LIMITED TOXICITY AND MUTAGENICITY TESTING OF FIVE UNICHARGE PROPELLANT COMPOUNDS

EVALUATION OF TWO UNICHARGE PROPELLANTS IN THE PRIMARY EYE IRRITATION

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WAVERLY, PA 18471

JANUARY 31, 1992

FINAL REPORT

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FORT DETRICK, FREDERICK, MARYLAND 21702-5012

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LIMITED TOXICITY AND MUTAGENICITY TESTING OF FIVE UNICHARGE PROPELLANT COMPOUNDS

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Fort Detrick
Frederick, Maryland 21702-5012

Subtitle: Evaluation of Two Unicharge Propellants in the Primary Eye Irritation

Bis (2,2-dinitropropyl) acetal/formal (-50/50 mixture) ± diphenyl amine stabilizer (BDNPA/F±DPA) were tested for eye irritation. One group of six rabbits per study were administered 0.1 mL of the test article directly into the right eye. The treated eyes were examined at 1, 24, 48 and 72 hours after treatment and grades of ocular reaction were recorded. Positive ocular scores were observed in both treatment groups at the 1 hour observation period. All scores were normal in both treatment groups for the remainder of the study. Based upon these observations BDNPA/F±DPA were determined to be eye irritants. The Toxicity Category for Eye Irritation for both test articles is Class IV.
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In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

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In the conduct of research utilizing recombinant DNA, the Investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.
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Evaluation of Two Unicharge Propellants in the Primary Eye Irritation

EXECUTIVE SUMMARY

Test articles bis-(2,2-dinitropropyl) acetal with diphenyl amine stabilizer and bis-(2,2-dinitropropyl) formal without diphenyl amine stabilizer were instilled in the right eye of six rabbits each at 0.1 mL/treated eye. The eyes were examined at 1, 24, 48 and 72 hours after administration.

Positive ocular scores of the conjunctivae were observed in four bis-(2,2-dinitropropyl) acetal with diphenyl amine stabilizer treated animals at the 1 hour observation period. The remaining two animals exhibited vessels injected above normal at the 1 hour observation period. All scores returned to normal at 24 hours.

Positive ocular scores of the conjunctivae were observed in two bis-(2,2-dinitropropyl) formal without diphenyl amine stabilizer treated animals at the 1 hour observation period. The remaining four animals exhibited vessels injected above normal at the 1 hour observation period. All scores returned to normal at 24 hours. Both treatment groups were terminated following the 72 hour observation period.

Based upon the observations made in the Primary Eye Irritation studies in rabbits, bis-(2,2-dinitropropyl) acetal with diphenyl amine stabilizer and bis-(2,2-dinitropropyl) formal without diphenyl amine stabilizer were determined to be eye irritants. The Toxicity Category for Eye Irritation for both test articles is Class IV (minimal effects cleaning in less than 72 hours).
Evaluation of Two Unicharge Propellants in the Primary Eye Irritation

PH 421-US-001, 002-91

STUDY DESCRIPTION

Sponsor: U.S. Army Medical Research and Development Laboratory
Fort Detrick
Frederick, MD 21702-5010

P.O. Box 609
Waverly, PA 18471

Test Facility
Study Conduct
S.O.P. No.: PH-421
Study Numbers: PH 421-US-001-91
PH 421-US-002-91

Purpose of the Study: To determine the irritant and/or corrosive effects on eyes of rabbits.

Ownership of the Study: The sponsor owns the study. All raw data, analyses and reports are the property of the sponsor.

Study Monitor: Major Nathaniel Powell, U.S. Army Medical Research and Development Laboratory

Study Director: Victor T. Mallory, B.S., RLAT, Pharmakon Research International, Inc.

Technical Performance: Thomas O’Neill, B.S., LAT and Kim DiLeo, B.S., LAT

O.A.U. Responsible Personnel: Leslie J. Pinnell, M.S.

Date Study Director Signed Protocols: September 23, 1991

Evaluation of Two Unicharge Propellants in the Primary Eye Irritation
PH 421-US-001, 002-91

Good Laboratory Practices
Statement: These studies were conducted in compliance with the Good Laboratory Practice Regulations. There were no deviations from the GLP Regulations which affected the quality or integrity of the study. Q.A.U. findings from the inspections conducted of this study and from the audit of the final report are documented and have been provided to the study director and the test facility management.

