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

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MAY 7 1987

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Captafol

FROM: Esther Rinde, Ph.D. E. Rinde 5/7/87
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769c)

TO: Addressees

The Toxicology Branch Peer Review Committee met on Feb. 4, 1987 to discuss and evaluate the weight-of-the-evidence on Captafol. At that meeting the Committee agreed to assign a tentative classification of B for captafol, pending completion of the review of two worker epidemiology studies.

This review has now been completed and Mr. Jerome Blondell of the HED Exposure Assessment Branch concluded that "... no excess risk was demonstrated" in one study, and that the second study "...was poorly done and no conclusions can be drawn based on the analysis" (the complete review is attached).

Therefore, based on these findings, captafol should be classified as B2 "probable human carcinogen" (refer to footnotes on pg. 15 of the Peer Review Document 4/10/87).

PLEASE REVIEW THE ATTACHMENTS AND PROVIDE ANY COMMENTS TO ME NO LATER THAN MAY 15, 1987. IF A REPLY IS NOT RECEIVED BY THAT TIME, I WILL PRESUME THAT YOU CONCUR WITH THE ABOVE CONCLUSIONS AND HAVE NO FURTHER COMMENTS.

Attachment

ADDRESSEES:

Theodore M. Farber
William L. Burnam
Anne Barton
Stephen Johnson
Reto Engler
Richard Hill
Diane Beal
Louis Kasza
Richard Levy
Robert Beliles
John A. Quest
Judith Hauswirth
Esther Rinde
Marion P. Copley
Bernice Fisher
Steven Saunders
Irving Mauer

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

APR 24 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Addendum to the weight-of-the-evidence and oncogenic properties of captafol.

Tox. Chem. No. 828

TO: The Peer Review Committee for Captafol
Toxicology Branch
Hazard Evaluation Division (TS-769C)

FROM: Marion P. Copley, D.V.M., D.A.B.T. Marion P. Copley 4/24/87
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Judith W. Hauswirth, Ph.D., Acting Section Head
Section VI, Toxicology Branch Judith W. Hauswirth 4/24/87
Hazard Evaluation Division (TS-769C)

The attached data were requested by the Peer Review Committee and should be considered addenda to the data evaluation report (DER) for the Peer Review of Captafol. Include are:

1. Summary
2. Epidemiology reviews by Jerome Blondell (EAB)
3. A reevaluation of the qualitative risk assessment
4. Additional historical control (mouse and rat) data
5. FYI - Minutes of meeting with Chevron (2/19/87)

COPLEY, PC1\CAPTAFOL\PR1.160, Proj.7-0100C,4/23/87

ADDENDUM TO THE TOXICOLOGY SUMMARY FOR

THE PEER REVIEW OF CAPTAFOL

Table of Contents

1. SUMMARY

The Toxicology Branch (TB) Peer Review Committee met on Feb. 4, 1987 and discussed the weight-of-the-evidence on Captafol. It was determined at that time that additional information was needed to complete the determination of the oncogenic classification of captafol and quantitative risk assessment for captafol. Exposure Assessment Branch, HED reviews of the two epidemiology studies indicate that "no excess risk was demonstrated". The TB statistical section's reevaluation of the qualitative risk assessment confirmed that lymphosarcomas in female mice are the most sensitive tumor type to increasing doses of Captafol. Therefore, the potency estimate of Captafol remains at .051 $(mg/kg/day)^{-1}$ in human equivalents (see memorandum from B. Fisher to Lois Rossi, dated 3/27/87). The additional historical data submitted by the company supported the previous conclusions.

2. ONCOGENIC CLASSIFICATION

The committee stated that due to the evidence already presented, the oncogenic classification of captafol should be at least a B. However, it could not determine whether the classification should actually be a B_1, B_2 or A, until two worker epidemiology studies were reviewed. The attached epidemiology reviews (Section 2.) by Jerome Blondell, resolve this concern. It was concluded for the first study (Cause-Specific Mortality Among Employees of the Chevron Chemical Company Facility at Richmond) that there was no significant excess mortality in the group of workers exposed to captafol. However, the review states that the study's power to detect a significant excess was limited due to the small numbers of deaths. The review of the second study (A Health Survey of Difolatan Plant Employees) states that the study did not adequately address whether the employee's health problems "were due to conditions at the plant where captafol was manufactured".

