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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: [redacted] (PC CODE 081301) Captan - Response to Recommendations made in the Health Effects Division RfD/Peer Review Report (Jan. 31, 1994)
Tox. Chem. Number: 159
DP Number: N/A
MRID Number: 00120315; 00125293; 418269-01; 00078622; 00078623; 00086803; 00126348; 00130848
Submission Number: N/A

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EXECUTIVE SUMMARY:

On January 31, 1994, Captan was presented to the Health Effects Division RfD/Peer Review Committee for the purposes of establishing an RfD for the chemical and to provide a quality assurance of the Data Evaluation Reports (DERs). As a result of that meeting, Toxicology Branch I was requested to provide the following additional information:

Item 1.

Summary tables for reproductive indices, parental and pup body weights and viability/survival for both reproductive studies (Tables 1-7) from 1 generation and 3 generation reproductive studies (MRID Number: 00120315; 00125293).

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Item 2.

Summary tables for parental body weights (Table 8) and maternal and fetal observations at cesarean section (Table 9) in the developmental toxicity study in hamsters (MRID No. 00078623).

Item 3.

RfD Committee recommended a developmental neurotoxicity study for captan be conducted based on the findings of encephalocoele and dilation of brain ventricles in rabbits and exencephaly in hamsters.

Toxcicology Branch I response to these requests are listed below:

Item 1:

Summary tables for reproductive indices, parental and pup body weights and viability/survival for both reproductive studies extracted from 1 generation and 3 generation reproductive studies (MRID Number: 00120315; 00125293) are generated and are shown in Tables 1-7.

Item 2:

Summary tables for parental body weights (Table 8) and maternal and fetal observations at cesarean section (Table 9) in the developmental toxicity study in hamsters are generated and they are shown below (MRID No. 00078623):

The above generated tables do not alter the conclusions stated in the previous DERs. This memorandum will serve as a supplement to the original DERs.

Item 3:

Rereview of DERs involved revealed that the incidence of encephalocoele and dilation of brain ventricles in rabbit developmental toxicity is limited to one fetus at the highest dose tested, and incidence of exencephaly in hamster developmental toxicity study occurred in the control group only. Because neurotoxicity was not observed in the developmental toxicity studies in both rabbits and hamsters, Toxicology Branch I is not requiring a developmental neurotoxicity study.

In the developmental toxicity study in rabbits, external defects observed was encephalocoele (brain hernia with protrusion) in one fetus (# 70K) at the highest dose tested (100 mg/kg/day). Also at this dose, two fetuses from one litter had two major visceral defects. One (# 72B) had omphalocoele (# 72B) and the other fetus (# 72D) had extreme dilation of the mid brain ventricles.

In addition, skeletal defects observed was fused maxillae in two fetuses (#72D and # 72G) from one litter (see Table 10 below). For details, see summary of the type and incidence of major defects shown in Table 11 attached (Source: MRID Number: 418269-01; CTL/P/3039).

In the developmental toxicity study in hamsters, exencephaly was found only in the control group and incidence of exencephaly was not observed in the 400 mg/kg/day treatment group as pointed out by the RfD committee (see Table 10 below). For details, see summary of the type and incidence of malformations shown in Table 12 attached (Source: ACC No. 249681; HED Doc. 002447).

The study type, HED Document Nos., and MRID Nos. used for this memorandum are shown below:

I. 3-Generation Reproduction Study in Rats; MRID Number: 00125293; HED Document No. 004470

II. 1-Generation Reproduction Study in Rats; MRID Number; 00120315; HED Document No. 004470

III. Developmental Toxicity Study in Rabbits; MRID Number: 41825901; HED Document No. 009537

IV. Developmental Toxicity Study in Hamsters; MRID Number: 00078622 [pilot study]; 00078623; 00086803; 00126348; 00130848); HED Document No. 002447; 004548; 004692

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Table 1. Summary of parental body weights in 3 generation reproductive study (Source: HED Doc. No. 004470 dated Aug. 12, 1983)

Statistically Significant Weight Decreases in Parents (% of control)[a]

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

a: Control = 100%

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Table 2. Summary of pup body weights in 3 generation reproductive study (Source: HED Doc. No. 004470 dated Aug. 12, 1983)

Statistically Significant Pup Weight Decreases (% of control)

