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

004597

MEMORANDUM:

OFFICE OF
PESTICIDES AND TOXIC SUBS

SUBJECT: Registration # 239-2230, Captafol: Toxicology data submitted in response to the Registration Standard, additional rat and mouse onco study data.

Tox. Chem. No.: 828
Accession No.: 257907

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

FROM: Marion P. Copley, D.V.M. MPCopley 7/29/85
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Jane Harris, Ph.D., Section Head JH 7/26/85
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Background:

A registration standard and position document 1 (PD 1) have been completed for the fungicide Captafol (difolatan). The issues in the PD 1 were oncogenicity and hazard to wildlife. The following data gaps were listed in the registration standard:

Acute inhalation - rat[1]
90-day feeding - non rodent
90-day inhalation - rat[1]
chronic feeding - dog
teratagenicity - 1 species
oncogenicity - rat[2], mouse[2]
gene mutation - mammalian cells in culture

Chevron has submitted, for Toxicology Branch (TB) review: 1) addendum II to the chronic feeding/onco toxicity study in rats (difolatan), including additional hepatic and mammary histopathology data for the mid and low dose groups, 2) "The presentation of separate control data for SOCAL 1330 and SOCAL 1331" mouse onco study.

1 Data currently under review in TB
2 Discussed in this action.

1. A new oncogenic risk assessment (as recommended in the attached memo by Ann Barton (Aug. 13, 1984) will be done by the TB statistics department using the new data obtained from the mid and low dose rat feeding/onco study (see attached DER supplement). Tumors to be examined are: 1) liver - neoplastic nodules + hepatocellular carcinoma, 2) kidney - renal tubular cell carcinoma.

2. The mouse onco control data for SOCAL 1330, presented by the company, is discussed in the attached DER supplement. This study remains core-supplementary for the following reasons:

   - The incidence of lymphosarcoma/study for the control groups needs to be presented as indicated in the attached memo by M. Copley of 7/23/85.

   - Tables 1, 2 and 17 need to be corrected, resubmitted and evaluated by TB before the oncogenic risk can be reevaluated.

   - These tables need to be examined before TB can consider upgrading SOCAL 1330 from core-supplementary.

3. The above mentioned risk assessments will be discussed more fully in the PD 2/3.

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Reviewed by: Marion P. Copley, D.V.M. MPC 7/24/85
Section VI, Tox. Branch (TS-769C)
Secondary reviewer: Jane Harris, Ph.D. JH 7/26/85
Section VI, Tox. Branch (TS-769C)

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DATA EVALUATION REPORT - Supplement

STUDY TYPE: 2 yr feeding onco - mouse TOX. CHEM. NO.: 82

ACCESSION NUMBER: 257907

TEST MATERIAL: Captafol

SYNONYMS: Difolatan

STUDY NUMBER(S): SOCAL 1330

SPONSOR: Chevron Chemical Co.

TESTING FACILITY: not stated

TITLE OF REPORT: Presentation of separate control data from SOCAL 1330 and SOCAL 1331

AUTHOR(S): GH Eisenlord, ZA Wong

REPORT ISSUED: 4/16/85

CONCLUSION:

Classification: Core-supplementary

METHODS: The mouse onco study controls for SOCAL 1330 (Captafol) were combined with SOCAL 1331 controls (Folpet). At the request of Toxicology Branch (TB) the company has submitted summary tables separating these data for analyses.

Both groups of mice were born on the same day and obtained from the same group of animals from the supplier. They were started on study one day apart, housed in the same room and sacrificed within 2 weeks of each other, after 2 years.