3. REEVALUATION OF QUALITATIVE RISK ASSESSMENT AND ESTIMATE OF POTENCY (Q_1*)

The Peer Review Panel requested time-adjusted analyses of tumor data for lymphosarcomas and hemangiosarcomas (males and females) and Harderian adenomas (male) CD-1 mice to determine which was the most sensitive to increasing doses of Captafol. A reevaluation by the TB statistical section of these tumor types, confirmed that lymphosarcomas in female mice are the most sensitive tumor type to increasing doses of Captafol. Therefore, the statistical section has concluded (see Section 3. for memorandum from B. Fisher to Lois Rossi, dated 3/27/87^{+}) that the potency estimate (Q_1*) of Captafol remains at .051 $(mg/kg/day)^{-1}$ in human equivalents as originally stated in the Risk Assessment memorandum from B. Fisher, dated August 1, 1986.

4. HISTORICAL CONTROL DATA

The company has submitted historical control data from the appropriate testing laboratories for the CD-1 mouse. The lesions included lymphosarcoma, Harderian gland (hyperplasia and adenomas) and hemangiosarcomas. Also included are photocopies of pages from the Hazleton summary of control data for the Sprague-Dawley rat (renal tumors, hepatocellular carcinomas and neoplastic nodules and mammary tumors). This historical control data does not alter the conclusions presented to the Panel at the February 4, 1984 discussion.

+ This memorandum had incorrectly listed the Q_1^* as 5.1×10^{-1} $(mg/kg/day)^{-1}$ instead of 5.1×10^{-2} $(mg/kg/day)^{-1}$.

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Captafol Epidemiology Reviews

FROM: Jerome Blondell
Health Statistician
Exposure Assessment Branch (TS-769C)

TO: Spencer Duffy
Registration Division (TS-767C)

I have reviewed the Chevron (referals one and two) epidemiology studies of captafol, as requested. I conclude from the first study that it was competently done but that no excess risk was demonstrated. Though one of the two kidney cancer cases raises suspicion, it has no statistical significance.

The second study was poorly done and no conclusions can be drawn based on the analysis. To characterize reports of persistant cough, wheezing, shortness of breath and coughing up blood as subjective complaints, as was done in the conclusion for this study, is improper. I understand from talking to Keith Maddy (California Department of Food and Agriculture) that Calif. OSHA has investigated this plant and changed the TLV (threshold limit value) to better protect the workers.

Cause-Specific Mortality Among Employees of The Chevron Chemical Company Facility at Richmond

Study Reviewed by Jerome Blondell

Synopsis

This mortality study was based on 1,535 employees that worked at a Chevron plant for one year or more between 1958 and 1980. Vital status was determined on 94% of these employees as of December 1980. 88 workers were deceased and death certificates were compared to expected mortality rates in the U.S. population standardized for age, sex, and race. Overall mortality was 16% lower than expected. No significant excess in mortality was found for the diseases studied. There was one possibly related kidney cancer case but the numbers were far too small for statistical significance.

Comment

This study uses appropriate techniques for analyzing the mortality experience in a population of workers. The study does not address exposure to captafol in any detail; no measurements of exposure are given. The study does not address exposure to other chemicals the workers were using.

I agree with the author's conclusion that no significant excess mortality was demonstrated in this group of workers. However, given the small numbers of deaths, this study's power to detect any significant excess was very limited.

A Health Survey of Difolatan Plant Employees

Study Reviewed by Jerome Blondell

Synopsis

A study of respiratory problems was conducted at the Chevron Richmond plant where captafol has been manufactured since 1967. The study was initiated due to reports from some workers who complained of congestion, eye irritation, and shortness of breath. At the time of the study, the plant manufactured 12 to 16 million pounds of captafol and employed 73 male workers. Of the 73 employees, 49 agreed to participate in the study; a response rate of 67%. The control group consisted of 209 employees at a Chevron refinery plant. All participants filled out a self-administered questionnaire, had a physical exam, pulmonary function tests, blood tests and x-rays. Workers at the captafol plant were subdivided into more or less exposure based on a job evaluation by an industrial hygienist in consultation with the safety engineer.

