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

DATE: October 8, 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

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

FROM: Jess Rowland
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THROUGH: K. Clark Swentzel K. Clark Swentzel 10/8/97
Chairman, Hazard Identification Assessment Review Committee
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BACKGROUND: On September 23, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Methidathion 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 Methidathion as required by the Food Quality Protecting Act (FQPA) of 1996. 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 Methidathion 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 Methidathion 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 clinical or histopathological signs of neurotoxicity were seen in hens given single oral doses of Methidathion at 175 or 350 mg/kg (MRID No. 00011704). The Committee noted that the study did not assess for the potential of Methidathion to inhibit neurotoxic esterase (NTE) in hens.

- In an acute neurotoxicity study, Sprague-Dawley rats were given an oral administration of Methidathion at 0, 1, 4, 8 or 15 mg/kg. For neurotoxicity, the NOEL was 4 mg/kg and he LOEL was 8 mg/kg based on decreased maze activity and differences in FOB parameters including tremors, bizzare behavior, abnormal gait, atxia, low arousal, decrease in forelimb grip strength, uncoordinated righting reflex. For cholinesterase inhibition, the NOEL was < 1 mg/kg (MRID Nos. 43145903 and 43590304).

- In a subchronic neurotoxicity study, Sprague-Dawley rats were fed diets containing Methidathion at 0, 3, 10, 30 or 100 ppm (0.2, 0.6, 1.9, or 6.3 mg/kg/day in males and 0.2, 0.7, 2, or 7.2 mg/kg/day, in males and females, respectively) for 90 days. The NOEL was 3 ppm (0.2 mg/kg/day) and the LOEL was 10 ppm (0.6 mg/kg/day) based on statistically and biologically significant decreases in red blood cell, serum and brain cholinesterase activity (MRID No. 43582501).

2. Developmental Toxicity

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

- In a developmental toxicity study pregnant Crl:CD(SD) BR rats received oral doses of Methidathion in 3% corn starch at 0, 0.25, 1.0, or 2.25 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 1.0 mg/kg/day and the LOEL was 2.25 mg/kg/day based on one death, decreases in body weight gain and food consumption, cholinergic signs indicative of cholinesterase inhition, exopthalmia, raspy respiration and vaginal bleeding. For developmental toxicity, the NOEL was 2.25 mg/kg/day (HDT); a LOEL was not established (MRID No. 40079807).

- In a developmental toxicity study, pregnant New Zealand White rabbits were given oral doses of Methidathion at 0, 2, 6, or 12 mg/kg/ day during gestation day 7 through 19. For maternal toxicity, the NOEL was 6 mg/kg/day and the LOEL was 12 mg/kg/day based on clinical signs indicative of cholinergic activity. For developmental toxicity, the NOEL was 12 mg/kg/day (HDT); a LOEL was not established (MRID Nos. 40079809 and 40079810).

3. Reproductive Toxicity

- In a one-generation reproduction study, Sprague-Dawley rats were fed diets containing Methidathion at 0, 5, 50, or 100 ppm (changed to 25 ppm at weaning of F_{1a} litters) for one generation. These doses were equivalent to 0,0.25, 2.5, or 5 (1.25) mg/kg/day. There was no increased sensitivity of pups over the adults. The parental/systemic NOEL was 5 ppm (0.25 mg/kg/day) and the LOEL was 50 ppm (2.5 mg/kg/day) based on tremors and decreased food consumption during lactation.. For reproductive toxicity, the NOEL was 5 ppm (0.25 mg/kg/day) and the LOEL was 50 ppm (2.5 mg/kg/day) based on decreased pup birth weight and pup weight during lactation.

- In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing Methidathion at 0, 5, 25, or 50 ppm (0,0.25, 1.25, or 2.5 mg/kg/day) for two sucessive generations. There was no increased sensitivity of pups over the adults. The parental/systemic NOEL was 5 ppm (0.25 mg/kg/day) and the LOEL was 25 ppm (1.25 mg/kg/day) based on tremors and decreased food consumption during lactation and decreased ovarian weight. 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 decreased pup weight and an increased incidence of hypothermia with the appearance of starvation (MRID No. 40079811-13).

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 Methidathion. These include acceptable developmental toxicity studies in rats and rabbits as well as a 1 and 2-generation reproduction studies in rats. In addition, no treatment-related neuropathology was seen in studies conducted in hen or 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 0.0015 mg/kg/day was derived from the NOEL of 0.15 mg/kg/day and an Uncertainty Factor (UF) of 100. The LOEL was based on elevated hepatic enzymes, gross hepatic lesions, chronic hepatitis and inhibition of red blood cell cholinesterase actitivity at 1.33 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

- 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 and red blood cell and brain cholinesterase activity at 0.6 mg/day in dogs. The NOEL was 0.2 mg/kg/day.

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 Methidathion for reasons stated below:

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

(ii) No increased sensitivity of 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 red blood cholinesterase inhibition and hepatic toxicity observed at 1.33 mg/kg/day (LOEL) in dogs. The NOEL was 0.15 mg/kg/day. An UF of 100 applied to the NOEL; 10 X each for inter and intra species variability. Thus an RfD of 0.0015 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 Methidathion **Therefore, the RfD remains at 0.0015 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 Methidathion as shown below:

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

(ii) Multi generation reproduction toxicity studies in rats showed no increased sensitivity of pups as compared to adults and offsprings.