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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

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

FROM: Jess Rowland *Jess Rowland 9/18/97*
Branch Senior Scientist,
Science Analysis Branch, Health Effects Division (7509C)

THROUGH: K. Clark Swentzel *K. Clark Swentzel 9/18/97*
Chairman, Hazard Identification Assessment Review Committee
Toxicology Branch II, Health Effects Division (7509C)

TO: Karen Whitby
Chief, Risk Characterization & Analysis Branch, Health Effects Division (7509C)

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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 Ethion, 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 Ethion 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 Ethion, 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 Ethion as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Ethion Reregistration Eligibility Document.

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

1. Neurotoxicity:

- In an acute delayed neurotoxicity study, no clinical or histopathological signs of neurotoxicity were seen in hens given a single oral dose of Ethion at 2792 mg/kg (LD₅₀). The Committee noted that this study did not assess for the potential of Ethion to inhibit neurotoxic esterase (NTE) in hens (MRID No. 00158376).
- No treatment-related pathological lesions of the central or peripheral nervous system were observed in the 90-day neurotoxicity study in rats, which is currently under review, or in the chronic toxicity studies in mice or rats (MRID Nos. 00148989 and 00148991).

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 Ethion and comparable NOELs were established for adults and off-spring.
- In a developmental toxicity study, pregnant Charles River rats received oral doses of Ethion at 0, 0.2, 0.6 or 2.5 mg/kg/day on gestation days 6 through 15. For maternal and developmental toxicity, the NOEL was 0.6 mg/kg/day and the LOEL was 2.5 mg/kg/day. The LOEL was based on signs of hyperactivity in the dams (maternal) and on delayed ossification of pubes in the fetuses (developmental) (MRID No. 00131852).
- In the other developmental toxicity study, pregnant New Zealand White rabbits were given oral doses at 0, 0.6, 2.4 or 9.6 mg/kg/day during gestation days 6 through 18. For maternal toxicity the NOEL was 2.4 mg/kg/day and the LOEL was 9.6 mg/kg/day based on decreases in body weight gain, reduced food consumption and clinical signs (orange colored urine). For developmental toxicity, the NOEL was 9.6 mg/kg/day (highest dose tested, HDT); a LOEL was not established (MRID No. 00131853).

3. Reproductive Toxicology

- In a 3-generation reproduction study, when administered in the diet at 0, 2, 4, or 25 ppm (1, 0.2 or 1.25 mg/kg/day, respectively) to Charles River rats, no increased sensitivity to pups over the adults was seen. For parental systemic toxicity, the NOEL was 0.2 mg/kg/day and the LOEL was 1.25 mg/kg/day based on significant decreases in plasma cholinesterase activity in F₁ and F₂ female adults (MRID No. 00148990). For reproductive toxicity, the NOEL was 1.25 mg/kg/day (HDT); a LOEL was not established.

4. Cholinesterase Inhibition

- In the 3-generation reproduction study, ChE activity was not measured in the F₀ parental animals and therefore, for this endpoint, a comparison could not be made with the pups. However, the dose (1.25 mg/kg/day) at which plasma ChE inhibition (ChEI) was seen in the F₁ and F₂ adult female rats in the reproduction study is comparable to the dose (2 mg/kg/day) at which ChEI was observed in adult rats in the chronic toxicity study with rats (00148991).

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

6. Reference Dose (RfD)

- A RfD of 0.0005 mg/kg/day was derived from the LOEL of 0.05 mg/kg/day and an Uncertainty Factor (UF) of 100. The LOEL was based on cholinergic signs observed at the lowest dose tested in human volunteers given oral doses of Ethion at 0.05, 0.075, 0.10 or 0.15 mg/kg/day for 21 days. The UF of 100 included a 10 to account for the difference in sensitivity within the human population and an additional 10 to account for the lack of a NOEL in the critical study.

7. Data Gaps

- The Committee noted that a data gap exists for an acute neurotoxicity study 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 clinical signs of cholinesterase inhibition observed at 0.05 mg/kg/day (LOEL) on day 19 in male volunteers. A NOEL was not established. In general, when the dose identified is a LOEL, an additional UF would be applied due to the lack of a NOEL in the critical study. In this case, however, since a human study was used and the effects seen occurred on day 19, an UF of 10 was appropriate.

Therefore, for acute dietary risk assessment, the Committee determined that **an additional UF of 10** to account for enhanced sensitivity to infants and children (as required by FQPA) **is not warranted. A Margin of Exposure of 10 is adequate** to ensure protection of this population from acute (single) exposure to Ethion for reasons specified below:

- (I) The endpoint identified was cholinesterase inhibition in adult human (males) subjects.
- (ii) There is no evidence of maternal or developmental toxicity attributable to an acute (single dose) *in utero* exposure of Ethion in developmental toxicity studies.

2. Chronic Dietary Risk Assessment

The endpoint selected for chronic dietary risk assessment is based on cholinergic signs observed at 0.05 mg/kg/day in human volunteers (LOEL). A NOEL was not established. An UF of 100 was applied to this LOEL; 10 to account for the difference in sensitivity within the human population and an additional 10 to account for the lack of a NOEL in the critical study. Thus an RfD of 0.0005 mg/kg/day was derived.

Therefore, for chronic dietary risk assessment, the Committee determined that **an additional UF of 10** to account for enhanced sensitivity of infants and children (as required by FQPA) **is not warranted. The present UF of 100 is adequate** to ensure the protection of this population from exposure to Ethion. **Thus the RfD remains at 0.0005 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 Ethion 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.