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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Difenoconazole

CASRN. 119446-68-3
EPA Chem. Code: 128847
Caswell No. 955

FROM: George Z. Ghali, Ph.D. G. Ghali
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (H7509C)

TO: Cynthia Giles-Parker, PM 22
Fungicide-Herbicide Branch
Registration Division (H7505C)

The Health Effects Division RfD/Peer Review Committee met on January 06, 1994 to discuss and evaluate toxicology data submitted in support of Difenconazole registration and to assess the Reference Dose (RfD) for this chemical.

The Committee considered the chronic toxicity study in rats **(83-1a)**, the long-term toxicity study in dogs **(83-1b)**, the carcinogenicity studies in rats and mice **(83-2a and -2b)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)** and the reproductive toxicity study in rats **(83-4)** to be acceptable and the data evaluation records, except that of the dog study, to be adequate. Reevaluation of the dog study was recommended to ascertain the no-observable effect level established in this study. The Committee indicated that the no-observable effect level (NOEL) established for the dog study will not be used for the setting of the reference dose. Minor revisions to the data evaluation records for the two-generation reproduction and developmental toxicity studies in rats were also recommended. The Committee recommended to include summary tables of tumor incidences for the rat and mouse carcinogenicity studies.

The Committee recommended that an RfD be established on the basis of a NOEL of 0.96 mg/kg/day for hepatotoxicity observed at 24.12 mg/kg/day in males and 32.79 mg/kg/day in females in a long-term feeding study in rats. An uncertainty factor (UF) of 100 was used to account for the inter-species extrapolation and intra-

species variability. On this basis the **RfD** was calculated to be **0.01 mg/kg/day.** It should be noted that this chemical has not been evaluated by the World Health Organization (WHO) up to this date.

The Committee considered the high dose tested in the rat study to be appropriate for carcinogenicity testing based on hepatotoxicity. The incidence of neoplastic lesions in treated rats was comparable to controls. In the mouse carcinogenicity study, the high dose tested was considered to be adequate for carcinogenicity testing based on liver weight changes and hepatotoxicity including histopathological and clinical chemistry changes. The treatment appeared to increase hepatocellular adenoma and/or carcinoma in males of the two high dose levels. The Committee referred the carcinogenicity issue to the Health Effects Division-Carcinogenicity Peer Review Committee for a weight of the evidence evaluation.

There was no evidence, based on the available data, to suggest that Difenconazole was associated with significant reproductive and developmental toxicity.

A. Individuals in Attendance

1. Peer Review Committee Members and Associates present (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

Reto Engler

Marcia Van Gemert

Karl Baetcke

Henry Spencer

William Sette

Roger Gardner

James Rowe

Esther Rinde

George Ghali

Rick Whiting

2. Scientific Reviewer (Committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

Jess Rowland

3. Others:

D. McCall and P. Hurley of HED as observers.

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Marcia Van Gemert
Jess Rowland
James Kariya
Flora Chow
RfD File
Caswell File

B. Material Reviewed

Material available for review included data evaluation records for chronic toxicity/carcinogenicity studies in rats **(83-5 or 83-1a and -2a)**, a carcinogenicity study in mice **(83-2b)**, a chronic toxicity study in dogs **(83-1b)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)** and a reproductive toxicity study in rats **(83-4)**, and a tox. one-liner.

1. Cox, R. H. (1989). Combined chronic toxicity and oncogenicity study of CGA 169374 technical in rats. MRID No. 42090019, 42090020, 42710010, HED Doc No. 009689, 010588.

Core Classification: Core minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in Sprague-Dawley rats at 10, 20, 500 and 2500 ppm (0.48, 0.96, 24.12 and 123.76 mg/kg/day in males and 0.64, 1.27, 32.79 and 169.67 mg/kg/day in females). The NOEL/LOEL were considered to be 20 and 500 ppm based on increased mean liver weights and hepatotoxicity including histopathological and clinical chemistry changes. The Committee considered the high dose tested in the rat study to be appropriate for carcinogenicity testing based on effects described above (increased mean liver weights and hepatotoxicity including histopathological and clinical chemistry changes). The dose selection was also based on the results of a subchronic toxicity study in rats. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. The study was considered to be acceptable and the data evaluation record was considered to be adequate. The Committee recommended the addition of summary tumor tables to the data evaluation record and referral of the carcinogenicity issue to the Carcinogenicity Peer Review Committee for a weight of the evidence evaluation. This study satisfies data requirements 83-1a and 83-2a of subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

