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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Registration No. 239-1246. CAPTAN. Review of a Lifetime Oral Oncogenicity Study of Captan in Mice, Bio/dynamics, Project No. 80-2491, April 6, 1983. Submitted by Chevron Chemical Company, EPA Accession Nos. 249942-249948.

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)

Budd 10/21/83

Summary

Captan was administered in the diet at 0, 100, 400, 800 and 6000 ppm (actual average dose in mg/kg/day calculated as 0, 15.1, 60.9, 122.8, and 924.8 for the males and 0, 17.7, 70.4, 141.9 and 1042.7 for the females) to CD-1 Charles River mice. The study was terminated at 22 months due to increased mortality especially for the high dose males. Of 100 mice per sex per group, the percent surviving at final sacrifice were (males) 25, 20, 20, 24 and 7 at 0, 100, 400, 800 and 6000 ppm and (females) 28, 31, 35, 38, and 27 for 0, 100, 400, 800 and 6000 ppm, respectively. Body weights and food consumption was recorded. No interim sacrifices were performed and at necropsy, only gastrointestinal sections and grossly abnormal lesions were examined (except for lungs and mesenteric lymph nodes which were examined from animals in which gastrointestinal lesions were observed).

In addition to increased mortality, the high dose males showed reduced body weight and increased food consumption generally throughout the study. No consistent pattern was seen for the other groups, except for the high dose females which also showed reduced body weight throughout the study.

Pronounced alopecia around the eyes was noted for the high dose groups (males and females) throughout the study. Treatment related masses, raised areas, or nodules of the small intestine were seen in females at 800 ppm and at 6000 ppm. An increase of focal hyperplasia of the duodenum was reported in high dose males (4 in 85 examined vs. 1 in 84 controls) and high dose females (7 in 93 examined vs. 1 in 85 controls).

An increase in neoplastic lesions in the duodenum was seen in males at 100 and 6000 ppm (3 in 79 and 4 in 85 examined vs. 0 in 84 controls) and in females at 400, 800 and 6000 ppm (1 in 89, 1 in 82, and 4 in 93 examined vs. 0 in 85 controls). A similar increase was seen for neoplasms in the jejunum/ileum for females (0 in 85, 1 in 81, 2 in 78, 2 in 83, and 3 in 87 examined at 0, 100, 400, 800, and 6000 ppm, respectively). The stomach also had an increase in neoplastic lesions for males (0 in 97, 3 in 95, 0 in 98, 1 in 92, and 2 in 97) and for females (0 in 97, 0 in 96, 1 in 99, 1 in 96, and 3 in 97) at these same dose levels. These types of lesions are rare in mice. It is likely that these gastrointestinal neoplasms are related to the administration of captan.

Recommendations

This study should be utilized in conjunction with the Chevron mouse oncogenic study in CD-1 mice (SOCAL 1150, January 9, 1981, EPA Accession Nos. 244220 through 244226). The results of both studies have been referred to B. Litt, Toxicology Branch statistician, for further analysis and a risk assessment.

The registrants should check the discrepency between Table A, page 12 (Female hyperplastic lesions) and the pathology reports (Volume VI). Two cases of focal hyperplasia in the duodenum are reported in the controls and 8 in the high dose group but the pathology reports show only 1 and 7 respectively.

Core: Guideline - in conjunction with the above mentioned study.

Detailed Review of Study

Study Title and Description: A Lifetime Oral Oncogenicity Study of Captan in Mice, Bio/dynamics, April 6, 1983 was submitted by Chevron Chemical Company.

Identification: EPA Accession Numbers: 249942-249948, Bio/dynamics, Project No. 80-2491.

Laboratory: Bio/dynamics, Inc., East Millstone, New Jersey 08873

Test Material: Technical Captan, 89% pure crystalline solid
Lot: SX-1086

Study Methods

Animals: Male and female CD-1 mice from Charles River Breeding Laboratories, Wilmington, Mass. 01887. The mice were 29 days old when received and 42 days old at initiation of treatment.

Dosing: Captan was administered in the diet for 22 months at dose levels of 0, 100, 400, 800, and 6000 ppm. Captan intake in mg/kg/day was also calculated weekly through week 8 and biweekly thereafter based on nominal concentration of captan in the diet, body weight and food consumption. The diet was Purina Lab Chow® #5001 prepared fresh weekly, and was sampled for captan content weekly for the first 20 weeks and monthly thereafter. The diets and water were given ad libitum. Fresh diets were presented to the animals 3 times per week.

