

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

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FEB 5 1985

MEMORANDUM:OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: E.P.A. ID No. 11678-1; Captan: Rat historical control data for review.

Tox. Chem. No.: 159
Accession No.: 260078TO: H. Jacoby (PM 21)
Registration Division (TS-767C)FROM: Marion P. Copley, D.V.M., D.A.B.T. *MC 1/22/86*
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C)THRU: Jane Harris, Ph.D., Section Head *JRH 1/22/86*
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C)
and
Theodore M. Farber, Ph.D., Branch Chief
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Hazard Evaluation Division (TS-769C) *df/r 1/22/86*

Makhteshim Chemical Works Ltd. has submitted (Oct. 25, 1985) historical control data from Netherlands Organization for Appl. Sci. Res. for the SPF Wistar Cpb:WU strain rat.

BACKGROUND:

Captan is currently under special review (Position document 2/3 is completed) and a registration standard is almost completed. The following data gaps still exist for captan:

- Acute dermal toxicity
- Primary dermal irritation
- 21-day dermal toxicity
- Chronic (oral) - non-rodent
- Subchronic (inhalation)
- Metabolism

Makhteshim Chemical Works Ltd. has previously submitted a captan (Merpan) lifetime (131-week) study with rats (see acc. #s 252722-5). This study was classified as core-supplementary until historical control data from the testing facility (Netherlands Organization for Appl. Sci. Res.) for the SPF Wistar Cpb:WU strain rat was evaluated. There appeared to be an increased incidence of uterine sarcomas and pancreatic islet cell tumors (males).

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CONCLUSIONS:

The incidence of islet cell tumors occurring in the Merpan lifetime rat study is within the range of historical controls. Therefore it does not appear that Merpan is associated with an increased incidence of islet cell tumors in the male rat.

It does appear however, that the increased incidence of uterine sarcomas at 2000 ppm (high dose) may be associated with the ingestion of Merpan. The historical control range for the incidence of uterine sarcomas for this laboratory is 0 to 2 % (7 of 8 studies showed no sarcomas in controls) as compared to 8 % in the high dose treatment group.

The company may wish to reread the uterine slides to confirm that sarcoma, a relatively uncommon tumor in the Wistar rat, was the correct diagnosis rather than fibromatous polyp. Until such time as additional information is received, Merpan (captan) will be considered weakly oncogenic for increasing the incidence of uterine sarcomas in the SPF Wistar Cpb:WU strain of rat.

Captan has already been classified as a type B2 oncogen (probable human oncogen), therefore the possible oncogenic potential indicated by this study would not have an impact on the risk assessment for this compound.

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Reviewed by: rion P. Copley, D.V.M., D ..B.T *WTC 1/27/86*
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DATA EVALUATION REPORT - Addendum

STUDY TYPE: Oncogenicity - Rat

TOX. CHEM. NO.: 159

ACCESSION NUMBER: 260078

(previously submitted as accession # 252722-5)
(original Tox. Br. DER is doc. # 4397)

TEST MATERIAL: Captan

SYNONYMS: Merpan

STUDY NUMBER(S): Report # B80-0153

SPONSOR: Makhteshim-Agan (America) Chemical Works Ltd.

TESTING FACILITY: Netherlands Organization for Applied Scientific
Research, Div. for Nutr. and Food Res. TNO, Zeist, Netherlands

TITLE OF ORIGINAL REPORT: Life-span oral carcinogenicity
study of Merpan in rats.

AUTHOR: H.P. Til, C.F.Kuper, H.E. Folke

TITLE OF SUBMISSION: Incidence of tumors in CPB: WU wistar
random rats. Data of control animals from long-term studies.

