US EPA ARCHIVE DOCUMENT

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

012401

DATE: November 10, 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

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

FROM: Jess Rowland 11/12/97
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THROUGH: K. Clark Swentzel, Chairman, 11/12/97
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
And
Mike Metzger, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Whang Phang, Branch Senior Scientist
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BACKGROUND: On November 4, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Ethoprop 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 Ethoprop as required by the Food Quality Protecting Act (FQPA) of 1996. The Committee's decisions are summarized below.

A. INTRODUCTION

The Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Ethoprop 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 Ethoprop as required by the Food Quality Protecting Act (FQPA) of 1996.

B. RESULTS

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 Ethoprop in corn oil at 6.5 mg/kg, followed by a second oral dose of 5.3 mg/kg 21-days later. (MRID No. 40609401). The Committee noted that this study did not assess for the potential of Ethoprop to inhibit neurotoxic esterase (NTE) in hens and that the HED RfD Committee recommended that a NTE study be performed based on structure activity relationship concerns (RfD Document 5/9/96).

- In an acute oral toxicity study, Sprague-Dawley rats were given a single oral administration of Ethoprop (95.7%) in corn oil at 0, 24.2 or 52 mg/kg/day to males and at 0, 15.7 or 33 mg/kg/day in females. The objective of this study was to evaluate the time-relaed effects of Ethoprop on cholinesterase activities in plasma, red blood cell (RBC) and four brain regions. The cholinesterase LOEL was $\leq$ 15.7 mg/kg/day based on inhibition of plasma, RBC and brain cholinesterase activity in females; a NOEL was not established (MRID No. 43442402).

- In an acute neurotoxicity study, Sprague-Dawley rats were given an oral administration of Ethoprop in corn oil at 0, 5, 50, or 75 mg/kg to males and at 5, 25 or 50 mg/kg/day for females. For neurotoxicity, the NOEL was 5 mg/kg in males and females and the LOEL was 50 mg/kg in males and 25 mg/kg/day in females based on transient neurobehavioral signs in both sexes related to cholinesterase inhibition (ChEI). For ChEI, the LOEL was 5 mg/kg based on plasma and red blood cell (RBC) ChEI in both sexes ; a NOEL was not established. Brain weight and neurohistopathology were not affected (MRID No. 43197701).

- In a subchronic neurotoxicity study, Sprague-Dawley rats were fed diets containing Ethoprop at 0, 4, 40, or 400ppm (0, 0.26, 2.6, or 27 mg/kg/day in males and 0, 0.31, 3.0 or 31 mg/kg/day in females , respectively) for 90 days.

For systemic/neurobehavioral effects, the NOEL was 40 ppm (2.6 mg/kg/day in males and 3 mg/kg/day in females) and the LOEL was 400 ppm (27 mg/kg/day in males and 31 mg/kg/day in females) based on decreased body weight gain and food consumption, decreased hindlimb grip strength, motor activity and analgesic response time in males and cholinergic signs in both sexes. In males, for plasma, RBC and brain ChEI, the NOEL was 0.26 mg/kg/day and the LOEL was 2.6 mg/kg/day. In females, for plasma and brain ChEI, the LOEL was 0.31 mg/kg/day; a NOEL was not established. For RBC ChEI, the NOEL was 0.31 mg/kg/day and the LOEL was 3 mg/kg/day (MRID No. 43442401).

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 Ethoprop and comparable NOELs were established for adults and offspring.

- In a developmental toxicity study pregnant SD rats received oral doses of Ethoprop (purity not known) in corn oil at 0, 0.16, 1.6, or 16 mg/kg/day during gestation days 6 through 15. Maternal toxicity in the high-dose group was reported as high mortality and decreased weight gain. Fetal toxicity was reported as incomplete ossification of all treated groups (NOEL $\leq$ 0.16 mg/kg/day). Although these results are suggestive of increased sensitivity in the offsprings, the Committee noted that the delayed ossification observed in the fetuses (upon which the NOEL/LOEL were based) did not occur in a dose-related manner, and that an unusually low incidence in the concurrent controls may have artificially created the statistical significance in all treated groups. No historical control data were available form the testing laboratory to determine if this was the case. It was also noted that maternal cholinesterase inhibition was not measured in this study, and that is unlikely that the actual maternal NOEL (were it to be based upon cholinesterase inhibition) is as high as 1.6 mg/kg/day. Also, greater confidence was placed in the recent study discussed below (MRID No. 00104532).

