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

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

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THROUGH: K. Clark Swentzel K. Clark Swentzel 9/25/97
Chairman, Hazard Identification Assessment Review Committee
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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 Coumaphos 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 Coumaphos 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 Coumaphos 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 Coumaphos 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 (via gelatin capsule) of Coumaphos at 50 mg/kg (MRID No. 00115167). The Committee noted that this study did not assess for the potential of Coumaphos to inhibit neurotoxic esterase (NTE) in hens.

- No acute or subchronic neurotoxicity studies are available and thus data on cholinesterase inhibition, behavioral effects and histopathology of the central and peripheral nervous systems are not available.

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 Coumaphos and comparable NOELs were established for adults and offspring.

- In a developmental toxicity study pregnant Crl:COBS-CD(SD) rats received oral doses of Coumaphos at 0, 1, 5 or 25 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 5 mg/kg/day and the LOEL was 25 mg/kg/day based on clinical signs of cholinesterase inhibition. For developmental toxicity, the NOEL was 25 mg/kg/day (HDT); a LOEL was not established. There was no evidence of teratogenicity (MRID No. 00131684).

- In a developmental toxicity study, pregnant American Dutch rabbits were given single oral dose of Coumaphos at 0, 0.25, 2, or 18 mg/kg/day during gestation days 7 through 19. For maternal toxicity, the NOEL was 2 mg/kg/day and the LOEL was 18 mg/kg/day based on mortality (2/17) and cholinergic signs. For developmental toxicity, the NOEL was 18 mg/kg/day (HDT); a LOEL was not established. There was no evidence of teratogenicity (MRID No. 00131683).

3. Reproductive Toxicity

- In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing Coumaphos at 0, 1, 5 or 25 ppm (0, 0.07, 0.3, or 1.79 mg/kg/day in males and 0, 0.08, 0.34 or 2.02 mg/kg/day in females, respectively). There was no increased sensitivity to pups over the adults. For parental/systemic toxicity, the NOEL was 25 ppm (1.79 mg/kg/day, (HDT); a LOEL was not established. For reproductive toxicity, the NOEL was 25 ppm (1.79 mg/kg/day); a LOEL was not established (MRID No. 430611701).

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 measured in adults and pups. There was dose-related decreases in plasma and red blood cell cholinesterase activity in dams at 5 and 25 ppm. Generally, no differences were seen on day 47 and day 91 measurements. Brain levels were biologically significantly inhibited (30%) in F_0 and F_1 adult females at 25 ppm, and in F_0 adult males at 25 ppm. In pups, no significant changes in red blood cell or brain cholinesterase activity were seen on day 4, but on day 21 changes were seen at 25 ppm. In F_1 pups, plasma and red blood cell ChE inhibition of 38-44% was seen, while in F_2 pups, only plasma was affected (31-44%). The only significant brain inhibition in pups was an 8% decrease in F_1 females on day 21. The NOEL was 5 ppm for cholinesterase inhibition in dams and in pups on day 21 (MRID No. 430611701).

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 Coumaphos. These include acceptable developmental toxicity studies in rats and rabbits and a 2-generation reproduction study in rats. 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 0.00025 mg/kg/day was derived from the NOEL of 0.025 mg/kg/day and an Uncertainty Factor (UF) of 100. The LOEL was based on inhibition of plasma and red blood cell cholinesterase activity observed at 0.75 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 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 red blood cell cholinesterase activity at 0.5 mg/kg/day in rats (LOEL). The NOEL was 0.2 mg/kg/day. A Margin of Exposure of 100 was recommended.

For acute dietary risk assessment, the Committee determined that the **10 x** 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 Coumaphos because of the:

(i) Lack of acute and subchronic neurotoxicity studies. Data on cholinesterase inhibition, FOB, and histopathology of the central and peripheral nervous system following a single exposure to Coumaphos are not available.

2. Chronic Dietary Risk Assessment

The endpoint for chronic dietary risk assessment is based on plasma and red blood cell cholinesterase inhibition observed at 0.7 mg/kg/day (LOEL) in dogs. The NOEL was 0.025 mg/kg/day. An UF of 100 applied to the NOEL; 10x each for inter and intra species variability. Thus an RfD of 0.00025 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.** Thus, **a total UF of 300** (i.e., 10 for inter-species variation x 10 for intra-species variation x 3 for FQPA) **is required** to ensure protection of this population from chronic exposue to Coumaphos. The UF of 300 is required because of the:

(i) Lack of acute, subchronic neurotoxicity studies. Data on cholinesterase inhibition, FOB, and histopathology of the central and peripheral nervous system following repeated exposures to Coumaphos are not available.