RESULTS AND DISCUSSION: Survival - Although deaths in males in SOCAL 1331 occured earlier (week 27) then in SOCAL 1330 (week 39), the survival at the end of 2 years was similar, 48.08 % and 46.15 % for Socal 1330 and Socal 1331, respectively. Deaths in SOCAL 1331 females started later (week 59)than in SOCAL 1330 (week-29). Again the 2 year survival rate was similar, 59.62 % and 61.54 % for SOCAL 1330 and SOCAL 1331, respectively.
Body weight and weight gains - They appeared to be similar between groups for both males and females.
Food consumption - Food consumption for females was similar between the 2 groups. Males in group SOCAL 1330 ate about 0.35 gm/mouse/day less than SOCAL 1331 males, an 8 % decrease.

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Clinical observations - Most visible lesions had similar incidences and onsets between studies. The following table lists those that were noticably different for either incidence or onset.

group	SOCAL 1330 mean week of onset	SOCAL 1330 incidence	SOCAL 1331 mean week of onset	SOCAL 1331 incidence
males				
agression	-	0	51	6
alopecia	-	0	68	2
bite marks	-	0	26	4
darkened/pale eyes	90.3	3	-	0
hyperactivity	78	3	80.3	6
preputial swilling	49.1	28	65.2	22
females				
exophthalmos	-	0	76.8	5
hyperactivity	48.1	7	52.8	4
lens/corneal opacity	81.4	8	82.0	15
scruffiness	88.7	14	82.9	21
skin irritation	77.0	6	-	0

The significance of these differences can not be determined. They may be due to animal variation.

Hematology - Hematology parameters were similar between the 2 groups with the following exceptions, presented as mean (SD):

group	SOCAL 1330 n=10	SOCAL 1331 n=10
2 yr females		
WBC (x 10^3 cells)	7.680 (4.084)	14.210 (12.564)
monocytes (% of differential)	10.1 (5.259)	4.2 (2.573)

Three SOCAL 1331 mice have WBC values above $20x10^3$ while all SOCAL 1330 mice have WBC values below $17x10^3$. Percent monocytes is increased in SOCAL 1330 mice due to three mice with greater than 14% monocytes in the differential, SOCAL 1331 mice have no more than 8 %. These differences have no impact on the interpretation of the treatment group values.

Histology - The summary values from tables 1 and 2 often did not agree with table 17 summary values. Several examples of discrepenci in non-neoplastic lesions are noted in the following table (this is not a complete list).

lesion	SOCAL 1330 table I,II	SOCAL 1330 table 17	SOCAL 1331 table I,II	SOCAL 1331 table 17
females				
blood smear	14	15	8	9
bone/marrow	4	6		
gonads	28	33	27	30
kidneys	28	35	27	35
liver	27	32	28	32
spleen	31	33	40	47

Histologic lesions can not be adequately compared for the following reasons: 1) tables 1 and 2 summary values are often not in agreement with Summary of Pathology Data in table 17. 2) new diagnoses for all myeloproliferative disease (MPD) diagnoses (a malignant neoplasm) have been submitted by the company (mostly lymphosarcoma). These involve several tissues of several mice in both groups. The new diagnoses were not represented in table 17. The incidence of these diagnoses in table 1 and 2 could not be determined as the pathology was listed by organ. MPD and lymphosarcoma have to be summarized by animal with the neoplasm since it may occur in multiple organs. This was discussed in more detail in a TB memo by M. Copley of 7/23/85 (see attached). The incidence of lymphosarcoma for each study control group needs to be presented as indicated in the attached memo. All values on tables 1 and 2 should be checked against table 17 and the individual animal values. Complete corrected tables should be submitted. These tables need to be evaluated before TB can reevaluate the oncogenic risk and consider upgrading this study from core-supplementary.

Most intergroup differences appeared small enough to justify combining the two control groups. Histological parameters, however could not be evaluated for the above mentioned reasons.

Comments and questions:

- The incidence of lymphosarcoma/study control group needs to be presented as indicated in the attached memo by M. Copley of 7/23/85.
- Tables 1, 2 and 17 need to be corrected, resubmitted and evaluated by TB before the oncogenic risk can be reevaluated.
- These tables need to be examined before TB can consider upgrading SOCAL 1330 from core-supplementary.