Records Maintained: All raw data, final report documentation and protocol will be maintained in the archives of Pharmakon Research International, Inc.

Recordings: Standard Pharmakon Notebook

Notebook Reference: Notebook #1449, pages 173-174, 176-177

<table>
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<tr>
<th>TEST ARTICLES</th>
<th>DESCRIPTION</th>
<th>LOT #</th>
<th>pH</th>
<th>CAS #</th>
<th>DATE SUBMITTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>bis-(2,2-dinitropropyl) acetal with diphenyl amine stabilizer (BDNPA/F+DPA)</td>
<td>yellow liquid</td>
<td>Set #1</td>
<td>5</td>
<td>5108-69-0</td>
<td>9/19/91</td>
</tr>
<tr>
<td>bis-(2,2-dinitropropyl) formal without diphenyl amine stabilizer (BDNPA/F-DPA)</td>
<td>yellow liquid</td>
<td>Set #2</td>
<td>5</td>
<td>5917-61-3</td>
<td>9/19/91</td>
</tr>
</tbody>
</table>

Analysis of Purity: The purity, identity, strength and stability of the test articles were the responsibility of the sponsor.

Stability: There was no apparent change in the physical appearance of the test articles during administration.

TEST SYSTEM
Species: Rabbit
Strain: New Zealand White
Evaluation of Two Unicharge Propellants in the Primary Eye Irritation
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Supplier (Source):
CAMM Research Lab Animals, Wayne, NJ

Sex:
Male and female

Age at Initiation:
8-12 weeks

Weight Range:
1.741-1.992 kilograms

No. on Study:
Six (6) (three males and three females) per study

Method and Justification for Randomization:
Selection of rabbits based upon body weight.

Acclimation Period:
Minimum of five (5) days

System of Identification:
Cage cards were marked with the study number, animal number, dose level and sex. Rabbits were ear tagged.

HUSBANDRY

Research Facility Registration:
U.S.D.A. Registration No. 23-R-107 under the Animal Welfare Act 74: SC 2131 et seq.

Animal Rooms:
Separate isolation by test system
Light cycle - 12 hours light, 12 hours dark
Temperature/Relative Humidity - Every attempt was made to maintain a temperature of 20°C ± 3°C (63-73°F) and a relative humidity of 30 to 70%.

Any excursions outside the temperature or humidity ranges were of small magnitude and/or brief duration and did not adversely affect the validity of the study.

Housing:
Rabbits were housed individually in cages sized in accordance with the "Guide for the Care and Use of Laboratory Animals" of the Institute of Laboratory Animal Resources, National Research Council.

Sanitization:
Waste material was removed twice weekly. Cages and feeders were sanitized every two weeks.

Food:
Purina Lab Rabbit Chow H.F. R ad libitum. Food was checked daily and added or replaced as
Evaluation of Two Unicharge Propellants in the Primary Eye Irritation
PH 421-US-001, 002-91

needed. Feeders are designed to reduce soiling, bridging and scattering.

Food Analysis: There were no contaminants that were reasonably expected to be present in the dietary material known to be capable of interfering with the purpose or conduct of the study.

Water: Fresh tap water, \textit{ad libitum}.

Water Analysis: Water is monitored for contaminants at periodic intervals according to Standard Operating Procedure PH-018.

METHODS

Rationale for Test System: A variety of experimental animals have been used, but it is recommended that testing will be performed using healthy adult albino rabbits. Commonly used laboratory strains will be used.

Compound Preparation: The test articles were dosed as received.

Dose Administration: 0.1 mL/treated eye

Rationale for Dose Selection: According to the EPA Federal Register, Vol. 50, No. 188, Friday, September 27, 1985.

Route of Administration: The test articles were administered directly into the eye.

Rationale for Route of Administration: To evaluate the irritant potential of the test article on the eye.