Study conduct: Male and female mice were randomly assigned to groups of 100 of each sex housed individually at each dose level of 0 (control), 100, 400, 800, and 6000 ppm. The mice were observed three times a day for gross toxicological effects and mortality from the start of dosing, October 8, 1980 to March 3, 1982 (17 months). For the remainder of the study (terminal sacrifice on 7/27-29/82 and 8/1-2/82), the mice were observed six times a day. A more extensive physical observation and palpation for tissue masses was performed weekly.

Body weights and food consumption were recorded weekly for the first 8 weeks and biweekly thereafter. No interim sacrifices were performed, however animals dying prior to termination of the study or animals found in a moribund condition were subjected to the same examination as those animals surviving to termination. After a gross examination (which included a very thorough examination of the entire alimentary canal and especially the intestines), the following tissues were taken from all animals, stained (hematoxylin and eosin) and examined histopathologically:

all grossly abnormal tissues and lesions
cecum
colon
duodenum, including pyloris of stomach (defined as upper 1/3 of small intestine)
esophagus
ileum (defined as lower 1/3 of small intenstine)
jejunum (defined as middle 1/3 of small intestine)
rectum
stomach, including forestomach, transition zone and glandular stomach

Lungs and mesenteric lymph nodes were also examined for those mice which had gastrointestinal lesions.

Results

Survival

The study was terminated after 22 months due to reduced survival. The high dose males' rate of mortality increased sharply after 11 months whereas the mortality rate for the other groups followed a similar trend but did not increase sharply until approximately 13 to 14 months. Only 7 mice survived until final sacrifice in the high dose male group. The survival at final sacrifice varied from 20 to 38 in the other groups and showed no dose relationship (Table 1). The increased mortality in the high dose male groups is considered to be related to the administration of captan.

Body Weight

The body weights of the high dose males and females were generally reduced from the weights of the controls throughout the study although the food consumption in the high dose group was generally higher in the males and varied with no definite pattern in the females. The body weights of the males in the lower dose groups were reduced after the first week of dosing, however, only a sporadic value was significantly lower during the remainder of the study. No consistent pattern was seen in the females. The decreased body weights in the high dose males and females were considered to be related to the administration of captan.

Organ Weights

No organ weights were recorded.

Food Consumption

Food consumption was generally higher in the males in all dose groups especially in the high dose group. The females exhibited considerable variability in food consumption both higher and lower than control values throughout the study and in all dose groups. No pattern or trend was evident.

Table 1

Mice Surviving

Month

Group (ppm)	Sex	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
0	M	100	–	–	–	–	–	–	–	98	97	96	95	94	90	85	76	58	51	45	36	32	29	25
	F	100	–	–	–	–	–	99	98	97	94	93	90	88	85	81	78	72	63	58	49	44	34	28
100	M	100	–	–	–	–	–	–	–	99	–	–	90	96	95	87	77	69	61	54	43	37	26	20
	F	100	–	99	–	–	–	–	97	–	–	–	95	94	89	87	85	78	65	60	51	47	40	31
400	M	100	–	–	–	–	–	–	99	98	–	–	97	96	93	89	86	81	65	50	42	32	24	20
	F	100	–	–	–	–	–	–	99	98	–	–	–	96	94	93	91	86	77	64	57	48	40	35
800	M	100	–	–	–	–	–	99	–	–	–	97	–	95	91	84	81	72	59	51	39	33	28	24
	F	100	–	98	–	–	–	97	96	95	–	93	–	92	91	89	83	77	72	62	55	50	46	38
6000	M	100	99	–	98	–	97	–	96	–	94	92	–	87	76	65	55	39	31	18	15	9	8	7
	F	100	–	–	–	–	–	99	99	–	–	98	–	96	92	86	79	72	61	53	46	40	33	27

Actual Dose Levels

The actual intake levels (mg/kg/day) of captan were calculated using the individual food consumption and body weight figures (Table 2).

