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

JAN 29 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: 1-Bromo-3-chloro-5,5-dimethylhydantoin: Review of toxicology data.
Barcode No: D228516 Submission No.: S509229
Case No.: 800363 Rereg. Case No.: 3055
PC Code No.: 006315 Tox. Chem. No.: 114A

To: Michael Metzger, Chief
Risk Analysis and Coordination Branch
Health Effects Division (7509C)

From: Raymond K. Locke, Toxicologist Raymond K. Locke 1/22/97
Section 2, Toxicology Branch I
Health Effects Division (7509C)

Thru: Joycelyn E. Stewart, Ph.D., Section Head 1/22/97
Section 2, Toxicology Branch I
Health Effects Division (7509C)

Registrant: Great Lakes Chemical Corporation,
Lafayette, IN

Action Requested: Review toxicology data [MRID No.: 44063901; 18-month oncogenicity study (83-2b) in mice, including an Amendment to the Final Report (pages 1-12)] to support reregistration of 1-bromo-3-chloro-5,5-dimethylhydantoin, and indicate whether these data meet the guideline requirements for oncogenicity testing (83-2b).

Conclusions:

This 18-month oncogenicity study of 5,5-dimethylhydantoin (DMH) in mice (MRID No. 44063901) is classified as **acceptable/guideline** and fulfills the regulatory requirements of guideline 83-2(b) for oncogenicity testing in mice.

This 18-month oncogenicity study of DMH (MRID No. 44063901) may be summarized as follows:

In a mouse oncogenicity study (MRID 44063901), DMH (97.1-97.3% a.i.) was administered to CD-1 mice (80/sex/group) for 18 months at 0, 100, 320, or 1,000 mg/kg/day.

No significant differences were observed in survival rates in male or female mice in any of the treated groups throughout the study when compared to the respective control groups. Overall body weight gains, leukocyte differential counts, absolute and relative organ weights, gross necropsy, as well as microscopic findings for both sexes at all doses were unaffected by treatment with DMH.

Negligible systemic toxicity was characterized by statistically significant decreases in mean body weights in males receiving the 1,000 or 320 mg/kg/day diets (↓3-5%; $p < 0.05$ or 0.01) and increases in mean feed consumption by the high-dose animals (↑3.8-9.8%; $p < 0.05$ or 0.01). The biological significance of these small, but statistically significant differences in mean body weights and feed consumption is unknown.

The NOEL is ≥1000 mg/kg/day and the LOEL was not observed.

Under the conditions of this study, there was no evidence of carcinogenic potential.

Dosing was considered adequate because the highest dose of 1,000 mg/kg/day represents a "limit dose".

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DATA EVALUATION RECORD

DIMETHYLHYDANTOIN (DMH)

Study Type: 83-2(b); 18-Month Dietary Oncogenicity Study in Mice with DMH

Work Assignment No. 2-33A (MRID 44063901)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Mary L. Menetrez, Ph.D.

Signature: Mary L. Menetrez
Date: 10/16/96

Secondary Reviewer:
Sandra Daussin

Signature: Sandra Daussin
Date: 10/21/96

Project Manager:
William Spangler, Ph.D.

Signature: William J. Spangler
Date: 11/1/96

Quality Assurance:
Michael Norvell, Ph.D.

Signature: Michael Norvell
Date: 10/28/96

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: R. Locke, Toxicologist Raymond K. Locke Date 1/9/97
Review Section II, Toxicology Branch I (7509C)
EPA Secondary Reviewer: M. Copley, DVM, DABT M. Copley Date 1/10/97
Review Section IV, Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Oncogenicity Study in Mice

OPPTS Number:	870.4200	OPP Guideline Number:	§83-2(b)
DP BARCODE:	D228516	SUBMISSION CODE:	S509229
P.C. CODE:	006315	TOX. CHEM. NO.:	114A

TEST MATERIAL (PURITY): DMH (94.9-97.1% a.i.)

