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

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SEP 20 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: TERBUTHYLAZINE. ID NO. 080814. Response to Company Reevaluation of Developmental Toxicity Study in Rabbit. Amendment to Study Evaluation on Selection of NOEL/LOEL for Developmental Toxicity. Executive Summary for Rabbit 28-Day Dermal Toxicity Study.

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CONCLUSIONS

TB-I has reviewed the response by FMC corporation to the selection of the developmental toxicity NOEL/LOEL in the HED reevaluation of the review of the rabbit developmental toxicity study on terbuthylazine (MRID 00103744; HED doc. nos. 003581 and 010953). Based on the additional information submitted, TB-I agrees with the Registrant that the NOEL for developmental toxicity should be changed to 4.5 mg/kg/day from 1.5 mg/kg/day. The recalculated value is not statistically significant and within historical control range for post-implantation loss observed at that time. Details are provided in the Discussion section, below. The revised Executive Summary is as follows:

EXECUTIVE SUMMARY: In a developmental toxicity study in rabbit (MRID 00130744), female New Zealand White rabbits were dosed by gavage from day 7 through 19 of gestation with terbuthylazine (GS 135259, 98.5% purity) in 1% methylcellulose, 14 animals at 0, 13 at 0.5, 15 at 1.5 and 17 at 4.5 mg/kg/day. Animals were sacrificed on day 29 of gestation.

There were no signs of maternal toxicity or developmental toxicity at any dose in the main study. In a preliminary study, body weight loss was observed at 12.5 mg/kg/day, but not at 5 mg/kg/day. **The maternal and developmental NOELs are equal to or greater than 4.5 mg/kg/day. The maternal and developmental LOELs are greater than 4.5 mg/kg/day.**

This study is classified as core-minimum data for developmental toxicity (83-3b) and satisfies the guideline requirement for a developmental toxicity study in rabbits. Although a LOEL was not determined in this study, it is considered acceptable for regulatory purposes because (1) the NOELs for developmental and maternal toxicity are similar in rat and rabbit, indicating that rabbit is not more sensitive to this chemical and (2) the developmental range-finding study for terbuthylazine in rabbits demonstrated maternal toxicity at 12.5 mg/kg/day.

An executive summary, below, was also prepared for a 28-day dermal toxicity study in rabbits (MRID 00151622; originally reviewed in HED doc. no. 005210). Although this study was classified as Core-supplementary, a summary is provided because the study was used in determination of appropriate endpoints for less-than-lifetime exposures.

EXECUTIVE SUMMARY: In a 28-day dermal toxicity study (MRID 00151622), male and female New Zealand White rabbits were dermally exposed to terbuthylazine (technical, 99.8% a.i.) at 0, 5, 50 or 500 mg/kg/day (10 animals/sex at 500 mg/kg/day; (5 animals/sex at all other dose levels). Doses were administered in an aqueous vehicle of 0.1% polysorbate/0.5% carboxymethylcellulose. Animals were exposed for 6 hrs/day, 5 days/week. Five high dose animals/sex were sacrificed at 29 days and 5 after a 2-week recovery period.

At 5.0 mg/kg/day, several clinical signs classified as minimal were observed among males and females. During the first 7 days of the study, clinical signs were observed only in 1 - 2 males (dyspnea, piloerection, sedation) and 1 - 2 females (curved body position). Thereafter, all animals developed dyspnea, piloerection, sedation and curved body posture, a few developed tremors (1 male, 2 females) and 1 female had ataxia. Dermal irritation was also observed in treated animals. At 50 and 500 mg/kg/day, clinical signs occurred earlier and with greater severity (classified as moderate). At 500 mg/kg/day, body weight gain was decreased compared to controls (87% less, males and 73% less, females) and food consumption was decreased during weeks 1 and 2 (42% - 71% less than controls, males; 23% - 37%, females). **The LEL of 5.0 mg/kg/day is based on clinical signs in males and females. The NOEL is less than 5.0 mg/kg/day.**

This study is classified as Core-supplementary data for repeated-dose dermal toxicity in rabbit (guideline 82-3) and is not considered acceptable for regulatory purposes due to the following study deficiencies: small number of animals (5) tested at each dose except high dose, a tissue inventory for microscopic evaluation was not included, NOEL not established. However, the study does provide adequate information to determine that toxicity was observed at the doses tested and the time of onset of toxicity (clinical signs).

ACTION REQUESTED

On August 15, 1994 FMC Corporation responded to the review by TB-I of the developmental toxicity in rabbit on terbuthylazine (MRID 00103744, HED Doc. Nos. 003581 and 010953). The Registrant disagreed with selection of the developmental NOEL/LOEL. In support of their position, FMC submitted historical control data on post-implantation loss and recalculated post-implantation loss values excluding non-treatment related abortions.

DISCUSSION

(1) Recalculation of mean post-implantation loss: Mean post-implantation loss was recalculated excluding does with abortions (table of group mean litter data is attached). One mid-dose and one high-dose female aborted during the study but these were not considered treatment-related effects and were therefore excluded in the recalculations of post-implantation loss. Table 6 (attached to this memorandum) provided by the Registrant shows recalculated values alongside the original values for comparison. Original post-implantation loss at 0, 0.5, 1.5 and 4.5 mg/kg/day was calculated at 11.5%, 13.2%, 14.9% and 22.8%; when recalculated excluding abortions, the mid- and high dose groups were 8.8% and 17.9%, respectively. The recalculated mean post-implantation loss at 4.5 mg/kg/day is not significantly increased compared to controls (Kruskal-Wallis test).

(2) Historical control data: Historical control data for developmental toxicity studies conducted around the same time as this study on terbuthylazine (see attached table) show a range of post-implantation loss ranging from 5.5% to 22.0% and a mean of 12.6%. Spontaneous abortions or total litter loss from resorption were observed in several of the control groups. The post-implantation loss of 17.9% is therefore within the observed range among control groups during that time.

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