



Note - Dave Wms has a report on this that could not be merged

EPA  
INFO. CONTROL BRANCH

1981 MAY 13 AM 11:39

GLYCO INC.

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PENNSYLVANIA 17701  
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May 4, 1981

Mr. Merenda  
Document Control Officer  
Management Support Division  
Office of Toxic Substances (WH-557)  
Environmental Protection Agency  
401 M. Street S.W.  
Washington, D. C. 20460

8EHQ-0581-0382 Follow-up  
88-8100228

Dear Mr. Merenda:

Re: EPA Document Control No: 8EHQ-0281-0382

In response to your February 24, 1981 letter received by Glyco on March 6, we are submitting the data requested. The toxicology reports submitted include a summary of the results obtained, the identity of the testing laboratory and procedures, documentation attesting the validity of the results, and that Good Laboratory Practices were employed, when appropriate. The raw data is not included. If necessary, the raw data will be submitted when Glyco completes its pesticide registration program under FIFRA.

The following is a summary of the data and information being submitted.

1. Bromochlorodimethylhydantoin (BCDMH)

✓ 2,4-imidazolidinedione, 3-bromo-1-chloro-5,5-dimethyl-

CAS No. 126-06-7

- A. Acute Oral LD50 Assay in Mice (EPA-FIFRA)
- B. Acute Oral LD50 Assay in Rats (EPA-FIFRA)
- C. Acute Dermal Dose Range Finding Study in Rabbits (EPA-FIFRA)
- D. Acute Dermal Toxicity Study in Rabbits (EPA-FIFRA)
- E. Primary Skin Irritation in Rabbits (EPA-FIFRA)
- F. Primary Eye Irritation Study in Rabbits
- G. Dermal Sensitization Study, Böhler Test of Glyco 609-64-A (BCDMH) in Guinea Pigs.
- H. Inhalation Toxicity - Incomplete.

(The above reports were submitted to Glyco by Food & Drug Research Laboratories, Inc.).

Glyco Inc. to  
Document Control Officer  
Management Support Div.  
Office of Toxic Substances (WH-557)  
Environmental Protection Agency  
5/4/81

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II. Dichlorodimethylhydantoin (DCDMH)  
2,4-imidazolidinedione, 1,3-dichloro-5,5-dimethyl-

CAS No. 118-52-5

- A. Wyandotte Chemicals Corporation summary of Acute Oral Toxicity, Skin Irritation, Eye Irritation, and 30-day Subacute Oral Toxicity tests performed by Industrial Bio-Test Laboratories.
- B. Acute Toxicity Tests on Halane\* (Report to Wyandotte by Industrial Bio-Test Laboratories).
- C. An Acute Inhalation Toxicity Study of Dantoin DCDMH in the Rat. (Report to Glyco by Bio/dynamics Inc.).
- D. Thirty-Day Subacute Oral Toxicity of Halane - Albino Rats (Report to Wyandotte by Industrial Bio-Test Laboratories).
- E. Addendum Report to Wyandotte, 30-Day Subacute Oral Toxicity of Halane - Albino Rats (Industrial Bio-Test Laboratories).
- F. Mutagenicity Evaluation of Dantoin DCDMH in the Ames Salmonella/ Microsome Plate Test (Report to Glyco by Litton Bionetics).
- G. NCI Carcinogenesis Bioassay Experimental Design Status Report, 2/22/78.
- H. Acute Dermal Toxicity Study in Rabbits (Report to Glyco by Bio/dynamics Inc.).

III. Dibromodimethylhydantoin (DBDMH)  
2,4-Imidazolidinedione, 1,3-dibromo-5,5-dimethyl-

CAS No. 77-48-5

- A. Acute Oral Toxicity Study in Rats.
- B. Rabbit Eye Irritation Study.
- C. An Acute Inhalation Toxicity Study of Dantoin DBDMH in the Rat.
- D. Acute Dermal Toxicity Study in Rabbits
- E. Primary Dermal Irritation Study in Rabbits.  
(The above reports were prepared for Glyco by Bio/dynamics Inc.).
- F. Mutagenicity Evaluation of Dantoin DBDMH in the Ames Salmonella/ Microsome Plate Test (Prepared for Glyco by Litton Bionetics).

\*Wyandotte trade name for DCDMH.

'Glyco' Inc. to  
Document Control Officer  
Management Support Div.  
Office of Toxic Substances (WH-557)  
Environmental Protection Agency  
5/4/81

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- IV. New Employee Safety Check List (Exhibit 1)
- V. TSCA Section 8(e) - Substantial Risk Employee Report (Exhibit 2)
- VI. Glyco Safety Policy for the Use of All Types of Respirators (Exhibit 3)
- VII. Notice to Employees Regarding Toxicology of the Halogenated Hydantoins (Exhibit 4)
- VIII. Record of Monthly Safety Meeting Report (Exhibit 5)
- IX. Memo to Dantoin Employees re Eye and Respiratory Protection (Exhibit 6)
- X. Notice to Customers of the Toxicology of the Halogenated Hydantoins (Exhibit 7)
- XI. MSDS - BCDMH (Exhibit 8)
- XII. MSDS - DCDMH (Exhibit 9)
- XIII. SMDS - DBDMH (Exhibit 10)

Discussion

New Glyco employees are instructed in safe working practices by Glyco's Safety Director and the Supervisor of the department where the new employee will work. This indoctrination is reinforced by the Safety Check List (Exhibit 1). Each employee is provided with a summary of the TSCA requirements for reporting "substantial risk" (Exhibit 2). In addition, each employee is advised of Glyco's safety policy for the use of respirators (Exhibit 3). Monthly safety meetings are conducted by the Supervisor of each department.

On February 2, 1981 employees involved with manufacturing the halogenated hydantoins were advised of the toxicological findings (Exhibit 4). The significance of these results was then discussed with each Dantoin employee to be certain of complete understanding of the information available. Record of these meetings is shown in Exhibit 5. The need for eye and respiratory protection was stressed in a memo to Dantoin employees on January 30, 1981.

On March 2, 1981, Glyco customers were advised of the toxicological properties of the halogenated dimethylhydantoins (Exhibit 7) and provided with Material Safety Data Sheets (Exhibits 8, 9, 10).

I hope this report satisfactorily provides you with the information needed.

Sincerely yours,

GLYCO INC.

