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

DEC 29 1986

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Captan, Caswell No: 159

FROM: Reto Engler, Ph.D., Chief
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769c)

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

The Toxicology Branch Peer Review Committee met on Dec. 5, 1985 to discuss and evaluate the weight-of-the-evidence on Captan, with particular reference to its oncogenic potential. Captan was already classified as a B2 Oncogen in the PD 2/3; the Peer Review Committee was assembled to reassess this determination.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with peer review unless otherwise stated).

William L. Burnam

Reto Engler

Richard Hill

Louis Kasza

Herbert Lacayo

Stephen Saunders

2. Reviewers: (Non-panel members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Marion Copley

for Jane Harris

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3. Peer review members in absentia: (Committee members who were not able to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Theodore M. Farber

Stephen Johnson

Anne Barton

John A. Quest

Judith Hauswirth

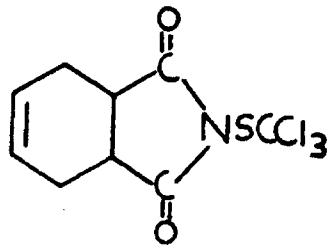
Esther Rinde

B. Material Reviewed:

The material available for review consisted of background summaries of oncogenicity studies in the Charles River CD rat and the CD-1 mouse, expanded incidence tables for relevant oncogenicity studies and summaries of the data for studies in additional rat and mouse strains, a report of the Science Advisory Panel for Captan, "One-Liners" for Captan, and statistical analyses from the Tox. Branch Statistical Team. A copy of the material reviewed is appended to this report.

C. Background Information:

Captan, N-trichloromethyl-thio-4-cyclohexene-1,2-dicarboximide, is a protectant fungicide, structurally related to two other fungicides, captafol and folpet. In August, 1980 EPA issued a notice of Rebuttable Presumption against Registration and Continued Registration of Pesticide Products containing Captan (45 FR 54938) based on oncogenicity and mutagenicity; teratogenicity, fetotoxicity, hypersensitivity, and acute toxicity were other possible adverse effects also considered at that time. In June, 1985 the Position Document 2/3 determined that risks of concern included oncogenicity, reproductive effects and possibly teratogenicity; however, analysis of new information as presented in the registration standard, determined that captan is not a teratogen. The oncogenic lesions in question were: 1) renal cortical/tubular cell adenoma and carcinomas in rats and 2) adenoma/polyps and adenocarcinomas in the upper gastrointestinal tract in mice. On Sept. 26, 1985, the FIFRA Scientific Advisory Panel concurred with the Toxicology Branch, that captan is oncogenic at high levels in the mouse intestine and that the oncogenicity data in the rat kidney were equivocal.



CAPTAN

D. Evaluation of Oncogenicity Evidence for Captan:

1. Two-year Oral Toxicity Carcinogenicity Study of Captan in Charles River CD Rats.

Testing facility: IRDC for Stauffer/Chevron, 1982
Total rats in study: 70/sex/group (10/sex/group sacrificed at 1 yr.)

Rats were treat [1] for up to 2 years with either 0, 500, 2000 or 5000 ppm of captan in the[1] diet.

Dose: (ppm)	0	500	2000	5000
(mg/kd/d)	0	25	100	250
# Male rats examined[2]	70	70	70	70
# " " surviving >1 yr.	58	57	58	57
Renal cortical/tubular cell:				
adenoma	1	0	2	3
carcinoma	0	1	1	1
combined[1]	1	1	3	4*

[1]The number of animals with either renal adenoma, carcinoma or both.
[2]Includes rats that died prior to, or were sacrificed at 1 year. There were no renal tumors prior to that time.
*p = 0.05 by Cochran Armitage

There was a dose-related trend for combined adenoma and carcinomas of the kidney in male rats. The first renal cortical/tubular cell tumor was observed on day 529 of the study. There was no increased incidence of renal cortical/tubular cell neoplasias in females.

The NOEL for systemic effects was 500 ppm. The LEL of 2000 ppm was based on hepatocellular hypertrophy (males); increased relative organ weight for kidneys (males and females); increased relative organ weight for heart, brain, liver and thyroid/parathyroid (males); and decreased mean weight body weight for males (12%) and females (19%) from controls. (The MTD was apparently exceeded at 2000 ppm.) High dose rats tended to die sooner, although the final survival at 104 weeks was similar among all groups.

D. Evaluation of Oncogenicity (continued)

2. Bioassay of Captan for Possible Carcinogenicity in Osborne Mendel Rats.

Testing facility: Gulf Research Institure for the National Cancer Institute Cancer Institute Carcinogen Bioassay Program (1977).
Number of rats in study: 50/sex/treated group; 10/sex/controls; 65/sex for pooled controls.

