



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
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OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

May 31, 1994

MEMORANDUM

SUBJECT: Health Effects Division (HED)  
Carcinogenicity Peer Review Committee  
Draft Document on DIFENOCONAZOLE (Dividend)

FROM: Esther Rinde, Ph.D. *E.R.*  
Manager, HED Carcinogenicity Peer Review  
Science Analysis Coordination Branch  
Health Effects Division (7509C)

TO: Addressees

Attached for your review is the draft document of the Carcinogenicity Peer Review Committee on Difenconazole. This is a revised new "Streamlined Format", a response to the curtailment of SAB contract support. Your comments on the first document of this kind (Cacodylic Acid), have been helpful and changes in the format have been incorporated accordingly.

Please provide your comments on the draft document and return to me no later than June 17, 1994. If a reply is not received by that time, it will be presumed that you concur and have no comments.

Should you need a few extra days for a thorough review, please let me know that your comments are forthcoming.

ADDRESSEES

|                 |                          |
|-----------------|--------------------------|
| P. Fenner-Crisp | E. Doyle                 |
| R. Engler       | R. Hill                  |
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MEMORANDUM

SUBJECT: DRAFT Carcinogenicity Peer Review of  
DIFENOCONAZOLE [DIVIDEND]

FROM: Jess Rowland, M.S, Toxicologist  
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: Cynthia Giles-Parker  
Product Manager #22  
Fungicide/Herbicide Branch  
Registration Division (7505C)

THROUGH: Penelope Fenner-Crisp, Ph.D.  
Director, Health Effects Division (7509C)

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on May 18, 1994 to discuss and evaluate the weight-of-the-evidence on Difenoconazole with particular reference to its carcinogenic potential. The CPRC concluded that Difenoconazole 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 quantitation of human risk. This was based on statistically significant increases in liver adenomas, carcinomas and combined adenomas/carcinomas in both sexes of CD-1 mice, only at doses which were considered to be excessively high for carcinogenicity testing.

A. Individuals in Attendance at the meetings:

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

Penny Fenner-Crisp \_\_\_\_\_  
Reto Engler \_\_\_\_\_  
William Burnam \_\_\_\_\_  
Marcia Van Gemert \_\_\_\_\_  
Elizabeth Doyle \_\_\_\_\_  
Hugh Pettigrew \_\_\_\_\_  
Esther Rinde \_\_\_\_\_  
Yin Tak Woo \_\_\_\_\_

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

Jess Rowland<sup>1</sup> \_\_\_\_\_  
Clark Swentzel \_\_\_\_\_  
Lori Brunsman \_\_\_\_\_  
Bernice Fisher \_\_\_\_\_  
Lucas Brennecke<sup>2</sup> \_\_\_\_\_  
(PAI/Clement)

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<sup>1</sup>Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

<sup>2</sup>Signature indicates concurrence with pathology report.

## SUMMARY

Administration of Difenoconazole in the diet to CD-1 mice resulted in statistically significant increases in liver adenomas, carcinomas, and adenomas/carcinomas in both sexes only at doses which the Carcinogenicity Peer Review Committee (CPRC) determined to be excessively toxic to the mice, based on liver necrosis and decreases in body weight gains. There was no apparent increase in tumors when Difenoconazole was administered in the diet to Sprague Dawley rats at doses considered to be adequate for carcinogenicity testing. Difenoconazole is a member of a class of chemicals, many of which have been associated with liver tumors in CD-1 mice. Difenoconazole does not appear to have mutagenic activity.

The Committee concluded that the top doses in the mouse study (2500 and 4500) ppm were excessive in both sexes. At 4500 ppm, 11/70 males and all females died within the first 2 weeks of the study. Both sexes exhibited severe liver necrosis at 2500 ppm; there were also decrements in body weight gain  $\geq 10$  at 2500 ppm at 13 weeks both in the sub-chronic study and in the carcinogenicity study. Weight gain decrements were greater in females, however females did not appear to show signs of toxicity. In male mice there was also significant toxicity (including liver necrosis) at 300 ppm. Females at 300 ppm showed neither toxicity nor significant increases in tumor incidence. The remaining doses (10 and 30 ppm) did not have statistically significant increases in liver tumors in either sex. The CPRC noted that there were no doses between 300 and 2500 ppm; because of the excessive toxicity at the highest doses the CPRC concluded that this may not have been an appropriate test. [Details are provided in Section F. "The Weight of Evidence".]

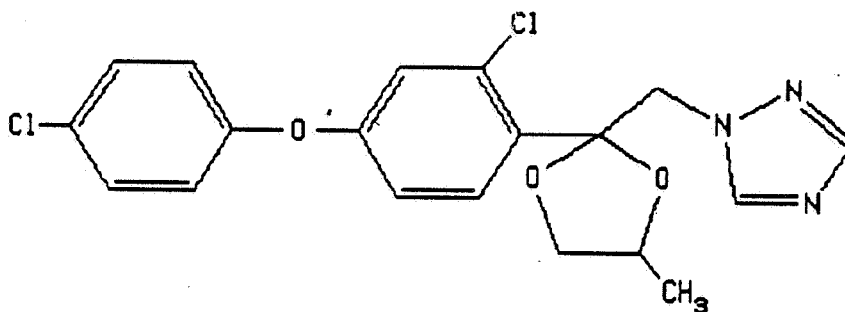
The classification of Difenoconazole as a Group C - possible human carcinogen - was based on the statistically significant increased incidence of liver tumors in both sexes of mice, by both pair-wise and trend analysis, and analogy to other structurally related chemicals with similar activity. However, since the dosing in the mouse study was considered to be excessive, and there was no apparent genotoxicity concern, the CPRC recommended that for the purpose of risk characterization, the Reference Dose [RfD] approach should be used for quantification of human risk.

## B. Materials Reviewed:

The material available for review consisted of Data Evaluation Records and other data summaries prepared by Jess Rowland, and statistical analyses prepared by Lori Brunsman. Also included was a Position Document entitled: "Assessment of the Liver Tumors Observed in CD-1 Mice Fed Excessive Levels of Difenconazole [CGA 169374]: A Mitogenic Response". Submitted by the Registrant, Ciba-Geigy Corporation. The material reviewed is attached to the file copy of this report. Studies were submitted by Ciba-Geigy Corporation.

