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DATA EVALUATION REPORT

STUDY TYPE: Teratology

TOX. CHEM. NO.: 716A

ACCESSION NUMBER: 262546

PROJ NO.: 1850

TEST MATERIAL: Pyridate Tech 92%

SYNONYMS: CL-11344

STUDY NUMBER(S): 055934

SPONSOR: Chemie Linz, Welser-Str. 42
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TESTING FACILITY: Research & Consulting Co A.G.
CH 4452 Itingen, Switzerland

TITLE OF REPORT: Embryotoxicity (including teratogenicity) study with Pyridate Technical in the rat

AUTHOR(S): Becker, H.; Schafroth, P.; Vogel, W.; Sachsse, R.; and Terrier,C.

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CONCLUSION: The Tox Branch reviewer has concluded the Based on the results presented, Pyridate Tech 92% was not teratogenic when administered to pregnant Wistar/HAN rats from day 6 through day 15 of pregnancy. The developmental NOEL was 165 mg/kg.

Classification: Guideline

MATERIALS: The test compound was prepared daily in 4% carboxymethylcellulose in distilled water just prior to compound administration. The carboxymethylcellulose solution served as the vehicle control. Pregnant Wistar/HAN rats were the test animals.

METHODS: One hundred thirty five Wistar/HAN rats(Kfm: WIST,Outbred SPF) weighing 189 to 232 grams were used in the study. The control group contained 35 rats,and each treatment group contained 25 rats. Animals were housed individually, and fed a standard laboratory diet. Food and water were available ad libitum. The females were housed with sexually mature males until daily vaginal smears were either sperm positive or a copulation plug was observed. The day either sperm or the copulation plug was observed

was designated day zero of pregnancy. The pregnant females were randomly assigned to groups receiving 0, 55, 165, or 495 mg/kg of the test compound. Dosages were based on the results of a previous dose range finding study. The test compound was administered by gavage daily from day 6 through day 15 of pregnancy in a volume of 10 ml/kg. Thirteen females receiving 495 mg/kg of the test compound died after administration of the first dose. A fifth group receiving 400 mg/kg was added to the study at this point, and the control group was increased to 35 animals.

The pregnant animals were observed daily for mortality and clinical signs,and were weighed daily. Food consumption was recorded on days 6, 11, 16 and 21. On day 21, all surviving females were sacrificed, and the pups removed by Caesarian section. All maternal internal organs were examined grossly, and the uterine contents, position of fetuses, number of corpora lutea recorded. Fetuses were sexed, weighed, and examined for external abnormalities. Half of each litter was examined by Wilson's technique for visceral abnormalities, while half was cleared and stained with alizarin Red for examination of skeletal abnormalities by a modification of Dawson's technique.

The uteri of all females found not pregnant at necropsy were placed in aqueous ammonium sulfide solution to be examined for implantation sites.

TEST COMPOUND

ANALYSIS: The concentration and homogeneity of the dosing mixtures were analysed by spectrophotometry. All samples were reported to be within 10% of target concentration. Details of the analysis were not given.

STATISTICAL

ANALYSIS: Maternal data were analysed by one way analysis of variance. Dunnett's test was used for intergroup comparisons (single treatment groups against the control group). Fetal data were compared by Fisher's exact test. The level of significance was considered to be 5%.

RESULTS: Sixteen females from group 4 (495 mg/kg) and 5 from group 5(400 mg/kg) died during the study. Thirteen of the group 4 and all of the group 5 females died after a single administration of the test compound. The remaining group 4 females which died did so after receiving 5, 6 and 10 doses of the test compound respectively. Somnolence, ruffled fur and dyspnea were observed in these animals prior to their deaths.

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Of the animals in Groups 4 and 5 (495 mg/kg and 400 mg/kg) which died on study, all but one (#92) were pregnant.

Total implantations and corpora lutea in these animals were similar to those which survived to termination of the study.

No toxic signs were reported in the control, 55 mg/kg or the 165 mg/kg groups. In the 495 mg/kg and the 400 mg/kg groups respectively, the following signs of toxicity were reported after the first and/or second test compound administraton: ventral body position, dyspnea, sedation, and loss of reaction to external stimuli. Mean maternal food consumption was significantly reduced in the 400 mg/kg and 495 mg/kg dams relative to the controls during the treatment period from day 6 to day 15 of gestation, and mean maternal body weight was significantly decreased from day 10 to day 21 of gestation. No stillbirths were reported in any treatment group. No significant differences between control and treated animals were reported with respect to the number of implantations, corpora lutea, resorptions, or fetuses per dam. Mean fetal body weight was slightly lower than control in the 400 mg/kg group(4.2%), and the 495 mg/kg group (8.3%). These data are shown in the following table:

Summary of Reproduction Data

Dosage mg/kg	0	55	165	495	400
No of dams	35	24	23	9	16
Implantations	12.1* ± 2.4	12.4 ± 1.7	13.0 ± 1.5	12.3 ± 1.1	11.3 ± 2.8
Corpora lutea	13.5 ± 2.4	13.0 ± 1.4	13.5 ± 1.5	13.1 ± 1.1	13.4 ± 2.1
Fetuses/ dam	11.2 ± 2.6	11.8 ± 1.9	12.0 ± 1.6	11.6 ± 1.7	10.7 ± 3.1
Resorptions	1.0	0.6	1.1	0.8	0.6
Fetal body wt.	4.8 ± 0.4	4.9 ± 0.4	4.8 ± 0.4	4.4 ± 0.4	4.6 ± 0.5

*Data are expressed as Mean and Std. Deviation

The sex ratio of pups was similar in control and treated animals.

No external or visceral abnormalities were reported. One control fetus was a runt. The following skeletal abnormalities were reported:

Control group(197 fetuses/35 litters):3 fetuses with missing sternebrae ; 1 fetus with irregularly ossified sternebra.

55 mg/kg group(143 fetuses/24 litters):1 fetus with irregularly ossified sternebra 4.

165 mg/kg group(138 fetuses/23 litters):2 fetuses with missing sternebrae and absent thoracic vertebral bodies.

400 mg/kg group (103 fetuses/19 litters):3 fetuses with missing sternebrae, 1 fetus with irregularly ossified sternebrae, and 1 with a bipartite sternebra.

495 mg/kg group (52 fetuses/9 litters): 3 fetuses with a missing thoracic vertebral body, 2 fetuses with absent sternebrae, and 2 fetuses with wavy ribs.

The investigators concluded that Pyridate did not demonstrate a teratogenic response in Wistar rats under the conditions of this study. The decreased fetal body weight was considered a compound related effect.

DISCUSSION AND CONCLUSIONS:

Administration of Pyridate Technical 92% to pregnant Wistar/HAN rats at dosage levels of 0, 55, 165, 400, and 495 mg/kg from day 6 through day 15 of gestation resulted in mortality at the two highest dosage levels (5/25 and 16/25 respectively), and significant decreases in body weight gain in those which survived to study termination. No adverse effects were noted on gestational parameters (implantations, corpora lutea, resorptions), or the number of live births. No compound related teratogenic effects were reported. However, an increased incidence of missing and/or unossofied sternebrae and a dose related decrease in mean fetal body weight were observed at the two highest doses. Based on these findings, the NOEL

However since 2 highest dose levels demonstrated maternal mortality and signif decrease in body wt gain of survivors

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for embryo/fetotoxicity is 165 mg/kg.

$$\text{A/D ratio} = \frac{\text{maternally toxic dose}}{\text{developmentally toxic dose}} = \frac{400 \text{ mg/kg}}{400 \text{ mg/kg}} = 1$$

Core Classification : Guideline