1. Phosmet

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

MAY 11 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: RfD/Peer Review Report of **Phosmet** (Imidan) [N-(mercaptomethyl) phthalimide S-(O,O-dimethylphosphorodithioate).

CASRN. 732-11-6
EPA Chem. Code: 059201
Caswell No. 543

FROM: George Z. Ghali, Ph.D. G. Ghali
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Health Effects Division (H7509C)

TO: George LaRocca, PM 13
Insecticide-Rodenticide Branch
Registration Division (H7505C)

Lois Rossi, Chief
Re-registration Branch
Special Review and Re-registration Division (H7508W)

The Health Effects Division RfD/Peer Review Committee met on March 3, 1994 to discuss and evaluate the existing toxicology data in support of Phosmet re-registration and to re-assess the Reference Dose (RfD) for this chemical in light of recently submitted data.

Material available for review included data evaluation records for two chronic toxicity/carcinogenicity studies in rats (83-1a and -2a, or 83-5), a carcinogenicity study in mice (83-2b), a long-term feeding study in dogs (83-1b), a two-generation reproduction in rats (83-4), a developmental toxicity study in rats (83-3a) and two developmental toxicity studies in rabbits (83-3b).

The RfD for this chemical was first assessed by the Health Effects Division RfD Committee on May 21, 1986 and verified by the Agency RfD Work Group on June 10, 1986. Subsequently, the RfD for this chemical was reassessed by the RfD Committee on March 4, and October 21, 1988. At that time the RfD was based on a two-year feeding study in rats with a no-observable effect level (NOEL) of 2.0 mg/kg/day. Decreased body weight gain and increased liver cell vacuolization were observed at the next dose level of 20 mg/kg/day. An uncertainty factor (UF) of 100 was used to account for inter-

species extrapolation and intra-species variability. On this basis the **RfD** was calculated to be 0.02 mg/kg/day.

Subsequently, a new chronic toxicity study in rats was submitted demonstrating a threshold NOEL of 1.1 mg/kg/day. Red blood cell (15-20%) and serum (5-36% in males and 15-25% in females) cholinesterase were inhibited at the next higher dose level (1.8 and 2.1 mg/kg/day in males and females, respectively). Systemic effects manifested as increased incidences of fatty changes in liver were observed in males at all dose levels including controls. The Committee discounted the toxicological significance of such an effect based on the fact that it was not well characterized, did not appear to be a dose-related effect and was not accompanied by other hepatic alterations at the low and mid-dose levels.

In the meeting of March 3, 1994 the Committee recommended that the RfD be based on a NOEL of 1.1 mg/kg/day established in the recent chronic toxicity study in rats described above. An uncertainty factor (UF) of 100 was used to account for inter-species extrapolation and intra-species variability. On this basis the **RfD was calculated to be 0.01 mg/kg/day**. It should be noted that this chemical had been reviewed and an acceptable daily intake (ADI) of 0.02 mg/kg/day has been established for this chemical by the World Health Organization (WHO) in 1979.

Although brain cholinesterase in the mouse study (83-2B, MRID No. 00141659, 00160114, 40595501) appeared to be inhibited at or below 1 mg/kg/day, the reduction in cholinesterase activity was inconsistent and was not dose-dependent indicating that cholinesterase measurement in this study was not reliable. Therefore, the NOEL for cholinesterase inhibition demonstrated in the mouse study was not considered in the setting of the RfD for this chemical.

The Committee considered the chronic toxicity study in rats (83-1a, MRID No. 41916401) to be acceptable and the data evaluation record (HED Doc. No. 009828) to be adequate. The adequacy of the chronic toxicity study in dogs (83-1b, MRID No. 00062651, 00075419, 00076436, 00080431, 00080556) and/or the data evaluation record for this study (HED Doc. No. 001999) were questioned by the Committee. The data evaluation record for this study was very brief and inconclusive. Revaluation of the study was considered necessary by the Committee. However, the general consensus was to limit any additional work on this study to updating the data evaluation record by including data summary tables to confirm the findings and conclusions reported (Note: as of the date of this report the study has already been reevaluated and the data evaluation record has been updated, HED Doc. No. 010826). There was another chronic toxicity study in rats (MRID No. 00062651, 00075419, 00076436, 00080431, 00080556) not classified. This study and the data evaluation record were considered to be inadequate.