## C. Background Information

Difenconazole [CGA-169374 Technical]; 1-[2-(2-chloro-4-(4-chlorophenoxy)phenyl)-4-methyl-1,3-dioxolan-2-yl)-methyl]-1H-1,2,4-triazole] is a triazole fungicide. The P.C Code is 128847 and the Caswell Number is 955. The Registrant, Ciba-Geigy, is requesting tolerances allowing import of wheat, barley, and rye grain harvested from Difenconazole treated seed as well as domestic tolerances of this fungicide in straw and forage of wheat and barley. The structure of Difenconazole is provided below:



## D. Evaluation of the carcinogenic potential

### 1. Carcinogenicity Study in Mice:

Reference: Cox, R.H. Oncogenicity Study in Mice. Project Report 483-250. Hazleton Laboratories, Report issued, April 3, 1989. MRID # 420900-15 & 427100-06. HED Document # 009689 & 010588

#### a. Experimental Design

Groups of 60-70 male and 60-70 female Crl:CD-1 mice were fed diets containing difenconazole at 0, 10, 30, 300, 2500 or 4500 ppm [males only] for 78 weeks. The mean daily test article intake was 1.5, 5, 46, 423 and 819 mg/kg/day in males and 2, 6, 58 and 512 mg/kg/day in females, respectively. Ten animals per sex from each group were sacrificed after 52 weeks of treatment. Ten additional animals, allocated to the control, 2500 ppm and 4500 ppm dose groups were kept for a four week recovery period after one year on the study.

b. Discussion of Tumor Data

As shown in Table 1, male mice exhibited significant [ $p < 0.05$ ] increasing trends in hepatocellular adenomas, carcinomas, and combined adenomas/carcinomas. Pair-wise comparison showed a significant [ $p < 0.05$ ] increase in hepatocellular adenomas at 300 ppm [9/56, 16%] when compared to controls [4/68, 6%]. Pair-wise comparison showed significant [ $p < 0.05$ ] increases in hepatocellular adenomas [13/70, 19%] and adenomas/carcinomas combined [16/70, 23%] at 2500 ppm when compared to controls [adenomas: 4/68, 6%; adenomas/ carcinomas combined, 5/68, 7%]. Pair-wise comparison showed significant [ $p < 0.01$ ] increases in adenomas [20/56, 36%], carcinomas [13/56, 23%] and adenomas/ carcinomas combined [28/56, 50%] at 4500 ppm when compared to controls [adenomas: 4/68, 6%; carcinomas, 1/68, 1%; and adenomas/carcinomas combined, 5/68, 7%].

As shown in Table 2, female mice exhibited significant [ $p < 0.01$ ] dose-related increasing trends in hepatocellular adenomas, carcinomas, and adenomas/carcinomas combined. Pair-wise comparison showed a significant increase in hepatocellular adenomas at 2500 ppm [16/59, 27%;  $p < 0.01$ ], carcinomas [4/39, 10%;  $p < 0.05$ ], and adenomas/ carcinomas combined [17/59, 29%;  $p < 0.01$ ] when compared to none of each in the controls.

**Table 1. Hepatocellular Tumor Rates<sup>+</sup> and Peto's Prevalence Test Results in MALE MICE**

| ppm        | 0       | 10    | 30    | 300    | 2500                | 4500                |
|------------|---------|-------|-------|--------|---------------------|---------------------|
| mg/kg/day  | 0       | 1.51  | 4.65  | 46.29  | 423.16              | 818.87              |
| Adenomas   | 4/68    | 10/57 | 8/58  | 9/56   | 13 <sup>a</sup> /70 | 20/56               |
| %          | 6       | 18    | 14    | 16     | 19                  | 36                  |
| p =        | 0.000** | 0.053 | 0.078 | 0.035* | 0.036*              | 0.000**             |
| Carcinomas | 1/68    | 0/57  | 1/58  | 0/56   | 5/70                | 13 <sup>b</sup> /56 |
| %          | 1       | 0     | 2     | 0      | 7                   | 23                  |
| p =        | 0.000** | --    | 0.546 | --     | 0.093               | 0.000**             |
| Combined   | 5/68    | 10/57 | 9/58  | 9/56   | 16 <sup>c</sup> /70 | 28 <sup>c</sup> /56 |
| %          | 7       | 18    | 16    | 16     | 23                  | 50                  |
| p =        | 0.000** | 0.114 | 0.128 | 0.061  | 0.023*              | 0.000**             |

\* No. of tumor bearing animals / No. of animals examined [excluding those that died or were sacrificed before observation of first tumor.

<sup>a</sup> First adenoma observed at week 53, dose 2500 ppm.

<sup>b</sup> First carcinoma observed at week 53, dose 4500 ppm.

<sup>c</sup> Includes animals with more than one tumor type [i.e., adenomas + carcinomas]

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. Hepatocellular Tumor Rates<sup>+</sup>/Exact Trend Test/Fisher's Exact Test Results in FEMALE MICE

|            |         |       |       |       |                     |
|------------|---------|-------|-------|-------|---------------------|
| ppm        | 0       | 10    | 30    | 300   | 2500                |
| mg/kg/day  | 0       | 1.90  | 5.63  | 57.79 | 512.61              |
| Adenomas   | 0/57    | 0/56  | 0/56  | 1/56  | 16 <sup>a</sup> /59 |
| %          | 0       | 0     | 0     | 2     | 27                  |
| p=         | 0.000** | 1.000 | 1.000 | 0.496 | 0.000**             |
| Carcinomas | 0/47    | 0/45  | 1/44  | 0/45  | 4 <sup>b</sup> /39  |
| %          | 0       | 0     | 2     | 0     | 10                  |
| p=         | 0.002** | 1.000 | 0.484 | 1.000 | 0.039*              |
| Combined   | 0/57    | 0/56  | 1/56  | 1/56  | 17 <sup>c</sup> /59 |
| %          | 0       | 0     | 2     | 2     | 29                  |
| p=         | 0.000** | 1.000 | 0.496 | 0.496 | 0.000*              |

\* No. of tumor bearing animals / No. of animals examined [excluding those that died or were sacrificed before observation of first tumors, Week 53 for adenomas and combined, and Week 58 for carcinomas].

<sup>a</sup> First adenoma observed at week 53, dose 2500 ppm.

<sup>b</sup> First carcinoma observed at week 72, dose 2500 ppm.

<sup>c</sup> Includes animals with more than one tumor type [i.e., adenomas + carcinomas]

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 for hepatocellular adenomas and carcinomas observed in Charles River CD-1 mice from 10 studies conducted at the testing laboratory [Hazleton Labs] are presented in Table 3. Historical control data were not available for combined adenomas/carcinomas.

