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

MEMORANDUM

SUBJECT: Fifth Carcinogenicity Peer Review of Propiconazole

FROM: Elizabeth Doyle, Ph.D., Section Head E.A. Doyle 8/6/92
Review Section IV, Tox Branch II (H7509C)

and
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TO: Susan Lewis
Product Manager #21
Herbicide/Fungicide Branch
Registration Division (H7505C)

The Health Effects Division Carcinogenicity Peer Review Committee met on April 15, 1992 to discuss and evaluate the weight-of-the-evidence on propiconazole with particular reference to its carcinogenic potential.

The Peer Review Committee agreed that propiconazole should be classified as Group C - possible human carcinogen and recommended that for the purpose of risk characterization the Reference Dose (RfD) approach should be used for quantification of human risk.

A. Individuals in Attendance:

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

Karl Baetcke Karl D. Baetcke

for Marcia Van Gemert James N. Rowe 8/10/92

Reto Engler

Robert Beliles Robert P. Beliles

Lucas Brennecke Linda H. Brennecke

Marion Copley Marion Copley

George Ghali

Jean Parker

Hugh Pettigrew

William Sette

Yin-Tak Woo

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

Elizabeth Doyle[1] E. A. Doyle 8/6/92

Bernice Fisher

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Penelope Fenner-Crisp Penelope A. Fenner-Crisp

William L. Burnam

Kerry Dearfield

Esther Rinde

Julie Du

Richard Hill

for John Quest James N. Rowe 8/10/92

4. Other Attendees: (Observers)

Eve Andersen (Clement)
Jon Fleuchaus
Ann Clevenger
Jim Rowe
Robert Friche
Lori Brunsman
Linnea Hansen

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

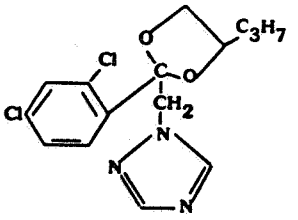
B. Material Reviewed:

The material available for review consisted of DER's, and other data summaries prepared by Elizabeth Doyle; tables and statistical analysis by Bernice Fisher. The material reviewed is attached to the file copy of this report. The data reviewed are based on studies submitted to the Agency by Ciba-Geigy Corp.

C. Background Information:

The Caswell (or Tox Chem) Number of propiconazole is 323EE
The Chemical Abstracts Registry Number (CAS No.) is 60207-90-1.

The structure of propiconazole is



Propiconazole has to date been the subject of four Peer Reviews and one SAP meeting. The following summaries of the preceding meetings are taken, in part, from the fourth Peer Review Document for this compound.

1. Initial Peer Review Committee Meeting Findings

The chemical was originally evaluated by the Peer Review Committee on January 15, 1987 and was classified as a Group C (possible human) carcinogen with a recommendation made for the quantification of estimated potential human risk using a linearized low-dose extrapolation. The classification was based upon the increased incidence of hepatocellular adenomas, carcinomas, and adenomas/carcinomas combined in CD1 male mice at 2500 ppm, the highest dose tested. The increase was statistically significant by pairwise comparison and trend analysis. The Committee found that the tumors progressed at an accelerated rate in the treated animals. There were no indications of treatment-related hepatocytic hyperplasia or necrosis. The incidence of nonneoplastic lesions in treated mice of both sexes, and neoplastic lesions in females were comparable to controls. The Committee felt, at this time, that the high dose might have been excessively toxic in males, based upon increased mortality in the first 52 weeks of the study, and the elevation of liver enzymes (SAP, SGOT, SGPT). There was also an increase in liver weight in the mid-, and high-dose males at interim and terminal sacrifice. Statistically significant increases in liver weights at interim and terminal sacrifice suggested that for females the high-dose level was appropriate for testing the carcinogenic potential of propiconazole.

In a second carcinogenicity study in Sprague-Dawley CD rats, treatment did not alter the spontaneous tumor profile for this strain under the conditions tested.

The group C classification was supported further by the structural similarity of propiconazole to other triazole fungicides such as Bayleton, Baytan, and etaconazole, all of which were reported to be associated with increased incidence of hepatocellular adenomas in male or female mice or both.