AUTHOR: J.P. Bruyntjes

REPORT ISSUED: Dated April 1984

Original report date: Nov. 1983

CONCLUSIONS:

Classification: Core-minimum

Weakly oncogenic for uterine sarcomas at 2000 ppm (HDT)

A. MATERIALS (original report):

1. Test Compound: Merpan tech., Description: White powder,
92.0 % a.i.
2. Test Animals: Species: rat; Strain: SPF Wistar Cpb:WU
random bred rats, Age: 4.5 weeks at start of study;
Weight (gm): 35-50; Source: TNO.

B. HISTORICAL DATA:

1. Pancreatic islet cells: adenomas (benign) and adenocarcinomas
(malignant) in males.

The mean incidence of islet cell tumors in male
rats (SPF Wistar Cpb:WU random bred rats) for 8 studies
(at TNO lab.) was 4 % with a range of 0 to 14 % (see
table).

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Table: Incidence (%) of islet cell tumor (benign unless otherwise stated) bearing males in 8 studies.

| | | | | | | | | |
|-------------------|----|----|----|----|----|----|------|-------|
| Duration (months) | 27 | 30 | 30 | 24 | 28 | 30 | 29 | 30 |
| Incidence (%) | 0 | 0 | 2* | 2 | 4 | 4 | 10** | 14*** |

*control for the Merpan (captan) study in question.

** 4% were malignant

*** 2% "

The number of islet cell tumor bearing males in the rat oncogenicity study using Merpan was:

Table: Pancreas (males)

| | dose (ppm)0 | 125 | 500 | 2000 |
|---------------------------|-------------|-----|-----|------|
| no. examined | 50 | * | * | 50 |
| islet cell adenoma | 1 | 2 | 0 | 4 |
| islet cell adenocarcinoma | 0 | 0 | 0 | 1 |
| adenoma + adenocarcinoma | 1 | 2 | 0 | 5 |

* only visible lesions were examined

The high dose male rats had a combined incidence of pancreatic adenoma and adenocarcinoma of 5 out of 50 (10 %). Although this is statistically increased over control values, the combined incidence is within the range of historical controls. There was also no evidence of progression toward malignancy from adenoma to adenocarcinoma. It does not appear that Merpan is associated with an increased incidence of islet cell tumors in the male rat.

2. Uterus: Fibromatous polyps and fibrosarcomas

The mean historical control incidence (%) of fibromatous polyps is 20 % with a range of 11 to 30 % (see table). There was only 1 (.2 %) sarcoma in the 8 studies, a total of 422 rats, and a range of 0 to 2 %.

Table: Incidence (%) of uterine fibromatous tumor bearing females in the controls of 8 studies.

| | | | | | | | | |
|-------------------|----|----|-----------------|-----------------|-----------------|-----------------|-----------------|----|
| Duration (months) | 24 | 27 | 28 | 29 | 30 ¹ | 30 | 30 | 30 |
| Fibromatous polyp | 11 | 21 | 14 ² | 30 ³ | 17 ³ | 18 ³ | 26 ³ | 26 |
| Fibrosarcoma | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |

¹ control for the Merpan (captan) study in question.

² 6 % of the rats had multiple polyps.

³ 1-2 % of the rats had multiple polyps.

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The tumor incidence in the rat oncogenicity study using Merpan was:

Table: Uterus

| | dose (ppm) | 0 | 125 | 500 | 2000 |
|-------------------|------------|----|-----|-----|------|
| no. examined | | 48 | 49 | 50 | 50 |
| fibromatous polyp | | 8 | 12 | 13 | 12 |
| sarcoma | | 0 | 0 | 0 | 4 |

It appears that the ingestion of 2000 ppm of Merpan is associated with a small increased incidence of uterine sarcomas. The historical control range for the incidence of sarcomas in this laboratory is 0 to 2 % as compared to 8 % in the high dose treatment group.

comments:

The company may wish to reread the uterine slides to confirm that sarcoma was the correct diagnosis. Until such time as additional information is received, Merpan (captan) will be considered a weak oncogen for uterine sarcomas in this strain of rat.

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