- In a developmental toxicity study pregnant Sprague-Dawley rats received oral doses of Ethoprop (95.6%) in corn oil at 0, 2, 9, or 18 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 2 mg/kg/day and the LOEL was 9 mg/kg/day based on decreases in body weight gain and increased soft stool. For developmental toxicity, the NOEL was $\geq$ 18 mg/kg/day (HDT); a LOEL was not established (MRID No. 41304402).

- In a developmental toxicity study, pregnant New Zealand White rabbits were given oral doses of Ethoprop (95.6%) in corn oil at 0, 0.625, 1.25, or 2.5 mg/kg/ day during gestation day 6 through 18. For maternal and developmental toxicity, the NOEL was $\geq$ 2.5 mg/kg/day (HDT); a LOEL was not established. Although neither maternal nor developmental toxicity was observed, dosing was judged to be adequate because the highest dose tested (2.5 mg/kg/day) was close to a lethal dose (5 mg/kg/day) (MRID No. 41304403).

3. Reproductive Toxicity

- In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing Ethoprop (95.3%) at 0, 1, 30 or 300/150 ppm (0, 0.08, 2.3, 24/13 mg/kg/day) for two successive generations. The high dose of 300 ppm was reduced to 150 ppm due to excessive mortality in the F1a litter. There was no increased sensitivity of pups over the adults. The parental/systemic NOEL was 30 ppm (2.3 mg/kg/day) and the LOEL was 150 ppm (13 mg/kg/day) based on decreases in body weight gain. For offspring toxicity, the NOEL was 30 ppm (2.3 mg/kg/day) and the LOEL was 150 ppm (13 mg/kg/day) based on increased mortality in F1a pups between days 21 and 28 post partum and decreases in body weight gain in both generations. Although pup deaths occurred at the same dose that caused only clinical signs of toxicity in adults the Committee determined that this was not a true indication of increased sensitivity because: (i) pup mortality was seen between days 21 and 28 post partum; (ii) during that period (i.e., later portion of lactation), young rats consume approximately twice the diet per unit body weight as an adult rat consumes (i.e., 1 ppm in the diet of a young rat is approximately 0.1 mg/kg/day where as in the older rats, this ppm level is equal to 0.05 mg/kg/day) and (iii) the estimation of the test substance intake in pre-weaning animals is likely to be more than double the adult intake because of the availability of the test material both via the milk (lactation) and food, particularly near the mid point of lactation. (MRID No. 41921201).

4. Cholinesterase Inhibition

- Cholinesterase activity was not measured in the adults and offspring in the developmental toxicity studies in rats and rabbits and was measured only in adults 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 Ethoprop. 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 0.0001 mg/kg/day was derived from a NOEL of 0.01 mg/kg/day established in the 5-month and 1-year (combined) studies in dogs and an Uncertainty Factor (UF) of 100. The LOEL was based on significant inhibition of plasma cholinesterase activity in both sexes of dogs at 0.025 mg/kg/day. The UF of 100 included a 10 x for intra-species and 10 x 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 cholinesterase activity at 0.075 mg/day in male dogs on day 2 in a 90-day study in dogs. The NOEL was 0.025 mg/kg/day.

For acute 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**. **A Margin of Exposure of 100 is adequate** to ensure protection of this population from acute exposure to Ethoprop 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) There are no data gaps.

2. Chronic Dietary Risk Assessment

The endpoint for chronic dietary risk assessment is based on significant plasma cholinesterase inhibition at 0.025 mg/kg/day (LOEL) in 5-month and 1-year (combined) studies in dogs. The NOEL was 0.01 mg/kg/day. An UF of 100 applied to the NOEL; 10 x each for inter and intra species variability. Thus an RfD of 0.0001 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 Ethoprop. **Therefore, the RfD remains at 0.0001 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 Ethoprop 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.

(iii) There are no data gaps.