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

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10/21/83

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Marilyn Mautz, PM#16
Registration Division (TS-767)

THRU: William L. Burnam, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Review of Curacron Rabbit Teratology Study
Accession No. 250451 CASWELL#266AA

Registrant: Ciba-Geigy Corp.
410 Swing Road
Greensboro, North Carolina 27409

Recommendation:

It is recommended that this study be classified as Supplementary Data. It is requested that historical control data for malformations and variations in this strain at this laboratory be submitted and that additional statistical analysis, as described below, be submitted. The NOEL for teratogenicity and fetotoxcity appear to be 60 mg/kg and it appears that a NOEL for maternal toxicity has not been established; however, the setting of firm NOELs must await the submission of the requested data.

Review of Data:

Teratology, Rabbits. Conducted at Science Applications, Inc., La Jolla, California and submitted by Ciba-Geigy, study number 283003, dated June 1, 1983.

New Zealand White rabbits, 4-5 months old, were acclimated for 9 days after arrival from the supplier (Holbert's Rabbitry, Spring Valley, CA). Does were bred naturally and, after the observation of mating, were injected with pituitary lutenizing hormone (.5 mg/kg). Mating took place over a 7 day period.

On day 6 of gestation, 16 rabbits per dose level were administered either 0, 30, 60, 90 or 175 mg/kg of Curacron technical (purity 90.8%). A 0.2% solution of carboxymethyl cellulose was prepared in distilled water and used as a vehicle. Dosing was via gavage. Animals were observed at least daily. Animals were weighed on days 0, 6, 9, 12, 15, 18, 25 and 30 of gestation.

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On day 30, animals were sacrificed via injection of "T-61", identified only as a "non-narcotic euthanasia solution". All does were necropsied and particular attention was paid to the reproductive organs. The gravid uterus was weighed and fetuses and resorption sites were recorded.

Each fetus was examined externally and viscerally using a modified Staples technique. After fixation, all fetuses were examined for skeletal abnormalities.

Results:

Twelve does died during the course of the study (9 mortalities at 175 mg/kg, 2 mortalities at 60 mg/kg and 1 mortality in the control group). Most deaths occurred following a period of anorexia and diarrhea. Pinpoint hemorrhages of the stomach were observed for 8 of 9 animals dying in the high dose group and one animal dying at 60 mg/kg. Actual mean body weight gains (day 30 minus day 6) were depressed in a dose related manner (438.5, 366.7, 350.0, 293.3 and 185.7 grams for the 0, 30, 60, 90 and 175 mg/kg dose levels, respectively). The mean change in body weight from day 6 to day 30 of the treated groups compared to controls was also clearly decreased when expressed on a percentage of control basis (84, 80, 69 and 42 percent of control for the 30, 60, 90 and 175 mg/kg/day groups, respectively). Although a statistical comparison of this data by the sponsor did not find statistical significance, it is suggested the a reanalysis be conducted in which the mean percentage change for the control, 30, 60, and 90 mg/kg/day groups be compared using analysis of variance.

The total number of implantations was similar at dose levels of 0, 30, 60 and 90 mg/kg, but was somewhat less at 175 mg/kg. The percent of fetuses delivered alive were similar in each dose group. Fetal weights were similar in all dose groups. Sex ratios were also similar in all groups.

External malformations consisted only of "runting", with 5, 0, 1, 11 and 5 runts observed in the 0, 30, 60, 90 and 175 mg/kg/day groups. A slight increase in the incidence of runting is observed at the 90 and 175 mg/kg/day dose level (9 and 10% vs. 5% in the control group). The number of litters having one or more runts is 2/13 examined, 0/13, 1/12, 3/15, and 2/7 for the 0, 30, 60, 90 and 175 mg/kg/day groups, respectively. The submission of historical data may help to clarify whether the apparent effect at 90 and 175 mg/kg/day is real.

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Visceral malformations consisted only of a single incidence of missing left kidney in a control fetus, incomplete partioning of the lungs in a 30 mg/kg fetus and an ovarian mass in a 30 mg/kg fetus. These did not appear to be associated with treatment.

The incidence of skeletal malformations were similar in the control and dosed animals. The incidences of several skeletal variations were increased in the high dose group. These variations consisted of several sites of incomplete ossification and an extra ossification center in sternebrae 5 and 6. Incomplete ossification of metacarpal 1 was increased from a mean of 3.3% in the control group to 7.4% per litter in high dose group, incomplete ossification was increased from 0% to 1.8% per litter in the high dose group and incomplete ossification of middle phalange 5 was increased from 0% in the control group to 3.6% per litter in the high dose group.

Core Classification:

Supplementary Data. The NOEL for fetal toxicity appears to be 60 mg/kg. An increase in the incidence of runting occurs at dose levels of 90 and 175 mg/kg/day. A NOEL for maternal toxicity cannot be established from this study. Submission of historical data for variations and malformations is requested as well as a statistical analysis as described in the above review.

Gary J Burin 10/25/83

Gary J. Burin, Toxicologist
Toxicology Branch/HED (TS-769)

10/25/83

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