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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Cyproconazole (Third Meeting): Reclassification from a Group C with Quantitation to a Group B_2 Carcinogen

TO: Carl Grable
Product Manager (21)
Registration Division (H7505C)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 11/12/92
Toxicology Branch II, Section II
Health Effects Division (H7509C)

Decision from the Third HED Carcinogenicity Peer Review of Cyproconazole

The HED Carcinogenicity Peer Review Committee (CPRC) met on October 21, 1992, and the decision was made to change the classification of Cyproconazole with respect to its carcinogenicity potential from a Group C carcinogen with quantitation to a Group B_2 carcinogen. The CPRC considered the absence of an adequate carcinogenicity study in rats and the structural relationship of Cyproconazole to closely related analogues shown to have carcinogenic activity as adequate justification for this decision. Previous considerations of the CPRC, as well as numerous deliberations between HED and the registrant regarding the inadequacy of the rat study, are discussed below.

A. Individuals in Attendance:

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

Karl Baetcke Karl D. Baetcke

William L. Burnam William L Burnam

Marcia Van Gemert Marcia Van Gemert

Kerry Dearfield Kerry O'Dearfield

Esther Rinde Esther Rinde

William Sette

Yin-Tak Woo

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

Linda Taylor[1]

Clark Swentzel

Lori Brunsman

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

Reto Engler

Marion Copley

Julie Du

George Ghali

Richard Hill

Jean Parker

Hugh Pettigrew

John Quest

4. Other Attendees:

Bernice Fisher

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

B. Background

Cyproconazole,[α-(chlorophenyl)-α-(1-cyclopropylethyl)-1H-4-1,2,triazole-1-ethanol], is a turf fungicide manufactured by Sandoz Crop Protection Corporation proposed for use on golf courses and sod farms. **Caswell No.** 272E; **PC No.** 128993.

C. Initial Carcinogenicity Peer Review Committee Meeting

The first CPRC met on June 20, 1990 and classified Cyproconazole as a Group C carcinogen with a Q_1*, based on the increased incidence of liver adenomas and carcinomas in both sexes of treated mice. The CPRC further concluded that the high-dose level used in the rat carcinogenicity bioassay was not adequate as evidenced by the lack of any biologically significant inhibition of body-weight gain, the absence of any histopathological changes accompanying the increase in relative liver weight, and the lack of any increase in the liver enzyme activity in females and the inconsistency of such change in the high-dose males. It was recommended that the carcinogenic phase of the rat study be repeated. Because of the lack of a complete data base, reconsideration and final determination of the cancer classification was subject to the evaluation of the results of the repeat study.

D. Second Carcinogenicity Peer Review Committee Meeting

The Registrant responded to the first CPRC by objecting to quantitation of the cancer potency by the use of the linearized multistage model, requesting a reconsideration by the CPRC with respect to cytotoxicity in the mouse liver. Additionally, arguments were submitted with respect to the adequacy of the dose levels used in the rat study. The CPRC was not persuaded by the arguments/issues submitted and reiterated its original conclusions that Cyproconazole be classified a Group C carcinogen with a Q_1* and that the carcinogenic phase of the rat study be repeated (second CPRC meeting on Cyproconazole, January 15, 1992).

Following the second CPRC decision, the Registrant submitted a "comprehensive summary of arguments" as to why the rat study should not be repeated, including a statistical analysis designed to test the hypothesis that at some higher but presumedly adequate dose (than that used in the rat study), a significant increase in tumors would have occurred in the rat but that a cancer potency estimate no greater than that estimated from the mouse data would result. This analysis was assessed by HED's Senior Science Advisor, who concurred with the Registrant in that a postulated tumor response in the rat at doses above 350 ppm would not alter the **quantitative** risk (i.e., Q_1*) assessment for Cyproconazole. "In fact it seems that the rat would appear to be at least 10-fold less

sensitive to the induction of tumors than the mouse" (memo, Engler to Swentzel, dated 9/21/92). The Registrant is no longer arguing against quantitation of risk but, as of October 21, 1992, remains unwilling to repeat the rat study.

E. Third Carcinogenicity Peer Review Committee Meeting

The CPRC met for a third time on Cyproconazole (October 21, 1992) to consider the statistical analyses performed by the Registrant and the HED Senior Science Advisor and concurred with the assessment that the estimation of carcinogenic potency would most likely not be increased were biologically significant tumors to be observed in a repeat rat carcinogenicity study. Moreover, it was emphasized that were tumors to be observed in a repeat rat carcinogenicity study, Cyproconazole would be reclassified as a Group B_2 carcinogen.

F. Precedent

The decision of the CPRC during the third Peer Review of Cyproconazole is consistent with the classification change made during the third Peer Review of Verdict (memorandum, Quest to Schnaubelt, September 18, 1989). Verdict also induced liver tumors in mice and it has structural similarity to other herbicides known to produce liver tumors in mice and in some cases, rats. The dosages in the rat carcinogenicity study on Verdict also were considered inadequate. In the absence of an adequate rat study as a critical part of the data base, the classification of Verdict was changed from a Group C carcinogen with quantitation to a Group B_2 carcinogen. This precedent was discussed during the third Peer Review of Cyproconazole.

G. Conclusions and Recommendations

The Peer Review Committee considered the information received from the Registrant and reached the following consensus opinions:

1. Cyproconazole should be reclassified as a Group B_2 (probable human) carcinogen. This reclassification from a Group C (possible human) carcinogen was based upon the demonstration of liver tumors in both sexes of mice administered adequate doses of Cyproconazole, the possible clastogenic activity of Cyproconazole, tumors in mice administered structurally-related analogues from the same chemical class (e.g., Propiconazole, Bayleton, Uniconazole, and Etaconazole), tumors in rats administered structurally-related chemical analogues (e.g., Hexaconazole and Etaconazole), and the lack of an adequate rat carcinogenicity study to show that it does not possess the carcinogenic potential of these analogues.

Since the first CPRC in 1990, which recommended Group C with a Q_1^* and a repeat of the carcinogenicity phase of the rat study, the Registrant has made it clear that they do not intend to repeat the rat study. Therefore, HED's only option is to assume, for the reasons stated above, a positive response in the rat study, thereby supporting the re-classification of the compound to a Group B_2 carcinogen.

2. The unit risk (Q_1^*) value of 3.0×10^{-1} $(mg/kg/day)^{-1}$ would continue to be derived from liver tumor data obtained in male mice. Thus, the reclassification of Cyproconazole to Group B_2 because of the probability that it will induce tumors in rats would <u>not</u> alter the **quantitative** dose-response assessment.

3. The Registrant could elect to perform a repeat rat carcinogenicity study in an effort to demonstrate that Cyproconazole does not induce a carcinogenic response in rats. Under those circumstances, assuming that the study was judged to be adequate, the CPRC would revise the carcinogenicity classification to a Group C carcinogen with a Q_1^*.