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SEP 22 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Fipronil [5-Amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-(1,R,S)-(trifluoromethyl)sulfinyl)-1H-pyrazole-3-carbonitrile]

CASRN. 120068-37-3
EPA Chem. Code: 129121

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

G. Ghali

Rick J. Whiting
Health Effects Division (7509C)

Rick J. Whiting

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

W. Burnam

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

Reto Engler

TO: Robert Brennis, PM 10
Insecticide-Rodenticide Branch
Registration Division (7505C)

The Health Effects Division RfD/Peer Review Committee met on July 21, 1994 to discuss and evaluate toxicology data submitted in support of Fipronil registration and to assess the Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DERs) for a chronic toxicity/oncogenicity study in rats (83-5 or 83-1a and -2a), a carcinogenicity study in mice (83-2b), a chronic toxicity study in dogs (83-1b), a multigeneration reproductive toxicity study in rats (83-4), developmental toxicity studies in rats and rabbits (83-3a and -3b), subchronic studies in rats and dogs (82-1a and -1b), a 21-day dermal toxicity study in rabbits (82-2) and an acute neurotoxicity study in rats (81-8).

The Committee considered the chronic toxicity studies in rats (83-1a, MRID No. 42918648) and dogs (83-1b, MRID No. 42918645) to be acceptable and the data evaluation records (HED Doc. No. 011086)



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to be adequate. However, some revisions to Table 2 of the DER of the two-year feeding study in rats were recommended.

The Committee considered the carcinogenicity phase of the chronic toxicity/carcinogenicity study in rats (MRID No. 42918648) and the carcinogenicity study in mice (MRID No. 42918649) to be acceptable and the data evaluation records (HED Doc. No. 011086) to be adequate. The Committee considered the dose levels tested to be adequate for carcinogenicity testing in rats and mice. Based on increased incidences of follicular cell thyroid tumors in both sexes of the rat, the Committee recommended referral of the carcinogenicity issue to the Health Effects Division-Carcinogenicity Peer Review Committee (HED-CPRC) for weight of the evidence evaluation.

The reproductive toxicity study in rats (83-4, MRID No. 42918647) and the developmental toxicity study in rats (83-1a, MRID No. 42977903) and rabbits (83-3b, MRID No. 42918646) were considered to be acceptable and the data evaluation records (HED Doc. No. 011086) were considered to be adequate. There was no evidence, based on the available data, that Fipronil was associated with significant reproductive or developmental toxicity under the testing conditions. However, the Committee recommended that a developmental neurotoxicity study be conducted.

The Committee considered the acute neurotoxicity study in rats (81-8, MRID No. 42918635) to be acceptable and the data evaluation record (HED Doc. No. 011086) to be adequate. In view of the neurotoxic effects observed in both the acute neurotoxicity and the chronic rat studies (included seizures and other excitatory effects), and considering all the available information for potential inhibition of GABA receptors by Fipronil, the Committee concluded that a chronic neurotoxicity study in adult rats must be submitted.

The Committee recommended that an RfD for this chemical be established based on a two-year feeding study in rats (MRID No. 42918648) with a NOEL of 0.5 ppm (0.019 and 0.025 mg/kg/day for males and females, respectively). In this study, rats were administered Fipronil in the diet at dose levels of 0, 0.5, 1.5, 30 and 300 ppm (Male: 0, 0.019, 0.059, 1.27 and 12.68 mg/kg/day; Female: 0, 0.025, 0.078, 1.61 and 16.75 mg/kg/day). Evidence of systemic toxicity included: 1) neurotoxicity (including seizures which resulted in death) in the 1.5, 30 and 300 ppm group males and females; 2) decreased body weight gain in the 300 ppm group males and females and the 30 ppm group females; decreased food consumption and food conversion efficiency in the 300 ppm group males and females at the beginning of the study; 4) decreased hematology parameters in the 300 ppm group males and females in comparison to the control groups; 5) alterations in clinical chemistry (increased cholesterol and calcium values; protein alterations with increased total protein, decreased albumin and

increased globulins) mostly in the 30 and 300 ppm group males and females; protein alterations were seen in the 1.5 ppm group males after 76 and 81 weeks of treatment; 6) alterations in thyroid hormones (increased TSH and decreased T4 levels) in all treated groups at some time with the 30 and 300 ppm group males and females consistently affected; 7) alterations in urinalysis parameters in the 30 and 300 ppm groups; 8) changes on gross necropsy in the 30 and 300 ppm group males and females; 9) increased absolute and relative weights of the liver and thyroid in the 30 and 300 ppm group males and females; and 10) increased incidence and severity of progressive senile nephropathy in the 30 and 300 ppm group males and females.

