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

MEMORANDUM JUL 28 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Henry M. Jacoby, Product Manager #21
Registration Division (TS-767)

THRU: Albin B. Kocialski, Acting Section Head ABK
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: EPA Reg. Nos. 239-533 and 239-1246. Response to Discussion Received from Chevron Chemical Company Regarding Comments by Registration Division to Chevron for the Purpose of Summarizing the Lifetime Oncogenic Feeding Study of Captan.

TOX Chem. No. 159

REFERENCES:

1. Letter from Registration Division to Mr. Don F. Dye, Chevron Chemical Company, March 9, 1982.

2. Lifetime Oncogenic Feeding Study of Captan Technical, SOCAL 1150. January 19, 1982. EPA Accession Nos. 244220 thru 244226.

We have reviewed the subject response from Chevron to Registration Division.

We do not find in the response any new data or arguments which would induce us to change our conclusions to the Lifetime Oncogenic study of Captan (reference No. 2).

D G Van Ormer

David G. Van Ormer, Toxicologist
Toxicology Branch
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Chevron Chemical Company
940 Hensley Street, Richmond, CA 94804

Research and Development
Agricultural Chemicals Division

May 19, 1982

ORTHOCIDE 50 Wettable (239-533)
Chevron Captan Technical (239-1246)
Lifetime Oncogenic Feeding Study:
EPA Accession Numbers 244220 through 244226

Mr. Henry M. Jacoby
Product Manager (21)
Registration Division (TS-767)
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, Virginia 22202

Dear Mr. Jacoby:

On March 9, 1982, you sent us your comments on our Lifetime Oncogenic Feeding Study of Captan Technical, SOCAL 1150 (submitted to you on January 22, 1981, and assigned EPA Accession Nos. 244220 through 244226). Below we discuss your comments on the report. The numbers correspond to the same numbers used in your March 9, 1982 letter....

1. You state, "The report does not tabulate data to permit good assessment of the effect of test material on tumor latency."

   Oncogenicity studies such as this, conducted in accordance with the proposed FIFRA testing guidelines, are not designed to assess tumor latency. In order to generate the type of data required to assess tumor latency, frequent interim sacrifices must be conducted throughout the study period. The only type of study that could credibly produce tumor latency data without interim sacrifices would be a skin painting study where the incidence of skin tumors would be readily apparent. Otherwise, oncogenicity studies reveal only the incidence of tumors occurring at death or final sacrifice. Appendix M in the final report does provide, by group, the mean week of death and the incidence of tumors in each organ/tissue .

2. You state, "The report notes several parameters which exhibit a negative dose response, (and that) the data of this study do not provide evidence that these (negative dose response) effects would impinge significantly upon a risk assessment performed on mouse duodenal carcinomas produced with positive dose response in mice by the test material."

   The reasons for disregarding negative dose-response data are neither clear nor justified. Negative as well as positive dose-response effects should definitely be considered in the risk assessment of Captan Technical. Negative correlations with dose should not be ignored simply because the "causative factors" are unknown. These "causative factors" are rarely, (if ever), known, even for positive correlations.

Scientific consideration should be given to the validity and significance of these negative observations. For example, the observed decreases in liver and lung tumors in treated males are valid and appropriate for consideration in risk assessment for the following reasons:

(a) The negative effects were dose-related and statistically highly significant ($p < 0.01$).

(b) Survival was excellent. Sufficient numbers of male mice were at risk for the development of these tumors. The decreased incidences of lung adenocarcinomas and hepatocellular adenomas in low-, mid-, and high-dose males were not artifacts created by early mortality.

(c) The effect was highly site specific. Only liver and lung tumors were decreased.

(d) The effect is reproducible. It was previously demonstrated in an NCI study (DHEW Publication No. (NIH) 77-815:1977).

One interpretation of the data is that dietary exposure to high concentrations of Captan Technical did not enhance the animal's susceptibility to tumor induction but, instead, apparently increased the incidence of a particular tumor type. It may be possible that these marked decreases in spontaneous tumor types are biologic indications that massive doses of Captan Technical produced a grossly artificial state in the animal. From a scientific point of view, both negative and positive dose-related effects should be considered.