2. Cox, R. H. (1989). Oncogenicity study in mice. MRID No. 42090015, 42710006, HED Doc No. 009689, 010588.

Core Classification: Core minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in Crl:CD-1 mice at 10, 30, 300, 2500 and 4500 ppm (1.51, 4.65, 46.29, 423.16 and 818.87 mg/kg/day for males and 1.9, 5.63, 57. 79 and 512.61 mg/kg/day in females). The NOEL/LOEL were considered to be 30 and 300 ppm for increased mean liver weights (in females) and hepatotoxicity including histopathological and clinical chemistry changes. The Committee

considered the high dose tested in the mouse study to be adequate for carcinogenicity testing based on increased mean liver weights and hepatotoxicity including histopathological and clinical chemistry changes. The dose selection was also based on the results of a subchronic toxicity study in mice. The treatment was associated with increased incidence of liver adenomas and/or carcinoma in both males and females of the 2500 ppm group. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. The study was considered to be acceptable and the data evaluation record was considered to be adequate. The Committee recommended the addition of summary tumor tables to the data evaluation record and referral of the carcinogenicity issue to the Carcinogenicity Peer Review Committee for a weight of the evidence evaluation. This study satisfies data requirements 83-2b of subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in rats.

3. Rudzick, M. W. et al. (1988). CGA 169374 technical 52-week oral toxicity study in dogs. MRID No. 42090014, 4271005, HED Doc. No. 009689, 010588.

Core Classification: Core minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in beagle dogs at 20, 100, 500 and 1500 ppm (0.71, 3.4, 16.4 and 51.2 mg/kg/day for males and 0.63, 3.7, 19.4 and 44.3 mg/kg/day in females). The NOEL/LOEL were considered to be 100 and 500 ppm, respectively, based on decreased body weight gain and food consumption in males and females. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. However, the Committee questioned the NOEL established in this study and recommended further evaluation of the study to ascertain this NOEL. The study was considered to be acceptable. However, the data evaluation record should be updated to reflect the results of the reevaluation. This study satisfies data requirements 83-1b of subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. Gikinis, M. L. A. (1988). A two-generation reproductive study in albino rats. MRID No. 009689, HED Doc No. 010588.

Core Classification: Core minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in Sprague-Dawley rats at 25, 250, 2500 ppm (1.25, 12.5, and 125 mg/kg/day). Parental NOEL/LOEL were considered to be 1.25 and 12.5 mg/kg/day based on decreased body weight gain and food consumption. Reproductive NOEL/LOEL were considered to be 1.25 and 12.5 mg/kg/day based on significant

reduction in pup body weights. The Committee generally agreed with the reviewer's evaluation and interpretation of data and classification of the study. However, the Committee felt that a combined systemic/reproductive NOEL/LOEL would appear to be appropriate using the lowest and middle dose levels tested. The F1 paternal body weight reductions for days 0-21 and 35 along with the statistical significant reductions in F1 body weight gain during the first 70 days are generally consistent with some of the body weight gain reductions observed in the females (at least the F0 day 0-7 of gestation). These body weight reductions are supported by the reductions in pup body weight at the middle dose and high dose which was statistically significant by day 21 in the F0 generation males and similarly lowered (not statistically significant in the middle dose tested) in the females. The study was considered to be acceptable but the data evaluation record should be revised in accordance with the Committee's recommendations. This study satisfies data requirements 83-4 of subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

5. Lochry, E. A. (1987). Developmental toxicity study of CGA-169374 technical (FL-851406) administered orally via gavage to Crl:COBS CD (SD) BR presumed pregnant rats. MRID No. 42090016, HED Doc No. 009689, 010588.

