Sarkaryotic Inhibition Potential of 
Sarcoplasma Titin in Rabbits 

James O. Johnson, BS 
W. Richardson, MED 

takes M. PhD, MD, MS 

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FREEMASON, SAN FRANCISCO, CALIFORNIA 94120
**Primary Dermal Irritation Potential of Guanidine Nitrte in Rabbits (U)**

Yvonne C. LeTellier, Joy W. Bauserman, Don W. Korte, Jr.

The primary dermal irritation potential of guanidine nitrate was determined in male and female New Zealand White rabbits using a modified Draize method. The test compound was classified as a severe primary irritant with corrosive properties. Erythema, edema, and eschar formation (injuries in depth) were detected at 24, 48, and 72 hours after dosing. Irreversible skin damage was apparent at the time of sacrifice, 14 days after dosing.

(Exxpt: triple base propellants cause physiology)
ABSTRACT

The primary dermal irritation potential of guanidine nitrate was determined in male and female New Zealand White rabbits using a modified Draize method. The test compound was classified as a severe primary irritant with corrosive properties. Erythema, edema, and eschar formation (injuries in depth) were detected at 24, 48, and 72 hours after dosing. Irreversible skin damage was apparent at the time of sacrifice, 14 days after dosing.

KEY WORDS: Primary Dermal Irritation, Guanidine Nitrate, Nitroguanidine, Munitions, Mammalian Toxicology, Rabbit
PREFACE

TYPE REPORT: Primary Dermal Irritation GLP Study Report

TESTING FACILITY:
US Army Medical Research and Development Command
Letterman Army Institute of Research
Presidio of San Francisco, CA 94129-6800

SPONSOR:
US Army Medical Research and Development Command
US Army Biomedical Research and Development Laboratory
Fort Detrick, Maryland 21701-5010
Project Officer: Gunda Reddy, PhD

GLP STUDY NUMBER: 84012

STUDY DIRECTOR: MAJ Don W. Korte Jr, PhD, MSC
PRINCIPAL INVESTIGATOR: Yvonne C. LeTellier, BS
CO-PRINCIPAL INVESTIGATOR: Joy W. Bauserman, MEd

REPORT AND DATA MANAGEMENT: A copy of the final report, study protocol, SOPs, raw data, analytical, stability, and purity data of the test compound, and an aliquot of the test compound will be retained in the LAIR Archives.

TEST SUBSTANCE: Guanidine Nitrate

INCLUSIVE STUDY DATES: 21 June - 24 July 1984

OBJECTIVE: The objective of this study was to determine the primary dermal irritation potential of guanidine nitrate in male and female New Zealand White rabbits.
ACKNOWLEDGMENTS

MAJ Earl W. Morgan, VC, and SPC Steven K. Sano, BS, provided research assistance. Richard D. Spieler, Richard Katona, Charlotte Speckman, and Roosevelt Cunningham provided animal care and facility management. Callie B. Crosby, MA, Colleen S. Kamiyama, and Julie Peacock provided secretarial assistance.
SIGNATURES OF PRINCIPAL SCIENTISTS AND MANAGERS INVOLVED IN THE STUDY

We, the undersigned, declare that GLP Study 84012 was performed under our supervision, according to the procedures described herein, and that this report is an accurate record of the results obtained.

DON W. KORTE JR., PhD / DATE
MAJ, MSC
Study Director

YVONNE C. LETELLIER, BS / DATE
DAC
Principal Investigator

JOY W. BAUSERMAN, MD / DATE
Co-Principal Investigator

CONRAD W. WHEELER, PhD / DATE
DAC
Analytical Chemist
MEMORANDUM FOR RECORD

SUBJECT: GLP Compliance for GLP Study 84012

1. This is to certify that in relation to LAIR GLP Study 84012, the following inspections were made:
   
   24 February 1984  -  Protocol Review
   11 July 1984      -  Scoring


Caroline M. Lewis
CAROLYN M. LEWIS
Chief, Quality Assurance
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Primary Dermal Irritation Potential of Guanidine Nitrate in Rabbits--LeTellier et al

