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

17 AUG 1993

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MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: RfD/Peer Review Report of Cyproconazole

CASRN. 111578-32-6
EPA Chem. Code: 129025
Caswell No. 551F

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

TO: Susan Lewis, PM 21
Fungicide-Herbicide Branch
Registration Division (H7505C)

The Health Effects Division RfD/Peer Review Committee met on May 13, 1993 to discuss and evaluate the toxicology data submitted in support of Cyproconazole registration and to assess the Reference Dose (RfD) for this chemical.

The Committee considered the long-term feeding studies in rats and dogs **(83-1a and -1b)** to be acceptable. The chronic toxicity phase of the mouse carcinogenicity study was also examined to confirm the systemic NOEL established in this study. The Committee discussed the developmental toxicity studies in rats and rabbits **(83-3a and -3b)** and the reproductive toxicity study in rats **(83-4)** and recommended the referral of the reproductive/ developmental toxicity issue to the Health Effects Division Reproductive/Developmental Toxicity Peer Review Committee for a weight of the evidence evaluation. The Committee recommended that the NOEL in the reproduction study should be revised.

The Committee recommended that a Reference Dose (RfD) should be established on the basis of a NOEL of 1.0 mg/kg/day established in the long-term toxicity study in dogs for hepatotoxicity and organ weight changes observed at 3.2 mg/kg/day. 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.**

The carcinogenic potential of this chemical has been addressed and classified by the Health Effects Division Carcinogenicity Peer

Review Committee on June 20, 1990 and again on January 15, 1992 (HED reports dated September 26, 1990 and April 29, 1992). Subsequently, Cyproconazole was reclassified as a "Group B2" carcinogen on October 21, 1992 (HED report dated November 12, 1992).

Until the developmental toxicity issue is addressed by the Health Effects Division Reproductive/Developmental Toxicity Peer Review Committee, and until exposure data become available, no conclusion can be made regarding a potential acute toxicity concern with respect to developmental toxicity.

There were no data available for review to address or characterize the hazard of a one-time or one-day exposure for other toxicological end-points. However, data available for review did not indicate that a one-day exposure to the chemical would be of such concern as to warrant the need for acute exposure studies to be used in an acute dietary risk assessment.

A. Individual in Attendance

1. Peer Review Committee Members and Associates present in at least one of the two meetings (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

Karl Baetcke

Henry Spencer

William Sette

Roger Gardner

Stephen Dapson

Esther Rinde

John Tice

George Ghali

Rick Whiting

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

Reto Engler

Marcia Van Gemert

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

Linda Taylor 7/8/93

Clark Swentzel 7/12/93

4. Others:

Stephanie Willett of CCB/HED as observer.

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Rick Whiting
Linda Taylor
Clark Swentzel
Mrcia Van Gemert
James Kariya

B. Material Reviewed

Material available for review included data evaluation records for a long-term toxicity study in dogs **(83-1a)**, a chronic toxicity/carcinogenicity study in rats **(83-5 or 83-1b and -2a)**, a carcinogenicity study in mice **(83-2b)**, 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. Warren, S. et al. (1988). Chronic toxicity/oncogenicity feeding study in rats. MRID No. 41164701, HED Doc No. 007871.

Core Classification: The chronic toxicity phase is classified as Core-minimum, the carcinogenicity phase is classified as Core-supplementary according to the data evaluation records.

Committee's Conclusions and Recommendations:

The chemical was tested at 20, 50 and 350 ppm in Wistar albino rats. The Committee agreed with the reviewer's evaluation and interpretation of data and classification of the chronic toxicity phase of the study. The carcinogenic potential of this chemical has been addressed by the Health Effects Division Carcinogenicity Peer Review Committee (CPRC). The data evaluation record is adequate as presented. This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats.

2. Warren, S. et al. (1988). Chronic oral toxicity by dietary administration to Beagle dogs for one year. MRID No. 41212901, HED Doc. No. 007871.

Core Classification: Core-minimum (according to the data evaluation record)

Committee's Conclusions and Recommendations:

The chemical was tested at 30, 100 and 350 ppm in Beagle dogs. The Committee agreed with the reviewer's evaluation and interpretation of data and classification of the study. The data evaluation record is adequate as presented. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in a non-rodent species.

3. Warren, S. et al. (1989). The potential oncogenicity of SAN 619F by prolonged dietary administration to mice. MRID No. 41147201, HED Doc No. 008009.

