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

APR 10 1987

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCE

SUBJECT: Peer Review of Captafol

FROM: Esther Rinde, Ph.D. E. Rinde 3/12/87
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769c)

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

The Toxicology Branch Peer Review Committee met on Feb. 4, 1987 to discuss and evaluate the weight-of-the-evidence on Captafol, with particular reference to its oncogenic potential.

A. Individuals in Attendance:

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

William L. Burnam
Reto Engler
Louis Kasza
Richard Levy
Robert Beliles
John A. Quest
Judith Hauswirth
Esther Rinde

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

Marion P. Copley
Bernice Fisher
Steven Saunders
Irving Mauer

A. 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

Anne Barton

Richard Hill

Stephen Johnson

Diane Beal

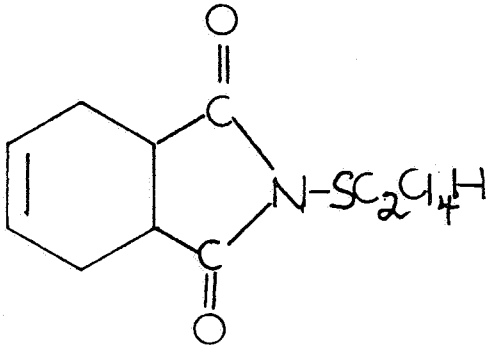
B. Material Reviewed:

The material available for review consisted of the following: DER's, 1-liners, and summary tables for tumor incidences and other data (mutagenicity, non-oncogenic effects, etc) prepared by the reviewer. A copy of the material reviewed is appended to this report.

C. Background Information:

Captafol (Difolatan): cis-N-[1,2,2-tetrachloroethyl)thio]-4-cyclohexene-1,2-dicarboximide, is a protectant fungicide structurally related to two other fungicides, captan and folpet, both of which have been classified as B2 carcinogens in Peer Review.

In the PDl, a notice of Special Review for pesticide products containing Captafol was issued (January 1985), based on oncogenic potential and toxicity to fish.



CAPTAFOL

D. Evaluation of Oncogenicity Evidence for Captafol:

1. Two-year Chronic Toxicity Study in Rats with Captafol Technical (SX-945)

Strain: Charles River Crl:CD Sprague Dawley Br albino rats - 50/sex/group
Testing Facility: Hazleton Labs for Chevron, 1983

Rats were treated for up to 2 years with either 0, 75, 300 or 1200 ppm (nominal dose) of captafol in their diet. Due to instability of captafol in the diet, the average measured concentrations were 0, 56, 241, and 1096 ppm, respectively.

Mammary fibroadenomas and hepatic neoplastic nodules* were statistically increased in high dose females. Renal tubular cell adenomas (males) and carcinomas (males and females) were also increased. The incidences of treatment related lesions are given in Tables I and II. (Note: dosages given in these tables represent actual concentrations in the diet.)

*The pathologist for this study (submitted in 1984) describes the (main) histopathologic lesions in these rat livers as neoplastic nodules, in keeping with the 1975 Squire-Levitt recommendation. The majority of Committee members felt, however, that neoplastic nodules should be interpreted as being adenomas, unless and until the Sponsor re-evaluates the slides using the recently revised nomenclature[1].

MTD: Apparently achieved at the high dose, both sexes, based on a weight loss of 10-12%. Signs of toxicity at the high dose were: reduced globulin (males), increased albumin:globulin ratios (males), decreased SGPT (females), hyperplasia of the renal tubular epithelium with megalocytic cells (males and females), gastric hemorrhage, erosion/ulceration, hyperkeratosis/acanthosis, increased ground substance (mucosal glands), and increased incidence of dilated gastric pits (males and females). There were no treatment related increases in non-neoplastic hepatocellular lesions in either sex. Survival was not apparently adversely affected by captafol treatment.

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[1]EPA is well aware of the confusion and controversy surrounding the term (neoplastic nodule) which has been used to describe both neoplastic (adenoma) and non-neoplastic (hyperplasia) lesions of the rat liver [U.S.EPA (1986) Proliferative Hepatocellular Lesions of the Rat. Review and Future Use in Risk Assessment. EPA/625/3-86/011]. Recently, NTP has proposed to change the nomenclature for classifying rat hepatocellular proliferative lesions in their chronic toxicity testing program [Maronpot, R.R. et al. (1986) NTP Nomenclature for Hepatocellular Lesions of Rats. Toxicol. Pathol. 14, 263-273]. Under the new classification scheme, NTP will no longer use the term "neoplastic nodule" in future pathological diagnoses; instead, it will use hyperplasia and hepatocellular adenoma.