SYNONYMS: Dimethylhydantoin

CITATION: Naas, D. J. (1996) 18-Month Dietary Oncogenicity Study in Mice with DMH. WIL Research Laboratories, Inc., Ashland, OH. Laboratory Study No. WIL-12257, May 23, 1996. MRID 44063901. Unpublished.

SPONSOR: Great Lakes Chemical Corporation, PO Box 2200, West Lafayette, IN

EXECUTIVE SUMMARY:

In a mouse oncogenicity study (MRID 44063901), DMH (97.1-97.3% a.i.) was administered to CD-1 mice (80/sex/group) for 18 months at 0, 100, 320, or 1,000 mg/kg/day.

No significant differences were observed in survival rates in male or female mice in any of the treated groups throughout the study when compared to the respective control groups. Overall body weight gains, leukocyte differential counts, absolute and relative organ weights, gross necropsy, as well as microscopic findings for both sexes at all doses were unaffected by treatment with DMH.

Negligible systemic toxicity was characterized by statistically significant decreases in mean body weights in males receiving the 1,000 or 320 mg/kg/day diets (↓3-5%; $p < 0.05$ or 0.01) and increases in mean feed consumption by the high-dose animals (↑3.8-9.8%; $p<0.05$ or 0.01). The biological significance of these small, but statistically significant differences in mean body weights and feed consumption is unknown.

The NOEL is ≥1000 mg/kg/day and the LOEL was not observed.

Under the conditions of this study, there was no evidence of carcinogenic potential.

Dosing was considered adequate because the highest dose of 1,000 mg/kg/day represents a "limit dose".

The submitted study is classified as **acceptable/guideline** and does satisfy the guideline requirements for a carcinogenicity study [§83-2 (b)] in mice.

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

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: DMH
   Description: Technical; white, crystalline, odorless solid
   Lot/Batch #: Lot #6 used from the initiation of dosing until study week 30; Lot #2412-67-DI used from study week 30 through study termination
   Purity: At 6 months 97.1% (Lot #2412-67-DI) and 97.3% (Lot #6). At study termination, 94.9% (Lot #2412-67-DI). Conducting laboratory assumed 100% purity for calculations
   Stability of compound: Compound is stable in the diet for up to 14 days when stored at ambient temperature.
   CAS #: Not provided
   Structure: Not provided

2. Vehicle and/or positive control: Diet

3. Test animals: Species: Mouse
   Strain: Crl:CD-1® (ICR)BR
   Age and weight at study initiation: approximately 6 weeks; 22.7-29.2 g (males) and 17.2-25.6 g (females)
   Source: Charles River Laboratories, Portage, MI
   Housing: Animals were housed one/cage in suspended wire-mesh cages.
   Diet: Purina Certified Rodent Chow® #5002, ad libitum
   Water: Tap water, ad libitum
   Environmental conditions:
   Temperature: 72 ±4 F
   Humidity: 30-70%
   Air changes: Not provided
   Photoperiod: 12 hr dark/12 hr light
   Acclimation period: 13 days

B. STUDY DESIGN:

1. In life dates - Start: 9/3/92 End: 3/3/94

2. Animal assignment: Animals were assigned to treatment groups as indicated in Table 1 using a set of computer-generated random numbers.

TABLE 1: STUDY DESIGN

			Number of Animals	
Test Group	Actual Dose to Animals (mg/kg/day) M/F	Nominal Dose to Animals (mg/kg/day)	Males	Females
Control	0	0	80	80
Low	100.6/100.8	100	80	80
Mid	321.1/321.9	320	80	80
High	1007.3/1008.5	1,000	80	80

3. Dose Selection: The rational for dose selection was based on results from a previously conducted 90-day study in mice (WIL-12186). The study results and conclusions were not provided.