Rats were treated for 80 weeks with no treatment for the last 33 weeks. The initial doses were 0, 8000, and 16,000 ppm in their diet, however doses were lowered at week 21, based on severe unspecified toxicity. The calculated time-weighted averages for the treatment groups were 2525 (126 mg/kg/d) and 6050 (302.5 mg/kg/d) ppm.

There was no increased incidence of renal cortical/tubular cell neoplasms in either male or female rats.

The systemic NOEL was 2525 ppm. The LEL was 6050 ppm, based on lower mean body weight than matched controls (about 10-15% less in males; variable but apparently, slightly less than 10% in females). (The MTD was apparently reached at the high dose - these rats are apparently less sensitive to the toxic effects of captan than are the Charles River rats - see D.1.)

3. Life-Span Oral Carcinogenicity Study of Merpan (Captan) in Wistar Cpb:WU Rats

Testing facility: Netherlands Organization for Applied Sci.Res. for Makhteshim-Agan (1983)
Total rats in study: 50/sex/group

Rats were treated for 30 months with either 0, 125, 500 or 2000 ppm (0, 6.25, 24, 98 mg/kg/d, respectively) in their diet.

There was no increase in the incidence of renal cortical/tubular cell neoplasms. There was a slight but statistically significant increase in uterine sarcomas (4/50 vs 0/48 in controls) noted in the high dose group, however historical control data from the laboratory was not available at the time of the meeting. Subsequently, the following data were submitted [M. Copley Memo 2/5/86].

Incidence (%) of uterine fibromatous tumor bearing females in the controls of 8 studies.

Duration (months)	24	27	28	29	30[1]	30	30	30
Fibromatous polyp	11	21	14[2]	30[3]	17[3]	18[3]	26[3]	26
Fibrosarcoma	0	0	0	2	0	0	0	0

[1]control for the Merpan (captan) study in question.
[2]6 % of the rats had multiple polyps.
[3]1-2 % of the rats had multiple polyps.

The MTD was apparently approached at the high dose (10% body weight decrease).

D. Evaluation of Oncogenicity (continued)

4. Bioassay of Captan for Possible Carcinogenicity in B6C3F1 Mice

Testing facility: Gulf Research Institute for the NCI Carcinogen Bioassay Program (1977).
Number of mice in study: 50/sex/treated group; 10/sex/matched controls; 65/sex for pooled controls.

Mice were treated for 80 weeks followed by no treatment for 33 weeks. Dose levels were 0, 6000 and 16,000 ppm.

Dose (ppm)	0	6000	16,000
" (mg/kg/d)	0	900	2,400
Male			
Duodenum, # examined	68	43	48
adenoma/polyps	0	2	2
carcinoma	0	1	3
combined	0	3	5
Female			
Duodenum, # examined	68	49	46
adenoma/polyps	1	1	0
carcinoma	0	0	3
combined	1	1	3

Male and female mice had an increased incidence in combined duodenal adenoma/polyps or adenocarcinomas at the 16,000 ppm level, with the first reported tumor at 91 weeks. The sponsor noted a positive linear trend in males ($p=0.008$) and the Fisher exact test in high-dosed males gave a probability of $p=0.009$. There was a minimal increase in hyperplasia of the duodenal mucosa noted in the high dose males.

Dose (ppm)		0	6000	16,000
Duodenum, # examined	M	68	43	48
	F	68	49	46
mucosal hyperplasia	M	0	0	3
	F	0	0	0

The systemic NOEL was 6000 ppm and the LEL was 16,000, based on decreased mean body weight from matched controls (about 10% less in both sexes). (The MTD was apparently approached at 16,000 ppm). There was no treatment related increase in mortality.

D. Evaluation of Oncogenicity (continued)

5. Lifetime Oncogenic Feeding Study of Captan Technical (SX-944) in (ICR Derived) CD-1 Mice

Testing facility: Chevron Environmental Health Center (1982)
Total mice in study: 80/sex/group

Mice were treated for 113 weeks with captan. The initial concentrations of 0, 2000, 6000 and 10,000 ppm were increased after 4 weeks to 0, 6000, 10,000 and 16,000 ppm for the remainder of the study.