D. 1. Two-Year Oncogenicity Study in Rats with Captafol, Contd.

Table I: Incidence (%) of treatment related neoplasia

	males				females			
ppm	0	56	241	1096	0	56	241	1096
mg/kg/day	0	2.8	12	55	0	2.8	12	55
tissue								
liver, neoplastic nodule (NN)	—	—	—	—	4/50	2/49	2/50	17/50***(34)
hepatocell. carcinoma (HCC)	—	—	—	—	0/50	0/49	1/50	2/50 (4)
NN + HCC[1]	—	—	—	—	4/50	2/49	3/50	17/50***(34)
mammary, fibroadenoma	—	—	—	—	18/49	26/49	28/50	33/50** (66)
renal[2]								
adenoma	1/50	0/50	0/50	3/50	1/50	0/50	0/50	0/50
carcinoma	0/50	1/50	0/50	4/50(8)	0/50	0/50	0/50	3/50****(6)
ad + carc[1]	1/50	1/50	0/50	7/50*(14)	1/50	0/50	0/50	3/50. (6)

[1] animals with tumors in this organ are counted only once.
* significantly greater than controls ($p \leq 0.05$)
** significantly greater than controls ($p \leq 0.01$)
*** significantly greater than controls ($p \leq 0.001$)
by captafol treatment.

[2] It was suggested by Dr. Farber (subsequent to the Peer Review Meeting) that the Sponsor be asked to recut the renal tissue and stain for hyaline droplets to further test the hypothesis that some chemicals (eg: unleaded gasoline) induce tumors primarily in male rats, because of alpha-2u-globulin, a component of hyaline droplets, which is present in only very low levels in female rat kidneys, mice and humans.

Table II: Incidence of select treatment related non-neoplastic lesions

	males				females			
ppm	0	56	241	1096	0	56	241	1096
mg/kg/day	0	2.8	12	55	0	2.8	12	55
Stomach incr. ground substance	0/48	1/49	40/48***	49/50***	0/50	0/50	17/50***	34/50***
Liver cellular alteration	43/50	27/34	24/32	43/50	39/50	19/29	22/37	44/50
Kidney hyperplasic tubular epith	2/50	1/50	1/50	13/50**	1/50	1/50	2/50	3/50
megalocytic cells	0/50	0/50	0/50	47/50***	0/50	0/50	0/50	48/50***

** significantly greater than controls ($p < 0.01$)
*** significantly greater than controls ($p < 0.001$)

D. 2. Lifetime Oncogenic Feeding Study of Captafol Technical in Mice

Strain: CD-1 (ICR Derived) - 80/sex/group (52/sex for controls)[1]
Testing Facility: Chevron Chemical Co.

Mice were fed 0, 300, 1000 or 3000 ppm (nominal dose) in their diet for 110-111 weeks.

There was a treatment associated increase of lymphosarcomas in high dose males and females. Harderian gland adenomas were significantly increased only in mid-dose males. Total hemangiosarcomas were increased in both mid and high dose male and female groups; for high dose male, $p<0.05$. When considered by site, however, the increases were not statistically significant. The incidence of hemangiosaracomas in the heart was: males, 33% at mid- and high dose; females, 53% at mid, 0% in high-dose. Tumor incidences are given in Table III. The incidences of non-neoplastic lesions are given in Table IV (pg. 6).

Table III: Incidence (%) of treatment related neoplasia (affected/treated)

	males				females			
ppm	0	300	1000	3000	0	300	1000	3000
mg/kg/day	0	45	150	450	0	45	150	450
Tissue or lesion								
lympho-sarcoma[4]	0/52	3/80 (4)	4/80 (5)	13/80*(16)	6/52	8/80	10/80	21/80**(26)
hemangio-sarcoma[2]	††1/52	0/80 (0)	5/80 (6)	6/80***(8)	†0/52	1/80	3/80	6/80**(8)
Harderian adenoma	0/104[3]	8/80(10)	19/80**(24)	2/80 (3)	—	—	—	—

* significantly greater than controls ($p < 0.001$)
** significantly greater than controls ($p \leq 0.05$)
*** $p = 0.16$

† $p \leq 0.05$ for treatment related trend (only given for hemangiosarcoma)
†† $p \leq 0.01$ for treatment related trend

[2] Each hemangiosarcoma bearing animal is only counted once.
[3] The additional 52 controls mentioned earlier are included.
[4] Myeloproliferative disease was originally reported as increased in high dose males, but on reexamination, the majority of these diagnoses were changed to lymphosarcoma.