Table 2*

Nominal Dose (ppm)	Actual Mean Dose (Range): mg/kg/day Males	Females
100	15.1 (9.4-22.1)	17.7 (11.3-27.1)
400	60.9 (43.0-100.7)	70.4 (50.5-120.1)
800	122.8 (91.1-210.8)	141.9 (90.7-238.6)
6000	924.8 (588.1-1686.4)	1042.7 (677.3-1934.0)

* as reported by IRDC

Hematology

None reported

Clinical Signs From Physical Examination

Alopecia was noted in all dose groups in similar frequency to that of the controls except for the high dose male and female groups. A much greater frequency (greater than 50%) and severity of alopecia (usually near the eyes) was seen in the high dose groups throughout the study. No other physical signs were considered related to the treatment since no dose response or increased frequency was found. The increased alopecia in the high dose males and females was considered to be related to the administration of captan.

Pathology

The pathology report, dated 4/5/83, was signed by Alexander L. Knezevich, D.V.M., Senior Vice President - Pathology. The pathologist was Henry F. Bolte, D.V.M., Ph.D.

Gross Pathology

The only treatment related gross lesions noted were masses, raised areas, or nodules of the small intestine in females in the intermediate (800 ppm) and high dose (6000 ppm) groups. No other lesions were seen with a dose related effect.

Histopathology

Several non-neoplastic lesions, particularly chronic interstitial nephritis in the kidneys and endometrial cystic hyperplasia in the uteri, were reported but, with the exception of focal hyperplasia in the duodenum (see below), no dose-response effect was seen.

No dose-response was reported for overall primary neoplastic lesions (Table 3).

Table 3. Overall Primary Neoplastic Lesions

Males

Dose (ppm)	Malignant*	Benign*	Total*
0	20/100 (20)	2/100 (2)	22/100 (22)
100	15/100 (15)	9/100 (9)	24/100 (24)
400	13/100 (13)	6/100 (6)	18/100 (18)
800	19/100 (19)	5/100 (5)	22/100 (22)
6000	11/100 (11)	8/100 (8)	18/100 (18)

Females

Dose (ppm)	Malignant	Benign	Total
0	17/100 (17)	5/100 (5)	19/100 (19)
100	20/100 (20)	3/100 (3)	22/100 (22)
400	20/100 (20)	9/100 (9)	29/100 (29)
800	15/100 (15)	6/100 (6)	21/100 (21)
6000	19/100 (19)	14/100 (14)	32/100 (32)

* Animals with one or more tumors/number of animals examined (percent).

These lesions included alveologenic carcinoma in the lungs, and malignant lymphoma and histiocytic sarcoma in the lymphoreticular system.

It should be noted, however, that histopathology was done on most organs only if a gross lesion was observed at necropsy or if gastrointestinal lesions were found (for lungs and mesenteric lymph nodes only).

The gastrointestinal tract was sectioned and examined in detail. The following tables from the report summarize the reported findings:

Table 4

Summary of Animals with Hyperplastic Lesions in the Duodenum

Sex	Males					Females				
Dose (ppm)	0	100	400	800	6000	0	100	400	800	6000
Number examined	84	79	90	89	85	85	83	89	82	93
Lesion:										
focal hyperplasia	1	1	0	0	4	1[a]	2	0	3	7[b]

a. 2 were reported by the registrant, only 1 was found in the pathology reports.

b. 8 were reported by the registrant, only 7 were found in the pathology reports.

Summary of Animals with Neoplastic Lesions in the Stomach

Sex	Males					Females				
Dose (ppm)	0	100	400	800	6000	0	100	400	800	6000
Number examined	97	95	98	92	97	97	96	99	96	97
Lesion:										
adenoma/polyp(s)	0	2	0	1	2	0	0	1	1	2
carcinoma, primary	0	1	0	0	0	0	0	0	0	0
squamous cell carcinoma, primary	0	0	0	0	0	0	0	0	0	1

Summary of Animals with Neoplastic Lesions in the Duodenum

Sex	Males					Females				
Dose (ppm)	0	100	400	800	6000	0	100	400	800	6000
Number examined	84	79	90	89	85	85	83	89	82	93
Lesion:										
adenoma/polyp(s)	0	3	0	0	3	0	0	1	1	3
carcinoma, primary	0	0	0	0	1	0	0	0	0	1