Group comparisons were done between the subjects and controls and, among the subjects, between those in the "more" or "less" exposure groups. On average controls were 7 years older than subjects and had worked nine years longer. The subjects contained 12% more blacks than the controls. Similar comparisons were made to test for smoking differences, but no statistically significant differences were found.

The analysis for health effects was stratified on age, race, and smoking resulting in 30 different subgroups. Dichotomous outcomes on the questionnaire were evaluated with the Mantel-Haensel chi-square test which provides a summary odds ratio adjusting for age, race and smoking effects. Significant findings were found between subjects and controls for congestion, wheezing, cough, shortness of breath, and coughing blood, but not between "more" and "less" exposed. However, when the results for the three groups were compared using a trend test the result was highly significant for the congestion and wheezing. The "more" exposed group had a sixfold increase and in risk when compared to controls by the trend test and a fourfold increase in risk when compared by the Mantel-Haensel chi-square. The physical exam, pulmonary function tests and x-rays did not reveal any statistically significant differences among the different groups. The blood tests revealed slight differences in SGPT, creatinine, hemoglobin and mean cell volume between subjects and controls but not between the "more" and "less" exposed groups.

Comment

Lack of appropriate design, inappropriate controls, low response rate and small numbers all conspire to prevent any meaningful conclusions being drawn from this study. Either a retrospective case-control approach or a prospective approach with documented exposure would have been preferable to the one employed. One can not be sure to what extent the subjects had been exposed or for how long.

The use of refinery workers as controls is highly suspect. It seems likely that refinery workers may have considerable opportunity for exposure to fumes or gases that put them at increased risk for respiratory illness. Even worse, the refinery workers were significantly older and had worked longer than the subjects. Matching, at least on age and sex, would have been preferable to the stratified analysis.

If workers first expressed concerns about repiratory illness, why was the response rate only 67 percent? Efforts to encourage worker participation are not described. It appears that the physicians responsible for this study made little effort to keep nonresponse to a minimum.

Because of the inadequate design 30 strata or subgroups were used in the final analysis. As a result, the number of workers in a particular subgroup was often very small (2-5 workers) and the power of this study to detect any significant differences particularly between the "more" and "less" exposed groups was greatly weakened. This lack of statistical power was not properly discussed.

There is no question that captafol workers participating in this study exhibit poor health: 35% of them report congestion at work; 18% report persistant cough; 24% have shortness of breath; and 10% report coughing blood when examined and 14% did so in the past. (Whether this is 14% in addition to the 10% or 14% overlapping the 10% is not explained). The present study does not adequately address whether these health problems were due to the conditions at the plant where captafol was manufactured.

that female mice are the most sensitive to increasing doses of Captafol in terms of their increasing lymphosarcoma tumors, i.e. the potency estimate of Captafol remains the same(5.1×10^{-2} in human equivalents$(mg/kg/day)^{-1}$).

Since it was determined by the Peer Review Committee that the MTD was exceeded in the study, time-adjusted pairwise comparisons of controls with low and mid dose groups in both sexes (for both lymphosarcomas and hemagiosarcomas) were also evaluated. The results did not produce any significant differences and thus the previous comparisons of controls with the highest dosed groups contained the only pairwise significant differences in both sexes for both tumor types.

Evaluations

The Peer Review Committee, on February 12, 1987 requested a review of the qualitative risk assessment based upon the lifetime oncogenic feeding study of Captafol Technical in mice. Chevron Chemical Company's submission consisted of data on the CD-1 strain of mice, both sexes, in groups of 80/sex/group (52/sex for controls) that were fed 0, 300, 1000, 3000 ppm of Captafol for 110 to 111 weeks.