Core Classification: Core-Guideline according to the data evaluation records.

Committee's Conclusions and Recommendations:

The chemical was tested at 5, 15, 100 and 200 ppm in CD-1 mice. The Committee examined only the chronic toxicity phase of the study for systemic effects and agreed with the reviewer's evaluation and interpretation of data and classification of the chronic toxicity phase of the study. In addition to effects on body weight gain and organ weights in both sexes, the treatment caused effects on testicular germinal epithelial tissues in males. The carcinogenic potential of this chemical has been addressed by the Health Effects Division Peer Review Committee. The data evaluation record is adequate as presented. The acceptability of the carcinogenicity phase of the study was determined by the Health Effects Division Carcinogenicity Peer Review Committee.

4. Eschbach, B. et al. (1987). San 619F, 2-Generation study in rats. MRID No. 40607723, HED Doc. No. 007003, 007908.

Core Classification: Core-Minimum according to the data evaluation records.

Committee's Conclusions and Recommendations:

The chemical was tested at 4, 20 and 120 ppm in Wistar albino rats. The Committee dismissed the effect of treatment on the length of the gestation period. The effects on preimplantation was also dismissed on the ground that it only occurred in one generation. The Committee determined that the NOEL for systemic and reproductive effects to be 20 and >120 ppm respectively. The study was considered acceptable and the data evaluation record was considered adequate. However, the Committee recommended that the data evaluation record should be revised to reflect the Committee recommendations. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in a rats.

5. Klotzche, C. (1985). Teratogenicity study in rats with SAN 619F. MRID No. 40607721, HED Doc. 007730.

Core Classification: Core-Minimum according to the data evaluation records.

Committee's Conclusions and Recommendations:

The chemical was tested at 6, 12, 24, and 48 mg/kg/day in Wistar/ Han rats. After a brief discussion, and because of potential developmental toxicity concern, the Committee decided to refer the developmental toxicity issue to the Reproductive/Developmental Toxicity Peer Review Committee for a weight of the evidence evaluation. .

6. Muller, W. (1991). Teratogenicity study in the rabbits. MRID No. 42175401, HED Doc. 009735.

Core Classification: Core-Minimum according to the data evaluation records.

Committee's Conclusions and Recommendations:

The chemical was tested at 2, 10 and 50 mg/kg/day in New Zealand White rabbits. After a brief discussion of the findings, and because of potential developmental toxicity concern, the Committee decided to refer the developmental toxicity issue to the Reproductive/Developmental Toxicity Peer Review Committee for a weight of the evidence evaluation.

C. Conclusions and Recommendations

1. Data Base

The Committee considered the long-term feeding studies in rats and dogs **(83-1a and -1b)** to be acceptable. The chronic toxicity phase of the mouse carcinogenicity study was also examined to confirm the systemic NOEL established in this study. The Committee discussed the developmental toxicity studies in rats and rabbits **(83-3a and -3b)** and the reproductive toxicity study in rats **(83-4)** and recommended the referral of the developmental toxicity issue to the Health Effects Division Reproductive/Developmental Toxicity Peer Review Committee for a weight of the evidence evaluation. The Committee recommended that the NOEL in the reproduction study should be revised.

2. Reference Dose

The Committee recommended that a Reference Dose (RfD) should be established on the basis of a NOEL of 1.0 mg/kg/day established in the long-term toxicity study in dogs for hepatotoxicity and organ weight changes observed at 3.2 mg/kg/day. 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.**

3. Carcinogenicity

The carcinogenic potential of this chemical has been addressed and classified by the Health Effects Division Carcinogenicity Peer Reviewe Committee on June 20, 1990 and again on January 15, 1992 (HED report dated September 26, 1990 and April 29, 1992). Subsequently, Cyproconazole was reclassified as a "Group B2" carcinogen on October 21, 1992 (HED report dated November 12, 1992).

4. Acute Toxicity Concern

Until the developmental toxicity issue is addressed by the Health Effects Division Reproductive/Developmental Toxicity Peer Review Committee, no conclusion can be made regarding any potential acute toxicity concern with respect to developmental toxicity.

There were no data available for review to address or characterize the hazard of a one-time or one-day exposure for other toxicological end-points. However, the data available for review did not indicate that a one-day exposure to the chemical would be of such concern as to warrant the need for acute exposure studies for acute dietary risk assessment purposes.