[1] There were an additional 52 control mice/sex from a study (SOCAL 1331) conducted at the same time in the same rooms.

D. 2. Lifetime Oncogenicity Study in the CD-1 Mouse, Contd.

Table IV: % Incidence of select treatment related non-neoplastic lesions

	males				females			
ppm	0	300	1000	3000	0	300	1000	3000
mg/kg/day	0	45	150	450	0	45	150	450
Tissue or Lesion								
Pancreatic acinar atrophy	0%	6%*	58%**	82%**	2%	1%	89%**	64%**
Nasal turb gland. atrophy	6%	25%**	61%**	19%**	2%	24%**	64%**	1%
Salivary gland interstitial fibrosis	2%	4%	46%**	66%**	0%	0%	48%**	19%**
Harderian gland hyperplasia	3%	0%	8%	11%*	--	--	--	--

* significantly greater than controls ($p < 0.05$)
** significantly greater than controls ($p < 0.01$)

MTD (Refer to Table V): Appears to have been exceeded in all three male treatment groups, based on poor survival at term (28.8% at low-dose *, 21.3% at mid-dose and 0% at high-dose vs 49% for controls); all males and females in the high dose group were dead by 85 weeks. The MTD was exceeded at mid-dose in females, based on poor survival at that dose (1.3% vs 59.6% in controls). The cause of death according to the sponsor, was mostly attributable to lymphosarcoma in both sexes.

Table V: Percent Survival

	males				females			
ppm	0	300	1000	3000	0	300	1000	3000
mg/kg/day	0	45	150	450	0	45	150	450
61 weeks	94.2	87.5	96.3	47.5**	97.1	95.0	88.8	2.5**
85 weeks	76.9	68.8	75.0	0 **	84.6	83.8	42.5**	0 **
At term (110 weeks)	49	28.8**	21.3**	0 **	59.6	52.5	1.3**	0 **

** significantly greater than controls ($p \leq 0.01$)

The Committee concluded that the tumors in these mice were significant, even though the MTD was exceeded, because there was no evidence that tumors would not have occurred at less toxic levels.

* It was also argued that the MTD may not have been exceeded at this dose, since the survival rate at term was greater than 50% of the control.

6

D. 3. Carcinogenicity of Captafol in B6C3F1 Mice by Ito, et al.

This is a journal article which did not present individual animal data, therefore, the study could not be completely analyzed.

The methodology (storage and contamination; captafol is unstable, particularly when contaminated with urine and feces) has been questioned by the Registrant (Chevron), who is presently conducting its own study with the B6C3F1 mouse.

4. Other - Chronic Rat - Makhteshim

Chevron has notified the Agency of a Makhteshim chronic study using Fisher 344 rats. Only preliminary data summaries were available.

The Peer Review Committee agreed that no conclusions could be reached based on either of the above two studies.

D. 5. Historical Control Information

a) Charles River CD Rats

Recent control data from Hazleton was unavailable; the following total tumor incidence in female Charles River CD rats is from 4 studies run at Hazleton in late 1970:

Liver		Mammary Gland (Benign)
Neoplastic Nodules (NN)	(14/277) = 14%	(101/174) = 37%
Hepatocellular Carcinoma (HCC)	(6/277) = 2%	
NN + HCC	(20/277) = 7%	

Renal data from Hazleton was unavailable; the following data for Charles River CD rats is from IRDC:

Kidney	Males		Females	
Total incidence		(%, range)		(%, range)
adenoma	5/1279	(0.4, 0-1.7)	2/926	(0.2, 0-2.2)
adenocarcinoma	2/1279	(0.2, 0-2.1)	1/926	(0.1, 0-1.1)

(The incidences of all of the above tumors were exceeded in treated rats.)

b) Charles River Swiss CD-1 Mice (ICR derived)

The following were the ranges of tumor incidence in historical controls, as included with the mouse oncogenicity study:

Incidence of lymphosarcoma:	2% - 14%
Incidence of hemangiosarcoma(all sites):	0 - 2%
Incidence of Harderian Gland adenoma:	<1 - 6%

(The incidences of the above tumors were exceeded in treated mice.)