*T. A. Girard*

T. A. Girard

Senior Vice President

jg

3

NEW EMPLOYEE ORIENTATION

SAFETY CHECK LIST

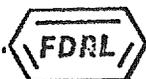
EXHIBIT 1

PAGE 0017

1. Safety Equipment Supplied
  - A. Hard Hats
  - B. Safety Glasses with Side Shields
  - C. Safety Toe Shoes
  - D. Respirators
  - E. Gloves
  - F. Special Equipment -
2. Reporting Accidents
3. Proper Use of Tools
4. Proper Clothing (ie) Minimum Requirements
5. Entering Vessels and Enclosures
6. Housekeeping
7. Hazardous Materials
  - A. Those used as raw materials.
  - B. Those manufactured.
  - C. Handling
8. TSCA Section 8(e) - Substantial Risk Employee Report

The above subjects were explained to me as part of the  
Company Policy.

Date \_\_\_\_\_ Signed \_\_\_\_\_



**FOOD AND DRUG**  
*Research* **LABORATORIES, INC.**

BCDMH  
3

WAVERLY DIVISION  
Route 17C  
P.O. Box 107  
Waverly, New York 14892  
(607) 565-2931

RAC 0042

REPORT: ACUTE DERMAL DOSE RANGE FINDING STUDY  
IN RABBITS (EPA-FIFRA)

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

Date: December 18, 1980

FDRL Study No.: 6711<sub>A</sub>

TEST ARTICLE:

FDRL ID: 80-1012  
Description: A white powder.  
Sponsor ID: Bromochlorodimethylhydantoin;  
No. 609-64-A; October 17, 1980

EXPERIMENTAL PROCEDURES: See Appendix I.

RESULTS: See Table below. See Appendix II (Raw Data).

Dosage <sup>a</sup> Level g /kg	No. Rabbits Dosed	Time to Death							Cumulative Mortality
		1	2	3	4	5	6	7	
2.0	2 M	0	0	0	0	0	0	0	0/2
2.0	2 F	0	0	0	0	0	0	0	0/2
4.0	2 M	0	0	0	0	0	0	0	0/2
4.0	2 F	0	0	0	0	0	0	0	0/2

a) Administered as received.

CONCLUSION: The test article was applied to the abraded skin of rabbits at the above levels. No animals died during the 7 day observation period following application. In accordance with 43 CFR 163.81-2 (c) (1) (iii) (S) (i) (EPA-FIFRA) an acute dermal toxicity study will be conducted rather than a Dermal LD50 Assay. The data suggests that the LD50 of Bromochlorodimethylhydantoin is greater than 2.0 g/kg of body weight.

NOTICE

The information contained in this report is the property of Glyco Inc. It is not to be used by any third party parties for any purpose whatsoever without the knowledge and permission of Glyco Inc., 51 Weaver St. Greenwich, Conn. 06870.

*Joseph C. Siglin*  
Joseph C. Siglin, B.A.,  
Assistant Toxicologist/  
Study Director

*Peter J. Becci*  
Peter J. Becci, Ph. D.,  
Director of Toxicology

*Richard A. Parent*  
Richard A. Parent, Ph.D.,  
Vice President/Director  
Waverly Research Center

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REC 0043

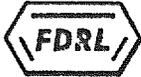
This final report was reviewed for accuracy as required by Good Laboratory Practice Regulations for non-clinical laboratory studies, 21 CFR Part 58. Inspections were accomplished as determined by a random sampling approach and reported to the study director and management immediately following their completion. The inspection record for study number *6711A* is available in the Quality Assurance Unit.

Raw data for this study are retained at the Waverly Research Center of FDRL, Inc.

*Frederick F. Paul*  
Frederick F. Paul,  
Quality Assurance Unit

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**FOOD AND DRUG  
Research LABORATORIES, INC.**

BCDMH  
4

WAVERLY DIVISION  
Route 17C  
P.O. Box 107  
Waverly, New York 14892  
(607) 565-2931

REPORT: ACUTE DERMAL TOXICITY STUDY IN RABBITS  
(EPA-FIFRA)

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

Date: December 11, 1980

FDRL Study No.: 6711<sub>A</sub>

TEST ARTICLE:

FDRL ID: 80-1012  
Description: White powder  
Sponsor ID: Bromochlorodimethylhydantoin;  
No. 609-64-A; October 17, 1980

EXPERIMENTAL PROCEDURES: See Appendix I and II (Raw Data).

RESULTS: See Table 1 for significant observations and Table 2 for mean body weight data.

Dosage <sup>a</sup> Level g /kg	No. Rabbits Dosed	Time to Death															Cumulative Mortality
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
2.0	5 M	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	2/5
2.0	5 F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5

a) Administered as received.

CONCLUSION: Two animals died during the 15 day observation period. The 95% confidence interval for this 20 % rate of mortality is 3 to 61 % when the test article was applied to the abraded skin of rabbits at a level of 2.0 g/kg of body weight.

NOTICE

Peter J. Becci, Ph.D.  
Director of Toxicology

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Joseph C. Siglin, B.A.,  
Assistant Toxicologist/  
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Richard A. Parent, Ph. D.,  
Vice President/Director  
Waverly Research Center

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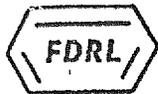


Table 1

Significant Observations<sup>a</sup>

Dosage Level g /kg	Clinical Observations <sup>b</sup>	Necropsy Observations
<u>Males</u>		
2.0	Eschar formation, Lacrimation, Small feces (2M), Decreased activity, Salivation (3M), Nasal discharge (2M).	Body Cavity: fluid filled (2M).
<u>NOTICE</u>		
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<u>Females</u>		
2.0	Eschar formation, Lacrimation (4F), Small feces (2F), Decreased activity, Salivation (2F).	Lungs: puffy (2F). Stomach: fluid filled (2F).

MAY 0 14 5

Table 2

Mean Body Weight Data<sup>a,c</sup>

Dosage Level g /kg	Day 1	Day 8	Day 15	at Death
	----- kg -----			
<u>Males</u>				
2.0	2.97 ±0.10(5)	2.79 ±0.12(4)	2.95 ±0.04(3)	2.83 ±0.09(2)
<u>Females</u>				
2.0	2.96 ±0.17(5)	2.72 ±0.32(5)	2.75 ±0.49(5)	-----

- a) Based on five animals per group unless otherwise specified in parenthesis.  
 b) To be significant, findings have to occur in 2/5 animals per sex.  
 c) Values indicated are Mean ± S.D., where appropriate. Individual animal weights may be found in Appendix II (raw data).



PH 0046

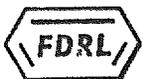
This final report was reviewed for accuracy as required by Good Laboratory Practice Regulations for non-clinical laboratory studies, 21 CFR Part 58. Inspections were accomplished as determined by a random sampling approach and reported to the study director and management immediately following their completion. The inspection record for study number 6711 A is available in the Quality Assurance Unit.

