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

JUN 10 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **MANEB** - 18-Month Carcinogenicity Study in Mice

TO: Terri Stowe
PM Team Reviewer (71)
SRRD/RB (H7508W)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 5/25/93
Toxicology Branch II, Section II,
Health Effects Division (H7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 6/7/93
Section II Head, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D. Marcia van Gemert 6/8/93
Chief, Toxicology Branch II/HFAS/HED (H7509C)

Registrant: ELF ATOCHEM North America, Inc.
Chemical: manganese ethylene-1,2-bisdithiocarbamate
Synonym: Maneb
Caswell No.: 539
Case No.: 818618
Submission No.: S435690
Identifying No.: 014505
DP Barcode: D188352
MRID No.: 426424-01
Action Requested: Please review the maneb data for GLN 83-2b Onco. - mouse study (MRID 42642401).

Comment: In response to the Generic Maneb Data Call In Notice of 4/1/87, the Registrant has submitted an 18-month Maneb mouse carcinogenicity study [WIL-134008]. This study has been reviewed, and the DER is appended.

Under the conditions of the study, oral administration of Maneb Technical to mice at dose levels in the diet of 60, 240, and 2400 ppm for 18 months resulted in a doubling of the number of deaths in the mid- and high-dose males compared to the control males, but adequate numbers of mice were available at termination for the assessment of the carcinogenic potential of Maneb. Decreased body

weights/body-weight gains were observed at the mid-dose (♀♀) and the high-dose (♂♂ & ♀♀) levels. Treatment-related decreases were observed in RBC's, hemoglobin, and hematocrit in both sexes, although $p<0.05$ was not always attained. T_4 values were decreased at all dose levels (dose-related) in females, and no NOEL for this effect was established. A treatment-related increase in thyroid weight (absolute and relative) was observed at termination in both sexes at the high-dose level, and a dose-related increase in absolute brain weight was observed in females at study termination. No treatment-related gross lesions were observed at any dose level. There was a treatment-related increase in the incidence of hepatocellular adenomas in both sexes at the high-dose level, and an apparent increase in the incidence of alveologenic adenomas in the high-dose males.

Classification: Core-Minimum. This study satisfies the guideline requirement (83-2) for a carcinogenicity study in mice.

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Reviewed by: Linda L. Taylor, Ph.D. Linda Lee Taylor 5/25/93
Section II, Tox. Branch II (H7509C)
Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 6/7/93
Section II Head, Tox. Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Carcinogenicity-mouse TOX. CHEM NO: 539

MRID NO.: 426424-01 Shaughnessy #: 014505

TEST MATERIAL: Maneb Technical

SYNONYMS: Manganese ethylene-1,2-bisdithiocarbamate

STUDY NUMBER: WIL-134008

SPONSOR: Maneb Registration Group; c/o NPC, Inc., Sterling, VA

TESTING FACILITY: WIL Research Laboratories, Inc., Ashland, OH

TITLE OF REPORT: 18-Month Dietary Oncogenicity Study in Mice with Maneb Technical

AUTHOR(S): EC Tompkins

REPORT ISSUED: September 15, 1992

Quality Assurance: Both a quality assurance and a GLP statement were provided.

CONCLUSION: Treatment of mice with Maneb Technical at dose levels in the diet of 60, 240, and 2400 ppm for 18 months resulted in a doubling of the number of deaths in the mid- and high-dose males compared to the control males, but adequate numbers of mice were available at termination for the assessment of the carcinogenic potential of Maneb. Decreased body weights/body-weight gains were observed at the mid-dose (♀♀) and the high-dose (♂♂ & ♀♀) levels. Treatment-related decreases were observed in RBC's, hemoglobin, and hematocrit in both sexes, although $p<0.05$ was not always attained. T_4 values were decreased at all dose levels (dose-related) in females, and no NOEL for this effect was established. A treatment-related increase in thyroid weight (absolute and relative) was observed at termination in both sexes at the high-dose level, and a dose-related increase in absolute brain weight was observed in females at study termination. No treatment-related gross lesions were observed at any dose level. There was a treatment-related increase in the incidence of hepatocellular adenomas in both sexes at the high-dose level, and an apparent increase in the incidence of alveologenic adenomas in the high-dose males.

Classification: Core-Minimum. This study satisfies the guideline requirement (83-2) for a carcinogenicity study in mice.

A. MATERIALS

1. Test compound: Maneb Technical; Description: buff-colored powder; Batch #: Lot # not provided; Purity: 89.5%; Source: Pennwalt Holland, Rotterdam, The Netherlands.

