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

APR
12 1985

004397

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Captan (Merpan) Lifetime (131-week)
Oncogenicity Study in Wistar rats; EPA ID #11678-1
Accession Number: 252722-252732;
Caswell #159

TO: H. Jacoby
Registration Division (TS-767)
PM #21

FROM: Jane E. Harris, Ph.D. JEH 4/4/85 11/12/85
Section Head, Section VI
Toxicology Branch/HED (TS-769)

Request: Review lifetime oral carcinogenicity study in Wistar rats on Merpan [92% a.i., N-(trichloromethylthio) cyclohex-4-ene 1,2-dicarboximide] submitted by Makhteshim Chemical Works Ltd., Israel, dated November 1983.

Recommendation and Conclusions:

At the highest dose tested (2000 ppm in the diet), there was a statistically significant increased incidence of sarcomas of the uterus and a nonstatistically significant increase of tumors in the pancreatic islet cells of males. Historical control data for this strain of Wistar rat from this testing laboratory (Netherlands Organization for Applied Scientific Research) and others, are required to interpret whether the increased incidence of sarcomas in the uterus and adenomas or carcinomas of the pancreatic islet cells in males at the highest dose tested might be related to treatment with captan.

Core Classification: Supplementary until historical control data as indicated above are provided.

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EPA: 68-01-6561
TASK: 23
March 20, 1985

DATA EVALUATION RECORD

MERPAN

Oncogenicity - Rat

CITATION: Til, H.P., Kuper, C.F., Folke, H.E. Life-span oral carcinogenicity study of Merpan in rats. An unpublished study prepared by Netherlands Organization for Applied Scientific Research (Report No. B80-0153) for Makhteshim Chemical Works Ltd. Beer-Sheva, Israel. Dated November 1983.

REVIEWED BY:

William L. McLellan, Ph.D.
Senior Scientist
Dynamac Corporation

Signature: William L. McLellan
Date: 20 March, 1985

F. Cavender, Ph.D.
Senior Scientist
Dynamac Corporation

Signature: Ira Cecil Felkner
Date: 3-20-85

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: Ira Cecil Felkner
Date: 3-20-85

APPROVED BY:

J. E. Harris
~~W. Schneider~~, Ph.D.
EPA Scientist

Signature: Jane E. Harris
Date: 3-20-85

DATA EVALUATION RECORD

STUDY TYPE: Oncogenicity - rat.

CITATION: Til, H.P., Kuper, C.F., Folke, H.E. Life-span oral carcinogenicity study of Merpan in rats. An unpublished study prepared by Netherlands Organization for Applied Scientific Research (Report No. B80-0153) for Makhteshim Chemical Works Ltd. Beer-Sheva, Israel. Dated November 1983.

ACCESSION NUMBER: 252722 - 252725.

LABORATORY: Netherlands Organization for Applied Scientific Research, Division for Nutrition and Food Research TNO, Zeist, the Netherlands.

QUALITY ASSURANCE STATEMENT: A Quality Assurance statement signed and dated November 17, 1983 was present.

TEST MATERIAL: Merpan technical, a white crystalline powder was used in the study. The material was 92.0 percent active ingredient, N-(trichloromethylthio) cyclohex-4-ene 1,2-dicarboximide.

PROCEDURES:

1. Weanling SPF Wistar Cpb:WU random bred rats (source: Central Institute for the Breeding of Laboratory Animals, TNO, Zeist, the Netherlands), were used in this study. The rats were 3.5 weeks old when received and weighed 35 to 50 g. They were acclimated to laboratory conditions for 7 days. Merpan was administered in the diet at levels of 125, 500 or 2000 ppm to groups of 50 males and 50 females. Controls (50 males and 50 females) received standard diet. The animals were housed 5/sex/cage in suspended stainless steel cages with wire mesh floors in temperature ($23 \pm 1^\circ \text{C}$) and humidity (40-70%) controlled rooms with a 12-hour light/dark cycle. Food and fresh tapwater were provided ad libitum.
2. The dose levels chosen were selected on the basis of a 4-week feeding study at levels of 2,000, 4,000, and 12,000 ppm Merpan (CIVO - Report No. R 6241). This latter report, although not available for review, apparently presented results indicative of a dose-related growth retardation in all dosed groups of males and females.