	Male				Female			
Dose (ppm)	0	6000	10,000	16,000	0	6000	10,000	16,000
" (mg/kg/d)	0	900	1,000	2,400		900	1,500	2,400
# treated	80	80	80	80	80	80	80	80
Small intestine								
adenomas	1	12	9	12	4	12	9	13
carcinomas	2	11	20	32	1	21	17	21
combined	3	19	22	39	3	26	21	29
Duodenum, mucosal hyperplasia	3	40	38	25	8	33	37	34
Jejeunum/Ileum, mucosal hyperplasia	2	5	9	3	4	11	12	16
Stomach, mucosal hyperplasia	10	29	25	16	6	21	16	11

There was a marked increased ($p<0.001$) incidence of small intestinal (primarily duodenal) adenoma/polyps and carcinomas at all dose levels. A positive dose-related trend for carcinomas in both sexes ($p<0.005$) was also observed. Proliferative duodenal changes appeared to occur earlier in the high dose males. There was also a marked increase in gastric and duodenal hyperplasia in both sexes; and in jejeunal hyperplasia in females. Stomach neoplasias were not reported.

The LEL was 6000 ppm based on decreased weight gain and food consumption. Both high dose males and females weighed about 25% less than controls. In high dose males and females, the mortality was signifigantly higher, suggesting that the MTD was exceeded.

D. Evaluation of Oncogenicity (continued)

6. A Lifetime Oral Oncogenicity Study of Captan in Charles River CD-1 Mice

Testing facility: Bio/Dynamics for Chevron Chemical Co. (1983)
Total mice in study: 100/sex/group

Mice were treated with 0, 100, 400, 800 or 6000 ppm captan in the diet. The study was terminated at 22 months due to increased mortality in the high dose males.

Dose (ppm)	0	100	400	800	6000
" (mg/kg/d)	0	15	60	120	900
Total # treated/sex	100	100	100	100	100
Male					
stomach tumors	0	3*	0	1	2
smalll intestine tumors	0	4	1	0	5*
TOTAL UPPER GI TRACT[1]	0	7	1	1	7
Female					
Stomach tumors	0	0	1	1	2
Small intestine tumors	0	1	2	3	7**
TOTAL UPPER GI TRACT[1]	0	1	3	4	9
Male					
Duodenum, hyperplasia	1	1	0	0	4
Jejeunum/Ileum, hyperpl.	0	0	0	0	0
Female					
Duodenum, hyperplasia	1	2	0	3	7
Jejunum/Ileum, hyperpl.	1	1	0	1	0

*1 carcinoma **two carcinomas

[1]Combination of small intestinal and gastric tumors (animals counted only once).

There was a small increase[1] in small intestinal tumors (benign and malignant) in the male (6%) and female (8%) high dose groups (controls = 0%). The low dose males also had an increased incidence (5%) over controls. When stomach (glandular) and small intestinal (benign and malignant) neoplasms were combined, the total incidence at the high dose became 7% (males) and 8% (females). The first duodenal tumor in the males occurred at 72 weeks, and in the females at 95 weeks. Increased incidence of focal hyperplasia was observed in the duodenum (no hyperplasia was reported for the stomach).

The systemic NOEL was 800 ppm and the LEL was 6000 ppm based on increased mortality in males; reduced weight gain throughout the study (males and females). (The MTD appears to have been exceeded at the high dose.)

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[1]These results were considered questionable by the Committee, because the low intestinal tumor incidence at 6000 ppm was not consistent with that obtained at the same dose, in the same mouse strain, in 2 other studies (Stauffers 1985 and Chevron 1982 - Nos. 7 and 5 of this report).

The results of an agency audit of this study, completed subsequent to the Peer Review Meeting, suggested that there "was a problem with achieving and maintaining the appropriate dose levels throughout the study" [Copley Memo 4/23/86, (page 9, this report)].

REVIEWER

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

005041

APR 23 1986

MEMORANDUM:

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: E.P.A. I.D. #239-Q: Captan; Laboratory audit of the two-year mouse feeding study conducted at Bio/Dynamics

Tox. Chem. No.: 159
Accession No.: N.A.

TO: H. Jacoby (PM 21)
Registration Division (TS-767C)

FROM: Marion P. Copley, D.V.M., D.A.B.T.
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Jane Harris, Ph.D., Section Head
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C)

The Agency has completed an audit of the 2 year mouse feeding study conducted by Bio/Dynamics, referred to as the low dose study (LDS). The results of the audit suggest that there was a "problem with achieving and maintaining the appropriate dose levels throughout the study." There was a series of correspondence between Chevron (the sponsor) and Bio/Dynamics (the testing facility) discussing sample stability and homogeneity. The actual sample concentrations were not presented in the audit therefore the adjusted actual doses could not be independently determined by Toxicology Branch (TB). These results, however would not significantly alter the results in the Registration Standard for Captan. The study of major importance was the high dose study (HDS) conducted by Chevron in 1982. The incidence of intestinal tumors at 6000 ppm from the latter HDS (Chevron) is consistent with that obtained in a recently performed single dose (6000 ppm) study conducted by Stauffers. Since the low intestinal tumor values reported in the 6000 ppm level in the Bio/Dynamics study were not consistent with the two previously mentioned studies, TB considered them questionable. The results from all the studies used in the risk assessment were similar, therefore no one study had a major impact on the risk assessment outcome.

