Institute Report No. 349

Primary Dermal Irritation Potential of Ball Powder® in Rabbits

Larry D. Brown, DVM, LTC, VC
and
Don W. Korte, Jr., PhD, LTC, MSC

MAMMALIAN TOXICOLOGY BRANCH
DIVISION OF TOXICOLOGY

July 1989

Toxicology Series: 128

LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129

Primary Dermal Irritation Potential of Ball Powder® in Rabbits (Toxicology Series 128)--
Brown and Korte

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for Richard A. Kokinis 11 July 1989

Edwin S. Beatrice (date)
COL, MC
Commanding

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The primary dermal irritation potential of Ball Powder® was determined in 4 male and 4 female New Zealand White rabbits by using a modified Draize method. Two Ball Powder® skin application sites were evaluated on each animal following a 4-hour application to closely clipped skin. Very slight erythema was observed in 1 rabbit at 1 hour after wrap removal and in 2 rabbits at 24 hours after wrap removal. All rabbits had returned to normal by 48 hours after dosing. Neither edema nor any other recognizable skin reaction was detected at any time during the 14-day observation period. Ball Powder® was classified as a non-irritant under conditions of this study.

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ABSTRACT

The primary dermal irritation potential of Ball Powder® was determined in 4 male and 4 female New Zealand White rabbits by using a modified Draize method. Two Ball Powder® skin application sites were evaluated on each animal following a 4-hour application to closely clipped skin. Very slight erythema was observed in 1 rabbit at 1 hour after wrap removal and in 2 rabbits at 24 hours after wrap removal. All rabbits had returned to normal by 48 hours after dosing. Neither edema nor any other recognizable skin reaction was detected at any time during the 14-day observation period. Ball Powder® was classified as a non-irritant under conditions of this study.

KEY WORDS: Primary Dermal Irritation, Ball Powder®, Propellant, 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, MD 21701-5010
Project Officer: Gunda Reddy, PhD

PROJECT/WORK UNIT/APC: 3E162720A835/180/TLB0

GLP STUDY NUMBER: 84033

STUDY DIRECTOR: LTC Don W. Korte, Jr., PhD, MSC
Diplomate, American Board of Toxicology

PRINCIPAL INVESTIGATOR: LTC Larry D. Brown, DVM, VC
Diplomate, American College of Veterinary
Preventive Medicine, American Board of Toxicology

PATHOLOGIST: LTC Lance O. Lollini, DVM, VC
Diplomate, American College of Veterinary Pathologists

REPORT AND DATA MANAGEMENT:

A copy of the final report, study protocol, retired 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: Ball Powder®

INCLUSIVE STUDY DATES: 24 January - 27 February 1985

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

ACKNOWLEDGMENTS

SP4 John R.G. Ryabik, BS, assisted in the research; SP4 James J. Fisher, SP4 Scott L. Schwebe, Richard A. Spieler, and Charlotte Speckman provided care for the animals; and Colleen S. Kamiyama, Dorothy Davis, and Dianna Johnson provided secretarial assistance.

SIGNATURES OF PRINCIPAL SCIENTISTS INVOLVED IN THE STUDY

We, the undersigned, declare that GLP Study 84033 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 11 July 89

DON W. KORTE, JR., PhD / DATE
LTC, MS
Study Director

Larry D. Brown 13 July 1987

LARRY D. BROWN, DVM / DATE
LTC, VC
Principal Investigator

Conrad Wheeler 10 July 89

CONRAD WHEELER, PhD/ DATE
DAC
Analytical Chemist

DEPARTMENT OF THE ARMY
LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129-6800

REPLY TO
ATTENTION OF:

SGRD-ULZ-QA 5 July 1989

MEMORANDUM FOR RECORD

SUBJECT: GLP Compliance for GLP Study 84Ø33

1. This is to certify that the protocol for LAIR GLP Study 84Ø33 was reviewed on 1 November 1984.

2. The institute report entitled "Primary Dermal Irritation Potential of Ball Powder in Rabbits," Toxicology Series 128, was audited on 23 July 1987.