INTRODUCTION

Guanidine nitrate is an intermediate and an anticipated by-product of nitroguanidine production. Nitroguanidine, a primary component of US Army triple-base propellants, is now produced in a Government-owned contractor-operated ammunition plant. The US Army Biomedical Research and Development Laboratory (USABRDL), as part of its charge to evaluate the environmental and health hazards of military-unique pollutants generated by US Army munitions-manufacturing facilities, reviewed the nitroguanidine data base and identified significant gaps in the toxicity data (1). The Toxicology Branch, LAIR, was tasked by USABRDL to develop a genetic and mammalian toxicity profile for nitroguanidine and related intermediates/by-products of its manufacture or environmental degradation products.

Objective of Study

The objective of this study was to determine the primary dermal irritation potential of guanidine nitrate in male and female New Zealand White rabbits.

MATERIALS

Test Substance

Chemical name: Guanidine nitrate

Chemical Abstracts Service Registry No.: 506-93-4

Structural formula:

\[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{C} = \text{NH}_2 \\
\text{NO}_3^-
\end{array}
\]

Molecular structure: \( \text{CH}_6\text{N}_4\text{O}_3 \)

Other test substance information is presented in Appendix A.
LeTellier et al.--2

Vehicle

The vehicle for guanidine nitrate was physiological saline (0.9%) for injection, obtained from Travenol Laboratories Inc., Deerfield, IL. The lot number used was 7C950X0, and the expiration date was Oct 85.

Animal Data

Four male and four female New Zealand White rabbits (Elkhorn Rabbitry, 5265 Starr Way, Watsonville, CA) were identified individually with ear tattoos numbered 84F429, 84F432-84F435, and 84F438-84F440 inclusive and assigned to the study. The animal weights on the day of dosing ranged from 2.6 to 3.3 kg. Additional animal data appear in Appendix B.

Husbandry

The rabbits were housed individually in stainless steel, battery-type cages with screened bottoms and automatically flushing dump tanks. The diet consisted of 150 g/day of Certified Purina Chow Diet 5322 (Ralston Purina Company, Checkerboard Square, St. Louis, MO); water was provided by continuous drip from a central line. The animal room temperature was maintained at 14.1 to 21.1°C with a relative humidity range of 40 to 70% except during a steam outage when it increased to 80% for several hours. The photoperiod was 12 hr of light per day.

METHODS

Group Assignment/Acclimation

This study was conducted in accordance with EPA guidelines (2) and LAIR SOP-OP-STX-34 (3).

Study animals were quarantined/acclimated for 19 days before the study. During this period, the animals were given one application of Canex® mineral oil (Pitman-Moore, Inc., Washington Crossing, NJ) for ear mite prevention. After quarantine, the rabbits were maintained in the same toxicology animal room for the remainder of the study. For assignment of chemicals to application sites on individual animals, a 4 x 8 Standard Latin Square (3) dosing scheme was used in conjunction with the RANDOM Program on the Data General C-330 computer.
Dosage Levels

A standard dose of 0.5 g of guanidine nitrate was used for the test compound sites. Physiological saline (0.5 ml) was used for the control sites.

Compound Preparation

The test compound was moistened with a few drops of physiological saline (0.9%) to make a thick paste.

Chemical Analysis of Dosing Solution

The pH of a saturated solution of guanidine nitrate in physiological saline was 4.74 (the pH of the physiological saline was 5.2). A pH of 4.74, which would be the anticipated pH of the guanidine nitrate in contact with the skin, is within the pH range for conducting this test (2).