Study[1]	Q_1^* (mg/kg/day)$^{-1}$
male mice HDS	3.9 x 10^{-3}
male mice LDS	1.0 x 10^{-3}
female mice HDS	3.: x 10^{-3}
female mice LDS	2.0 x 10^{-3}
male rats	2.4 x 10^{-3}

[1]HDS (high dose study) chronic mouse feeding, conducted by Chevron
LDS (low dose study) chronic mouse feeding, conducted by Bio/Dynamics

The Registration Standard reported the geometric mean for the upper 95 % bound of the five pooled Q_1^* values to be 2.3 x 10^{-3}. When the values for the Bio/Dynamics study (LDS) are deleted, the geometric mean increases slightly to become 3.2 x 10^{-3}.

While the audit information does support the Agency's concern about nominal dose levels tested in the LDS conducted at Bio/Dynamics, TB feels no further action is needed at this time since the study was not used (by itself) to toxicologically support the registration of captan. Furthermore, removal of the study from consideration would not significantly erode the data base or alter TB recommendations concerning the use of captan.

BACKGROUND:

Captan is currently under special review (Position document 2/3 was completed and a Registration Standard was completed in March 1986. The following data gaps still exist for captan:

- Acute dermal toxicity
- Primary dermal irritation
- 21-day dermal toxicity
- Chronic (oral) - nonrodent
- Subchronic (inhalation)
- Metabolism

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D. Evaluation of Oncogenicity (continued)

7. Identification of Preneoplastic Alteration Following Administration of Captan Technical to Charles River CD-1 Mice.

Testing facility: Stauffer Chemical Company (1985)
Number of animals: Most groups had 14 to 26 animals.

Male mice were treated with either 0 or 6000 ppm captan technical in the diet for 3, 6, 9, 12 or 18+ months (the company combined animals sacrificed at 18 and 20 months for statistical purposes and referred to them as 18+). Some mice were then allowed to recover for 6 to 12 months.

Incidence data for intestinal tumors and hyperplastic lesions is given in appendix B of the Peer Review package. Focal intestinal hyperplasia was present as early as 3 months (75% of treated animals) with all treated mice affected by 9 months (0% in controls until 18 months). This incidence decreased to control levels after recovery periods of 6 to 12 months. Although tumors did not occur in controls until 18 months (1 adenocarcinoma, 4%), there was an increased ($p<0.01$) incidence (25%) of intestinal adenomas in treated groups, after only 9 months of treatment. After 12 months of treatment followed by a 6 month recovery period, the incidence of tumors was still statistically ($p<0.05$) increased over controls (4%). Tumors and focal hyperplasia were usually located within the first 7 cm of the small intestine. This study is consistent with the hypothesis that although mucosal hyperplasia may regress after removal of the causative agent, it does have the potential to progress to benign or malignant neoplasias.

8. Historical Control Information

a) Organ/lesion: Renal neoplasms (renal cortical/tubular cell adenoma and adenocarcinoma)
Species/strain: C rles River CD Rats
Laboratory: IRDC
Study type: 2 year feeding study (for study A).

Study Date	males incidence	(%)	females incidence	(%)
2/16/79	0/90		1/90[c]	(1.1)
7/2/79	0/80		0/77	
10/[illegible]/79	1/60[a]	(1.7)	1/60[a]	(1.7)
[illegible]	0/50		0/50	
8/29/80	0/85		0/85	
10/3/80	1/70[a]	(1.4)	0/70	
11/25/80	0/[illegible]5		0/5[illegible]	
2/9/81	0/100		0/[illegible]	
6/4/81	0/50		0/49	
8/7/81	0/[illegible]		0/[illegible]	
9/8/81	0/110		0/110	
10/29/81	0/58		0/60	
11/27/81	1/48[c]	(2.1)	1/[illegible][c]	(2.2)
12/8/81	3/350[a]	(0.9)		
	1/350	(0.3)		
Total incidence		(%, range)		(%, range)
adenoma	5/1279	(0.4, 0-1.7)	2/926	(0.2, 0-2.2)
adenocarcinoma	2/1279	(0.2, 0-1.1)	1/926	(0.1, 0-1.1)

