CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

007067

WASHINGTON, DC 20460

MAR 13 1989

MEMORANDUM

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Maneb - Response to Data Call-In; 21-Day Dermal Study in Rabbits and Supplemental Data on Dermal Absorption Study

TO: Susan Lewis
Product Manager (21)
Registration Division (TS-767C)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor C 3/8/89
Toxicology Branch II, Section II
Health Effects Division (TS-769C)

THRU: K. Clark Swentzel K. Clark Swentzel 3/8/89
Acting Section II Head, Toxicology Branch II
Health Effects Division (TS-769C)

and

Marcia van Gemert, Ph.D. Marcia van Gemert 3/13/89
Acting Chief, Toxicology Branch/HFAS/HED (TS-769C)

Registrant: Penwalt Corporation
Chemical: Manganese ethylene-1,2-bisdithiocarbamate
Project: 9-0479
Caswell No.: 539
Record No.: 235857
Identifying No.: 4581-35S
MRID No.: 408761-00, 408847-00
Action Requested: Review data.

Comment: In response to the Maneb Comprehensive Data Call-In (4/1/87), the Maneb Registration Group (Penwalt Corporation) has submitted a 21-day dermal study in rabbits. Additionally, a supplement to the final report entitled "Dermal Absorption of Radiolabeled Maneb in Male Rats" was submitted in response to the request for additional data concerning $^{14}C$ activity in the carcasses.

1. The DER of the 21-day dermal study is attached. There was some evidence that the thyroid was a target (slightly increased thyroid weights and follicular cell hypertrophy in the high-dose animals) following dermal exposure to technical Maneb at levels of 100, 300, and 1000 mg/kg/day. Slight dermal irritation at the site of application was observed at all dose levels. The systemic NOEL can be set at 100 mg/kg and the LEL at 300 mg/kg, based on histological changes in the thyroid.

2. With regard to the supplemental data on the dermal absorption study, the previous reviewer (not this reviewer, LLT) requested information on the amount of radioactivity remaining in the carcasses in order to obtain a more precise measurement of the amount of Maneb absorbed after dermal application.

The data provided indicate that less than 1% of the dose remained in the carcasses. Additionally, it is noted that 92-105% of the dose was accounted for in the original final report.

What can be cleaned from this study is that, over a short time period, approximately 1% of the applied dermal dose of Maneb is absorbed, and there is evidence of accumulation, i.e., the amount adsorbed/absorbed appeared to increase slightly with time. There is the potential for a greater amount of Maneb to be absorbed following longer periods of exposure.

It can be concluded that Maneb is absorbed through the skin following dermal exposure, and there is the potential for accumulation.

007067

Reviewed by: Linda L. Taylor, Ph.D. Linda Lee Taylor 3/8/89
Section II, Tox. Branch II (TS-769C)
Secondary reviewer: K. Clark Swentzel K. Clark Swentzel 3/8/89
Acting Head Section II, Tox. Branch II (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: 21-Day Dermal Toxicity - Rabbits TOX. CHEM. NO.: 539

MRID NO.: 408761-01

TEST MATERIAL: Maneb Technical

SYNONYMS: manganese ethylene-1,2-bisdithiocarbamate

STUDY NUMBER: HLA 153-139

SPONSOR: Pennwalt Corporation

TESTING FACILITY: Hazleton Laboratories America, Inc.

TITLE OF REPORT: 21-Day Dermal Toxicity Study in Rabbits With Maneb Technical

AUTHORS: Janet A Trutter, M.S., D.A.B.T.

REPORT ISSUED: September 27, 1988

CONCLUSIONS: Three groups of 5 rabbits/sex were treated via dermal application with Maneb technical (100, 300, and 1000 mg/kg/day) once daily (5 days a week) for 15 days and compared to sham treated controls (5 rabbits/sex).

No deaths occurred and clinical findings, body weight changes, food consumption, hematology, serum chemistry, and organ weights were comparable among the groups; i.e., no statistical significance was attained. However, there was some evidence that the thyroid is a target (slightly increased thyroid weights and follicular cell hypertrophy in the high-dose animals) following dermal exposure. Feeding studies have identified the thyroid as a target organ for Maneb.

The systemic toxicity NOEL for Maneb technical via repeated dermal exposure can be set at 100 mg/kg, and a conservative LEL at 300 mg/kg, based on histological changes in the thyroid. Slight dermal irritation at the site of application was observed at all dose levels.

Classification: core minimum.

QUALITY ASSURANCE: A quality assurance statement was provided.

A. MATERIALS:

1. Test compound: manganese ethylene-1,2-bisdithiocarbamate; Description: a yellow powder; Batch No. 8607-584/25; Purity: 86%; Composition and stability: on file with sponsor.

2. Test animal: Species: Rabbit; Strain: Hra:(NZW)SPF; Age: not specified; Weight: 2064-2429 g (males), 2140-2444 g (females); Source: Hazleton Research Products, Inc. Denver, PA.