Raw data for this study are retained at the Waverly Research Center of FDRL, Inc.

*Frederick F. Paul*  
Frederick F. Paul,  
Quality Assurance Unit

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FOOD AND DRUG  
*Research* LABORATORIES, INC.

BCDMI  
5

WAVERLY DIVISION  
Route 17C  
P.O. Box 107  
Waverly, New York 14892  
(716) 565-2931

REC'D 10/17

REPORT: PRIMARY SKIN IRRITATION IN RABBITS (EPA-FIFRA)

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

Date: November 6, 1980

Laboratory No. 6711<sub>A</sub>

TEST ARTICLE:

FDRL ID: 80-1012  
Description: White powder  
Sponsor ID: Bromochlorodimethylhydantoin;  
No. 609-64-A; Oct. 17, 1980

EXPERIMENTAL PROCEDURES: See Appendixes I and II.

RESULTS: Scoring of the effects produced by the test material is shown in Table 1.

CONCLUSION: Average score is 6.98 (See Table 1). The test article identified above is extremely irritating to the skin of rabbits.

NOTICE

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Joseph C. Siglin  
Joseph C. Siglin, B.A.,  
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Peter J. Becci  
Peter J. Becci, Ph. D.,  
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Richard A. Parent  
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Vice President/Director,  
Waverly Research Center



PHC 0048

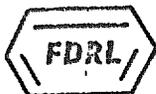
This final report was reviewed for accuracy as required by Good Laboratory Practice Regulations for non-clinical laboratory studies, 21 CFR Part 58. Inspections were accomplished as determined by a random sampling approach and reported to the study director and management immediately following their completion. The inspection record for study number *6711 A* is available in the Quality Assurance Unit.

Raw data for this study are retained at the Waverly Research Center of FDRL, Inc.

*Frederick F. Paul*  
Frederick F. Paul,  
Quality Assurance Unit

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Appendix II

Skin Reaction Code\*

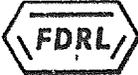
64049

	<u>Value</u>
<b>Erythema and eschar formation:</b>	
No erythema .....	0
Very slight erythema (barely perceptible).....	1
Well-defined erythema .....	2
Moderate to severe erythema .....	3
Severe erythema (beet redness) to slight eschar formations (injuries in depth) .....	4
<b>Edema formation:</b>	
No edema .....	0
Very slight edema (barely perceptible) .....	1
Slight edema (edges of area well defined by definite raising) .....	2
Moderate edema (raised approximately 1 millimeter). ..	3
Severe edema (raised more than 1 millimeter and extending beyond the <u>area of exposure</u> ) .....	4

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\* Draize, John H., Woodard, Geoffrey, and Calvery, Herbert O., "Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes", J. Pharm. & Exp. Ther. 82, 337 (1944).





**FOOD AND DRUG  
Research LABORATORIES, INC.**

BCDMH  
6

WAVERLY DIVISION  
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P.O. Box 107  
Waverly, New York 14892  
(607) 565-2931

FILE 0050

REPORT: PRIMARY EYE IRRITATION STUDY IN RABBITS

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

Date: November 19, 1980

Laboratory No. 6711<sub>A</sub>

TEST ARTICLE:

FDRL ID: 80-1012  
Description: White powder  
Sponsor ID: Bromochlorodimethylhydantoin;  
No.: 609-64-A; October 17, 1980

EXPERIMENTAL PROCEDURES: See Appendixes I, II and III.

RESULTS: See Table 1.

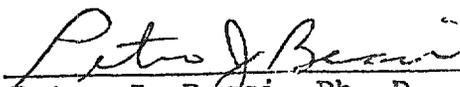
Mean Scores (± SEM)	Hours			Days			
	24	48	72	4	7	10	13
No Washout	99.3 ±4.5	99.7 ±4.6	103.0 ± 4.1	103.0 ± 4.1	103.0 ± 4.1	103.0 ± 4.1	102.3 ± 3.9
With Washout (30-Seconds)	78.3 ±6.7	78.3 ±6.7	78.3 ±6.7	78.3 ±6.7	78.3 ±6.7	70.3 ±7.4	69.0 ±8.3

CONCLUSION: Based on the scoring system described in Appendixes II and III, the test article is considered to be extremely irritating to the rabbit eyes without or with a washout 30-seconds after instillation.

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Joseph C. Siglin, B.A.,  
Assistant Toxicologist/  
Study Director

  
Peter J. Becci, Ph. D.,  
Director of Toxicologist

  
Richard A. Parent, Ph.D.,  
Vice President/Director,  
Waverly Research Center

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FILE 051

This final report was reviewed for accuracy as required by Good Laboratory Practice Regulations for non-clinical laboratory studies, 21 CFR Part 58. Inspections were accomplished as determined by a random sampling approach and reported to the study director and management immediately following their completion. The inspection record for study number 6711A is available in the Quality Assurance Unit.

Raw data for this study are retained at the Waverly Research Center of FDRL, Inc.

*Frederick F. Paul*  
Frederick F. Paul,  
Quality Assurance Unit

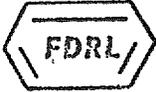
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Appendix III

Classification of Test Material\*  
Based on Eye Irritation Properties



Rating	Range of Mean Score*	Definition**
Non-Irritating	0.0 - 0.5	To maintain this rating, all scores at the 48-hour reading must be zero; otherwise, increase rating one level.
Practically Non-Irritating	Greater than 0.5 - 2.5	To maintain this rating, all scores at the 48-hour reading must be zero; otherwise, increase rating one level.
Minimally Irritating	Greater than 2.5 - 15.0	To maintain this rating, all scores at the 72-hour reading must be zero; otherwise, increase rating one level.
Mildly Irritating	Greater than 15.0 - 25.0	To maintain this rating, all scores at the 7-day reading must be zero; otherwise, increase rating one level.
Moderately Irritating	Greater than 25.0 - 50.0	To maintain this rating, scores at 7 days must be less than or equal to 10 for 60% or more of the animals. Also, mean 7-day score must be less than or equal to 20. If 7-day mean score is less than or equal to 20 and more than 60% of animals show scores less than 10, then no animal among those showing scores greater than 10 can exceed a score of 30 if rating is to be maintained; otherwise increase rating one level.
Severely Irritating	Greater than 50.0 - 80.0	To maintain this rating, scores at 7 days must be less than or equal to 30 for 60% or more of the animals. Also, mean 7-day score must be less than or equal to 40. If 7-day mean score is less than or equal to 40 and more than 60% of the animals show scores less than or equal to 30, then no animal among those showing scores greater than 30 can exceed a score of 60 if rating is to be maintained, otherwise, increase rating one level.
Extremely Irritating	Greater than 80.0 - 110.0	

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\* Mean score for rating is taken from the observation time which has the highest mean score.  
 \*\* Where responses are persistent, ratings will be increased by only one level.

