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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

OCT 23 1996

J. Michael Kelley, Ph.D.
Director of Regulatory Affairs
Great Lakes Chemical Corporation
P.O Box 2200
West Lafayette, IN 47906

SUBJECT: Review of Chronic (One-year) Feeding Study in the Dog Supporting the Reregistration of 1-bromo-3-chloro-5,5-dimethylhydantoin, Case # 3055, AI 006315.

Dear Dr. Kelley:

The Agency has completed its review of MRID 43813301 which you submitted in support of the reregistration of 1-bromo-3-chloro-5,5-dimethylhydantoin. The chronic toxicity study in the dog is acceptable and satisfies the data requirements for guideline 83-1(b).

There were no treatment-related effects on mortality, clinical signs, body weight, body weight changes, food consumption, hematology, clinical chemistry, urinalysis, organ weights, organ/body weight or organ/brain weight ratios, ophthalmological parameters, or gross or microscopic results from histologic examination of selected tissues. The LOEL is greater than 1000 mg/kg/day (HDT), based on the lack of any observable toxic effects. The NOEL is $\geq$ 1000 mg/kg/day.

A copy of the Data Evaluation Report is enclosed. If you have any questions regarding this letter, please call Patricia Leopard in the Accelerated Reregistration Branch on (703) 308-8065.

Sincerely yours,

Kathleen Depukat, Acting Section Chief
Reregistration Section 1
Accelerated Reregistration Branch
Special Review and Reregistration Division

Enclosure: Data Evaluation Report

cc: Raymond K. Locke, HED

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J. Michael Kelley, Ph.D.
Director of Regulatory Affairs
Great Lakes Chemical Corporation
P.O Box 2200
West Lafayette, IN 47906

SUBJECT: Review of Chronic (One-year) Feeding Study
Supporting the Reregistration of 1-bromo-3-c
dimethylhydantoin, Case # 3055, AI 006315

Dear Dr. Kelley:

The Agency has completed its review of MRID 43813301 v
support of the reregistration of 1-bromo-3-chloro-5,5-dimethylhyd
study in the dog is acceptable and satisfies the data requirements fc

There were no treatment-related effects on mortality, clinical signs, body weight, body weight changes, food consumption, hematology, clinical chemistry, urinalysis, organ weights, organ/body weight or organ/brain weight ratios, ophthalmological parameters, or gross or microscopic results from histologic examination of selected tissues. The LOEL is greater than 1000 mg/kg/day (HDT), based on the lack of any observable toxic effects. The NOEL is ≥ 1000 mg/kg/day.

A copy of the Data Evaluation Report is enclosed. If you have any questions regarding this letter, please call Patricia Leopard in the Accelerated Reregistration Branch on (703) 308-8065.

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Kathleen Depukat, Acting Section Chief
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Accelerated Reregistration Branch
Special Review and Reregistration Division

Enclosure: Data Evaluation Report

cc: Raymond K. Locke, HED

CONCURRENCES								
SYMBOL	ARB							V
SURNAME	P Leopard							
DATE	10/21/96							

012060

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

SEP 20 1996

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: 1-Bromo-3-chloro-5,5-dimethylhydantoin. Review of Toxicology Data.
DP Barcode: D220580. Submission #: S496247
Rereg. Case No.: 3055 ID#: 006315-005785
Case No.: 800363 Tox. Chem. No.: 114A

To: Kathleen Depukat/Tom Myers, PM# 51
Reregistration Branch
Special Review and Reregistration Division (7508W)

From: Raymond K. Locke, Toxicologist Raymond K. Locke
Section II, Toxicology Branch I
Health Effects Division (7509C)

Thru: Joycelyn E. Stewart, Ph.D., Section Head 9/11/96
Section II, Toxicology Branch I
Health Effects Division (7509C) 9/16/96

Registrant: Great Lakes Chemical Corporation
West Lafayette, IN

Action Requested: Review toxicology data submitted on 5,5-dimethylhydantoin to support the reregistration of 1-bromo-3-chloro-5,5-dimethylhydantoin and indicate whether these data meet the requirements for a chronic (one-year) feeding study in the dog (guideline 83-1b).

