



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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

COMMERCIAL/FINANCIAL INFORMATION IS NOT INCLUDED

Subject: Dantobrom S. EPA ID No.38906-13 and Dantobrom P
EPA ID No. 38906-15
Caswell No ~~114A/306/309C~~; Project No 2333/2334
366D, 568E

From: Joycelyn E. Stewart, Ph.D. *JS 4/23/87*
Section VII, Toxicology Branch (TS-769C)
Hazard Evaluation Division

To: Jeffrey Kempter/Barbara Pringle, PM# 32
Disinfectants Branch(TS-767C)
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Thru: Albin B. Kocialski, Ph.D.
Supervisory Pharmacologist
Toxicology Branch (TS-769C)
Hazard Evaluation Division

*ABK
4/28/87
Wesley Collins
5/14/87*

Registrant: Glyco Inc.
Norwalk, Connecticut 06856-5100

Action Requested: Review developmental toxicology study in rats and rabbits, and 90 day oral study in rats of 5 ethyl, 5 methylhydantoin (EMH) and 5,5,dimethylhydantoin (DMH), the organic moieties of Dantobrom. Dantobrom consists of: bromochlorodimethylhydantoin 60%; dichlorodimethylhydantoin 27.4%; and dichloroethylmethylhydantoin 10.6%. The sponsor is seeking registration of Dantobrom P and Dantobrom S as disinfectants for swimming pools and spas. [REDACTED]

Recommendations:

The teratology study in Sprague-Dawley rats using EMH and DMH at the "limit dose" demonstrated no embryo/fetotoxic potential of these compounds. However, the study is classified core-Supplementary pending clarification of the composition and purity of the test substances.

The teratology study in New Zealand White rabbits using EMH and DMH does not give a clear indication of the embryo/fetotoxic potential of these compounds. The study is classified core-Supplementary. The study may be upgraded on submission and review of historical control data on the incidence of fetal resorptions and on fetal body weights

observed in the investigators' laboratory on the strain of rabbits used in the study. The sponsor is also requested to clarify the chemical composition and purity of the test compounds.

The 90 day oral study is classified core-Supplementary based on the absence of individual animal data supporting the investigators' conclusions. The chemical composition and purity of the test compounds also need to be delineated. The study may be upgraded when the requested information is supplied and reviewed.

Reviewed by: Joycelyn Stewart, Ph.D.
Section VII, Tox. Branch (TS-769C).
Secondary reviewer: Albin B. Kocialski, Ph.D.
Section VII. Tox. Branch (TS-769C)

005876

DATA EVALUATION REPORT

STUDY TYPE: Teratology

TOX. CHEM. NO.: ~~114A/306/309C~~ ^{366D + 568E}

ACCESSION NUMBER: 26503³0/265040(Duplicate)

PROJ. NO.: 2333/2334

TEST MATERIAL: 5,5-Dimethylhydantoin; 5 Ethyl,5 methylhydantoin

SYNONYMS: DMH; EMH

STUDY NUMBER(S): T86M0007G

SPONSOR: Glyco Inc.
P.O. Box 3187
Williamsport, Pa 17701

TESTING FACILITY: Findley Research Inc.
420 Airport Rd.
Fall River, Ma 02720

TITLE OF REPORT: Developmental Toxicity Study in Rabbits on
Ethylmethylhydantoin and Dimethylhydantoin.
Limit Test - TSCA Guidelines.

AUTHOR(S): R.M. Hoar. D.A. Olson

REPORT ISSUED: 7/6/86

CONCLUSION: The data presented did not demonstrate a clear
NOEL for embryo/fetotoxicity under the experimental conditions.

Classification: Supplementary

MATERIALS:

Dimethylhydantoin(Batch 1083.32) and Ethylmethylhydantoin
(Batch 1083.31) were the test chemicals. Sterile Water for
Injection USP was the vehicle control. The positive control compound
was 6-aminonicotinamide. The test animals were New Zealand White
rabbits.