2. FIFRA Scientific Advisory Panel Evaluation

The Peer Review Committee's decision was presented to the FIFRA Scientific Advisory Panel (SAP) on March 2, 1988. The Panel did not concur with the Committee's overall assessment of the weight-of-evidence on the carcinogenicity of propiconazole. The Panel recommended placing the chemical in Group D. The Panel indicated that "there is only minimal evidence for placing propiconazole in this category [Group C] . . ." This minimal evidence, according to the SAP "is based on the incidence of liver tumors in male mice given the agent at a dose that was excessive (demonstrated by increased mortality in the first year of the study, and increased SGOT, SAP, and SGPT in these animals)".

3. Second Peer Review - Evaluation of the SAP Findings

The HED Peer Review Committee met on March 30, 1988, to examine the issues raised by the SAP with respect to the classification of the carcinogenicity of propiconazole and the need for quantification of the estimated potential human risk.

Upon reconsideration, the Committee still concluded that the data available on the mouse demonstrated sufficient evidence of carcinogenicity in the male mice and, therefore, the Group C classification was appropriate. The Committee based its decision on the following:

a. Administration of propiconazole was associated with a highly significant increase ($p < 0.01$) of benign as well as malignant tumors in male CD1 mice.

b. No evidence of overt toxicity to the liver.

c. Mortality in males of the high-dose group was not dramatically increased, and the increase was limited to the first year of the study.

d. The uncommon biological behavior of these tumors, in that they were considered a contributing factor to death in many male mice at the high dose level and in some cases, the mice were sacrificed because of a distended abdomen due to the underlying liver enlargement caused by the tumors.

e. Structural similarity to homolog etaconazole (associated with liver adenomas and carcinomas in male and female mice), analog Baytan (Group C based on hepatocellular adenomas in female mice), and Bayleton, another triazole fungicide (associated with hepatocellular adenomas in male and female mice).

The Committee took as precedent the SAP's classification of triadimenol (Baytan) as a Group C oncogen based on a marginal increase in liver adenomas in female mice in spite of a dose-related increase in liver enzymes (SGOT, SAP, and SGPT) and liver hyperplasia in that study.

The Committee also considered that a risk assessment using a linearized low-dose extrapolation model in this case was appropriate. The Committee based its decision on the fact that the treatment resulted in a highly significant increase of tumors, increased malignancy, and an accelerated response in these animals. Furthermore, the dose selection and spacing in the mouse study was such that the mid dose of 500 ppm could not provide any information on the carcinogenic response of propiconazole.

4. Third Peer Review - Evaluation of Registrant's Rebuttal

This meeting was called on April 26, 1989 to reconsider the Agency's position regarding the carcinogenicity of propiconazole in light of comments submitted by the registrant, Ciba-Geigy, in a position document entitled "Rationale for using a risk safety factor approach with propiconazole for risk management purposes," received August 30, 1988.

In this position document, the registrant questioned the relevance of the elevated incidence of both benign and malignant tumors in male mice at a dietary level of 2500 ppm which was excessive. The registrant further contended that an adequate dose had been reached at the mid-dose level, i.e., 500 ppm.

With respect to the registrant's question regarding the relevance of the elevated incidence of both benign and malignant tumors in male mice, the Committee believed that this effect was treatment-related for the following reasons:

a. The increase was highly significant ($p < 0.01$), and included increases in malignancy and multiplicity and occurred at an accelerated rate.

b. The uncommon biological behavior and morphology of these tumors, in that the tumors in the high-dose males were larger in size, reported in multiple and progressed in an aggressive manner. These tumors were considered a contributing factor to death. In some cases, the mice had to be sacrificed because of distended abdomens due to the underlying liver enlargement caused by the tumor.

c. Additional data were provided indicating that propiconazole is metabolized in a manner similar to etaconazole, another triazole which has been associated with a significant increase in liver adenomas and carcinomas in both male and female mice.

The Committee recommended that the classification of propiconazole should remain unchanged until further evaluation of individual animal data to ascertain the number of animals with multiple liver cell tumors and the extent of liver enlargement and discoloration in the treatment and control groups.

No official report was issued at that time, and the recommendations of the Committee were conveyed in a brief memorandum to the Fungicide-Herbicide Branch of the Registration Division/OPP. The Committee decided to reconvene at a future date to continue the discussion once the requested information was available.

5. Fourth Peer Review Meeting

The HED Peer Review Committee reconvened to consider further the registrant's arguments that the MTD had been exceeded at the 2500 ppm treatment level. A detailed presentation of the results of a reevaluation of the mouse oncogenicity study was made.