In males, the incidence of hepatocellular adenomas at 300 ppm [9/56, 16%], at 2500 ppm [13/70, 19%] and at 4500 ppm [20/56, 36%] exceeded both the weighted average of the historical control incidences [7.4%] from all studies and the historical control range [2 - 11%]. Hepatocellular carcinomas [13/56; 23%] at the 4500 ppm also exceeded the weighted average of the historical control incidences [3%] from all studies and the historical control range [0 - 8.2%]. The incidence of hepatocellular adenomas and carcinomas in the concurrent untreated males was 6% and 1%, respectively.

In females, the incidence of hepatocellular adenomas [16/59; 27%] at 2500 ppm [HDT] also exceeded the weighted average of the historical control incidences [1.4%] from all studies and the historical control range [0 - 6.1%]. Hepatocellular carcinomas [4/39; 10%] at the HDT exceeded both the weighted average of the historical control incidences [0.6%] from all studies and the historical control range [0 - 2.1%]. No liver tumors were seen in the concurrent untreated females.

**Table 3. Historical Control: Hepatocellular Adenomas and Carcinomas in CD-1 Mice<sup>a</sup>**

| Study Identification    | Adenomas [%] | Carcinomas [%] |
|-------------------------|--------------|----------------|
| <b>MALES</b>            |              |                |
| 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]      |
| <b>Weighted Average</b> | <b>[7.4]</b> | <b>[3.0]</b>   |
| <b>FEMALES</b>          |              |                |
| 5DE                     | 0/40 [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]     |
| <b>Weighted Average</b> | <b>[1.4]</b> | <b>[0.6]</b>   |

<sup>a</sup> Historical control data were obtained from 10 chronic/carcinogenicity studies with Charles River CD-1 mice conducted at Hazleton Laboratories between April 1984 and April 1987. All studies were 78 weeks in duration.



c. Non-neoplastic Lesions

Treatment-related non-neoplastic histopathological changes were confined to the liver and included: necrosis of individual hepatocytes; focal/multifocal necrosis; hepatocellular hypertrophy; inflammation; bile stasis; and fatty changes. These lesions were observed at the interim and terminal sacrifices in males at 300 ppm and above and in the females at 300 and 2500 ppm. Hepatic lesions are summarized below in Table 4.

**Table 4. Non-Neoplastic Lesions in the Liver of Mice fed Difenoconazole.**

| Hepatic Lesions                    | 0 ppm |    | 10 ppm |    | 30 ppm |    | 300 ppm |    | 2500 ppm |      | 4500 ppm |    |
|------------------------------------|-------|----|--------|----|--------|----|---------|----|----------|------|----------|----|
|                                    | M     | F  | M      | F  | M      | F  | M       | F  | M        | F    | M        | F' |
| Sex No. Examined                   | 70    | 60 | 60     | 60 | 60     | 60 | 70      | 70 | 70       | 70   | 70       |    |
| Necrosis of individual hepatocytes | 5     | 3  | 5      | 0  | 2      | 0  | 13*     | 6  | 52**     | 27** | 53**     |    |
| Focal/multifocal necrosis          | 4     | 4  | 2      | 2  | 4      | 0  | 6       | 7  | 11*      | 6    | 16**     |    |
| Hypertrophy                        | 17    | 2  | 16     | 7  | 15     | 2  | 26*     | 7  | 61**     | 53** | 57**     |    |
| Inflammation                       | 18    | 13 | 5      | 13 | 8      | 7  | 12      | 18 | 21       | 12   | 7        |    |
| Bile stasis                        | 1     | 0  | 0      | 0  | 0      | 0  | 3       | 3  | 56**     | 50** | 50**     |    |
| Fatty changes                      | 2     | 0  | 1      | 0  | 0      | 2  | 4       | 2  | 13**     | 9**  | 32**     |    |

# Females were not dosed at this level.

\* =  $P \leq 0.05$ ; \*\* =  $P \leq 0.01$ ; significantly different from the controls.

d. Toxicological Effects

The statistical evaluation of mortality indicated a significant increasing trend in mortality with increasing doses of Difenoconazole in male mice [Table 5]. Females showed no significant incremental changes in mortality with increasing doses of the test compound [Table 6]. At 4500 ppm, 11/70 males and all females died within the first two weeks of the study. Prior to death, clinical signs of toxicity included thinness, hunched posture and rough haircoat in the high-dose females. These signs were also seen with increased incidence throughout the study in both sexes at 2500 ppm and in the remaining males at 4500 ppm. In spite of comparable food consumption, cumulative body weight gain at 13 weeks was approximately 16%, 19% and 64% lower [statistically significant at  $p < 0.05$ ] than the weight gain of the control males at 300, 2500 and 4500 ppm, respectively [Table 7]. At termination, the values for male mice were 12%, 10% and 34% at 300, 2500 and 4500 ppm, respectively. In females, at 13 weeks, reductions in body weight gain were 16% at 300 ppm and 33% at 2500 ppm. At termination, the values were 7% at 300 ppm and 22% at 2500 ppm [Table 7]. Alterations in clinical chemistry were manifested by elevations in alanine aminotransferase, SAP and SDH in males at 2500 and 4500 ppm and in females at 2500 ppm.

Table 5. Mortality Rates<sup>+</sup> In Male Mice and Cox or Generalized K/W Test Results

| Dose<br>(mg/kg/day) | Study Weeks                      |                 |       |                 |                    | Total (%)    |
|---------------------|----------------------------------|-----------------|-------|-----------------|--------------------|--------------|
|                     | 1-52                             | 53 <sup>i</sup> | 53-56 | 57 <sup>i</sup> | 57-80 <sup>f</sup> |              |
| 0                   | 2/70                             | 10/68           | 1/58  | 9/57            | 17/48              | 20/51 (39)** |
| 1.51                | 2/60                             | 10/58           | 0/48  | 0/48            | 16/48              | 18/50 (36)   |
| 4.65                | 2/60                             | 10/58           | 3/48  | 0/45            | 18/45              | 23/50 (46)   |
| 46.29               | 4/60                             | 10/56           | 0/46  | 0/46            | 22/46              | 26/50 (52)   |
| 423.16              | 0/70                             | 10/70           | 0/60  | 10/60           | 16/50              | 16/50 (32)   |
| 818.87              | 13 <sup>#</sup> /69 <sup>a</sup> | 10/56           | 0/46  | 10/46           | 20/36              | 33/49 (67)** |

<sup>+</sup> No. of animals that died during interval / No. of animals alive at the beginning of the interval.

<sup>#</sup> All 13 of these animals died within the first 25 weeks of the study; 11 of 13 died before week 4.

<sup>a</sup> One accidental death at week 39, dose 818.87 mg/kg/day.

<sup>i</sup> Interim sacrifices at weeks 53 and 57.

<sup>f</sup> Final sacrifice at week 79.

Note: Time intervals were selected for display purposes only.