Core Classification: Core minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in Crl:COBS CD (SD) BR rats at 2, 20, 100 and 200 mg/kg/day. Maternal toxicity NOEL/LOEL were considered to be 16 and 85 mg/kg/day based on significant decreases in maternal body weight gain and food consumption and increased incidence of excess salivation. Developmental toxicity NOEL/LOEL were considered to be 85 and 171 mg/kg/day. There was a non-significant reduction in the mean number of fetuses per dam, and non-significant increases in the mean number of resorptions per dam and percent postimplantation loss in the 200 mg/kg/day group. There was a slight decrease in mean fetal body weight at the 200 mg/kg/day. The following represents the significant alterations in the development of fetuses in the 200 mg/kg/day group. The incidence of bifid or unilateral ossification of the thoracic vertebrae was significantly increased on the fetal basis. There were also significant increases in the average number of sternal centers of ossification (per fetus per litter). The average number of ribs was significantly increased (with accompanying increases in the number of thoracic vertebrae), and decreases in the number of lumbar vertebrae in this group. These findings may be related to maternal toxicity. The Committee generally agreed with the reviewer's evaluation and interpretation of data and classification of the study. However, the actual dose levels need to be corrected to reflect the second reevaluation of the chemical analysis of the test compound. The NOEL's established in this study should not be

used for risk assessment of acute exposures. The study was considered to be acceptable and the data evaluation record was considered adequate. This study satisfies data requirements 83-3a of subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

6. Hummel, H. E. et al. (1987). CGA-169374 technical: teratology teratology study in rabbits. MRID No. 42090017, 42710008, HED Doc No. 009689, 010588.

Core Classification: Core minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in New Zealand rabbits at 1, 25 and 75 mg/kg/day. Maternal toxicity NOEL/LOEL were considered to be 25 and 75 mg/kg/day. Maternal toxicity was observed in this study as the death of one doe and abortions observed in two other high dose does. In addition, significant reductions in body weight gain was observed in the high dose does. However, this decrease in body weight gain corresponds with reduced food consumptions in the same time intervals. Developmental toxicity NOEL/LOEL were considered to be 25 and 75 mg/kg/day. Slight nonsignificant increases in postimplantation loss and resorptions/doe were observed in the high dose group. The significant decrease in fetal weight in the high dose group may have been due to treatment. The significant difference in fetal weight observed at the low and mid dose were apparently not due to treatment. The Committee generally agreed with the reviewer's evaluation and interpretation of data and classification of the study. The study was considered to be acceptable and the data evaluation record was considered adequate. This study satisfies data requirements 83-3b of subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

C. Conclusions and Recommendations

1. Data Base

The Committee considered the long-term feeding study in rats **(83-1a)**, the chronic toxicity study in dogs **(83-1b)**, the carcinogenicity studies in rats **(83-2a)** and mice **(83-2b)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)** and the reproductive toxicity study in rats **(83-4)** to be acceptable and the data evaluation records, except that of the dog study, to be adequate. Further reevaluation of the dog study was recommended to ascertain the no-observable effect level established in this study. However, the Committee indicated that the no-observable effect level established for the dog study will not be used for the setting of the Reference Dose. Minor revisions to the data evaluation records for the two-generation reproduction study and the developmental toxicity study in rats were also recommended.

2. Reference Dose

The Committee recommended that an RfD be established on the basis of a NOEL of 0.96 mg/kg/day for hepatotoxicity observed at 24.12 mg/kg/day in males and 32.79 mg/kg/day in females in a long-term feeding study in rats. An uncertainty factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability. On this basis the **RfD** was calculated to be **0.01 mg/kg/day**. It should be noted that this chemical has not been reviewed by the World Health Organization (WHO) upto this date.

3. Carcinogenicity

The Committee considered the high dose tested in the rat study to be appropriate for carcinogenicity testing based on increased mean liver weight and hepatotoxicity. The incidence of neoplastic lesions in treated animals was comparable to controls. In the mouse carcinogenicity study, the high dose tested was considered to be adequate for carcinogenicity testing based on liver weight changes and other hepatotoxicity signs including histopathological and clinical chemistry changes. The treatment appeared to increase hepatocellular adenoma and/or carcinoma in males of the two high dose levels. The Committee referred the carcinogenicity issue to the Health Effects Division-Carcinogenicity Peer Review Committee for a weight of the evidence evaluation.

4. Reproductive and Developmental Toxicity

There was no evidence, based on the available data, to suggest that Difenconazole was associated with significant reproductive and developmental toxicity.

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