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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

AUG 12 1983

MEMORANDUM

SUBJECT: EPA Registration No. 239-1246. Captan. Review of Three Generation Reproductive Study in Rats. IRDC, # 153-096, January 7, 1982. Submitted by Stauffer Chemical Company and Chevron Chemical Company. EPA Accession No. 249334.

TOX. Chem. No. 159.

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

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

8/9/83

SUMMARY

Captan was administered in the diet at 0, 25, 100, 250, and 500 mg/kg/day to male and female COBS CD rats for three generations. For each generation 15 males were mated with 30 females. Litter parameters recorded were: survival, weight, gross appearance and macroscopic pathology. A teratology examination was performed on 30 F2 females.

No treatment related effects due to the administration of captan in the diet were seen with the exception of body weight reduction and food consumption.

A dose related decrease in both male and female parent body weight was reported at 100, 250, and 500 mg/kg/day. A related decrease in food consumption was reported for all groups except for 25 mg/kg/day in the F1 males and F2 females and 100 mg/kg/day in the F2 females.

It is not possible to establish a NOEL since pup litter weights were decreased in all dosage groups.

LEL = 25 mg/kg/day
Core supplementary

DETAILED REVIEW OF STUDY

Study Title and Description: Three Generation Reproduction Study in Rats, IRDC, January 7, 1982, was submitted by Chevron Chemical Company.

Identification: EPA accession number: 249334, IRDC Laboratory Study number: 153-096.

Laboratory: International Research and Development Corporation (IRDC) Mattawan, Michigan 49071.

Test Material: Captan technical SX 944, 89% pure
Jugs No. 1-9, 3/24/78.
Jugs No. 10, 1/24/78.
5 cans, 20 kg each, 11/23/78.

STUDY METHODS

Animals:

Male and female COBS CD weanling rats from the Charles River Breeding Laboratories, North Wilmington, Massachusetts.

Dosing:

The diet included captan at dosage levels of 0, 25, 100, 250, and 500 mg/kg/day, adjusted weekly for body weight and food consumption, and was prepared weekly. All the rats received the diet (after weaning).

Study conduct:

Males were mated with two females each (figure 1). All litters were handled similarly. Pup survival was recorded at birth (lactation day 0) and at lactation days 1, 4, 7, 14, and 21. Litters were randomly reduced to 10 pups on lactation day 4. Litters were weighed as a group on days 1, 4, 7, and 14. Individual pup weights and physical observations were recorded on lactation day 21.

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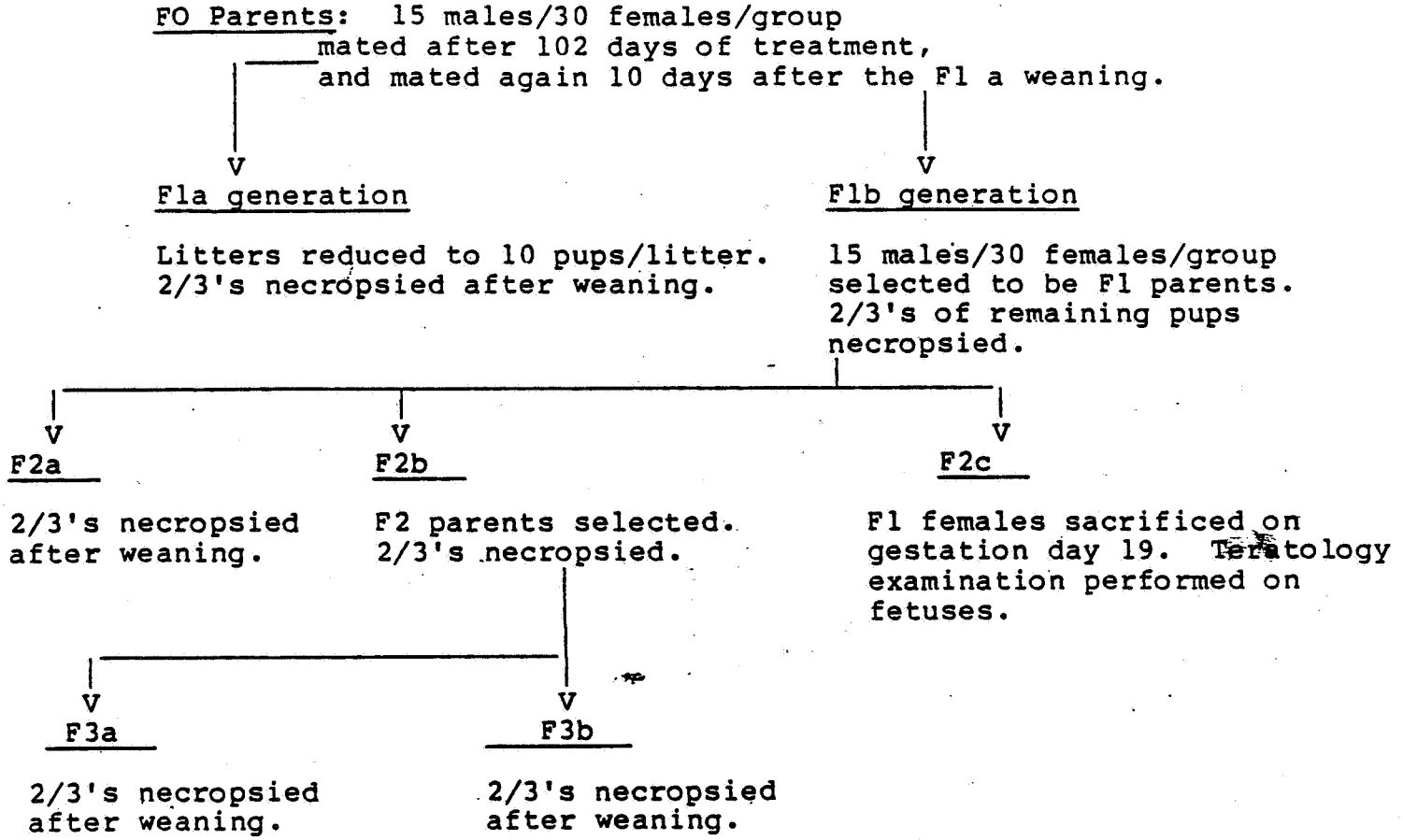
Figure 1