4. Diet Preparation and Analysis: Premixes and test diets were prepared weekly and stored at room temperature. Prior to the start of the study, homogeneity was tested in samples taken from each of three levels (top, middle, and bottom) of test formulations prepared at 100, 320, and 1,000 mg/kg/day. Stability was determined after 7 and 14 days of storage under ambient and frozen conditions (temperatures were not reported). Concentration analyses were performed on all diets once prior to the start of the study and during weeks 1, 2, 3, 7, 11, 24, 37, 50, 63, and 76.

Results: Homogeneity Analysis: The mean concentrations for the 100, 320, and 1,000 mg/kg/day diets were 103-107% of the intended concentrations with relative standard deviations (RSD) of 1.0-6.0%.

Stability Analysis: The mean concentrations of the test substance in the 100, 320, and 1,000 mg/kg/day diets when stored at ambient temperature for 7 days were 88-96% (0.65-1.8% RSD) of the target concentration; 102-103% (1.1-1.7% RSD) when stored frozen for 7 days; 89.8-92.1% (1.5-3.4% RSD) when stored at ambient temperature for 14 days; and 104-105% (0.82-3.1% RSD) when stored frozen for 14 days.

Concentration Analysis: The mean concentrations of the analyzed diets (all dose levels) were 110-115% (5.7-9.5% RSD) of the intended concentrations.

The analytical data indicated that the mixing procedure was adequate for preparing trial diets and that the variance between nominal and actual dosage to the animals was acceptable.

5. Statistics: Body weight, body weight change, food consumption, organ weight, and leukocyte differential count data were subjected to an analysis of variance followed by Dunnett's test. Differences in mortality were tested by Fisher's Exact Test and no statistically significant differences were observed.

C. METHODS:

1. Observations: Animals were observed twice daily for mortality and moribundity. Clinical examinations were performed daily and significant findings recorded. Detailed physical examinations were performed weekly beginning one week prior to the initiation of dosing. The appearance and progress of palpable masses were recorded during these weekly examinations.

2. Body weight: Animals were weighed at weekly intervals beginning one week prior to dosing.

3. Feed consumption and compound intake: Feed consumption for each animal was determined weekly and the weekly average reported. Feed intake was calculated as g/animal/day. Mean compound intake values (mg/kg/day) were calculated from the mean feed consumption (g/kg/day) and the targeted concentration in the diet.

4. Ophthalmoscopic examination: Data from ophthalmoscopic examinations were not reported.

5. Blood Analyses: Blood smears were obtained from all animals at the 52- and 79-week intervals, and from all unscheduled sacrifices. Differential leukocyte counts

were performed on all control and high-dose animals and all animals euthanized *in extremis*. For these hematological analyses, samples were obtained from the tip of the tail or from the vena cava.

6. Urinalysis: Data on urinalyses were not submitted. These data are not required for carcinogenicity studies based on Subdivision F.

7. Sacrifice and Pathology: All animals that died or were sacrificed in a moribund condition and those sacrificed on schedule were subjected to gross pathological examination. Histological examinations were performed on the CHECKED (X) tissues collected from all animals that died or were sacrificed in a moribund condition and the control and the high-dose animals that were sacrificed on schedule. In the animals treated at 100 and 320 mg/kg/day, the adrenals, kidneys, liver, lungs, masses, and all gross lesions suspected of being treatment related were examined microscopically. Additionally, the (XX) organs were weighed from all animals euthanized at the terminal necropsy.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta	XX	Brain
X	Salivary glands	XX	Heart	X	Peripheral nerve
X	Esophagus	X	Bone marrow	X	Spinal cord (3 levels)
X	Stomach	X	Lymph nodes	X	Pituitary
X	Duodenum	X	Spleen	X	Eyes (optic n.)
X	Jejunum	X	Thymus		GLANDULAR
X	Ileum		UROGENITAL	X	Adrenal glands
X	Cecum	XX	Kidneys	X	Preputial gland
X	Colon	X	Urinary bladder	X	Mammary gland
X	Rectum	XX	Testes	X	Parathyroids
XX	Liver	X	Epididymides	X	Thyroid
X	Gall bladder	X	Prostate		OTHER
X	Pancreas	X	Seminal vesicles	X	Bone
	RESPIRATORY	XX	Ovaries	X	Skeletal muscle
X	Trachea	X	Uterus	X	Skin
X	Lungs	X	Vagina	X	All gross lesions and
	Nose	X	Clitoral gland		
	Pharynx				
	Larynx				

The XX organs were weighed.