E. Additional Toxicology Data on Captafol:

1. Metabolism:

Following oral administration, captafol appears to be extensively hydrolyzed at the N-S bond to tetrahydrophthalamide (THPI) and tetraethylthio (TES). Figure I shows the metabolic pathway in the rat, suggested by two Chevron studies with C^{14} (carbonyl) labeled captafol. Figure II shows the proposed metabolic pathway for both rats and mice, obtained with captafol labeled (C^{14} or Cl^{36}) in the tetrachloroethylthio side chain. Most of the radioactivity appears to be excreted within 3 to 4 days, primarily in the urine. Unmetabolized captafol was found in feces, but not in urine. The metabolism of captafol appears to be qualitatively similar in rats and mice and no major differences were observed between males and females.

2. Non-Oncogenic Toxicological Effects

The LD_{50} of captafol technical in rats is 1.6 g/kg (oral) and >5 g/kg (dermal). Captafol is a moderate primary skin irritant and sensitizer and causes severe eye irritation with irreversible corneal opacities (Category I). In dogs, 2 mg/kg/day captafol causes ballooning degeneration of the urinary tract transitional epithelium. Captafol has not been demonstrated to be teratogenic in the rabbit or rat using standard protocols, and there was no evidence of developmental toxicity noted in the mouse somatic cell mutation assay ("mouse spot test"). There were no reproductive effects observed in a 2 generation rat reproduction study.

