Government of Canada / Gouvernement du Canada

MEMORANDUM NOTE DE SERVICE

CANCELL FILE

Dr. C.T. Miller
Coordinator
Task Force for Reassessment
of Chemical Safety

FROM / DE
Dr. C.E. Mendoza
Task Force for Reassessment
of Chemical Safety

SECURITY CLASSIFICATION / CLASSIFICATION DE SÉCURITÉ

OUR FILE - N/ RÉFÉRENCE

YOUR FILE - V/ RÉFÉRENCE

DATE
12 December, 1980

SUBJECT / OBJET
Audit and validation: Additional information submitted by Chevron Chemical Co. on May 8, 1980 regarding "Dominant lethal studies with metepa and MMS, and Captan technical, albino mice".

IBT No.: 622/623-05998*

Date: January 7, 1977

Test material: Captan technical

Common name: Captan

Synonyms: SR406, Orthocide 406

Petitioner: Chevron Chemical Co.

File under: Captan

Recommendation: Valid but requires re-interpretation

*There were 3 studies included under 622/623-05998

1) IBT 622-05998; "Pilot study with MMS and metepa in albino mice; December 26, 1974. (MMS = methylmethane sulfonate) (Phase I)

2) IBT 623-05998; "Dominant lethal study with metepa and MMS in albino mice exposed for 8 weeks to the chemicals in the diet"; August 7, 1975 (Phase II)

3) IBT 623-05998; "Dominant lethal study with captan technical in albino mice exposed for 8 weeks to the chemical in the diet"; January 7, 1979. (Phase III).

Audit and validation: Additional information submitted by Chevron Chemical Co. on May 8, 1980 regarding "Dominant lethal studies with metepa and MMS, and Captan technical, albino mice"

The initial audit and validation report (July 9, 1979) from HPB indicated that this study was invalid. The overall comments are quoted verbatim:

> "The audit and validation of this report indicate that the study cannot be validated from the available raw data. Of prime importance was the lack of histopathological raw data and the failure of any of the data to show any signatures and for only a small portion of the data to be dated. It was also disturbing to find little difference between the mutation rate of treated and control animals after the company had complained that there were differences and later had this page replaced by IBT".

The present report was based on the re-validation of IBT Study 623-05998 in the light of additional data submitted by Chevron Chemical Co. on May 8, 1980. The additional data, received by HPB on May 21, 1980, include the following items:

1. Response prepared by Dr. R.A. Zimmerman, Chevron's toxicologist, to the HPB comments on the study.

2. Appendices:

   a) Diet stability analyses by Chevron.

   b) Analyses of Phase III diets by Chevron.

   c) Original pages of the IBT report: Pages 9, 19, 20 and 22.

   d) Replacement pages: 7A, 9, 19, 20 and 22.

   e) Statistical analyses performed by Chevron.

The response prepared by Dr. R.A. Zimmerman, dated and signed April 30, 1980, to HPB validation includes the following items:

1. That there were sufficient raw data available to indicate that the study took place as reported and that the study closely followed the protocol submitted by Chevron.

2. That the diets were prepared in adequate fashion.

3. Statistical analyses performed by Chevron on the raw data available indicated that the positive control data were adequate and that captan did not exhibit a dominant lethal effect.

   That Chevron is concerned with MMS was less efficacious as a mutagen in Phase III than in Phase II.

4. That the histopathology on the testes was neither a requirement in the protocol submitted by Chevron nor is it a routine in dominant lethal studies.

Our response to Chevron's position prepared by Dr. Zimmerman, April 30, 1980 should be as follows:

1) There were sufficient raw data available to indicate that the study took place and to validate the study.

2) The study should have been considered invalid initially since there were inadequate diet preparation records in the microfiche data received on July 9, 1979. However, chemical analyses conducted by Chevr indicated that the diets were adequately prepared during the course of the study. It should be noted, however, that the diet samples were received from IBT 2 weeks after the termination of the study and they were identified by week numbers only, not dates of preparation.

3) The argument concerning the positive control prepare by Chevron (Item 3, April 30, 1980) applies to the safety-in-use evaluation not the audit and validatic Chevron was concerned that MMS was less efficacious as a mutagen in Phase III than in Phase II. Chevron conclusion that Captan did not exhibit a dominant lethal effect is subject to safety-in-use re-evaluat of the data, particularly for the 7000 ppm level.

4) Raw data indicated that histopathology was neither a requirement nor routine in dominant lethal studies. There were no aggravating circumstances to indicate that histopathology of the testes should be required to interpret the overall results.

5) It should be emphasized that in microfiche 536 the following was noted: "fresh diets offered daily - 4 days a week". The original 7 was replaced with 4 (days), which agrees with the food consumption dat (Table III, IBT final report) for 4 days per week fo

consumption. There was no information to indicate what type of diet was offered to the animals during the intervening 3 days each week for 8 weeks.