2. Test animals: Species: mouse; Strain: Crl:CD-1®(ICR)BR; Age: ≈ 28 days on receipt and 6 weeks old at study initiation; Weight: males 21.7-36.7 g, females 16.4-29.5 g at time of selection for study; Source: Charles River Breeding Laboratories, Inc., Portage, Michigan.

B. STUDY DESIGN

1. Animal assignment

Prior to study initiation, the animals were acclimated for 13 (♂♂) or 14 (♀♀) days; all mice were checked twice daily pre-test for mortality and general changes in appearance or behavior, and body weight and food consumption were recorded. The mice were housed individually, and had access to feed [Purina® Certified Rodent Chow® #5002] and tap water ad libitum. After the acclimation period, the mice were assigned to groups by the computer randomization procedure (based on body weight stratification in a block design). There were 75 mice/sex/group. The mice were fed diets containing 0, 60, 240, or 2400 ppm (adjusted for active moiety) test material for at least 78 weeks (≈ 18 months).

2. Diet preparation

An appropriate amount of test material was weighed, added to an appropriate amount of basal diet for each dose level, and mixed thoroughly. Fresh test material:diet mixtures were prepared weekly and stored at room temperature. Prior to study initiation, stability and homogeneity tests were performed on samples from all dose levels. The test diets were analyzed for test material concentration weekly for all dose levels.

RESULTS

The procedures developed for dose preparation prior to the study were found to provide homogeneous mixtures. The test material was found to be stable in the diet for 2 weeks at room temperature and for 4 weeks when frozen. The overall mean concentrations of test material in the diets were within 10% of the stated concentrations. The means of the target values are listed below for each dose.

Table 1. Mean and Percent of Target Value Attained

Dose Level (ppm)	Mean [ppm] (% of Target Value)
0	ND
60	58.3 (97.1)
240	237 (98.8)
2400	2425 (101)

ND = not detected

3. Statistics - The following procedures were utilized: body weight, body-weight change, food consumption, clinical pathology parameters, and absolute and relative organ weight- one-way analysis of variance followed by Dunnett's Test. Treatment groups were compared to controls, by sex. All statistical tests were 2-tailed, with $p \leq 0.05$ and $p \leq 0.01$ used as levels of significance. All statistical tests were performed by a Digital® Microvax 3400 computer with appropriate programming.

C. METHODS AND RESULTS

1. Observations

The mice were observed twice daily for moribundity, mortality, and signs of obvious toxicity. A detailed physical examination (with palpation) was performed once a week, starting one week prior to study initiation. Each mouse was weighed pretest (week -1), weekly for the first 13 weeks, every other week through week 17, and weekly thereafter. Individual food consumption was recorded weekly, starting at week -1 through week 16 and every other week thereafter. The mean amounts of test material consumed (mg/kg/day) by each sex were calculated from the mean food consumption (g/kg/day) and the appropriate concentration of Maneb in the food (ppm, based on 89.5% purity).

RESULTS

Toxicity/Mortality (survival): There were no statistically significance differences in survival among the groups of either sex, although males at the mid- and high-dose levels displayed a doubling of the number of deaths compared to the control and low-dose groups. There was no common probable cause of death established. The number surviving in each group is adequate for each sex for the assessment of carcinogenic potential. There were no differences observed in the clinical findings that could be attributed to treatment. NOTE: The interim sacrifice of 20 mice/sex/group occurred during weeks 52-53.

Table 2. Survival (# of animals)

# Survivors/ Dose level (ppm)	MALES				FEMALES			
	0	60	240	2400	0	60	240	2400
Termination	49	49	43	42	42	48	39	38
26 weeks	75	75	75	75	74	75	74	74
54 weeks	55	54	52	55	50	52	50	52
77 weeks	50	49	43	45	43	48	39	39
# dying	6	6	12	13	12	7	14	16

Bodyweight: Statistically significant decreases were observed in body weight at the mid-dose level in females and the high-dose level in both sexes throughout the study, but the magnitude of the differences was small (1-3 grams; ≤ 8% below control values). Body-weight gains were decreased at the high-dose level in males compared to the control values during the first 2 weeks on test. Females at all dose levels displayed decreased body-weight gains (0.8 for treated vs 1.4 for control) compared to the control during the week prior to the start of dosing. During week 1 of dosing, there was a dose-related negative body-weight gain at the mid- and high-dose levels (♀♀) and a dose-related increase in body-weight gain compared to the control at these dose levels during week 2. The overall gain for the high-dose males was 90% of the control value. For females, the mid-dose gain was 93% and the high-dose gain was 84% of the control value.

