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

DATE: October 20, 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

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

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BACKGROUND: On September 30, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Phostebupirim 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 Phostebupirim as required by the Food Quality Protecting Act (FQPA) of 1996. The Committee's decisions are summarized below.

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A. INTRODUCTION

The Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Phostebupirim 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 Phostebupirim as required by the Food Quality Protecting Act (FQPA) of 1996.

B. RESULTS

1. Neurotoxicity

- In an acute delayed neurotoxicity study, no delayed neurotoxicity or neuropathology was seen in hens given single oral doses of Phostebupirim at 10 mg/kg on day 0 and a second administration at the same dose on day 22 (MRID No.42088901).

- In a separate acute oral neurotoxicity study in chickens, NTE was measured, but the significance of the results was not apparent due to the large range of responses, the omission of technical details, and the lack of statistical analysis (MRID No. 420005439).

- Acute and subchronic neurotoxicity studies are not available and thus data on cholinesterase inhibition and FOB as well as histopathology on the central and peripheral nervous systems are not available for evaluation after single or repeated exposures to Phostebupirim.

2. Developmental Toxicity

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

- In a developmental toxicity study pregnant Wistar rats were given oral doses of Phostebupirim in distilled water with 0.5% Cremaphor at doses of 0, 0.25, 0.5 or 0.75 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 0.5 mg/kg/day and the LOEL was 0.75 mg/kg/day based on mortality, clinical signs (salivation, tremors, dyspnea and ataxia), decreased body weight and food consumption, and inhibition of plasma, red blood cell and brain cholinesterase activity on gestation day 16. For developmental toxicity, the NOEL was $\geq$0.75 mg/kg/day (HDT); a LOEL was not established (MRID No.42005454).

- In a developmental toxicity study, pregnant Himalayan rabbits received oral doses of Phostebupirim in deionized water with 0.5% Cremaphor at 0, 0.03, 0.1, or 0.3 mg/kg/ day during gestation days 6 through 18. For maternal toxicity, the NOEL was 0.1 mg/kg/day and the LOEL was 0.3 mg/kg/day based on a suggested adverse effect on the number of resorptions and fetuses, as well as inhibition of erythrocyte cholinesterase activity on gestation days 14 and 19. For developmental toxicity, the NOEL was ≥0.3 mg/kg/day (HDT); a LOEL was not established (MRID No. 42005455).

3. Reproductive Toxicity

- In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing Phostebupirim at 0, 1, 5 or 25 ppm (0, 0.05, 0.25, or 1.25 mg/kg/day, respectively) for two successive generations. There was no increased sensitivity in pups over the adults. The parental/systemic NOEL was 1 ppm (0.05 mg/kg/day) and the LOEL was 5 ppm (0.25 mg/kg/day) based on cholinesterase inhibition. Plasma and red blood cell cholinesterase activity were inhibited in adult males at 5 ppm and brain cholinesterase activity was inhibited in F1 females at 1 ppm. Additional findings in both generations at 25 ppm included reduced stools size and tremors in dams, decreased body weight gain (first generation male and females for 14 days, females during gestation and lactation), decreased fertility index and more extensive cholinesterase inhibition (plasma, red blood cell and brain). For reproductive toxicity, the NOEL was 5 ppm (0.25 mg/kg/day) and the LOEL was 25 ppm (1.25 mg/kg/day) based on tremors in neonates, decreased pup body weight gain, increased number of pup deaths, and cholinesterase inhibition (plasma, red blood cell and brain) in pups on postnatal day 21, but not postnatal day 4 (MRID No. 42005456).

4. Cholinesterase Inhibition

- Cholinesterase activity was measured only in the adults but not in the pups in the developmental toxicity studies. Therefore, no comparisons could be made for this endpoint between adults and offspring. In addition, data gaps exists for acute and subchronic neurotoxicity studies.

5. Developmental Neurotoxicity

- There are sufficient data available to adequately assess the potential for toxicity to young animals following pre-and/or post-natal exposure to Phostebupirim. These include acceptable developmental toxicity studies in rats and rabbits and a 2-generation reproduction study in rats. However, data gaps exists for acute and subchronic neurotoxicity studies. Therefore, the requirement for a developmental neurotoxicity was placed in *reserve status* until submission and review of the neurotoxicity studies.

6. Reference Dose (RfD)

- An RfD of 0.0002 mg/kg/day was derived from the NOEL of 0.02 mg/kg/day and an Uncertainty Factor (UF) of 100. The LOEL was based on inhibition of plasma, red blood cell and brain cholinesterase activity observed at 0.13 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 Neurotoxicity Study in Rats
- Subchronic Neurotoxicity Study in Rats

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 from a developmental toxicity study in rabbits for acute dietary risk assessment is based on resorptions and number of fetuses, as well as inhibition of red blood cell cholinesterase activity at 0.3 mg/day in rabbits. The NOEL was 0.1 mg/kg/day.

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 reduced to 3 x.** Therefore, **a Margin of Exposure of 300 is required** to ensure protection of this population from acute exposure to Phostebupirim. A MOE of 300 is required because:

(i) Athough additional sensitivity of young rats or rabbits following pre- and/or post natal exposure to Phostebupirim was not observed, data gaps exists for acute and subchronic neurotoxicity studies. These studies would have provided cholinesterase inhibition and FOB data as well as histopathology of the central and peripheral nervous system following a single exposure to Phostebupirim.

2. Chronic Dietary Risk Assessment

The endpoint for chronic dietary risk assessment is based on plasma, red blood cell and brain cholinesterase inhibition in dogs at 0.13 mg/kg/day. The NOEL was 0.02 mg/kg/day. An UF of 100 applied to the NOEL; 10 x each for inter and intra species variability.

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 reduced to 3 x for a total UF of 300** (i.e., 10 for inter-species variation x 10 for intra-species variation x 3 for FQPA) to ensure protection of this population from chronic exposure to Phostebupirim. **Thus, the revised RfD is 0.00007 mg/kg/day.** The UF of 300 is required because:

(i) Athough additional sensitivity of young rats or rabbits following pre- and/or post natal exposure to Phostebupirim was not observed, data gaps exists for acute and subchronic neurotoxicity studies. These studies would have provided cholinesterase inhibition and FOB data as well as histopathology of the central and peripheral nervous system following a single exposure to Phostebupirim.