Conclusion: This study (MRID No.: 43813301) was adequately conducted and supports the reregistration of 1-bromo-3-chloro-5,5-dimethylhydantoin. The data presented demonstrate that, under the study conditions, the study may be classified as follows:

MRID No.: 43813301. Chronic (One-Year) Toxicity (Dog). In a chronic toxicity study (MRID 43813301), 5,5-dimethylhydantoin (97.4% a.i.) was administered to 32 beagle dogs (4/sex/dose) by capsule at dose levels of 0, 250, 500, or 1000 mg/kg/day for 52 weeks (capsules given 7 days/week). There were no treatment-related effects on mortality, clinical signs, body weight, body weight changes, food consumption, hematology, clinical chemistry, urinalysis, organ weights, organ/body weight or organ/brain

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weight ratios, ophthalmological parameters, or gross or microscopic results from histologic examination of selected tissues. **The LOEL is greater than 1000 mg/kg/day (HDT), based on the lack of any observable toxic effects. The NOEL is ≥ 1000 mg/kg/day.**

Classification: Acceptable

EPA Reviewer: Raymond K. Locke, Toxicologist Raymond Locke Date 8/22/96
Review Section 2, Toxicology Branch I (7509C)
EPA Secondary Reviewer: Joycelyn E. Stewart, Section Head JS Date 9/10/96
Review Section 2, Toxicology Branch I (7509C)

DATA EVALUATION RECORD

012060

STUDY TYPE: Chronic Oral Toxicity (Capsule-Dog); OPPTS 870.4100 [§83-1(b)]

DP BARCODE: D220580 SUBMISSION CODE: S496247
P.C. CODE: 006315 TOX. CHEM. NO.: 114A

TEST MATERIAL (PURITY): 5,5-Dimethylhydantoin (97.4% a.i.); Lot# 1

SYNONYMS: DMH; DMH-P

CITATION: Chengelis, C. (1995). One-year oral toxicity study in dogs with DMH. WIL Research Laboratories, Inc., Ashland, OH. Laboratory Study No.: WIL-12274, March 14, 1995. MRID No.: 43813301. Unpublished.

SPONSOR: Great Lakes Chemical Corporation
P.O. Box 2200
West Lafayette, IN

EXECUTIVE SUMMARY:

In a chronic toxicity study (MRID 43813301), 5,5-dimethylhydantoin (97.4% a.i.) was administered to 32 beagle dogs (4/sex/dose) by capsule at dose levels of 0, 250, 500, or 1000 mg/kg/day for 52 weeks (capsules given 7 days/week). There were no treatment-related effects on mortality, clinical signs, body weight, body weight changes, food consumption, hematology, clinical chemistry, urinalysis, organ weights, organ/body weight or organ/brain weight ratios, ophthalmological parameters, or gross or microscopic results from histologic examination of selected tissues. **The LOEL is greater than 1000 mg/kg/day (HDT), based on the lack of any observable toxic effects. The NOEL is ≥ 1000 mg/kg/day.**

This chronic toxicity study in the dog is acceptable and does satisfy the guideline requirement for a chronic oral study [83-1(b)] in the dog.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: DMH-P (dimethylhydantoin, purified)
   Description: White crystalline odorless solid
   Lot/Batch #: 1
   Purity: 97.4% a.i.
   Stability of compound: Determined to be stable for 52 weeks (duration of study)
   CAS #: Not given

2. Vehicle and/or positive control: None (Undiluted solid was added to empty gelatin capsules; controls received empty capsules only.)

3. Test animals: Species: Dog
   Strain: Beagle
   Age and weight at study initiation: Males: 6.3-8.6 kg, 6 months of age; Females: 5.6-7.2 kg, 6 months of age
   Source: Ridglan Farms, Inc., Mt. Horeb, WI
   Housing: Individual stainless steel cages
   Diet: Purina® Certified Canine Chow® (400 g) was offered for 1-2 hours each day
   Water: Municipal tap water, ad libitum
   Environmental conditions:
   Temperature: 71.6-75.8°F
   Humidity: 34.7-87.2%
   Air changes: No data
   Photoperiod: 12 hr light/dark cycle
   Acclimation period: 19 days

B. STUDY DESIGN:

1. In life dates - start: 11/3/92 end: 11/3/93

2. Animal assignment

   Animals were assigned randomly to the test groups in listed in Table 1:

TABLE 1: STUDY DESIGN[a]

Test Group	Dose to animal (mg/kg/day)	Main Study (52 months)	
		male	female
Control	0	4	4
Low (LDT)	250	4	4
Mid (MDT)	500	4	4

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6. Urinalysis

Urine was collected from animals (not stated whether animals were fasted or not) at two times (week -1 and week -2) prior to study initiation and during study weeks 12, 25, and 51. Urine was collected by catheter at week -2, but metabolism cages were used instead for week -1 and all other collections. The CHECKED (X) parameters were examined.