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 6. Mortality Rates<sup>+</sup> In Female Mice and Cox or Generalized K/W Test Results

| Dose<br>(mg/kg/day) | Study Weeks                      |                 |       |                 |                    | Total (%)   |
|---------------------|----------------------------------|-----------------|-------|-----------------|--------------------|-------------|
|                     | 1-52                             | 53 <sup>i</sup> | 53-56 | 57 <sup>i</sup> | 57-81 <sup>f</sup> |             |
| 0                   | 2/59 <sup>a</sup>                | 10/57           | 0/47  | 0/47            | 23/47              | 25/49 (51)  |
| 1.90                | 2/59 <sup>b</sup>                | 10/57           | 1/47  | 0/46            | 11/46              | 14/49 (29)* |
| 5.63                | 3/59 <sup>c</sup>                | 10/56           | 2/46  | 0/44            | 15/44              | 20/49 (41)  |
| 57.79               | 4/60                             | 10/56           | 1/46  | 0/45            | 10/45              | 15/50 (30)  |
| 512.61              | 10 <sup>#</sup> /69 <sup>d</sup> | 10/59           | 10/49 | 10/49           | 10/39              | 20/49 (41)  |

<sup>+</sup> Number of animals that died during interval/Number of animals alive at the beginning of the interval.

<sup>#</sup> All 10 of these animals died within the first 16 weeks of the study; 9 of 10 died before week 4.

<sup>a</sup> One accidental death at week 6, dose 0 mg/kg/day.

<sup>b</sup> One accidental death at week 51, dose 1.90 mg/kg/day.

<sup>c</sup> One accidental death at week 19, dose 5.63 mg/kg/day.

<sup>d</sup> One accidental death at week 7, dose 512.61 mg/kg/day.

<sup>i</sup> Interim sacrifices at weeks 53 and 57.

<sup>f</sup> Final sacrifice at week 79 for all animals except the 10 animals in the 512.61 mg/kg/day dose group that were originally in the control group which were sacrificed at week 81.

Note: Time intervals were selected for display purposes only.

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 7. Selected Cumulative Body Weight Gain [G] in Mice Fed Difenoconazole**

| Study Week | Males      |     |     |      |      |       | Females |      |      |      |      |
|------------|------------|-----|-----|------|------|-------|---------|------|------|------|------|
|            | 0          | 10  | 30  | 300  | 2500 | 4500  | 0       | 10   | 30   | 300  | 2500 |
| ppm        | 0          | 10  | 30  | 300  | 2500 | 4500  | 0       | 10   | 30   | 300  | 2500 |
| 1          | 1.2        | 1.1 | 1.0 | 0.3  | -2.8 | -5.5  | 0.6     | 0.6  | 0.7  | 0.3  | -4.4 |
| 4          | <u>3.2</u> | 3.2 | 3.1 | 1.9* | 0.9* | -1.3* | 2.6     | 2.7  | 2.5  | 2.1  | 0.9* |
| 8          | 4.4        | 4.6 | 4.5 | 4.0  | 2.9* | -0.1* | 4.7     | 4.2  | 4.5  | 4.3  | 2.9* |
| 13         | 5.8        | 5.8 | 5.6 | 4.9* | 4.7* | 2.1*  | 5.8     | 5.4  | 5.8  | 4.9* | 3.9* |
| 40         | 8.3        | 8.8 | 7.9 | 6.7* | 6.3* | 5.5*  | 8.6     | 8.1  | 8.3  | 8.4  | 6.5* |
| 52         | 8.5        | 8.9 | 8.1 | 7.2* | 6.7* | 5.8*  | 10.0    | 9.2  | 9.8  | 9.2  | 7.7* |
| 60         | 8.8        | 9.1 | 9.3 | 7.8  | 7.5  | 7.1   | 10.3    | 9.9  | 10.0 | 10.5 | 8.1  |
| 76         | 8.5        | 9.0 | 8.0 | 7.5  | 7.7  | 5.6*  | 11.6    | 11.0 | 10.2 | 10.8 | 9.0* |

\* Significantly different from control at  $p \leq 0.05$

e. Adequacy of Dosing for Assessment of Carcinogenic Potential

The highest dose tested [2500 ppm in females and 4500 ppm in males] induced **toxicological** [mortality,  $\geq 10\%$  reductions in body weight/body weight gain and clinical signs], **pharmacological** [changes in liver enzymes indicative of liver damage], and **histopathological** [non-neoplastic and neoplastic hepatic lesions] changes in both sexes of mice. However, this dose appears to be excessively high for carcinogenicity testing due to severe body weight decreases and liver necrosis in both sexes, and that the 4500 ppm dose tested in female mice was excessive due to the high mortality rate.

2. Chronic Toxicity/Carcinogenicity Study in Rats:

Reference: Cox, R.H. Combined Chronic Toxicity and Oncogenicity Study of CGA 169374 Technical in Rats. Project Report 483-249. Hazleton Laboratories, Report issued, March 31, 1989. MRID # 420900-19 & 427100-10. HED Document # 009689 & 010588.

a. Experimental Design

Groups of 80 male and 80 female Sprague-Dawley rats were fed diets containing Difenconazole at 0, 10, 20, 500 or 2500 ppm for 104 weeks. The mean daily test article intake was 0.48, 0.96, 24.1 and 124 mg/kg/day in males and 0.64, 1.27, 32.8 and 170 mg/kg/day in females, respectively. Ten animals per sex from each group and were sacrificed after 52 weeks of treatment. Ten additional animals, allocated to the control and 2500 ppm dose groups were kept for a four weeks recovery period after one year on the study.

b. Discussion of Tumor Data

Difenconazole did not increase the neoplastic lesions commonly seen in this strain/age of rats. Statistical analyses of tumor data showed no significant treatment-related or dose-related tumors in either sex of rats.

c. Non-neoplastic Lesions

As shown in Table 8, treatment-related non-neoplastic histopathological changes were limited to an increased incidence of hepatocytic hypertrophy [centrilobular to diffuse to focal/multifocal] in both sexes at 500 and 2500 ppm. The lesions were characterized by the presence of lightly stained enlarged hepatocytes with poorly distinguishable cell borders.

