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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Addendum to Clements' Review of Captan: Robens, J. F., 1970, Teratogenic Activity of Several Phthalimide Derivatives in the Golden Hamster. Toxicology Appl. Pharmacol. 16: 24-34.

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Albin B. Kocialski 6/22/84

Background:

A review conducted by Clements' Associates under EPA Toxicology Branch contract concluded that there was "strong evidence of the teratogenicity and fetotoxicity of captan." A recent study (Hamster Teratology Study of Captan. IRDC, 2/16/79, Acc. No. 238658, Reg. No. 239-1246.) at lower dose levels enable us to reevaluate the Robens study (which should be classified as core supplementary since not all fetuses were stained and sectioned and it was incompletely reported).

Reported Results:

Table 1

Total dose (mg/kg)	Day(s) of gestation treated	No. dams died/No. treated	Fetal mortality %	Terata %
Captan				
2500	6-10	1/5	46.9	3.7
1500	6-10	2/8	25.9	0
1000	6-10	0/4	9.1	0
500	6-10	0/2	0	0
1000	7 or 8	3/9	56.2	22.9
750	7 or 8	2/9	14.4	13.7
600	7 or 8	3/8	18.8	7.7
500	7 or 8	0/10	11.5	4.6
400	7 or 8	0/8	6.5	0
300	7 or 8	0/9	4.3	8.1
200	7 or 8	0/3	12.5	0

Table 2 lists malformations.

Table 2
(From Robens, J., 1970)

Total Dose (mg/kg)	No. of Administration	Day(s) of Gestation treated	No. of litters with fetuses	No. malformed/ total no. of fetuses	Exencephaly	Cranial pimple	Fused ribs	Cleft palate or harelip	Short or curved tail	Limb defects	Umbilical hernia
Captan											
2500	5	6-10	3	1/27	-	-	1	-	-	-	-
1000	1	7	2	5/18	3	1	-	1	-	-	-
1000	1	8	4	3/17	-	-	-	-	-	-	-
750	1	7	5	10/46	8	2	8	-	-	-	-
600	1	8	1	4/15	-	-	2	-	-	2	-
500	1	7	5	4/58	1	3	1	-	-	1	-
500	1	8	5	1/51	-	-	-	-	1	1	1
300	1	8	5	9/67	1	-	8	-	-	-	-

No individual animal data are included and the summary tables are incomplete. For example, at the 1000 mg/kg dose at 8 days, 3 malformed fetuses were reported in Table 2 but they do not appear in Table 2. In other cases, the number of defects shown are greater than the total number of malformed fetuses; possibly some fetuses had multiple defects. Since the litter numbers are small, the malformations often may have come from the same litter which would greatly reduce the significance of the findings.

The most common malformation reported by both Robens and IRDC was fused ribs. The 1979 study by IRDC in hamsters showed an increased number of fused ribs in treated groups although no dose response by litter was evident. As reported in the Toxicology Branch review (Schneider, 1984) of the 1979 IRDC study, Neil Chernoff (EPA, HERL, Research Triangle Park, N.C.) has recently shown that fused ribs may be caused by maternal (restraint) stress in the mouse. Delayed ossification and other fetotoxicity was also seen in the IRDC study. Fused ribs are most likely a fetotoxic manifestation of maternal stress.

Exencephaly was the other effect of concern reported by Robens. The only case of exencephaly in the IRDC study was in the control group. It is impossible to tell from the Robens report which day of gestation some of the dose levels were administered. Another problem is that the doses with no malformation were not reported. The following table is the best we can compile from the information reported.

Exencephaly

Dose (mg/kg)	Day of treatment	Exencephaly (%) of total fetuses
1000	8	8.6
750	7**	17.4
600	8**	0
500	7	1.9
500	8	0
400	*	0
300	8**	1.5
200	*	0

* These groups may have been dosed on day 7 or day 8, or there may have been two groups at this dose (day 7 and day 8).

** There may also have been a second group at this dose level at day 7 or 8 with no malformations.

Conclusions:

There is not enough information available from this report to evaluate the possible teratogenicity of captan. The main problem area is exencephaly. There appears to be an effect at 750 mg/kg and the NOEL would be 600 mg/kg. Excessive fetal mortality is demonstrated at 600 mg/kg.

Fetotoxicity, as demonstrated by fused ribs caused by maternal stress is seen at 300 mg/kg and a NOEL is 200 mg/kg.

A new and definitive study should be performed to examine the possibility of teratogenicity (exencephaly in the Golden syrian hamster) at a single dose at gestation day 7 and day 8. This study, as reported, is suggestive for teratogenicity.

Study Classification: Core supplementary: insufficient data to fully evaluate.

Fetotoxicity NOEL = 200 mg/kg

Possible teratogenicity: NOEL = 600 mg/kg

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