011081

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

OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

JUN 23 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Paclobutrazol [1-(4-chlorophenyl)-4,4-dimethyl-2-(1H-1,2,4-triazol-1-yl)pentan-3-ol]

CASRN. 76738-62-0
EPA Chem. Code: 125601
Caswell No. 628C

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

Rick J. White 6/21/94 for

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

Lois Rossi, Chief
Reregistration Branch
Special Review and Re-registration Division (7508W)

The Health Effects Division RfD/Peer Review Committee met on March 3, 1994 to discuss and evaluate the existing toxicology data in support of Paclobutrazol re-registration and to re-assess the Reference Dose (RfD) for this chemical in light of recently submitted data.

Material available for review included data evaluation records for a chronic toxicity/carcinogenicity study in rats (83-1a and -2a or 83-5), a carcinogenicity study in mice (83-2b), a chronic toxicity study in dogs (83-1b), a multi-generation reproductive toxicity study in rats (83-4), two developmental toxicity studies in rats (83-3a), two developmental toxicity studies in rabbits (83-3b), and short-term toxicity studies in rats and dogs (82-1a and -1b).

The RfD for this chemical was first assessed by the Health Effects Division RfD Committee on July 25, 1986 and verified by the Agency RfD Work Group on September 2,, 1986. At that time the RfD

was based on a subchronic feeding study in rats with a no-observable effect level (NOEL) of 12.5 mg/kg/day. Increased liver weights, microsomal enzymes activity and serum cholesterol level were observed at the next higher dose level of 62.5 mg/kg/day. An uncertainty factor (UF) of 100 was applied to account for inter-species extrapolation and intra-species variability. An additional UF of 10 was used to account for the lack of chronic and reproductive toxicity data in rats. On this basis the RfD was calculated to be 0.013 mg/kg/day.

In the meeting of March 10, 1994 the Committee considered all data submitted since the last meeting and recommended that the RfD be based on the reproductive toxicity study in rats with a NOEL of 2.5 mg/kg/day, the lowest dose tested. Reproductive/systemic toxicity effects including increased incidence of chromodacryorrhea and thickened eyelids in both generations were observed at 12.5 mg/kg/day, the middle dose. An uncertainty factor (UF) of 100 was applied to account for the inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.025 mg/kg/day.

It should be noted that this chemical had been reviewed and an acceptable daily intake (ADI) of 0.1 mg/kg/day has been established by the joint meeting of the WHO/FAO on pesticide residues (JMPR) in 1988. The following studies were considered to be critical in the ADI evaluation: 1) a mouse study with a NOEL of 15 mg/kg/day, 2) a developmental toxicity study in rats with a NOEL of 10 mg/kg/day (based on fetotoxicity), and 3) a dog study with a NOEL of 75 mg/kg/day. No information about the Safety factor was provided. However, it appears that ADI was based on a NOEL of 10 mg/kg/day and a Safety Factor of 100 was applied.

The Committee considered the chronic toxicity study in rats (83-1a, MRID No. 40734301), the chronic feeding study in dogs (83-1b, MRID 00132691, 00143166) to be acceptable and the data evaluation records (HED Doc. No. 011061; 003813, 004352) to be acceptable. The Committee questioned the biological significance of the fatty degenerative and liver weight changes reported in the data evaluation record of the chronic feeding study in rats. The NOEL for this study was considered to be 12.5 mg/kg/day, the mid-dose tested and should be based on increased liver hypertrophy/ steatosis observed at 62.5 mg/kg/day, the high-dose tested in both sexes.

The carcinogenicity phase of the chronic toxicity/ carcinogenicity study in rats (MRID No. 40734301) and the carcinogenicity study in mice (MRID No. 40762501) were considered inadequate. The dose levels tested were considered to be inadequate for carcinogenicity testing in both species. Body weight gain decrease observed in the rat study was attributed to reduction in food consumption. Effects seen at the high dose levels in the rat and mouse studies, though sufficient to establish

a regulatory NOEL for chronic toxicity, were not considered severe enough to indicate that the animals in this study were tested at a sufficiently high dose level for an adequate negative carcinogenicity testing in rats or mice. Furthermore, a statistically significant increase at all dose levels with a positive trend was observed for benign stromal polyps in female rats. A borderline, but statistically significant, increase in Leydig cell tumors was observed in high dose male mice. This increase demonstrated a statistically significant positive trend with increasing dose. However, there was no historical control data available for review by the Committee. On the basis of these two studies, the chemical was classified as a "Group D". The Committee noted that new carcinogenicity studies may be required if the current use pattern changes (i.e. food uses or uses which are in the high exposure category and require carcinogenicity data).

