

US EPA ARCHIVE DOCUMENT



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

10-21-83

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

OCT 21 1983

MEMORANDUM

SUBJECT: Spa-Brom; Review of Toxicity Studies on  
Dimethylhydantoin

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10/21/83

Compound: Dimethylhydantoin

Registration No. 1729-122  
1729-123

Accession Nos. 250552, 55, 56, 57, 58, 59, 60, 61 and 83.

Tox. Chem. No. 114A

Registrant: Hydro Tech Chemical Corp.  
Great Lakes Chemical Corp.

Action: Review 9 toxicology Studies, requested by  
the Agency, of dimethylhydantoin.

Background

Spa-Brom utilizes 1-Bromo-3-chloro-5,5-dimethylhydantoin as a source of bromine and chlorine as a disinfectant in spas and hot tubs. Based on the toxicity of the drug diphenylhydantoin, concern has been generated about the possible

toxicity of the dimethylhydantoin moiety. Diphenylhydantoin is an antiepileptic drug which has been established as a teratogen and oncogen in experimental animals and in man. The data available at the Agency on dimethylhydantoin was essentially nil. The Agency therefore asked the Registrant to supply teratogenicity, 90-day subchronic and metabolism studies and a mutagenicity battery on dimethylhydantoin. In addition, the Registrant agreed to commission an independent expert to compare and contrast the metabolism of dimethylhydantoin with the metabolism of diphenylhydantoin. Based on this information the Agency would determine if the safety of dimethylhydantoin could be defined satisfactorily or if additional studies were necessary.

The studies requested have been supplied and are reviewed in the attached DERs.

### Results

In the rat teratogenicity study, dimethylhydantoin was not teratogenic at doses up to 4.5 gm/kg/day. Toxicity to dams and pups consisting of dose related weight depression at 2 and 4.5 gm/kg/day was observed. No effect was observed of 0.5 gm/kg/day.

In the 90-day rat study dimethylhydantoin was administered orally, by gavage, at 2, 5 or 10 gm/kg/day. A generally mild, nonspecific and dose related toxicity was observed at all doses. The basic toxic effect appeared in the kidney, particularly in the males and appeared to be due to the relatively massive solute load imposed by the compound. Increases in SGPT and alkaline phosphatase paralleled the kidney effects. A NOEL was not demonstrated in this study.

The metabolism study in rats showed that dimethylhydantoin was rapidly absorbed by the oral route and rapidly excreted in the urine essentially unchanged. There was no evidence of bioaccumulation or of a change in metabolic pattern following 14 days of dosing.

The in vitro cell transformation assay and the mouse lymphoma forward mutation assay were negative at doses up to 1000 ug/ml both without and with activation. The in vivo bone marrow cytogenetic assay in male and female rats was negative at doses up to 2 gm/kg P.O.

The comparison of the metabolism of dimethylhydantoin and diphenylhydantoin was performed by Gary P. Carlson Ph.D., Professor of Toxicology, Purdue University. Dr. Carlson points out the extensive metabolism of the phenyl group on the diphenyl compound compared to the complete lack of metabolism of the dimethyl compound.

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The data considered clearly implicates the highly reactive intermediate (arene oxide) in the teratogenicity and oncogenicity of diphenylhydantoin.

The review also points out that the metabolism and excretion of the diphenyl is affected by both the dose and duration of administration.

#### Discussion and Recommendation

Dimethylhydantoin has been shown by the studies reported to differ significantly in toxicity and metabolism from the human drug diphenylhydantoin. Diphenyl is teratogenic in rats at 150 mg/kg/day while dimethyl is not teratogenic at 4.5 gm/kg/day. Orally in rats, diphenyl is lethal at doses in the order of 3 gm/kg by a central depression. Rats tolerated oral doses of 10 gm/kg/day dimethyl for 90 days without visible signs of toxicity.

In addition, dimethyl is inactive in the mutagenicity tests both with and without metabolic activation. Diphenyl is mutagenic in several test systems but requires metabolic activation.

Dimethyl is excreted rapidly and metabolically unchanged. Diphenyl is excreted in a complex dose-dependent pattern and is metabolized through formation of a highly reactive arene oxide on a phenyl ring.