3. Batches of diets (30 kg) containing the test material were reported as being prepared every 2 to 3 weeks and stored in metal containers at ambient temperature. Test material and diet were mixed for 2 min. with a mechanical mixer. The mid-dose and low-dose diets were prepared by diluting the high-dose diets.

Merpan in diets was determined by gas chromatography after toluene extraction; electron capture was the method of detection. Diets were analyzed at 1 to 3 month intervals.

4. Clinical observations for signs of toxicity were made daily and animals were palpated for masses and examined in detail weekly. From about 18 months, animal cages were checked 2 times daily for dead or moribund animals. Animals in unthrifty condition were removed from the cages and housed individually. Ophthalmologic examinations were performed on all males and females in the control and 2000 ppm groups at weeks 27, 52, 77, and 104.
5. Body weights were measured weekly for the first 12 weeks and biweekly thereafter. Food intake was measured for weekly intervals during the first 12 weeks and for one week at 3 month intervals throughout the remainder of the study. Gram weight gain per gram food consumed was calculated over the first 12 weeks of the study.
6. Hematology determinations were performed on all rats at weeks 13, 27, 53, 79, and 105. The following parameters were measured: hemoglobin, hematocrit, RBC count, total and differential WBC count, and prothombin time. The mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentrations (MCHC) were calculated.
7. All animals still alive were killed in week 131 by ether anesthesia and aortic bleeding. A complete postmortem examination was performed on all animals that died or were sacrificed. Any lesions suggestive of neoplasia were recorded, noting location, size, and multiplicity.
8. The following organs were weighed at final sacrifice: heart, kidneys, liver, spleen, brain, testes/ovaries, pituitary, thyroid with parathyroid, and adrenals.
9. Samples of 40 tissues from each animal were preserved in 4% buffered formaldehyde. All nodules, tissue masses, and lesions suspected of being tumors were preserved along with samples of adjacent tissues.

All organs and tissues of all male and female rats of the control and 2,000 ppm groups were examined microscopically for hyperplastic, preneoplastic and neoplastic lesions. All organs and tissues for 20 males and females in the same groups were examined for non-neoplastic lesions. For all animals in the 125 and 500 ppm groups liver, spleen, pituitary, thyroid, adrenals, grossly observed tumors and gross lesions suspected of being tumors were examined histologically.

10. Statistical analyses were performed on body weight data, hematology, and organ weight data, using a one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test. Food intake data were evaluated by ANOVA followed by the LSD test. White cell data were analyzed by the Mann-Whitney U-test and ophthalmoscopic examination results were evaluated with the chi-square test. Gross and histopathologic findings and mortality data were analyzed by the Fisher exact one tailed test.

RESULTS:

Dietary Preparation and Analysis: The frequency of diet preparation could not be validated from the information reported. Levels of test compound in the diet were measured 11 times during the study, at approximately 1 to three months intervals. At the 125 ppm dose, the range of analyzed concentrations immediately after mixing was between 110-131 ppm, with a mean of 124 ppm; at the 500 ppm dose levels the range was between 439 and 565 ppm, with a mean of 504 ppm; at 2000 ppm the analyzed concentrations ranged from 1940 to 2190 ppm with a mean of 2083 ppm. Levels in control diet were all below the level of detection (< 0.2 ppm). The homogeneity of material in diets had a coefficient of variation (standard deviation \div mean $\times 100$) of less than 5%. The test material was not stable in the diets under the conditions of storage. After 5 week of storage at room temperature, there was 64, 48, and 28 percent loss of Merpan in diets containing 125, 500, and 2000 ppm; after 2 weeks of storage losses were 44, 6, and 1 percent at 125, 500, and 2000 ppm, respectively. Since the diets were stored "less than 3 weeks" the authors stated that the average daily levels in the diets were about 100, 475, and 1950 ppm.

