

SUMMARY

Doses tested

0, 10, 30, 300, 2500, 4500 ppm

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.

**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.



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

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