METHODS:

Sixty virgin female New Zealand White rabbits weighing 3.0 -
4.0 kg were artificially inseminated with semen from healthy
male New Zealand White rabbits. Semen from each male was used
to inseminate several females in each group. The insemination
day was designated day zero of gestation. The females were ran-

randomly assigned to test groups receiving DMH 1000 mg/kg, EMH 1000 mg/kg, 6-AN 3 mg/kg, or the vehicle control. The test compounds were administered orally by gavage. The positive control compound was administered as a single oral dose on day 9 (8 females) day 10 (3 females) or day 11(4 females). EMH, DMH, and the vehicle were administered on gestation days 6 through 18. Females were observed daily for toxic signs. Food and water were available ad libitum. Food consumption was measured weekly. Body weights were recorded on gestation days 0, 6, 12, 18, 21 and 29. Animals found dead were necropsied. Females showing signs of abortion or premature delivery were sacrificed and examined.

All surviving does were sacrificed on gestation day 29, and the pups removed by Caesarian section. Maternal internal organs were examined, and the uterine contents, number and position of fetuses, implantation sites, corpora lutea recorded. Fetuses were weighed, sexed, and examined for external, visceral and skeletal abnormalities. For skeletal examination, fetuses were fixed, cleared and stained using the KOH Alizarin Red S method. For soft tissue examination, viscera were preserved in ethyl alcohol or 10% buffered formaldehyde.

TEST COMPOUND ANALYSIS:

The DMH and EMH solutions used in the study were analysed by ultraviolet spectroscopy and reported to be within 10% of target concentration.

STATISTICAL ANALYSIS:

Results generated from the test groups were compared independently with the vehicle control group as follows: maternal data were analyzed by analysis of variance and Fisher's exact test. Fetal data were compared by analysis of variance for homogeneity with Satterthwaite's "t" test for intergroup comparison and the Mann-Whitney U test. The level of significance was 5%.

RESULTS:

The investigators reported that the pregnancy rate was 73% in the vehicle controls as compared with 93%, 87%, and 93% in the EMH, DMH and 6-AN groups. All animals survived the study. Clinical signs of alopecia and nasal discharge were reported with equal frequency among all groups. Food consumption was reported to be significantly increased in the 6-AN group in Weeks 2 and 3 ($p \leq 0.05$). Mean maternal body weight was similar among all groups. One, 4, 2, and 1 pregnant rabbits of the control, EMH, DMH and 6-AN groups respectively aborted. All females but one which aborted were inseminated with sperm from the same buck (#60190), and data from these animals were excluded from the study.

The pregnancy rate and the number of corpora lutea were reported to be similar among all groups; while resorptions were reported significantly increased over the controls in all treated groups. Litter size was reported to be decreased in EMH treated rabbits but not significantly so. No dead fetuses were reported in any treatment group. Mean fetal body weight was significantly reduced among the EMH, DMH, and 6-AN treated groups when compared to the vehicle controls ($p < 0.05$). The investigators regarded these occurrences as biological variations rather than consequences of EMH and DMH treatment. They described the resorption rate (7.8%) and mean fetal body weights (44.1 gram) observed in the controls as unusual, and state that these values usually range from 10 to 14% and from 35 to 39 gram. The reproductive data are summarized below:

TABLE 1
REPRODUCTIVE DATA OF RABBITS IN TERATOLOGY STUDY OF
DMH AND EMH

	Control	EMH 1000 mg/kg	DMH 1000 mg/kg	6-AN 3 mg/kg
Pregnancy Rate	11/15	14/15	13/15	14/15
Abortions	1	4	2	1
Corpora Lutea	11.7 \pm 3.1	13.5 \pm 4.0	13.2 \pm 2.5	12.3 \pm 2.8
Implantation Sites	7.7 \pm 2.4	7.2 \pm 3.1	8.9 \pm 3.5	9.0 \pm 2.6
Resorption Rate(%)	7.8	18*	16.3*	23.9*
Mean Litter Size	7.1 \pm 2.5	5.9 \pm 2.4	7.5 \pm 2.6	7.4 \pm 2.6
Fetal Body Weight	44.1 \pm 6.5	40.4 \pm 6.0*	38.4 \pm 9.3*	38.3 \pm 5.9*