Clinical Observations: There were no overt toxic signs related to treatment with Merpan. There were no remarkable changes in appearance or behavior in any group of rats for the first 18 months of the study. Subsequently, all groups of rats had an increased incidence of signs of poor condition; this was related to the aging process and was not compound related. The conclusions were supported by tabular data showing the number of animals in each group of males and females with specific signs during each 13 week interval of the study (Appendix 1 of the study). Individual animal data were not presented.

Mortality: There was no effect of test compound on mortality. Survival at 18 months ranged from 92-98% in males and 94-98% in females; at 24 months, survival ranged from 66-76% in males and 74-80% in females. Data are summarized for 18, 24, and 30 months in Table 1.

Ophthalmologic Observations: There was a statistically significant increased incidence of females with vacuoles in the lens at 52 weeks at the 2000 ppm dose (7/50) when compared to controls (1/50). However at 77 and 104 weeks the incidence was similar in control and high dose females. There was a statistically significant increased incidence in cataracts in females dosed at 2000 ppm at 104 weeks compared to controls (18/37 compared to 8/40) but there was no similar trend in males (18/33 in

TABLE 1. Mortality and Survival in Rats Fed Merpan for 30 Months^a

	Dose Level in Males (ppm)				Dose Level in Females (ppm)			
	0	125	500	2000	0	125	500	2000
<u>18 months</u>								
Mortality	4	2	1	1	1	3	2	3
% survival	92	96	98	98	98	94	96	94
<u>24 months</u>								
Mortality	17	14	12	16	10	11	12	13
% survival	66	72	76	68	80	78	76	74
<u>30 months</u>								
Mortality	27	24	30	31	26	26	22	30
% survival	46	52	40	38	48	48	56	40

^a There were initially 50 rats/sex/group.

controls and 20/34 at 2000 ppm). Individual animal data supported the incidence data. The ophthalmologic findings were "not considered of toxicological importance" by the authors since these are common findings in rats of this age.

Body Weights and Food Consumption: The mean body weights of both males and females at the 2,000 ppm dose were slightly but significantly lower than controls beginning at week 1 and throughout the study. The overall decrease was about 10% in both sexes at 24 months; at 30 months the decrease was 11% in males and about 5% in females. This reviewer noted that after week 16 of the study incremental weight gains were similar in all groups (Table 2).

The authors stated that "the dose level chosen for the top-dose group is considered adequate for the purpose of the present study" (see Discussion).

Food consumption in males and females dosed at 2000 ppm was slightly lower than in controls throughout the study. The difference was statistically significant for about 24 weeks in males and 47 weeks in females. According to the authors, food efficiency, which was calculated weekly for the first 12 weeks of the study, was similar in all groups of males and females. This reviewer, however, noted that food efficiency (g gain/g food) in males dosed at 2000 ppm (0.293) was significantly lower ($p < 0.001$) than in controls (0.416) at week one but not during weeks 2 to 12.

Hematology: There were no test-compound related effects on hematology parameters.

TABLE 2. Mean Body Weights and Mean Weight Gains at Selected Intervals of Rats Fed Merpan

Weeks	MALES			FEMALES		
	Control	grams	(Δ grams)	Control	grams	(Δ grams)
			Percent less than control			Percent less than control
0	79.7	79.5		71.8	73.0	
4	224.6(144.9) ^a	192.6*(113.1)	14.2	149.4 (77.6)	137.8* (64.8)	7.8
8	309.4 (84.8)	269.7* (27.1)	12.8	184.2 (34.8)	169.8* (32.0)	7.8
12	353.5 (44.1)	312.3* (42.6)	11.6	202.6 (18.4)	188.4* (18.6)	7.0
16	378.1 (24.6)	334.0* (21.7)	14.3	214.4 (11.8)	199.2* (10.8)	6.2
Months						
6	423.5 (45.1)	378.4* (44.4)	10.6	233.0 (18.6)	216.8* (17.6)	6.9
12	500.6 (77.1)	461.7* (83.3)	12.2	279.0 (46.0)	251.0* (34.2)	10.0
24	523.5 (22.9)	477.5* (15.80)	7.7	327.1 (48.1)	293.7* (42.7)	10.2
30	457.5(-65.8)	407.7*(-69.8)	10.9	292.8(-34.3)	280.1 (-13.6)	4.3

^a Calculated for the interval by this reviewer

* Statistically different from controls at a p value of < 0.05.

