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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

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121026

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Halofenozide [N'-(4-chlorobenzoyl)-N-(t-butyl)benzoyl-hydrazide].

CASRN: 112226-61-6
EPA Chem. Code: 121026
Caswell No.:

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

THRU: William Burnam
Chairman, RfD/QA Peer Review Committee
Health Effects Division (7509C)

TO: Rick Keigwin, PM 10
Insecticide-Rodenticide Branch
Registration Division (7505C)

The Health Effects Division-RfD/Peer Review Committee met on October 10, 1996 to discuss and evaluate the toxicology data submitted in support of Halofenozide registration and to assess the Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DERs) for an acute neurotoxicity study in rats **(81-8)**, a combined subchronic toxicity **(82-1a)**/subchronic neurotoxicity study **(82-7)** in rats, a subchronic feeding toxicity study in dogs **(82-1b)**, a 14-week range-finding feeding study in dogs, developmental toxicity studies in rats and rabbits **(83-3a and -3b)**, a subchronic dermal toxicity study in rats **(82-3)**, and a battery of mutagenicity studies **(84-2)**.

A. Chronic and Subchronic Toxicity:

There were no chronic toxicity studies in rats or dogs (83-1a, and -1b) available for review by the Committee.

There was a combined subchronic toxicity/neurotoxicity study in rats (82-1a and -7, MRID No. 43714501)) available for review by the Committee. The Committee considered the subchronic feeding toxicity phase of the study to be supplementary and the data evaluation record (HED Doc. No. 012062) to be adequate. The NOEL/LOEL were considered to be 75 ppm (5.53 and 5.88 mg/kg/day, in males and females, respectively) and 750 ppm (52.72 and 54.61 mg/kg/day in males and females, respectively) based on body weight gain decrease, reduction in food consumption, hematological effects, alteration in blood chemistry parameters, increased liver weight, and histopathological changes.

The Committee considered the subchronic toxicity study in dogs (82-1b, MRID No. 43701610) to be acceptable and the data evaluation record (HED Doc. No. 012062) to be adequate. The NOEL/LOEL were considered to be 100 ppm (3.7 and 4.0 mg/kg/day, respectively, in males and females) and 300 ppm (11.0 mg/kg/day) based on absolute and relative liver weight increases, histopathological changes in the liver and spleen, erythroid hyperplasia of bone marrow. The Committee did not discuss the 14-day range-finding study in dogs

The Committee considered the subchronic dermal toxicity study in rats (82-3, MRID No. 43642819, HED Doc. No. 011893) to be acceptable and the data evaluation record to be adequate. The systemic toxicity NOEL/LOEL were considered to be 40 and 200 mg/kg/day based on hematological and clinical chemistry changes and hepatic hypertrophy in males. No dermal irritation was noted in this study.

B. Carcinogenicity:

There were no carcinogenicity studies in rats or mice (83-2a and -2b) available for review by the Committee.

C. Reproductive and Developmental Toxicity:

The was no reproductive toxicity study in rats (83-4) available for review by the Committee.

The Committee considered the developmental toxicity study in rats (83-3a, MRID No. 43642819, HED Doc. No. 011893) to be acceptable and the data evaluation record to be adequate. The maternal toxicity NOEL/LOEL were considered to be 30 and 180 mg/kg/day, respectively, based on decreases in food consumption, body weight, body weight gain, and carcass weight, hematological changes, and increased mortality. The developmental toxicity NOEL/LOEL were considered to be 30 and 180 mg/kg/day, respectively,

based on decreased fetal body weight/litter, decreased ossification of caudal vertebrae and forelimb metacarpals.

The Committee considered the developmental toxicity study in rabbits (83-3b, MRID No. 43642820, HED Doc. No. 011893) to be acceptable and the data evaluation record to be adequate. The maternal toxicity NOEL/LOEL were considered to be 10 and 20 mg/kg/day, respectively, based on clinical signs (tremors). The developmental NOEL was considered to be 120 mg/kg/day, the highest dose level tested.

D. Acute and Subchronic Neurotoxicity:

The Committee considered the acute neurotoxicity study ~~neurotoxicity study in rats (81-8, MRID No. 43701609, HED Doc. No.~~ 012062) to be acceptable and the data evaluation record to be adequate. The NOEL/LOEL were considered to be 200 and 400 mg/kg/day, respectively, based on clinical signs, and effects on FOB parameters.

The Committee considered the neurotoxicity phase (82-7) of the combined subchronic feeding/neurotoxicity study in rats (MRID No. 43714501, HED Doc. No. 012062) to be acceptable and the data evaluation record to be adequate. The LOEL for neurotoxicity was considered to be 750 ppm (52.72 and 54.61 mg/kg/day in males and females, respectively), and the NOEL for neurotoxicity 75 ppm (5.53 and 5.88 mg/kg/day in males and females, respectively) based on decreased forelimb grip strength in males and females and decreased rears in females at the high dose level.

E. Mutagenicity:

The Committee considered the following mutagenicity studies to be acceptable:

1) Salmonella typhimurium reverse gene mutation assay (MRID No. 43642821; HED Doc. No. 011893). The test was negative up to 2000 ug/plate, the highest concentration tested, in the presence or absence of metabolic activation. Minor revisions were suggested to the data evaluation record.