*Significantly different from control $p < 0.05$

No abnormalities were reported in fetuses from DMH treated does. Two does in the EMH treated group had offspring with abnormalities. One had a single pup with cleft palate/cranial meningocele, and one had a pup with interventricular septal defect. All does in the positive control group had pups with abnormalities, distributed as follows: 74% external, 37% soft tissue and 88% skeletal abnormalities. The vehicle controls had 3 fetuses with enlarged lateral ventricles, and one fetus with microphthalmia. No treatment related skeletal variations were reported. The number and types of skeletal variations were similar among all groups and consisted of the presence of 13th ribs. and absence or incomplete sternebral ossification.

Based on these results, the investigators concluded that neither EMH nor DMH demonstrated any teratogenic potential under the conditions of the study.

DISCUSSION:

The study was a "limit test" study employing a single oral dose level of 1000 mg/kg of EMH or DMH from gestation days 8 through 16 in New Zealand White rabbits. No maternal toxicity and no teratogenic responses were reported in the animals administered the test compounds, while the positive control animals produced offspring with numerous external, soft tissue and skeletal abnormalities.

Based on the data submitted, it is not clear whether the decrease in fetal body weight and the number of resorptions observed in the EMH and DMH treated does were treatment related. The sponsors are therefore requested to submit historical control data on fetal body weight and resorption rate of New Zealand White rabbits used in the investigators' laboratory in order that a full evaluation of the data may be made. The composition and purity of the test material also need to be delineated. Pending submission and review of the requested information, the study is classified core-Supplementary.

Reviewed by: Joycelyn Stewart, Ph.D.
Section VII, Tox. Branch (TS-769C)
Secondary reviewer: Albin Kocialski, Ph.D.
Section VII, Tox. Branch (TS-769C)

005876

DATA EVALUATION REPORT

STUDY TYPE: Teratology

TOX. CHEM. NO.: 114A 366D
306
309C 568E

ACCESSION NUMBER: 265031/265041 (Duplicate)

PROJ. NO.: 2333/2334

TEST MATERIAL: 5,5 Dimethylhydantoin; 5 Ethyl,5 methylhydantoin

SYNONYMS: DMH; EMH

STUDY NUMBER(S): T86M0006G

SPONSOR: Glyco Inc.
P.O. Box 3187
Williamport, Pa 17701

TESTING FACILITY: Findley Research Inc
420 Airport Rd.
Fall River, Me 02720

TITLE OF REPORT: Developmental Toxicity Study in Rats on EMH and
DMH. Limit Test- TSCA Guidelines.

AUTHOR(S): R.M. Hoar, D.A. Olson

REPORT ISSUED: 8/12/86

CONCLUSION: DMH and EMH did not demonstrate teratogenic effects
when administered to pregnant Sprague-Dawley rats
from day 6 to day 15 of pregnancy.

Classification: Supplementary

MATERIALS: 5,5 Dimethylhydantoin Batch 1083.32, and 5 Ethyl,5 methyl-
hydantoin Batch 1083.31 were the test chemicals. Sterile
Water for Inj. USP was the vehicle control. The positive
control compound was 6-aminonicotinamide(6-AN). The
test animals were Sprague-Dawley rats.

METHODS:

One hundred female Sprague-Dawley rats were mated with sexually mature males until copulation plugs were observed. The day the plugs were observed was designated day zero of pregnancy. The pregnant females were randomly assigned to four test groups: vehicle control; DMH 1000 mg/kg; EMH 1000 mg/kg; and the positive control compound AN-6 8 mg/kg.