Again, under paragraph 2 you state, "The literature contains references for the chemical induction of intestinal neoplasms in both rats and mice."

The reason for this comment is not apparent. A search of the available literature was conducted to determine the spontaneous tumor rates of various organs and tissues in several strains of mice, including CD-1 mice. Because of the increased incidence of intestinal tumors observed in SOCAL 1150, an effort was made to obtain any literature information concerning the natural incidence of intestinal neoplasms in mice. Thus, in Appendix P, complete references were cited if they contained pertinent mouse data on intestinal neoplasms, regardless of whether or not other species were also mentioned.

3. You state, "Data are not present on organ weights, blood chemistry, urinalysis, and reticulocyte counts. The latter is desirable to clarify the evidence of anemia in males."

We acknowledge that organ weights, blood chemistry, urinalysis and reticulocyte counts were not performed in SOCAL 1150. This study was specifically intended to determine the oncogenicity potential of Captan Technical and, therefore, general chronic toxicity data as mentioned were not considered in the evaluation.

A reticulocyte count is not considered necessary to clarify the hematologic data of the mid-dose males because of the following reasons:

(a) The "anemia" effect was not apparent in the high-dose males.

(b) Red blood cell (RBC), hemoglobin (HGB), and hematocrit (HCT) values for the mid-dose males have been compared statistically to our available control data for CD-1 mice, and no statistical significance ($p \leq 0.05$) was observed. Therefore, there is no apparent biological significance to the observed values for RBC, HGB, and HCT. It should be kept in mind that the sample size in SOCAL 1150 was relatively small (n = 8/group).

(c) Low values for RBC, HGB, and HCT are common findings in aged mice. These mice were 113 weeks old when they were bled, an extremely old age for CD-1 mice.

We trust that our response will serve to clarify the comments you sent us. Please let us know if we can be of further assistance.

Sincerely,

L. R. Stelzer, Manager
Registration & Regulatory Affairs

THL:rb/D2-18

MAR 9 1982

Chevron Chemical Company
Ortho Agricultural Chemicals Division
940 Hensley Street
Richmond, CA 94804

Attention: Don F. Dye

Gentlemen:

Subject: Orthocide 50 Wettable
EPA Registration No. 239-533
Chevron Captan Technical
EPA Registration No. 239-1246
Your Letter Dated January 22, 1981

The Lifetime Oncogenic Feeding Study of Captan Technical submitted with the subject letter has been reviewed by our scientific staff. The following comments were made:

1. According to the data of this study, the test material is established as an oncogen by at least two criteria: a) increased tumor incidence, and b) appearance of tumors in organs where spontaneous tumors are rare. The report does not tabulate data to permit good assessment of the effect of test material on tumor latency.

2. The report notes several parameters which exhibit a negative dose response, and other parameters for which the mid-dose is lower than would be expected by a linear relationship. Possible causative factors include competing biological effects with some organ specificity, dose-specific effects, and diet formulation variance. Without further data we are unable to comment on the possible competing bio-effects of the test material. The data of this study do not provide evidence that these effects would impinge significantly upon a risk assessment performed on mouse duodenal carcinomas produced with positive dose response in mice by the test material. The literature contains references for the chemical induction of intestinal neoplasms in both rats and mice.

3. Judgment of the overall toxicity of the test material indicates that for non-neoplastic, non-hyperplastic lesions the low dose may be accepted as a provisional no-effect level. This study partially satisfies require data for a chronic lifetime study. Data are not present on organ weights, blood chemistry, urinalysis and reticulocyte counts. The latter is desirable to clarify the evidence of anemia in males. We agree that unpalatability may have seriously decreased the usefulness of body weight as a toxicity parameter.

Sincerely,

Henry M. Jacoby
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Fungicide-Herbicide Branch
Registration Division (TS-767)

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6