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

DATE: September 18, 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

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

FROM: Jess Rowland Jess Rowland 9/15/97
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THROUGH: K. Clark Swentzel K. Clark Swentzel 9/18/97
Chairman, Hazard Identification Assessment Review Committee
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TO: Karen Whitby
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BACKGROUND: On September 2, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Fenamiphos 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 Fenamiphos 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 Fenamiphos 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 Fenamiphos as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Reregistration Eligibility Document.

B. RESULTS: Evaluation of the toxicology data base indicated the following:

1. Neurotoxicity

- In an acute delayed neurotoxicity study, no clinical signs of neurotoxicity or neuropathology were seen in hens following single oral doses of Fenamiphos at doses up to and including 10 mg/kg. The Committee noted that this study did not assess the potential of Fenamiphos to inhibit neurotoxic esterase (NTE) in hens (HED Doc. No. 001308).

- No treatment-related pathological lesions were seen in the central or peripheral nervous systems in an acute neurotoxicity study in Wistar rats following single oral doses at 0, 0.4, 1.6 or 2.4 mg/kg/day or in the subchronic neurotoxicity study in Fisher 344 rats following dietary administration at dose levels of 0.08, 0.8 or 3.98 mg/kg/day for 90-days. In the acute study, the LOEL was 0.4 mg/kg/day based on plasma and red blood cell (RBC) ChE inhibition (ChEI); a NOEL was not established. In the subchronic study, the NOEL was 0.08 mg/kg/day and the LOEL was 3.98 mg/kg/day based on plasma and RBC ChEI (MRID Nos. 44041501 and 44051401).

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 Fenamiphos and comparable NOELs were established for adults and offspring.

- In a developmental toxicity study with CD rats, pregnant animals were given oral doses of Fenamiphos at 0, 0.25, 0.85 or 3.0 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 0.85 mg/kg/day and the LOEL was 3.0 mg/kg/day based on increased mortality, reduction in body weight gain and food consumption, cholinergic signs and plasma and RBC ChEI. For developmental toxicity, the NOEL was 3.0 mg/kg/day (HDT); a LOEL was not established (MRID No. 41225401).

- In a developmental toxicity study, artificially pregnant Chinchilla rabbits received oral doses of Fenamiphos at 0, 0.1, 0.5 or 2.5 mg/kg/day during gestation days 6 through 18. For maternal toxicity the NOEL was 0.5 mg/kg/day and the LOEL was 2.5 mg/kg/day based on cholinergic signs. For developmental toxicity, the NOEL was 2.5 mg/kg/day (HDT); a LOEL was not established (MRID No. 40347602).

3. Reproductive Toxicity

- In a 2-generation reproduction study, when administered in the diet at 0, 2.5, 10 or 30 ppm (0, 0.17, 0.64 or 2.8 mg/kg/day for males and 0, 0.2, 0.73 or 3.2 mg/kg/day for females) to Sprague-Dawley rats, no increased sensitivity to pups over the adults was seen. For parental systemic toxicity, the NOEL was 0.17 mg/kg/day for males and <0.2 mg/kg/day for females. The LOEL was 0.64 mg/kg/day for males and 0.2 mg/kg/day for females. In both sexes, the LOELs were based on inhibition of plasma and RBC cholinesterase activity. For toxicity to the offspring and for reproductive toxicity, the NOELs were 3.2 mg/kg/day (HDT); LOELs were not established (MRID Nos.41908901 and 42491701).

- In a 3-generation reproduction study, when administered in the diet at 0, 3, 10 or 30 ppm (0, 0.15, 0.5 or 1.5 mg/kg/day, respectively) to rats, no increased sensitivity to pups over the adults was seen. For parental toxicity, the NOEL was 0.5 mg/kg/day and the LOEL was 1.5 mg/kg/day based on reduced body weight gain in F1 males. For reproductive and offspring toxicity, the NOEL was 1.5 mg/kg/day (HDT); a LOEL was not established (MRID No.00037979).

4. 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 Fenamiphos. These include acceptable developmental toxicity studies in rats and rabbits as well as 2-generation and 3-generation reproduction studies in rats. In addition, no treatment-related neuropathology was seen in studies conducted in hens or rats (acute and subchronic). Therefore, based upon a weight-of-the-evidence consideration of the data base, the Committee determined that a developmental toxicity study in rats is not required

5. Reference Dose

- A Reference Dose (RfD) of 0.0001 mg/kg/day was derived from the NOEL of 0.01 mg/kg/day and an Uncertainty Factor (UF) of 100. The NOEL was based on plasma ChEI observed at 0.3 mg/kg/day in a 1-year feeding study in dogs. The UF of 100 included a 10 to account for intra-species and a 10 for inter-species variations.

6. Data Gaps

- None

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 (males and females) and red blood cell (males) cholinesterase activity at 0.37 mg/kg/day (LOEL) in an acute neurotoxicity study with rats. A NOEL was not established in this study. Since the dose identified is a LOEL, an additional UF of 3 was recommended.

Therefore, for acute dietary risk assessment, the Committee determined that the **10 x** factor to account for enhanced sensitivity to infants and children (as required by FQPA) **should be reduced by 3-fold for a total UF of 300** (10 for inter-species variability x 10 for intra-species variability x 3 for lack of a NOEL). Consequently, **A MOE of 300 is required** to ensure protection of this population from exposure to Fenamiphos for the following reasons:

(I) The endpoint identified was cholinesterase inhibition in adult rats.

(ii) There was no evidence of maternal or developmental toxicity attributable to a an acute (single dose) *in utero* exposure of Fenamiphos in developmental toxicity studies.

(iii) An additional UF of 3 was applied to account for the lack of a NOEL in the critical study.

2. Chronic Dietary Risk Assessment

The endpoint selected for chronic dietary risk assessment is based on plasma ChEI observed at 0.3 mg/kg/day (LOEL) in a 1-year feeding study in dogs. The NOEL was 0.01 mg/kg/day. An UF of 100 was applied to the NOEL; 10 to account for intra-species and a 10 for inter-species variations. Thus a RfD of 0.0001 mg/kg/day was derived.

For chronic dietary risk assessments, the Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be removed.** The present **UF of 100 is adequate** to ensure the protection of this population from exposure to Fenamiphos. **Thus the RfD remains at 0.0001 mg/kg/day.** An UF of 100 is adequate since there was no indication of increased sensitivity to young animals following pre-and/or post-natal exposure to Fenamiphos as shown below:.

(I) Developmental toxicity studies showed no increased sensitivity to fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.

(ii) A 2-generation and a 3-generation reproduction toxicity studies in rats showed no increased sensitivity to pups as compared to adults.