**Table 8. Non-Neoplastic Lesions in the Liver of Rats fed Difenconazole.**

| Hepatic Lesions                  | 0 ppm     |          | 10 ppm   |          | 20 ppm    |          | 500 ppm    |            | 2500 ppm   |            |
|----------------------------------|-----------|----------|----------|----------|-----------|----------|------------|------------|------------|------------|
|                                  | M         | F        | M        | F        | M         | F        | M          | F          | M          | F          |
| No. Examined:<br>70/Dose         |           |          |          |          |           |          |            |            |            |            |
| Hepatocytic #<br>hypertrophy [%] | 7<br>[10] | 4<br>[6] | 5<br>[7] | 0<br>[0] | 8<br>[11] | 0<br>[0] | 29<br>[41] | 17<br>[24] | 39<br>[56] | 36<br>[51] |

d. Toxicological Effects

Treatment caused no adverse effect on survival. Over the first year of treatment, body weight gain of the 500 and 2500 ppm groups was 94% and 80% of the control values in males and 90% and 59% in the females [statistical significance at  $p < 0.05$ ], respectively. The mean body weights of the rats at 2500 ppm remained consistently below the control values reaching 89% of the control values in the males and 63% in the females, respectively at termination [Table 9]. The only remarkable changes seen in clinical chemistry parameters were consistently [at Weeks 28, 53, 79 and 105] increased albumin and decreased globulin concentrations in the males at 2500 ppm which resulted in an increased albumin/globulin ratio. At both the interim and terminal sacrifices, absolute and relative liver weights were elevated at 2500 ppm. After 52 weeks of treatment, the liver-to-body weight ratio amounted to 114% of the control value in males and 148% in females, respectively. The values were in the same range at terminal sacrifice.

Table 9. Selected Cumulative Body Weight Gain [G] in Rats Fed Difenoconazole

| Study Week | Males |     |     |      |      | Females |     |     |     |      |      |
|------------|-------|-----|-----|------|------|---------|-----|-----|-----|------|------|
|            | ppm   | 0   | 10  | 20   | 500  | 2500    | 0   | 10  | 20  | 500  | 2500 |
| 1          |       | 52  | 49  | 49   | 47   | 25      | 20  | 19  | 20  | 18   | 6    |
| 4          |       | 160 | 152 | 147  | 143  | 116     | 61  | 61  | 62  | 55   | 38   |
| 8          |       | 237 | 225 | 225  | 222  | 183     | 93  | 91  | 91  | 84   | 62   |
| 13         |       | 287 | 276 | 272* | 265* | 222*    | 115 | 113 | 115 | 104* | 77*  |
| 40         |       | 399 | 393 | 391  | 374* | 321     | 196 | 201 | 205 | 189  | 128  |
| 52         |       | 423 | 417 | 416  | 398* | 339*    | 232 | 234 | 237 | 209* | 139* |
| 60         |       | 425 | 417 | 415  | 407  | 349     | 242 | 237 | 239 | 219  | 141  |
| 76         |       | 410 | 405 | 398  | 397  | 350     | 252 | 262 | 254 | 237  | 159  |
| 88         |       | 395 | 379 | 377  | 394  | 345     | 256 | 269 | 259 | 239  | 158  |
| 104        |       | 332 | 340 | 352  | 359  | 294*    | 251 | 270 | 269 | 238  | 158* |

\* Significantly different from control at  $p \leq 0.05$

e. Adequacy of Dosing for Assessment of Carcinogenic Potential

The highest dose tested [2500 ppm] induced **toxicological** [ $\geq 10\%$  reductions in body weight/body weight gain], **pharmacological** [liver effects indicative of enhanced functional load], and **histopathological** [non-neoplastic hepatic lesions] changes. Therefore, it is concluded that the dose levels employed in this study were adequate to assess the chronic toxicity and the carcinogenicity potential of Difenoconazole in rats.

## E. Additional Toxicology Data on Difenconazole

### 1. Metabolism

Reference: Absorption, Distribution and Metabolism Studies in Rats with Difenconazole.  
MRID # 420900-28/29/30/31; 427100-13/14; HED Document # 009689 & 010588

The biotransformation of Difenconazole is shown in Figure 1. The compound undergoes successive oxidation and conjugation reactions. One of its metabolites, CGA-205375, accounts for 6-24% of the applied dose and is found only in urine and feces of oral high-dose (300 mg/kg) rats. The presence of this intermediate in excreta of only high-dose rats, suggests that its rate of further biotransformation has reached saturation at the high dose. Additionally, excretion of radioactivity in bile, feces and urine of rats orally dosed with [<sup>14</sup>C]-difenconazole is consistent with saturation g.i. absorption of the chemical at 300 mg/kg.

### 2. Mutagenicity

Reference: Mutagenicity Studies with Difenconazole.  
MRID # 420900-25; 427100-11 & 427100-12 HED Document # 09689 & 010588

Difenconazole was nonmutagenic with or without metabolic activation, when tested at concentrations ranging from 340 to 5447 µg/plate in two independently performed microbial/mammalian microsome plate incorporation assays using *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2uvrA. In an *in vivo*, micronucleus assay, no increase in micronucleated polychromatic erythrocyte counts were seen in the bone marrow cells of mice given oral administration of difenconazole at 0, 400, 800 or 1600 mg/kg/day. Difenconazole was negative in an *in vitro* UDS assay with primary rat hepatocytes at concentrations up to 50.0 µg/mL.

### 3. Subchronic and Chronic Toxicity

Reference: 13-Week Feeding Study in Mice. MRID# 420900-21; HED Document # 009689

In a subchronic toxicity study CD-1 mice [15/sex/dose] were fed diets containing Difenconazole at 0, 20, 200, 2500, 7500 or 15,000 ppm for 13 weeks. These levels were equivalent to approximately 0, 3, 30, 375, 1125 or 2250 mg/kg/day, respectively. All but 2 mice fed 7500 ppm and all mice fed 15,000 ppm died during the first three weeks of the study. Clinical signs seen prior to death were thinness, hunched posture, languidness and tremors. At 2500 ppm, the cumulative body weight gains were decreased by 9% for males and 41% for females and the absolute and relative liver weights were significantly increased in both sexes. Histopathology revealed erosion/ulceration of the glandular stomach and hyperkeratosis of the non-glandular stomach as well as diffused hepatocellular enlargement and necrosis in many of the mice that died. Histopathology showed hypertrophic and cytotoxic changes in the liver at feeding levels ≥ 2500 ppm; hepatocellular enlargement was seen in all mice [10/sex] while vacuolation was seen in 7 males and 7 females at 2500 ppm. Results indicate that the MTD is lower than 2500 ppm. A LOEL of 200 ppm [30 mg/kg/day] was based on mortality, reductions in body weight gain, and histopathologic alterations in the liver. The NOEL was 20 ppm [3 mg/kg/day].