The reevaluation of the study resulted in confirmation of the increased incidence of hepatocellular adenomas and carcinomas in male mice from the 2500 ppm treatment group. The reviewer reemphasized that a marked increase in multiple tumors occurred in this group.

With regard to the increased mortality observed in the high dose males, this argument was not taken as evidence dosing was excessive in that many of the mice were sacrificed moribund or for humane reasons because of the occurrence of large liver tumors. In some cases, the livers were so enlarged due to tumor burden as to result in abdominal distension.

Arguments that the 500 ppm treatment level constituted an adequate top dose were not accepted. None of the criteria for an adequate dosing were achieved at this dose level. The body weight decrement indicated by the registrant as statistically significant was found to not be biologically significant in as much as the difference between body weights for the 500 ppm group and control males was generally only one gram.

The Committee concluded that the classification of propiconazole as a Group C carcinogen with quantification of potential human risk should not be changed on the basis of arguments presented by the registrant.

6. Fifth Peer Review - April, 1992

The registrant has provided an additional submission requesting further consideration of the issue of the MTD for propiconazole in mice. The registrant continues to argue that the high-dose was excessive in the mouse oncogenicity study (Acc. No. 073919, 250784-250786, 251237). They further argue that the data from the high dose (2500 ppm) should not be included in the evaluation of carcinogenic potential of propiconazole.

In support of these arguments, the registrant has provided two subchronic oral toxicity studies in mice in an attempt demonstrate that chronic studies exceeded appropriate dosing to assess carcinogenicity.

Ciba-Geigy also has provided a reread of the pathology slides from the study by J Hardisty, DVM, which they feel indicates sufficient concurrent liver toxicity at 2500 ppm to document that this dose was excessive. These data were not present in the original pathology report by JM Offer, DVM, of

Huntingdon Research Centre. Due to the inconsistency in the reports, Tox Branch requested that an independent (third) evaluation of the slides be made to determine if the pathology reported in Hardisty's report could be confirmed. L Brennecke, DVM, has performed this evaluation which was limited to the control, mid and high dose groups to determine if sufficient toxicity exists to exclude the high dose group.

D. Evaluation of Tumor Data

The registrant has challenged the argument that the tumors produced in the male mice are morphologically different from the background tumors in the control and lower dose mice. This particular discussion arises from the use of difference in morphology as a factor in deciding to quantify the carcinogenic risk from propiconazole.

The PRC determined that, although the adenomas observed in the treated animals were larger and more numerous than those in controls, the tumor type (adenomas) was the same. The numbers of hepatocellular tumors in the control animals was also high. No excessive numbers of tumors were found in female mice.

The statistical evaluation of the incidence of male mouse liver tumors are shown in the following tables. The adenomas were statistically increased by both trend and pair-wise comparison at the high doses ($p<0.01$). The carcinomas were statistically increased by trend analysis, and were increased at the high-dose ($p<0.05$) when the analysis of 2 pathologists were used (26155 or 25155 affected), but not using the analysis of the third pathologist (20154 affected). Statistical analysis of the combined adenomas/carcinomas yielded significant increases ($p<0.01$) for both the trend and pair-wise comparison at the high dose.

Propiconazole - Male Mouse Study, Hepatocellular Adenoma Only Tumor Rates and Peto's Prevalence Test Results (p values)

Tumors	Dose (ppm) 0	500	2500
Adenomas Only			
J.M. Offer (%)	13/64 (20)	10[a]/62 (16)	22/56 (39)
p=	0.001**	0.668(n)	0.007**
J. Hardisty (%)	12/64 (19)	13[b]/62 (21)	23/56 (41)
p=	0.000**	0.419	0.001**
L.J. Brennecke (%)	13/64 (20)	12[c]/62 (19)	28/56 (50)
p=	0.000**	0.514(n)	0.000**

* Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

n Negative change from control.