FIGURE 1

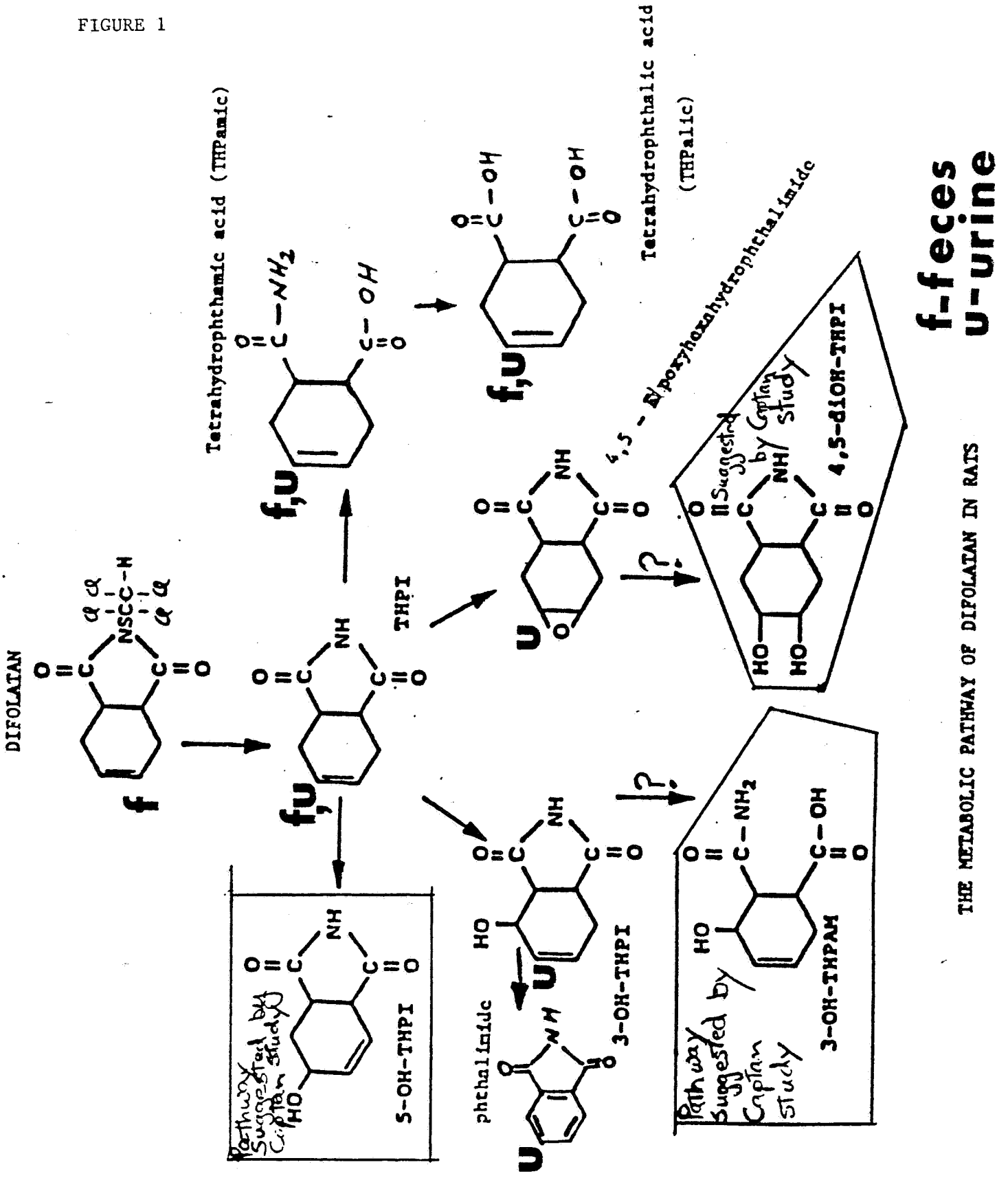

DIFOLATAN
THPI
Tetrahydrophthamic acid (THPamic)
Tetrahydrophthalic acid
(THPalic)
4,5 - Epoxyhexahydrophthalimide
Suggested by Captan study
4,5-DIOH-THPI
5-OH-THPI
Pathway Suggested by Captan study
phthalimide
3-OH-THPI
Pathway Suggested by Captan study
3-OH-THPAM
f-feces
u-urine
THE METABOLIC PATHWAY OF DIPOLATAN IN RATS

FIGURE 2 **Proposed Major Metabolic Pathway of [^{14}C-TES] captafol In Rats and Mice**

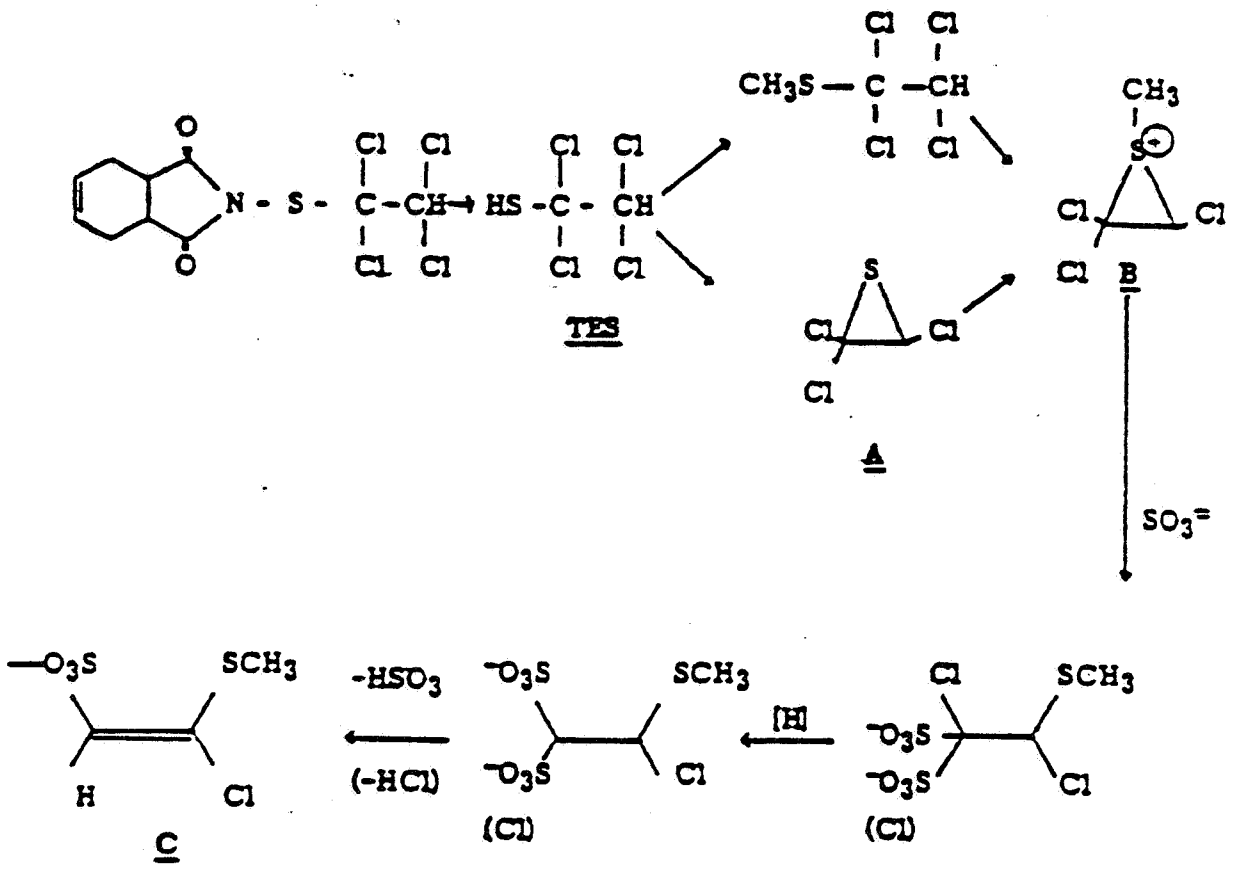
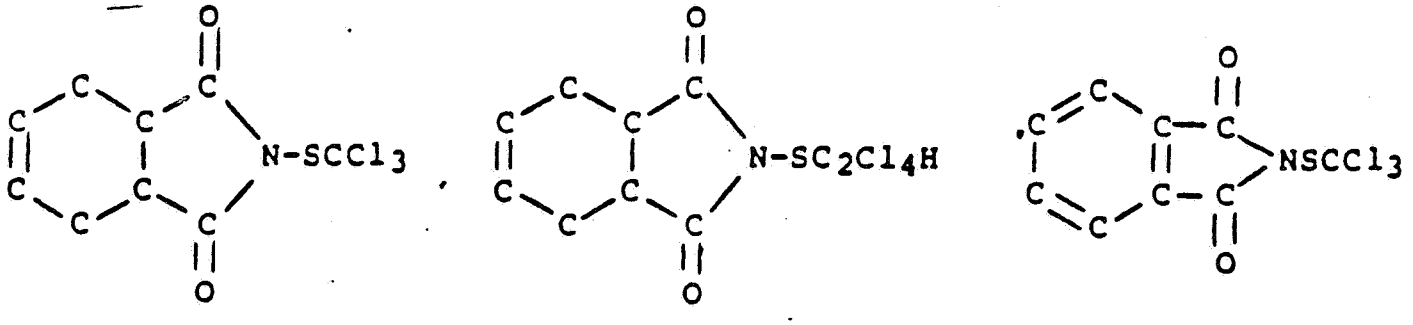