The data available are sufficient to show that dimethylhydantoin lacks the chemical properties that make diphenylhydantoin a teratogen and a carcinogen. These properties lie in the metabolic pattern of the phenyl rings of diphenylhydantoin.

There is, however, a problem with the results of the 90-day rat study with dimethylhydantoin. The study shows clear evidence of a nonspecific kidney damage in the rats, particularly males, which is probably due to excretion of excessive solute with accompanying precipitation in collecting ducts, kidney pelvis, ureter, bladder and urethra. This is shown by histopathology, blood in the urine and increased SGOT and alkaline phosphatase. A NOEL was not demonstrated at the lowest dose, 2 gm/kg/day orally by gavage. Demonstration of a NOEL is necessary particularly to insure that the changes in blood chemistry are associated with the kidney effect and not indicative of some other toxic effect. A NOEL is also necessary to indicate a margin of safety for the human exposure (dose) expected with hot tub-spa use.

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An additional study is required to provide a NOEL. The study may be either a second 90-day rat study or a 2-year rat study. The study chosen must be performed at lower doses. It is strongly recommended that the Registrant consult with the Agency on choice of study and dose.

DCR-32818:Zendzian:TOX-24:CM#2:RM-824:557-1511:8/30/83:efs  
REVISED-9/2/83:DCR-32821:TOX-24:efs

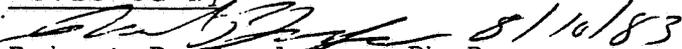
DATA EVALUATION REPORT

Compound Dimethylhydantoin

Citation

Four Week Range-Finding Oral Gavage Study in Rats with Dimethylhydantoin (DMH)  
M. LaQuire & D.A. Mayher  
Will Research Laboratories Inc., May 1983.

Reviewed by

  
Robert P. Zendzian, Ph.D.  
Pharmacologist

Core Classification Supplementary

Tox Category: N/A

Conclusion:

Signs of compound toxicity were observed at 9 and 12.5 gm/kg/day. Two female rats died after a single dose of 12.5 gm/kg/day. Toxicity was nonspecific depression.

Materials

Dimethylhydantoin 899 00 00 from Great Lakes Chemical Co.

Young male and female CD Sprague Dawley rats from Charles River Breeding Laboratories.

Methods

Rats were randomly assigned, 5 males and 5 females to 5 test groups and dosed orally, by gavage, with 0, 2.5, 5.0, 9.0 or 12.5 gm/kg/day of dimethylhydantoin for 28 days. Compound was administered as a suspension in 0.59% methylcellulose.

Rats were observed twice daily for signs of toxicity, weighed weekly and food consumption measured weekly. Survivors were sacrificed and necropsied at termination.

Results

Following the first dose one female was found dead and a second female was sacrificed moribund in the high dose group.

Lethargy and salivation were observed in groups dosed with 9.0 and 12.5 gm/kg/day.

No specific abnormalities were observed at necropsy.

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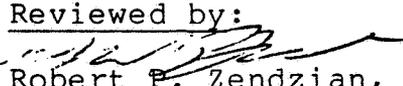
## DATA EVALUATION REPORT

Compound: Dimethylhydantoin

Citation:

A Range-Finding Teratology Study in Rats with 5,5-Dimethylhydantoin, D.E. Rodwell, WIL Research Laboratories Inc.  
December 21, 1983

Reviewed by:

 8/16/83  
Robert P. Zendzian, Ph.D.  
Pharmacologist

Core Classification: Supplementary

Toxicology Category: N/A

Conclusion

Signs of maternal toxicity were observed at 5, 7.5 and 10 gm/kg/day. No signs of maternal or fetal toxicity were observed at doses of 2.5 mg/kg/day or lower.

Materials

Dimethylhydantoin (899 00 00) from Great Lakes Chemical Corporation.

Sexually mature female Sprague-Dawley COBS CD rats from Charles River Breeding Laboratories.

Methods

Females were caged individually with males until a copulatory plug was evident and then were caged individually. Bred females were assigned, serially, to one of six treatment groups and dosed orally with 0, 1, 2.5, 5, 7.5 or 10 gm/kg/day on day 6 through 19 of gestation. *Oral.*

Females were observed twice daily through gestation and weighed on days 0, 6, 9, 12, 16 and 20. Surviving females were sacrificed, by CO<sub>2</sub> asphyxiation on gestation day 20 and necropsied. The uterus and ovaries were examined and number of corpora lutea, viable and non-viable fetuses, early and late implantations and the total number of implantation sites determined.