[a] First adenoma observed at week 44, dose 500 ppm.
[b] First adenoma observed at week 44, dose 500 ppm.
[c] First adenoma observed at week 44, dose 500 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Propiconazole - Male Mouse Study, Hepatocellular Carcinoma Tumor Rates* and Peto's Prevalence Test Results (p values)

	Dose (ppm)		
	0	500	2500
Tumors			
Carcinomas			
Pathologist			
J.M. Offer (%)	15/62 (24)	15/60 (25)	26[a]/55 (47)
p=	0.003**	0.511	0.010*
J. Hardisty (%)	16/62 (26)	13/60 (22)	25[b]/55 (45)
p=	0.006**	0.75(n)	0.035*
L.J. Brennecke (%)	14/60 (23)	11/58 (19)	20[c]/54 (37)
p=	0.028*	0.801(n)	0.050

* Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first carcinoma.

n Negative change from control.

[a] First carcinoma observed at week 50, dose 2500 ppm.
[b] First carcinoma observed at week 50, dose 2500 ppm.
[c] First carcinoma observed at week 53, dose 2500 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Propiconazole - Male Mouse Study, Hepatocellular Tumor Rates* and Peto's Prevalence Test Results (p values)

	Dose (ppm)		
Tumors Combined (Adenoma &/or Carcinoma)	0	500	2500
Pathologist			
J.M. Offer	28/63	25/62	48/56
(%)	(44)	(40)	(86)
p=	0.000**	0.702(n)	0.000**
J. Hardisty	28/63	26/61	48/56
(%)	(44)	(43)	(86)
p=	0.000**	0.693(n)	0.000**
L.J. Brennecke (%)	27/63	23/62	48/56
	(43)	(37)	(86)
p=	0.000**	0.718(n)	0.000**

* Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

n Negative change from control.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then p<.05 and if ** then p<.01.

E. Evaluation of Supportive Data

1. Subchronic Toxicity Studies

Subchronic Dietary Toxicity Study with CGA-64250 in Mice. MRID 420505-01. RF Potrepka and JC Turnier. Ciba-Geigy Corp., Farmington CN. April 30, 1991.

Groups of 20 male and 20 female Crl:CD-1 (ICR) BR (Swiss) mice were given 0, 20, 500, or 2500 ppm propiconazole in the diet for 17 weeks. An additional two groups of 20 males each were given diet containing 850 or 1450 ppm. Mice were seven weeks old at the initiation of the study.

No effect on body weight gain was reported. No treatment related mortality or toxic signs were reported.

Treatment related increases in ALT/SGPT were reported for males receiving ≥850 ppm and females given 2500 ppm. High dose females also had increased levels of AST/SGOT. Cholesterol levels were decreased in males receiving ≥850 ppm (Table 1).

Significantly increased liver weights (absolute, relative to body weight and relative to brain weight) were reported in males at treatment levels ≥500 ppm and in females given 2500 ppm (Table 2). Increased weights were accompanied by increased evidence of histopathological lesions which exhibited a dose related increase in both frequency and severity (Table 3). At 500 and 850 ppm, all diagnosed hypertrophy in the males was mild; moderate hypertrophy was present in 9/20 and 18/20 animals in the 1450 and 2500 ppm groups, respectively. In high dose females, 14/20 had minimal to mild hypertrophy while 3/20 were classified as moderate. Necrosis was present in males receiving ≥500 ppm and increased in frequency and severity with increasing dose. It occurred as scattered individual cell foci and/or multicellular areas. Severity at all doses was minimal to mild. Significant vacuolation occurred only in high dose males. The severity rating was minimal in 2/20, mild in 7/20 and moderate in 1/20 animals.

Based on these findings, the PRC determined that the 1450 and 2500 dose levels were very toxic, and that the MTD was 850 ppm.

Table 1: Clinical Chemistry Findings

Analyte (units)	Week of Study	Dose Level (ppm) 0	20	500	850	1450	2500
Male							
Cholesterol (mg/dl)	13	120	108	121	108	70**	71**
	17	119	104	105	91**	66**	67**
Alanine Amino-transferase (U/l)	13	52	31	39	43	65	81
	17	17	33	28	29	65**	128**
Female							
Aspartate Amino-transferase (U/l)	13	67	60	61	---	---	68
	17	45	47	55	---	---	68**
Alanine Amino-Transferase (U/l)	13	27	24	27	---	---	64**
	17	17	20	21	---	---	61**

** $p < 0.01$

Table 2: Absolute and relative liver weights of male and female mice

Dose Level (ppm)	Absolute (g)	% of Body Weight	% of Brain Weight
Male			
0	1.445	3.961	286.3
20	1.408	4.108	283.8
500	1.660*	4.486**	332.2*
850	1.792**	5.131**	363.0**
1450	2.450**	6.701**	480.2**
2500	2.773**	8.102**	555.0**
Female			
0	1.177	4.182	230.6
20	1.267	4.533	250.9
500	1.215	4.414	243.9
2500	2.110**	7.684**	435.5**