PGM-122  
12/22

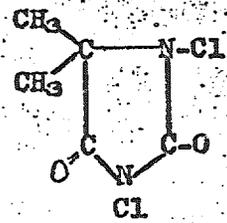
HALANE  
TOXICOLOGICAL STUDIES

XX ✓  
TEP  
40-572  
40PP  
8EHQ-0581-0382  
F-2

DCDM.  
1

HALANE is a registered trade mark of Wyandotte Chemicals Corporation covering the compound 1,3-dichloro-5,5-dimethylhydantoin, which has the following structure:

88-8100-228  
NOV 1958



A sample of this compound was submitted to Industrial Bio-Test Laboratories, Inc., Northbrook, Illinois for determination of Acute Oral Toxicity, Skin Irritation, Eye Irritation, and 30-day Subacute Oral Toxicity.

A summary of the results of these tests is as follows:

Acute Oral Toxicity - Albino Rats

The acute oral mean lethal dose (LD<sub>50</sub>) of HALANE was found to be 542 mg./kg.

Skin Irritation Tests - Albino Rabbits

<u>Compound</u>	<u>Type of Preparation</u>	<u>Rating</u>
HALANE	Powder, <u>as received</u>	Severely Irritating
HALANE	Aqueous Solution, 600 ppm "available chlorine"	Slightly Irritating
Sodium Hypochlorite	Aqueous Solution, 600 ppm "available chlorine"	Slightly Irritating

Eye Irritation Tests - Albino Rabbits

<u>Compound</u>	<u>Type of Preparation</u>	<u>Rating</u>
HALANE	Aqueous Solution, 600 ppm "available chlorine"	Mildly Irritating
Sodium Hypochlorite	Aqueous Solution, 600 ppm "available chlorine"	Mildly Irritating

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2.

30-Day Subacute Oral Toxicity

Body Weights and Water Consumption. Thirty-day ingestion of water containing HALANE or Sodium Hypochlorite at concentrations furnishing 20 ppm of "available chlorine" did not affect growth patterns or water consumption as compared to data for untreated control rats.

It was calculated that total ingestion of "hydantoin residue" (after liberation of the "available chlorine" from 1,3-dichloro-5,5-dimethyl-hydantoin) was 101 mg. for each rat during this test.

Mortality, General Reactions, and Observations. There were no deaths or untoward behavioral reactions noted during the study.

Hematologic Studies and Urine Analysis. The results of blood and urine studies conducted on rats of all groups were within normal limits.

Pathology. Gross and microscopic findings upon examination of representative tissues and organs of animals from the HALANE and Sodium Hypochlorite groups were comparable to those found for untreated control rats.

A discussion of the test procedures and the test results follows.

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4900314

SKIN IRRITATION TESTS

REC 0066

Albino rabbits were used as test animals in evaluating the primary skin irritating properties of HALANE (both as the dry solid and as an aqueous solution adjusted to 600 ppm available chlorine). Sodium hypochlorite in the form of an aqueous solution was used as a control, at a concentration of 600 ppm available chlorine. The test procedure employed was modeled after that of Draize et al.<sup>1</sup>

[Draize, Woodward and Calvert, J. Pharm. and Exp. Ther., 82 4 (1944)]

Prior to the application of the test materials, the hair was clipped from the backs and flanks of each of six rabbits. The test sites on each rabbit were located at the corners of a square, approximately ten centimeters on a side. Two of the four sites selected, diagonally opposite from one another, were abraded by making four epidermal incisions, two perpendicular to the other two, at each site. The other two skin sites remained intact. Two rabbits were employed in testing each preparation.

The HALANE powder, moistened slightly at the time of application, was applied to the skin sites in 0.5 gram quantities; aqueous preparations of HALANE and sodium hypochlorite were applied in 0.5 ml. quantities. All applications were in the form of square gauze patches, 2.5 cm. on a side, containing the 0.5 gram or 0.5 ml. quantities of test material. These were affixed directly over the skin test sites and secured in place by means of thin strips of adhesive tape. Following the patch applications, the entire trunk of each test animal was wrapped in an impervious plastic sheeting.

At the end of 24 hours, the plastic wrappings and patches were removed and the skin sites individually examined and scored for both erythema and edema. After 72 hours had elapsed, the sites were reexamined and rescored. Results of these tests are summarized in Tables II, III and IV.

TABLE II

PRIMARY SKIN IRRITATION: HALANE POWDER

Animal Number	Intact Skin		Abraded Skin		Combined Average	Max. Poss. Score
	24 hours	72 hours	24 hours	72 hours		
1	6.0	6.0	6.0	6.0		
2	6.0	6.0	6.0	6.0		
mean	6.0		6.0		6.0	8.0

Primary Irritation Rating, HALANE Powder; Severely Irritating

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0051

TABLE III

PRIMARY SKIN IRRITATION: HALANE AS AQUEOUS SOLUTION  
(600 ppm Available Chlorine)

Animal Number	Intact Skin		Abraded Skin		Combined Average	Max. Poss. Score
	24 hours	72 hours	24 hours	72 hours		
1	0.5	0.0	1.0	0.0		
2	1.5	0.0	1.5	0.0		
mean	0.50		0.62		0.56	8.0

Primary Irritation Rating, HALANE as aqueous solution, 600 ppm available chlorine: Slightly Irritating

TABLE IV

PRIMARY SKIN IRRITATION: SODIUM HYPOCHLORITE CONTROL  
(600 ppm Available Chlorine)

Animal Number	Intact Skin		Abraded Skin		Combined Average	Max. Poss. Score
	24 hours	72 hours	24 hours	72 hours		
1	1.0	0.0	1.5	0.0		
2	1.0	0.0	1.0	0.0		
mean	0.50		0.62		0.56	8.0

Primary Irritation Rating, Sodium hypochlorite as aqueous solution, 600 ppm available chlorine: Slightly Irritating

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PNE 0057

EYE IRRITATION TESTS

Albino rabbits, two groups of five animals each, were used as test animals. One group of animals was treated with an aqueous solution of HALANE and one group with sodium hypochlorite, both as aqueous solutions with concentrations of 600 ppm. as available chlorine. Exactly 0.1 ml. of test solution was instilled into the conjunctival sac of the right eye of each test rabbit; the left eye of each animal served as a scoring control.

