CASWELL FILE 30

MEMORANDUM NOTE DE SERVICE

Z. 131

TO A: Mr. D. J. Clegg,
Head, Pesticide Section,
Toxicological Evaluation Division.

FROM DE: Pesticide Section,
Toxicological Evaluation Division.

DATE: June 18, 1980.

SUBJECT OBJET: Validation of the Study: "Rat Teratogenic Study - Captan, Difolatan and Phaltan".
Second Audit & Validation - See individual compound file.

IBT No. P-5397

Dated October 11, 1967.

159.
828
464

Common name:	Trade name:
Captan	Orthocide-406
Captafol	Difolatan
Folpet	Phaltan

Petitioner: Chevron Chemical Company,
Ortho Division

Note that the present study covers 3 different compounds. A copy of the present memo should be filed in each compound's file, i.e. in Folpet file, in Captafol file and in Captan file.

OVERALL COMMENTS: Examination of available raw data indicates very poorly performed study, e.g.administratio of the test material and eventual euthanasia within the same group was not performed at the same time but spread up to a difference of 3 days; controls and principals were not run at the same time; recording of gross observati is incomplete and of questionable nature; anim were not properly identified; 15 other compoun were tested apparently in the same run, etc. The present experiment looks like a crude pilo study rather than structured investigation.

Skeletal examination data are not available on microfiche. There is no indication that the i ternal development examination was performed.

"Rat Teratogenic Study - Captan, Difolatan and Phaltan"

AUDIT

1. Report No.: IBT No. P-5397

   Dated October 11, 1967.

2. Date of Study: Proposed start: June 1, 1967.

   Proposed termination: Indefinite.

3. Sponsor: Chevron Chemical Company
   Ortho Division.

4. Protocol: Proposed protocol not available on microfiche.

5. Test material: IBT internal memo of 6-1-67 states that the test material is "on hand".

6. Animal suitability: Information is not available on microfiche on age, strain and origin of animals. Pairing and mating are not available on Microf

7. Raw data: Incomplete.

VALIDATION OF EVALUATION:

Dates: as seen below, "Day 6" varied among and/or within the same group from May 28 to July 2 and the autopsy dates varied from June 3 to August 8 (? 1967).

Group	Dose	"Day 6" date(s)	Autopsy date(s) Day 21
Control I		7-6, 7 & 8	7-27, 28 & 29
Control II			
"Control 2nd phase"	Corn Oil	Dosed from 5-28 through 6-5	
Trypan blue	50	7-10 & 11	7-31 & 8-1
Captan	50	7-1 & 2	7-22 & 23
"	100	6-27 & 28	7-18 & 19
"	250	7-18	8-8
"	500	Dosed from 5-28 through 5-30-67 (sacrificed) 6-10-67)	
"	1000	" " 6-2, 4 through 6-3, 4 & 5	
"	2000	Dosed from 6-3, 4 & 5	
Difolatan	100	6-29 & 29	7-19 & 20
"	500	Dosed from 5-27 through 5-29-67 (sacrificed 6-9-67)	
Phaltan	100	6-29, 30 & 7-1	7-20, 21 & 22
"	500	Dosed from 5-28 through 5-30-67 (sacrificed 6-10-67)	

The above table covers only dates available on raw data.
Dates are given using US system.

Personnel: Report prepared by: Gerald Kennedy, B.S.
Staff Assistant.

Report approved by: E. Fancher, Ph.D.
Director

&

J. C. Calandra, M.D. & Ph.D.
President.

EXECUTION OF THE STUDY;

The information available on microfiche consists of limited correspondence, a copy of the final report and raw data for body weights and gross examination of females and their progeny.

The corrected Table I shows discrepancies and omissions in the outline of the experiment. Since several females were not accounted for and were not properly identified, the comparison of raw body weights and corresponding results given in the final report is difficult; no attempt therefore will be made to establi the presence and/or extent of discrepanci

The corrected Table III giving summary of results, corrected Table IV giving abnorm fetuses and corrected Table VI giving summary of fetal body weights, all show the discrepancies and omissions in respective results.

Raw data are not available on microfiche skeletal development.

OVERALL COMMENTS:

Examination of available raw data indicat very poorly performed study, e.g. adminis tration of the test material and eventual euthanasia within the same group was not performed at the same time but spread up a difference of 3 days; controls and principals were not run at the same time;

recording of gross observations is incomplete and of questionable nature; animals were not properly identified; 15 other compounds were tested apparently in the same run, etc. The present experiment looks like a crude pilot study rather than structured investigation.

Skeletal examination data are not available on microfiche. There is no indication that the internal development examination was performed.

In view of the above, the present study is considered as invalid.