a adenoma
c carcinoma

b) Organ/lesion: Duodenum (adenoma/polyp and carcinoma)
Species/strain: Mouse (strain unspecified), concurrent studies (number unspecified) with the CD-1 mouse study (for study F) at Bio/Dynamics
Laboratory: Bio/Dynamics (1983)
Study type: Chronic mouse feeding studies
Total incidence: males - 1/718 (duodenal carcinoma)
females - 0/737
NOTE: Because the NCI study identified the duodenum as a possible target organ of captan, six or seven duodenal sections were examined in the Bio/dynamics captan study which may have increased the incidence of tumors observed. Most studies examine only one section of each intestinal segment.

c) Organ/lesion: Gastrointestinal tract tumors
Species/strain: CD-1 HaM/ICr mice
Laboratory: Reported in the J. N. C. I. 46:1045, 1971 (referenced in the Chevron mouse 2 year study report E)
Study type: unspecified
Incidence of lower gastrointestinal tumors: less than 1%.

E. Additional Toxicology Data on Captan:

1. Metabolism: Captan is decomposed in vitro at the N-S bond when combined with inorganic sulfites and thiosulphates as well as with thiols of biological origin (glutathione and cysteine). Captan also undergoes rapid hydrolysis at the N-S bond in the blood and gastro-intestinal tract. At blood pH and in the presence of thiols, captan hydrolyzes to tetrahydrophthalimide (THPI) (Figure 1) and derivatives of the trichloromethylthio side chain (Figure 1). In the gut however, there is evidence of a rapid reaction with thiols and sulfites resulting in the formation of THPI (Figure 1) and several derivatives of the side chain (Figure 2). One proposed metabolic scheme is the conversion of the side chain moiety to a thiophosgene intermediate. After inter-peritoneal injection (of side chain labelled captan), only metabolite C is found in the urine, while A, B and C are all observed after oral administration of captan (see Figure 2).

Captan and its metabolites do not appear to bioaccumulate.

2. Non-Oncogenic Toxicological Effects:

The acute and subacute toxicity of captan has been determined in a large number of animal species, including rats, swine, sheep, cattle, chicken, hamsters, rabbits and monkeys. Captan is not acutely toxic and lab animals can tolerate very high levels in their diet; the acute oral LD_{50} in rats is 9 g/kg.