Test Procedures

The backs of eight rabbits were close-clipped and divided into 4 quadrants designated I - IV (4, 5). Areas I and IV were intact on all animals, and areas II and III were abraded by making two perpendicular scratches in the stratum corneum of the skin about 1 in long with an escarifier (6). Each animal had two sites treated with the test compound: one site was treated with the vehicle, and one was a sham patch. The guanidine nitrate paste was placed on a 1-in. square gauze patch which was taped to the appropriate site. Biendor® (Medical Products Division of 3M, St. Paul, MN), a semi-impervious hypoallergenic surgical tape, was used to hold the patches in place. Vet Wrap® (Animal Care Products, Division of 3M, St. Paul, MN) was then wrapped securely around the animal, followed by Conform® elastic tape (The Kendall Company, Boston, MA). The test compound was left in contact with the skin for 24 hr. At the end of the exposure period, the wrapping and patches were removed, the skin was wiped if the material adhered, and the areas were scored.

Observations

Dermal reactions were graded and scored according to Table 1 (6). Observations were made daily from 11 to 24 July 1984. Scoring and grading of dermal reactions were performed at 1, 2, 3, 7, and 14 days after application.
<table>
<thead>
<tr>
<th></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No erythema</td>
<td>0</td>
</tr>
<tr>
<td>Very slight erythema</td>
<td>1</td>
</tr>
<tr>
<td>Well-defined erythema</td>
<td>2</td>
</tr>
<tr>
<td>Moderate-to-severe erythema</td>
<td>3</td>
</tr>
<tr>
<td>Severe erythema (beet redness to slight eschar formation injurious in depth)</td>
<td>4</td>
</tr>
<tr>
<td>Possible total erythema score</td>
<td>4*</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>No edema</td>
<td>0</td>
</tr>
<tr>
<td>Very slight edema (barely perceptible)</td>
<td>1</td>
</tr>
<tr>
<td>Slight edema (edges of area well-defined by definite raising)</td>
<td>2</td>
</tr>
<tr>
<td>Moderate edema (edges raised approximately 1 mm)</td>
<td>3</td>
</tr>
<tr>
<td>Severe edema (raised more than 1 mm and extending beyond area of exposure)</td>
<td>4</td>
</tr>
<tr>
<td>Possible total edema score</td>
<td>4*</td>
</tr>
<tr>
<td>Possible total score for primary irritation</td>
<td>8</td>
</tr>
</tbody>
</table>

*Any skin reaction more serious than severe edema, vesiculation, ulceration, or necrosis places the chemical in Category V.
Duration of Study

Appendix C is a complete listing of historical events.

Changes/Deviations

This study was conducted in accordance with all applicable SOPs and addenda with the following exceptions: Approximately 150 g/day of rabbit chow was provided to each animal rather than ad libitum as stated in the protocol. Also, the animals were scored at 48 hr, in addition to the 24- and 72-hr observations required by the protocol, to follow more closely the progression of dermal signs in each animal. These deviations had no effect on the results of the study.

Raw Data and Final Report Storage

A copy of the final report, study protocols, raw data, SOPs, and an aliquot of the test compound will be retained in the LAIR Archives.

RESULTS

Results from scoring the dermal irritation in each rabbit are tabulated in Appendix D.

Controls

Animals were scored for erythema and edema at each patch site. No erythema or edema was observed with the sham patch, and well-defined (score 2) erythema was observed with the vehicle patch in only one animal (#84F429) at 24 hr. The erythema had resolved in this case by 48 hr.

Guanidine Nitrate: Intact Sites

Upon removal of the wrappings at the intact sites, erythema was present in all animals with scores ranging from slight (score 1) to severe (score 4). Edema, ranging from very slight (score 1) to slight (score 2), was observed at the intact sites of each of the 8 rabbits. All signs of edema cleared by Day 7 for 6 animals, and edema was barely perceptible in the remaining 2 rabbits (84F432, 84F435) on that day. The edema had resolved in all animals by Day 14.
When the wraps were removed, the abraded sites of each of the 8 rabbits exhibited well-defined (score 2) to severe (score 4) erythema with obvious areas of devitalized tissue surrounding the abrasion itself. All sites became necrotic with eschar formation within the first week, with lesions on 6 animals spreading well beyond the area covered by the gauze patch. Edema at the abraded sites was more pronounced than at the intact sites and was graded as severe (score 4) for one animal (84F439) at 1, 2, and 3 days and for another animal (84F440) on Day 2. No edema was present in either animal by Day 7. The remaining 6 animals exhibited very slight to slight edema formation which had resolved by Day 7 in all but Rabbit 84F432. The edema in this rabbit had resolved by Day 14.