* $p < 0.05$, ** $p < 0.01$

Table 3: Incidence of Histopathological Lesions in the Liver

Lesion	Dose Level (ppm)					
	0	20	500	850	1450	2500
Male						
Total Livers Examined	20	20	20	20	20	20
Hypertrophy	0	0	4	14**	20**	20**
Necrosis	1	0	2	4	8*	12**
Individual Cell	0	0	0	0	2	12**
Total Affected	1	0	2	4	10**	18**
Vacuolation	0	0	6*	2	3	10**
Individual Cell	0	0	0	0	0	6**
Total Affected	0	0	6*	2	3	16**
Female						
Total Livers Examined	20	20	20	20	20	20
Hypertrophy	0	0	0	---	---	17**
Necrosis	0	0	0	---	---	6*
Individual Cell	0	0	0			1
Total Affected	0	0	0			6*
Vacuolation	0	0	0	---	---	2
Individual Cell	0	0	0			1
Total Affected	0	0	0			3

* $p < 0.05$, ** $p < 0.01$

13-Week Toxicity Study with CGA-64250 in Male Mice: MRID 420505-02. RF Potrepka and JC Turnier. Ciba-Geigy Corp., Farmington, CN. April 30, 1991.

Groups of 40 male Crl:CD-1 (ICR) BR (Swiss) mice were given 0, 20, 500, 850, 1450, or 2500 ppm propiconazole in diet. They were 37 days old at initiation of the study. Ten animals from each group were sacrificed at 4 and 8 weeks. The remaining 20 mice from each group were sacrificed at 13 weeks. No unscheduled deaths or toxic signs were reported during this study. A slight body weight decrement was reported for the 2500 ppm treatment group, with a difference of about 1 gram at week 8. No further difference was reported. At week 8, the 2500 ppm group had gained 0.9 g less than the control group. However, no further change occurred during the study.

Mice exhibited significantly decreased cholesterol levels at treatment levels ≥850 ppm (Table 4). This response to treatment was dose related. ALT/SGPT and sorbitol dehydrogenase were increased in a dose related manner at treatment levels ≥850 ppm. None of the effects reported exhibited a time related change. Differences were established by Week 4 and persisted until the Week 13 sacrifice.

Table 4: Clinical Chemistry Findings

Parameter (units)	Week of Study	Dose Level (ppm)			
		0	850	1450	2500
Cholesterol (mg/dl)	4	129	92**	81**	47**
	8	114	104	58**	57**
	13	122	86**	75**	67**
Alanine Amino transferase (U/l)	4	24	42	56**	86**
	8	24	30	53**	74**
	13	22	35	53**	79**
Sorbitol Dehydrogenase (U/l)	4	26	45*	58**	66**
	8	27	30	47**	59**
	13	22	31*	45**	58**

** $p<0.01$

Absolute and relative liver weights were increased in a dose related manner in treatment groups receiving feed containing ≥500 ppm (Table 5). At necropsy, increased prominence in the lobular architecture was reported in the 1450 and 2500 ppm treatment groups. Incidence increased with duration of treatment.

Table 5: Absolute and relative liver weights

Dose Level (ppm)	Absolute (g)	% of Body Weight	% of Brain Weight
0	1.307	4.524	266.7
20	1.194	4.335	251.1
500	1.523*	5.339**	317.8
850	1.709**	6.078**	356.5**
1450	1.984**	7.043**	414.5**
2500	2.382**	8.776**	512.0**

* $p < 0.05$, ** $p < 0.01$

A dose related increase in both the incidence and severity of hypertrophy, necrosis and vacuolation was reported, beginning with the 500 ppm treatment group (Table 6). Hypertrophy was graded as mild to moderate with the more severe lesions occurring at the 1450 and 2500 ppm dose levels. Necrosis was either single cell foci or multiple cell clusters. Necrosis and vacuolation were graded from minimal to moderate with the more severe effects at higher doses. In addition, the frequency and severity increased with increasing time on treatment. Based on these findings, the MTD appears to be 850 ppm.