X		X	
X	Appearance*	X	Glucose*
X	Volume*	X	Ketones*
X	Specific gravity*	X	Bilirubin*
X	pH	X	Blood*
X	Sediment (microscopic)*	X	Nitrite
X	Protein*		Urobilinogen
		X	White blood cells

* Required for chronic studies

7. Sacrifice and Pathology

All animals that died (none in this study) and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. All tissues listed were examined microscopically for all animals. The (XX) organs, in addition, were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
	Tongue	X	Aorta*	XX	Brain*
X	Salivary glands*	XX	Heart*	X	Periph.nerve*
X	Esophagus*	X	Bone marrow*‡	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*		
X	Duodenum*	X	Spleen*	X	Pituitary*
X	Jejunum*	X	Thymus*	X	Eyes (optic n.)*
X	Ileum*		UROGENITAL		GLANDULAR
X	Cecum*	XX	Kidneys*+		
X	Colon*	X	Urinary bladder*		
X	Rectum*†	XX	Testes*+	XX	Adrenal gland*
XX	Liver*+	XX	Epididymides		Lacrimal gland
X	Gall bladder*	X	Prostate	X	Mammary gland*
X	Pancreas*		Seminal vesicle	XX	Parathyroids*++
	RESPIRATORY	XX	Ovaries*+	XX	Thyroids*++
XX	Trachea*	X	Uterus*		
XX	Lung*				OTHER
	Nose				
	Pharynx			X	Bone (femur)*
	Larynx			X	Skeletal muscle*
				X	Skin*
				X	All gross lesions and masses*

* Required for chronic studies based on Subdivision F Guidelines.
+ Organ weight required in chronic studies.

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++ Organ weight required for non-rodent studies.
† Rectum inadvertently not collected from 7, 3, 5, and 5 animals in the control, 250, 500 and 1000 mg/kg/day groups, respectively.
‡ In addition, bone marrow smears were taken at necropsy, but not placed in formalin.

II. RESULTS

A. Observations

1. Toxicity - No treatment-related toxicity was observed at any dose level of DMH tested. There were increased incidences of red tongue and increased salivation in almost all DMH treatment groups primarily during weeks 13-20 of the study. However these clinical signs are most likely indicative of "trench mouth" (fusospirochetosis) rather than a treatment-related effect. During the last 6 months of the study, increased salivation was observed only once in high-dose (1000 mg/kg/day) males--the group in which this observation was most prominent (78 observations in 3 of 4 males throughout the 52-week study). The animals apparently tolerated and recovered from this oral infection well, since no concurrent infection-related effects on body weight, food consumption, other clinical signs, or clinical pathology were observed.

2. Mortality - All animals on test survived to scheduled sacrifice.

B. Body weight DMH, at all doses tested, elicited no treatment-related effects on body weight. There were no statistically significant differences in mean body weights for any treatment group when compared with controls. There were nine statistically significant differences in body weight gain in various DMH treatment groups throughout the course of this study; however, these differences included both increases and decreases and showed no trends. Therefore these differences in body weight gains are not considered to be treatment-related. Representative body weight data are presented in the following Table 2:

Table 2. Mean Body Weights (g) Observed During a One-Year Chronic Toxicity Study of DMH in Dogs[a]

Males				
Study Week	0 mg/kg/day	250 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
0	7502± 827.2[b]	7364± 952.9	7339± 748.4	7627± 814.9

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13	11266± 1584.0	10233± 492.4	10805± 822.0	11289± 1185.9
26	12500± 1590.2	11209± 301.7	12162± 842.6	12404± 1000.1
52	12962± 1606.2	11931± 641.7	13175± 995.7	12715± 723.3
Females				
0	6388± 582.2	6458± 581.1	6271± 674.2	6466± 586.2
13	8908± 1014.4	8884± 971.9	8151± 994.9	9008± 1001.8
26	9765± 1323.6	9412± 1350.0	8918± 1081.6	9578± 1335.3
52	10196± 1254.0	9605± 1406.0	9247± 1328.1	10143± 1285.1

[a]Data extracted from pages 52-73 of this submission (MRID No.: 43813301).
[b]Mean and standard deviation.

C. Food consumption

1. Food consumption - DMH, at all dose levels tested, had no effects on food consumption during this one-year study. The only statistically significant difference from control values was a 27% decrease in the mean weekly food consumption in the 250 mg/kg/day males during week 21-22. Representative food consumption data are presented in the following Table 3.