Body-Weight Data [grams (% of control)]

Body weight/gain/ time/dose	MALES				FEMALES			
	0 ppm	60 ppm	240 ppm	2400 ppm	0 ppm	60 ppm	240 ppm	2400 ppm
week -1	27.2	27.2	27.2	27.2	22.5	22.6	22.5	22.6
0	29.3	29.4	29.2	29.4	24.0	23.4	23.3	23.3
1	30.7	30.4	30.3	29.8*(97)♦	24.2	23.7	23.3**(96)	23.0**(95)
2	31.2	31.0	30.6	29.6**(95)	25.2	25.0	24.6	24.5*(97)
3	32.0	31.6	31.8	30.5**(95)	25.6	25.5	25.0	24.9*(97)
8	34.3	34.2	34.3	33.1**(97)	27.7	27.5	27.2	27.2
13	35.9	35.8	35.7	34.4**(96)	29.5	29.1	28.3**(96)	28.0**(95)
26	38.0	37.7	37.8	36.2**(95)	31.8	31.1	30.4**(96)	29.9**(94)
52	39.8	39.2	39.3	37.3**(94)	34.8	33.4*(96)	32.9**(95)	31.9**(92)
79/78	39.9	39.4	39.2	38.9(97)	35.5	35.0	34.0(96)	33.0**(93)
-1-0	2.1	2.2	2.0	2.2	1.4	0.8**	0.8**	0.8**
0-1	1.4	1.0	1.1	0.4**	0.2	0.3	-0.1	-0.3**
1-2	0.5	0.6	0.3	-0.2**	1.0	1.3	1.3*	1.4**
0-79/78	10.5	10.0	10.0	9.5(90%)♥	11.5	11.6	10.7	9.7(84%)♥

* p<0.05; p <0.01; ♦ % of control value; ♥ statistics not performed

Food consumption and compound intake: The mid- and high-dose males displayed decreased food consumption (g/mouse/day) during the first 5 weeks of dosing and then only during a few intervals thereafter. On a g/kg/day basis, the mid- and high-

dose males displayed a dose-related decrease in intake during weeks 1 and 3. Thereafter, food intake was comparable or greater than the control value for these groups. For females, the high-dose displayed decrease intake (g/mouse/day) during the first 10 weeks and then periodically during the first year of treatment. On a g/kg/day basis, the high-dose females displayed a decrease in intake during the first week and between weeks 6-8 and 12-13. Thereafter, their intake was comparable to or greater than the control value. The average compound consumption values for the 78-week study are listed below.

Table 3. Average Compound Consumption (mg/kg/day)

Dose level (ppm)	MALES	FEMALES
60	8.6	10.8
240	34.8	45.0
2400	354.7	439.3

2. Clinical Pathology Evaluations

Blood samples were taken from the vena cava from 20 mice/sex/group at the interim and terminal sacrifices. Ten males and 10 females per group were evaluated for hematology parameters, and the serum from the remaining 10/sex/group was assayed for the thyroid hormones triiodothyronine (T_3; pooled samples of 10 mice) and thyroxine (T_4; individual samples) and for thyroid stimulating hormone (TSH; individual samples). The hematology parameters determined were: leukocyte count, erythrocyte count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, differential WBC count [control and high-dose mice] and platelet count.

RESULTS

Hematology: The high-dose level mice displayed several differences in the measured parameters (decreased erythrocyte counts, hemoglobin, and hematocrit), compared to the control values (as shown below), which the author attributed to treatment. Since there are no pretest values, a definitive conclusion regarding the differences observed cannot be made, especially those for males. The female values for these three parameters do appear to be decreased at termination compared to the interim values relative to control, but there is no dose-response and different mice were utilized at each interval.