Summary of Animals with Neoplastic Lesions in the Jejunum/Ileum

Sex	Males					Females				
Dose (ppm)	0	100	400	800	6000	0	100	400	800	6000
Number examined	81	78	77	74	79	85	81	78	83	87
Lesion:										
adenoma/polyp(s)	0	1	1	0	0	0	1	2	2	2
carcinoma, primary	0	0	0	0	0	0	0	0	0	1

DISCUSSION

On examination of the summary tables reported by the registrants, I can not find two focal hyperplasia lesions in the pathology reports. The registrant should check the discrepancy between the number of hyperplastic lesions for females (controls and high dose) reported in Table A, page 12, and the pathology reports, Volume VI. Two cases of focal hyperplasia in the duodenum are reported in the controls and 8 in the high dose and I can find only 1 and 7 respectively.

This study would be graded as core supplementary by itself; however, it was designed as such since the intention of the study was to examine the duodenum tumors found at higher doses in this same strain of mouse in an earlier study. In conjunction with the earlier (high dose) study, however, it is classified as Core-Guideline.

Relatively low numbers of animals with duodenal tumors were found in this study compared to the previous high dose experiment. The figures in this low-dose study are somewhat suspect since the lowest dose (6000 ppm) in the high dose

experiment (Lifetime Oncogenic Feeding Study of Captan Technical (SX-944) in CD-1 Mice (ICR Derived), Chevron Environmental Health Center. Report: SOCAL 1150, January 9, 1981. Accession Nos. 244220 thru 244226) was the same as the highest dose in this experiment, and the previous experiment showed many more duodenal tumors at this dosage level (Table 5).

Table 5

Number of Animals with Neoplastic Lesions in the Duodenum

Dose (ppm)	High Dose Study				Low Dose Study				
	16000	10000	6000	0	6000	800	400	100	0
			Males						
Number examined	75	72	73	74	85	89	90	79	84
Number of Adenomas (%)*	11(15)	7(9.7)	11(15)	1(1.4)	3(3.5)	0(0)	0(0)	3(3.8)	0(0)
Number of Adenocarcinoma (%)**	30(40)	14(19)	10(14)	1(1.4)	1(1.2)	0(0)	0(0)	0(0)	0(0)
Total Number with Duodenal Neoplasms (%)	39(52)	21(29)	20(27)	2(2.7)	4(4.7)	0(0)	0(0)	3(3.8)	0(0)
			Females						
Number examined	76	76	78	72	93	82	89	83	85
Number of Adenomas (%)*	12(16)	8(11)	10(13)	2(2.8)	3(3.2)	1(1.2)	1(1.1)	0(0)	0(0)
Number of Adenocarcinoma (%)**	20(26)	14(18)	17(22)	0(0)	1(1.1)	0(0)	0(0)	0(0)	0(0)
Total Number with Duodenal Neoplasms (%)	29(38)	19(25)	24(31)	2(2.8)	4(4.3)	1(1.2)	1(1.1)	0(0)	0(0)

*Described as adenoma/polyp(s) in Low Dose Study.
**Described as primary carcinomas in Low Dose Study.

It can be seen that in the high dose study, at 6000 ppm, 27% of the males and 31% of the females had duodenal neoplasms whereas in the low dose experiment, at the same dose, only 4.7% of the males and 4.3% of the females had duodenal neoplasms.

The answer to this discrepancy might be found in the survival rates. If we look at the high dose study we find that survival was better. (Table 6).

Table 6

Survival of Mice (%)

Males

	52 Weeks		75 Weeks		Termination*	
Experiment:	High Dose	Low Dose	HD	LD	HD	LD
Controls	94	94	83	36	43	25
6000 ppm	96	87	79	15	40	7
Females						
Controls	95	88	85	49	33	28
6000 ppm	96	96	89	46	51	27

* Termination was at 22 months in the low dose study and at 26 months in high dose study.

The survival of the mice (low dose study) with duodenal lesions can be found in the pathology report and is summarized in Table 7.

Table 7

Time of Death of Animals With Lesions in the Duodenum.