The test compounds were administered by gavage daily from day 6 to day 15 of pregnancy. The positive control was given as a single oral dose on gestation day 15. A supplemental positive control group of 8 females was given 10 mg/kg of 6-AN on day 10, and an additional group of 18 pregnant females was given 8 mg/kg of AN-6 on day 10 of gestation.

The pregnant animals were housed individually and were observed daily for mortality and clinical signs. Food and water were available ad libitum. Body weight was recorded on days 6, 11, 16 and 20. Food consumption was measured weekly. On day 20, all surviving females were sacrificed, and the pups removed by Caesarian section. All maternal internal organs were examined grossly. The uterine contents, number and position of fetuses, and number of corpora lutea were recorded. Fetuses were sexed, weighed, and examined for external abnormalities. Half of each litter was cleared and stained with alizarin Red S for examination for skeletal abnormalities, while half was examined for visceral abnormalities using a modification of Wilson's technique.

TEST COMPOUND ANALYSIS:

Aqueous solutions of DMH and EMH were analyzed by ultra violet spectroscopy. DMH samples were reported to be 95.2 to 122 percent, and EMH samples were 98 to 122 percent of target concentration.

STATISTICAL ANALYSIS:

Maternal data were analyzed by "t" test with F test for homogeneity and Fisher's exact test. Fetal data were compared by analysis of variance with Satterthwaite's "t" test for inter-group comparison of means and the Mann-Whitney U test. The level of significance was 5%.

RESULTS:

One DMH and one EMH female died from intubation accidents during the study. No toxic signs were observed in either the DMH or EMH treated groups which could be attributed to administration of the test compounds. Nasal discharge and/or a reddish ocular exudate was reported in a few animals from both control and test compound treated animals. No toxic signs were observed in the positive control group given 8 mg/kg 6-AN on day 15, therefore a supplemental positive control group of 8 animals was added at 10 mg/kg on day 10. Severe toxicity, including one death was observed at that dose. The investigators concluded that the MTD had been exceeded, so the dose was reduced to 8 mg/kg and given by gavage on gestation day 10. These two positive control groups were used throughout the study. Toxic signs reported in these two groups were: lethargy, ataxia, irritability, and tremors. Of the 8 rats administered 10 mg/kg of 6-AN on day 10, the following gross necropsy findings were reported: one was found dead on day 14, two had completely resorbed litters, and two were not pregnant.

Except for the 6-AN(10 mg/kg) group at week 2, the maternal food consumption and body weight were similar among control and treated groups. The mean body weight gain in the 8 mg/kg 6-AN group was 28% as compared to 33% in the control and the DMH and EMH treated groups, and was 13% in the 10 mg/kg 6-AN group. One EMH treated female delivered spontaneously. Except for the positive controls no difference was reported between groups in mean number of corpora lutea, implantations, litter size, and litters with dead fetuses. The resorption rate was significantly increased in the positive control groups ($p \leq 0.01$). Fetal body weight and sex ratio were similar among all groups except the 10 mg/kg 6-AN group, which showed a significant decrease in fetal body weight ($p < 0.01$). The reproductive data are summarized below.

Summary of Reproductive Effects

	Vehicle Control	DMH 1000 mg/kg	EMH 1000 mg/kg	6-AN 8 mg/kg day 15	^a 6-AN 10 mg/kg day 10
No. of Dams ^{1/}	19	21	20	20	18
Implantations	13.2 \pm 2.9	13.6 \pm 2.0	13.9 \pm 2.4	13.7 \pm 1.8	13.7 \pm 2.6
Corpora lutea	20.9 \pm 4.9	22.4 \pm 5.7	23.1 \pm 5.1	22.1 \pm 6.4	17.8
Fetuses/dam	12.7 \pm 3.2	12.9 \pm 2.1	13.2 \pm 2.6	12.7 \pm 2.0	11.1 \pm 3.9
% Resorptions	3.9	5.3	5.3	6.9*	33.8*
Fetal body weight (gm)	3.8 \pm 0.5	4.0 \pm 0.07	3.7 \pm 0.3	3.0 \pm 0.5	2.3 \pm 0.06