FIGURE 3



Captan Captafol Folpet

E. 3. Mutagenicity:

Captafol can produce mutagenic events in bacteria, and mammalian cells (in culture). Metabolic activation (S9), blood, serum and thiol containing amino acids can decrease or eliminate the mutagenic activity of captafol. Captafol has not yet been demonstrated to be mutagenic in vivo.

The PD 2/3 for captan, which has the same profile for mutagenic activity, 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."

Summary of the mutagenic potential of captafol.

Positive gene mutation studies:
- E. coli WP2
- B. subtilis H17/M45
- S. typhimurium TA1535, TA100, and TA102
- Chinese hamster ovary V-79 (in culture)

Positive for induction of DNA repair:
- Bacillus subtilis
- mammalian cells (in culture)
  Chinese hamster ovary V79 cells

Positive for chromosome aberrations in culture for:
- Chinese hamster ovary V79 cells

Negative or reduced mutagenic activity:
- in studies with metabolic activation, i.e. -
  S9 activation with S. typhimurium TA100 reduced mutagenic activity; with TA98 and CHO/HGPRT there was negative activity.

- in host mediated assays, negative mutagenic activity:
  - when cysteine or glutathione was added to the test system, mutagenic activity of captafol in S. typhimurium TA102 was completely inhibited.
  - when captan was preincubated with blood, urine and plasma, mutagenic activity was markedly reduced 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 in 2 chromosomal aberration (bone marrow) tests.
- Negative in a dominant lethal test.
- Negative in 2 mouse color coat spot tests.

E. 4. Structure-Activity Correlations:

Captafol is structurally related to captan and folpet. Captan has the same ring structure as captafol and both are initially hydrolyzed to THPI (tetrahydroxyphthalimide).