B. STUDY DESIGN:

Methodology

Rabbits were assigned (using computerized weight randomization program) to the following test groups.

| Test Group | Test Material (mg/kg/day) | Males | Females |
|---|---|---|---|
| 1 | 0 (sham treated) | 5 | 5 |
| 2 | 100 | 5 | 5 |
| 3 | 300 | 5 | 5 |
| 4 | 1000 | 5 | 5 |

The hair from the back of each animal was clipped from shoulder to rump (10% of total body surface area), approximately 24 hours before study initiation and thereafter as necessary during the study, before application of the test material. The neat test material (powder) was dermally applied uniformly to the exposure site using gauze moistened sufficiently with distilled water to ensure good contact with the skin. The control and high-dose received 4 ml, the low dose 2 ml and the mid dose 3 ml. The test material was held in contact with the skin for approximately 6 hours each day with gauze dressing secured to an overlying porous bandage with staples. The porous bandage was secured with non-irritating tape. The controls were treated in a similar manner but did not receive the powder. Following the 6-hour exposure period, the occlusion was removed and the test site was wiped with gauze to remove any remaining test material. The treatment was once daily, 5 days a week, for 15 days.

Observations

All rabbits were examined twice daily for mortality and moribundity, and once a day (apparently after exposure) for toxic effects. Prior to each application and on the day of terminal sacrifice, the skin of each animal was graded according to the Draize system. During exposure, the animals were observed approximately once every hour for signs of discomfort or distress. Detailed clinical observations were made on treatment days 1, 6, and 11 and at termination (day 22 or 23).

Body weights were recorded on treatment days 1, 6, 11, 15, and on the day of terminal sacrifice. Food consumption was recorded daily. Purina Certified High Fiber Rabbit Chow® #5325 was provided in a daily ration of approximately

120 grams; water ad libitum.

Clinical Pathology

Blood was collected from each animal at necropsy (during week 4) for hematology and clinical analyses. The CHECKED (X) parameters were examined.

a. Hematology

| | | | |
|---|---|---|---|
| X | Hematocrit (HCT) | X | Leukocyte differential count |
| X | Hemoglobin (HGB) | | Mean corpuscular HGB (MCH) |
| X | Leukocyte count (WBC) | | Mean corpuscular HGB conc.(MCHC) |
| X | Erythrocyte count (RBC) | | Mean corpuscular volume (MCV) |
| X | Platelet count | | Nucleated red blood cell count |
| | | X | Cellular morphology |

b. Clinical Chemistry

| | Electrolytes: | | Other: |
|---|---|---|---|
| X | Calcium | X | Albumin |
| X | Chloride | X | Blood creatinine |
| | Magnesium | X | Blood urea nitrogen |
| X | Phosphorous | | Cholesterol |
| X | Potassium | X | Globulins |
| X | Sodium | X | Glucose |
| | Enzymes | X | Total Bilirubin |
| | Alkaline phosphatase | X | Total Serum Protein |
| | Cholinesterase | | Triglycerides |
| | Creatinine phosphokinase | | Serum protein electrophoresis |
| | Lactic acid dehydrogenase | | |
| X | Serum alanine aminotransferase (also SGPT) | | |
| X | Serum aspartate aminotransferase (also SGOT) | | |
| | Gamma glutamyl transferase | | |
| | glutamate dehydrogenase | | |

Gross Pathology

All animals were sacrificed (after overnight food fast) within 3 to 4 days of the last dose and were subjected to gross pathological examination, which included an examination of the following.

external surface
all orifices
cranial cavity
carcass
external and cut surfaces of brain and spinal cord
nasal cavity and paranasal sinuses
thoracic, abdominal and pelvic cavities and their viscera
cervical tissues and organs

The liver, kidneys, testes (with epididymides), and thyroid/parathyroid were weighed at necropsy.

Histopathology

The following organs and tissues were preserved* from all animals, and the control and high-dose animals were examined microscopically.

treated and untreated skin
liver
kidneys
thyroid/parathyroids
testes with epididymides

Based on the findings in the high-dose group, the treated skin and thyroid from the low- and mid-dose animals were also examined.

(*testes with epididymides were not examined histologically; neither gross lesions nor organ weight findings indicated a need for such examination, according to the author)

Statistics

Data were analyzed as diagrammed in Figure 1, attached.

c. RESULTS

Survival

No deaths occurred during the study.

Clinical Signs and Derral Irritation

All animals appeared normal throughout the study, with the exception of one high-dose male. This animal was examined by a veterinarian because it appeared thin and was anorexic on Day 8. By Day 11, it appeared to be recovering. A second animal (control male) was also examined because of a weight loss during the weight interval preceeding Day 18. No disease was noted.

No erythema or edema was observed in any of the control or low-dose animals during the study. One mid-dose male showed very slight erythema on Day 7 of treatment only. One mid-dose female showed very slight erythema on Day 7 and Day 13, only.