Table 3. Mean Weekly Food Consumption (Grams/Animal/Day) Observed in a Chronic Toxicity Study of DMH in Dogs[a]

Males				
Study Week	0 mg/kg/day	250 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
0-1	249± 47.9[b]	237± 24.4	284± 48.6	248± 27.1
13-14	297± 48.1	250± 26.0	287± 27.3	264± 18.3
26-27	302± 62.8	262± 8.9	283± 38.3	286± 16.0
51-52	300± 33.7	256± 24.1	307± 19.9	293± 49.3

Females				
0-1	252± 40.0	228± 11.7	225± 39.1	227± 29.8
13-14	253± 59.1	224± 29.1	281± 43.3	237± 42.6
26-27	245± 60.2	203± 29.0	228± 18.7	219± 45.4
51-52	255± 62.7	227± 47.3	247± 34.0	240± 42.0

[a]Data extracted from pages 96-117 of this submission (MRID No.: 43813301).
[b]Mean and standard deviation.

D. Ophthalmoscopic examination - No treatment-related lesions were observed during any of the ophthalmological examinations.

E. Blood work

1. Hematology - DMH, at all doses tested, elicited no changes in hematological parameters when compared with the appropriate controls. The single statistically significant difference from control values was an increased (111% control) activated partial thromboplastin time (APTT) at week 11 for low-dose (250 mg/kg/day) males. Since no dose or time relationship was observed for this effect, it is not considered to be treatment-related.

2. Clinical chemistry - The only treatment-related clinical chemistry finding was a decrease in blood urea nitrogen (BUN) as compared with appropriate controls. This finding, illustrated in Table 4 below, might indicate severe liver damage. However, as described later, no concurrent liver effects were observed during gross or microscopic examinations of the livers of the animals exhibiting this decrease in BUN. It should also be noted that, although control males and females for some unknown reason exhibited increasing blood BUN values with time, the BUN values for treated males and females remained closer to pre-treatment values. Therefore, the biological significance of the dose- and time-related decreases in BUN in treated animals with respect to controls (exhibiting increased BUN values) is unknown. Incidental statistically significant (*=$p<0.05$; **=$p<0.01$) differences from controls exhibiting no time or dose relationships included: decreased* creatinine in high-dose (1000 mg/kg/day) males at 51 weeks; decreased* glutamyl transferase activity at 25 weeks in mid-dose (500 mg/kg/day) males; increased* glutamyl transferase activity at 25 weeks all female groups (250, 500, and 1000 mg/kg/day); decreased* blood phosphorus at 51 weeks in low- and mid-dose females; decreased* blood glucose in mid-dose females at 51 weeks; increased* blood sodium in high-dose males at 25 weeks; and decreased** blood potassium in high-dose males at 51 weeks.

Table 4. Blood Urea Nitrogen Concentrations (mg/dL) Observed in a Chronic Toxicity Study of DMH in Dogs[a]

Males				
Study Week	0 mg/kg/day	250 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
-2	12.7± 1.40[b]	11.9± 1.28	14.2± 5.54	9.2± 2.19
11	14.3± 1.65	12.3± 1.56	14.1± 1.85	12.8± 1.56
25	17.4± 1.65	15.0± 2.03	14.3± 1.02	13.3± 1.93*
51	15.5± 2.06	14.4± 2.66	14.3± 1.85	12.1± 1.62
Females				
-2	12.4± 1.81	10.4± 1.79	10.8± 2.85	12.0± 3.66
11	13.9± 1.16	14.4± 3.16	14.1± 1.72	13.4± 2.54
25	16.8± 1.91	14.8± 2.18	12.8± 1.55*	11.7± 1.43**
51	17.3± 1.83	13.5± 0.25	12.2± 3.58*	11.4± 1.71**

[a]Data extracted from pages 148-171 of this submission (MRID No.: 43813301).
[b]Mean and standard deviation.

F. Urinalysis - No treatment-related effects were observed for any urinary parameters measured for any level of DMH tested. Sporadic statistically significant differences ($p < 0.05$ in all cases) from control values exhibiting no time or dose relationships included the following: increased specific gravity in mid-dose (500 mg/kg/day) females at week 12; and increased pH in the low-dose (250 mg/kg/day) females at weeks 12 and 25.