2) In vitro chromosome aberrations in Chinese hamster ovary (CHO) cells (MRID No. 43701614, HED Doc. No. 011893). The test is negative up to cytotoxic levels (150 ug/ml) in the presence or absence of metabolic activation. Minor revisions were suggested to the data evaluation record.

3) Test for chemical induction of gene mutation at the HGPRT locus in cultured Chinese hamster ovary (CHO) cells with and without metabolic activation. There were no increased induced mutation rate over solvent control values in any test culture treated up to precipitating levels, 49 to 99 ug/ml. Minor

revisions were suggested to the data evaluation record.

4) Micronucleus assay in CD-1 mouse bone marrow cells (MRID No. 43701615, HED Doc. No. 011893): There were no significant increases over solvent control values in micronucleated polychromatic erythrocytes at doses producing systemic toxicity (704 and 1408 mg/kg) or cytotoxicity (141 mg/kg and above). Minor revision were recommended to the data evaluation record.

No other genetic toxicology data requirements have been identified at this time. The Committee concluded that the acceptable studies satisfy the current mutagenicity initial testing battery guidelines.

F. Reference Dose (RfD):

The Committee recommended that an RfD for this chemical not to be established at this time.

It should be noted that this chemical has not been reviewed by the FAO/WHO joint committee meeting on pesticide residue (JMPR) and that an acceptable daily intake (ADI) has not been established by that Committee.

G. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (Chief, SAB; Chairman, RfD/Peer Review Committee), George Ghali (Manager, RfD/Peer Review Committee), Karl Baetcke (Chief, TB I), Mike Ioannou (Acting Chief, TB II), Stephen Dapson, Roger Gardner, Byron Backus, Kit Farwell, Guruva Reddy, William Sette, and Henry Spencer. In attendance also were Debbie McCall HED/RCAB and Rick Keigwin of RD as observers.

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

Brian Dementi Brian Dementi

Edwin Budd Edwin Budd

Respective Branch Chief (Committee member; signature indicates concurrence with the peer review unless otherwise stated)

Karl Baetcke

CC: Stephanie Irene
Albin Kocialski
Karl Baetcke
Edwin Budd
Brian Dementi
Beth Doyle
Amal Mahfouz (OW)
RfD File
Caswell File

H. Material Reviewed:

1. Morrison, R. D. et al. (1994). RH-70, 345: Acute Oral (Gavage) Neurotoxicity Study in Rats. MRID No. 43701609. HED Doc No. 012062. Classification: Acceptable. This study satisfies data requirement 81-8 of Subpart F of the Pesticide Assessment Guideline for acute neurotoxicity testing in rats.

2. Anderson, D. M. et al. (1995). RH-70, 345: Three-Month Dietary Toxicity/Neurotoxicity Study in Rats. MRID No. 43714501. HED Doc. No. 012062. Classification: Supplementary data for the subchronic feeding toxicity phase (82-1a) and acceptable for the subchronic neurotoxicity phase of the study (82-7). This study satisfies data requirement 82-7, but not 82-1a of Subpart F of the Pesticide Assessment Guideline.

3. Kaminski, E. J. et al. (1994). RH-70, 345: Three-Month Dietary Toxicity Study in Dogs. MRID No. 43701610. HED Doc No. 012062. Classification: Acceptable. This study satisfies data requirement 82-1b of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in dogs.

4. Nuttall J. (1994). RH 70, 345: 14 Day Oral (Dietary Administration) Dose Range-Finding Study in the Dog. MRID No. 43701612. HED Doc. No. 012062. Classification: Supplementary data. This range-finding study was not discussed by the Committee.

5. Foss, John A. (1994). Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of RH-70, 345 Administered Orally Via Gavage to Crl: CDBR VAF/Plus Presumed Pregnant Rats. MRID No. 43642819, HED Doc. No. 011893. Classification: Acceptable. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

6. Danberry, T. L. and Shuey, D. L. (1995). RH-70, 345 Technical: Oral (Gavage) Developmental Toxicity Study in Rabbits. MRID No. 43642820. HED Doc. No. 011893. Classification: Acceptable. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

7. Craig, L. P. et al. (1995). RH-70,345: Thirteen Week Dermal Toxicity Study in Rats. MRID No. 43642818. HED Doc. No. 011893. Classification: Acceptable. This study satisfies data requirement 82-3 of Subpart F of the Pesticide Assessment Guideline for subchronic dermal toxicity testing in

rats.

8. Sames, J. and Elia, M. (1994). RH-70,345: Salmonella typhimurium Gene Mutation Assay (Ames Test). MRID No. 43642821, HED Doc. No. 011893. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

9. Pant, K. (1994). Test for Chemical Induction of Gene Mutation at the HGPRT Locus in Cultured Chinese Hamster Ovary (CHO) Cells with and Without Metabolic Activation. RH-70,345. MRID No. 43701613, HED Doc. No. 011893. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

10. Kumaroo, P. (1994). Test for Chemical Induction of Chromosome Aberration Using Monolayer Cultures of Chinese Hamster Ovary (CHO) Cells with and without Metabolic Activation. RH-70,345. MRID No. 43701614, HED Doc. No. 011893. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

11. Sames, J. and Elia, M. (1994). RH-70,345: Micronucleus Assay in CD-1 Mouse Bone Marrow Cells. MRID No. 43701615, HED Doc. No. 011893. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.