Carolyn M. Lewis

CAROLYN M. LEWIS, MS
Diplomate, American Board of Toxicology
Quality Assurance Auditor

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Primary Dermal Irritation Potential of Ball Powder® in Male and Female Rabbits–Brown and Korte

INTRODUCTION

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 mission to evaluate the environmental and health hazards of military-unique propellants generated by US Army munitions-manufacturing facilities, conducted a review of the nitroguanidine data base and identified significant gaps in the toxicity data (1). The Division of Toxicology, LAIR, was tasked by USABRDL to develop a genetic and mammalian toxicity profile for nitroguanidine, related intermediates/by-products of its manufacture, and its environmental degradation products. A genetic and acute mammalian toxicity profile of Ball Powder®, a fielded nitrocellulose-based propellant, was also requested as a baseline against which future formulations will be compared.

Objective of Study

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

MATERIALS

Test Substance

Name: Ball Powder® (Olin WC 844 double base spheroidal propellant)

LAIR Code Number: TA45

Chemical Composition:

Component	Percent
Nitroglycerin	10.235
Dinitrotoluene	0.685
Diphenylamine	1.105
Dibutylphthalate	5.255
Nitrocellulose	83.23
Total Volatiles	1.045
Moisture and Volatiles	0.895
Residual Solvent	0.49
Calcium Carbonate	0.09
Sodium Sulfate	0.12

Source: Badger Army Ammunition Plant
Baraboo, WI 53913

Other test substance information is presented in Appendix A.

Vehicle

Viaflex® sterile isotonic saline (Travenol Laboratories, Deerfield, IL) was used as the vehicle for Ball Powder®. The expiration date for the saline (lot 7C950X0) used in this study was Oct 85.

Animal Data

Four male and four female New Zealand White rabbits (Elkhorn Rabbitry, 5265 Starr Way, Watsonville, CA), identified individually with ear tattoos numbered 85F018 to 85F021 (females) and 85F022-85F025 (males) inclusive, were assigned to the study. The animal weights on dosing day (13 Feb 85) ranged from 3.41 to 4.25 kg. Additional animal data appear in Appendix B.

Husbandry

The rabbits were housed individually in stainless steel, screen-bottomed, battery-type cages with automatically flushing dump tanks. The diet consisted of 150 g per 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 15.5° to 20.5°C with a relative humidity range of 39% to 63% with short spikes up to 70% associated with room cleaning. The photoperiod was 12 hours of light per day.

METHODS

Group Assignment/Acclimation

Study animals were acclimated for 5 days to the study room following a 14-day quarantine by the Division of Animal Care and Services (DACS). During this period they were observed daily for signs of illness. They were treated prophylactically for ear mites with a single dose of Canex® and mineral oil instilled in the ears.

Test Procedures

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

The backs of 8 rabbits were close-clipped 24 hours before the actual dosing. The clipped area was divided into 4 quadrants designated I-IV (4, 5). Site I was designated a sham patch site. Sites II and III were test compound sites. Site IV was a saline control patch site. A standard dose of 0.5 g of Ball Powder® was moistened with enough (usually 0.5 ml) 0.9% sodium chloride solution to make a thick paste. This paste was placed on 1-inch (2.5 cm) square gauze patch that was taped to the appropriate site. Blenderm® (Medical Products Division of 3M, Saint Paul, MN), an occlusive, hypoallergenic surgical tape, was used to hold the patches in place. Vet Wrap® (Animal Care Products Division of 3M, Saint Paul, MN) was then wrapped securely around the animal and taped down with Conform® elastic tape (Kendall Company, Boston, MA). The test compound was left in contact with the skin for 4 hours. At the end of the exposure period the wrapping and patches were removed, and the skin was gently wiped with a saline-moistened gauze to remove any test material remaining on the skin.

