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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: October 22, 1981

SUBJECT: Teratogenicity Study in Himalayan Rabbits for inclusion into Triforine data base.

FROM: Charles Frick, Toxicologist E.F. 10/22/81 FDC 11/3/81
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Study conducted by E. Merck, Darmstadt
Experiment T-9127
Document No. 102AC-451.3
Date - 2/20/81
Study Director - J. Gleich

Compound Tested

Triforine (N,N'-1,4-piperazinediylbis(2,2,2-trichloroethylidene)[bis [formamide])(Technical)

Protocol

Triforine was administered orally by stomach tube to pregnant Himalayan rabbits from days 6 to 18 of pregnancy in daily doses as follows:

0.0 mg/kg (group 1)
5.0 mg/kg (group 2)
25 mg/kg (group 3)
125 mg/kg (group 4)

Fifteen animals per group.

Dosage was given in the form of a suspension in 5 ml of 0.5% carboxymethyl cellulose mucilage. The animals of trial group 1 were dosed with vehicle only.

1074

Cesarean section was performed on day 29 post-coitus. All of the fetuses were macroscopically examined for external malformations and, after x-rays had been taken, they were examined for skeletal malformations. After necropsy the organs were examined for malformations.

In all test groups, the frequency distribution of corpora lutea and implantations per dam, as well as the resorption rates, abortions, the number of dead fetuses and runts, and the viability of the offspring over the 24-hour incubation period were recorded.

In each group, mean values and standard deviations were calculated from body weight of the dams. The mean weekly feed consumption and the total feed consumption of the experimental animals were calculated. Mean fetus weights per dam were also recorded.

The behavior and general condition of the animals were checked daily. All of the animals were weighed at 3 to 4 day intervals until the end of the trial period. The feed consumption was determined once per week by back-weighing the feed not consumed.

Results

Clinical Observations

Control: Group I

One animal with vaginal hemorrhage on day 24 p.c.

One animal with total abortion on day 22 p.c. (6 normally developed fetuses were observed).

Group II:

One animal with vaginal hemorrhage on day 20 p.c. This animal aborted but this was not noted in study summary - (No. 2078).

One animal with total abortion on day 24 p.c. (4 normally developed fetuses were observed).

Group III:

Four animals had total abortion.

Group IV:

One animal had a partial abortion on day 21 p.c. (one aborted early resorption was observed).

One animal had a total abortion on day 26 p.c. (4 normally developed fetuses were observed).

One animal had a total abortion on day 21 p.c. (6 normally developed fetuses were observed).

One animal, not noted in summary ; aborted - animal No. 2116.

2

Body Weight Gain (Dams)

The test compound appeared to have little toxic effects on the dams or fetuses at 5 mg/kg (Group II) but a slight systemic toxic effect on the dams (temporarily reduced feed intake and body weight loss or reduced body weight gain) was noted in the 25 and 125 mg/kg test groups (Group III & IV).

Mortality:

No animals died.

Number of Pregnant Animals:

	Pregnant	Animals Used
Group I (control)	9	15
Group II	8	15
Group III	12	15
Group IV	10	15

Corpora Lutea:

The frequency distribution of the corpora lutea in trial groups 2, 3 and 4 corresponded to that of the control group.

Implantations:

The distribution of implantations in all test groups did not significantly differ from the control group.

Abortions:

In the control group, one animal had an abortion. In test group II, two animals aborted, test groups III and IV each had four animals abort. The investigators did not judge these incidences of abortions to be significant - this reviewer must consider the incidence of abortion to be at least an indication of maternal toxicity.

Resorption:

The early and late resorption rates in the test groups did not significantly differ from the control group.

3

Fetuses:

As was stated, the frequency distribution of live fetuses per dam in trial groups 2 to 4 was not significantly different from the control group (Group I). The percentage of live fetuses in trial Groups 2 and 4 was less than Group I because of the total abortions.

Fetal Weight:

The male offspring in trial group 4, and the female offspring in Group 3 and 4 were lighter (mean relative weights) than control animals.

Sex Distribution:

Not extraordinary.

Variations and Malformations:

Visceral changes - Not extraordinary
Skeletal changes - Not extraordinary

Conclusions:

Maternal Effects - NOEL = 5 mg/kg - Body weight effects noted at 25 and 125 (HLT) mg/kg.

Fetotoxicity - NOEL = 5 mg/kg (fetal weight)

Teratogenic Effect - No teratogenic effects observed at 125 mg/kg (HLT)

Study Classification: Core-Minimum

TS-769:th:TOX/HED:CFrick:10-22-81:card 2