No erythema or edema was observed in three of the five high-dose males. Very slight erythema was observed in one high-dose male on treatment days 3, 4, 6, 7 and well-defined erythema was observed on Day 5. This same male also displayed edema (very slight) on Days 5 through 7. None of the high-dose females displayed edema and two high-dose females were free of erythema also. Very slight erythema was observed in one high-dose female on Day 7 only, in another on Days 5 and 7, and in a third high-dose female on Days 6 through 8 and on Day 14.

No dermal irritation was observed in the sham-treated controls. Epidermal scaling was observed in one low-dose male on Day 7 and at termination and in one low-dose female on Days 13 and at termination. Four of five males

and 4 of 5 females in the mid-dose group displayed epidermal scaling as follows.

| MALES | FEMALES |
|---|---|
| Days 13 and 14 | Days 12 through 15 |
| Days 12 through 15 | Days 6 through termination |
| Days 7, and 11 through 13 | Days 6 through 15 |
| Days 11, 14, and at termination | At termination only |

All high-dose animals displayed epidermal scaling, generally from day 6 through termination.

Body Weight and Food Consumption

There were no distinct treatment- or dose-related effects reported in body weight. The only statistically significant finding was a decreased body-weight gain in the low-dose males during treatment days 11-15. Food consumption was also reported to be comparable among the groups, although the mean total food consumption for the high-dose females was significantly decreased compared to control (2400 vs 2382 g). The magnitude of this decrease is not considered to be significant. In reviewing the daily consumption values, it was noted that the high-dose males consumed considerably less food during treatment days 3 through 8, which can be attributed to the male that was found to be anorexic.

| | Body Weight Increase During Exposure Mean % | |
|---|---|---|
| Group | Males | Females |
| Control | 9 | 8 |
| Low | 7 | 6 |
| Mid | 10 | 5 |
| High | 6 | 8 |

Clinical Pathology

No compound-related findings were reported in the clinical pathology data, and there were no statistically significant differences observed. It is to be noted that these parameters were only examined at study termination.

Gross Pathology

There was no evidence of any effect on the viscera. Treated site observations were as follows.

| | Control | | Low | | Mid | | High | |
|---|---|---|---|---|---|---|---|---|
| | M | F | M | F | M | F | M | F |
| desquamation/scaling of skin | 0 | 0 | 1 | 1 | 1 | 2 | 2 | 5 |
| dark area or yellow stain | 0 | 0 | 2 | 3 | 4 | 4 | 3 | 2 |

Organ weights

The mean absolute and relative thyroid weights of the high-dose males were increased compared to control, but statistical significance was not attained.

| THYROID | Absolute (g) | Relative (%) |
|---|---|---|
| males | | |
| Control | 0.174±0.053 | .0071±.0023 |
| Low | 0.203±0.075 [120]* | .0087±.0032 [123]* |
| Mid | 0.197±0.062 [113] | .0083±.0037 [117] |
| High | 0.226±0.041 [130] | .0094±.0020 [132] |

* % control

Relative kidney weights were decreased (dose-related) in males, with the high-dose males displaying a 15% decrease from control values (a $p < 0.05$ was not attained). The decrease in kidney weight in the high-dose females was not dose-related, nor statistically significant. There was a dose-related increase in testis/epididymides weight (absolute and relative) with increasing dose. The high-dose value was 16-17% greater than the control value.

Histology

Follicular cell hypertrophy was observed in all high-dose males and in two high-dose females. Increased colloid material was observed in the thyroid of four high-dose females, two mid-dose females, and one low- and one control females. Follicular cysts were present in two males and two females of the control group and in four females of the high-dose group.

Slight dermal irritation (acanthosis and/or hyperkeratosis) was evident in all treated groups but not in the controls. Mid- and high-dose animals displayed a yellow pigment on the epidermal surface at the exposure site.

| | MALES | | | | FEMALES | | | |
|---|---|---|---|---|---|---|---|---|
| | Control | Low | Mid | High | Control | Low | Mid | High |
| Acanthosis | - | - | | 3 | - | - | 1 | 5 |
| Hyperkeratosis | - | 1 | 3 | 2 | - | 3 | 5 | 5 |
| Pigment | - | - | 1 | 5 | - | - | 4 | 5 |

CONCLUSION

No deaths occurred following dermal exposure to technical Maneb and clinical findings, body weight changes, food consumption, hematology, serum chemistry, and organ weights were comparable among the groups; i.e., no statistical significance was attained. However, there was some evidence that the thyroid is a target organ (slightly increased thyroid weights and follicular cell hypertrophy in the high-dose animals) following dermal exposure to Maneb.

The NOEL for systemic toxicity can be set at 100 mg/kg, and a conservative LEL can be set at 300 mg/kg, based on microscopic thyroid changes. Slight dermal irritation at the site of application was observed at all dose levels.

MANEB 014505

Page 9 is not included in this copy.

Pages _____ through _____ 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 product 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.