G. Sacrifice and Pathology

1. Organ weight - DMH, at all doses tested, exerted no effects on absolute organ weights or the ratios of organ/body weight or organ/brain weight. The only statistically significant ($p < 0.05$) difference from control values noted was a decreased (87% control) heart/body weight ratio in males in the 500 mg DMH/kg/day group.

2. Gross pathology - No treatment-related lesions were observed in any DMH treatment group. There was a slight increase in the incidences of red ileo-cecal junctions and white cortico-medullary junctions in the kidneys in high-dose (1000 mg/kg/day) females, but

these increases were slight, the effects were also observed in the female control (0 mg/kg/day) group, and no similar increases in the incidences of these effects occurred in high-dose (1000 mg/kg/day) males. In addition, no confirmatory abnormal histopathology was observed in the ileum, cecum, or kidneys of these animals. Therefore, the biological significance of these increased incidences is unknown.

3. Microscopic pathology

a) Non-neoplastic - No treatment-related lesions were found during microscopic examination. The lesions observed, presented in Table 5, do not exhibit a dose relationship or they represent lesions normally present in older beagle dogs, are therefore not considered to be treatment-related.

Table 5. Microscopic Lesions Observed in a Chronic Toxicity Study of DMH in Dogs[a]

Males				
Lesion	0 mg/kg/day	250 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
Sternebra- Osteomalacia (minimal)	0/4[b]	0/4	0/4	1/4
Brain- Meningitis (minimal)	0/4	1/4	0/4	0/4
Epididymides- Polyarteritis (moderate)	1/4	1/4	0/4	0/4
Kidneys- Mineralization (minimal) Mild inflammation	0/4 0/4	1/4 0/4	1/4 0/4	0/4 1/4
Liver- Mild inflammation	1/4	0/4	0/4	0/4
Lymph node, Mesenteric- Hyperemia, medulla Minimal Mild	0/4 3/4	0/4 2/4	0/4 1/4	1/4 2/4

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Lungs-				
Lymphoid peribronchiolar hyperplasia				
Mild	1/4	0/4	0/4	0/4
Moderate	1/4	0/4	0/4	0/4
Mild suppurative inflammation	1/4	0/4	1/4	0/4
Granulomatous inflammation				
Minimal	0/4	0/4	1/4	0/4
Mild	0/4	0/4	1/4	1/4
Pituitary-				
Cyst, pars distalis	0/4	3/4	1/4	0/4
Prostate-				
Lymphocyte infiltration				
Minimal	0/4	1/4	0/4	0/4
Mild	1/4	0/4	0/4	0/4
Spleen-				
Capsular fibrosis				
Minimal	0/4	0/4	1/4	1/4
Mild	0/4	3/4	2/4	2/4
Stomach-				
Mild polyarteritis	1/4	0/4	0/4	0/4
Testes-				
Aspermatogenesis	1/4	1/4	1/4	0/4
Polyarteritis	0/4	1/4	0/4	0/4
Thymus gland-				
Minimal hemorrhage	1/4	0/4	0/4	0/4
Thyroid glands-				
C-Cell hyperplasia	1/4	0/4	2/4	2/4
Lymph node, supra-				
Pigmented	1/4	2/4	2/4	1/4
Hyperemia, medulla	1/4	0/4	0/4	0/4

Lymph node, cervical-[c]				
Pigmented	NE[d]	2/2	1/1	3/4
Mediastinal hemorrhage	NE	NE	NE	2/4
Bronchial hemorrhage	NE	NE	NE	2/4
Females				
Sternebra-				
Mild osteomalacia	0/4	0/4	0/4	1/4
Brain-				
Mild encephalitis	0/4	0/4	1/4	0/4
Kidneys-				
Mineralization, medulla	0/4	0/4	1/4	1/4
Inflammation	0/4	0/4	0/4	2/4
Hyperplasia	0/4	0/4	0/4	1/4
Liver-				
Inflammation	1/4	0/4	0/4	1/4
Necrosis	0/4	0/4	0/4	1/4
Lymph Node, mesenteric-				
Hyperemia, medulla	2/4	2/4	0/4	1/4
Inflammation, mild	0/4	0/4	1/4	0/4
Lungs-				
Mild hyperplasia, lymphoid peribronchiolar	0/4	1/4	0/4	0/4
Moderate suppurative inflammation	0/4	0/4	1/4	0/4
Perivascular lymphoid hyperplasia	0/4	2/4	0/4	0/4
Granulomatous inflammation	0/4	0/4	1/4	1/4
Ovaries-				
Active follicle proliferation	0/4	2/4	1/4	1/4
Parathyroid-				
Cyst, ductal	0/4	0/4	2/4	1/4
Pituitary-				
Cyst, pars distalis	0/4	0/4	2/4	1/4