Reviewed by: Marion P. Copley, D.V.M MPC 7/26/85
Section VI, Tox. Branch (TS-769C)
Secondary reviewer: Jane Harris, Ph.D. JH 7/26/85
Section VI, Tox. Branch (TS-769C)

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DATA EVALUATION REPORT - Supplement

STUDY TYPE: 2 yr feeding/onco - rat TOX. CHEM. NO.: 828

ACCESSION NUMBER: 257907

TEST MATERIAL: Captafol

SYNONYMS: Difolatan

STUDY NUMBER(S): Hazleton Project No. 2107-103

SPONSOR: Chevron Chemical Co.

TESTING FACILITY: Hazleton

TITLE OF REPORT: Chronic toxicity study in rats, Addendum II

AUTHOR(S): RN Cox

REPORT ISSUED: 4/2/85

CONCLUSION: This study satisfies the registration standard for 1 rodent onco/feeding study.

Classification: Core-minimum

RESULTS AND DISCUSSION: Hepatic and mammary histology was reported for all mid and low dose females. The following table summarizes the incidences of 1) neoplastic nodules and hepatocellular carcinoma of the liver, 2) fibroadenoma, adenocarcinoma and adenoma of the mammary gland, and 3) renal tubular cell carcinoma of the kidney. Animals are counted only once for each tissue.

tissue of	males				females			
neoplasm	0	75ppm	300ppm	1200ppm	0	75ppm	300ppm	1200 ppm
liver	--	--	--	--	4/50	2/49	3/50	17/50
mammary	--	--	--	--	18/49	26/49	28/50	33/50
kidney	0/50	1/50	0/50	4/50	0/50	0/50	0/50	3/50

-- treatment groups not different from controls

There was an increased incidence of renal abnormalities discussed in the initial review of this study, however renal neoplasia was not addressed. The incidence of renal tubular cell carcinoma, a rare tumor in rats, was significantly increased in high dose males and females. There was also an increased incidence of renal tubular cell hyperplasia in the high dose. This may be the preneoplastic form of the carcinoma and further suggests that renal neoplasia may be treatment related.

Quantative risk assessment using the incidences of renal and hepatic tumors, as listed in the table as requested in the memo by Ann Barton (Aug 13, 1984, see attached) is being done by the statistics department of the Toxicology Branch.

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

00459

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

AUG 13 1984

MEMORANDUM

SUBJECT: Preliminary Risk Assessment for Captafol

FROM: Anne Barton, Deputy Director
Hazard Evaluation Division (TS-769)

TO: Esther Saito,
Science Integration Staff
Hazard Evaluation Division (TS-769)

This quantitative risk assessment is preliminary until the required additional information on the rat and mouse oncogenicity studies are received and more complete analyses are done on both studies. The need for additional analyses is described below. I recommend we not publish specific risk numbers until the additional analyses are completed.

The Q* for neoplostic liver lesions in female rats is 5×10^{-2}. The Q* for lymphosarcomas in mice depends upon the sex and number of dose groups used but ranges from 5×10^{-3} to $5 \times 10^{-}$. For simplicity, I am using 10^{-2} as the slope in the preliminary risk calculations.

The TMRC of 1.46 mg/day is equivalent to .02 mg/kg/day for a 60kg person. This corresponds to a preliminary risk estimate of 2×10^{-4}. The actual dietary exposure is lower than the TMRC, of course. I see no point, however, in attempting actual residue estimates until the risk assessment on the complete data set can be done, since the Q* may increase.

Preliminary risk estimates for applicators are shown in Table 1. The dermal absorption assumption used in these calculations is the same as that used in the captan PD 2/3. Since there is some doubt about the appropriateness of the Captan data for Captafol absorption, the preliminary risk estimates assuming 100% absorption are provided in Table 2.