The analysis of survival patterns by increasing dose levels for both sexes indicated statistically significant

($p < .01$) increases in mortality with these incremental doses. The evaluation was based upon the application of the D.G. Thomas, H. Breslow and J.J. Gart "Trend and Homogeneity Analysis of Proportions and Life Table Data" computer program. See Table 1 for the details.

Table 1. Captafol - Mouse Study, Mortality Rates+ and Cox or Generalized K/W Test Results

A. Males

Dose (ppm)	Weeks 0-52	53-78	79-104	105-110	Total
0	5/52	2/47	15/45	5/30	27/52 (52)**
300	6/80	14/74	34/60	3/26	57/80 (71)*
1000	0/80	10/80	44/70	9/26	63/80 (79)**
3000	22/80	55/58	3/3	-	80/80 (100)**

B. Females

Dose (ppm)	Weeks 0-52	53-78	79-104	105-111	Total
0	1/52	6/51	13/45	1/32	21/52 (40)**
300	1/79	7/78	22/71	5/49	35/79 (44)
1000	4/80	25/76	48/51	2/3	79/80 (99)**
3000	54/80	26/26	-	-	80/80 (100)**

+ Number of Animals Died/Number of live animals
() Percent

Note - The above group of selected time interval data were not individually evaluated.

Significance of Trend Analysis denoted at control
Significance of pairwise comparison with control denoted at dose level
* $p < .05$
** $p < .01$

In view of the two conditions: (1)significant increases in mortality with incremental dose levels of Captafol and (2)the significant increases in fatal (as determined by Dr.Kasza, Staff Pathologist) tumors such as lyphosarcomas and hemanigiosarcomas, the statistical evaluation of their trends as well as the pairwise comparisons (control versus a dose level) was based upon the application of the above mentioned Thomas, Breslow and Gart program. See Tables 2. and 3. for details.

Table 2. Captafol - Mouse Study, Lymphosarcoma Rates+ and Cox or Generalized K/W Test Results

A. Males

Dose (ppm)	Weeks 0-52	53-78	79-104	105-110	Total
0	0/5	0/2	0/15	0/5	0/52 (0)**
300	0/6	1/14	3/34	0/3	4/80 (5)
1000	0/0	0/10	4/44	0/9	4/80 (5)
3000	10/22	2/55	0/3	-	12/80 (15)**

B. Females

Dose (ppm)	Weeks 0-52	53-78	79-104	105-111	Total
0	0/1	1/6	4/13	1/1	6/52 (12)**
300	0/1	2/7	5/22	1/5	8/79 (10)
1000	3/4	5/25	1/48	1/2	10/80 (13)
3000	21/54	0/26	-	-	21/80 (26**

+ Number of Tumor Bearing Animals/Number of Animals Examined
( ) Percent

Note: The above group of selected time interval data were not individually evaluated.

Significance of Trend Analysis denoted at control
Significance of pairwise comparison with control denoted at dose level
* $p < .05$
** $p < .01$

Table 3. Captafol - Mouse Study, Hemangiosarcoma Rates+ and Cox or Generalized K/W Test Results

A. Males

Dose (ppm)	Weeks 0-52	53-78	79-104	105-110	Total
0	0/5	0/2	1/15	0/5	1/52 (2)**
300	0/6	0/14	0/34	0/3	0/80 (0)
1000	0/0	0/10	2/44	3/9	5/80 (6)
3000	0/22	5/55	1/3	-	6/80 (8)**

B. Females

Dose (ppm)	Weeks 0-52	53-78	79-104	105-111	Total
0	0/1	0/6	0/13	0/1	0/52 (0)**
300	0/1	0/7	1/22	0/5	1/79 (1)
1000	0/4	1/25	2/48	0/2	3/80 (4)
3000	4/54	2/26	-	-	6/80 (8)**

+ Number of Tumor Bearing Animals/Number of Animals Examined
( ) Percent

Note - The above group of selected time interval data were not individually evaluated.

Significance of Trend Analysis denoted at control
Significance of pairwise comparison with control denoted at dose level
* $p < .05$
** $p < .01$

In addition, the Peer Review Committee recommended the statistical investigation of another increasing tumor rate, Harderian adenomas in the male mice. Since Harderian adenomas are not fatal, the method of evaluating these data was conducted by the Peto Prevalence method. See Table 4. for results.