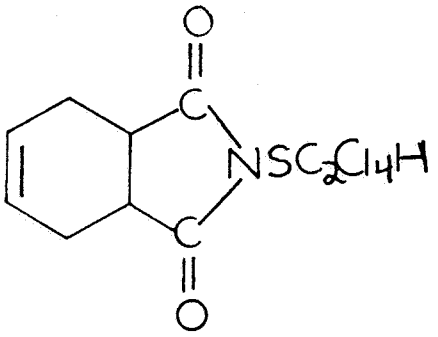
Captan, associated with an increase in duodenal tumors (mice) and renal tumors (rats), as well as folpet, also associated with duodenal tumors (mice) have been classified as B2 oncogens by the Tox Branch Peer Review Committee.

Captan appears to be associated with an increased incidence of renal tumors in Charles River CD male rats at about 100 mg/kg/day. It is likely that the renal tumors observed with both captan and captafol (at 55 mg/kg/day primarily in males and to a lesser extent, females), are associated with the cyclohexene moiety (or its metabolites) which is present in both compounds. Folpet, which has an unsaturated phthalimide ring, was not associated with an increase in renal tumors in the rat. All three compounds have mutagenic potential in vitro for gene mutation, DNA repair and chromosomal aberration. This is reduced following addition of inorganic or organic thiols. All are negative for in vivo assays including chromosomal aberration, dominant lethal and mouse color coat spot test.

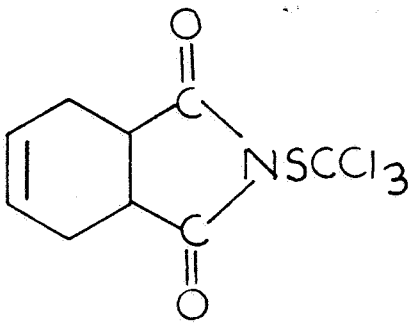
Table 1 relates the similarities among these three compounds.

TABLE 1

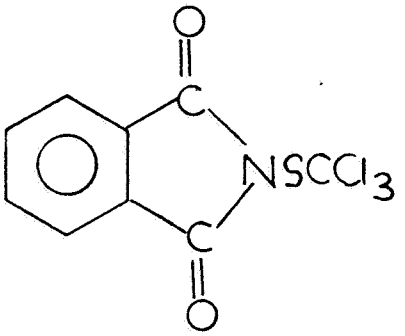
	captafol	captan	folpet
Intestinal tumors, mice	-	X	X
Renal tumors, rats	X	X	-
Mutagenicity (in vitro)	X	X	X
Teratagenicity	-	-	X



CAPTAFOL



CAPTAN



FOLPET

F. Weight of Evidence Considerations:

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

Captafol fed in the diet to Sprague Dawley rats, produced a statistically significant increase in mammary fibroadenomas and hepatic adenomas (see pg.3) in females at the high dose (1200 ppm - nominal dose); renal adenomas/carcinomas (combined) were significantly increased in males (1200 ppm), and there was a treatment related trend for carcinomas and adenomas/carcinomas (combined) in females.

Captafol fed in the diet to CD-1 mice: A treatment associated increase in lymphosarcomas in males and females, at the high dose (3000 ppm); total hemangiosarcomas were significantly increased in both mid (1000 ppm) and high dose males and females, with a treatment related trend; the increase in harderian gland adenomas was statistically significant only in males, and only at the mid dose (1000 ppm).

It was noted that lymphosarcomas in the mouse are often associated with the presence of a murine virus and that the high dose may have enhanced the response to this oncogenic virus, however the Committee did not consider this sufficient basis for dismissing these tumors.

In the mouse study, the MTD appeared to have been exceeded in all three male treatment groups (see footnote, pg. 6) and in females at the mid-dose; the Committee nevertheless considered these tumors to be significant, because the degenerative lesions were seen at all dose levels, and there was no evidence that the mouse metabolizes captafol differently at high doses.

Captafol is mutagenic in bacterial systems and in mammalian cells in culture. Mutagenic activity is reduced or abolished in the presence of S-9, cysteine, glutathione, and when preincubated with blood, urine or plasma. Captafol is negative in in vivo assays.

Captafol is structurally related to captan and folpet. Captan has the same ring structure as captafol and both are initially hydrolyzed to tetrahydroxy-phthalimide. Both captan and folpet were evaluated as B2 carcinogens in Peer Review. Captan and captafol produced renal tumors in rats; and captan and folpet produced intestinal tumors in mice. All three compounds have mutagenic activity in vitro, which is reduced upon addition of inorganic or organic thiols. All three are negative in in vivo assays.