N. Platonow.

D. J. Clegg.

TABLE I (corrected)

TEST MATERIALS: Captan, Difolatan and Phaltan

Outline of Experiment

Albino Rats

Group	Test Material	Dose Level (mg/kg of body weight/day)	Treated on Gestation Days	Number of Females
Control (C-I)	Corn Oil	500	6-15	~~10~~ 11**
Control (C-II)	Corn Oil	500	8-10	7
Control "2nd phase"	Corn oil		6-13	5
Positive Control (PC)	Trypan Blue	50*	8-10	10/5
Cap-I	Captan	50	6-15	~~6~~ 7
Cap-II	Captan	100	6-15	7 —
Cap-III	Captan	250	~~6-15~~ a	5 —
Cap-IV	Captan	500	~~8-10~~ a	5 —
Cap-V	Captan	1000	~~8-10~~ a	5 —
Cap-VI	Captan	2000	~~8-10~~ a	5 —
Dif-I	Difolatan	100	6-15	9/12
Dif-II	Difolatan	500	~~8-10~~ a	5
	Phaltan "2nd phase"	100	6-13	5
Phal-I	Phaltan	100	6-15	~~10~~ 7
Phal-II	Phaltan	500	~~8-10~~ a	5 —

* Trypan Blue was injected subcutaneously.

** Number of females listed and available on raw data

*** Number of females pregnant

a - raw data not available

TABLE III ("corrected)

TEST MATERIALS: Captan, Difolatan and Phaltan

Teratogenic and Reproduction Effects

Albino Rats

Summary of Results

oup	Pregnant Females Examined	Corpora Lutea Total	Implantation Sites Total	Resorption Sites Total	Fetuses Total	Abnormal Fetuses Total
:	~~10~~	~~135~~ 141	~~126~~ 133	~~8~~ 2	~~123~~ 131	~~1~~ 0
:I	~~7~~	~~84~~ 102	~~80~~ 92	~~3~~ 3	~~78~~ 71	0
	~~105~~	~~129~~ 141	~~116~~ 56	~~5~~ 4	~~61~~ 22	~~1~~ 3
p-I (50 mg/kg)	6	93	79	~~2~~ 15(?)	77(?)	0
p-II 0 mg/kg)	~~7~~	~~91~~	~~86~~ 84	4	~~82~~ 90	0
p-III 0 mg/kg)	~~5~~ 4	49	49	4	45	0
p-IV 0 mg/kg)	~~5~~	59	58	10	48	0
p-V 00 mg/kg)	5	~~65~~ 74	~~63~~ 75(?)	~~4~~ 3	59	3
p-VI 00 mg/kg)	5	64	60	0	~~60~~ 51	~~1~~(?)
-I (100 mg/kg)	~~9~~ 10	~~13~~2	121	~~11~~ 4	117	0
-II(500 mg/kg)	5	66	64	~~3~~ 1	63	0
al-I(100mg/kg)	10	~~134~~ 121[a]	124	4	120	0
al-II(500mg/kg)	4**	51	51	2	49	1

One female died following the three doses.

TABLE IV ("corrected")

TEST MATERIALS: Captan, Difolatan and Phaltan

Abnormal Fetuses

Albino Rats

Group	Fetuses Examined	Finding	Incidence
C-I	~~125~~ 131	Normal	~~125~~ 131
		Abnormal	~~0~~
		~~Subdermal hematoma~~	~~0~~
C-II	~~78~~ 71	Normal	~~78~~ 71
		Abnormal	0
PC	~~61~~ 22	Normal	~~41~~ 18
		Abnormal	~~17~~ 3
		Clubbing of extremities **	6
		Undeveloped rear limbs	1 ✓
		Absent tail **	8
		Shortened tail **	2
		Exencephalic	1 ✓
		Anophthalmic **	2
		Shibori	1 ✓
Cap-I (50 mg/kg)	77	Normal	77
		Abnormal	0
Cap-II (100 mg/kg)	~~82~~ 90	Normal	~~82~~ 90
		Abnormal	0
Cap-III (250 mg/kg)	45	Normal	45
		Abnormal	0
Cap-IV (500 mg/kg)	48	Normal	48
		Abnormal	0

* Some fetuses exhibited more than a single abnormality.

TABLE VI (corrected)

TEST MATERIALS: Captan, Difolatan and Phaltan

Summary of Fetal Body Weights

Albino Rats

Group	Number of Fetuses	Mean Body Weights (grams) Males	Fem
C-I	123 131	5.5	
C-II	~~28~~ 71	5.9	
PC	~~24~~ 22	6.4	
Cap-I (50 mg/kg)	77	4.9	
Cap-II (100 mg/kg)	~~82~~ 90	5.5	
Cap-III (250 mg/kg)	45	5.6	
Cap-IV (500 mg/kg)	48	5.2	
Cap-V (1000 mg/kg)	59	4.5	
Cap-VI (2000 mg/kg)	~~60~~ 51		
Dif-I (100 mg/kg)	117	5.8	
Dif-II (500 mg/kg)	63	5.4	
Phal-I (100 mg/kg)	120	5.0	
Phal-II (500 mg/kg)	49	5.0	