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II. RESULTS

A. Observations

1. Toxicity - There were no clinical observations nor palpable masses detected that were related to dietary levels of DMH in any of the animals.

2. Mortality - No significant differences were observed in survival rates in male and female mice in any of the treated groups throughout the study when compared to the respective control groups. At 78 weeks, survival rates ranged from 66-81% in males and 74-80% in females.

B. Body weight - Mean body weights for the low-dose males and all treated females were similar to the concurrent controls. From weeks 29 to 77 (except weeks 68, 71, and 74), the mean body weights of the high-dose males were slightly, but statistically significantly, lower than the controls (↓3-5%; $p < 0.05$ or 0.01) (Table 2). The mean body weights of the 320 mg/kg/day males were also slight, but statistically significantly, lower than the controls (↓3-4%; $p < 0.05$ or 0.01) during weeks 32 through 37, and weeks 72, 76, and 77. The biological significance of these small decreases in body weights is unknown.

There were statistically significant ($p<0.05$ or 0.01) differences observed in mean body weight gain data in all the treated groups. These differences were minor, intermittent, and not dose related and were therefore not considered to be of toxicological concern.

C. Feed consumption and compound intake

1. Feed consumption - Feed consumption was calculated at weekly intervals. At twenty intervals throughout the study (consistently during weeks 58 through 67), increased mean feed consumption (↑3.8-8.2%; $p<0.05$ or 0.01) was observed in the high-dose males. Statistically significant increases in mean feed consumption (↑5.2-9.8%; $p<0.05$ or 0.01) were also observed in the high-dose females at 12 intervals throughout the study (consistently during weeks 65 through 69). This small increase in feed consumption in the high-dose animals is of unknown biological significance. Sporadic statistically significant differences observed in feed consumption in the 100 and 320 mg/kg/day animals compared to the controls were also judged to be not of toxicological concern.

Table 2. Mean body weight (g) at selected intervals in male mice fed DMH for up to 78 weeks.[a]

Males				
Weeks	Dietary Level (mg/kg/day)			
	0	100	320	1,000
-1	23.3	23.1 (↓0.9)	23.1 (↓0.9)	23.0 (↓1.3)
29	37.3	36.7 (↓1.6)	36.3 (↓2.7)	36.1* (↓3.2)
32	37.5	36.7 (↓2.1)	35.9** (↓4.3)	35.7** (↓4.8)
37	38.2	37.5 (↓1.8)	37.0* (↓3.1)	36.6** (↓4.2)
52	38.8	38.0 (↓2.1)	37.5 (↓3.4)	37.1* (↓4.4)
77	39.0	38.6 (↓1.0)	37.4* (↓4.1)	37.2* (↓4.6)
78	39.1	39.0 (↓0.3)	37.6 (↓3.8)	37.5 (↓4.1)

[a] Numbers listed parenthetically are percent difference from controls and were calculated by the reviewers. These data were extracted from study report, Table 5, pages 129-145.
*Significantly different from controls $p < 0.05$.
**Significantly different from controls $p < 0.01$.

2. Compound consumption - Mean compound intake values (mg/kg/day) calculated from the mean feed consumption (g/kg/day) and the targeted concentration in the diet are summarized in Table 1.

3. Feed efficiency - Feed conversion efficiency data were not submitted.

D. Blood analyses:

Leukocyte differential counts - No significant differences were observed in leukocyte differential counts in the high-dose animals at the 52 and 79 week intervals and in all unscheduled sacrifices compared to controls.