Spleen-				
Mild hyalinosis	1/4	0/4	0/4	0/4
Capsular fibrosis	0/4	0/4	1/4	2/4
Accessory splenic tissue	0/4	1/4	0/4	0/4
Thyroid glands-				
C-Cell hyperplasia	2/4	2/4	0/4	0/4
Cell infiltration	0/4	0/4	1/4	0/4
Ultimobranchial cyst	0/4	0/4	0/4	1/4
Vagina-				
Epithelial estrogenic stimulation	0/4	2/4	1/4	1/4
Inflammation	0/4	1/4	1/4	0/4
Lymph node, supra-				
Pigmented	0/4	0/4	1/4	0/4
Hyperemia, medulla	1/4	0/4	0/4	1/4
Lymph nodes-[c]				
Cervical, pigmented	2/3	1/2	1/2	3/3
Mediastinal, hemorrhage	2/3	1/2	0/2	1/3
Bronchial, inflammation	0/3	0/3	1/3	0/3

[a]Data extracted from pages 197-215 of this submission (MRID No.: 43813301).
[b]Number of animals exhibiting lesion/total number of animals examined.
[c]Examined only in certain animals.
[d]Indicates that, for a particular group, this tissue was not examined.

b) Neoplastic - No neoplastic lesions were observed.

III. **DISCUSSION**

A. DMH, at all dose levels tested, exerted no biologically significant effects on mortality, clinical signs, body weight, body weight changes, food consumption, organ weights, organ/body weight or organ/brain weight ratios, blood chemistry or urinary parameters, ophthalmological parameters, or macroscopic or microscopic results from examination of selected tissues. Based on these data, **the systemic LEL is greater than 1000 mg/kg/day (HDT), based on the lack of any observable systemic effects. The NOEL is ≥ 1000 mg/kg/day.**

B. Study deficiencies This study contains no significant deficiencies.

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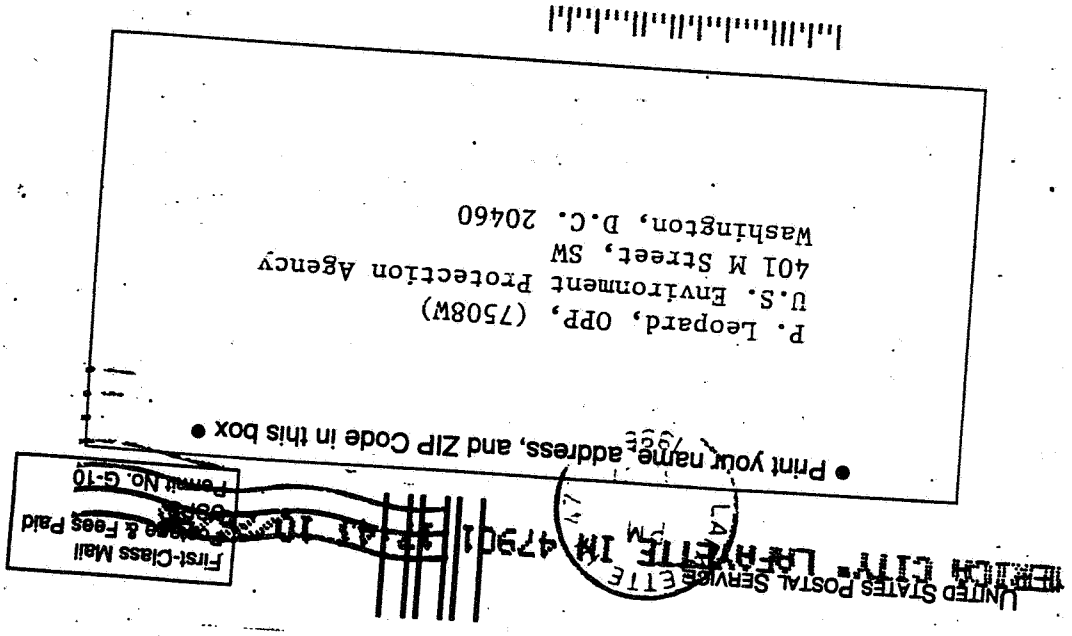

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J. Michael Kelley, PH.D.
Director of Regulatory Affairs
Great Lakes Chemical Corporation
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