Results

Toxicity was observed in females dosed with 5 or more gm/kg/day. One female died at 7.5 and two at 10 gm/kg/day. The remaining females demonstrated ataxia and depression. Decreases in body

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weight and weight gain were observed. No apparent compound-related effects were observed at sacrifice and necropsy and in reproductive parameters.

## DATA EVALUATION REPORT

Compound: Dimethylhydantoin

Citation:

Mouse Lymphoma Forward Mutation Assay Dimethylhydantoin  
M.G. Farrow  
Hazleton Laboratories America Inc.  
October 29, 1982

Reviewed by:

*Robert P. Zendzian* 8/17/83  
Robert P. Zendzian, Ph.D.  
Pharmacologist

Core classification: Minimum.

Tox Category: N/A

Conclusion:

Dimethylhydantoin is not mutagenic in the activated or unactivated L5178Y mouse lymphoma mutation assay.

Materials

Dimethylhydantoin was supplied by Great Lakes Chemical Corporation.

Ethylmethane sulfonate (EMS) unactivated positive control.

3-methylcholanthrene (MCA) activated positive control.

L5178Y heterozygens TK<sup>+/-</sup> mouse lymphoma cells, subline 3.7.2C

Methods

The test system was exposed to dimethylhydantoin at concentrations of 3, 10, 30, 100, 300 or 1000 µg/ml with or without metabolic activation for the toxicity test. The forward mutation assay was performed at concentrations of 82, 117, 168, 240, 343, 490, 700 or 1000 µg/ml dimethylhydantoin with or without metabolic activation.

EMS, the positive unactivated control, was utilized at 620 µg/ml and MCA, the positive activated control, was utilized at 1 µg/ml.

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Results

Dimethylhydantoin was not toxic at the doses used. The compound was not mutagenic in the nonactivated and or the activated test.

DCR-11760:Zendzian:Tox-18:CM#2:Rm821:557-1511:8/11/83:efs  
REVISED-8/12/83:DCR-11678:TOX-18:efs

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## DATA EVALUATION REPORT

Compound: Dimethylhydantoin

Citation:

1. Cell Transformation Assay, Dimethylhydantoin without Metabolic Activation  
M.G. Farrow and R.C. Sernan  
Hazleton Laboratories America Inc.  
January 18, 1983.

2. Cell Transformation Assay, Dimethylhydantoin with Metabolic Activation  
M.G. Farrow and R.C. Sernan  
Hazleton Laboratories American Inc.  
January 18, 1983.

Reviewed by:

 8/17/83  
Robert P. Zendzian, Ph.D.  
Pharmacologist

Core Classification: Minimum

Tox Category: N/A

Conclusion:

Dimethylhydantoin did not induce cell transformation in the C3H/10T 1/2 (Clone 8) cell line at doses up to 1000 mg either without or with metabolic transformation.

Materials

Dimethylhydantoin from Great Lakes Chemical Corporation.

Benzo(a)pyrene positive without activation control, from Aldrich. Lot No. 021897.

Cyclophosphomid positive with activation control, from Adams Chemical Co.

C3H/10% 1/2 (Clone 8) cells from Dr. Charles Heidelberser.

Methods

In the first study C3H10T 1/2 (Clone 8) mouse fibroblast cells were exposed to 1000, 300, 100, 30 and 10 ug/ml of dimethylhydantoin, 10 ug/ml of benzo(a)pyrene, and a negative control, all without metabolic activation.

In the second study C3H/10T 1/2 (Clone 8) mouse fibroblast cells were exposed to 1000, 300, 100, 30 and 100 ug/ml of dimethylhydantoin, 4 ug/ml cyclophosphamid and a negative control all with metabolic activation.

Results

Dimethylhydantoin did not produce cell transformation either without or with metabolic activation. Positive controls were active in both conditions.