E. Sacrifice and Pathology:

1. Organ weights - No treatment related effects on organ weights were observed in mice dosed with DMH for up to 78 weeks. The minor difference compared to controls in relative heart weight in the 320 mg/kg/day females (↓6%; $p<0.05$) was not attributed to treatment.

2. Gross pathology - There were no treatment related gross necropsy findings. Necropsy findings observed both in the control and treated groups occurred with comparable frequency and are commonly seen in this strain/age of mice.

3. Microscopic pathology:

a) Non-neoplastic - There were no treatment related histopathologic changes in mice dosed with DMH for up to 18 months. There was an increased incidence of minimal nephropathy in the 320 mg/kg/day males and the high-dose females. In the mid-dose males, nephropathy was observed in 48/65 dosed animals (minimal 40/48; moderate 3/48) vs. 33/64 controls. In the high-dose females, nephropathy was observed in 27/64 dosed animals (minimal 18/27; moderate 4/27) vs. 17/65 controls. Because the minimal nephropathy is a common finding in aging mice and a clear dose response was not evident, these observations were not considered to be treatment related.

b) Neoplastic - No increases in the incidences of any neoplasm was observed in dosed animals. All tumors occurred at the expected incidence for mice of this strain, age, and sex. No historical control data were submitted.

III. DISCUSSION

A. Investigators Conclusions- Dietary administration of DMH resulted in decreases in mean body weights of the 320 and 1,000 mg/kg/day males and increased feed consumption in the high-dose animals.

There was no evidence of a carcinogenic effect in mice treated with DMH in the diet for up to 18 months.

B. Reviewer's Discussion/Conclusions- Male and female mice were fed diets containing DMH at 0, 100, 320, and 1,000 mg/kg/day for 18 months. Dietary analyses at select study intervals confirmed that nominal diet concentrations of DMH were achieved.

No significant differences were observed in survival rates in male or female mice in any of the treated groups throughout the study when compared to the respective control groups. At 78 weeks, survival rates ranged from 66-81% in males and 74-80% in females. Overall body weight gain, leukocyte differential counts,

absolute and relative organ weights, gross necropsy, as well as microscopic findings for both sexes at all doses were unaffected by treatment with DMH.

Mean body weights were lower than controls in the high-dose males (↓3-5%; p <0.05 or 0.01) and the 320 mg/kg/day males (↓3-4%; p <0.05 or 0.01) during the final two-thirds of the study. Mean feed consumption was increased in the high-dose males (↑3.8-8.2%; p<0.05 or 0.01; twenty weekly intervals throughout the study, consistently during weeks 58 through 67) and the high-dose females (↑5.2-9.8%; p<0.05 or 0.01; 12 intervals throughout the study, consistently during weeks 65 through 69). The biological significance of these small changes is unknown.

In conclusion, the dose levels employed in this study were adequate to characterize the carcinogenic potential of DMH in both sexes of CD-1 mice because the highest dose represents a "limit dose". No increases in the incidences of any neoplasm was observed in dosed animals.

The NOEL is ≥1000 mg/kg/day systemic; the LOEL was not observed.

C. Study deficiencies - The rational for dose selection was based on results from a previously conducted study in mice and the study results and conclusions were not provided; this deficiency should not alter the conclusions. The submitted study is classified as **acceptable/guideline** and does satisfy the guideline requirements for a carcinogenicity study [§83-2(b)] in mice.

DP BARCODE: D228516 REREG CASE # 3055

CASE: 800363 DATA PACKAGE RECORD DATE: 08/01/96
SUBMISSION: S509229 BEAN SHEET Page 1 of 1

* * * CASE/SUBMISSION INFORMATION * * *

CASE TYPE: REREGISTRATION ACTION: 627 CORE DATA
CHEMICALS: 006315 1-Bromo-3-chloro-5,5-dimethylhydantoin 100.00 %