The Committee considered the developmental toxicity studies in rats (83-3a, MRID No. 00132693; 00143158) and rabbits (83-3b, MRID No. 40734302) and the reproductive toxicity study in rats (MRID No. 40734303) to be acceptable and the data evaluation records for these studies (HED Doc. No. 003813; 004352; 011061; 011061) to be adequate as presented. The other developmental toxicity study in rabbits (MRID No. 00132692) was considered to be inadequate. The Committee recommended combining the NOEL's for reproductive and systemic toxicity in the reproductive toxicity study. The data evaluation record for this study should be revised accordingly.

There was no evidence, based on the available data, to suggest that Paclobutrazol was associated with significant developmental or reproductive effects under the testing conditions.

A. Individuals in Attendance

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

William Burnam

Marcia Van Gemert

Karl Baetcke

Henry Spencer

Roger Gardner

James Rowe

Esther Rinde

William Sette

Stephen Dapson

George Ghali

Rick Whiting

2. Peer Review Committee Members and associates in absentia (Signature indicates concurrence with the peer review unless otherwise stated).

Reto Engler

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

Roger Gardner

Pam Hurley

4. Others:

T. McMahon, John Tice, and K. Locke of HED as observers

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Karl Baetcke
Roger Gardner
Pam Hurley
James Kariya
RfD and Caswell Files

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Karl Baetcke
Roger Gardner
Pam Hurley
James Kariya
RfD and Caswell Files

B. Material Reviewed

Material available for review included data evaluation records for a chronic toxicity/carcinogenicity study in rats (83-1a and -2a or 83-5), a carcinogenicity study in mice (83-2b), a chronic toxicity study in dogs (83-1b), a multi-generation reproductive toxicity study in rats, two developmental toxicity studies in rats (83-1a), two developmental toxicity studies in rabbits (83-3b), and short-term toxicity studies in rats and dogs (82-1a and -1b).

1. Shaw, D. C. (1986). Paclobutrazol: 104-week oral (dietary administration) combined toxicity and carcinogenicity study in the rat with a 52-week interim kill. MRID No. 40734301, HED Doc. No. 011061. Classification: Core-minimum data for chronic toxicity; Core-supplementary data for carcinogenicity. This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats, but does not satisfy data requirement 83-2a for carcinogenicity testing in rats.

2. Shaw, D. C. (1986). Paclobutrazol: 104-week oral (dietary administration) combined toxicity and carcinogenicity study in the mouse with a 52-week interim kill. MRID No. 40762501, HED Doc. No. 011601. Classification: Core-minimum data for chronic toxicity; Core-supplementary data for carcinogenicity. This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rodents, but does not satisfy data requirement 83-2b for carcinogenicity testing in mice.

3. Clapp, M. J. L. et al. (1983). Paclobutrazol: One year oral dosing study in dogs; interim report after 26 weeks. MRID No. 00132691, 00143166, HED Doc. No. 003813, 004352, 011061. Classification: Core-minimum data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. Wickramaratne, G. A. (1987). Paclobutrazol: two-generation reproduction study in rats including individual animal data. MRID No. 40734303, HED Doc. No. 011061. Classification: Guideline data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

5. Killick, M. E. et al. (1983). Paclobutrazol: teratogenicity study in the rat. MRID No. 00132693, HED Doc. No. 003813, 011061. Classification: Core-minimum data. This study satisfies data

011081

requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

6. Killick, M. E. et al. (1984). Paclobutrazol: second teratogenicity study in the rat. MRID No. 00143158, HED Doc. No. 004352, 011601. Classification: Core-minimum data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

7. Killick, M. E. et al (1986). Paclobutrazol: second teratogenicity study in the rabbit including individual animal data. MRID No. 40734302, HED Doc. No. 011061. Classification: Guideline data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.