Table 4. Summary Hematology Values

Parameter/sex/ dose (ppm)/ interval	MALES				FEMALES			
	0	60	240	2400	0	60	240	2400
Erythrocytes♦								
interim	9.01	9.18	8.73	8.05**	9.69	9.58	9.38	8.93*
terminal	9.10	8.72	7.88	8.00	8.97	8.03*	8.24	7.59**
Hemoglobin♦								
interim	14.4	14.8	14.4	13.5	15.7	15.8	15.3	14.8
terminal	13.8	13.6	12.9	13.1	14.2	12.7*	13.1	12.0**
Hematocrit♦								
interim	47.4	48.8	46.9	44.8	50.5	50.8	49.5	47.4
terminal	47.6	46.9	41.9	43.2	46.6	41.2**	43.7	39.4**

* $p<0.05$; ** $p<0.01$; ♦ mil/μL; ♣ g/dL; ♠ %

Thyroid Function Assays: Mean thyroxine (T_4) values were decreased in both sexes at the high-dose level at both the interim and terminal sacrifices compared to the control values. Additionally, the females displayed a dose-related decrease in this parameter, with all groups displaying statistical significance at study termination. No treatment-related differences were observed in either triiodothyronine (T_3) or thyroid stimulating hormone values at either sacrifice. Since there was a large degree of variation in TSH data, no data were available for the control females at termination, and ≥ 25% of the animals evaluated had values less than the detectable range, no definitive assessment of these data is possible.

Thyroid Function Assay Values

Parameter/sex/ dose (ppm)/ interval	MALES				FEMALES			
	0	60	240	2400	0	60	240	2400
T_3 (ng/mL)								
interim	0.85	0.83	1.02	1.00	0.84	0.92	1.00	0.86
terminal	1.75	1.63	2.05	2.02	1.40	1.46	1.67	1.56
T_4 (μg/dL)								
interim	2.21	2.94	2.51	1.10**	3.07	2.83	2.65	1.09**
terminal	3.05	2.69	2.63	1.20	2.98	1.72**	1.45**	0.81**
TSH (ng/mL)								
interim	0.59	0.72	0.71	1.01	0.70	0.70	0.79	0.95
terminal	0.48	0.38	0.28	0.57	NA	1.47	0.39	0.29

NA-not available due to accident

3. Sacrifice and Pathology

All animals that died or were sacrificed on schedule were subjected to a complete gross pathological examination, which included an examination of the external surface, all orifices, and the cranial, thoracic, pelvic, and abdominal cavities, including viscera. The brain, kidneys, liver, adrenals, heart, thyroid gland with parathyroids, and testes (males) of all mice sacrificed at the interim and terminal periods were weighed. The CHECKED (X) tissues were collected from all animals. All tissues of those found dead or sacrificed

moribund and all mice in the control and high-dose groups were examined microscopically; examination of the tissues of the interim-sacrificed mice was limited to the liver, kidneys, thyroid/parathyroid, masses, and gross lesions thought to be treatment-related. The liver, lungs, kidneys, thyroid/parathyroid, masses, and gross lesions were examined from the low- and mid-dose mice of both sexes.

X		X		X	
Digestive system		Cardiovasc./Hemat.		Neurologic	
	Tongue	X	Aorta	X	Brain (3 levels)
X	Salivary glands♦	X	Heart	X	Periph. nerve (sciatic)
X	Esophagus	X	Bone marrow	X	Spinal cord (3 levels)
X	Stomach	X	Lymph nodes*	X	Pituitary
X	Duodenum	X	Spleen	X	Eyes (optic n.)
X	Jejunum	X	Thymus	Glandular	
X	Ileum	Urogenital		X	Adrenal gland
X	Cecum	X	Kidneys		Lacrimal gland
X	Colon	X	Urinary bladder	X	Mammary gland ♀♀
X	Rectum	X	Testes	X	Parathyroids
X	Liver	X	Epididymides	X	Thyroids
X	Gall bladder	X	Prostate	Other	
X	Pancreas	X	Seminal vesicle	X	Bone (femur)
Respiratory		X	Ovaries	X	Skeletal muscle
X	Trachea	X	Uterus	X	Skin
X	Lung w/bronchi	X	Oviducts	X	All gross lesions
	Nasal passages	X	Vagina		and masses
	Pharynx	X	Clitoral gland	X	Preputial gland ♂♂
	Larynx				

♦ submaxillary; * mesenteric and mandibular

RESULTS

Organ weight - High-dose males and females displayed increased thyroid weights (both absolute and relative) at both the interim ($p<0.05$ was not attained) and terminal (statistically significant) sacrifices. At the interim sacrifice, mid- and high-dose males displayed statistically significant decreases in testes weights (absolute for both groups; relative for mid-dose only), but the mid-dose displayed the greater decrease and a comparable effect was not observed at the terminal sacrifice. Increased relative kidney and liver weights were observed at the high-dose level in both sexes compared to the control values at both the interim and terminal sacrifices (terminal relative liver weight of the males did not attain $p<0.05$). Relative heart weight was increased at the terminal sacrifice in both sexes at the high-dose level and at the interim sacrifice in the high-dose females. Absolute brain weight was decreased in females at the mid- and high-dose levels (dose-related). Relative brain weight was increased in the same groups at the interim sacrifice (not dose-related) and statistical significance was not attained at the terminal sacrifice.

