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

FEB - 7 1996

January 31, 1996

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

SUBJECT: Phorate - Amendment to RfD report

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

FROM: Yung G. Yang, Ph.D. Yung G. Yang 1/31/96
Toxicology Branch II, Section II
Health Effect Division (7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 1/31/96
Section Head, Section II
Toxicology Branch II, HED (7509C)

and

Stephanie R. Irene, Ph.D. Stephanie R. Irene 2/6/96
Acting Branch Chief
Toxicology Branch II, HED (7509C)

Chemical: Phorate
Caswell No.: 660
PC No.: 057201
Registrant: American Cyanamid Co.

As a result of the January 23, 1996 HED Less Than Lifetime Hazard Assessment meeting of phorate, it was decided that an amendment should be attached to the HED/RfD/Peer Review Report (Ghali, 12/30/93) for the following changes:

5. Teratology study with phorate in rabbits (MRID# 40174528):

For developmental toxicity:

- Change the **NOEL from 0.5 mg/kg/day to 1.2 mg/kg/day** (HDT)

- The change is based on the conclusion that the increase in the incidence of angulated hyoid arches was an artifact. Also the incidence was not dose related.

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DEC 30 1993

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MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: RfD/Peer Review Report of Phorate (Thimet)

CASRN. 298-02-2
EPA Chem. Code: 057201
Caswell No. 660

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

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

Lois Rossi, Chief
Reregistration Branch
Special Review and Reregistration Division (H7508W)

The Health Effects Division RfD/Peer Review Committee met on September 16, 1993 to evaluate the existing toxicology data in support of Phorate re-registration and to re-reassess the Reference Dose (RfD) for this chemical.

The RfD for this chemical was first assessed by the Health Effects Division RfD Committee on June 13, 1986 and again reassessed on May 5, 1986. Verification by the Agency RfD Work Group was deferred once on August 5, 1986 and again on July 20, 1988 pending a final Agency position on cholinesterase issue. At that time the RfD, as proposed by the RfD Committee, was based on a no-observable effect level (NOEL) of 0.05 mg/kg/day for depression of red blood cell and brain cholinesterase activity and tremors in males and females observed at 0.25 mg/kg/day in a one-year feeding study in dogs. An Uncertainty Factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.0005 mg/kg/day. In the meeting of September 16, 1993 the RfD Peer Review Committee recommended that the existing RfD remain unchanged. It should be noted that a regulatory value of 0.0002 mg/kg/day was established for this chemical by the World Health Organization (WHO) in 1985.

The Committee considered the chronic toxicity study in rats

A. Individual 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

William Sette

James Rowe

John Tice

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

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

Clark Swentzel

3. Others

L. Hansen, A. Protzel and D. McCall as observers

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Marcia Van Gemert
Clark Swentzel
James Kariya
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tables. This study satisfies data requirement 83-1a and 83-2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

3. Goldsmith, L. A. et al. (report 1981, addendum 1982). 18-Month chronic toxicity and potential carcinogenicity study in mice. MRID No. 00092853, HED Doc. No. 007010.

Core Classification: Core-minimum data.

Committee's Conclusion and Recommendation:

The chemical was tested in Swiss Albino (CD-1) mice at 1, 3 and 6 ppm (equivalent to 0.15, 0.45 and 0.9 mg/kg/day). The NOEL/LOEL were considered to be 0.45 and 0.9 mg/kg/day based on slight decrease in weight gain in females in the first 25 weeks. The dose level tested was considered adequate for carcinogenicity testing based on the results of the range finding study. The treatment did not alter the spontaneous tumor profile in this strain of mice. The study was considered to be acceptable and the data evaluation record was considered to be adequate as is. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

4. Beliles, R. P. and Weir, R. J. (1979). Teratology study in rats. MRID No. 00122775, HED Doc. 007010.

Core Classification: Guidline data.

Committee's Conclusion and Recommendation:

The chemical was tested in CRL:COBS CD(SD)BR rats at 0.125, 0.25 and 0.5 mg/kg/day. Maternal toxicity NOEL/LOEL were considered to be 0.25 and 0.50 mg/kg/day. The developmental NOEL/LOEL were considered to be 0.25 and 0.50 mg/kg/day based on heart enlargement. The Committee agreed with the reviewer's evaluation and interpretation of data. The study was considered to be acceptable and the data evaluation record was considered to be adequate as is provided that a table for selected skeletal variations will be added. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

5. Schroeder, R. (1987). Teratology study with phorate in rabbits. MRID No. 40174528, HED Doc. 007010.

Core Classification: Core-minimum data.

Committee's Conclusion and Recommendation:

The chemical was tested in New Zealand rabbits at 0.15, 0.50, 0.90

C. Conclusions and Recommendations

1. Reference Dose

The RfD for this chemical was first assessed by the Health Effects Division RfD Committee on June 13, 1986 and again reassessed on May 5, 1986. Verification by the Agency RfD Work Group on was deferred once on August 5, 1986 and again on July 20, 1988 until a final Agency position on cholinesterase issue is defined by the Risk Assessment Forum. At that time the RfD, as determined by the RfD Committee, was based on a no-observable effect level (NOEL) of 0.05 mg/kg/day for depression of red blood cell and brain cholinesterase activity and tremors in males and females observed at 0.25 mg/kg/day in a one-year feeding study in dogs. An Uncertainty Factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.0005 mg/kg/day. In the meeting of September 16, 1993 the RfD Peer Review Committee recommended that the existing RfD remain unchanged. It should be noted that a regulatory value of 0.0002 mg/kg/day was established for this chemical by the World Health Organization (WHO) in 1985.

2. Data Base

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

3. Carcinogenicity

The Committee considered the high dose levels tested in the carcinogenicity studies in rats and mice to be adequate for carcinogenicity testing. This conclusion was based on cholinesterase inhibition observed in the rat study and on the results of a range-finding study in mice. The treatment did not alter the spontaneous tumor profile in these strains of rats and mice. The chemical was classified as a "Group E" carcinogen.

4. Developmental and Reproductive Toxicity

There was only limited evidence, based on the available data, to suggest that the chemical was associated with significant reproductive or developmental toxicity under the testing conditions. However, since Phorate is a potent cholinesterase inhibitor, the Committee recommended that a reproductive/developmental neurotoxicity study be conducted in accordance with the Agency Guideline.