The developmental toxicity studies in rats (83-3a, MRID No. 41962902) and rabbits (83-3b, MRID No. 41962901) and the reproductive toxicity study in rats (83-4, MRID No. 41520001) were considered to be acceptable. The data evaluation records for the developmental toxicity studies (HED Doc. No. 009422; 009422) were considered to be adequate as presented. The data evaluation record for the reproductive toxicity study in rats (HED Doc. No. 010205) appeared to be inadequate as presented. The Committee recommended reevaluation of the reproductive toxicity study to preclude any possible effect on mating behavior resulting from cholinesterase inhibition (Note: as of the date of this report the study has already been reevaluated and the data evaluation record has been updated (HED Doc. No. 010898). It was concluded that "the conclusions as stated in the previous DER are supported by the results....."). The Committee recommended to lower the maternal toxicity NOEL in the rat developmental toxicity study to 5 mg/kg/day based on body weight gain decrease during the dosing period (HED Doc. No. 010898). There was another developmental toxicity study in rats (MRID No. 005102) classified as supplementary. This study was considered to be inadequate. There was no evidence, based on the available data, to suggest that phosmet was associated with significant reproductive or developmental effects under the testing conditions.

The Committee was informed that acute and subchronic neurotoxicity studies have already been requested.

The carcinogenicity studies in rats (83-2a, MRID No. 00041916401) and mice (83-2b, MRID No. 00000141659, 00160114, 40595501) were not discussed by the RfD Peer Review Committee. The carcinogenicity issue has already been addresses by the Health Effects Division-Carcinogenicity Peer Review Committee (HED-CPRC). The chemical was classified as a "Group C", possible human carcinogen, based on mouse liver tumor (HED report dated March 7, 1994).

A. Individuals in Attendance

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

Marcia Van Gemert

Karl Baetcke

Henry Spencer

Roger Gardner

James Rowe

William Sette

Stephen Dapson

George Ghali

2. Peer Review Committee Members and associates in absentia (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

Reto Engler

Rick Whiting

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

[redacted]

William Greear

4. Others:

T. McMahon and K. Locke of HED as observers

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Karl Baetcke
Marion Copley
William Greear
James Kariya
RfD and Caswell Files

RfD and Caswell Files

B. Material Reviewed

Material available for review included data evaluation records for two chronic toxicity/carcinogenicity studies in rats (83-1a and -2a, or 83-5), a carcinogenicity study in mice (83-2b), a long-term feeding study in dogs (83-1b), a two-generation reproduction in rats (83-4), a developmental toxicity study in rats (83-3a) and two developmental toxicity studies in rabbits (83-3b).

1. Chang, J. C. F. et al. (1991). Two-year chronic toxicity/ oncogenicity study with R-1504 in rats. MRID No. 41916401, HED Doc. No. 009828, 010758. Classification: Core-minimum data. This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats.

2. Woodard, G. (1966). Imidan: Safety evaluation by two-year feeding studies in the rat and the dog. MRID No. 0062651, 00075419, 00076436, 00080431, 00080556, HED Doc. No. 001999, 010826*. Classification: Core-minimum data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

3. Meyer, L. S. and Walberg, J. A. (1990). A two-generation reproduction study in rats with R-1504. MRID No. 41520001, HED Doc. No. 010205, 010898*. 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.

4. Hodge, M. C. E. (1991). Phosmet: teratogenicity study in rats. MRID No. 41962902, HED Doc. No. 009422, 010898*. Classification: Guideline data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

5. Moxon, M. E. (1991). Phosmet: teratogenicity study in rabbits. MRID No. 41962901, HED Doc. No. 009422. 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.

6. Katz, A. (1984). Two-year dietary oncogenicity in mice with Imidan technical. MRID No. 00141659, 00160114, 40595501, HED Doc. No. 005304, 006853. Classification: Guideline data. For more information about this study, please see the carcinogenicity peer review report dated March 7, 1994.

*Completed subsequent to the March 3, 1994 meeting.