DATA EVALUATION RECORD PAGE OF

CASE PM002649

CHEM Chlorsulfuron (formerly DPX-W4189)

BRANCH Toxicology DISC TOPIC Teratogenicity

FORMULATION Technical (information known to reviewer)

FICHE/MASTER ID CONTENT CAT

Teratology Study in Rabbits
Haskell #12,700
Revised Final Report
HLO-534-80
MR-3582-001
A. M. Hoberman et al. July 17, 1980
Hazleton Laboratories America, Inc.

SUBST. CLASS =

OTHER SUBJECT DESCRIPTORS

DIRECT RVW TIME = 3 hours START-DATE END DATE

REVIEWED BY: Ladd W. Smith
TITLE: Toxicologist
ORG: Biochemicals Dept., E. I. du Pont de Nemours & Co., Inc.
Wilmington, DE 19898
LOC/TEL: B-12360
(302) 774-6342

SIGNATURE: Ladd W. Smith DATE: 11/13/81

APPROVED BY:
TITLE:
ORG:
LOC/TEL: 201-536

SIGNATURE: DATE:

Conclusion:

A. Core Minimum
B. A NOEL of 75 mg/kg body weight was established for teratogenic effects based on the absence of significant effects when chlorsulfuron was given in oral doses of 0, 10, 25, and 75 mg/kg body weight to pregnant female rabbits on days 6-19 of gestation. A NOEL of 25 mg/kg body weight was established for fetotoxicity based on an increased incidence of resorptions and lower fetal viability at 75 mg/kg body weight.
C. This study generally conforms to EPA Proposed Guidelines in Section 163.83-3 (Federal Register 43: 37383, 8/22/78).

Methods:

Chlorsulfuron was administered by oral intubation on days 6 through 19 of gestation to 16 to 17 pregnant New Zealand white rabbits at levels of 0, 10, 25, or 75 mg/kg of body weight. Corn oil (1 ml/kg) was used as a vehicle. Rabbits were singly housed in stainless steel cages and fed Purina® Lab Rabbit Chow® and water ad libitum. Does were impregnated by artificial insemination. Ovulation was induced by intravenous administration of human chorionic govadotropin. Criteria evaluated for evidence of compound effect were individual maternal body weight change on days 0, 6, 11, 15, 19, and 29 of gestation, individual food consumption, daily clinical observations, survival, gross pathology, implantation efficiency, and offspring viability and development.

Surviving

On day 29 of gestation, all surviving females in each group were sacrificed by an injection of T-61® Euthanasia Solution. The fetuses were taken by cesarean section, the does were examined for visceral gross pathology and the following information was recorded for each litter: the number of corpora lutea per ovary and ovarian weight(s); uterus weight with and without fetuses; and the number and placement of implantations, resorptions, live fetuses, and dead fetuses. Each fetus was tagged for identification, examined externally, and the weight and crown-rump distance were recorded. Fetuses were sacrificed by injection with Nembutal®, and opened by a longitudinal incision. The sex was determined, and the visceral examined grossly. Approximately one-third of the fetuses from each litter were examined without fixation by Staples' Technique. Major organs were inspected in situ with special attention given to the heart and major blood vessels. The heads of these fetuses were removed, fixed in Bouin's solution, sectioned by Wilson's freehand razor technique and sealed in plastic. The prepared sections were examined against a light box with the aid of magnification.

The remaining two-thirds of the fetuses from each litter were eviscerated, skinned, and placed in 96% ethyl alcohol. After proper fixation and dehydration, the skeletons were stained in a potassium hydroxide-alizarin red solution and finally cleared in a solution of glycerol, ethyl alcohol, and benzyl alcohol. Each skeleton was examined with the aid of magnification on a light box for anomalies and the degree of ossification.

The maternal body weight gain, food consumption, and uterine and ovarian weight data, as well as the mean (per litter by sex) fetal weights and lengths of the control group were compared statistically to the treated groups by Bartlett's test for homogenicity of variance and one-way classification analysis of variance (ANOVA). If significant results were from both Bartlett's test an ANOVA, a multiple pair-wise comparison procedure was used to compare the group mean values. If a significant result was not obtained from Bartlett's test, but was obtained from ANOVA, Scheffe's multiple pair-wise comparison procedure was used to compare the group mean values. The reproduction and viability indices were analyzed by Wilcoxin's nonparametric comparison of group means. The litter was used as the experimental unit. All analyses were evaluated at the 5.0% probability level.

Results:

A statistically insignificant dose-related weight loss occurred during treatment; all groups gained weight over the entire study period. Food consumption was generally decreased in the treated groups.

The incidences of gross pathological findings increased slightly, in a dose-related fashion. Pale kidneys and pale or nutmeg livers were the most frequent occurrences.

Uterine weights, ovarian weights, corpora lutea and implantations showed no significant differences among groups.

The incidences of resorptions were increased and fetal viability was decreased in all treated groups; only the effects in the high-dose group were significant. Fetal body weights and lengths were comparable in all groups.

	0	10	25	75
Mean Number of Resorptions	0.7	1.4	0.7	1.9
Nean Incidence of Resorptions %	11.6	23.9	13.8	31.3
Mean Incidence of Fetal Viability %	88.5	76.3	79.2	59.8

The incidences of visceral anomalies and of skeletal and visceral variants were not significantly different among groups. No skeletal anomalies were noted.

A NOEL of 75 mg/kg body weight was established for teratogenic effects based on the absence of significant effects when chlorsulfuron was given in oral doses of 0, 10, 25, and 75 mg/kg body weight to pregnant female rabbits on days 6-19 of gestation. A NOEL of 25 mg/kg body weight was established for fetotoxicity based on an increased incidence of resorptions and lower fetal viability at 75 mg/kg body weight.

Discussion:

The study was conducted by acceptable methods and the collected data support the reported conclusions.

Pregnancey rates were higher in treated groups than in the control group; rates were 81%, 88%, 100%, and 94% for the 0, 10, 25, and 75 mg/kg dose groups, respectively.