Frequency of Administration: Once (1) per test article

No. of Animals Per Dose Group: Six (6)

No. & Code of Dose Groups: 

<table>
<thead>
<tr>
<th>Rabbit No.</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>5501-5506</td>
<td>0.1 mL/treated eye [bis-(2,2-dinitropropyl) acetal with diphenyl amine stabilizer]</td>
</tr>
<tr>
<td>5291-5296</td>
<td>0.1 mL/treated eye [bis-(2,2-dinitropropyl) formal without diphenyl amine stabilizer]</td>
</tr>
</tbody>
</table>
Evaluation of Two Unicharge Propellants in the Primary Eye Irritation
PH 421-US-001, 002-91

Length of Studies:
Seventy two (72) hours

Method of Study
Performance:
Both eyes of each experimental animal provisionally selected for testing were examined within 24 hours before testing started by the same procedure used during the test examination. Animals showing eye irritation, ocular defects or pre-existing corneal injury were not used. The test substance was placed in the conjunctival sac of the right eye of each animal after gently pulling the lower lid away from the eyeball. The lids were then gently held together for about one second in order to limit loss of the material. The other eye, which remained untreated, served as a control.

Type and Frequency of Test, Analysis and Measurements to be Made:
The eyes were examined at 1, 24, 48 and 72 hours after treatment. The grades of ocular reaction were recorded at each examination period.

Data Analysis:

RESULTS

Positive ocular scores of the conjunctival were observed in four bis-(2,2-dinitropropyl) acetal with diphenyl amine stabilizer treated animals at the 1 hour observation period. The remaining two animals exhibited vessels injected above normal at the 1 hour observations period. All scores returned to normal at 24 hours.

Positive ocular scores of the conjunctivae were observed in two bis-(2,2-dinitropropyl) formal without diphenyl amine stabilizer treated animals at the 1 hour observation period. The remaining four animals exhibited vessels injected above normal at the 1 hour observation period. All scores returned to normal at 24
hours. Both treatment groups were terminated following the 72 hour observation.

CONCLUSIONS

Based upon the observations made in the Primary Eye Irritation, bis-(2,2-dinitropropyl) acetal with diphenyl amine stabilizer and bis-(2,2-dinitropropyl) formal without diphenyl amine stabilizer were determined to be eye irritants. The Toxicity Category for Eye Irritation for both test articles is Class IV (minimal effects cleaning in less than 72 hours).
Evaluation of Two Unicharge Propellants
in the Primary Eye Irritation
PH 421-US-001, 002-91

TABLE I

Scale for Scoring Ocular Lesions*

(1) Cornea
   (A) Opacity-degree of density (area most dense taken for reading)
      No opacity..............................................0
      Scattered or diffuse area, details of iris clearly visible........1**
      Easily discernible translucent areas, details of iris slightly obscured........2
      Opalescent areas, no details of iris visible, size of pupil barely discernible.....3
      Opaque, iris invisible................................4

(2) Iris
   (A) Values
      Normal.................................................0
      Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reactions are positive)...............................1**
      No reaction to light, hemorrhage, gross destruction (any or all of these).........2

(3) Conjunctivae
   (A) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)
      Vessels normal........................................0
      Vessels definitely injected above normal........1
      More diffuse, deeper crimson red, individual vessels not easily discernible........2**
      Diffuse beefy red....................................3
   (B) Chemosis
      No swelling............................................0
      Any swelling above normal (includes nictitating membrane)..............................1
      Obvious swelling with partial eversion of lids........................................2**
      Swelling with lids about half closed............3
      Swelling with lids about half closed to completely closed..............................4

**Figures indicates lowest grades considered positive under the Federal Hazardous Substances Act Regulations at 16 CFR 1500.42
TABLE I (continued)

Toxicity Categories for Eye Irritation

<table>
<thead>
<tr>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrosive (irreversible destruction of ocular tissue) or corneal involvement or irritation persisting for more than 21 days</td>
<td>Corneal involvement or irritation clearing in 8-21 days</td>
<td>Corneal involvement or irritation clearing in 7 days or less</td>
<td>Minimal effects clearing in less than 24 hours</td>
</tr>
</tbody>
</table>
### Summary of Ocular Lesion Scores of Two Unicharge Propellants in the Primary Eye Irritation

