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WASHINGTON, D.C. 20460

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SEP 7 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Flumiclorac Pentyl [Pentyl 2-chloro-4-fluoro-5-[(3,4,5,6-tetrahydrophthalonyl)phenoxy acetate]

CASRN. 87546-18-7
EPA Chem. Code: 128724
Caswell No. 958A

FROM: George Z. Ghali, Ph.D.
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (7509C)

THRU: William Burnam
Co-Chair, RfD/Peer Review Committee
Health Effects Division (7509C)

Reto Engler, PhD
Co-Chair, RfD/Peer Review Committee
Health Effects Division (7509C)

TO: Joanne Miller, PM 23
Insecticide-Rodenticide Branch
Registration Division (7505C)

The Health Effects Division RfD/Peer Review Committee met on August 25, 1994 to discuss and evaluate toxicology data submitted in support of Flumiclorac Pentyl registration and to assess the Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DER's) for a chronic toxicity/carcinogenicity study in rats (83-5 or 83-1a and -2a), a carcinogenicity study in mice (83-2b), a long-term feeding toxicity study in dogs (83-1b), developmental toxicity studies in rats and rabbits (83-3a and -3b), a two-generation reproductive toxicity study in rats (83-4), two subchronic toxicity studies in rats (82-1a) and subchronic toxicity studies in mice and dogs (82-1b).

The Committee considered the chronic toxicity studies in rats (MRID No. 42187406, 42883906) and dogs (MRID No. 42825817) to be acceptable and the data evaluation records (HED Doc. 010848) to be

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adequate. In the rat study, the Committee felt that the only reliable parameter to set the NOEL was the organ weight changes. Increased activity of the gamma-glutamyl transpeptidase was discounted by the Committee. In the dog study, the Committee noted that there were only marginal effects observed at the lowest effect level. In the data evaluation records of the dog study, the Committee noted that the dose levels were sometimes erroneously expressed in some tables as parts per million while in fact these values should have been in mg/kg/day (the chemical was administered in this study in gelatin capsules).

The Committee considered the carcinogenicity phase of the chronic toxicity/carcinogenicity study in rats (MRID No. 42187406, 42883906) and the carcinogenicity study in mice (MRID No. 42883905) to be acceptable and the data evaluation records (HED Doc. No. 010848) to be adequate. The Committee noted that there was no statement in the executive summary in the data evaluation record of the rat carcinogenicity study regarding the conclusion of the carcinogenicity study. However, no changes to the data evaluation record were recommended. The dose levels tested in the rat and mouse studies were considered to be adequate for carcinogenicity testing since the highest dose levels tested were at least at the limit dose as defined in Subpart F of the Pesticide Assessment Guideline. The Committee concluded that the treatment did not alter the spontaneous tumor profile in these strains of rat and mouse under the testing conditions. The chemical was classified as a "Group E".

The reproductive toxicity study in rats (83-4, MRID No. 42169835) and the developmental toxicity studies in rats (83-3a, MRID No. 42169832) and rabbits (83-3b, MRID No. 42169830) were considered to be acceptable and the data evaluation records (HED Doc. No. 009587) were considered to be adequate. The Committee generally agreed with the reviewer's evaluation and interpretation of data. The Committee noted a marginal increase in the incidence of visceral variations (accessory subclavian anterior/posterior to left subclavian) in the rabbit developmental toxicity study at the middle dose level; however, these effects were questionable as treatment-related developmental toxicity effects since they were marginal, dose related, and often occur spontaneously in rabbits. Therefore, no changes to the data evaluation records were recommended. There was no evidence, based on the available data, that Flumiclorac was associated with major developmental or reproductive toxicity.

The Committee recommended that an RfD for this chemical be established based on a two-year feeding study in rats with a NOEL of 35.4 mg/kg/day. Organ weight changes were observed at the next higher dose of 360.4 mg/kg/day. 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 0.35 mg/kg/day. It should be noted that this chemical has

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not been reviewed by the World Health Organization (WHO) and an acceptable daily intake (ADI) has not been generated.

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Individuals in Attendance

Peer Review Committee members and associates present were William Burnam (Chief, SAB, Co-chair), Reto Engler (HED, Senior Science Advisor, Co-Chair), Karl Baetcke (Chief, TB I), Marcia Van Gemert (Chief, TB II), George Ghali (Manager, HED-RfD/QA), Rick Whiting, Susan Makris and Myron Ottley.

Scientific reviewer (Committee or non-committee member(s) responsible for data presentation; signature (s) indicate technical accuracy of panel report)

Robert Fricke

Robert Fricke

Susan Makris

Susan Makris

Respective branch chief (Committee member; Signature indicates concurrence with the peer review unless otherwise stated)

Marcia Van Gemert

Marcia Van Gemert

CC: Richard Schmitt
Stephanie Irene
Marcia Van Gemert
Susan Makris
Robert Fricke
Debra Edwards
Kerry Dearfield
James Kariya
RfD File
Caswell File

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Material Reviewed

1. Adachi, H. (1992). Combined chronic toxicity and carcinogenicity study of S-23031 by dietary administration in rats. MRID No. 42187406, 42883906, HED Doc. No. 010848. Classification: Guideline data. This study satisfies data requirement 83-1a and -2a (or 83-5) of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

2. Adachi, H. (1992). Oncogenicity study of S-23031 by dietary administration in mice. MRID No. 42883905, HED Doc. No. 010848. Classification: Guideline data. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

3. Dalgard, D. W. (1992). Chronic oral toxicity study in dogs. MRID No. 42825817, HED Doc. No. 010848. Classification: Guideline data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. Nemec, M. D. (1991). A dietary two-generation reproduction study of S-23031 in rats. MRID No. 42169835, HED Doc. No. 009587. 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. Lemen, J. K. (1991) Rat teratology study with S-23031. MRID No. 42169832, HED Doc. No. 009587. Classification: Guideline data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

6. Lemen, J. K. (1991). Rabbit teratology study with S-23031. MRID No. 42169830, HED Doc. No. 009587. Classification: Guideline data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

7. Yoshida, Y. (1990). Three-month subacute toxicity study of S-23031 by dietary administration in rats. MRID No. 42169826, HED Doc. No. 009587. Classification: Guideline data. This study satisfies data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rats.

8. Tamano, S. (1990). 13-Week subchronic toxicity study of S-23031 pure in rats. MRID No. 42883903, HED Doc. No. 010848. Classification: Guideline data. This study satisfies data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rats.

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9. Nakano, M. (1991). Three-month oral toxicity study of S-23031 in dogs. MRID No. 42169827, 42310802, HED Doc No. 009587. Classification: Guideline data. This study satisfies data requirement 82-1b of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in dogs.

10. Yamada, H. (1990). Three month subacute toxicity study of S-23031 by dietary administration in mice. MRID No. 42883904, HED Doc. No. 010848. Classification: Core-supplementary data. This study does not satisfy data requirement 82-1b of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in mice.