Organ Weights: Mean organ weights were similar in all groups of animals. There was a slight but statistically significant increase in liver weight relative to body weight in 2000 ppm males (37.6%) when compared to controls (32.7%) but it was stated by the authors that since there was no effect on absolute liver weight and no accompanying histologic changes in the organ, the effect was not regarded as related to treatment.

Gross Pathology: The notable gross findings are presented in Table 3. The report stated that the incidence of kidneys with a granular appearance was increased in 2000 ppm males compared to controls but that "no other discernible differences in type, incidence or severity of gross lesions occurred among the groups."

Histopathology: Summary tabulations of neoplastic, pre-neoplastic, and non-neoplastic lesions are presented in Tables 4, 5, and 6, respectively. The authors stated that there was no evidence of tumorigenicity related to compound administration. They noted that there were leiomyosarcomas in the small intestine of small numbers of males receiving 125 ppm and "that sarcomas of the uterus, an uncommon tumor in this strain of rat, was found in a small number of animals dosed at 2000 ppm...there was, however, no statistically significant difference in incidence of any tumor type between test groups and controls" and no dose-response relationship. The authors found no association between occurrence to tumors and the presence of hyperplastic or pre-neoplastic lesions. The non-neoplastic lesions were not considered of "any toxicology significance" by the authors of the report who noted that the highest incidence of these lesions observed in test groups compared with historical background data for this strain of rat in their testing laboratory.

DISCUSSION:

The authors concluded that "feeding Merpan to rats at dietary levels of 125, 500, or 2000 ppm for the major part of their lifetime did not cause any distinct deleterious effect. There was no evidence of Merpan affecting condition, behavior, survival, hematology, or neoplastic and non-neoplastic lesions;" and based on a "slight growth depression" in the high-dose group, the dose level chosen was "considered adequate for the purpose of the present study."

This reviewer, however, noted that there was a statistically significant ($p < 0.05$) increase in the incidence of sarcomas of the uterus in females receiving 2000 ppm (4/50) compared to controls (0/50). The authors did not indicate that this was statistically significant but commented that it was not a tumor type common in the strain of rat used. The four tumors were found on days 378, 565, 860, and 915 (average, 680 days). There was also a statistically significant increase in benign adrenal pheochromocytomas in males receiving 500 ppm Merpan compared to controls; a

TABLE 3. Gross Finding in Rats Fed Merpan^a

	Males/Dose (ppm)				Females/Dose (ppm)			
	0	125	500	2000	0	125	500	2000
Skin								
mass	4	6	11	3	3	2	0	6
Clitoris								
inflammation					1	5	1	5
Abdomen								
mass	1	0	1	3	0	0	0	0
ascites	2	1	0	7	1	2	1	1
Adrenals								
discolored	2	2	6	6	0	1	2	1
spotted	2	2	5	2	5	11	13	12
enlarged	6	5	5	3	8	12	10	6
Kidney								
granular surface	10	12	18	25*	3	2	4	2
discolored	9	8	9	14	2	1	3	4
Pancreas								
pale	1	1	1	3	0	0	0	1
Liver								
prominent	6	4	5	9	6	10	13	10
lobular pattern								
discolored	1	5	3	3	2	1	2	5
Thorax								
hydrothorax	4	1	2	7	2	2	2	1
Lungs								
spotted	6	5	8	9	5	7	5	5
Aorta								
dilated	3	4	8	8	1	1	0	2
Lachrymal glands								
spotted	3	7	3	4	0	0	0	0
Pituitary								
hemorrhage	0	3	0	1	4	4	3	6

^a Only findings that were increased over controls in dosed groups are included; suspect tumors in visceral organs were not included. The information was tabulated by this reviewer. It was verified that 50 animals/group were examined.

* Statistically different from control at a p value of < 0.01 with the Fisher exact one-tailed test (analysis by reviewer).

