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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: February 12, 1998

MEMORANDUM

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

FROM: Jess Rowland 2/11/98
Executive Secretary,
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: Melba Morrow,
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BACKGROUND: On February 3, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee met to re-assess the FQPA requirement for Phorate. The Committee's decisions are summarized below.

I. INTRODUCTION

On September 8, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) determined that the **10 x factor** to account for enhanced sensitivity of infants and children (as required by FQPA) **should be retained** to ensure protection from exposure to Phorate for the following reasons:

(i) Data gap for acute and subchronic neurotoxicity studies. Data on cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology on the central and peripheral nervous system were not available for evaluation after single or repeated exposures to Phorate.

(ii) Data gap for a two-generation reproduction toxicity study in rats which precluded an evaluation of potential susceptibility in offsprings as compared to adults.

Since the September 8, 1997 meeting, the Agency has received and reviewed a developmental toxicity study in rats and a two-generation reproduction study in rats.

On February 3, 1998, the HIARC met to evaluate these studies and re-assess the FQPA factor in light of these studies. The Committee's conclusions are presented below:

II. Evaluation of the New Data:

In a developmental toxicity study, pregnant Crl:CD®BR rats (24-25/dose) received oral administration of Phorate (92.1%) in corn oil at dose levels of 0, 0.1, 0.2, 0.3 or 0.4 mg/kg/day from days 6 through 15 of gestation. For maternal toxicity, the NOEL was 0.3 mg/kg/day and the LOEL was 0.4 mg/kg/day, based on mortality, clinical signs indicative of neurotoxicity, decreases in body weight and body weight gain and food consumption and gross pathology. Developmental toxicity was manifested as decreased fetal weights and increased incidence of skeletal variations (delayed ossification of the sternum and pelvis). For developmental toxicity, the NOEL was 0.3 mg/kg/day and LOEL was 0.4 mg/kg/day (MRID No. 44422301).

In a two-generation reproduction study, groups of male and female Sprague-Dawley rats (25/sex) were fed diets containing Phorate (92.1%) at dose levels of 0, 1, 2, 4, or 6 ppm (0, 0.087, 0.176, 0.359 or 0.603 for males and 0, 0.103, 0.210, 0.420 or 0.727 for females) for two successive generations. For parental systemic toxicity, the NOEL was 2 ppm (0.2 mg/kg/day) and the LOEL was 0.4 mg/kg/day based on clinical signs (tremors) and inhibitions of plasma and brain cholinesterase activity (F_1 females only). For offspring toxicity, the NOEL was 0.2 mg/kg/day and the LOEL was 0.4 mg/kg/day based on decreased pup survival and pup body weight. The decrease in pup survival was seen during early lactation and the decrease in pup body weights was seen during the later part of lactation (MRID No. 44422302).

III. Determination of Developmental Neurotoxicity Study

The HIARC at the September 8, 1997 meeting re-affirmed the previous RfD Committee's recommendation of a combined reproductive/developmental neurotoxicity study in rats.

The Agency has received a new developmental toxicity study in rats and a 2-generation reproduction toxicity study in rats that do not show increased susceptibility. In addition, these studies do not demonstrate any findings indicative of effects on the developing nervous system. Although this would provide support for not requiring a developmental neurotoxicity, it was noted that histopathological evaluation of perfused tissue in rats was not available in the data base. Due to concerns regarding the potency of this chemical, and in the absence of this histopathological data, the HIARC, at the February 3, 1998 meeting decided to place the requirement for this study under **reserve** status pending receipt of the acute and subchronic neurotoxicity studies. A combined reproductive/developmental neurotoxicity study is no longer considered necessary, since an adequate assessment of reproductive toxicity has been provided.

IV. Re-assessment of FQPA Factor

The core studies required under 40 CFR Part 158, for the assessment of effects following pre-and postnatal exposure, have been received by the Agency and were found to be adequate. However, uncertainties still exists regarding the need for a developmental neurotoxicity study and an assessment of functional development.

The developmental toxicity studies showed no increased susceptibility in fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits. Similarly, the two generation reproduction toxicity study in rats showed no increased sensitivity in pups when compared to adults. However, the Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be reduced to 3 x** for the following reason:

- Data gap exists for acute and subchronic neurotoxicity studies. Therefore, data on cholinesterase inhibition, neurobehavioral effects (FOB) and histopathology on the central and peripheral nervous system were not available for evaluation after single or repeated exposures to Phorate.

V. Determination of Uncertainty Factors (UFs)and Margins of Exposures (MOEs)

1. Acute Dietary Risk Assessment: The Committee determined that a **MOE of 300 is required** for the protection of the U.S. General Population including infants and children from acute exposure to Phorate. This MOE includes the conventional 100 and 3 x for FQPA.

2. Chronic Dietary Risk Assessment: The Committee determined that an **UF of 300 is required** for the protection of the U.S. General Population including infants and children from chronic exposure to Phorate. Based on the UF of 300 (10 x for inter-species, 10 x for intra-species variations and 3 x for FQPA), the Reference Dose (RfD) is revised as follows:

Revised RfD = $\frac{\text{0.05 mg/kg/day (NOEL)}}{\text{300 (UF)}}$ = **0.0002 mg/kg/day**

3. Occupational/Residential Risk Assessments. The Committee determined that a **MOE of 300 is required** for the protection of the U.S. General Population including infants and children from occupational/residential exposures to Phorate.

VI. Toxicology Endpoints Selected for Risk Assessments

The doses and endpoints for acute and chronic dietary as well as occupational/residential exposure risk assessments are tabulated below. The reader is referred to the RfD/Peer Review report (12/30/93) and the Toxicology Endpoint Selection Document (1/29/96) for Executive Summaries and rationales employed in selecting the doses and endpoints for the various risk assessments.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE REQUIRED
Acute Dietary	NOEL=0.05	Inhibition of RBC and brain cholinesterase activity	Chronic Toxicity - Dog	300
Chronic Dietary	NOEL=0.05	Inhibition of RBC and brain cholinesterase activity	Chronic Toxicity - Dog	300
	300			
Short-Term (Dermal) [a]	Oral NOEL=0.05	Inhibition of RBC and brain cholinesterase activity	Chronic Toxicity - Dog	300
Intermediate-Term (Dermal) [a]	Oral NOEL=0.05	Inhibition of RBC and brain cholinesterase activity	Chronic Toxicity - Dog	300
Long-Term (Dermal) [a]	Oral NOEL=0.05	Inhibition of RBC and brain cholinesterase activity	Chronic Toxicity - Dog	300
Inhalation (Any time period) [a]	Oral NOEL=0.05	Inhibition of RBC and brain cholinesterase activity	Chronic Toxicity - Dog	300

a = Appropriate route-to-route extrapolations should be performed for these risk assessments [i.e., the dermal and inhalation exposure components using the appropriate absorption rates (100% default value for dermal and for inhalation) should be converted to equivalent oral doses and compared to the oral NOEL).