UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

004853

MEMORANDUM

SUBJECT: Imazalil (Fungaflor/Fecundal). Addendum to PP#5F3250. Caswell No. 497AB

FROM: Carlos A Rodriguez
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THRU: Jane E. Harris, Section Head
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Toxicology Branch
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Applicant: Janssen Pharmaceutica
40 Kingsbridge Road
Piscataway, NJ 08854

Action:

Janssen Pharmaceutica through the Data Call-In Program has been requested to submit a teratology study in a second species for Imazalil. This data will be made part of PP#5F3250 submission.

Recommendation(s):

This study is classified "Supplementary" because no maternal or fetal toxicity was observed at the highest dose tested (40 mg/kg bwt/day). The study will be part of PP#5F3250 files.

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Review

Study ID:

Study Title: Oral Embryotoxicity and Teratogenicity of Imazalil in Cobs Mice.

Accession No.: 258128

Sponsor: Janssen Pharmaceutica

Testing Laboratory: Research Dept., Janssen Laboratories, France.

Study No.: 85-02

Study Director: G. Sanz

Study Head: J. M. Gillardin

Dates: February 7, 1985 to March 22, 1985

Report Date: March 25, 1985

Test Substance: R 27180 Imazalil

Test Animals:

Ninety-six young virgin female mice supplied by Charles River Society were used in this study.

Methods:

Sexually mature virgin female cobs mice, weighing between 25 and 34 grams were mated (one breeding male for three females) with adult males of the same strain. A vaginal smear was taken daily from the female at each mating and examined for mucous vaginal plug. The day when the mucous vaginal plug was found was considered to be the day one of pregnancy. The test material was dissolved in arabic gum and administered orally by gavage in a volume of 0.2 mL per 20g of body weight on day 6 through 16 of gestation to 4 groups 24 pregnant female mice at levels of 0, 2.5, 10, and 40 mg/kg.

Observations for signs of waning health, behavior, appearance, and signs of toxic and pharmacological response were made daily.

Records of food consumption were made on day 6, 17, and 19 during the study.

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Body weights were recorded on day 1, 6, 17, and 19 of pregnancy.

Prior to sacrifice, a complete physical examination was performed on all surviving mice.

At the termination of the experiment on day 19 of gestation all surviving animals were sacrificed by decapitation. Autopsy was performed in animals sacrificed and in all animals that died during the study and any macroscopic pathological changes were recorded.

The uterus was removed, the weight recorded, and the dams examined for the number and distribution of live and dead fetuses in each uterine horn, number of implantation sites in each horn, litter size and individual weight, number of live, dead, and resorbed fetuses, and abnormalities.

Two-thirds of the fetuses were randomized for dissection and one-third cleared and stained for skeletal abnormalities.

The following adult mice parameters were analyzed statistically: mortality, food consumption, body weight, and pregnancy rate.

Litter data statistically analyzed were: body weight, live fetuses, dead fetuses, resorbed fetuses, and abnormalities.

Results:

A. Adult Mouse Data (Tables 1-5 of the Report)

Mortality - No mortality occurred during the study as a result of treatment with the test material.

Body Weight - All treated groups body weight gain was comparable with the control group. No statistically significant differences were noted.

Food Consumption - The various treated groups' food consumption during the study was comparable to the control group.

Pregnancy - The percentage of pregnancy of the treated groups were comparable to the control group. No significant differences were noted.

B. Litter Data

Cesarean Data: (Tables 1-5 of the Report)

All measured parameters (number of live fetuses per litter, number of dead fetuses per litter, litter size, number of resorptions, number of implantations, weight of living pups) were similar in all groups.

Abnormalities: (Pages R4-R5 of the Report)

The most common observed abnormal variation was "talipes valgus." This abnormality appears to be more common in the control group and is considered not to be related to compound administration.

One fetus (out 263, 0.4%) from the high-dose group (40 mg/kg/day) was noted to have an external malformation. This fetus had exencephaly. This malformation appears to be incidental and not related to the compound administration.

Conclusions:

Imazalil is not teratogenic to mice at 40 mg/kg/day (HDT) in this study. Systemic Maternal NOEL > 40 mg/kg/day (HDT). Fetotoxic NOEL > 40 mg/kg/day (HDT). This study is classified "Supplementary." The highest dose tested (40 mg/kg/day) did not produce any evidence of maternal or fetal toxicity. We suggest a rate finding study be performed to determine the maximum tolerated dose (MTD) which will induce some maternal or fetal toxicity.

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