3-10-87

DATA EVALUATION REPORT

STUDY TYPE: Teratology Study in Rabbits.

ACCESSION NUMBER: 265796 Project No. 7-0227

CASWELL NO.: 323EE RECORD NO.: 185584

TEST MATERIAL: CGA 64250 Technical; 92.1% purity

SYNONYMS: Propiconazole; Tilt

SPONSOR: Agricultural Division, CIBA-GEIGY Corp.

TESTING FACILITY: Research Department, Pharmaceuticals Division, CIBA-GEIGY Corp., Summit, NJ.

CITATION: Raab, D.M., Youreneff, M.A., Giknis, M.L.A., et al. (1986). CGA-64250 Technical: A Teratology Study in New Zealand White Rabbits. Report No. 86043 (MIN 852172); CIBA-GEIGY Corp., NJ. (Aug 1, 1986).

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CONCLUSIONS: Groups (19/group) of pregnant rabbits were administered CGA-62450 at doses of 100, 250, and 400 mg/kg from gestation days 7 through 19. At 250 and 400 mg/kg, the treated animals showed decreased food consumption and body weight gain during the treatment period. At 400 mg/kg, treated rabbits also showed increased incidence of abortion. There was, however, no evidence of developmental toxicity.

Based upon the data, the NOEL for maternal toxicity was estimated to to be 100 mg/kg; LOEL, 250 mg/kg. The NOEL for developmental toxicity was estimated to be 400 mg/kg (HDT).

Classification: Core Supplementary. The report must contain the data on the animals which were sacrificed before the termination of the study, specifically those rabbits which had aborted or delivered early in the study.

A. MATERIALS:

1. Test compound: CGA-64250, Description: not specified. Batch #: FL 850083, Purity: 92.1%.

2. Test animals: Species: rabbits; Strain: New Zealand White; Age: "Sexually" mature; Weight: 6-7 lbs; Source: HARE-MARLAND, Hewitt, NJ.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Dose (mg/kg/day)	No. of Animals female
1	0	19
2 low dose	100	19
3 mid dose	250	19
4 high dose	400	19

2. Dosage Preparation

Appropriate amounts of CGA-64250 were mixed in 0.5% Tween 80 and 3% aqueous corn starch. The chemical analysis of the stability of the test solution was not submitted.

The animals were dosed by gavage.

3. Animals received food and water ad libitum.

4. Mating: Females were artificially inseminated. The day of insemination was designated as day 0 of gestation.

5. All animals were observed daily for clinical signs. They were also weighed on day 0, 7, 10, 14, 20, 24, and 29.

6. Food consumption of the pregnant females was measured daily for gestational days 5 to 29.

7. On day 29 of gestation, females were sacrificed and the fetuses were removed. In addition, the following observations and measurements were made:
   a). Macroscopic abnormalities of the reproductive tract of the dam.
   b). Number of corpora lutea in each ovary.
   c). Weight of gravid uterus.
   d). Numbers of live fetuses and number and distributions of resorption sites in each uterine horn.
   e). Placental weights.
   f). Fetal weights.

g). External abnormalities and sex of each fetus were determined.
h). Each fetus was sacrificed; soft tissue and skeletal abnormalities were examined.

8. Statistics - The following procedures were utilized in analyzing the numerical data: Bartlett's test, Dunnett's method of multiple comparision, and Healy Analysis.

9. Quality assurance: A quality assurance statement was submitted.

C. RESULTS:

Maternal Toxicity

1). Survival Rates: The survival rates were good for all treated and control animals. There were two deaths, one doe from the control and the other from mid dose animals. The death of one of the animals was due to a dosing accident.

In high-dose animals, 5/19 does were sacrificed early due to abortion or early delivery. In the mid dose group, one doe aborted early. One control animal delivered early.

2). Necropsy and Clinical Observations:

Among animals of the high dose group, there was an increased incidence of stool alterations, which could be compound related because similar results were not observed in the corresponding controls. There was also an increased incidence of abortion (Table I). Other parameters were comparable between the control and treated animals.

3). Food Consumption:

During the dosing period (days 7-19), the high and mid dose groups consistently consumed less food. The decrease in food intake was significantly different from that of the controls. Subsequent to the termination of dosing, the food consumption of these animal was increased (Table II).

4). Body Weight:

The body weight gain of the mid and high dose animals was supressed between the gestation days 7-20 (Table III). Similar to food consumption, the body weight gain of the affected groups of animals rebounded to normal after withdrawal of the test compound.

Developmental effects:

The developmental parameters were relatively similar between the controls and treated animals (Table IV). Although there appeared to be an increase in the value of Mean No. Resorption, the apparant increase was heavily influenced by a completely resorbed litter.

Fetotoxicity:

The Mean No. of Live Fetuses and the Mean Fetal Weights were comparable between control and treated groups (Table IV and V).

There were no significant differences in visceral and skeletal malformations between the treated and control fetuses (Table VI, VII, and VIII). Although increased incidence of the formation of 13th rib was observed, this incidence was shown to be associated with the maternal toxicity in other studies (Kavlock et al., 1985).

Discussion:

Based upon the reported data, CGA-62450 Technical at 250 and 400 mg/kg caused decreases in food consumption and body weight in treated does. At 400 mg/kg, the test compound also induced early delivery and abortion in pregnant rabbits. The report has a major deficiency; the data on food consumption, body weight gain, and other parameters of the animals which delivered or aborted early in the study were not presented in the report. These data are important in evaluating the possible maternal toxicity of the test agent, and they should be submitted for review.

The experimental results did not shown any increase in the incidence of cleft lip or palate in treated animals. Based upon the available data, the LOEL for maternal toxicity was estimated to be 250 mg/kg; NOEL, 100 mg/kg. The NOEL for developmental toxicity was estimated to be 400 mg/kg (HDT).

Reference

Kavlock, R.J., Chernoff, N., and Rogers, E.H. (1985). The effect of Acute Maternal Toxicity on Fetal Development in the Mouse. Teratogenisis, Carcinogenesis , and Mutagenesis 5: 3-25 (1985).

TILT CGA-64250 Reviews

The next 8 page(s) is/are not included in this copy of the TILT reviews.

The material not included contains the following type of information:

___ Identity of product inert ingredients

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