a Dosage changed to 8 mg/kg on day 10

* Significantly different from control $p \leq 0.05$

^{1/} Litters with viable fetuses

No external abnormalities were reported in fetuses from the DMH and EMH treated rats. One control fetus was reported to have an umbilical hernia, and one was reported with lowset jaws and no mandible. Numerous external anomalies were reported for the positive controls including cleft lip, cleft palate, fused digits and rudimentary digits. The number and types of soft tissue abnormalities were similar in fetuses from control, DMH and EMH treated rats and are summarized as follows: bilateral renal pelvis dilation, 8, 2, 1; unilateral renal pelvis dilation, 4, 4, 1; umbilical eventration, 1, 0, 0, in fetuses from the control, DMH, and EMH treated groups respectively. One control fetus was reported with fused vertebral bodies (L2-L3 on left; L2-L4 on right); one DMH fetus with bilateral wavy ribs; one EMH fetus with unossified vertebral bodies C1-C3. An increased incidence of supernumerary ribs was reported in fetuses of DMH and EMH treated rats. The incidence of unossified or incompletely ossified sternbrae was similar in negative control and DMH and EMH treated fetuses, while the incidence of these findings was increased in the 6-AN treated fetuses. Several skeletal and soft tissue abnormalities were reported in fetuses of 6-AN treated animals at both dosage levels.

Based on these observations, the investigators concluded that DMH and EMH were not teratogenic when administered under the conditions of the study.

DISCUSSION:

Administration of DMH and EMH to pregnant Sprague-Dawley rats at dosage levels of 1000 mg/kg from gestation days 6 through 15 did not result in mortality, significant toxicity to the dams, adverse effects on gestational parameters, (corpora lutea, resorptions), the number of live births, fetal body weights, or sex ratio of the offspring. No compound related teratogenic effects were reported. Although the fetuses from each litter were not individually identified, enough data were presented to adequately support the investigators' conclusions that the test compounds did not exhibit any teratogenic potential.

Maternal NOEL = > 1000 mg/kg

Embryofetotoxic NOEL = > 1000 mg/kg

$$\begin{aligned} \text{A/D Ratio} &= \frac{\text{maternally toxic level}}{\text{fetal toxic level}} \\ &= \frac{1000 \text{ mg/kg}}{1000 \text{ mg/kg}} = 1 \end{aligned}$$

Core Classification: Supplementary. The study may be upgraded after identification of the composition and purity of the test material.

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Section VII, Tox. Branch (TS-769C)
Secondary reviewer: Albin B. Kocialski, Ph.D
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005876

DATA EVALUATION REPORT

STUDY TYPE: Subchronic Oral

TOX. CHEM. NO.: ~~N4A 568E~~
~~306~~ 366D
~~309C~~

ACCESSION NUMBER: 265032/265042(Duplicate)

PROJ. NO.: 2333/2334

TEST MATERIAL: 5,5 dimethylhydantoin(DMH); 5 ethyl,5 methylhydantoin

SYNONYMS: dimethylhydantoin(DMH); ethylmethylhydantoin(EMH).

STUDY NUMBER(S): T86M0023G

SPONSOR: Glyco Inc., Williamsport, Pa 17701

TESTING FACILITY: Findley Research Inc.
Fall River, Maine 02720

TITLE OF REPORT: 90 day oral toxicity study on EMH and DMH in Rats.

AUTHOR(S): J.A. Salinas; J. Fredette; D.A. Olson; R. Baker; H.E.Griffin
J. Reynolds; and I.E. Smiley.

REPORT ISSUED: 7/24/1986

CONCLUSIONS: The study as reported does not adequately assess the subchronic oral toxicity of EMH and DMH. The study may be upgraded when the raw data supporting the investigators' conclusions and the chemical composition and purity of the test chemical have been submitted and reviewed.