TABLE 4. Tumor Incidence in Rats Fed Merpan^a

	Male/Dose (ppm)				Female/Dose (ppm)			
	0	125	500	2000	0	125	500	2000
<u>Adrenal</u>	(50) ^b	(50)	(49)	(47)	(49)	(47)	(50)	(49)
pheochromocytoma (B) ^c	6	6	14*	5	0	0	0	0
" (M)	5	3	0	1	0	0	0	0
cortical adenoma	6	0	1	2	0	0	0	0
<u>Kidney</u>	(49)	(-)	(-)	(50)	(48)	(-)	(-)	(49)
nephroblastoma	0	-	-	2	0	-	-	0
<u>Liver</u>	(49)	(49)	(50)	(50)	(50)	(49)	(50)	(49)
cholangioma	0	1	0	1	0	0	0	2
<u>Mammary gland</u>	(48)	(-)	(-)	(48)	(49)	(-)	(-)	(48)
fibroadenoma	0	-	-	0	19	17 ^d	13	13
adenocarcinoma	0	-	-	0	4	6	4	2
<u>Pancreas</u>	(50)	(-)	(-)	(50)	(46)	(-)	(-)	(48)
islet cell adenoma	1	2	-	4	0	-	-	0
islet cell carcinoma	0	0	0	1	0	-	-	0
islet cell adenoma or carcinoma	1	2	0	5	0	-	-	0
<u>Prepuce/clitoris</u>	(49)	(-)	(-)	(48)	(45)	(-)	(-)	(44)
carcinoma, squamous	0	1	0	2	1	1	2	2
<u>Pituitary</u>	(46)	(45)	(49)	(50)	(48)	(49)	(49)	(46)
hemorrhagic tumor	8	7	3	10	15	16	15	14
solid tumor	1	3	2	1	1	3	2	1
<u>Small intestine</u>	(50)	(-)	(49)	(50)	(46)	(-)	(-)	(48)
leiomyosarcoma	0	0	3 ^e	0	0	0	0	0
<u>Zymal gland</u>	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
carcinoma, squamous	0	1	1	0	-	-	-	-
<u>Urinary bladder</u>	(49)	(-)	(-)	(50)	(46)	(-)	(-)	(46)
papilloma	0	0	2	0	0	-	-	0
<u>Thyroid</u>	(46)	(47)	(48)	(50)	(45)	(46)	(46)	(47)
adenoma, follicular	0	1	0	0	0	0	0	0
" , small	2	0	0	1	1	0	0	0
adenoma, light cell	3	3	5	3	1	0	1	1
carcinoma, polymorpho- follicular	0	0	1	0	0	0	0	1
carcinoma, light cell	0	0	0	0	0	2	0	1
total thyroid tumors	5	4	6	4	2	2	1	3

TABLE 4. Tumor Incidence in Rats Fed Merpan^a (Continued)

	Male/Dose (ppm)				Female/Dose (ppm)			
	0	125	500	2000	0	125	500	2000
<u>Uterus</u>					(48)	(49)	(50)	(50)
fibromatous polyp ^f					8	12	13	12
adenocarcinoma					6	4	5	7
sarcoma					0	0	0	4*
papilloma					0	0	1	0
<u>Skin</u>	(50)	(-)	(-)	(50)	(48)	(-)	(-)	(49)
malignant ^g	3	5	1	0	1	2	0	0
benign ^h	5	2	6	3	1	3	1	0

^a Number of animals with tumor; this table does not include tumors if they only occurred in a single test animal (however; tumors were included if different types in a specific organ might be combined for statistical analysis).

^b No. of tissues examined histologically. For several tissues at 125 and 500 ppm, only lesions identified as suspect tumors were examined histologically.

Where is could not be determined how many tissues were examined a dash is entered.

^c B = benign, M = malignant.

^d One fibroadenoma with a focal malignant area was not included.

^e One tumor, a leiomyosarcoma in the abdomen infiltrating the intestines, was not included since its primary source could not be determined.