**Bis-(2,2-Dinitropropyl) Acetal with Diphenyl Amine Stabilizer**

<table>
<thead>
<tr>
<th>Rabbit No.</th>
<th>Sex</th>
<th>Observations</th>
<th>1</th>
<th>24</th>
<th>48</th>
<th>72</th>
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<td>Cornea</td>
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<td></td>
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<td>0</td>
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<tr>
<td></td>
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<td>M</td>
<td>Cornea</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Iris</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Iris</td>
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<td>0</td>
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</tr>
<tr>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Iris</td>
<td>0</td>
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<tr>
<td></td>
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<td></td>
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<td>Iris</td>
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<tr>
<td></td>
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<td>Iris</td>
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</tr>
</tbody>
</table>

Cornea = degree of opacity  
Iris = degree of iritis  
Conjunctivae = redness, chemosis
TABLE II (continued)

Summary of Ocular Lesion Scores of Two Unicharge Propellants in the Primary Eye Irritation

PH 421-US-001, 002-91

Bis-(2,2-Dinitropropyl) Formal without Diphenyl Amine Stablizer

<table>
<thead>
<tr>
<th>Rabbit No.</th>
<th>Observations</th>
<th>Hours</th>
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<td>48</td>
<td>72</td>
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<tr>
<td></td>
<td>Iris</td>
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<td>0</td>
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<tr>
<td></td>
<td>Conjunctivae</td>
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<tr>
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<tr>
<td></td>
<td>Conjunctivae</td>
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<td>5293</td>
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<td>Iris</td>
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<tr>
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<td>Iris</td>
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<td>0</td>
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<tr>
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<tr>
<td></td>
<td>Conjunctivae</td>
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<td>0,0</td>
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</tr>
</tbody>
</table>

Cornea = degree of opacity
Iris = degree of iritis
Conjunctivae = redness, chemosis
### TABLE III
Summary of Positive Scores of Two Unicharge Propellants in the Primary Eye Irritation

PH 421-US-001, 002-91

**Bis-(2,2-Dinitropropyl) Acetal with Diphenyl Amine Stabilizer**

<table>
<thead>
<tr>
<th>Hours</th>
<th>1</th>
<th>24</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornea Opacity</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
</tr>
<tr>
<td>Iritis</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
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<tr>
<td>Conjunctivae Redness</td>
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<td>0/6</td>
</tr>
<tr>
<td>Chemosis</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
</tr>
</tbody>
</table>

**Bis-(2,2-Dinitropropyl) Formal without Diphenyl Amine Stabilizer**

<table>
<thead>
<tr>
<th>Hours</th>
<th>1</th>
<th>24</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornea Opacity</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
</tr>
<tr>
<td>Iritis</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
</tr>
<tr>
<td>Conjunctivae Redness</td>
<td>2/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
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<tr>
<td>Chemosis</td>
<td>0/6</td>
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<td>0/6</td>
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</tbody>
</table>
Table IV. Summary of Body Weights (g) of Two Unicharge Propellants in the Primary Eye Irritation

PH 421-US-001, 002-91

Bis-(2,2-Dinitropropyl) Acetal with Diphenyl Amine Stabilizer

<table>
<thead>
<tr>
<th>Animal Number</th>
<th>Sex</th>
<th>Initial</th>
<th>Final</th>
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Bis-(2,2-Dinitropropyl) Formal without Diphenyl Amine Stabilizer

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QUALITY ASSURANCE UNIT STATEMENT

Study Nos.: PH 421-US-001-91
PH 421-US-002-91

Study Director: **Victor T. Mallory**

The Quality Assurance Unit conducted the inspections listed below and reported the results to the study director and to management on the dates indicated.

The following inspections were performed:

<table>
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<th>Interval</th>
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<td>Reporting Phase</td>
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**Date OAU Report Issued**

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<th>To Study Director</th>
<th>To Management</th>
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<td>January 29, 1992</td>
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[Signature]

Quality Assurance

[Signature]

Date

Jan 29, 1992
COMPLIANCE STATEMENT

This study was conducted in compliance with the Principles of Good Laboratory Practices (GLP) as promulgated by the following regulatory agencies.

EPA as stated in the Federal Register, 40 CFR Parts 160 and 792.


U.S. Food and Drug Administration as stated in 58 CFR Part 21.

Study Nos.: PH 421-US-001-91
PH 421-US-002-91

To the best of my knowledge, this study was conducted in accordance with applicable Good Laboratory Practice regulations; there were no deviations from these regulations that impacted on study conclusions.

Study Director

Date

May 29, 1993