Classification: core-Supplementary

A. MATERIALS:

1. The test compounds were DMH (Batches 1083:32 and 1083:45) and EMH (Batches 1083:31 and 1083:46) dissolved in Water for Injection USP. The purity and composition of the test compounds were not stated.

2. The test animals were Sprague-Dawley rats obtained from Taconic Farms, Germantown, NY. Age and weight were not given.

3. Animals were housed in individual cages in an animal room maintained at $22 \pm 3^{\circ}\text{C}$ with relative humidity at $50 \pm 20\%$ and a 12 hour light and dark cycle. They were given a standard rodent laboratory diet (Prolab RMH 3000) and water ad libitum. Food was withheld for 15-20 hours prior to terminal sacrifice.

B. STUDY DESIGN:

1. Animal assignment - Animals were assigned randomly to the following test groups:

Test Group	Dose in diet (ppm)	Main Study 3 months		Interim Sac. 1 month	
		male	female	male	female
1 Cont.	0	15	15	5	5
2 EMH	0	15	15	5	5
3 DMH	0	15	15	5	5

2. The test animals were gavaged with either DMH or EMH at dosage levels of 1000 mg/kg body weight 5 days/week for 90 days. Control animals received distilled water by gavage. The test solutions used in the study were analyzed by u.v. spectrophotometry and were found to contain 95.2% - 122% (DMH) and 98-122% (EMH) of target concentration. The test compound concentrations were adjusted weekly so that the required dose was contained in 2 ml/100 g of body weight.
3. Observations - Animals were inspected daily for signs of toxicity and mortality.
4. Body weight - They were weighed weekly throughout the study.
5. Ophthalmological examinations were performed on 5 animals/sex at the beginning and end of the study.
6. Blood was collected for hematology and serum biochemistry from 10 males and 12 females from the same stock of animals used in the study at start of the study, from 5 animals/sex/group at 30 days, and from 5/sex of the DMH and EMH treated and 6/sex of the controls at 90 days. The CHECKED (X) parameters were examined.

a. Hematology -

X	Hematocrit (HCT)*	X	Total plasma protein (TP)
X	Hemoglobin (HGB)*	X	Leukocyte differential count
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)*	X	Mean corpuscular HGB conc. (MCHC)
X	Platelet count*	X	Mean corpuscular volume (MCV)

b. Clinical Chemistry

Electrolytes:		Other:	
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
X	Phosphorous*	X	Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
Enzymes		X	Total Bilirubin*
X	Alkaline phosphatase	X	Total Protein*
X	Lactic acid dehydrogenase	X	Triglycerides
X	Serum alanine amino- transferase(SGPT)*	X	BUN/Creatinine Ratio
X	Serum aspartate amino- transferase (SGOT)*	X	A/G Ratio
		X	Iron
		X	Uric Acid

* Required for subchronic and chronic studies.

6. Urinalysis - Urinalysis was not performed in this study. The CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose*
	Volume*		Ketones*
	Specific gravity*		Bilirubin*
	pH		Blood*
	Sediment (microscopic)*		Nitrate
	Protein*		Urobilinogen

* Required for chronic studies.

7. Sacrifice and Pathology - All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

Digestive system		Cardiovasc./Hemat.		Neurologic	
	Tongue		Aorta*	XX	Brain*
X	Salivary glands*	X	Heart*	X	Periph. nerve*
X	Esophagus*		Bone marrow*	a	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*	a	Eyes (optic n.)*
X	Jejunum*		Thymus*	Glandular	
X	Ileum*		Urogenital	XX	Adrenals*
X	Cecum*	XX	Kidneys*	a	Lacrimal gland
X	Colon*	X	Urinary bladder*	a	Mammary gland*

X	Rectum*	XX	Testes*	X	Parathyroids*
XX	Liver*	X	Epididymides	X	Thyroids*
	Gall bladder*	X	Prostate		Other
X	Pancreas*	X	Seminal vesicle	a	Bone*
	Respiratory	XX	Ovaries	a	Skeletal muscle*
	Trachea*		Uterus*	a	Skin
X	Lung*			X	All gross lesions and masses

* Recommended by Subdivision F (Oct. 1982) guidelines for chronic studies.

a. Preserved in formalin but not microscopically examined since there was no indication of toxicity of the target organ.