Reference: 13-Week Feeding Study in Rats; MRID # 420900-22; HED Document # 009689

In a subchronic toxicity study Sprague-Dawley rats [15/sex/dose] were fed diets containing Difenoconazole at 0, 20, 200, 750, 1500 or 3000 ppm for 13 weeks. These levels were equivalent to 0, 1.23, 11.3, 47.8, 99.3, and 189 mg/kg/day in males and 0, 1.43, 15.5, 61.8, 124 and 194 mg/kg/day in females, respectively. The body weight gains were significantly reduced in males at 3000 ppm and in females at 200 ppm and above. At the high dose, the overall body weight gain amounted to 85% of the control value in males and 62% in females, respectively. The absolute and relative liver weights were significantly increased in males at 750 and above and in females at 200 ppm and above. Although no changes in key liver marker enzymes were observed, histopathology revealed a dose-related increased incidence of diffuse hepatocellular enlargement in both sexes treated at 1500 ppm and above. Results indicate that the MTD was exceeded at 3000 ppm due to severe depression in body weight gain. A LOEL of 200 ppm [11.3 mg/kg/day in males and 15.5 mg/kg/day in females] was based on reductions in body weight gain and increased liver weights. The NOEL was 20 ppm [1.23 mg/kg/day in males and 1.43 mg/kg/day in females].

Reference: 52-Week Feeding Study in Dogs.  
MRID #420900-14 & 427100-05 HED Document # 009689 & 010588

In a chronic toxicity study, beagle dogs [4/sex/dose] were fed diets containing Difenoconazole at 0, 20, 100, 500 or 1500 ppm for 52 weeks. These levels were equivalent to 0, 0.71, 3.4, 16.4 or 51.2 mg/kg/day in males and 0, 0.63, 3.7, 19.4 or 44.3 mg/kg/day in females, respectively. The body weight gain was consistently diminished in females at 500 and 1500 ppm; at termination the body weight gain was 60% and 69% of the control values, respectively. No reductions in body weight gain were seen in male dogs at any dose level. Male dogs exhibited dose-related increases in serum alkaline phosphatase activity on Days 85, 175 and 359 with the increase reaching statistical significance at the high dose. No treatment-related histopathologic changes were seen. A LOEL of 500 ppm [16.4 mg/kg/day in males and 19.4 mg/kg/day in females] was based on reductions in body weight gain. The NOEL is 100 ppm [3.4 mg/kg/day in males and 3.7 mg/kg/day in females]

Reference: 78-Week Feeding Study in Mice.  
MRID # 420900-15 & 427100-06. HED Document # 009689 & 010588

In a carcinogenicity study [discussed in detail on Page 8], CD-1 mice [60-70/sex/dose] were fed diets containing Difenoconazole at 0, 10, 30, 300, 2500 or 4500 ppm [males only] for 78 weeks. The systemic LOEL of 300 ppm [46.29 mg/kg/day in males and 57.79 mg/kg/day in females] was based on reductions in cumulative body weight gain. The NOEL was 30 ppm [4.65 mg/kg/day in males and 5.63 mg/kg/day in females].



Reference: 104-Week Feeding Study in Rats.  
MRID # 420900-15 & 427100-06. HED Document # 009689 & 010588

In a chronic toxicity/carcinogenicity study [discussed in detail on Page 13], Sprague-Dawley rats were fed diets containing difenoconazole at 0, 10, 20, 500 or 2500 ppm for 104 weeks. The systemic LOEL of 500 ppm [24.12 mg/kg/day in males and 32.79 mg/kg/day in females] was based on reductions in cumulative body weight gain. The NOEL was 20 ppm [0.96 mg/kg/day in males and 1.27 mg/kg/day in females].

#### 4. Registrant's Rebuttal Concerning Carcinogenicity of Difenconazole in Mice.

Reference: Position Document entitled: "Assessment of the Liver Tumors Observed in CD-1 Mice Fed Excessive Levels of Difenconazole [CGA 169374]: A Mitogenic Response". Submitted by Ciba-Geigy Corporation. MRID # 429728-03

The Registrant contends that the carcinogenic response was noted 1) at excessive dietary levels where the hepatocytotoxic maximum tolerated dose was exceeded; 2) liver tumors were accompanied by a clear sequela of non-neoplastic changes which clearly support a hepatotrophic effect; and 3) liver damage is most likely to result in mitogenesis [cell replication] in the liver. The Registrant, therefore, asserts that the liver tumors observed in the mouse study are not germane to the toxicological assessment of human exposure to difenoconazole.

The weight of evidence for a mitogenic response is as follows:

- o Subchronic studies in mice, rats, and dogs showed that difenoconazole is well tolerated at relatively high dietary levels [greater than 50 mg/kg/day selectively results in hepatocyte damage];
- o In rats and dogs, liver damage is manifested by liver enlargement, hepatocyte hypertrophy and elevation of key liver marker enzymes. These may be described as adaptive reactions of the liver and reflect functional overload of this organ at high levels. These changes were reversible and there were no corroborative histopathological changes in the liver in these species.
- o Similar to rats and dogs, liver was the target organ in mice. Mouse liver exhibited the same pattern of liver enlargement, hepatocyte hypertrophy, elevation of liver marker enzyme. But, these alterations were corroborated with a clear profile of liver pathology characterized by necrosis, fatty infiltration, and vacuolation.
- o The cross-species hepatotrophic and hepatotoxic effects can partially be explained by the fact that Difenconazole is a mixed phenobarbital-type and steroidal microsomal enzyme inducing agent. A similar profile of cellular hypertrophy accompanied by cytotoxicity is seen with other hepatic enzyme inducing agents

- o In the absence of specific cell proliferation studies, to determine an association exists between the degenerative process and the presence of a tumor, odds ratios were calculated. The odds ratios expressed the increased likelihood of tumor presence when a specific degenerative process was present. As shown below, a clear association was seen between the formation of liver tumors and the *a priori* cytotoxic event. Therefore, the tumor response can be ascribed to a mitogenic error that results from the homeostatic regeneration of hepatocytes to replace damaged tissue. The odds ratio showing the likelihood of tumor presence when a specific degenerative process is present below:

| Degenerative Process | Odds Ratio | P-Value | 95% Confidence Bounds |             |
|----------------------|------------|---------|-----------------------|-------------|
|                      |            |         | Lower Bound           | Upper Bound |
| Necrosis             | 1.862*     | 0.002   | 1.251                 | 2.773       |
| Inflammation         | 0.749      | 0.320   | 0.418                 | 1.343       |
| Hypertrophy          | 2.023**    | 0.001   | 1.318                 | 3.105       |
| Fatty Changes        | 2.438**    | <0.001  | 1.621                 | 3.665       |
| Bile Stasis          | 2.752**    | <0.001  | 1.865                 | 4.060       |

\* Significantly different from the control at  $P \leq 0.05$

\*\* Significantly different from the control at  $P \leq 0.01$

- o Metabolism data provide evidence that Difenoconazole is absorbed from the intestinal tract, is rapidly metabolized and is quickly eliminated. No accumulation of the compound in individual tissues or animal products has been detected.
- o No evidence of mutagenicity was seen in a battery of tests which covered different endpoints in procaryotes an eucaryotes *in vivo* and *in vitro*.