The individual scores for guanidine nitrate at 1 and 3 days were used to determine the primary dermal irritation index. The intact score was calculated by dividing the sum of scores for both erythema and edema at 1 and 3 days by twice the number of intact sites (37/16 = 2.31). The abraded score was calculated in a similar manner (72/16 = 4.5). The total score, or primary dermal irritation index, is the sum of the intact and abraded scores divided by the total number of intact and abraded sites [(37+72)/32 = 3.41].

DISCUSSION

The severe erythema and necrosis observed with guanidine nitrate in this evaluation of its dermal irritation potential indicate that the test compound should be considered a severe irritant. Guanidine nitrate was categorized using a primary irritation index adapted from McCreesh and Steinberg (7). According to this classification scheme, non-irritating compounds (Category I) have a primary irritation index of 0.50 or less, mild irritants (Category II) have indices between 0.51 and 2.0, moderate irritants (Category III) have indices between 2.1 and 5.0, and severe irritants (Category IV) have combined indices between 5.1 and 8.0 and there is necrosis, vesiculation, ulceration, and/or eschars. Compounds that are impossible to classify because of staining or masking of effects due to physical properties are placed in Category V.

The primary dermal irritation index for guanidine nitrate was 3.41. This is considered a Category III response. However, accurate observation of edema was made difficult by the severity of the erythema and necrosis. This
may have produced an artificially low value for the index. If erythema alone were calculated, guanidine nitrate would be considered a Category IV compound. Moreover, since necrosis and corrosion were also observed, guanidine nitrate was classified as a severe (Category IV) irritant.

The irreversible skin damage observed in this study is consistent with findings from other studies conducted in the Institute in which guanidine nitrate was applied locally in the eye (8). The irreversible corneal erosion observed in the ocular irritation study supports the classification of guanidine nitrate as a severe dermal irritant in this study.

CONCLUSION

Guanidine nitrate is a severe primary dermal irritant under the conditions of this assay.
REFERENCES


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Appendix A: CHEMICAL DATA

Chemical Name: Guanidine Nitrate

Lot Number: 123820

Chemical Abstracts Service Registry No.: 506-93-4

LAIR Code: TP030

Chemical Structure:

H₂N⁺
C == NH₂
H₂N⁻
NO₃⁻

Molecular Formula: CH₆N₃·NO₃

Molecular Weight: 122.1

Physical State: White crystalline powder

Melting Point: 214°C¹

Analytical Data:

Infrared spectrophotometry was performed, and the spectrum obtained² was identical to the Sadtler spectrum³ for Guanidine Nitrate. Major absorption peaks were observed at 3400 (broad), 3200, 1665, 1575, 1400, 1385, and 825 cm⁻¹. The grade of material obtained for this study is referred to as the Ultralog Grade by the manufacturer. The label on the bulk container states that the purity is at least 99.99%.

Source: Chemical Dynamics Corporation
Hadley Road, P.O. Box 395
South Plainfield, NJ

Appendix A (cont.): CHEMICAL DATA

Stability:

The stability of guanidine nitrate in aqueous solution is demonstrated by the absorbance values obtained for a standard solution containing 20 μg/ml of guanidine nitrate. This solution was prepared on 25 May and kept at room temperature over the period of analysis. From 25 May to 6 June, four assays of this solution were performed yielding statistically identical absorbance values. Since the Voges-Proskauer assay is specific for unsubstituted and mono-substituted guanidines, the data demonstrate that aqueous solutions of guanidine nitrate are stable for a period of at least 12 days (Table 1).