8. Statistics - The following procedures were utilized in analyzing the numerical data:

Non-parametric data were analysed according to Wilcoxon/Mann Whitney U-test for two samples.

Parametric data were analysed by Students "t" test comparing comparing each experimental group with the control group. The incidence of certain histopathology findings were analysed for significance using 2x2 contingency tables (Fisher Exact Test).

9. Quality assurance inspections were conducted periodically during the study. A signed and dated Quality Assurance statement is included in the submission.

C. RESULTS:

Hair loss on legs was reported to be distributed among all treatment groups. Chromodacryorrhea was observed in 2 animals/sex from the DMH treated group, and in 2 males and 1 female from the EMH group. One female from the EMH group died on day 84. Gross examination demonstrated that this animal had an ulcerated liver, enlarged spleen, hemorrhagic thymus and mesenteric lymph nodes.

Body weight in male rats were 98.3% and 106.7% of control, while female body weights were 105% and 104% of control in the animals administered DMH and EMH respectively. No ophthalmological abnormalities were observed in either control or treated animals as determined by the Draize test.

The following hematological parameters were reported to be significantly different from controls (<0.05): in DMH treated males: decreased RBC, WBC, lymphocytes, MCHC and increased segmented WBC, MCV; in DMH treated females: decreased lymphocytes, MCH and MCHC. In EMH treated males:

decreased RBC, WBC, Hgb, MCHC and increased MCV and MCH; and decreased lymphocytes, WBC and increased segmented WBC in females. The biochemical changes observed which were statistically significantly different from control ($p < 0.05$) were: in DMH treated males; decreased albumin, increased phosphate, and SGPT, and in DMH treated females, increased uric acid and BUN/creatinine. In EMH treated males, total protein and albumin were decreased and iron increased, while BUN/creatinine, LDH, alkaline phosphatase, chloride, SGOT and SGPT were increased in females. These changes were not considered to be biologically significant since they were not consistent in both sexes and were not accompanied by any histopathological changes. Moreover, the RBC and WBC values were reported to be within the range reported in the literature (7.25 - 8.45 for RBC; 10.0 - 17.2 for WBC).

Significantly lower ($p < 0.05$) absolute and relative liver weights were reported in DMH treated males; significantly higher absolute kidney and adrenal weight ($p < 0.01$) were reported in EMH treated rats. Relative, but not absolute lower brain weights were observed in EMH treated male rats ($p < 0.01$). DMH treated females had significantly higher spleen weights ($p < 0.01$).

Slight to moderate mottling of the lung was observed in 1/10, 2/10, and 4/10 males and in 2/10, 1/10, and 1/10 females of the control, EMH and DMH groups respectively. No other gross abnormalities were reported.

No histological findings attributable to DMH or EMH administration were reported. The incidence of focal chronic hepatitis was reported to be similar among all groups, and nephrocalcinosis was reported among all female groups. Isolated incidences of focal chronic myocarditis and thyroid hyperplasia were reported.

D. DISCUSSION:

The study was done according to the "limit" test procedure in which 1000 mg/kg of EMH and DMH were administered by gavage 5 days/week for 90 days to Sprague-Dawley rats. No toxicity was observed which could be attributed to administration of the test compounds. Therefore the investigators concluded that that neither EMH nor DMH was toxic to Sprague-Dawley rats under the study conditions. However, the raw data

supporting the investigators' conclusions were not included in the submission. The composition and purity of the test material also needs to be delineated. Based on these deficiencies, the study is classified core-Supplementary. The study may be upgraded when the missing information has been submitted and reviewed.