## 5. Structure-Activity Relationships

Difenoconazole is structurally related to Azaconazole, Baycor, Bayleton, Baytan, Cyproconazole, Etaconazole, Fenbuconazole, Hexaconazole, Propiconazole, Tebuconazole, and Uniconazole. The structural formulas of these compounds are shown in Table 10. The tumor types and cancer classifications of these compounds are provided below:

**Azaconazole:** 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.

**Baycor:** Non carcinogenic in male and female mice and male and female rats at doses up to and including 500 ppm.

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

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

**Cyproconazole:** Group B2 carcinogen; based on hepatocellular adenomas and carcinomas in male and female CD-1 mice and the absence of an acceptable carcinogenicity in rats.

**Etaconazole:** No classification; increased the incidence of liver adenomas and carcinomas; registration voluntarily withdrawn.

**Fenbuconazole:** Group C (Q) carcinogen; based on thyroid follicular cell adenomas and/or combined adenomas/carcinomas in male Sprague-Dawley rats in two studies. Increased incidence of hepatocellular adenomas and/or carcinomas in CD-1 mice fed inadequate doses.

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

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

**Tebuconazole:** Group C (nq) carcinogen; based on hepatocellular adenomas, carcinomas, and combined adenomas/carcinomas in both sexes of NMRI mice.

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

## F. Weight of Evidence Considerations

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

1. Male and female CD-1 mice were fed diets containing Difenconazole at 0, 10, 30, 300, 2500 or 4500 ppm for 78 weeks. The highest dose tested, 4500 ppm was determined to be excessively high for carcinogenicity testing due to high mortality where 11/70 males and all females died within the first two weeks of the study. The next lower dose, 2500 ppm, was also determined to be too high for carcinogenicity testing due to severe reductions [statistically significant] in body weight gain by week 13 in both sexes. At 13 weeks, treated males and females exhibited a 16% and 33%, respectively, lower body weight gain compared to that of the weight gain of the control animals. In addition, histopathology revealed statistically increased incidences of liver necrosis in both sexes of mice at this dose. **Because of the excessive dosing in this study, the relevance to carcinogenicity in humans of the tumors occurring at these doses [2500 and 4500 ppm] was questioned by the Committee.** The next lower dose [300 ppm] was considered to be an adequate dose to assess carcinogenicity in male mice but not in female mice. This was based on the fact that while males exhibited body weight loss as well as liver necrosis, females exhibited only body weight loss without any other toxicological effects.

In male mice, there was a significant [ $p=0.000$ ] increasing trend in hepatocellular adenomas, carcinomas, and combined adenomas/carcinomas. At 300 ppm, hepatocellular adenomas [16%] were significantly [ $p=0.035$ ] increased when compared to controls [6%]. At 2500 ppm, hepatocellular adenomas [19%;  $p=0.036$ ] and combined adenomas/carcinomas [23%;  $p=0.023$ ] were significantly increased when compared to controls [adenomas: 6%; combined adenomas/carcinomas: 7%]. At 4500 ppm, adenomas [36%], carcinomas [23%] and combined adenomas/carcinomas [50%] were significantly [ $p < 0.000$ ] increased when compared to controls [adenomas: 6%; carcinomas: 1%; and combined adenomas/carcinomas: 7%]. In addition, there was a statistically significant positive trend [ $p = 0.000$ ] for adenomas, carcinomas, and adenomas/carcinomas.

In female mice, there was a significant [ $p < 0.01$ ] dose-related increasing trend in hepatocellular adenomas, carcinomas, and combined adenomas/carcinomas. At 2500 ppm, hepatocellular adenomas [27%;  $p=0.000$ ], carcinomas [10%;  $p=0.039$ ], and combined adenomas/carcinomas [29%;  $p=0.000$ ] when compared to none in the controls. In addition, there was a statistically significant positive trend [ $p = 0.000$ ] for adenomas, carcinomas, and adenomas/carcinomas.

2. When compared to historical control data, in male mice, the dose-related increases in the incidence of hepatocellular adenomas [16% at 300 ppm, 19% at 2500 ppm and 36% at 4500 ppm] exceeded the concurrent controls [6%] as well as both the weighted average of the historical control incidence [7.4%] and the historical control range [0 - 11%]. Similarly, hepatocellular carcinomas [10%] at the HDT also exceeded the concurrent controls [1%] as well as the weighted average of the historical control incidence [3%] and the historical control range [0 - 8.2%].

3. When compared to historical control data, in female mice, the incidence of hepatocellular adenomas [27%] at the HDT exceeded the concurrent controls [0%] and the weighted average of the historical control incidence [1.4%] and the historical control range [0 - 6.1%]. Similarly, hepatocellular carcinomas [29%] at the HDT exceeded the concurrent controls [0%] and both the weighted average of the historical control incidence [0.6%] and the historical control range [0 - 2.1%].
4. Difenoconazole has been shown to be nonmutagenic both *in vivo* and *in vitro*. It was negative for gene mutations in a *Salmonella*/microsomal assay, did not cause an increase in micronucleated polychromatic erythrocytes in a mouse micronucleus assay, and was negative in an UDS assay with primary rat hepatocytes.
5. Difenoconazole is structurally related to other triazole pesticides such as Cyproconazole, Fenbuconazole, Propiconazole, Tebuconazole, and Uniconazole] known to have induced hepatocellular adenomas, carcinomas, and/or adenomas and carcinomas combined in several strains [CD-1, Swiss, NMRI, and CF1-W74] mice. An other analog, Bayleton, induced thyroid follicular tumors in rats.
6. Carcinogenicity in animals -- Difenoconazole

After a full evaluation of all of the data and supporting information regarding animal carcinogenicity, the Committee concludes that exposure to Difenoconazole resulted in an increased incidence of adenomas, carcinomas and combined adenomas/carcinomas in mice. Although there is some question about the relevance of these tumors, since they occurred only at doses considered to be excessively toxic to the mice, the increased tumor incidences support the finding that Difenoconazole is an animal carcinogen. The relevance of the tumor data to an evaluation of Difenoconazole's potential for human carcinogenicity is discussed elsewhere in this report.