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

* B.C. = Before culling
**A.C. = After culling
Control = 100%

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Table 3. Summary of viability/survival data for F1a and F1b litters in 3 generation reproductive study

Dosage group mg/kg/day	Survival Index on Lactation day[1]					
	F1a	1	4	7	14	21
0		315/317 (99)	314/317 (99)	251/251 (100)	251/251 (100)	251/251 (100)
25		241/242 (100)	239/242 (99)	201/202 (100)	200/202 (99)	200/202 (99)
100		243/247 (98)	242/247 (98)	200/200 (100)	200/200 (100)	200/200 (100)
250		192/208 (92)	191/208 (92)	169/169 (100)	168/169 (99)	168/169 (99)
500		167/174 (96)	161/174 (93)	151/151 (100)	151/151 (99)	150/151 (99)
	F1b					
0		316/316 (100)	313/316 (99)	222/223 (100)	222/223 (100)	222/223 (100)
25		265/265 (100)	265/265 (100)	206/206 (100)	206/206 (100)	206/206 (100)
100		306/318 (96)	301/318(95)	208/209 (100)	208/209 (100)	207/209 (99)
250		264/268 (99)	247/268 (98)	205/205 (100)	205/205 (100)	204/205 (100)
500		235/242* (97)	226/242 (93)	202/205 (99)	192/205 (94)	191/205 (93)

[1] Survival index are defined as follows:

1 day survival index = (pups surviving 1 day/live pups at birth) x 100

4 day survival index = (pups surviving 4 days/live pups at birth) x 100

7 day survival index = (pups surviving 7 days/pups retained at 4 days) x 100

14 day survival index = (pups surviving 14 days/pups retained at 4 days) x 100

21 day survival index = (pups surviving 21 days/pups retained at 4 days) x 100

* Significantly different from control group, $p<0.05$
** Significantly different from control group, $p<0.01$
Sources: Tables 16-18 of the study report.

Table 4. Summary of viability/survival data for F2a and F2b litters in 3 generation reproductive study

Dosage group mg/kg/day	Survival Index on Lactation day[1]					
	F2a	1	4	7	14	21
0		324/324 (100)	321/324 (99)	245/245 (100)	245/245 (100)	245/245 (99)
25		356/356 (100)	353/356 (99)	269/269 (100)	259/269 (96)	258/269 (96)
100		341/344 (99)	338/344 (98)	258/258 (100)	258/258 (100)	258/258 (100)
250		347/360* (96)	340/360* (95)	290/290 (100)	290/290 (100)	290/290 (100)
500		254/293** (87)	249/293** (85)	230/230 (100)	214/230 (92)	214/230 (92)
	F2b					
0		354/356 (99)	353/356 (99)	262/262 (100)	262/262 (100)	262/262 (100)
25		376/377 (100)	367/377 (97)	282/282 (100)	282/282 (100)	282/282 (100)
100		359/360 (100)	353/360 (98)	267/269 (99)	267/269 (99)	267/269 (99)
250		316/317 (100)	316/317 (100)	257/257 (100)	257/257 (100)	257/257 (100)
500		262/270 (97)	258/270 (96)	222/226 (98)*	222/226 (98)	222/226 (98)*

[1] Survival index are defined as follows:

1 day survival index = (pups surviving 1 day/live pups at birth) x 100

4 day survival index = (pups surviving 4 days/live pups at birth) x 100

7 day survival index = (pups surviving 7 days/pups retained at 4 days) x 100

14 day survival index = (pups surviving 14 days/pups retained at 4 days) x 100

21 day survival index = (pups surviving 21 days/pups retained at 4 days) x 100

* Significantly different from control group, $p<0.05$
** Significantly different from control group, $p<0.01$
Sources: Tables 20-22 of the study report.