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PD 1

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Additonal Data and Analyses Needed

The submitted mouse study report compared results in the Captafol treated groups to the combined controls of the captafol and folpet mouse studies. Results for the separate controls have been requested. In this preliminary assessment, I have assumed no neoplasms in controls.

There was a significant increase in mortality in the mid and high dose mice, frequently accompanied by neoplastic lesions. This preliminary assessment does not take these early deaths-with-tumor into account. When the additional control data have been received, a time-to-tumor assessment will be done.

The rat study failed to complete the histopathology for the low and mid doses. This prliminary assessment is based on results for the high dose and controls only. The remaining histopathology must be completed and included in the final risk assessment.

The result of the final risk assessment may be a higher or lower slope than that used in the preliminary risk assessment, but it is unlikely to be greatly lower. Dietary exposure, however, may be much lower than estimated here.

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

JUL 23 1985

004574

MEMORANDUM:

OFFICE OF PESTICIDES AND TOXIC SUBST

SUBJECT: Registration # 239-2230, Captafol: Miscellaneous data submitted in response to the Registration Standard.

Tox. Chem. No.: 828
Accession No.: 257492

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

FROM: Marion P. Copley, D.V.M.
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)

Background:

A registration standard and position document 1 (PD 1) have been completed for the fungicide Captafol (difolatan). The issues in the PD 1 are oncogenicity and hazard to wildlife. The following are still considered data gaps in the registration standard:

Acute inhalation - rat[1]
90-day feeding - non rodent
90-day inhalation - rat[1]
chronic feeding - dog
teratagenicity[2]
oncogenicity - rat[1], mouse[1]
gene mutation - mammalian cells in culture

The following reports on difolatan were reviewed by the Toxicology Branch (TB):

1. One-year subchronic oral toxicity study in dogs. Chevron Captafol technical. Fifty-two-week progress report. Hazleton Laboratories America Inc. March 6, 1985.

2. Final report addendum. A reevaluation of myeloproliferative disease. Chevron Env. Health Ctr. SOCAL-1330. Feb. 22, 1985 (Addendum to lifetime oncogenic feeding study of difolatan technical (SX-945) in CD-1 (ICR derived) mice.

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[1]Data currently under review in TB
[2]Need additional hamster historical data (as discussed in the meeting of 6/20/85 with Chevron) in order to consider upgrading

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3. Microbial/mammalian microsome mutagenicity plate incorporation assay: Comparison of captan technical (SX-1086), Chevron folpet technical (SX-1388), and Chevron captafol technical (SX-945). Chevron Env. Health Ctr. SOCAL 2042. Dec. 18, 1984. S-2229.
4. Metabolism studies of [^{14}C-TES] captafol in rats and mice following oral dosing. Chevron Chemical company and Chevron Env. Health Ctr. SOCAL 1879, Sept. 1 1983.

TB evaluations:

1. One-year oral - dog - progress report. The study will be evaluated when the final report is received. There are no apparent problems with this study (review attached).

2. Two year oral - mouse - addendum to final report.
Core-supplementary
All myeloproliferative disease diagnoses were changed after reevaluation of the slides, most to lymphosarcoma (murine leukemia). The control data needs to be separated into the individual studies (SOCAL 1330 - captafol, SOCAL 1331 - folpet) see below.

Chevron has reevaluated all tissues with the diagnosis of myeloproliferative disease (MPD) in order to "provide a more definitive diagnosis". These results are attached (table 1A). TB has no problem with these changes in diagnosis (mostly to lymphosarcoma). Lymphosarcoma, as used by the registrant refers to mouse lymphoma or murine leukemia. TB is aware that this neoplastic entity is directly related to a virus[1]. This complicates the risk concerns since it is impossible to conclude whether the compound may be a promoter or initiator[1] with regards to this tumor.