Based on an increased incidence of clinical signs and alterations in clinical chemistry and thyroid parameters, the LOEL for systemic toxicity was considered to be 1.5 ppm (0.059 and 0.078 mg/kg/day for males and females, respectively). The NOEL for systemic toxicity was considered to be 0.5 ppm (0.019 and 0.025 mg/kg/day for males and females, respectively). An uncertainty factor (UF) of 100 was applied to account for the interspecies extrapolation and intraspecies variability. On this basis the RfD was calculated to be 0.0002 mg/kg/day. It should be noted that this chemical has not been reviewed by the World Health Organization (WHO).

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), Rick Whiting, Henry Spencer, William Sette, Esther Rinde and James Rowe.

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

Virginia Dobozy

Virginia Dobozy

Mike Ioannou

J. M. Ioannou

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
Mike Ioannou
Virginia Dobozy
Debra Edwards
Kerry Dearfield
Beth Doyle
RfD File
Caswell File

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B. Material Reviewed

Material available for review consisted of data evaluation records (DER's) for a chronic toxicity/oncogenicity study in rats (83-5 or 83-1a and -2a), a carcinogenicity study in mice (83-2b), a chronic toxicity study in dogs (83-1b), multigeneration reproductive toxicity study in rats (83-4), developmental toxicity studies in rats and rabbits (83-3a and -3b), subchronic studies in rats and dogs (82-1a and -1b), a 21-day dermal toxicity study in rabbits (82-2) and an acute neurotoxicity study in rats (81-8).

1. Aughton, P. (1993). M&B 46030: Combined Oncogenicity and Toxicity Study by Dietary Administration to CD Rats for 104 Weeks including a 13-Week Reversibility Period on Completion of 52 Weeks of Treatment. MRID No. 42918648. HED Doc. No. 011086. Classification: Core-Minimum data. This study satisfies data requirement 83-1a and -2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.
2. Broadmeadow, A. (1993). M&B 46030: Oncogenicity Study by Dietary Administration to CD-1 Mice for 78 Weeks. MRID No. 42918649. HED Doc. No. 011086. Classification: Core-Minimum data. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.
3. Holmes, P. (1992). M&B 46030: Toxicity Study by Oral (Capsule) Administration to Beagle Dogs for 52 Weeks. MRID No. 42918645. HED Doc. No. 011086. Classification: Core-Guideline data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.
4. King, V. (1992). M&B 46030: Reproductive Performance Study in Rats Treated Continuously through Two Successive Generations. MRID No. 42918647. HED Doc. No. 011086. Classification: Core-Minimum data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.
5. Brooker, A. and John, D. (1991). The Effect of M&B 46,030 on Pregnancy of the Rat. MRID No. 42977903. HED Doc. No. 011086. 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.
6. King, V. (1990). M&B 46030: Teratology Study in the Rabbit. MRID No. 42918646. HED Doc. No. 011086. Classification: Core-Minimum data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.
7. Holmes, P. (1993). M&B 46030: Toxicity Study by Dietary

Administration to CD Rats for 13 Weeks. MRID No. 42918643. HED Doc. No. 011086. Classification: Core-Supplementary data. This study does not satisfy data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rodents. The study may be upgraded with the submission of the data from the neurological examinations.

8. Holmes, P. (1991). M&B 46030: Toxicity Study by Oral (Capsule) Administration to Beagle Dogs for 13 Weeks. MRID No. 42918642. HED Doc. No. 011086. Classification: Core-Guideline data. This study satisfies data requirement 82-1b of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in nonrodents.

9. Gill, M.W., Wagner, C.L. and Driscoll, C.D. (1993). M&B 46030: Single Exposure Peroral (Gavage) Neurotoxicity Study in Sprague Dawley Rats. MRID No. 42918635. HED Doc. No. 011086. Classification: Core-Minimum data. This study satisfies data requirement 81-8 of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in nonrodents.

10. Hermansky, S. and Wagner, C. (1993). M&B 46030: Twenty-One Day Repeated Cutaneous Dose Toxicity Study in New Zealand White Rabbits #2. MRID No. 42918644. HED Doc. No. 011086. Classification: Core-Guideline data. This study satisfies data requirement 82-2 of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in nonrodents.