DCR-11761:Zendzian:8/11/83:TOX-33:Rm821:CM#2:557-1511:efs  
REVISED-8/17/83:DCR-11770:efs:TOX-33

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DATA EVALUATION RECORD

Compound: Dimethylhydantoin

Citation: In Vivo Bone Marrow Cytogenetic Assay in Rats 5,5-Dimethylhydantoin (DMH)

M.G. Farrow, T. Cortina and M. Zite,  
Hazleton Laboratories America, Inc., October 26, 1982.

Reviewed by: *[Signature]* 8/17/85  
Robert P. Zendzian, Ph.D.  
Pharmacologist

Core Classification: Minimum

Tox Category: N/A

Conclusion: Dimethylhydantoin was negative in the in vivo bone marrow cytogenetic assay in male and female rats at doses of up to 2 gm/kg.

Materials: Dimethylhydantoin (DMH) was supplied by the sponsor.

Male and female Sprague-Dawley CD rats from Charles River Breeding Laboratories, Inc.

Method: Rats were assigned, randomly, to five groups of 15/sex/group. Groups were:

1. Vehicle control
2. Positive control cyclophosphamide 40 mg/kg
3. DMH 200 mg/kg
4. DMH 660 mg/kg
5. DMH 2000 mg/kg

The material was administered as a single oral dose by gavage at time zero. A single intraperitoneal dose of colchine (2 mg/kg) was administered two hours before the scheduled time of sacrifice which was according to the table from the report.

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Number of Animals Sacrificed at Each Time Interval  
Following Compound Administration

Group	Treatment	6 Hours		12 Hours		24 Hours		48 Hours		7 Days	
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
I	Polar Distilled H <sub>2</sub> O	3	3	3	3	3	3	3	3	3	3
II	Cyclophosphamide (40 mg/kg)	-	-	-	-	3	3	-	-	-	-
III	DMH (200 mg/kg)	3	3	3	3	3	3	3	3	3	3
IV	DMH (660 mg/kg)	3	3	3	3	3	3	3	3	3	3
V	DMH (2,000 mg/kg)	3	3	3	3	3	3	3	3	3	3

"The bone marrow cells were processed according to the modified techniques described by Evans (1976 and Kilian et al. (1977))." Slides were read blind and fifty cells in metaphase were examined for each rat. "Numbers and types of chromosomal aberrations, mitotic index, modal number and the vernier location of each metaphase containing damage were recorded."

"Chromosomal aberrations were characterized as follows:

- (1) chromatid breaks - including fragments and deletions
- (2) chromosome breaks - including acentric fragments, deletions, and minutes
- (3) chromatid and chromosome gaps
- (4) exchanges - rings, dicentrics, quadriradials and triradials
- (5) cells with >10 aberrations
- (6) pulverized cells"

Numerical data were analyzed statistically.

### Results

Positive results were produced by cyclophosphamid, the positive control. The test compound was negative.

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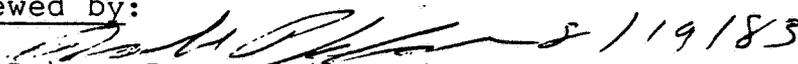
DATA EVALUATION REPORT

Compound Dimethylhydintoin

Citation: The Absorption and Elimination of Dimethylhydantoin  
<sup>14</sup>C by Rats

P. Rosnis and E.M. Craine  
Wil Research Laboratories Inc.  
Research Report, Analytical 85:4  
Project WIL-12003  
May 12, 1983.

Reviewed by:

 1/19/83  
Robert P. Zendzian, Ph.D.  
Pharmacologist

Core Classification: Guideline

Tox Catagory: N/A

Conclusions:

Dimethylhydantoin <sup>14</sup>C administered orally was rapidly absorbed and rapidly excreted in the urine. The compound was excreted essentially unchanged. No evidence of bioaccumulation was obtained.

Materials

Dimethylhydantoin from Great Lakes Chemical Corp.

Dimethylhydantoin - <sup>14</sup>C (DMH-<sup>14</sup>C)  
12.33 mCi/mM, ring labeled position two. From Pathfinder Laboratories.

CD Charles River White Rats from Charles River Breeding Laboratories Inc.

