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

APR 27 1993

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of **Phostebupirim**

CASRN. 96182-53-5
EPA Chem. Code: ~~129806~~ 129086

FROM: George Z. Ghali, Ph.D. G Ghali 4.7.93
Manager, RfD/Peer Review Committee
Health Effects Division (H7509C)

TO: Robert Forrest, PM 14
Insecticide-Rodenticide Branch
Registration Division (H7505C)

The Health Effects Division RfD/Peer Review Committee met on March 4, and again on April 1, 1993 to discuss and evaluate the toxicology data base submitted in support of Phostebupirim registration and to determine a reference (RfD) dose for this chemical.

The Committee recommended that a Reference Dose should be established based upon a NOEL of 0.02 mg/kg/day for plasma, red blood cell and brain cholinesterase inhibition observed at 0.13 mg/kg/day in a long-term feeding study in dogs, using an uncertainty factor (UF) of 100 to account for inter-species extrapolation and intra-species variability. On this basis the **RfD** was calculated to be **2 E-4 (0.0002 mg/kg/day)**.

The Committee considered the long-term feeding study in dogs **(83-1a)**, rats **(83-1b and -2a)** and mice **(83-2b)** to be acceptable and the data evaluation records to be adequate. The Committee considered the reproductive toxicity study in rats **(83-4)** and the developmental toxicity studies in rats **(83-3a)** and rabbits **(83-3b)** to be acceptable and recommended upgrading the reproductive toxicity study in rats from a Core-supplementary to a Core-minimum status. Except for minor revision to the data evaluation record of the chronic toxicity/carcinogenicity study in rats, the carcinogenicity study in mice and the reproductive toxicity study in rats, all the data evaluation records were considered adequate. The Committee recommended to the respective branch to revise the NOEL established in the data evaluation records of the long-term studies in rats and mice, redefine the NOEL/LOEL for reproductive toxicity, revise the NOEL/LOEL for maternal toxicity established in the data evaluation record of the reproduction study and upgrade this study to a Core-Minimum status.

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The need for additional data e. g. ninety-day neurotoxicity and ocular toxicity studies in accordance with the current Agency Guidelines was discussed by the Committee. However, the Committee deferred this issue to the respective branch for an action.

The high dose tested in the carcinogenicity studies in rats and mice were adequate based on cholinesterase inhibition. The chemical did not alter the spontaneous tumor profile in these strains of rats and mice under the test conditions. On the basis of these two studies, the Committee classified the chemical as a **"Group E"**.

A. Individual in Attendance

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

William Burnam

Reto Engler

Marcia Van Gemert

Karl Baetcke

Henry Spencer

William Sette

Roger Gardner

Stephen Dapson

David Anderson

Esther Rinde

George Ghali

Rick Whiting

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

Alan Levy

Elizabeth Doyle

3. Others:

Albin Kocialski, Stephanei Willet of CCB/HED as observers

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Marcia Van Gemert
Elizabeth Doyle
Alan Levy
James Kariya
Albin Kocialski

B. Material Reviewed

Material available for review included a reference dose summary document, 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. Porter, M. C. et al. (1991). Safety evaluation of MAT 7484: Chronic (1-year) feeding study in dogs. MRID No. 42005452, 42119301, HED Doc. 009954.

Core Classification: Core Minimum (according to the DER).

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer interpretation of data and classification of the study. The study is acceptable and the DER is adequate. This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in a non-rodent species.

2. Eiben, R. (1991). MAT 7484, Study of the chronic toxicity and carcinogenicity to Wistar rats (administered in the feed for 24 months). MRID No. 42005451, HED Doc. No. 009954.

Core Classification: Core Minimum (according to the DER).

Committee's Conclusions and Recommendations:

The Committee recommended to the respective branch to lower the NOEL for cholinesterase inhibition from 5 to 1 ppm. The Committee generally agreed with the reviewer interpretation of data and classification of the study. The high dose tested in this study was considered adequate for carcinogenicity testing. The study is acceptable and the DER is adequate. The treatment did not alter the spontaneous tumor profile for this strain of rats under the test conditions. This study satisfies data requirement 83-5 (83-1b and 83-2a) of Subpart F of the Pesticide Assessment Guideline for chronic toxicity and carcinogenicity testing in the rat.