Table 5. Summary of viability/survival data for F3a and F3b litters in 3 generation reproductive study

Dosage group mg/kg/day	Survival Index on Lactation day[1]					
	F3a	1	4	7	14	21
0		314/314 (100)	302/314 (96)	238/238 (100)	238/238 (100)	234/238 (98)
25		344/344 (100)	342/344 (99)	258/258 (100)	258/258 (100)	257/258 (100)
100		363/365 (99)	359/365 (98)	284/284 (100)	284/284 (100)	282/284 (99)
250		335/340 (99)	318/340* (94)	284/288 (99)	284/288 (99)	283/288 (98)
500		261/272* (96)	242/272** (89)	218/220 (99)	216/220 (98)	215/220 (98)
	F3b					
0		279/280 (100)	277/280 (99)	219/220 (100)	219/220 (100)	219/220 (100)
25		332/337 (99)	330/337 (98)	250/250 (100)	250/250 (100)	249/250 (100)
100		416/419 (99)	411/419 (98)	297/297 (100)	297/297 (100)	295/297 (99)
250		402/404 (99)	394/404 (98)	296/297 (100)	295/297 (99)	294/297 (99)
500		312/318 (98)	296/318* (93)	260/261 (100)	260/261 (100)	260/261 (100)

[1] Survival index are defined as follows:

1 day survival index = (pups surviving 1 day/live pups at birth) x 100

4 day survival index = (pups surviving 4 days/live pups at birth) x 100

7 day survival index = (pups surviving 7 days/pups retained at 4 days) x 100

14 day survival index = (pups surviving 14 days/pups retained at 4 days) x 100

21 day survival index = (pups surviving 21 days/pups retained at 4 days) x 100

* Significantly different from control group, $p<0.05$
** Significantly different from control group, $p<0.01$
Sources: Tables 24-26 of the study report.

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Table 6. Summary of parental body weights in 1 generation reproductive study

Dosage group mg/kg/day	Mean body weight at week					
	Males			Females		
	1	11	19	1	11	19
0	189	464	519	145	264	313
6	192	479	538	145	270	313
12.5	189	464	528	140	258	318
25	187	463	530	141	261	304

Source: Table 5 of the study report

Table 7. Summary of pup body weights in 1 generation reproductive study

Dosage group mg/kg/day	Mean litter body weight at lactation days 1 to 21					
	1	4		7	14	21
		B.R.	A. R.			Male Female
0	7.4	11.3	11.3	17.3	30.6	43.0 41.8
6	7.5	11.4	11.4	17.6	30.9	43.8 42.9
12.5	7.3	10.9	10.9	16.9	30.3	43.2 42.6
25	7.3	10.7	10.7	16.2	28.9	42.5 44.6

Source: Table 5 of the study report
B.R. = Before reduction
A.R. = After reduction

Table 8. Mean body weight

	Mean Body Weight (g)			
	Dose level (mg/kg/day)			
	0	50	200	400
Gestation days				
0	122	125	122	122
5	125	124	124	125
8	131	132	123	111
11	145	144	131	110
14	159	158	149	131

Source: Table 1 of the study report

Table 9. Summary of maternal and fetal observations at cesarean section

Observation	Dose level mg/kg/day			
	0	50	200	400
No. of dams on study	30	30	30	30
No. of dams died	0	0	1	4
No. nongravid	0	0	0	1
No. gravid	0	0	1	3
No. of dams which delivered	0	0	1	0
No. of dams examined at cesarean section	30	30	28	26
No. nongravid	2	4	3	2
No. gravid	28	26	25	24
No. of dams with resorptions only	0	0	0	1
No. of dams with live fetuses	28	26	25	23
No. of live fetuses/dams	12.2	11.1	11.2	8.8**
No. of post implantation losses/dam	0.9	0.8	1.1	3.2**
No. of implantations/dam	13.1	11.8	12.2	12.0
No. of corpora lutea/dam	13.6	12.7	13.0	12.1
Sex ratio male:female	161: 181	152: 136	128: 151	81**: 127**
Mean fetal body weight (g)	1.53	1.56	1.45	1.23**

Source: Table 2 of the study report
* Statistically significantly different from controls, $p \leq 0.05$.
** Statistically significantly different from controls, $p \leq 0.01$.

Table 10. Incidence of encephalocoele, dilation of brain ventricles, and maxillae fused in rabbits and exencephaly in hamsters

Observation	Dose level mg/kg/day			
	0	1	30	100
Rabbits				
Encephalocoele	0	0	0	1 (70K)
Dilation of brain ventricles	0	0	0	1 (72D)
Maxillae fused	0	0	0	2 (72D, 72G)
Hamsters	0	50	200	400
Exencephaly	1	0	0	0

Fetus identity is given in parentheses