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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Hamster Teratology Study of Captan. Amended Final Report, IRDC, January 17, 1983, Acc. No. 249681, Reg. No. 239-1246.

FROM: William R. Schneider, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Henry Jacoby, Product Manager #21
Registration Division (TS-767)

THRU: Jane Harris, Ph.D., Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769)

TOX Chem. No. 159

Registrant: Chevron Chemical Company
Richmond, California 94804

Contract Laboratory: International Research and Development Corporation
Mattawan, Michigan 49071

Chemical: Technical Captan

Background:

This study had been reviewed by Dr. Dykstra (10/2/79) who requested an evaluation of a numerical discrepency in Table 4 of the original submission. He did not make any conclusions regarding the teratogenicity of Captan pending receipt of the information. The registrant supplied information which explained the apparent discrepency, however, we requested further information to evalute the "rib anomalies" (review, Dr. Schneider, 1/27/83).

Recommendations:

Captan produces stress-related fetal effects but is not teratogenic in this study. NOEL for fetotoxicity is 200 mg/kg/day.

Classification: Core Minimum data.

Materials and Methods: See review, W. Dykstra, Ph.D. 10/2/79.

Results:

The original table showed rib anomalies. This resubmission has described them as fused ribs, bent ribs, and focal enlargement of ribs.

	Control mg/kg/day)	Captan (mg/kg/day) 50	200	400
No. of litters examined:	28	26	26	23
Total No. of fetuses examined externally:	342	288	284	210
Observations:	Number of Fetuses (No. of litters)			
Fused ribs	1 (1)	4 (4)	5 (4)	0 (0)
Bent ribs	0 (0)	0 (0)	0 (0)	5 (1)
Rib: Focal enlargement	0 (0)	0 (0)	1 (1)*	1 (1)
Total Rib anomalies:	1(1)	4(4)	5(4)	6(2)

* This fetus also had fused ribs.

Discussion:

The rib anomalies are increased in captan-treated groups at all doses; fused ribs were the most common anomaly seen in the Robens hamster study (Robens, J. F., 1970). However, as in the Robens study, a good dose response (especially considering the effect per litter) was not seen. Fused and bent ribs have generally been considered as terata, but a recent study (N. Chernoff, USEPA, HERL, Research Triangle Park, N.C., in press) has showed that fused, supernumery and bent ribs were induced by general maternal restraint stress in mice. There was definite maternal stress at the 200 and 400 mg/kg/day dose levels as indicated directly by mortality, reduced body weight gains, and body weight loss. These rib

effects may therefore represent another manifestation of the fetotoxicity, particularly the reduced ossification, seen at 400 mg/kg/day. Teratology litter data are sometimes transformed by an arc sine conversion but these numbers are too low for this to be appropriate so a one tailed Fisher exact test was performed.

Dose (mg/kg/day)	0	50	200	400
Rib anomalies	1	4	5	6
Fetuses examined	342	288	284	210
P statistic		0.138	0.071	0.014

This showed significance at $P < 0.05$ at 400 mg/kg/day, however, five of these six rib anomalies were in the same litter which decreases our confidence in the significance of this effect.

Conclusions:

Captan produces fetotoxicity and maternal toxicity in the Golden Syrian Hamster under the conditions of this study. The fetotoxic effects were reduced ossification and decrease in fetal body weights at 400 mg/kg/day. Other statistical significant effects at 400 mg/kg/day were decreases in male to female and the number of viable fetuses; and increases in the number of early and late "resorptions" and post-implantation losses. The NOEL for fetotoxicity is 200 mg/kg/day.

A previous hamster study (Robens, J.F., 1970) also showed increases in fused ribs, particularly using single dosing on day 7 and on day 8 of gestation. This study was inconclusive based on the information in the published article and the raw data was no longer available. To determine whether the increases in rib anomalies in Captan-treated groups in the present study are related to treatment, additional historical data on these rib effects would be useful in evaluating potential variability in spontaneous background rates. In lieu of such information, another teratology study in hamsters using single dose treatments on day 7 and day 8 would help to elucidate any rib effects induced by captan by reducing the confounding effects of fetotoxicity.

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MEMORANDUM

To : William Schneider

From : Quang Q. Bui 10/9/84

Thru : Larry Chitlik

RE : Teratology Study in Hamsters with Captan

As per your request, the teratology study with Captan in hamsters (IRDC. 415-005; 01/17/83) has been evaluated. The following comments are noted by this reviewer:

1. Dosage level of 400 mg/kg (highest dose tested) is associated with excessive maternal toxicity and fetotoxicity as evidenced by significant decreases in litter size and fetal weight and by significant increases in mean resorption sites.

2. In terms of malformations, most of the findings are associated with skeletal malformations (ribs, tail, limbs, jaw). Fetal anasarca is the only finding that was observed in all treated groups but the control. However, the incidence of fetal anasarca is relatively low in all treated groups and is statistically similar to that of the historical control data provided (4.6% of litter). For each malformation described, evidences of dose-response relationships are not present. However, the percentage of litters with malformations in all treated groups is higher than that of the control and historical control groups.

Historical Control	Malformations	:	9.3 %	of litters
Concurrent Control	"	:	14.3 %	" "
50 mg/kg group	"	:	23.1 %	" "
200 mg/kg group	"	:	23.1 %	" "
400 mg/kg group	"	:	30.4 %	" "

The two-fold increases in malformations observed at 400 mg/kg may be associated with excessive maternal toxicity observed at this dosage level. However, the increased litters with malformations at the 50 and 200 mg/kg groups could not be ignored.

3. In teratology study, either one of two observations will indicate whether or not an agent should have a high index of suspicion as a teratogen. The first is the finding of a marked increase in embryonic deaths with absence of any recognizable embryonic tissues in the gestation sacs at the time of recovery (early resorptions). The second observation is the finding of a marked retardation of growth as compared to the normal external morphology expected for that day of development.

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The following table summarizes these two observations in this study :

	Control	50 mg/kg	200 mg/kg	400 mg/kg
Early resorptions (Mean)	0.9	0.8	1.1	2.9**
Fetal weight (mean in grams)	1.53	1.56	1.45	1.23**

Both of these observations are evident in the highest dose group (400 mg/kg). However, the teratogenic potential of Captan still can not be assessed with certainty due to excessive maternal toxicity associated with this dosage level and the malformations observed may be secondary to the maternal and fetal toxic effects.

There is no doubt that the compound is fetotoxic at 400 mg/kg but to fully assess the teratogenic potential of Captan, another investigation is suggested. This further testing may be: single dosing on day 8th of gestation with dosage levels in the range of 50 - 200 mg/kg.

The eighth day of gestation is suggested since embryonic development in the hamster proceeds in a rapid manner which is quite striking during this day. Development proceeds within the next 24 hours (day 9 of gestation) with functional heart, completely closed neural tube, visceral arches, optic and otic placodes, and beginning of formation of limb buds. The dams may be sacrificed on day 10 of gestation and the fetuses observed for malformations. This approach may be helpful in evaluating the results and also prevent the resorptions of severely malformed fetuses which would eventually be excluded from statistical data.

The final decision is at your discretion.