2. Reevaluation of Histopathology Slides

Two reevaluations of the slides from the original study have been conducted. The initial reevaluation was conducted by Jerry Hardisty, DVM, of Experimental Pathology Laboratories, Inc. (Reexamination of the Liver Tumor Response in Male and Female Mice - Pathology Report, May 6, 1991). This evaluation was commissioned by Ciba-Geigy Corp. The purpose of this submission was to present evidence that excessive nonneoplastic lesions were present in the livers of male mice given 2500 ppm propiconazole in the diet for two years. These data were accompanied by arguments from the registrant that the original pathology report from Huntingdon Research Centre (HRC Report No. CBG/196/81827) understated the extent of concurrent nonneoplastic lesions, thereby causing misinterpretation of the data. They argued that the Hardisty evaluation was more correct and indicates that the 2500 ppm treatment level clearly exceeded the MTD.

Another re-evaluation of the slides was commissioned by HED to validate the report from EPL. This evaluation included only the livers from the control, 500 ppm and 2500 ppm male mice, those slides which reflect the questionable setting of the MTD. This evaluation was conducted by Lucas H. Brennecke, DVM, of Pathology Associates, Inc. (Histopathologic Review of Livers in Male Mice From the Long-Term Feeding Study in Mice With CGA 64 250 (Propiconazole), January 30, 1992).

As an initial evaluation of the similarity of the evaluations from JM Offer (HRC), J Hardisty (EPL) and L Brennecke (PAI), Bernice Fisher conducted a tumor rate analysis using Peto's Prevalence tests of trends and pair-wise comparison of controls and each dose level for each set of data from each pathologist (See attached memo). The increase in total hepatocellular tumors was essentially identical with respect to trends and pair-wise comparison to control for all three evaluations. All three evaluations indicated significant trend for hepatocellular carcinomas with treatment.

Table 6: Incidence of Histopathological Lesions in the Liver

Lesion	Dose Level (ppm)					
	0	20	500	850	1450	2500
Interval Period: 4 Weeks						
Total Livers Examined	10	10	10	10	10	10
Hypertrophy	0	0	2	6**	10**	10**
Necrosis	1	0	0	4	3	6
Individual Cell	0	0	1	0	5*	4
Total Affected	1	0	0	4	7*	7*
Vacuolation	0	0	0	0	1	6**
Individual Cell	0	0	0	0	1	2
Total Affected	0	0	0	0	2	8**
Interval Period: 8 weeks						
Total Livers Examined	10	10	10	10	10	10
Hypertrophy	0	0	5*	9**	10**	10**
Necrosis	0	0	2	2	4	6**
Individual Cell	0	0	0	0	8**	9**
Total Affected	0	0	2	2	9**	9**
Vacuolation	0	0	1	0	4	4
Individual Cell	0	0	0	0	0	7
Total Affected	0	0	1	0	4	7**
Interval Period: 13 weeks						
Total Livers Examined	20	20	20	20	20	20
Hypertrophy	0	0	3	20**	20**	20**
Necrosis	0	0	1	2	9**	5*
Individual Cell	0	0	0	1	10**	16**
Total Affected	0	0	1	3	15**	18**
Vacuolation	0	1	1	5*	6*	6*
Individual Cell	0	0	0	0	3	18
Total Affected	0	1	1	5*	9**	6**
Mineralization	0	0	0	2	0	6*

* $p < 0.05$, ** $p < 0.01$

Two of three evaluations (Offer and Hardisty) indicated significant pair-wise comparisons to the control, while the third (Brenneke) indicated borderline significance for increases in carcinomas. Comparison of the statistical analysis of hepatocellular adenomas also indicated the same significant results with increasing trends and significant pair-wise comparisons of the high dose to the controls. Although there was some difference in tumor count, this did not differentially affect the statistical results among the pathologists. Based upon the total tumor analysis, there is no evidence that the new pathology report would indicate a need for recalculation of the Q_1*.

With respect to the question of morphology of hepatocellular adenomas in the 2500 ppm treatment group, no difference was found with respect to tumor type relative to the lower dose groups and the controls. The difference in the high dose group was rather increased numbers and size of tumors of the same types seen in the controls.