Tumor incidence in the high dose group is significantly greater than controls at $p < 0.01$. Although historical data for this tumor shows wide variability in spontaneous rates, the significant increase of the high dose group over the low and mid groups (at least 3-fold in males and 2-fold in females) suggests a treatment related effect in the high dose animals. Although mortality is elevated in the high dose group it is impossible to say whether this is due to tumor formation or non-tumor related toxicity. For the above reasons TB feels that mouse lymphosarcoma as reported in this study should be considered when evaluating the oncogenic risk due to captafol.

Statistical analysis of the new data can not be completed until Chevron separates the incidences for lymphosarcoma by study (the control group, as presented, is a combination of studies SOCAL 1331 -folpet and SOCAL 1330 -captafol). This is needed in order to determine whether the two groups can be combined in the statistical analysis. The report containing separate summaries, by study (submitted in a separate action), can not be used for this lesion

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[1] "Tumors of the mouse hematopoietic system, their diagnosis and interpretation in safety evaluation tests", report of a study group, April, 1980.

for the following reasons: 1) lesions were presented by organ, not by ' sion/animal (: mphosarcoma can occur in multiple organs but should only be counted once). 2. the presentation of separate control data did not include the new d ;nu es.

The new table should contain all the information that is presented in table 1A (attached) of the addendum to the mouse onco study, as well as the following additional values for male and female controls: 1) original incidence by study, of MPD, lymphosarcoma and other tumors; 2. incidence after reclassification of MPD animals, by study, of lymphosarcoma and other tumors. This new table should be submitted as soon as possible to facilitate the analysis of this lesion and possible upgrading of the study from core-supplementary to core-minimum.

3. Mutagenicity study - acceptable.
Thiol containing compounds (cysteine and glutathion) can inhibit mutagenicity of captafol, captan and folpet in S. typhimurium. Review is attached.

Questions and comments:

- In figure 2A, which values were used when multiple values were present in the tail (10 ug/plate for ratio 1 and 5)?
- In figure 2A there appear to be errors in the positioning of solid circles for molar ratio 1 and up.

4. Metabolism study - unacceptable.

Comments and questions: This study will be reviewed in toto when the methods have been received for the supplementary examining the metabolism of [^{14}C(1-ES)]Captan.

Table 1A

Sex	Group	No.	Original Incidence			Incidence After Reclassificati of MPD Animals	
			MPD(a)	Lymphosarcoma(b)	Other Tumors(c)	Lympho-sarcoma	Other Tumors(c)
Male	Control	104	0	1	0	1	0
	300 ppm	80	1	3	0	3	0
	1000 ppm	80	2	3	0	4	1
	3000 ppm	80	9**(d)	7*(d)	0	12**(f)	2(g)
Female	Control	104	7	4	1	9	3
	300 ppm	80	1	7	0	8	0
	1000 ppm	80	4(e)	7(e)	0	10	0
	3000 ppm	80	6	16**	0	21**	1

a) Myeloproliferative disease, from revised main text, Volume I, p 48, Table 7.
b) Lymphosarcoma was frequently present in more than one tissue when it occu
The incidence of the condition was, therefore, determined by identifying al
animals in which the lesion occurred in any tissue; the animal was then co
only once, in spite of multiple tissue involvement. From main text, Volu
p 41, Table 5.
c) Animals with other lymphoreticular neoplasms.
d) Includes two 3000 ppm males (No. 478 and No. 479) which are included under
MPD and lymphosarcoma. Therefore, a total of 14 animals had either MP
lymphosarcoma.
e) Includes one 1000 ppm female (No. 379) which is included under both MPD
lymphosarcoma. Therefore, a total of 10 animals had either MPD or lymphosarco
f) Includes two males (No. 449 and No. 450) which had inconclusive "lymphosarcoma
g) Includes Animal No. 449 which had a granulocytic sarcoma and "lymphosarcon
This animal was also tallied under lymphosarcoma (footnote (f)).
h) One MPD animal in this group was reclassified as having granulocytic hyperplas

** Significantly greater than controls using the Fisher's Exact Test ($p \leq 0.0$
$p \leq 0.01$(**)).

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