Table 4. Captafol - Mouse Study, Male Harderian Adenoma Rates+ and Peto s Prevalence Test Results

A. All Dose Levels

Dose (ppm)	Weeks 38[a]-78	79-104	105-110	Total
0	0/7	0/15	0/30**	0/52*
300	2/18	2/34	4/26	8/78**
1000	0/10	10/44	9/26	19/80**
3000	2/71	0/30	0/0	2/74

B. Highest Dose Level Excluded

Dose (ppm)	Weeks 38[A]-78	79-104	105-110	Total
0	0/7	0/15	0/30**	0/52**
300	2/18	2/34	4/26	8/78**
1000	0/10	10/30	9/26	19/80**

+ Number of animals with tumor/number of animals examined.
[a] Appearence of the first tumor.

Note - Significance of Trend Analysis denoted at control
Significance of pairwise comparison with control denoted at dose level
* $p \leq .05$
** $p < .01$

CAPTAFOL

Page _____ is not included in this copy.

Pages 19 through 26 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

2/22/87

MEMORANDUM

SUBJECT: Captafol - Meeting with the Registrant, Chevron

TO: Addressees

Special Review Branch staff met with representatives from Chevron Chemical Company on Thursday, February 19, 1987 at Crystal Mall #2. The purpose of this meeting, which was requested by Chevron, was to discuss certain issues regarding the Special Review of captafol.

The following persons were present at the meeting:

Desmond Byrne - Chevron Chemical Company
C.D. McLaughlin - Chevron Chemical Company
Ward Richter - Chevron Chemical Company
Nancy Rachman - Chevron Chemical Company
Jan Auerbach - EPA Special Review Branch Chief
Spencer Duffy - EPA Special Review Branch

Chevron expressed concern about the research cost involved in meeting the data requirements for the Special Review of captafol in light of organization changes within the company resulting from its merger with Gulf Oil Company and the decline in demand for captafol on the world market.

Chevron indicated that sales of captafol have been dropping. Captafol's principal use is for fungus control on apples, cherries, cranberries, and citrus. Other uses include sweet corn, tomatoes, taro, and other fruits and vegetables. Most of the captafol produced in the United States is exported. Some of the major buyers are Germany, Brazil, Korea, and Taiwan. Some of these countries have withdrawn their registration, revoked tolerances, or otherwise reduced their use of captafol. Chevron indicated that it had stocks of captafol on hand, about 40% of which would be sold to foreign markets this year. The remaining 60 million pounds could be disposed of through normal domestic sales within about 2 years.

Chevron expressed a desire to voluntarily cancel its registration of captafol and requested procedural guidance from the Agency in executing this task. Chevron was informed that a written cancellation request should be sent to the Agency, which should include the reasons for wanting to voluntarily cancel the registration, a statement on the amount and a plan for handling existing stock, and a time estimate of how long it would take existing stocks of captafol to clear the market and the food chain.

Chevron was informed that if it requested a voluntary cancellation for captafol, the Agency would consider such a request and, if granted, would cooperate in the expeditious processing of the request. A fair and equitable existing stock provision is a major factor in considering a voluntary cancellation.

Chevron asked if it would be obligated to complete the research already started under the requirements of the Registration Standard and the 3(c)(2)(b) Notice. Chevron was informed that once a voluntary cancellation becomes effective the legal requirement for data generation would cease. However, there would be a period for public comment in which other concerned parties may assume the burden of generating the required data if they wished to support the registration of captafol.

Chevron agreed to submit a formal letter to SRB (with copies to FHB) expressing its decision on whether or not it wanted to voluntarily cancel the registration of captafol. Chevron agreed to submit this letter in 2 weeks. Upon receipt of this letter, the Agency will determine whether or not and under what terms and conditions the Special Review of captafol should continue.

Respectfully submitted,

Spencer L. Duffy
Review Manager

Addressees:
M. Copley
H. Day
L. Bradley
M. Pallitto
O. Butzen
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R. Farnsworth
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