TABLE 1: Stability Assay of a 20 μg/ml Standard Solution of Guanidine Nitrate

<table>
<thead>
<tr>
<th>Date of Analysis</th>
<th>Absorbance Values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 May 84</td>
<td>1.74 ± 0.02</td>
</tr>
<tr>
<td>29 May 84</td>
<td>1.76 ± 0.05</td>
</tr>
<tr>
<td>30 May 84</td>
<td>1.76 ± 0.02</td>
</tr>
<tr>
<td>6 Jun 84</td>
<td>1.76 ± 0.02</td>
</tr>
</tbody>
</table>

*Values are mean ± S.D. for three replicates.

Appendix B: ANIMAL DATA

Species: Oryctolagus cuniculus
Strain: New Zealand White (albino)
Source: Elkhorn Rabbitry
5265 Starr Way
Watsonville, CA 95076
Sex: Male and Female
Age: Young Adults
Animals in each group: 4 males and 4 females
Condition of animals at start of study: Normal
Body weight range at dosing: 2.65 - 3.33 kg
Identification procedures: Ear tattooing procedure (SOP OP-ARG-1), tattoo numbers 84F429, 84F432 - 84F435, 84F438 - 84F440 inclusive.

Pretest conditioning:
1. Quarantine from 21 June - 9 July 1984
2. Animals were close-clipped and examined 24 hours before dosing.

Model Justification: Laboratory rabbits are a proven sensitive animal model for dermal testing.
Appendix C: HISTORICAL LISTING OF STUDY EVENTS

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 Jun 84</td>
<td>Animals arrived at LAIR. They were tattooed, examined for illness, and placed under a two-week quarantine in the Toxicology Suite.</td>
</tr>
<tr>
<td>21 Jun - 5 Jul 84</td>
<td>Animals were checked daily.</td>
</tr>
<tr>
<td>5 Jul 84</td>
<td>Rabbits were removed from quarantine.</td>
</tr>
<tr>
<td>6 - 9 Jul 84</td>
<td>Animals were checked daily.</td>
</tr>
<tr>
<td>9 Jul 84</td>
<td>Animals were shaved and areas were marked.</td>
</tr>
<tr>
<td>10 Jul 84</td>
<td>Test substance was applied, and animals were weighed.</td>
</tr>
<tr>
<td>11-24 Jul 84</td>
<td>Animals were observed daily.</td>
</tr>
<tr>
<td>11 Jul 84</td>
<td>Bandages were removed, and areas were scored 24 hours after exposure.</td>
</tr>
<tr>
<td>12 Jul 84</td>
<td>Animals were scored 48 hours after exposure.</td>
</tr>
<tr>
<td>13 Jul 84</td>
<td>Animals were scored 72 hours after exposure.</td>
</tr>
<tr>
<td>17 Jul 84</td>
<td>Animals were scored 7 days after exposure.</td>
</tr>
<tr>
<td>24 Jul 84</td>
<td>Animals were scored 14 days after exposure and weighed.</td>
</tr>
<tr>
<td>25 Jul 84</td>
<td>Animals were sacrificed.</td>
</tr>
</tbody>
</table>
Appendix D: PRIMARY SKIN IRRITATION SCORES

Summary for Intact Sites*

<table>
<thead>
<tr>
<th>Rabbit Number</th>
<th>Patch Site</th>
<th>Erythema Day</th>
<th>Edema Day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1  2  3  7  14</td>
<td>1  2  3  7  14</td>
</tr>
<tr>
<td>FEMALE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>84F429</td>
<td>I</td>
<td>4  4  3  4  4</td>
<td>1  2  1  0  0</td>
</tr>
<tr>
<td>84F432</td>
<td>IV</td>
<td>2  4  4  4  4</td>
<td>1  0  1  1  0</td>
</tr>
<tr>
<td>84F433</td>
<td>IV</td>
<td>1  0  0  1  0</td>
<td>1  0  0  0  0</td>
</tr>
<tr>
<td>84F434</td>
<td>I</td>
<td>1  1  1  1  1</td>
<td>1  0  0  0  0</td>
</tr>
<tr>
<td>MALE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>84F435</td>
<td>I</td>
<td>2  2  1  4  *</td>
<td>1  0  1  1  0</td>
</tr>
<tr>
<td>84F438</td>
<td>IV</td>
<td>1  0  1  2  1</td>
<td>2  2  0  0  0</td>
</tr>
<tr>
<td>84F439</td>
<td>I</td>
<td>1  2  1  1  1</td>
<td>1  1  0  0  0</td>
</tr>
<tr>
<td>84F440</td>
<td>IV</td>
<td>1  2  1  1  1</td>
<td>1  2  0  0  0</td>
</tr>
</tbody>
</table>