3. Eiben, R. (1991). MAT 7484, Study of the chronic toxicity and carcinogenicity to B6C3F1 mice (administered in the feed for 24 months). MRID No. 42005453, HED Doc. No. 009954.

Core Classification: Core Minimum (according to the DER).

Committee's Conclusions and Recommendations:

The Committee recommended to the respective branch to lower the NOEL for cholinesterase inhibition from 9 to 1 ppm. The Committee generally agreed with the reviewer interpretation of data and classification of the study. The high dose tested in this study was considered adequate for carcinogenicity testing. The study is acceptable and the DER is adequate. The treatment did not alter the spontaneous tumor profile for this strain of mice under the test conditions. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity and carcinogenicity testing in the mice.

4. Becker, H. et al. (1989). Embryotoxicity study (including teratogenicity) with MAT 7484 technical in the rat. MRID No. 42005454, HED Doc. No. 009954.

Core Classification: Core Minimum (according to the DER).

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer interpretation of data and classification of the study. The study is acceptable and the DER is adequate. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in the rat.

5. Renhof, M. et al. (1989). MAT 7484, study of embryotoxicity effects on rabbits after oral administration. MRID No. 42005454, HED Doc. No. 009954.

Core Classification: Core Minimum (according to the DER).

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer interpretation of data and classification of the study. The study is acceptable and the DER is adequate. This study satisfies data requirement 83-3b of Suppart F of the Pesticide Assessment Guideline for developmental toxicity testing in the rat.

6. Clemens, G. R. et al. (1990). A two-generation reproduction study with MAT 7484 in the rat. MRID No. 42005456, HED Doc. No. 009954.

Core Classification: Core Minimum (according to the DER).

Committee's Conclusions and Recommendations:

The Committee generally agreed with the reviewer interpretation of data and classification of the study. However, the Committee recommended to the respective branch to upgrade the study to a Core Minimum status. The Committee also recommended to the respective branch to redefine the NOEL/LOEL for reproductive toxicity and to

revise the NOEL/LOEL for maternal toxicity. The NOEL for reproductive toxicity was considered to be 5 ppm based on decrease in fertility indices. The Study did not demonstrate a NOEL for Maternal toxicity in F1 adults. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in the rat.

C. Conclusions and Recommendations

1. Data Base

The Committee considered the long-term feeding study in dogs **(83-1a)**, rats **(83-1b and -2a)** and mice **(83-2b)**, the developmental toxicity studies in rats and rabbits **(83-3a and -3b)** and the reproductive toxicity study in rats **(83-4)** to be acceptable and the data evaluation records to be adequate. The Committee recommended some revisions to the data evaluation records of the long-term studies in rats and mice and the reproductive toxicity study in rats.

The need for additional data e. g. ninety-day neurotoxicity and ocular toxicity studies in accordance with the current Agency Guidelines was discussed by the Committee. However, the Committee deferred this issue to the respective branch for an action.

2. Reference Dose (RfD)

The Committee recommended that a Reference Dose (RfD) should be established based upon a NOEL of 0.02 mg/kg/day for plasma, red blood cell and brain cholinesterase inhibition observed at 0.13 mg/kg/day in a long-term feeding study in dogs, using an uncertainty factor (UF) of 100 to account for inter-species extrapolation and intra-species variability. On this basis the **RfD** was calculated to be **2 E-4 (0.0002 mg/kg/day)**.

3. Carcinogenicity

The high dose tested in the carcinogenicity studies in rats and mice was considered to be adequate for carcinogenicity testing. The chemical did not alter the spontaneous tumor profile in these strains of rats and mice under the test conditions. On this bases, the Committee classified the chemical as a **"Group E"**.

4. Acute Toxicity Concern

Although the chemical is considered a very potent cholinesterase inhibitor, the available data did not warrant dietary acute toxicity concern based on the current dietary exposure profile. No conclusion can be made regarding the occupational safety since no estimates on worker exposure were available to the Committee. The data did not warrant acute toxicity concern based on developmental toxicity.