A summary report (by sponsor) of a mortality study of Chevron Chemical Co. employees indicated 2 cases of kidney cancer and 1 case of liver cancer in a cohort study of 1446 employees, including those engaged in the manufacture of captafol products for more than 13 years. This study has not been reviewed by EPA and was not available at the time of the meeting. It has since been obtained and is being reviewed by an Epidemiologist; the Committee will meet again to finalize the classification of captafol as soon as the review is complete.

F. Classification of Oncogenic Potential:

Criteria contained in the EPA Guidelines [FR51: 3392-34003, 1986] for classifying a carcinogen were considered.

Captafol fed in the diet to Sprague Dawley rats produced mammary fibroadenomas ($p \leq 0.01$) and hepatic adenomas ($p<0.001$) in females at 1200 ppm; renal adenomas/carcinomas (combined) ($p<0.05$) in males at 1200 ppm, and a treatment-related trend ($p<0.003$) in females.

Captafol is oncogenic in the mouse, producing lymphosarcomas ($p<0.05$) in both sexes at 3000 ppm; total hemangiosarcomas in both sexes (1000 and 3000 ppm) and harderian gland adenomas ($p<0.05$) in males (1000 ppm). The Statistics Section has been asked to reanalyze the mouse tumor incidence data, taking survival into account.

Captafol also demonstrated mutagenic activity and is structurally related to captan and folpet which are also mutagenic; both captan and folpet were evaluated as B2 carcinogens in Peer Review.

Based on the above evidence, captafol meets the criteria for Group B - Probable Human Carcinogen (causes an "increased incidence of malignant or combined malignant and benign tumors in multiple species"). Additional evidence for this classification was provided by SAR and mutagenicity.

The Committee agreed to assign a tentative classification of B for captafol pending completion of the review of the epidemiology study, at which time they will reconvene to determine which of the following apply:

- A - if the evidence from the epidemiology study is sufficient[1]
- B1 - if the evidence is limited[2]
- B2 - if the evidence is inadequate[3].

A tentative estimate of potency (Q_1^*) has been set at 0.051 $(mg/kg/day)^{-1}$, based on the Hazleton 2-year rat study (see memorandum from B. Fisher dated Jan. 29, 1987). This value will be revised as appropriate.

As described on page 33999 of the Guidelines, the weight of evidence for carcinogenicity from studies in humans is classified as follows:

[1] Sufficient evidence of carcinogenicity, which indicates that there is a causal relationship between the agent and human cancer.

[2] Limited evidence of carcinogenicity, which indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be excluded.

[3] Inadequate evidence, which indicates that one of two conditions prevailed: (a) there were few pertinent data, or (b) the available studies, while showing evidence of association, did not exclude chance, bias, or confounding and therefore a causal interpretation is not credible.

G. References

1. Chronic Toxicity Study in Rats; Hazleton Laboratories America, Inc., Vienna, Va; June 15, 1983; Author: RN Cox; Sponsor: Chevron Chemical Co., Richmond, CA; EPA Accession Number: 250921-250924.

2. Lifetime Oncogenic feeding Study of Difolatan Technical in Mice; Chevron Chemical Co., Ortho Agricultural Chemical division, Richmond, CA; Jan. 11, 1980; EPA Accession Numbers: 242040, 248212, 257492, 257907.

3. N. Ito, T. Agiso, S. Fuhushima, M. Shibata and A. Hagiwara. (1984) Carcinogenicity of Captafol in B6C3F1 Mice. GANN 75: 853-865.

4. Chronic Study in Rats; Makhteshim: Preliminary Report.

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IRVING MAUER	DATE: 3/24	3/24

CHEMICAL NAME: CAPTAFOL

PLEASE SIGN AND RETURN TO S. BAILEY WITHIN 2 DAYS TO (RM. 821 CM-2 TS-769)

Need to change transmittal memo. Hank Jacobs is now in S/S/HED. (yes) but do we change signature page!! 4/19/87

I QUESTION THE RECAT OF TISSUES TO LOOK FOR HYPERPLASIA DYSPLASIA SINCE BOTH SEXES SHOW KIDNEY TUMORS.

- WHY IS MTD EXCEEDED IF TUMORS FOUND

- WHAT DOES THE STUDY BY IVO ET AL TELL US?

17

TOX 3/19

H.d587