Methods

Five male and five female rats, approximate 200 gm in weight, were dosed with dimethylhydantoin - <sup>14</sup>C at a single dose of 20 or 100 mg/kg. An additional 5 males and five females were dosed for 14 days with 20 mg/kg/day, dimethylhydantoin and then with a single dose of 20 mg/kg dimethylhydantoin-<sup>14</sup>C. Immediately after dosing the rats were placed in individual metabolism cages for seven days. Total urine and feces were collected at intervals of 4, 8, 12, 24, 36 and 48

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hours and 3, 4, 5, 6 and 7 days. Rats were then sacrificed and bone, brain, fat, gonads, heart, kidney, liver, muscle and spleen collected. All samples were analyzed for radioactivity.

Samples of urine were analyzed by thin layer chromatography for metabolites.

### Results

Dimethylhydantoin was essentially completely excreted in the urine during the collection period. No dose or treatment or sex related differences were observed. The majority of material was excreted within 24 hours. No tissue deposition was observed.

The radiolabeled compound was excreted at least 98% unchanged with no evidence of significant metabolites.

DCR-11286:Zendzian:Tox-28:7/19/83:CM#2:Rm821:557-7311:efs  
REVISED-7/20/83:DCR-11753:TOX-28:efs

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## DATA EVALUATION REPORT

Compound: Dimethylhydantoin

Citation:

90-Day Oral Gavage Study in Rats Dosed with Dimethyl-  
hydantoin  
B. J. Carling, R. Mudersbach F. W. Sigler & D. A. Mayhew  
WIL Research Laboratories Inc. January 10, 1983.

Reviewed by:

 5/17/83  
Robert P. Zendzian, Ph.D.  
Pharmacologist

Core Classification: Minimum

Tox Category: N/A

Conclusion:

Nonspecific kidney toxicity probably due to excretion of the large dose, was observed with some evidence of tissue damage. A NOEL was not demonstrated at the lowest dose administered, 2 gm/kg/day.

Materials

Dimethylhydantoin 899,00,000 from Great Lakes Chemical Corporation.

Young male and female Sprague-Dawley CD rats from Charles River Breeding Laboratories.

Methods

Rats were assigned randomly to four groups, of 20 males and 20 females, and dosed orally, by gavage, at 0, 2, 5 or 10 gm/kg/day dimethylhydantoin for 90 days.

Animals were observed twice daily and examined weekly for toxic effects. Animals were weighed weekly and food consumption recorded weekly.

Blood collections for hematology and clinical chemistry were made during week 1 (10/sex/dose), during week 4 (10/sex/dose) and during week 12 (10/sex/dose). Urine samples were collected one day prior to blood samples.

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Hematology

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White Blood Cell Count	Mean Corpuscular Hemoglobin Concentration
Red Blood Cell Count	Mean Corpuscular Volume
Hemoglobin	Mean Corpuscular Hemoglobin
Hematocrit	Differential White Blood Cell Count
Reticulocyte Count*	Platelet Count

\*Only to be determined if signs of anemia were present; no signs of anemia were apparent so reticulocyte count was not determined.

Clinical Chemistry

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Glucose	Alanine Aminotransferase (SGOT)
Urea Nitrogen	Aspartate Aminotransferase (SGPT)
Total Protein	Alkaline Phosphatase
Albumin (A)	Lactic Dehydrogenase
Globulin (G)	Calcium
Albumin/Globulin (A/G)	Potassium
Total Cholesterol	Total Bilirubin
Direct Bilirubin	

Urinalysis

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Specific Gravity	Bilirubin
pH	Ketones
Glucose	Urobilinogen
Protein	Microscopic Examination of Centrifuged Sediment
Blood	Color

At termination animals were sacrificed by CO<sub>2</sub> asphyxiation and necropsied. Brain, gonads, heart, kidneys and liver were weighed.

The following tissues were examined grossly and fixed:

Adrenals	Prostate
Aorta (thoracic)	Salivary Gland (mandibular)
Bone and Bone Marrow (sternabrae)	Sciatic Nerve
Brain (3 sections)	Seminal Vesicles
Cecum	Skeletal Muscle
Epididymis	Skin
Esophagus	Spinal Cord
Eyes	Spleen
Heart	Stomach
Intestines (3 levels)	Testes
Kidneys	Thymus
Liver (2 sections)	Thyroids (w/parathyroids)
Lung (with mainstem bronchi)	Trachea
Lymph Node (mesenteric)	Urinary Bladder

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Mammary Gland  
Ovaries  
Pancreas  
Pituitary

Uterus (corpus and cervix)  
Vagina  
All gross lesions

All tissues and lesions were processed and read in the control and high dose groups; in the low and mid dose groups the heart, kidneys, liver and lesions were processed and read.