^f Multiple polyps occurred in 1, 1, 1, and 2 females of the 0, 125, 500, and 2000 ppm groups and are included.

^g Sarcoma, fibrosarcoma, squamous cell carcinoma.

^h Fibroma, fibrous histiocytoma, sebaceous adenoma, lipoma, and ganglio-neuroma.

* Found to be statistically different from the control; analysis by this reviewer using the Fisher exact one-tailed test ($p < 0.05$). No statistical notations were made by the authors.

TABLE 5. Hyperplastic and Pre-neoplastic Lesions in Rats Fed Merpan

	Male/Dose (ppm)				Female/Dose (ppm)			
	0	125	500	2000	0	125	500	2000
<u>Adrenals</u>	(50 ^a)	(50)	(49)	(49)	(49)	(47)	(50)	(49)
ganglion cell proliferation	0	2	1	1	1	4	5	1
<u>Liver</u>	(49)	(49)	(50)	(50)	(50)	(49)	(50)	(49)
bile duct proliferation	16	24	25	15	6	8	9	1
<u>Pituitary</u>	(45)	(45)	(49)	(50)	(48)	(49)	(49)	(46)
clear cell, focus of cellular alteration	1	1	0	0	0	3	1	3
<u>Thyroid</u>	(45)	(47)	(48)	(50)	(45)	(46)	(46)	(47)
parafollicular cell proliferation	5	3	7	9	7	13	9	4

^a Number of tissues examined.

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TABLE 6. Percent Incidence of Non-neoplastic Histologic Findings in Rats Fed Merpan^a

Organ/Finding	Male/Dose (ppm)				Female/Dose (ppm)			
	0	125	500	2000	0	125	500	2000
<u>Adrenals</u>	(20) ^b	(50)	(48)	(20)	(19)	(47)	(50)	(19)
cortical vacuolization	25	42	39	10 ^c	32	11	22	16
sinusoidal dilation	0	0	2	0	16	19	24	11
<u>Liver</u>	(19)	(49)	(50)	-	(20)	(49)	(50)	(20)
hepatocellular vacuolization	31*	10	16	5				
RES aggregation/necrosis	0	6	8	5				
hepatocellular necrosis	0	4	2	5	0	4	4	10
<u>Lungs</u>	(20)	-	-	(19)	(19)	-	-	(20)
brown pigment accumulation	0			0	0	-	-	25*
<u>Pancreas</u>	(20)	-	-	(20)	(19)	-	-	(18)
periarteritis	10			10	26*	-	-	0
fatty atrophy	5			10	32*	-	-	0
<u>Pituitary</u>	(19)	(45)	(49)	(21)	(20)	(47)	(49)	(17)
focus of cellular alteration	11	20	20	10	0	0	0	14
<u>Spleen</u>	(20)	(50)	(50)	(20)	(19)	48	(50)	(18)
brown pigment accumulation	10	4	12	5	74	73	70	78
<u>Thymus</u>	(11)	-	-	(13)	(17)	-	-	(14)
involution	82	-	-	92	76	-	-	57
<u>Thyroid</u>	(20)	(47)	(47)	(22)	(18)	(46)	(46)	(18)
follicular dilation	0	2	0	5	0	2	7	0

* Statistically significant at a p value < 0.05; analyses by testing laboratory.

^a Compiled by this reviewer; only statistically significant differences or lesions increasing in dosed groups are tabulated.

^b Number of tissues with non-neoplastic histologic data recorded.

^c This is based on 2/20 animals determined by the checking of individual pathology sheets by the reviewer; the summary table in the report indicated 4 animals with this lesion.

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dose-related trend was not observed (Table 4). The significance of these findings was not indicated by the authors who stated that there was "no statistical significance in incidence of any tumor type between test groups and controls." There was also a nonsignificant increase in leiomyosarcomas in the small intestine of males receiving 500 ppm (3/50) without any corresponding tumors in controls, low- or high-dose males. There was an increase in adenomas or carcinomas in the islet cells of the pancreas in high-dose males (5/47) when compared to controls (1/50) but this was not significant using the Fisher exact test ($p > 0.05$). No historical control data for Wistar rats in this laboratory were provided for uterine sarcomas, adrenal pheochromocytomas or pancreatic islet cell tumors. These data would have been useful for evaluating the tumorigenic responses.