**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 Difenoconazole should be classified as a Group C - possible human carcinogen and that the RfD approach should be used for quantitation of human risk. This decision was based on increases in liver adenomas, carcinomas and combined adenomas/carcinomas in both sexes of CD-1 mice, which occurred only at doses considered to be excessively high for carcinogenicity testing. There was no apparent increase in tumors in Sprague Dawley rats and Difenoconazole does not appear to have mutagenic activity. Difenoconazole is a member of a class of chemicals, many of which have been associated with liver tumors in CD-1 mice.

The Committee concluded that the mouse study may not have been an appropriate test, due to the excessive toxicity in both sexes at the two top doses (4500 and 2500 ppm); there were also no doses between 2500 ppm and 300 ppm. The 300 ppm dose was considered adequate for assessing carcinogenicity in male, but not in female mice.

Table 10. Structurally Related Triazole Pesticides.

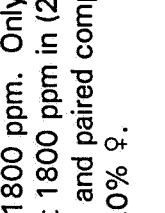
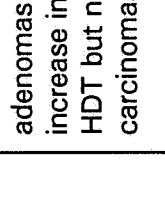
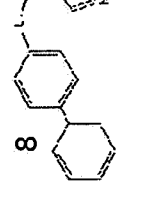
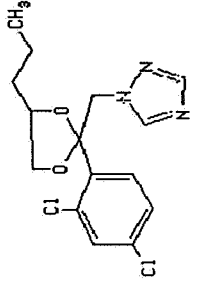
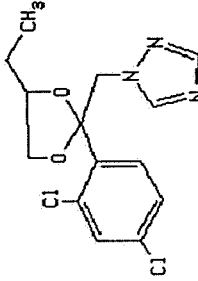
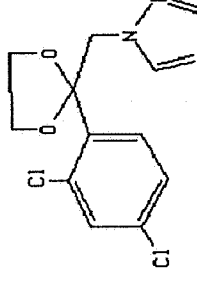
| Compound  | Structure   | Carcinogenic Effect   | Carcinogen Classification                            |
|---|---|---|--|
| <p>Bayleton<br/>                     PC Code 109901<br/>                     Tox. Chem. # 862AA</p> |      | <p>NMRI Mouse, 50, 300, &amp; 1800 ppm. Only hepatocellular adenoma,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

Table 10. Structurally Related Triazole Pesticides (Continued)

| Compound   | Structure   | Carcinogenic Effect  | Carcinogen Classification |
|--|---|--|---------------------------|
| <p><b>Propiconazole</b><br/>                     PC Code: 122101<br/>                     Tox. Chem. # 323EE</p> |    | <p><b>CD-1 Mouse, 100, 500 &amp; 2500 ppm.</b> Statistically significant trend and pairwise comparisons in liver adenomas and combined at 2500 ppm. For carcinomas only there were statistically significant trend and pairwise comparisons at the HDT for data from 2 of 3 pathologists; for the data from the third pathologist only the trend was significant (<math>p=0.028</math>), the pairwise comparison HDT vs. control had a <math>p = 0.050</math>.</p> | <p><b>C NO</b></p>        |
| <p><b>Etaconazole</b><br/>                     PC: None</p>  |    | <p><b>Swiss Mouse</b> increased incidence of liver adenomas and carcinomas in both sexes. Registration voluntarily withdrawn.</p>  | <p>None</p>               |
| <p><b>Azaconazole</b><br/>                     PC Code: 128882<br/>                     Tox. Chem. # 321A</p>    |  | <p><b>Mouse, 25,100 &amp; 400 ppm.</b> There is the question of whether the MTD was reached. No carcinogenicity effect.</p>  |                           |



**Table 10. Structurally Related Triazole Pesticides (Continued).**

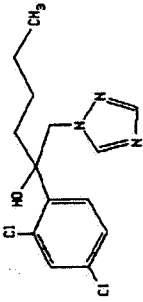
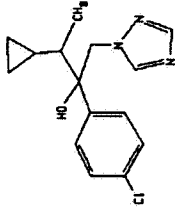
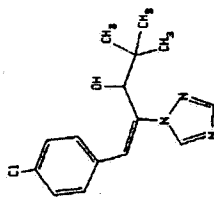
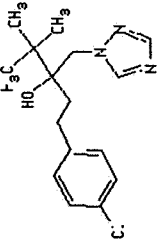
| Compound  | Structure   | Carcinogenic Effect  | Carcinogen Classification       |
|---|---|--|---------------------------------|
| <p><b>Hexaconazole</b><br/>PC Code: 128925<br/>Tox. Chem.#<br/>480G</p>   |    | <p><b>CD-1/Alpk Mouse, 5, 40 &amp; 200 ppm.</b> No carcinogenicity effect. Should be evaluated with caution since an MTD was not reached.<br/><b>ALpk:APfSD (Wistar derived) Rats, 10, 100, 1000 ppm.</b> There was a significant (<math>p &lt; 0.01</math>) 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 HDT (16%) exceeded historical control values of up to 6.0%</p> | <p>C Q (Based on rat Study)</p> |
| <p><b>Cyproconazole</b><br/>PC Code: 128993<br/>Tox. Chem. #<br/>272E</p> |   | <p><b>CD-1 Mouse, 5, 15, 100 &amp; 200 ppm.</b> Significant incidence of adenomas &amp; carcinomas at the MDT and HDT in males and at the HDT in females.</p>  | <p>B2</p>                       |
| <p><b>Uniconazole</b><br/>PC Code: 128976<br/>Tox. Chem. #<br/>207H</p>   |  | <p><b>CrI:CD-1(ICR)BR Mouse, 10, 40, 200 &amp; 1500 ppm.</b> Increased incidence of hepatocellular adenomas &amp; carcinomas in 1500 ppm males only.<br/><b>CrI:CD-1(ICR)SD Rat, 10, 40 200 &amp; 1000 ppm.</b><br/>No increase in neoplastic findings.</p>  | <p>C No Q</p>                   |

Table 10. Structurally Related Triazole Pesticides (Continued).

| <i>Compound</i>  | <i>Structure</i>  | <i>Carcinogenic Effect</i>  | <i>Carcinogen Classification</i> |
|--|---|---|----------------------------------|
| Tebuconazole<br>PC Code:<br>Tox. Chem. #<br># 463P       |  | NIMRI Mice, 0, 500 & 1500 ppm. Increased incidence of hepatocellular adenomas, carcinomas, and combined adenomas/ carcinomas at HDT | C NQ                             |
| Fenbuconazole<br>PC Code: 129011<br>Tox. Chem. #<br>723Q |   | Sprague-Dawley rat, 0, 8, 80, 800, 1600 ppm. Thyroid follicular cell adenomas and/or carcinomas in male rats in two studies.        | C Q                              |