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

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DATE: September 25, 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **PHORATE - *FQPA REQUIREMENT*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland Jess Rowland 9/25/97
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THROUGH: K. Clark Swentzel K. Clark Swentzel 9/25/97
Chairman, Hazard Identification Assessment Review Committee
Toxicology Branch II, Health Effects Division (7509C)

TO: Mike Metzger
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BACKGROUND: On September 8, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Phorate with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Phorate as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Reregistration Eligibility Document. The Committee's decisions are summarized below.

CC: Rick Whiting, Science Analysis Branch
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A. INTRODUCTION

The Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Phorate with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Phorate as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Reregistration Eligibility Document.

B. RESULTS

1. Neurotoxicity

- In an acute delayed neurotoxicity study, hens received an oral administration of a single dose of Phorate at 14.2 mg/kg (LD_{50}). A second administration, at the same dose, was given after a 21-day interval. Phorate did not cause neurological changes indicative of delayed neurotoxicity. The Committee noted that this study did not assess for the potential of Phorate to inhibit neurotoxic esterase (NTE) in hens (MRID No. 00152640).

- No acute or subchronic neurotoxicity studies are available and thus data on cholinesterase inhibition, FOB, and histopathology on the central and peripheral nervous system are not available for evaluation after single or repeated exposures to Phorate.

2. Developmental Toxicity

- The developmental toxicity studies in rats and rabbits showed no evidence of additional sensitivity to young rats or rabbits following pre- or postnatal exposure to Phorate and comparable NOELs were established for adults and offspring.

- In a developmental toxicity study pregnant Crl:COBS-CD(SD) rats received oral doses of Phorate in corn oil at 0, 0.125, 0.25 or 0.5 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 0.25 mg/kg/day and the LOEL was 05 mg/kg/day based on increased mortality, convulsions, and hypothermia. For developmental toxicity, the NOEL was 0.25 mg/kg/day and the LOEL was 0.5 mg/kg/day based on enlarged heart. The enlargement of heart was considered to be a physiological effect resulting from anticholinesterase activity of Phorate and not a true developmental effect. There was no evidence of teratogenicity (MRID No. 00122775).

- In a developmental toxicity study, pregnant New Zealand White rabbits were given single oral doses of Phorate 0, 0.15, 0.5, 0.9 or 1.2 mg/kg/day during gestation days 6 through 18. For maternal toxicity, the NOEL was 0.15 mg/kg/day and the LOEL was 0.5 mg/kg/day based on increased mortality and body weight loss. For developmental toxicity, the NOEL was 1.2 mg/kg/day (HDT); a LOEL was not established. There was no evidence of teratogenicity (MRID No. 40174528).

3. Reproductive Toxicity

- An acceptable two-generation reproductive toxicity study is not available in the data base.

4. Cholinesterase Inhibition

- No data are available to compare the effects of Phorate on cholinesterase activity in the adults and/or pups since this endpoint was not evaluated in the developmental toxicity studies in rats and rabbits. In addition, data gap exists for acute and subchronic neurotoxicity studies.

5. Developmental Neurotoxicity

- Data available to assess the potential developmental neurotoxicity of Phorate are limited due to the lack of neurotoxicity (acute and subchronic) as well as the reproductive toxicity studies. Since Phorate is potent cholinesterase inhibitor, the RfD Committee recommended that a combined reproductive/developmental neurotoxicity study be required as confirmatory data to support reregistration of Phorate (see RED). This Committee concurs with the recommendation made by the RfD Committee.

6. Reference Dose (RfD)

- An RfD of 0.0005 mg/kg/day was derived from the NOEL of 0.05 mg/kg/day and an Uncertainty Factor (UF) of 100. The LOEL was based on tremors and inhibition of red blood cell and brain cholinesterase activity observed at 0.25 mg/kg/day in dogs in a chronic toxicity study. The UF of 100 included a 10 for intra-species and 10 for inter-species variation.

7. Data Gaps

- Acute and subchronic neurotoxicity studies in rats

- A combined reproductive/developmental neurotoxicity study

C. CONCLUSIONS

The Committee's conclusions on the Uncertainty Factors for acute and chronic dietary risk assessments are as follows:

1. Acute Dietary Risk Assessment

The endpoint selected for acute dietary risk assessment is based on inhibition of plasma cholinesterase activity at 0.25 mg/day in dogs. The NOEL was 0.05 mg/kg/day. A Margin of Exposure of 100 was recommended.

For acute dietary risk assessment, the Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children **(as required by FQPA) should be retained**. Therefore, **a Margin of Exposure of 1000 is required** to ensure protection of this population from acute exposure to Phorate for reasons stated below:

(i) Lack of acute and subchronic neurotoxicity studies. Data on cholinesterase inhibition, FOB, and histopathology on the central and peripheral nervous system are not available for evaluation after a single exposure to Phorate.

(ii) Lack of a two-generation reproduction study which would have enabled an evaluation of sensitivity between adults and pups.

2. Chronic Dietary Risk Assessment

The endpoint for chronic dietary risk assessment is based on red blood cell and brain cholinesterase inhibition observed at 0.25 mg/kg/day (LOEL) in dogs. The NOEL was 0.05 mg/kg/day. An UF of 100 applied to the NOEL (10 x each for inter and intra species variability) to derive the RfD.

For chronic dietary risk assessment, the Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be retained for a total UF of 1000** (i.e., 10 for inter-species variation x 10 for intra-species variation x 10 for FQPA). **Therefore, the revised RfD is 0.00005 mg/kg/day.** An UF of 1000 is supported by the following factors:

(i) Lack of acute, subchronic neurotoxicity studies. Data on cholinesterase inhibition, FOB, and histopathology on the central and peripheral nervous system are not available for evaluation after repeated exposures to Phorate.

(ii) Lack of a two-generation reproduction study which would have enabled an evaluation of sensitivity between adults and pups.