Table 5. Organ Weight Data - Males

Parameter/dose (ppm)	MALES [interim/terminal]			
	0	60	240	2400
Thyroid				
absolute (g)	0.0043/0.0048	0.0049/0.0047	0.0047/0.0044	0.0051/0.0059**
relative-body♦	0.011/0.012	0.012/0.012	0.012/0.011	0.014/0.015**
Testes				
absolute (g)	0.2554/0.2160	0.2430/0.2199	0.2206**/0.2221	0.2266*/0.2126
relative-body♦	0.653/0.533	0.599/0.550	0.548**/0.554	0.595/0.550
Liver				
absolute (g)	1.9780/2.4112	1.9865/2.2956	2.0135/2.2952	2.1556/2.4309
relative-body♦	5.025/5.887	4.877/5.733	4.934/5.704	5.645**/6.237
Kidneys				
absolute (g)	0.7704/0.8389	0.8115/0.8313	0.8024/0.8435	0.8580/0.8582
relative-body♦	1.961/2.063	1.996/2.077	1.970/2.094	2.249*/2.215*
Heart				
absolute (g)	0.2150/0.2339	0.2148/0.2414	0.2221/0.2394	0.2205/0.2379
relative-body♦	0.547/0.576	0.528/0.603	0.547/0.593	0.579/0.615*
TERMINAL BODY WEIGHT (g)				
Interim	39.5	40.7	40.8	38.3
Final	40.8	40.1	40.6	38.7*

Table 6. Organ Weight Data - Females

Parameter/dose (ppm)	FEMALES [interim/terminal]			
	0	60	240	2400
Thyroid				
absolute (g)	0.0055/0.0049	0.0046/0.0049	0.0045/0.0047	0.0058/0.0062*
relative-body♦	0.015/0.014	0.013/0.014	0.014/0.014	0.018/0.019**
Liver				
absolute (g)	1.7866/2.0183	1.6915/1.9521	1.6924/1.9628	1.9369/2.2337
relative-body♦	4.916/5.604	4.941/5.535	5.178/5.701	6.016**/6.668**
Kidneys				
absolute (g)	0.5436/0.5591	0.5282/0.5681	0.5269/0.5587	0.5445/0.5911
relative-body♦	1.500/1.565	1.549/1.622	1.618/1.630	1.694**/1.782**
Heart				
absolute (g)	0.1842/0.2047	0.1755/0.1981	0.1726/0.2052	0.1848/0.2123
relative-body♦	0.510/0.571	0.513/0.565	0.531/0.598	0.577**/0.640**
Brain				
absolute (g)	0.5362/0.5380	0.5372/0.5294	0.5316/0.5241*	0.5124/0.5239*
relative-body♦	1.485/1.512	1.580/1.522	1.643**/1.536	1.602*/1.587
TERMINAL BODY WEIGHT (g)				
Interim	36.4	34.2	32.5**	32.2**
Final	36.0	35.2	34.4	33.3**

♦ g/100 g

b. Gross pathology - The incidence of macroscopic lesions was comparable among the groups (both sexes) at the interim sacrifice. At the terminal sacrifice, there was a treatment-related increase in the incidence of hepatic masses at the high-dose level in both sexes.

Incidence of Hepatic Masses

Dose/# (%) masses	0 ppm	60 ppm	240 ppm	2400 ppm
Males	8 (16)	5 (10)	10 (23)	15 (36)
Females	1 (2)	1 (2)	1 (3)	6 (16)

c. Microscopic pathology: 1) Non-neoplastic - Amyloid deposition was observed in various tissues in all groups, although the incidence in the high-dose mice (both sexes) that died or were sacrificed moribund was slightly increased. Since this is a common observation of mice of this strain and age, and there were no differences noted at either the interim or terminal sacrifice, the author considered the apparent increase to be unrelated to treatment. TB II notes that the incidence of this finding was greatest in the high-dose mice (both sexes) for most of the tissues in which it was observed ($p<0.05$ not attained); the significance of this finding could not be determined. There were no apparent treatment-related effects on the thyroid among the groups, and no increases were noted in any non-neoplastic lesion in either the liver or lung (see below under 2) Neoplastic).