Results

Four animals died on test, one control female, one mid dose female, one high dose female and one high dose male. At least two of these deaths were due to dosing trauma.

A dose related appearance of material-stains in the urogenital area and around the mouth was observed in the treated animals. This is probably related to the large amount of compound administered.

A statistically significant decrease in growth rate was observed in the high dose males in week 7 through 12. Increased food consumption was observed in all treated animals and it was statistically significant in mid and high dose females, in a dose related fashion.

A dose related decrease in platelets was observed in treated animals, which was statistically significant, as shown below.

Platllets/Thousands/ml

wk	Group 1	2	3	4
M/4	<del>867.5</del> 779.3	746.6	630.8*	537.3**
/12	779.3	689.5	641.8*	558.7**
F/4	798.4	721.0	748.7	502.1**
/12	709.2	763.1	684.5	628.8

\* P < 0.05  
\*\* P < 0.01

As shown in table B from the report, dose related increases in serum enzyme activity was observed at 4 and 12 weeks in both sexes. Such increases are considered indicative of tissue breakdown.

Urinalysis indicates a dose related appearance of blood, RBCs and protein particularly in the males. This can be considered indicative of some kidney/urinary bladder damage.

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TABLE 6

PROJECT NO.: WIL-81185  
 CLIENT: GREAT LAKES CHEMICAL CO.  
 CLIENT STUDY NO.:  
 \*\*\* SERUM CHEMISTRY VALUES--SUMMARY OF MEANS \*\*\*  
 90 DAY ORAL GAVAGE STUDY IN RATS WITH DIMETHYLHYDANTOIN  
 14:33 04-JAN-83 PAGE 1  
 WEEK 4

TEST	SEX	MALE				FEMALE			
		1	2	3	4	1	2	3	4
GLU	MG/DL	57.90	74.70	61.60	83.40*	70.40	71.30	69.00	76.70
ESW	MG/DL	15.60	17.00	16.40	16.60	16.10	15.50	16.10	19.10
TP	G/DL	7.16	7.00	7.18	6.89	7.58	7.02	7.41	7.53
ALB	G/DL	4.14	4.04	4.44	4.43	4.41	4.52	4.57	5.12**
CLB	G/DL	3.02	2.96	2.74	2.46	3.17	2.50**	2.64	2.41**
CA	MG/DL	10.63	11.23	10.55	10.37	10.97	10.39	11.13	10.89
CHOL	MG/DL	55.90	59.20	76.10	89.90**	85.80	64.80	83.90	87.40
BILI	MG/DL	0.70	0.59	0.79	0.78	0.75	0.88	0.76	1.18
UREL	MG/DL	0.60	0.09	0.02	0.02	0.02	0.02	0.02	0.02
SGOT	U/L	156.00	133.60	152.60	154.60	133.60	129.30	134.30	129.40
SGPT	U/L	24.20	20.20	36.30**	45.30**	25.30	39.20	33.70*	40.50**
ALP	U/L	159.50	190.80	216.80	515.60**	95.10	165.50	169.10	251.40**
LH	U/L	2010.50	1583.50	1699.10	1035.00	1400.00	1272.30	939.80	671.70*
K	MG/L	6.34	5.82	5.66*	5.39**	5.70	5.51	5.64	5.54
A/G	G/%	1.41	1.40	1.72	1.84*	1.41	1.88*	1.65	2.23**

\* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP AT .05 LEVEL USING DUNNETT'S TEST

\*\* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP AT .01 LEVEL USING DUNNETT'S TEST

UNIT CODE: MG/DL = MILLIGRAMS/DECILITER; G% = GRAMS PERCENT; U/L = INTERNATIONAL UNITS/LITER  
 G/DL = GRAMS/DECILITER; U/L = MILLIGRAMS/DLIS/LITER

Q = UNABLE TO ACCURATELY ASSAY DUE TO EXTENSIVE LITICHA AND HEMOLYSIS

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No treatment-related abnormalities were observed in gross necropsy.

