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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#8F2106; Stampede 3E Herbicide; Propanil on Wheat; Submission of teratology studies to satisfy conditions of tolerance. CASWELL#325 Accession#244328-332

FROM: William Dykstra, Toxicologist
Toxicology Branch, HED (TS-769) WD for LDC 3/9/81

TO: Robert Taylor (25)
Registration Division (Ts-767)
and
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

Recommendations:

1) The submitted teratology studies are acceptable as Core-Minimum Data. Stam, technical was not teratogenic in rats or rabbits at dosages up to 100 mg/kg/day during gestation.

Review:

1) Teratologic Evaluation of Stam technical in the Albino Rat (Snell Project#10065-008; February 29, 1980)

Groups of 25 pregnant BLU:(SD) rats received doses of 0, 0.8 mg/kg, 4.0 mg/kg, 20 mg/kg and 100 mg/kg of test material in corn oil at 10 ml/kg during the period of major organogenesis, days 6-15 of gestation.

Each animal was observed daily for pharmacological and toxicological effects. The body weight of each animal was recorded on the day of receipt and on days 6, 10, 15 and 20 of gestation. Food consumption was recorded for each animal on days 6, 10, 15 and 20 of gestation.

On day 20 of gestation, all animlas were sacrificed by exposure to CO_2 vapor. The uterine contents and genital tract were examined and the following recorded for each dam:

°number of corpora lutea per ovary
°number of implantation sites
°number of early and late resorption sites
°number of live and dead fetuses
°body weight of each live fetus
°sex of each fetus

At the time of uterine examination all fetuses were examined grossly for the presence of external congenital abnormalities.

One-third of the fetuses were examined for soft tissue anomalies by the Wilson technique.

The remaining two-thirds of the fetuses were examined by Alizarin staining for skeletal anomalies and ossification variations.

Statistical analyses of the data were performed.

Results:

All animals appeared thirfty throughout the study. However, a few scattered incidences of rales, diarrhea, red nasal discharge and alopecia were observed. These observations were not considered to be dose-related. There were no dose-related deaths. One of the one hundred twenty-five animals died during the course of the study: Dam#5119, Group V (100 mg/kg). Upon gross necropsy, the dam was apparently not pregnant. In addition, a red stomach lining and red fluid filling the intestines were osberved.

Body weights and food consumption were similar among all groups with the exception of the dams of the 4 mg/kg group sacrificed on the first day of caesarean sections. These dams were lighter ($p < .05$) than dams of all other groups. This effect is considered random and to be of no toxicologic signifcance. No significant difference was observed across groups for body weights minus the gravid uterine weights.

The average litter reproduction data was similar among all groups with the exception of differences in average pup weights in replicate 1 (day 1) and replicate 2 (day 2) among all groups including controls.

Observations at sacrifice indicated no effect attributable to administration of the test substance.

Other than trauma-induced lesions at the time of caesarean section, no gross findings were recorded for the pups. There were no significant dose-related occurrences of gross or soft tissue abnormalities detected in this study. However, smaller pups were seen in the high-dose group. The skeletal structure was not affected by daily treatment with up to 100 mg/kg of test material. No teratological effects were observed in stained skeletal preparations.

Conclusion:

The test material is not teratogenic in rats at doses up to 100 mg/kg. The NOEL is considered to be 20 mg/kg/day.

Classification: Core-Minimum Data

2. Stam Technical Teratogenicity Study in Rabbits (Argus Project#018-001; December 17, 1980)

Twenty rabbits were artificially inseminated on each of four consecutive days (insemination groups A, B, C and D). Five rabbits were assigned to each of the four treatment groups on each of the four insemination day. Each treatment group consisted of 20 rabbits.

Stam, technical (85.4% a.i.) was administered as a suspension in corn oil at dosages of 0 (vehicle), 4, 20 and 100 mg/kg/day of the active ingredient. Rabbits were given oral dosages of Stam, technical once daily on days 6 through 18 of gestation at volumes of 1 mg/kg/day. Daily adjustments in dosages administered were made on the basis of maternal body weight.

Pregnancy occurred in 18, 19, 15, and 17 rabbits given 0 (vehicle), 4, 20 and 100 mg/kg/day of Stam, technical. Reproductive parameters and fetal skeletal and soft tissue observations were made. Statistical analyses of the data were performed.

Results:

Treatment with 100 mg/kg/day resulted in the death of 5 rabbits. All of the rabbits which died were pregnant; 2 were resorbing all implantations. Deaths occurred during days 13 through 20 of gestation. No treatment-related physical signs were osberved in rabbits which died.

Abortion occurred in 1, 3, 0, and 4 control, low, middle, and high dosage group rabbits, respectively. Abortion was not dose-related. All of the high dosage group rabbits had blood in the cage pan at abortion. No other dosage-related physical sign occurred in rabbits which aborted.

Two low, one middle and one high dosage group rabbits delivered naturally on day 29 or 30 of gestation, prior to scheduled carsarean-sectioning.

Pregnant rabbits treated with 100 mg/kg/day of test material lost significantly more body weight ($p < 0.01$) than controls at the beginning of treatment (days 6 to 12 of gestation). The effect was transient and disappeared by day 30 of gestation.

Day 30 caesarean-sectioning observations were based on 17, 14, 14, and 7 pregnant rabbits which survived and did not abort or delivered naturally in the control, low, middle, and high-dose groups, respectively. Maternal treatment with Stam, technical did not significantly alter the number of corpora lutea, implantations, live and dead fetuses or early and late resorptions in caesarean-sectioned rabbits. Fetal sex ration and fetal body weight were also significantly unaltered by maternal treatment.

Totals of 113, 106, 65 and 49 in 16, 16, 14 and 8 control, low, middle, and high dosage group, respectively, caesarean-sectioned or natural delivery litters were evaluated for gross and skeletal variations. Soft tissue evaluations were based on 113, 106, 65, and 49 control, low, middle, and high dosage group fetuses or pups, respectively, in the same respective number of litters; autolysis precluded visceral examination of late resorptions. No gross, soft tissue or skeletal variation observed in fetuses, pups or late resoprtions was attributed to maternal treatment with Stam, technical. Variations occurred without dose-response or as single occurrences.

No differences in the average number of ossification sites in fetuses were considered to reflect maternal treatment with Stam, technical. Ossification site data were based on 113, 91, 56 and 41 liveborn fetuses in 16, 14, 13, and 7 control, low, middle, and high dosage group caesarean-delivered litters, respectively. Significantly fewer ($p < 0.01$) metacarpals were ossified in fetuses in 100 mg/kg/day dosage group litters than in controls because of 8 of 10 fetuses in one litter had 4 ossified metacarpals. Other ossification site data were similar in control and Stam-treated litters.

Conclusion:

Stam, technical was not teratogenic at dosages up to 100 mg/kg/day in rabbits. The NOEL is considered to be 20 mg/kg/day.

Classification: Core-Minimum Data

TS-769:TOX/HED:th:WDYKSTRA:3-9-81