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

FORTRESS

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

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THROUGH: K. Clark Swentzel 9/25/97
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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 Chlorethoxyfos 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 Chlorethoxyfos 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 Chlorethoxyfos 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 Chlorethoxyfos 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, no delayed neurotoxicity was seen in hens given a single oral doses of Chlorethoxyfos at 14.5 or 19 mg/kg (above the LD_{50}) (MRID No. 40898702). The Committee noted that a study to assess for the potential of Chlorethoxyfos to inhibit neurotoxic esterase (NTE) in hens was requested by the RfD Committee and a protocol has been reviewed .

- An acute neurotoxicity study has been submitted to the Agency and is in review. An overview of this study revealed the following: no treatment-related neuropathological findings; clinical signs in males at 0.75 mg/kg, the lowest dose tested (LDT); inhibition of plasma and red blood cell cholinesterase activity in males at 0.75 mg/kg; and red blood cell in females at 0.25 mg/kg).

- The requirement for a 90-day subchronic neurotoxicity study is placed in *Reserve* status on the basis that other subchronic studies provided sufficient data to characterize the potential neurotoxicity of Chlorethoxyfos.

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 Chlorethoxyfos and comparable NOELs were established for adults and offspring.

- In a developmental toxicity study pregnant Crl:CD(BR) rats received oral doses of Chlorethoxyfos in 0.5% aqueous methylcellulose at 0, 0.05, 0.25, 0.50 or 0.60 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 0.25 mg/kg/day and the LOEL was 0.50 mg/kg/day based on increased mortality and decreased body weight gain during gestation days 13-17. For developmental toxicity, the NOEL was 0.25 mg/kg/day and the LOEL was 0.5 mg/kg/day based on decreases in the number of live fetuses per litters. No treatment-related effects were seen in external, visceral or skeletal observations (MRID No. 40898705).

- In a developmental toxicity study, pregnant New Zealand White rabbits were given single oral doses of Chlorethoxyfos in 0.5% methylcellulose at 0, 0.76, 1.38, 2.1 or 2.8 mg/kg/ day during gestation day 7 through 19. For maternal toxicity, the NOEL was 0.76 mg/kg/day and the LOEL was 1.38 mg/kg/day based on mortality associated with cholinesterase inhibition. For developmental toxicity, the NOEL was 1.38 mg/kg/day and the LOEL was 2.1 mg/kg/day based on a statistically significant increase in the average number of early resorptions/litter relative to controls. This was supported by an increase in the number of litters with at least one early resorption per total litters. No treatment-related effects were seen in external, visceral or skeletal fetal observations (MRID No. 41290633 and 42559219).

3. Reproductive Toxicity

- In a two-generation reproduction study, Crl:CD BR rats were fed diets containing Chlorethoxyfos at 0, 0.25, 1, 4 or 8 ppm. These doses were equivalent to 0,0.018, 0.074, 0.296 or 0.607 mg/kg/day in males and 0, 0.022, 0.091, 0.357 or 0.776 mg/kg/day in females, respectively There was no increased sensitivity to pups over the adults. The parental/systemic NOEL was 4 ppm (0.296 mg/kg/day) and the LOEL was 8 ppm (0.607 mg/kg/day) based on increased incidence of tremors during lactation. For reproductive toxicity, the NOEL was 8 ppm (0.607 mg/kg/day); a LOEL was not established (MRID No. 41736836).

4. Cholinesterase Inhibition

- Cholinesterase activity was not measured in the adults and offspring in the developmental toxicity studies or in the reproduction study. Therefore, no comparisons could be made for this endpoint between adults and offspring.

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 Chlorethoxyfos. These include acceptable developmental toxicity studies in rats and rabbits and a 2-generation reproduction study in rats. In addition, there are outstanding reviews of an acute neurotoxicity study in rats and NTE hen data. Therefore, based upon a weight-of-the-evidence consideration of the data base, the Committee determined that a developmental neurotoxicity study in rats is not required at this time (i.e., contingent upon the findings of the acute studies in hen and rats).

6. Reference Dose (RfD)

- An RfD of 0.0006 mg/kg/day was derived from the NOEL of 0.06 mg/kg/day and an Uncertainty Factor (UF) of 100. The LOEL was based on inhibition of plasma cholinesterase activity observed at 0.6 mg/kg/day in dogs in subchronic and chronic toxicity studies. The UF of 100 included a 10 for intra-species and 10 for inter-species variation.

7. Data Gaps

- None. (An NTE study in hen and an acute neurotoxicity are due to be reviewed)

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 0.6 mg/day in dogs. The NOEL was 0.06 mg/kg/day. A Margin of Exposure of 100 was recommended.

For acute dietary risk assessment, the Committee determined that an the **10 x** factor to account for enhanced sensitivity of infants and children **(as required by FQPA) should be removed. A Margin of Exposure of 100 is adequate** to ensure protection of this population from acute exposure to Chlorethoxyfos for reasons stated below:

(i) No increased sensitivity to fetuses as compared to maternal animals following *in utero* exposure in developmental toxicity studies..

(ii) No increased sensitivity to pups as compared to adults in a multigeneration reproduction study.

(iii) No data gaps.

2. Chronic Dietary Risk Assessment

The endpoint for chronic dietary risk assessment is based on plasma cholinesterase inhibition observed at 0.6 mg/kg/day (LOEL) in dogs. The NOEL was 0.06 mg/kg/day. An UF of 100 applied to the NOEL; 10 X each for inter and intra species variability. Thus an RfD of 0.0006 mg/kg/day was derived.

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 removed. The present UF of 100 is adequate** to ensure protection of this population from chronic exposure to Chlorethoxyfos since there was no indication of increased sensitivity to young animals following pre-and/or post-natal exposure to Chlorethoxyfos 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 multi generation reproduction toxicity study in rats showed no increased sensitivity to pups as compared to adults and offsprings.