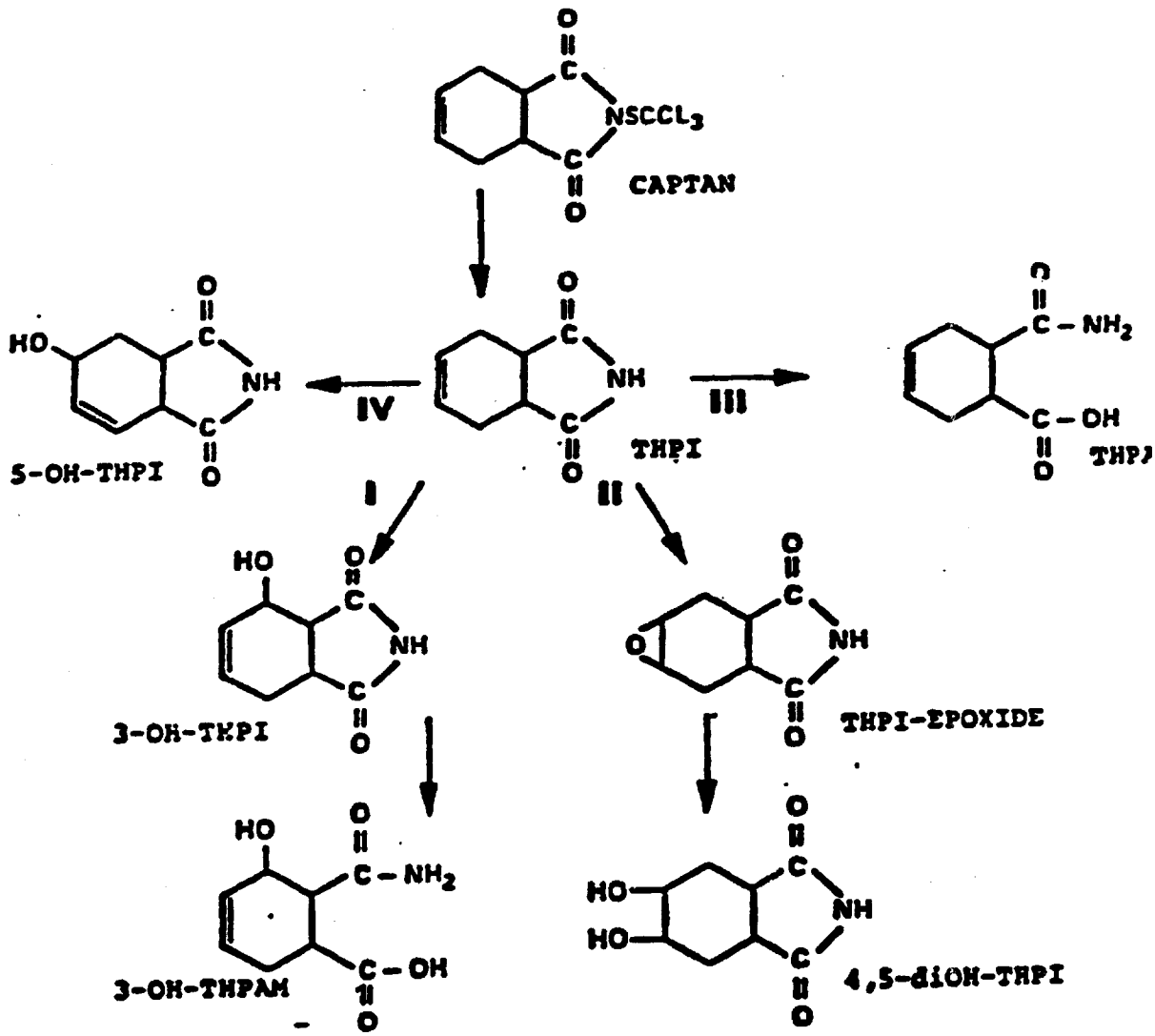


Figure 1. Urinary Metabolites of ^{14}C-Captan in the Rat

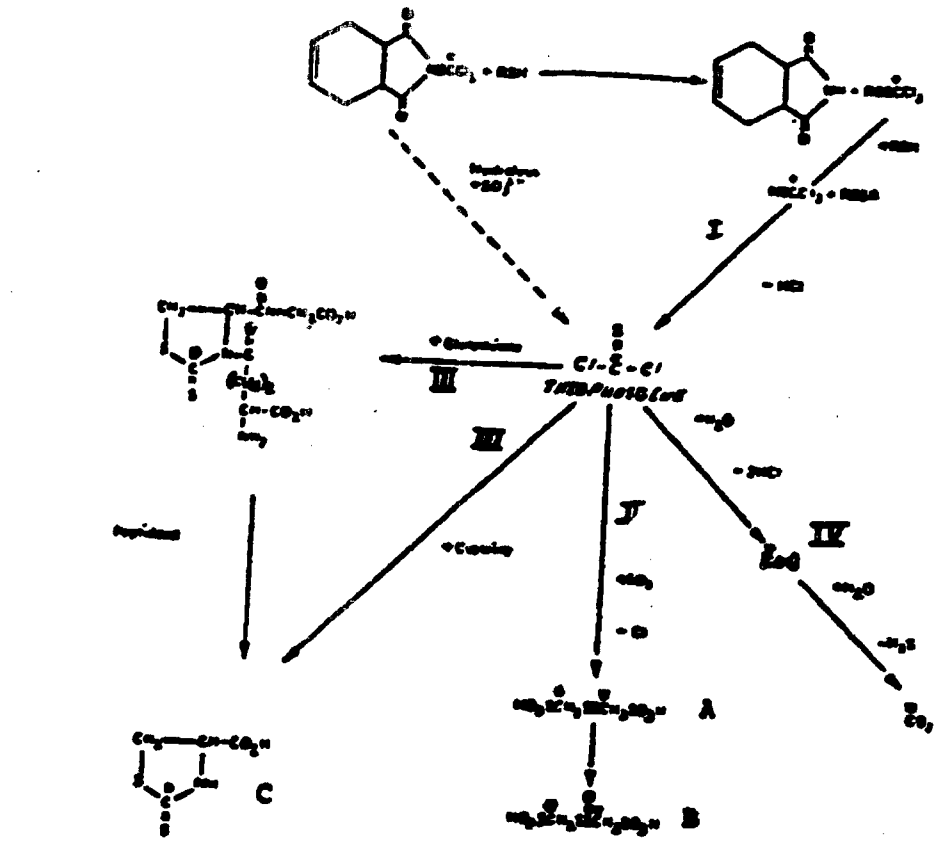


Figure 2. Proposed Metabolism of ^{14}C-Captan in the Rat

*C=^{14}C

3. Mutagenicity:

Captan can produce mutagenic events in bacteria, eukaryotic microorganisms, and mammalian cells (in culture). Metabolic activation (S9), urine, blood, serum and thiol containing amino acids can decrease or eliminate the mutagenic activity of captan. Captan has not yet been demonstrated to be mutagenic in vivo. The PD 2/3 concluded that, "Although captan may be able to cause somatic mutational events and may, therefore, have an oncogenic problem, the risk to humans of heritable mutagenicity is extremely low or does not exist and does not warrant further testing at this time."

The following is a summary of the mutagenic potential of captan.

Positive gene mutation studies:
- E. coli WP2
- S. typhimurium G46, TA 1950, TA1530, TA1535, TA1537, TA100, and TA98
- Aspergillus nidulans
- Chinese hamster ovary V-79 (in culture)
- lung fibroblasts (in culture)

Positive for induction of DNA repair:
- E. coli WP2
- Bacillus subtilis
- A. nidulans
- Saccharomyces cervesiae
- mammalian cells (in culture)
  - SV40 transformed human fibroblasts
  - Chinese hamster lung fibroblasts
  - Chinese hamster ovary V79 cells

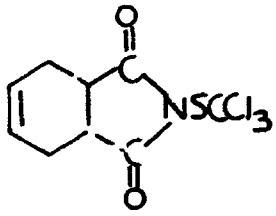
Positive for chromosome aberrations in culture for:
- human embryo lung cells
- rat kangaroo cells
- Chinese hamster ovary V79 cells

Negative or reduced mutagenic activity:
- in studies with metabolic activation, i.e. S9 activation with S. typhimurium TA100, TA 1535, and TA1537 reduced mutagenic activity.
- in host mediated assays, negative mutagenic activity
  - when bacteria (injected I.P.) were indirectly exposed to captan that was injected subcut.
  - when captan was preincubated with blood, urine and plasma (markedly reduced mutagenic activity in the reverse mutation assay with S. typhimurium, strain TA 1535).