Interpretation of non-neoplastic histologic findings was complicated by the fact that although 50 animals/sex were histologically examined in control and high dose groups, there was no recording of non-neoplastic lesions for 30 of these animals/group/sex; however neoplastic and preneoplastic lesions were recorded. The rationale for this omission is not evident to this reviewer. Major organs were examined for all animals in the mid and low dose groups (both neoplastic and neoplastic lesions being recorded); however, the kidneys were omitted from examination. The rationale for this omission is not evident since there was a dose-related increase (statistically significant) in gross lesions of kidneys of males (Table 3), and 2/50 males dosed at 2000 ppm had nephroblastomas whereas controls had none (Table 4).

A number of organs with grossly observed tumors were not weighed (pituitary, adrenals, gonads and kidney), so the mean organ weights do not correlate with histologic findings.

Three reporting deficiencies in the dosing of the animals were noted. These involved a) the instability of the test material in the diet, b) the lack of documentation of body weight decrement in the high dose animals as due to a toxic effect, and c) the absence of data to support test dose selection.

- a. Because of instability of test compound in the diet and the limited frequency of diet preparation (reported as being approximately every 3 weeks) the animals may not have received the intended amount of test material in their diets. The frequency of diet preparation could not be validated from the information reported and insufficient information on the gas chromatographic resolution of degradation products versus the test material were available to confirm or calculate the average daily intake of Merpan at each dose level. Consequently, the authors' estimates of compound intake could not be verified.
- b. The percent lower weights of males and females receiving 2000 ppm Merpan as compared to controls at selected intervals during the study, and the incremental weight gains of control and high-dose males and females (calculated by this reviewer) are given in Table 2. Males receiving 2000 ppm Merpan had mean weights from 7.7 to 14.3% lower than controls and females receiving 2000 ppm Merpan had mean weights

from 6.2 to 10.2 percent lower than controls. Incremental weight gains were lower in males and females at 2000 ppm than in controls for the first 8 and 4 weeks of the study, respectively, but were comparable throughout the remainder of the study. These decreased weight gains in general correlated with statistically lower food consumption which was found in high-dosed animals in the early part of the study. Food efficiency (grams of body weight gain/grams of food consumed) was statistically lower in males at 2000 ppm compared to controls for days 1-7 but was not statistically lower at any other time interval in the first 12 weeks of the study nor thereafter. Food efficiency in females was not affected by dosing at any time during the study. Consequently, it is not clear if the lower weights of the high dosed animals were due to a primary toxic effect or was secondary to a decreased food intake resulting from poor palatability of the high-dose diet.

- c. The selection of test doses was based on a 4-week feeding study. The authors stated that at levels of 2,000, 4,000, and 12,000 ppm of Merpan, there was a dose-related growth retardation. However, the report of this 4-week feeding study and its resulting data were not available for review.

Consequently, because of the above concerns, it cannot be clearly established that the animals received the stated doses, that the doses administered were adequate to achieve optimum test sensitivity, or that the animals could not have tolerated a higher dose level.

CONCLUSIONS:

Under the conditions of the study, there was a statistically significant increase in sarcomas of the uterus in females fed Merpan at levels of 2000 ppm and an increase in the incidence of benign pheochromocytoma in males at 500 ppm but not at the high dose when compared to controls. An increased incidence, although not statistically significant, of adenomas or carcinomas in the pancreatic islet cells of males was observed at 2000 ppm. In the absence of historical control data from this laboratory regarding sarcomas in the uterus and adenomas or carcinomas of the pancreatic islet cells, it is difficult to interpret the significance of these lesions. There were no overt toxic signs, decreased survival, effects on hematology, or increased incidence of nonneoplastic histologic lesions related to dosing. There was a slight decrease in weight gain in both males and females at the highest dose tested which might have been the result of compound administration. The animals may have been able to tolerate a higher dose level.

CORE CLASSIFICATION: Minimum.