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CASE PM

CHEM Chlorsulfuron Formerly DPY-W4189

BRANCH Toxicology DISC TOPIC Teratogenicity in Rat

FORMULATION Technical

FICHE/MASTER ID CONTENT CAT

Teratological Study of 2-chloro-N-[(4-methoxy-6-methyl-1, 3, 5-triazin-2-yl)aminocarbonyl] benzenesulfonamide (INW-4189) in Rats
Haskell Laboratory Report No. 583-78
Medical Research Project No. 2738
A. S. Rogers et al. October 11, 1978

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OTHER SUBJECT DESCRIPTORS

DIRECT RVW TIME = 4 hours START-DATE END DATE

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Conclusions:

A. Core Minimum Upgraded (no maternal toxicity produced).
B. A Noel of 2500 ppm was established based on the absence of significant effects when chlorsulfuron was fed to pregnant rats from day six through day fifteen of gestation at 0, 100, 500, and 2500 ppm. Chlorsulfuron was neither fetotoxic nor teratogenic at any test level.
C. This study generally conforms to EPA Proposed Guidelines in Sec. 163.83-3 (Federal Register 43: 37383, 8/22/78).

Methods:

Dietary levels of 0, 100, 500, and 2500 ppm chlorsulfuron were fed to 27 pregnant Charles River - CD Rats/groups on days 6 through 15 of gestation. Ground Purina Lab Chow was powdered ad libitum through day 5 of gestation and for days 16 through 21. Rats were housed in wire, mesh cages. Water was provided ad libitum, and temperature (72-74°) and humidity (50%) were controlled.

Individual food consumption was measured and recorded throughout the test. Rats were observed daily for clinical signs of toxicity and changes in behavior. They were weighed on the day of arrival and on days 6, 10, 16, and 21 of gestation.

All rats were sacrificed by chloroform inhalation on the twenty-first day of gestation. At the time of sacrifice, the abdominal wall of the female was opened and both ovaries and uterus were removed and inspected. The uterus was then opened and the fetuses removed and examined. The following observations and measurements were recorded:

1. Number of corpora lutea in each ovary.
2. Number of implantation sites in each horn.
3. Number and location of all live and dead fetuses.
4. Number and location of resorptions.
5. Weight of each live fetus (to 0.01 g)
6. Crown-rump length of each live fetus (to 0.01 cm)
7. Any gross anomaly which could be observed under a long focal length of 2 1/2X.

About one-half of the fetuses from each litter were preserved in 95% alcohol for subsequent maceration in 1% aqueous KOH, clearing and staining with Alizarin Red and examination to detect skeletal abnormalities. The remaining fetuses were fixed in Bouin's fluid for free-hand razor blade sectioning by a modified Wilson Method and examination under a dissecting microscope for visceral and neural anomalies. The uterus and ovaries of rats in all groups were examined for gross changes and those of pregnant rats were preserved in Bouin's fluid for possible histologic examination. Other tissues and organs were examined grossly and discarded if found to be normal.

For statistical evaluation of the data, the litter was considered the experimental unit of treatment and observation. Maternal and fetal body weights and fetal crown-rump measurements were treated statistically by analysis of variance and least significant difference tests. The Fisher Exact Probability test was used to evaluate the incidence of resorptions and abormalities among litters. The number of corpora lutea implantations and live fetuses per litter were analyzed by the Wilcoxon Rank Sum Test. In all cases, two-tailed significance tests were performed and significance was judged at the 0.05 probability level.

Results:

No meaningful effects occured in body weight, food consumption, or clinical signs of toxicity.

Average daily intakes of chlorsulfuron were 10, 49, and 241 mg/kg, at dietary levels of 100, 500, and 2500 ppm, respectively.

Mean litter size, resorptions per litter, and average fetal body measurements were not affected.

Small subcutaneous hematomas and petechial hemorrhages were found in fetuses from control and all treated groups; the 500 ppm group had a significantly higher incidence of hemorrhages.

Low incidences of minor visceral anomalies were found in all groups. Four major abnormalities were present in two of the test groups, each involving only one fetus. One fetus had hydrocepholms, and the other one showed multiple defects consisting of heart and lung abnormalities and exencgsholy. Both of these were from mothers fed 100 ppm. The other two were from mothers fed 500 ppm; one with an umbillical hernia and the other with a great vessel defect (absent left pulmonary artery). These were considered isolated occurrences rather than compound related. A NOEL of 2500 ppm was established since chlorsulfuron was neither fetotoxic nor teratogenic at any test level.

No malformations or major abnormalities of the skeletal system were noted. The incidences of minor anomalies and common variants were similar in all groups.

Discussion:

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

The number of litters with partial resorptions in the control group was unusally small. Historical controls at Haskell Laboratory have almost twice as many litters with partial resorptions. Charles River Breeding Laboratories report values of from 11-78%.

The major abnormalities seen in the four fetuses were believed to be due to genetic background because of the varied nature and the sporadic distribution. The study was run in connection with Reproductive Study HLR-557-81.