  - when rat liver homogenate, cysteine or whole rat blood was added to the system (mutagenic activity of captan in E. coli WP2 and S. typhimurium TA 1535 was inhibited or reduced).

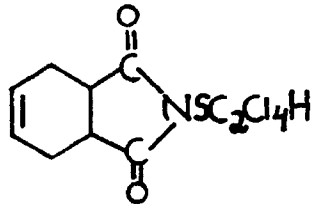
In vivo assays:
- Negative for chromosomal aberrations in bone marrow.
- Negative in 2 dominant lethal tests.
- Negative in the mouse color coat spot test.

4. Structure-Activity Correlations:

Captan is structurally related to captafol and folpet:



CAPTAN



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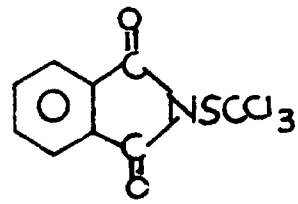

FOLPET

Captafol has the same ring structure as captan and both are initially hydrolyzed to THPI (Figure 1). Captafol appears to be associated with an increased incidence of renal tumors and hyperplasia in Charles River CD male rats at about 60 mg/kg - captan produced renal tumors and hyperplasia in the males of the same rat strain at 250 mg/kg.

Folpet and captan have the same side chain, (which may convert to thiophosgene, a highly reactive compound - see Figure 2). Both captan (6000 ppm or lower) and folpet (5000 ppm) are associated with an increased incidence of intestinal tumors in the CD-1 mouse following dietary exposure.

All three analogs have shown mutagenic activity in vitro.

F. Weight of Evidence Considerations:

The committee considered the following facts regarding toxicology data on captan to be of importance in a weight of evidence determination of oncogenic potential.

a. Rats - Oral administration of captan to:

Study 1. *Charles River CD rats resulted in an increase in combined renal cortical/tubular cell neoplasms in male rats at 2000 and 5000 ppm (dose-related trend). The tumors were first observed on day 529 of the study.

Study 2. *Osborne Mendel rats - did not result in increases of renal neoplasms in either sex at doses up to 16,000 ppm (HDT).

