9/87 - and Levy memo, 3/11/87 - appended).

H. References

1. "CGA 64 250; Long-Term Feeding Study in Mice" Huntingdon Research Centre, Huntingdon, Cambridgeshire, England; Final Report, No. CBG 196/81827

11/4/82; Authors: B. Hunter, N. Slater, R. Heywood, A. Street, D. Prentice, W. Gibson, C. Gopinath; Sponsor: CIBA-GEIGY Limited, Basle, Switzerland; EPA Accession Nos. 250784-250786; 252137

2. "CGA 64 250, Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats"; Huntingdon Research Centre, Huntingdon, Cambridgeshire, England; Report No. CBG 193/8284; Test No. 789023; 9/30/82; Authors: B. Hunter, N. Slater, R. Heywood, A. Street, D. Prentice, W. Gibson, C. Gopinath; Sponsor: CIBA/GEIGY Limited, Basle, Switzerland; EPA Accession Nos. 250787-250790.