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

DEC 30 1993

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

(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.

The Committee considered the high dose levels tested in the carcinogenicity studies in rats and mice to be adequate for carcinogenicity testing in these strains of rats and mice. 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 under the testing conditions. The chemical was classified as a "Group E" carcinogen.

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.

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
RfD File
Caswell File

B. Material Reviewed:

Material available for review by the Committee included data evaluation records for the chronic toxicity/carcinogenicity study in rats (83-1a), the long-term toxicity study in dogs (83-1b), the carcinogenicity study in mice (83-2b), the developmental toxicity studies in rats and rabbits (83-3a and -3b) and the reproductive toxicity study in rats (83-4) and the tox-one liner. The Committee focused the discussion on the following studies:

1. Shellenberger, T. and Tegeris, A. (1987). One-year oral toxicity study in purebred Beagle dogs with Ac 35,024. MRID No. 40174527, HED Doc. No. 007010.

Core Classification: Core-minimum data.

Committee's Conclusions and recommendations:

The chemical was tested in Beagle dogs at 0.005, 0.01, 0.05 and 0.25 mg/kg/day. The NOEL/LOEL for systemic toxicity were considered to be 0.05 and 0.25 mg/kg/day based upon slight decrease in body weight gain in males and tremors in both sexes. The NOEL for plasma and brain cholinesterase were considered to be 0.01 and 0.05 mg/kg/day, respectively. The Committee agreed with the reviewer's evaluation and interpretation of data. The study was considered acceptable and the data evaluation record was considered adequate. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

2. Goldsmith, L. A. et al. (1981). Twenty-four month chronic toxicity and carcinogenicity study. MRID No. 00122774, HED Doc. No. 007010.

Core Classification: Core-minimum data

Committee's Conclusions and Recommendations:

The chemical was tested in Charles River rats [CRL:COBS CD (SD) BR] at 1, 3 and 6 ppm (equivalent to 0.05, 0.15 and 0.3 mg/kg/day). A NOEL for plasma cholinesterase inhibition was not established in males, plasma cholinesterase inhibition was observed in males at 0.05 mg/kg/day and in females at 0.15 mg/kg/day. The NOEL for RBC cholinesterase inhibition was considered to be 0.3 mg/kg/day in males and 0.15 mg/kg/day in females. The NOEL for brain cholinesterase inhibition was considered to be 0.15 mg/kg/day in males and 0.05 mg/kg/day in females. The high dose level tested was considered adequate for carcinogenicity testing in both males and females based on cholinesterase inhibition. The treatment did not alter the spontaneous tumor profile in this strain of rats. The study was considered to be acceptable and the data evaluation record was considered to be adequate after the addition of tumor

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

and 1.20 mg/kg/day. The maternal toxicity NOEL/LOEL were considered to be 0.15 and 0.50 mg/kg/day, based on mortality and body weight loss. The developmental NOEL was considered to be 1.2 mg/kg/day, the highest dose tested. The Committee agreed with the reviewer's evaluation and interpretation of data. However, the Committee considered the developmental toxicity NOEL to be 0.50 mg/kg/day based upon a dose-related increase in the incidence of angulated hyoid arches. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

6. Morici, I. J. et al. (1965). Thimet systemic insecticide: successive generation studies with mice. MRID No. 00092853, HED Doc. No. 007010.

Core Classification: Core-minimum data.

Committee's Conclusion and Recommendation:

The chemical was tested in Albino mice at 0.6, 1.50 and 3.0 ppm (equivalent 0.12, 0.3 and 0.54 mg/kg/day in males and 0.13, 0.33 and 0.64 mg/kg/day in females). The reproductive toxicity NOEL/LOEL were considered to be 0.3 and 0.54 mg/kg/day in males and 0.33 and 0.64 mg/kg/day in females, based on effects on viability and lactation indices. The study was considered to be unacceptable. The Committee recommended to down-grade the study to a Core-supplementary status. This study does not satisfy data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rodents. A combined reproductive-developmental neurotoxicity study will be required to support the re-registration of this chemical.

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.