Study 3. *Wistar Cpb:WU rats resulted in an increase of uterine sarcomas (4/50 vs 0/48 in controls) at 2000 ppm (HDT), which was statistically significant, but did not result in increases of renal neoplasms in either sex.

b. Mice - Oral administration of captan to:

Study 4. *B6C3F1 mice resulted in an increased incidence of combined duodenal (relatively unusual site) adenomas/polyps or adenocarcinomas at the HDT (16,000 ppm) in both sexes, with the first tumor reported at 91 weeks (positive linear trend in males, which was statistically significant at the HDT).

Study 5. *CD-1 mice (ICR Derived - Chevron) resulted in a marked increase ($p < 0.001$) in the incidence of small intestinal (mainly duodenal) adenoma/polyps and carcinomas at all levels tested (6000 ppm and above) . A positive dose-related trend for carcinomas in both sexes ($p<0.005$) was also observed, and duodenal changes appeared to occur earlier in the high dose males. There was also a marked increase in gastric and duodenal hyperplasia in both sexes.

Study 6. *Charles River CD-1 mice (Bio/Dynamics) resulted in a slight increase in small intestinal tumors (benign and malignant) in male and female high dose groups (6000 ppm), however this study and its results were questioned by the Committee, and subsequent Agency audit suggested there were problems with maintaining dose levels throughout the study. There were also smaller increases in stomach tumors. The first duodenal tumor occurred at 72 weeks (in males).

Study 7. *Charles River CD-1 mice (Stauffer) resulted in a significant ($p<0.01$) increase in intestinal adenomas, after only 9 months of treatment at 6000 ppm. After 12 months of treatment, followed by 6 months of recovery, the incidence of neoplasias was still statistically ($p<0.05$) increased over controls.

In addition, focal hyperplasias were present as early as 3 months (75% of treated animals) with all treated mice affected by 9 months (vs 0% in controls up to 18 months into the study). After recovery periods of 6 to 12 months, the incidence of hyperplasia decreased to control levels.

F. Weight of Evidence (continued)

c. The PD 2/3 (pgs. II-38-44) elaborates on the mutagenicity of captan. These aspects were discussed by the Peer Review Committee, but no new or additional information was included in the discussion. The salient points on captan's mutagenicity are:

Captan has mutagenic activity in bacteria, eukaryotic microorganisms, and mammalian cells:
(1) Captan induced DNA repair in several test systems
(2) Captan produced chromosomal abberations in several mammalian cell systems
(3) Metabolic activation or reaction with sulfhydryl groups reduced or eliminated captan's mutagenicity
(4) In vivo tests for mutagenicity were mostly negative or inconclusive, presenting an equivocal picture
(5) The overall conclusion is that the mutagenicity assays on captan lend significant support to its classification as an oncogen, but there is little or no risk of its producing heritable mutagenic effects in humans.

d. Captan is structurally related to captafol and folpet; captafol appears to be oncogenic (renal tumors) in Charles River CD male rats; folpet is associated with intestinal tumors in the CD-1 mouse. Both of these analogs have also shown mutagenic activity in vitro.

G. Classification of Oncogenic Potential:

Criteria contained in the EPA Guidelines for classifying a carcinogen [FR 51: 3392-34003, 1986] were considered. These Guidelines state that -

For Group B - Probable Human Carcinogen:

"Sufficient evidence of carcinogenicity .... indicates that there is an increased incidence of malignant tumors or combined malignant and benign tumors:

a) in multiple species [MET] or strains [MET]; or
b) in multiple experiments [MET] (e.g., with different routes of administration or using different dose levels); or
c) to an unusual degree in a single experiment with regard to high incidence [MET], unusual site or type of tumor [MET], or early age at onset [MET].

Additional evidence may be provided by data on dose-response effects [MET], as well as information from short-term tests [MET] or on chemical structure [MET]".

B1 = "... limited evidence of carcinogenicity from epidemiology studies.."
B2 = "... inadequate evidence or no data from epidemiology studies..."

Thus, the evidence for captan meets all of the criteria for category B, any one of which alone can be sufficient for such a classification:

Captan produced an increased incidence of renal cortical/tubular cell neoplasms in male Charles River CD rats (tumors appeared somewhat early: day 529), and an increased incidence of uterine sarcomas in Wistar rats.

Captan produced an increased incidence of intestinal neoplasms in B6C3F1 mice; in ICR-Derived CD-1 mice (tumors appeared somewhat early and a dose-related trend for both sexes was observed); and in Charles River CD-1 mice (tumors appeared after 9 months).

Captan also demonstrated mutagenic activity and is structurally related to two oncogens (captafol and folpet), which also have mutagenic activity.

On the basis of the above evidence, the Peer Review Committee agreed to classify captan as a B2 "Probable Human Carcinogen" (there is no available data from epidemiology studies).