With respect to nonneoplastic lesions, effects reported by Hardisty and Brennecke were similar (Table 7). A dose related increase in incidence and severity of hepatocyte enlargement was reported by both pathologists beginning with the 500 ppm treatment level. In addition, eosinophilic foci were increased at 500 ppm. No other nonneoplastic effects were reported at this treatment level. In the 2500 ppm treatment group, the severity and incidence of hepatocyte vacuolation, chronic inflammation and pigmented Kupffer cells was increased. Effects in the high dose group were limited in severity to moderately severe for hepatocyte enlargement and chronic inflammation, and moderate for pigmented Kupffer cells and hepatocyte vacuolation. No other treatment related effects were reported. Hepatocyte necrosis in all dose groups was comparable to the control.

Table 7: Incidence of Histopathological Lesions in the Livers of Male Mice - Terminal Sacrifice and Early Deaths

Lesion	Dose Level (ppm)			
	0	100	500	2500
Total Livers Examined*	53 (53)	53 (0)	51 (53)	55 (55)
Eosinophilic Focus	1 (1)	1 (-)	5 (4)	6 (17)
Hepatocyte Enlargement	12 (20)	6 (-)	31 (30)	45 (49)
Minimal	4 (9)	3 (-)	15 (11)	0 (7)
Mild	7 (8)	3 (-)	14(13)	18 (11)
Moderate	1 (3)	0 (-)	2 (6)	26 (28)
Moderately Severe	0 (0)	0 (-)	0 (0)	1 (3)
Hepatocyte Vacuolation	7 (5)	5 (-)	7 (5)	19 (30)
Minimal	4 (3)	3 (-)	5 (0)	8 (10)
Mild	3 (1)	2 (-)	2 (4)	11 (16)
Moderate	0 (1)	0 (-)	0 (1)	0 (4)
Inflammation, Chronic	30 (28)	26 (-)	26 (29)	38 (41)
Minimal	12 (15)	11 (-)	17 (21)	11 (22)
Mild	13 (10)	9 (-)	6 (6)	14 (16)
Moderate	5 (3)	6 (-)	3 (2)	12 (3)
Moderately Severe	0 (0)	0 (-)	0 (0)	1 (0)
Pigmented Kupffer Cells	7 (3)	8 (-)	8 (2)	37 (33)
Minimal	7 (3)	6 (-)	8 (2)	7 (11)
Mild	0 (0)	2 (-)	0 (0)	22 (20)
Moderate	0 (0)	0 (-)	0 (0)	8 (2)

*Pathologist = Hardisty (Brennecke)

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on propiconazole in a weight-of-the-evidence determination of carcinogenic potential.

Increased numbers of adenomas (increased trend and pairwise comparision, $p<0.01$) were found in the livers of male CD1 mice given 2500 ppm of propiconazole in the diet. The treated animals also had earlier fatalities than the controls. The numbers of carcinomas also were increased (increased trend, $p<0.05$).

Although the adenomas observed in the treated animals were larger and more numerous than those in controls, the tumor type (adenomas) was the same. The numbers of hepatocellular tumors in the control animals also was high. No excessive numbers of tumors were found in female mice.

The Peer Review Committee determined that the high dose used in this study was excessively toxic but that the other doses were not adequate for assessing the carcinogenic potential of propiconazole. The 2500 ppm used in the two year chronic study exceeded the MTD demonstrated in the 90 day study based on the endpoint of hepatic necrosis. The 500 ppm used in the chronic study was inadequate to assess the carcinogenicity of propiconazole.

In a rat study conducted with acceptable doses of propiconazole, no excessive numbers of tumors were found.

Propiconazole is structurally related to other systemic triazole fungicides which are known to be carcinogenic.

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.

The Peer Review Committee agreed that the classification for propiconazole should be Group C - possible human carcinogen, based on the finding of increased numbers of adenomas ($p<0.01$ by pairwise comparison at the high dose) in the livers of male mice. The numbers of carcinomas were also increased using the trend analysis ($p<0.05$). The treated animals also had earlier fatalities than the controls.

For the purpose of risk characterization the Peer Review Committee recommended that the Reference Dose approach should be used for quantification of human risk (RfD). This decision was based on the new data submitted (90 day studies) which showed excessive toxicity at the high dose (2500 ppm); however, the middle dose (500 ppm) was not considered sufficiently high for assessing the carcinogenic potential of propiconazole. Therefore, there are no appropriate data for the calculation of a q1*.

The Peer Review Committee discussed the need to repeat the mouse study using adequate doses. This decision, however, was deferred to the HED Re-registration data review panel.

ATTACHMENT