One, 24, 48, 72, 96 hours, and 7 days following the initial instillations, the cornea, iris, and palpebral conjunctiva were examined individually and graded for irritation and injury. The maximum possible score at any one examination and scoring period is 110 points, which indicates maximal irritation and damage to all three ocular tissues. In the classification system used, special emphasis was placed upon irritation or damage to the cornea. Correspondingly less stress was placed upon conjunctival and iridial effects. The scores and ratings are summarized in Tables V and VI.

REF 0058

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Reference 2

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NOV 00 1970

REPORT TO  
WYANDOTTE CHEMICALS CORPORATION  
ACUTE TOXICITY TESTS ON  
HALANE

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I. Introduction

A sample of HALANE was received from Wyandotte Chemicals Corporation for toxicological evaluation. The following studies were conducted:

Acute Oral Toxicity - Albino Rats  
Skin Irritation Tests - Albino Rabbits  
Eye Irritation Tests - Albino Rabbits

In addition, skin and eye irritation tests were performed using Sodium Hypochlorite as a test comparison.

II. Acute Oral Toxicity - Albino Rats

A. Procedure

Healthy, young albino rats of the Sprague-Dawley strain with an average body weight of approximately 100 grams were used as test animals. The rats were divided into groups of four animals each for dosing purposes.

All animals used were kept under observation for five days prior to experimental use, during which period they were checked for general physical well-being and homogeneity. The animals were housed

individually in stock cages and permitted a standard laboratory rat diet\* plus water ad libitum until 16 hours immediately prior to oral intubation.

On the morning of the first test day, after a 16-hour fast (water permitted), the selected dose groups of four rats each were intubated with previously calculated doses of the test material which were administered as 10 per cent (w/v) aqueous suspensions. The test material was orally intubated at four graded dose levels. All doses were administered directly into the stomachs of the test rats using a hypodermic syringe equipped with a ball-pointed intubating needle.

Following oral administration of the test material, the rats were returned to their stock cages and observed for the succeeding 14 days. All significant reactions and mortalities which occurred were recorded. Particular attention was given to the observation during the first four hours after intubation.

At the end of the observation period, all data were collected and the acute oral mean lethal dose (LD50) of the test material was calculated, using the techniques of Weil\*\*, Thompson\*\*\*, and Thompson and Weil\*\*\*\*.

- \* Rockland Rat Diet, Rockland Farms, New City, New York.
- \*\* Weil, Carrol S.: Tables for Convenient Calculation of Median-Effective Dose (LD50 or ED50) and Instructions in Their Use. Biometrics, Sept. 1952.
- \*\*\* Thompson, William R.: Use of Moving Averages and Interpolation to Estimate Median-Effective Dose. Bact. Rev., Nov. 1947.
- \*\*\*\* Thompson, William R. and Weil, Carrol S.: On the Construction of Tables for Moving Average Interpolation. Biometrics, March, 1952.

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ME 0012

2. Reactions

No untoward reactions were observed among rats receiving a dose of 266.7 mg/kg.

Generalized tremors, salivation, hyperpnea, cyclic running and coma (in moribund animals) were observed in the order listed in rats dosed at 400, 600, and 900 mg/kg. The onset of reactions occurred approximately ten minutes after dosing. Severity of the reactions was roughly comparable to the increase in dose level. Deaths occurred within 18 hours after dosing.

Surviving animals in the 400 and 600 mg/kg dose groups exhibited generalized weakness 24 hours after dose administration. These animals appeared normal at the 48-hour point.

Necropsies of animals which died during the test period revealed hemorrhages of the gastro-intestinal tract. No other gross pathologic alterations were observed in the tissues and organs examined.

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ME 0071

III. Skin Irritation Tests - Albino Rabbits

A. Procedure

These tests were conducted on both HALANE and Sodium Hypochlorite.

Six albino rabbits were used in the evaluation of primary skin irritating properties of the test materials. The test procedure employed was modeled after that of Draize et al\*.

Prior to the application of the test materials, the hair was clipped from the backs and flanks of each of the six rabbits. The test sites on each rabbit were located at the corners of a square, approximately ten centimeters to a side. Two of the four sites selected, diagonally opposite from one another, were abraded by making four epidermal incisions, two perpendicular to the other two at each site. The other two skin sites remained intact.

HALANE was tested as received, i.e. in powder form, and also in the form of an aqueous solution (concentration adjusted to 600 ppm "available chlorine"). Sodium Hypochlorite was tested only in the form of an aqueous solution (concentration adjusted to 600 ppm "available chlorine"). Two rabbits were employed in testing each preparation. The HALANE powder\*\* was applied to the skin sites in 0.5 gram

\* "Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes", Draize, John H., Woodard, Geoffrey, and Calvery, Herbert O., J. Pharm. & Exp. Ther., 82, 4, December 1944.

\*\* The HALANE powder was moistened slightly at the time of application.

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REC-0074

quantities; aqueous preparations of HALANE and Sodium Hypochlorite were applied in 0.5 ml quantities.

All applications were in the form of square gauze patches, 2.5 cm on a side, containing 0.5 gram or 0.5 ml quantities of test material. These were affixed directly over the skin test sites and secured in place by means of thin strips of adhesive tape.

In the above manner, each test material was evaluated for primary irritation on each of two rabbits, a total of eight sites (four intact and four abraded) being employed.

Following the patch applications, the entire trunk of each test animal was wrapped in an impervious plastic sheeting. This helped to hold the patches in position and insured intimate contact of epidermis and test material.

At the end of 24 hours, the plastic wrappings and patches were removed. The skin sites were then individually examined and scored separately for both erythema and edema on a graded scale of 0 to 4. After 72 hours had elapsed, the sites were re-examined and rescored.

In evaluating the average irritation present, scores for individual intact and abraded sites were first averaged separately for each of the two scoring time intervals. The mean scores for the 24- and 72-hour grading periods were then averaged to obtain separate mean irritation grades for both intact and abraded skin. Finally, the latter two

means were averaged to give a combined average irritation score. The scoring criteria for erythema and edema are shown in Table II.

