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

DATE: September 25, 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

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

FROM: Jess Rowland 9/25/97
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THROUGH: K. Clark Swentzel 9/25/97
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TO: Karen Whitby
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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 Terbufos 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 Terbufos 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 Terbufos 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 Terbufos 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 dose of Terbufos at 40 mg/kg. A second administration, at the same dose, was given after a 21-day interval. The Committee noted that this study did not assess for the potential of Terbufos to inhibit neurotoxic esterase (NTE) in hens (MRID No. 00037472).

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

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 Terbufos and comparable NOELs were established for adults and offspring.

- In a developmental toxicity study pregnant Crl:COBS-CD(SD) rats received oral doses of Terbufos in corn oil at 0, 0.05, 0.1 or 0.2 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 0.2 mg/kg/day (HDT); a LOEL was not established. For developmental toxicity, the NOEL was 0.1 mg/kg/day and the LOEL was 0.2 mg/kg/day based on increases in early fetal resorptions, the number of litters with two or more resorptions, and post-implantation losses. There was no evidence of teratogenicity (MRID No. 00147533).

- In a developmental toxicity study, pregnant New Zealand White rabbits were given a single oral dose of Terbufos 0, 0.05, 0.10, 0.25 or 0.50 mg/kg/day during gestation days 7 through 19. For maternal toxicity, the NOEL was 0.1 mg/kg/day and the LOEL was 0.25 mg/kg/day based on decreased body weight gain and increased incidence of soft stools. For developmental toxicity, the NOEL was 0.25 mg/kg/day and the LOEL was 0.5 mg/kg/day based on a slight reduction in fetal body weight and an increase in resorptions. There was no evidence of teratogenicity (MRID No. 40886301).

3. Reproductive Toxicity

- In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing Terbufos at 0, 0.5, 1 or 2.5 ppm for 9 weeks prior to mating (males and females) as well as during both gestation and lactation. There was no increased sensitivity to pups over the adults. The maternal/offspring NOEL was 1 ppm (0.08-0.09 mg/kg/day) and the LOEL was 2.5 ppm (0.22-0.24 mg/kg/day) based on a decreased body weight gain in females during lactation and lower pup weights during lactation days 14 and 21. For reproductive toxicity, the NOEL was 1 ppm (0.07 mg/kg/day) and the LOEL was 2.5 ppm (0.17 mg/kg/day) based on a decrease in pregnancy rate and male fertility. For cholinesterase inhibition (measured only in adults), the NOEL was 0.5 ppm (0.04 mg/kg/day) and the LOEL was 1 ppm (0.08 mg/kg/day) based on >50% inhibition of plasma cholinesterase activity (MRID No. 43649402).

4. Cholinesterase Inhibition

- Cholinesterase activity was not measured in the adults and offspring in the developmental toxicity studies. In the reproduction study, ChE activity was measure only in adults and not in the pups. 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 Terbufos. These include acceptable developmental toxicity studies in rats and rabbits and a 2-generation reproduction study in rats. In addition, no treatment-related effects in the reproductive organs were seen in subchronic and chronic studies conducted in mice, rats and dogs. 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.

6. Reference Dose (RfD)

- An RfD of 0.00005 mg/kg/day was derived from the NOEL of 0.005 mg/kg/day and an Uncertainty Factor (UF) of 100. The LOEL was based on inhibition of plasma cholinesterase activity observed at 0.015 mg/kg/day in dogs in a 28 day study. The 6-month and 1-year studies are considered co-critical. 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

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 0.015 mg/day in dogs. The NOEL was 0.005 mg/kg/day. An Margin of Exposure of 100 was recommended.

For acute dietary risk assessment, the Committee determined that the **10 x** factor to account for enchanced 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 Terbufos because:

(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 expsoure to Terbufos.

(ii) Lack of evaluation of a critical endpoint (i.e., measurement of cholinesterase activity) in the developmental or reproduction studies which would have yielded a comparison of this endpoint in adults and offsprings.

2. Chronic Dietary Risk Assessment

The endpoint for chronic dietary risk assessment is based on plasma cholinesterase inhibition observed at 0.015 mg/kg/day (LOEL) in dogs. The NOEL was 0.005 mg/kg/day. An UF of 100 applied to the NOEL; 10 X each for inter and intra species variability. Thus an RfD of 0.00005 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 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 Terbufos. **Thus, the revised RfD is:0.00002**The UF of 300 is required because of the:

(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 repeated expsoures to Terbufos.

(ii) Lack of an evaluation of a critical endpoint (i.e., measurement of cholinesterase activity) in the developmental or reproduction studies which would have yielded a comparison of this endpoint in adults and offsprings.