Thyroid Lesions (all mice)

Lesion/Group	0 ppm	60 ppm	240 ppm	2400 ppm
THYROID				
hypertrophy				
males	0	0	4	1
females	0	4	4	2
amyloid deposition				
males	4	1	8	6
females	6	7	8	13

2) Neoplastic - There was a treatment-related increase in the incidence of hepatocellular adenomas in both sexes at the high-dose level at the terminal sacrifice and when all mice are considered. There was an apparent increase (doubling) in the incidence of alveologenic adenomas in the high-dose males at study termination and when all male mice are considered, but statistical significance was not attained.

Incidence of Neoplasia - **MALES** (# tumors/# examined)

Tumor/Group	0 ppm	60 ppm	240 ppm	2400 ppm
LIVER - adenoma				
terminal sacrifice	8/49	5/49	8/43	17/42*
all deaths	10/75	6/75	11/75	21/75*
LUNG - alveologenic adenoma				
terminal sacrifice	7/49	7/49	6/43	13/42
all deaths	8/75	9/75	7/75	16/75

Incidence of Neoplasia - **FEMALES** (# tumors/# examined)

Tumor/Group	0 ppm	60 ppm	240 ppm	2400 ppm
LIVER - adenoma				
terminal sacrifice	1/42	0/48	0/39	5/38
all deaths	1/75	0/75	0/75	8/75**

D. DISCUSSION

The administration of Maneb technical in the diet of mice at dose levels of 0, 60, 240, and 2400 ppm for an 18-month

period resulted in a slight decrease in the survival of the mid- and high-dose males, compared to the controls. Body weights and body-weight gains were decreased slightly in the mid-dose females and in the high-dose mice of both sexes, with an overall gain of 90% [♂♂]/84% [♀♀] for the high-dose mice compared to the control values. An initial decrease in food consumption was observed in both sexes. Erythrocyte, hemoglobin, and hematocrit values were decreased relative to control values at the high-dose level (♂♂ & ♀♀), although statistical significance was not always attained. TB II notes that similar decreases in these hematology parameters were observed in the chronic dog study. T_4 values were decreased in both sexes at the high-dose level at both the interim and terminal sacrifices and also in females at the low- and mid-dose levels (dose-related) at the terminal sacrifice. Several organ-weight differences were observed between the controls and high-dose mice of both sexes. A treatment-related increase in thyroid weight (absolute and relative) was observed at termination in both sexes at the high-dose level, and a dose-related increase in absolute brain weight was observed in females at study termination. No treatment-related gross lesions were observed at any dose level. Amyloid deposition in various organs was a common finding in all groups, although the high-dose mice dying on test or sacrificed moribund displayed a slightly greater incidence compared with the controls. There was a treatment-related increase in the incidence of hepatocellular adenomas in both sexes at the high-dose level, and an apparent increase in the incidence of alveologenic adenomas in the high-dose males.

E. CONCLUSION

The administration of Maneb technical to mice at dose levels in the diet of 60, 240, and 2400 ppm for 18 months resulted in a doubling of the number of deaths in the mid- and high-dose males compared to the control males, but adequate numbers of mice were available at termination for the assessment of carcinogenic potential of Maneb. Decreased body weights/body-weight gains were observed in the mid-dose females and the high-dose mice of both sexes. Treatment-related decreases were observed in several hematology parameters (RBC's, hemoglobin, hematocrit), and T_4 values were decreased at the high-dose level (♂♂ & ♀♀) at both sacrifice intervals and in females at the low- and mid-dose levels (dose-related) at the terminal sacrifice. A treatment-related increase in thyroid weight (absolute and relative) was observed at termination in both sexes at the high-dose level, and a dose-related increase in absolute brain weight was observed in females at study termination. No treatment-related gross lesions were observed at any dose level. The incidence of hepatocellular adenomas was increased in both sexes at the high-dose level, and an apparent increase was observed in the incidence of alveologenic adenomas in the high-dose males.

T_4 values were decreased at all dose levels (dose-related) in females and no NOEL for this effect was established. There was a treatment-related increase in the incidence of

hepatocellular adenomas in both sexes at the high-dose level [354.7 mg/kg ♂♂/439.3 mg/kg ♀♀], and an apparent increase in the incidence of alveologenic adenomas in the high-dose males. This study is classified Core Minimum, and it satisfies the guideline requirement (83-2) for a carcinogenicity study in mice.