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TABLE II

Scoring Criteria for Skin Reactions

AME 0013

Erythema and Eschar Formation

Very slight erythema (barely perceptible) . . . . .	1
Well-defined erythema . . . . .	2
Moderate to severe erythema. . . . .	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth) . . . . .	4
 Total Possible Erythema Score	 4

Edema Formation

Very slight edema (barely perceptible). . . . .	1
Slight edema (edges of area well defined by definite raising) . . . . .	2
Moderate edema (area raised approximately 1 mm) . . . . .	3
Severe edema (raised more than 1 mm and extending beyond area of exposure). . . . .	4
 Total Possible Edema Score	 4
 Total Possible Primary Irritation Score	 8

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#### IV. Eye Irritation Tests - Albino Rabbits

##### A. Procedure

These tests were conducted on both HALANE and Sodium Hypochlorite. Both test materials were employed in the form of aqueous solutions (concentrations adjusted to 600 ppm "available chlorine").

Two groups of five albino rabbits were used to evaluate the eye irritating properties of the test materials. Young adult, New Zealand strain animals were selected for the tests.

The test method employed was patterned after that of Draize et al\*. Exactly 0.1 ml of test solution was instilled into the conjunctival sac of the right eye of each test rabbit in a group of five animals. The left eye of each animal served as a scoring control.

One, 24, 48, 72, 96 hours, and 7 days following the initial instillations, the cornea, iris, and palpebral conjunctiva were examined individually and graded for irritation and injury according to a standard scoring system\*. The maximum possible score at any one examination and scoring period is 110 points which indicates maximal irritation and damage to all three ocular tissues. Zero score indicates no irritation whatever.

After the completion of the tests, the scores were analyzed and descriptive eye irritation ratings were assigned to the test materials. The criteria used for assignment of a descriptive rating were the frequency, the extent, and the persistence of irritation or damage which

\* See footnote \* page 5

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HE 0075

occurred to the three ocular tissues. In the classification system used, special emphasis was placed upon irritation or damage to the cornea. Correspondingly less stress was placed upon conjunctival and iridial effects.

The descriptive ratings assigned were one of the following, each of which characterizes a particular level of ophthalmic irritation and damage:

Non-Irritating  
Practically Non-Irritating  
Minimally Irritating  
Mildly Irritating  
Moderately Irritating  
Severely Irritating  
Extremely Irritating  
Maximally Irritating

#### B. Results

The scores and ratings are given in Tables VI and VII.

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V. Summary

1. Acute Oral Toxicity - Albino Rats

The acute oral mean lethal dose (LD<sub>50</sub>) of HALANE was found to be 542 mg/kg.

2. Skin Irritation Tests - Albino Rabbits

<u>Compound</u>	<u>Type of Preparation</u>	<u>Rating</u>
HALANE	Powder, <u>as received</u>	Severely Irritating
HALANE	Aqueous Solution 600 ppm "available chlorine"	Slightly Irritating
Sodium Hypochlorite	Aqueous Solution 600 ppm "available chlorine"	Slightly Irritating

3. Eye Irritation Tests - Albino Rabbits

<u>Compound</u>	<u>Type of Preparation</u>	<u>Rating</u>
HALANE	Aqueous Solution 600 ppm "available chlorine"	Mildly Irritating
Sodium Hypochlorite	Aqueous Solution 600 ppm "available chlorine"	Mildly Irritating

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

NOTICE

*John H. Kay*

Report prepared by: John H. Kay, Ph.D.  
Associate Director

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*J. C. Calandra*

Report approved by: J. C. Calandra, M.D., Ph.D.  
Director

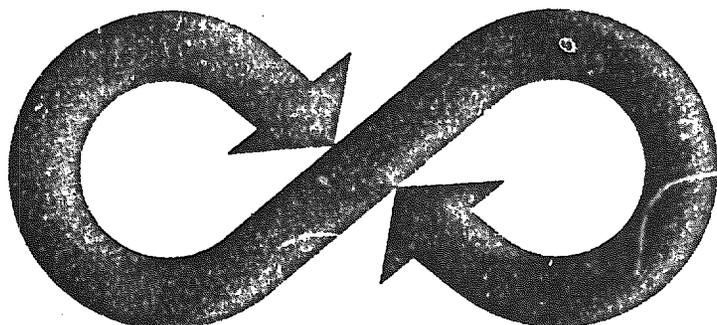
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**Bio/dynamics Inc.**

Division of Biology and Safety Evaluation

PROJECT NO.: 4740-77

ACUTE DERMAL TOXICITY STUDY IN RABBITS

COMPOUND: Dantoin DCDMH 837991

Submitted to: Glyco Chemicals, Inc.  
Williamsport, Pennsylvania

Date: April 11, 1979

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4740-77

PAGE 0106

I. GENERAL

An acute dermal toxicity study, described in 16 CFR 1500.40, was performed on rabbits using test material labeled: Dantoin DCDMH 40-572; 837991; DLB-457-28-1; 6/29/78. The test material was received on July 6, 1978 from Glyco Chemicals, Inc. and was in the form of a fine white powder.

II. EXPERIMENTAL

Sixteen albino rabbits, New Zealand White strain (Marland Breeding Farms, Inc., Hewitt, N.J.), weighing 2.6 to 3.5 kg, were prepared and treated according to the method described in 16 CFR 1500.40. The hair of each rabbit was clipped from the trunk so as to expose at least 10% of the body surface area. The skin of half the animals (4 males; 4 females) was abraded longitudinally every 2 or 3 centimeters so as to penetrate the stratum corneum but not so deep as to disturb the derma or produce bleeding.

The test material was administered as received to four animals (2/sex) at each of the following dose levels: 7.1, 10.0, 14.2, and 20.0 g/kg. Preliminary screening was performed to arrive at the appropriate dose levels. Each dose was individually weighed, placed onto gauze and sprinkled with a small amount of water until damp. The test material was held in contact with the skin by a sleeve made of impervious plastic sheeting designed to contain the dose without leakage or undue pressure. Collars designed to prevent the ingestion of the test material were worn by all animals throughout the study.

Observations for mortality and overt signs of effect were made at 0-2 and 4-6 hours following dosing, and daily thereafter for fourteen days. Following 24 hours of exposure, the sleeves were removed and observations were made

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II. EXPERIMENTAL (cont.)

for edema, erythema and eschar formation.<sup>1</sup> The exposed area was then wiped free of excess test material. Body weights were recorded initially and terminally. A gross necropsy was performed on spontaneous deaths.

III. RESULTS

Individual body weights and 24-hour dermal observations are presented in Table I. The scoring system used is presented with the table. A summary of in-life observations is presented in Table II.