In summary, the HPB validation report (July 9, 1979) indicated lack of the raw data in histopathology and the absence of dates and signatures in some of the raw data available. HPB was also concerned that little difference was shown between the mutation rates "after the company ahd complained that there were differences". Re-review of the data in question indicate that there were no significant changes made on the original final report (January 7, 1979) except for correction of the typographic error from 3000 to 7000 ppm. Biostatistical treatments were added later by Chevron. Discrepant data found later during audit and validation (see April 30, 1980) were inconsequential to the overall results.

GENERAL COMMENTS

The study should have been considered invalid during the initial validation of this report on the premise that insufficient raw data on diet preparations were available. However, Chevron subsequently submitted chemical analyses of the diets prepared by IBT during the course of the study which indicated that the diets were adequately prepared. In addition, the data in the final report are substantiated by the laboratory data except for those on diet presentation.

It should be emphasized that a question should be raised as to whether the animals were fed the test diet daily for 8 weeks without interruption, or not. It is noted in microfiche 536 the following "fresh diets offered daily - 4 days a week". The final report, likewise, stated 4 days a week food consumption for 8 weeks (Table III). It is, therefore, uncertain that the animals were fed the test diets during the intervening 3 days each week for 8 weeks.

Chevron's conclusion that Captan did not exhibit a dominant lethal effect is open to question, particularly for the 7000 ppm level. The exclusion of a datum for one female to obtain a statistically not significant result can be questioned. In addition, if the dosing regime was 4 days per week for 8 weeks, the study should be considered toxicologically inadequate to clearly demonstrate the lack of a dominant lethal effect of Captan in the species used.

4/

Thus, although this study may be considered valid in that the raw data largely substantiate the final report, the interpretation of the results should be reconsidered.

C.E. Mendoza

E.P. Arnold

C.T. Miller

5

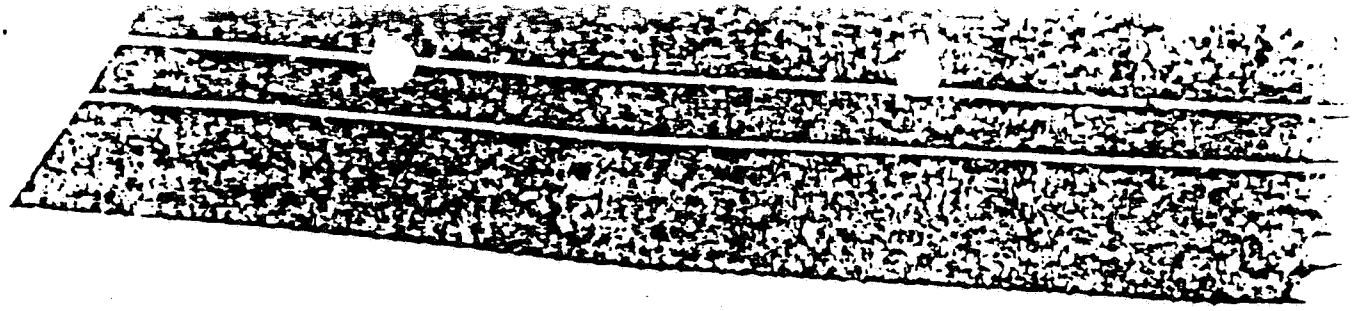
OVERALL COMMENTS:

The study should have been considered invalid during the initial validation of this report on the premise that insufficient raw data on diet preparations were available. However, Chevron subsequently submitted chemical analyses of the diets prepared by IBT during the course of the study which indicated that the diets were adequately prepared. In addition, the data in the final report are substantiated by the laboratory data except for those on diet presentation, as indicated below.

It should be emphasized that a question should be raised on whether the animals were fed the test diet daily for 8 weeks without interruption, or not. It is noted in microfiche 536 the following; "fresh diets offered daily - 4 days a week". The final report, likewise, stated 4 days a week food consumption for 8 weeks (Table III). It is, therefore, uncertain that the animals were fed the test diets the intervening 3 days each week for 8 weeks.

Chevron's conclusion that Captan did not exhibit a dominant lethal effect is open to question, particularly for the 7000 ppm level. The exclusion of a datum for one female to obtain a statistically not significant result can be questioned. In addition, if the dosing regime was 4 days per week for 8 weeks, the study should be considered toxicologically inadequate to clearly demonstrate the lack of a dominant lethal effect of Captan in the species used.

Thus, although this study may be considered valid in that the raw data largely substantiate the final report, the interpretation of the results should be reconsidered.



033-65948

Chevron

D/L = Caption

530

Mice arrive - 1/13 - make & check facility
(100 ♂'s & 200 ♀'s)

♂'s placed on diets 1/20 -
♂'s housed individually
Body weights recorded weekly for 8 weeks

Food consumption on 50 ♂'s/level weekly

Diets prepared fresh weekly — refrigerated
Fresh diets offered daily - 5 days a week.

Mating initiated 3/22 - 3 ♀'s / ♂ / week
females segregated by male

Sacrifice of mating - 6 weeks minimum -
if mice exhibited live 8 weeks.

7