ID#: 006315-005785
COMPANY: 005785 GREAT LAKES CHEM CORP
PRODUCT MANAGER: 51 KATHLEEN DEPUKAT 703-308-8587 ROOM: CS1 4F6
PM TEAM REVIEWER: KATHLEEN DEPUKAT 703-308-8587 ROOM: CS1 4F6
RECEIVED DATE: 07/31/96 DUE OUT DATE: 11/28/96

* * * DATA PACKAGE INFORMATION * * *

DP BARCODE: 228516 EXPEDITE: N DATE SENT: 08/01/96 DATE RET.: / /
CHEMICAL: 006315 1-Bromo-3-chloro-5,5-dimethylhydantoin
DP TYPE: 999 Miscellaneous Data Package
CSF: N LABEL: N

ASSIGNED TO	DATE IN	DATE OUT	
DIV : HED	8/7/96	1/29/97	ADMIN DUE DATE: 11/29/96
BRAN: TB-1	8/13/96	1/29/97	NEGOT DATE: / /
SECT: RS-2	8/23/96	1/22/97	PROJ DATE: / /
REVR :	8/23/96	1/22/97	
CONTR: DYNAMAC	8/23/96	/ /	

* * * DATA REVIEW INSTRUCTIONS * * *

The following study is submitted herewith for review for the reregistration of Case 3055, the dihalodialkylhydantoins:

GDLN 83-2
"18-Month Dietary Oncogenicity Study in Mice with DMH"
Volumes 1 through 8 - Study PJB-96-196
MRID 440639-01
Also included is an Amendment to the Final Report, pages 1-12.

If you have any questions, please call me at 308-8587.
Thanks for your help in this matter.

* * * DATA PACKAGE EVALUATION * * *

No evaluation is written for this data package

* * * ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION * * *

DP BC	BRANCH/SECTION	DATE OUT	DUE BACK	INS	CSF	LABEL

Great Lakes
Chemical Corporation

Kathleen Depukat will know who gets this.

440639-00

P.O. BOX 2200 • ONE GREAT LAKES BOULEVARD • WEST LAFAYETTE, IN 47906 • PHONE: 317-497-6100 • FAX: 317-497-6123

June 28, 1996

Mr. Tom Myers
Chemical Review Manager
Accelerated Reregistration Branch
Special Review and Reregistration Division (H7508W)
Office of Pesticide Programs
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Re: Study submission in support of Reregistration for Case No. 3055 (Dihalodialkylhydantoins) of Bromo-3-chloro-5,5-dimethylhydantoin (When responding, please refer to PJB-96-196)

Dear Mr. Myers:

Great Lakes Chemical Corporation is submitting three copies of the following final report in support of the reregistration of 1-bromo-3-chloro-5,5-dimethylhydantoin:

"18-Month Dietary Oncogenicity Study in Mice with DMH".

Also enclosed with this study is an "Amendment to the Final Report, pages 1-12".

This study meets the requirements for subdivision F, series 83-2. If the Agency has any questions regarding this study, please contact me at (317) 497-6223.

Sincerely,

John A. Biesemeier
Regulatory Toxicologist

PJB/
attachment

cc: Study File

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TRANSMITTAL DOCUMENT

1. NAME AND ADDRESS OF SUBMITTER:

Great Lakes Chemical Corporation
P.O. Box 2200
One Great Lakes Boulevard
West Lafayette, IN 47906-2200

2. REGULATORY ACTION IN SUPPORT OF WHICH THIS PACKAGE IS SUBMITTED:

Reregistration Eligibility Decision - Inorganic Halides

3. TRANSMITTAL DATE:

28 June 1996

4. LIST OF SUBMITTED STUDIES:

Volume 1 - 8: "18-Month Dietary Oncogenicity Study in Mice with DMH (Data Requirement F-83-2) 44063901

Amendment to the Final Report Pages 1 through 12

5. SUBMITTER REPRESENTATIVE:

John A. Biesemeier — Date 6/28/96

John A. Biesemeier
Regulatory Toxicologist
Corporate Regulatory Affairs
Phone: (317) 497-6223
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