Mortality at each of the dose levels was as follows:

<u>Dose Level</u> (g/kg)	<u>Mortality</u>
7.1	0/4
10.0	0/4
14.2	0/4
20.0	1/4

The dermal LD<sub>50</sub> for Dantoin DCDMH 837991 estimated from the above data is greater than 20.0 g/kg. According to 40 CFR 162.10, Dantoin DCDMH 837991 meets the criteria of Toxicity Category IV.

At 7.1 g/kg, moderate to severe erythema was noted in two animals and severe erythema to slight eschar formation was noted in the two remaining animals at the 24-hour dermal observation. In addition, moderate edema was noted in three animals and severe edema was noted in one animal. Three animals exhibited a weight loss and one animal exhibited a failure to gain weight at the termination of the study.

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<sup>1</sup> Draize, John H., et al. Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes. J. Pharm. Exp. Ther., 82: 337 (1944).

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-3-  
4740-77III. RESULTS (cont.):

At 10.0 g/kg, severe erythema to slight eschar formation and moderate edema were noted in all animals at the 24-hour dermal observations. Three animals exhibited a weight loss at the termination of the study.

At 14.2 g/kg, severe erythema to slight eschar formation was noted in all animals at the 24-hour dermal observation. In addition, moderate edema was noted in one animal and severe edema was noted in three animals. Three animals exhibited a loss of weight at the termination of the study.

At 20.0 g/kg, severe erythema to slight eschar formation and severe edema were noted in all animals at the 24-hour dermal observation. One animal was found dead on Day 6 of the study and a gross necropsy revealed dark red lungs, small and pale spleen, stomach wall white and thickened, and areas of distinct vascularization over the surface of the kidneys. Two of the three surviving animals exhibited a weight loss at the termination of the study.

Lethargy was persistent in all animals during the study. Ataxia was noted in all animals at the 20.0 g/kg dose level and in one animal each at the 7.1 and 14.2 g/kg/dose levels. Prostration was noted in two animals at the 20.0 g/kg dose on Day 5 (one of these animals was found dead on Day 6). Other in-life signs noted occasionally during the study included piloerection, clear nasal discharge, rapid respiration, abdominal griping, hair loss, soft stool and fecal staining of the abdomen.

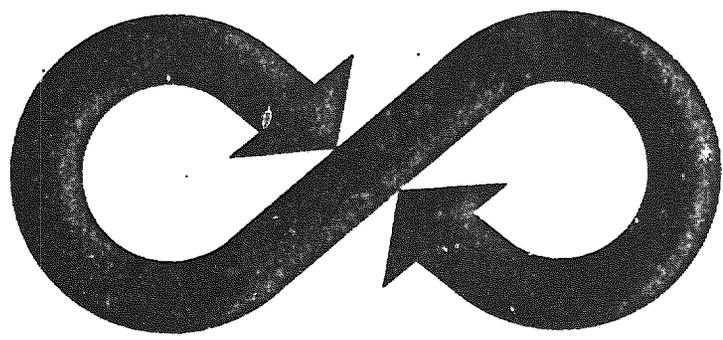
*Carol S. Auletta*

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William E. Rinehart, Sc.D.  
Vice-President

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# Bio/dynamics Inc.

Toxicological Resources Unit

PROJECT NO. 4744-77

RABBIT EYE IRRITATION STUDY

COMPOUND: Dantoin DBDMH ~~736635~~ NOTICE

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Submitted to: Glyco Chemicals, Inc.  
Williamsport, Pa.

Date: February 10, 1978

I. GENERAL

An eye irritation test, a modification of that described in 16 CFR 1500.42, was performed on rabbits using test material labeled: 9/29/77; Dantoin DBDMH 94-606; Batch 736635; DLB-440-21. The test material was received on October 5, 1977 from Glyco Chemicals, Inc., and was in the form of a fine white powder.

II. EXPERIMENTAL

Nine New Zealand White rabbits (Marland Breeding Farms, Inc., Hewitt, N.J.) were individually housed and equilibrated in this laboratory. Only animals which were determined to be free of ocular defects prior to compound administration were used in this study.

One-tenth cubic centimeter of the test material was instilled into one eye of each of the nine rabbits. The treated eyes of three rabbits were rinsed with 30 ml tap water (room temperature), 15 seconds following the instillation of the test material. The remaining six animals received no further treatment.

The eyes were examined and scored for ocular reactions<sup>1</sup> on Days 1, 2, 3, 4, 7, 10, and 14 following compound administration. A fluorescein wash was used when necessary in scoring ocular reactions. The scoring scale used is presented in Appendix A.

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<sup>1</sup>Draize, John H., et al. Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes. J. Pharm. Exp. Ther., 82: 337 (1944).

### III. RESULTS

Individual scores for ocular reactions are presented in Table I. A summary of positive scores and mean maximum Draize scores is presented in Table II.

All six unwashed eyes were assigned positive scores for corneal opacity and ulceration, iritis, conjunctival redness and chemosis, and necrosis/ulceration. Pannus was evident in each unwashed eye. Due to the severity of the corneal opacity, five of the six eyes could not be examined for all the parameters on Day 14. One eyeball ruptured on the final day of the study. Eschar formation was noted on the eyelids of each unwashed eye, beginning on Day 1. Signs of irritation were evident in each unwashed eye at the termination of the study.

Each eye washed at 15 seconds following compound administration was assigned positive scores for corneal opacity and ulceration, iritis, conjunctival redness and chemosis, and necrosis/ulceration. Pannus was noted in two of the three eyes. Due to severe corneal opacity the treated eye of one animal could not be examined for all the parameters on Days 10 and 14 of the study. Alopecia was noted around one treated eye. One eye was clear of signs of irritation on Day 10, while signs of irritation were evident in two eyes at the termination of the study.

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III. RESULTS (cont.)

Dantoin DBDMH 736635 is considered to be maximally irritating to the eye<sup>2</sup>.

Pamela R. Heenehan  
Pamela R. Heenehan, B.S.  
Staff Supervisor

William G. Braun  
William G. Braun, M.S.  
Manager

William E. Rinehart  
William E. Rinehart, Sc.D.  
Director, Division of Biology  
and Safety Evaluation

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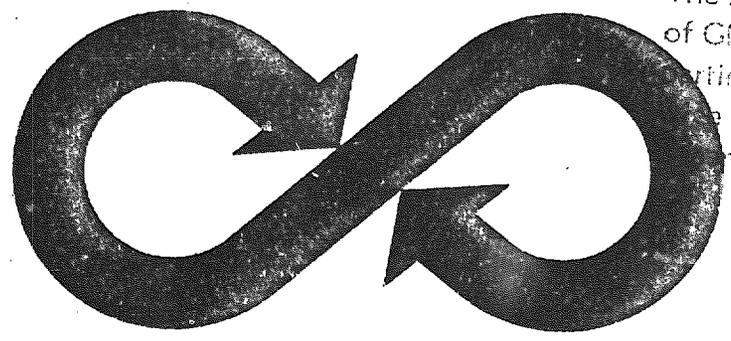
<sup>2</sup>Kay, John H. and Calandra, Joseph C., Interpretation of Eye Irritation Tests, Journal of the Society of Cosmetic Chemists, p. 281-289 (1962).