Males

Dose (ppm)	Pathology Number	Animal Number	Lesion	Day of Death	Weeks on Test	Months on Test
0	1026	125	Malignant lymphoma, metastatic	423	61	15
0	1037	136	Malignant lymphoma, metastatic	492	71	17

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0	1074	173	Mucosa: Focal Hyperplasia	659	95	23
100	2012	311	Benign Polyp(s)	498	72	17
100	2034	333	Benign Polyp(s)	435	63	15
100	2050	349	Mucosa: Focal Hyperplasia	661	95	23
100	2062	361	Benign Polyp(s)	651	93	23
100	2094	393	Carcinoma, invasive from stomach	400	58	14
400	NONE	—	—	—	—	—
800	4005	704	Malignant lymphoma, metastatic	523	75	18
6000	5022	921	Benign Polyp(s)	419	60	14
6000	5036	935	Benign Polyp(s)	660	95	23
6000	5050	949	Benign Polyp(s)	405	58	14
6000	5051	950	Mucosa: Focal Hyperplasia	396	57	14
6000	5057	956	Carcinoma, primary	538	77	19
6000	5076	975	Mucosa: Focal Hyperplasia	660	95	23
6000	5094	993	Mucosa: Focal Hyperplasia	339	48	12
6000	5096	995	Mucosa: Focal Hyperplasia	433	62	15
			Females			
0	1525	224	Malignant lymphoma, metastatic	555	80	19
0	1522	221	Mucosa: Focal Hyperplasia	648	93	22

100	2534	433	Mucosa: Focal Hyperplasia	415	60	14
100	2580	479	Mucosa: Focal Hyperplasia	665	95	23
400	3551	650	Benign Polyp(s)	664	95	23
400	3556	655	Malignant lymphoma, metastatic	531	75	18
400	3558	657	Malignant lymphoma, metastatic	664	95	23
400	3577	676	Malignant lymphoma, metastatic	196	28	7
800	4513	812	Mucosa: Focal Hyperplasia	642	92	22
800	4559	858	Mucosa: Focal Hyperplasia	664	95	23
800	4580	879	Mucosa: Focal Hyperplasia	521	74	18
800	4588	887	Benign Polyp(s)	665	95	23
6000	5506	1005	Mucosa: Focal Hyperplasia	660	95	23
6000	5520	1019	Mucosa: Focal Hyperplasia & Benign Polyp(s)	661	95	23
6000	5544	1043	Mucosa: Focal Hyperplasia	630	90	22
6000	5545	1044	Mucosa: Focal Hyperplasia	664	95	23
6000	5546	1045	Benign Polyp(s)	645	92	23
6000	5556	1055	Benign Polyp(s)	572	82	20
6000	5563	1062	Mucosa: Focal Hyperplasia	585	84	20
6000	5565	1064	Mucosa: Focal Hyperplasia	283	41	10
6000	5573	1072	Carcinoma, primary	536	77	19
6000	5591	1090	Mucosa: Focal Hyperplasia	576	83	20

From Table 7, we see that the two duodenal carcinomas (animal 956, male, and 1072, female) were found at the animal's death, both at week 77. From the survival table (Table 6) it is evident that only 15% of the males and 46% of the females still survived at this time in the high dose group (6000 ppm). It can also be seen that many of the mice with hyperplasia and "benign" lesions of the duodenum died before week 77. The hyperplasia and benign lesions might possibly be precursors of the carcinomas and it is probable that the high mortality in this study obscures the true tumor incidence.

The laboratory performing this study reports that the duodenal neoplasms normally are rare since, in concurrent studies in their facilities, one male and no female mice developed duodenal carcinomas out of 718 and 737 mice respectively. No other duodenal neoplasms were seen in these concurrent studies.

There was not always good correlation between the gross necropsy findings and the microscopic findings. In particular, animal number 1008 was reported to have a duodenal mass at gross necropsy but no masses were found on the histopathology examination (pathology number 5509).

The data from this study may still be useful in conjunction with the high dose study in performing a risk assessment if the survival and time-to-death of the mice is taken into account.

CONCLUSION

The data in this study demonstrate an increased incidence of focal hyperplasia (non-neoplastic lesions) and of adenoma/polyp(s) and primary carcinomas (neoplastic lesions) in the gastrointestinal tract of both male and female mice at the highest dosage level tested (6000 ppm) and possibly also at lower dosage levels. These types of neoplasms are rare in mice. It is likely that these lesions are related to the administration of captan. The results of this study (and the results of the earlier high dose study) have been referred to B. Litt, Toxicology Branch statistician, for further analysis and a risk assessment.

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