Protocol



Pathology:

Gross examination was done of two thirds of the pups (after litter reduction) from each litter except the F2c. Soft tissues, eyes, brain, reproductive organs and the heart were examined. Tissues and organs from 10 male and 10 female F3b pups and from parents dying during the study were preserved but no histopathology examination was done.

Teratology:

All fetuses from the F2c generation were removed by cesarean section on gestation day 19, weighed and examined externally. Approximately one half the fetuses were fixed in Bouin's for visceral sectioning and the other half were fixed, cleared and stained with Alizarin Red S for skeletal examination.

Results

Survival:

Parental survival - All of the F0 generation survived. In the F1 parents one male died at 26 weeks in the 250 mg/kg/day group and one female died at 16 weeks in the 100 mg/kg/day group. In the F2 parents, one female died after 17 weeks in the control group and another female died after 30 weeks in the 250 mg/kg/day dosage group.

Pup survival: No statistically significant differences were seen in the 25 and 100 mg/kg/day groups. Statistically significant differences were seen at 250 mg/kg/day at lactation days 1, and 4 on the F2a and lactation day 4 in the F3a litters and at 500 mg/kg/day at lactation days 1 and 4 in the F2a and F3a litters and at lactation days 7 in the F2b litter.

Body weights:

Parental weights: No statistically significant weight differences from the controls were noted in the 25 mg/kg/day group. Statistically significant reductions in body weights were noted for dose levels of 100, 250, and 500 mg/kg/day (Table 1).

TABLE 1

Statistically Significant Weight Decreases in Parents (%)

Dose level mg/kg/day		Generation, week								
		F0		F1			F2			
		14	34	34	47	66	67	79	98
100	M	-	92	85	-	-	-	-	-
	F	95	-	91	92	93	-	94	-
250	M	87	87	81	85	84	82	84	81
	F	91	92	83	84	86	87	86	89
500	M	83	82	63	72	73	70	79	76
	F	87	88	66	76	78	78	78	82

Pup weights: Statistically significant reductions in mean litter weights were seen in all dosage groups (Table 2).

TABLE 2

Statistically Significant Pup Weight Decreases (%)

Litter	Dose (mg/kg/day)	Lactation Day						
		1	4*	4**	7	14	21 M	21 F
$F1_a$	25	93	-	-	-	-	-	-
	100	92	88	88	86	92	91	90
	250	88	84	84	80	79	83	82
	500	82	75	76	67	65	66	65
$F1_b$	25	-	-	-	93	95	98	98
	100	92	-	-	90	89	93	93
	250	92	87	87	80	78	79	80
	500	83	73	73	62	60	62	60
$F2_a$	25	-	-	-	-	-	-	-
	100	-	92	91	91	90	87	87
	250	87	81	81	74	73	70	72
	500	83	74	74	63	60	56	60
$F2_b$	25	93	-	92	-	94	-	-
	100	93	89	88	86	85	87	87
	250	90	88	88	81	73	75	76
	500	90	83	82	73	69	69	68
$F3_a$	25	-	-	-	-	-	-	-
	100	-	-	-	-	-	92	-
	250	93	85	85	83	81	83	83
	500	86	76	75	71	64	67	68
$F3_b$	25	-	-	-	-	-	-	-
	100	-	-	-	89	91	93	91
	250	93	85	84	79	79	80	79
	500	87	76	76	64	62	61	61

* Before reduction
**After reduction

Food Consumption:

All treatment groups showed a decrease in food consumption compared to the controls except for F1 males (25 mg/kg/day) and F2 females (25 and 100 mg/kg/day).

Litter size:

A statistically significant decrease in litter size was seen only in the F1b litter (500 mg/kg/day).

Length of gestation:

No statistically significant differences or trends were seen in the length of gestation.

Fertility index:

A statistically significant decrease in fertility was seen in F1a males at 250 mg/kg/day and F1a females at 500 mg/kg/day. No other matings demonstrated a reduced fertility trend.

Teratology:

No statistically significant changes or trends were seen.

Pathology:

No macroscopic pathology was seen that could be attributed to the treatment.

DISCUSSION

No treatment related effects due to the administration of captan in the diet could be demonstrated for reproduction or teratology with the exception of food consumption, body weights, and pup survival.

A dose related decrease in body weight was seen in male and female parents at 100, 250, and 500 mg/kg/day. This agrees with the observed decrease in food consumption in all groups except for the F1 males (25 mg/kg/day) and F2 females (25 and 100 mg/kg/day).

Pup survival was reduced at 250 and 500 mg/kg/day. Of more concern is the decrease in pup litter weights in all dosage groups since a NOEL can not be determined for this effect.

The study was otherwise performed in a scientifically valid manner and may be classified as core supplementary.

A one generation reproduction study (EPA Accession No. 249332) was performed after this study. Although either study by themselves would be classified as core supplementary, they present enough information together to establish a NOEL of 12.5 mg/kg/day and a LEL of 25 mg/kg/day and may <u>together</u> be classified as core minimum.

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