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DBDMH

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# Bio/dynamics Inc.

Division of Biology and Safety Evaluation

PROJECT NO. 4742-77

ACUTE DERMAL TOXICITY STUDY IN RABBITS

COMPOUND: Dantoin DBDMH 736635

Submitted to: Glyco Chemicals, Inc.  
Williamsport, Pa.

Date: November 30, 1978

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4742-77

PAGE 0123

I. GENERAL

An acute dermal toxicity study, described in 16 CFR 1500.40, was performed on rabbits using test material labeled: 9/29/77. Dantoin DBDMH 94-606; Batch 736635; DLB-440-21. The test material was received on October 5, 1977 from Glyco Chemicals, Inc. and was in the form of a fine white powder.

II. EXPERIMENTAL

Six albino rabbits, New Zealand White strain (Marland Breeding Farms, Inc. Hewitt, N.J.), weighing 2.9 to 3.5 kg, were prepared and treated according to the method described in 16 CFR 1500.40. The hair of each rabbit was clipped from the trunk so as to expose at least 30% of the body surface area. The skin of half the animals (2 male; 1 female) was abraded longitudinally every two or three centimeters so as to penetrate the stratum corneum but no so deep as to disturb the derma or produce bleeding.

The test material was administered as a 1 g/ml slurry in tap water to six animals (3/sex) at a single dose level of 20.0 g/kg. The test material was held in contact with the skin by a sleeve made of impervious plastic sheeting designed to contain the dose without leakage or undue pressure. Collars designed to prevent the ingestion of the test material were worn by all animals throughout the study.

Observations for mortality and overt signs of effect were made at 0-2 and 4-6 hours following dosing, and daily thereafter for fourteen days. Following 24 hours of exposure, the sleeves were removed and observations were

made for edema, erythema and eschar formation.<sup>1</sup> The exposed area was then wiped free of excess test material. Body weights were recorded initially and terminally. A gross necropsy was performed on all spontaneous deaths.

### III. RESULTS

Individual body weights and 24-hour dermal observations are presented in Table I. The scoring system used is presented with the table.

One death occurred during this study. The dermal LD<sub>50</sub> for Dantoin DBDMH 736635 is greater than 20.0 g/kg. According to 40 CFR 162.10, this test material meets the criteria of Toxicity Category IV.

At the 24-hour dermal observation the following were noted: moderate to severe erythema in two animals; severe erythema to slight eschar formation in four and severe edema in all six animals.

Common in-life signs of effect observed during this study period included: lethargy and clear nasal discharge. In addition, soft stool, fecal staining of the abdomen and piloerection were noted in one animal. One animal died on Day 10 of the study and necropsy observations included mottled liver, pale spleen, mottled dark red and pink lungs and subcutaneous edema. A loss of weight was exhibited by one animal and a failure to gain weight was exhibited by two animals.

#### NOTICE

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<sup>1</sup> Draize, John H., et al. Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes. J. Pharm. Exp. Ther., 82: 337 (1944).

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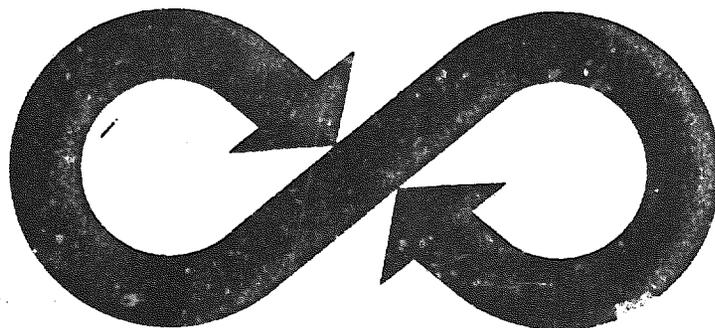
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DBDMH

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**Bio/dynamics Inc.**

Toxicological Resources Unit

PROJECT NO. 4743-77

PRIMARY DERMAL IRRITATION STUDY IN RABBITS

COMPOUND: Dantoin DBDMH 736635

Submitted to: Glyco Chemicals, Inc.  
Williamsport, Pa.

Date: January 4, 1978

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## I. GENERAL

A primary dermal irritation study, described in 16 CFR 1500.41, was performed on rabbits using test material labeled: 9/29/77; Dantoin DBDMH 94-606; Batch 736635; DLB-440-21. The test material was received on October 5, 1977 from Glyco Chemicals, Inc., and was in the form of a fine, white powder.

## II. EXPERIMENTAL

Six albino rabbits, New Zealand White strain, weighing 2.45 to 3.15 kg, were closely clipped over the back and sides with an electric clipper. There were two test sites per rabbit, each site 1" x 1" in area. A site to the left of the spinal column was abraded, while a site to the right of the spinal column was left intact. The abrasions were sufficiently deep so as to penetrate the stratum corneum, but not so deep as to disturb the derma or produce bleeding.

The test material was administered as a 1 g/ml aqueous slurry. In all cases 0.5 ml of the test material was applied beneath a surgical gauze square 1" x 1", eight single layers thick, placed directly on the test site and secured with Dermicel<sup>R</sup> tape. The animals were then wrapped with plastic sheeting secured with masking tape. After 24-hours the sheeting and gauze patches were removed.

Observations for signs of dermal irritation or systemic toxicity were recorded at 24 and 72 hours after application. At each observation all treated sites were scored for erythema, eschar, and edema formation<sup>1</sup>. The scores were used to calculate a primary dermal irritation index.

<sup>1</sup>Draize, John H., et al, Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes. J. Pharm. Exp. Ther., 82: 337 (1944).

III. RESULTS

The observations at 24 and 72 hours are presented in Table I. The scoring scale used in scoring the dermal reactions is presented along with the table.

The primary dermal irritation index of Dantoin DBDMH 736635 was found to be 5.9. This compound is considered to be moderately to severely irritating to the skin.<sup>2</sup>

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<sup>2</sup>Draize, John H. "Dermal Toxicity," Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, 2nd ed., p. 46. The Association of Food and Drug Officials of the United States, 1965.