* See Table 1 (page 4) for explanation of scores.
Appendix D: PRIMARY SKIN IRRITATION SCORES

Summary for Abraded Sites

<table>
<thead>
<tr>
<th>Rabbit Number</th>
<th>Patch Site</th>
<th>Erythema Day</th>
<th>Edema Day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 2 3 7 14</td>
<td>1 2 3 7 14</td>
</tr>
<tr>
<td>FEMALE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>84F429</td>
<td>III</td>
<td>4 4 4 4 4</td>
<td>1 2 1 0 0</td>
</tr>
<tr>
<td>84F432</td>
<td>II</td>
<td>2 4 4 4 4</td>
<td>1 0 2 1 0</td>
</tr>
<tr>
<td>84F433</td>
<td>III</td>
<td>2 4 1 4 4</td>
<td>1 0 0 0 0</td>
</tr>
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<td>84F434</td>
<td>III</td>
<td>2 2 2 4 4</td>
<td>2 2 0 0 0</td>
</tr>
<tr>
<td>MALE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>84F435</td>
<td>II</td>
<td>3 4 4 4 4</td>
<td>2 1 1 0 0</td>
</tr>
<tr>
<td>84F438</td>
<td>III</td>
<td>2 2 1 4 2</td>
<td>2 1 2 0 0</td>
</tr>
<tr>
<td>84F439</td>
<td>II</td>
<td>3 4 4 4 4</td>
<td>4 4 4 0 0</td>
</tr>
<tr>
<td>84F440</td>
<td>II</td>
<td>4 4 4 4 4</td>
<td>1 4 2 0 0</td>
</tr>
</tbody>
</table>

* See Table 1 (page 4) for explanation of scores.
Distribution List

Commander
US Army Biomedical Research and Development Laboratory (27)
ATTN: SGRD-UBZ-C
Fort Detrick, Frederick, MD 21701-5010

Defense Technical Information Center (DTIC) (2)
ATTN: DTIC-DLA
Cameron Station
Alexandria, VA 22304-6145

US Army Medical Research and Development Command (2)
ATTN: SGRD-RMI-S
Fort Detrick, Frederick, MD 21701-5012

Commandant
Academy of Health Sciences, US Army
ATTN: AHS-CDM
Fort Sam Houston, TX 78234

Chief
USAEHA Regional Division, West
Fitzsimmons AMC
Aurora, CO 80045

Chief
USAEHA Regional Division, North
Fort George G. Meade, MD 20755

Chief
USAEHA Regional Division, South
Bldg. 180
Fort McPherson, GA 30330

Commander
USA Health Services Command
ATTN: HSPA-P
Fort Sam Houston, TX 78234

Commandant
Academy of Health Sciences
United States Army
ATTN: Chief, Environmental Quality Branch
Preventive Medicine Division (HSHA-IPM)
Fort Sam Houston, TX 78234

Commander US Army Materiel Command
ATTN: AMSCG
5001 Eisenhower Avenue
Alexandria, VA 22333

Commander
US Army Environmental Hygiene Agency
ATTN: Librarian, HSDH AD-L
Aberdeen Proving Ground, MD 21010

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School of Medicine
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Bethesda, MD 20014

Commander
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Falls Church, VA 22041-3258

HQDA
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Washington, D.C. 20314