In both matings, all groups were similar, except that there were fewer F_{3b} litters. This reduced litter incidence was greatest in the control group, and was not caused by the test article. There were reportedly no abnormalities in any F_3 litters. Thirteen control F_{3a} weanlings were found to have congested lungs. In all other respects, the F_3 generations were similar for all groups. The liver, kidney, and heart weights were similar for all groups, and there were no compound-related histopathologic lesions.

CONCLUSIONS: There were no indications of toxicity, reproductive effects, or terata any dose or in any generation. The reproductive NOEL is >5.0 mg a.i./kg/day (100 ppm prometryn a.i.).

STUDY CLASSIFICATION: This study is Core SUPPLEMENTARY. The highest dose should have induced a toxic response, but no toxicity was seen in any group or any generation. Considering the much higher doses used in a previously performed rat chronic study (up to 1250 ppm, at which level no significant toxic effects were observed), it comes as no surprise that no effects were seen in this study. The occasional deaths were probably not compound-related. The report was lacking specifics on the strain of the test animals. There was no mention of whether the rats were dosed during mating, gestation, and lactation. The criteria for selecting pups for mating or examination were not described. Body weights were not measured for females during mating, gestation, and lactation. Organ weight data for the F_{3b} weanlings were presented only in absolute terms. This made interpretation difficult since there was a great deal of variability in age (and therefore weight and organ weight) at the time of weaning. Additional reproductive organs should have been evaluated histopathologically.

The day -1 weights of the F_0 rats were identical for all three groups of males and for all three groups of females. Specifically, there were the same number of rats in each sex group which weighed 39 g, 40 g, 41 g, etc., and the pattern of weights was identical. This would not happen by chance or by design and raises some question as to the validity of the study. No other such anomalies were found in the report.

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83-3 TERATOLOGY STUDY OF PROMETRYN IN RABBITS

Ciba-Geigy Corporation; Report No. 85158; December 31, 1985; Accession No. N/A; MRID No. 157995

PROTOCOL: Seventy-six sexually mature virgin New Zealand White rabbits (2.97-4.01 kg) were artificially inseminated with semen from a New Zealand White buck colony. They were randomly assigned to 4 groups of 19 does each, and dosed by gavage on gestation days 7 through 19 with formulated technical prometryn at doses of 0 (vehicle control), 2, 12, and 72 mg/kg/day. The test

article was formulated in 3% cornstarch in 0.5% Tween 80. The does were observed daily for clinical signs, and weighed on gestation days 0, 7, 10, 14, 20, 24, and 29. Food consumption was measured daily on gestation days 5-28. On gestation day 29, the does were asphyxiated with CO_2 and examined grossly. The uteri and their contents were examined and weighed, and the ovaries were examined and the corpora luteae counted. The fetuses were counted, weighed, sexed, and examined grossly. They were then clarified and stained with Alizarin Red S to facilitate skeletal examination.

RESULTS: Three dams died during the course of this study. A mid-dose dam was found dead on gestation day 21. The presence of blood in the cage suggested that it may have died in the course of abortion. A high-dose dam died on gestation day 20 because of a hairball in its stomach. Another high-dose dam died due to a dosing accident. Two high-dose dams aborted on gestation days 16 and 23, respectively. A control dam delivered early on gestation day 28. No other compound-related clinical signs were observed. Mean group food consumption was significantly decreased (10-36%, relative to the controls) in the high-dose group between gestation days 12 and 23. Mean group body weight gain was similar in all groups, however. There were no compound-related gross lesions in the does. The litter data were as follows:

Dose (mg/kg/d)	Pregnant/ Mated	Implantations /doe	Resorptions (%) Embryonic	Fetal	Early delivery and Abortions
0	18/19	9.2	0.5	0.4	1
2	18/19	9.6	0.2	0.6	0
12	17/19	9.6	0.6	0.4	0
72	16/19	9.1	0.6	1.1	2

Dose (mg/kg/d)	Live litters	Live Fetuses Fetuses/doe	% Live	Wt (g)	% Male
0	17	8.4	90	42.0	54
2	18	8.7	91	42.8	52
12	16	8.6	89	42.6	50
72	11	7.1	77	40.3	53

All groups had similar mean values for corpora lutea, implantations, embryonic resorptions, fetal sex ratios, and fetal weights. The high-dose had significantly decreased numbers of live litters and live fetuses/doe due to increased late resorption and abortion. It cannot be determined whether the abortions were due to maternal toxicity. The incidences of external, visceral, and skeletal anomalies were similar for all dosed and control groups. Prometryn was not teratogenic at the doses tested. The defined doses are:

Maternal toxicity NOEL = 12 mg/kg/day
Maternal toxicity LEL = 72 mg/kg/day (decreased food consumption)
Embryotoxicity NOEL >72 mg/kg/day (HDT)
Fetotoxicity NOEL = 12 mg/kg/day
Fetotoxicity LEL = 72 mg/kg/day (increased fetal resorptions)
Developmental toxicity NOEL >72 mg/kg/day (HDT)
Developmental toxicity index (A/D) = 72/72 = 1

STUDY CLASSIFICATION: This study is Core MINIMUM. The technical test article was used, but the purity was not reported. The dose concentration and stability data were not reported. This study received Quality Assurance review.

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