In treated males the mean kidney weight, both absolute and relative, was significantly increased at all doses in a dose related manner.

In treated females the mean kidney weight, both absolute and relative, was increased in a dose related manner but was significant only at the mid and high doses absolute and high dose relative. The mean liver weight, both absolute and relative, was increased in a dose related manner but was significant only at the mid and high doses absolute and high dose relative.

Histopathological examination identified kidney lesions, shown in the table, which may be compound related. The effects appear to be confined to the males although the pelvis urolithiasis seen in the female may have some compound relation.

SEX	Dose group	MALES				FEMALES			
		1	2	3	4	1	2	3	4
Kidneys									
Total No. Examined		20	20	20	19	19	20	19	18
Unremarkable		12	12	8	11	16	17	13	15
Glomerulonephrosis (progressive and diseased)		5	3	1	1	0	0	0	0
Hydronephrosis		1	1	4	2	0	0	1	0
Pelvic Urolithiasis		0	4	8*	4	2	2	5	2
Chronic Pyelonephritis		0	1	1	1	1	0	0	0
Chronic Interstitial nephritis		0	2	6	2	0	1	0	1
Total lesions:		6	11	20	10	3	3	6	3

\* = P < 0.05

### Discussion

The mild and generally nonspecific responses to large doses of dimethylhydantoin are indicative of a very low level toxicity.

The basic toxic effect appears in the kidney, particularly in the males. The increase in mean kidney weight, both absolute and relative, plus pelvic urolithiasis is indicative of a response to the relatively massive solute load imposed by the compound. The appearance of urogenital staining supports this explanation. The increase in serum

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enzyme activity can be attributed to excessive kidney activity. The effect on platelets cannot be readily explained.

A NOEL was not demonstrated at the lowest dose tested, 2 gm/kg/day.

DCR-11758:Zendzian:TOX-18:8/10/83:CM#2:Rm821:557-15611:efs  
REVISED-8/12/83:DCR-11767:efs:TOX-18

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## DATA EVALUATION REPORT

Compound: Dimethylhydantoin

Citation:

A Teratology Study in Rats with 5, 5-dimethylhydantoin  
D.E. Rodwell  
Wil Research Laboratories, Inc.  
January 5, 1983

Reviewed By

 8/4/85  
Robert P. Zenzian, Ph.D.  
Pharmacologist

Core Classification: Minimum

Toxicology Category: N/A

Conclusion

Dimethylhydantoin is not a teratogen in rats at doses of up to 4.5 gm/kg/day. Toxicity to dam and pups was observed ~~at~~ 2 and 4.5 gm/kg/day. The low dose, 0.5 gm/kg/day was a NOEL.

Materials

Dimethylhydantoin (Lot No. 899 00 00) supplied by the Great Lakes Chemical Company.

Sprague-Dawley COBS CD adult female rats from Charles River Breeding Laboratories.

Methods

Females were caged individually with males and examined daily for a copulatory plug. Upon detection of a plug the female was caged individually and assigned randomly to a treatment group until a total of 25 animals per group were obtained. Females were dosed orally by gavage, at 0, 500, 2000 or 4500 mg/kg dimethylhydantoin on gestation days 6 through 19.

Females were weighed on gestation days 0, 6, 9, 12, 16 and 20. Females were observed twice daily for signs of toxicity.

On gestation day 20 the females were sacrificed by CO<sub>2</sub> asphyxiation and necropsied. Reproductive organs were examined for number of corpora lutea, number of fetuses (live and dead) and number of implantation sites. All fetuses, were weighed, sexed and examined for abnormalities. Approximately half the fetuses were fixed for determination of soft tissue abnormalities, and the remaining half were fixed for skeletal examination.

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compound related toxic effects were observed in the females.  
dose related depression in weight gain was observed in the  
10 and 4500 mg/kg/day group.

only fetal effect observed was a dose related decrease  
mean fetal weights at 2000 and 4500 mg/kg/day. 500 mg/kg/day  
is a NOEL.

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