Observations

The grading and scoring for dermal reactions were performed according to Table 1. Scoring and grading for dermal irritation were performed at 30-60 minutes and approximately 24, 48, and 72 hours after removal of the patch. Observations for clinical signs were made daily from 14 to 27 February 1985. After 14 days the animals were submitted for necropsy and sections were taken from the application site for microscopic evaluation.

TABLE 1 (4)
Evaluation of Skin Reactions

Erythema and Eschar Formation		
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 formation [injurious in depth])	4	
Possible total erythema score		**4**
Edema Formation		
No edema	0	
Very slight edema (barely perceptible)	1	
Slight edema (edges of area well-defined by definite raising)	2	
Moderate edema (edges raised approximately 1 mm)	3	
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4	
Possible total edema score		**4**
Possible total score for primary irritation		**8**

Duration of Study

Appendix C is a complete historical listing of study events.

Changes/Deviations

This study was conducted in accordance with the protocol and addenda and all applicable SOPs.

Storage of Raw Data and Final Report

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

RESULTS

Animals were scored for erythema and edema at each patch site. Three rabbits (85F019, 85F021, 85F024) exhibited very slight erythema (dermal reaction score of 1) at test compound application sites. Three rabbits (85F018, 85F021, 85F024) exhibited very slight erythema (score of 1) at the sham site and two (85F019, 85F021) exhibited very slight erythema (score of 1) at the saline control site. Rabbits 85F019 (compound) and 85F021 (sham) were observed to have very slight erythema 1 hour after dosing. Rabbits 85F018 (sham), 85F021 (compound, sham, vehicle), and 85F024 (compound, sham) exhibited very slight erythema 24 hours after dosing. All rabbits had returned to normal by 48 hours after dosing. Neither edema nor any other recognizable skin reaction was detected at any time during the 14-day observation period. Results of scoring the dermal irritation potential in each rabbit are tabulated in Appendix D.

The quality control animal (85F038) submitted on 25 Jan 85 was unremarkable. Among the 8 rabbits dosed there were no gross pathological lesions attributable to the test compound or test procedures. Histopathological examination of tissues was unremarkable except for the incidental hepatic portal fibrosis in one rabbit (85F018). The Veterinary Pathology Report is presented in Appendix E.

DISCUSSION

The modified Draize dermal irritation test as performed for this study has proven reliable for detecting nonirritating substances and severe irritants but considerably less reliable for detecting mild and moderate irritants (5). Consequently, many systems have been used to score and categorize the dermal irritation potential of a test compound. The system used by the Toxicity Testing Program at LAIR is an adaptation of one used at the U.S. Army Environmental Hygiene Agency (6). It develops a dermal irritation index based on the peak net mean score, which is the maximum net mean score calculated during the 72-hour observation period. Nonirritating compounds have peak net mean scores of 0.0 to 0.5. Mild irritants have peak net mean scores of 0.51 to 2.0. Moderate irritants have peak net mean scores of 2.1 to 5.0. Severe irritants have peak net mean scores of 5.1 to 8.0. Ball Powder® produced very slight erythema in 3 of 8 rabbits. However, each time there was a similiar score at the corresponding vehicle and/or sham sites. Consequently, the peak net mean score was zero. Therefore, Ball Powder® was classified as a nonirritant.

Ball Powder® is insoluble in physiological solutions. In order for a compound to be irritating it must first be absorbed by the skin (7). Most of the Ball Powder® was still present on the skin when the patches were removed, which indicates that the compound was poorly absorbed. This lack of irritation was also observed in a dermal toxicity study performed at this Institute (8).

CONCLUSION

The test compound, Ball Powder®, is not a dermal irritant under conditions of this assay.

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8. Ryabik JRG, Lewis C, Mellick PW, Korte DW. Acute dermal toxicity of ballpowder in rabbits. Toxicology Series 120. Presidio of San Francisco, CA: Letterman Army Institute of Research, 1986; Institute Report No. 211.

Appendix A: CHEMICAL DATA

PROPELLANT DESCRIPTION SHEET

REPORTS CONTROL SYMBOL: EXEMPT - PARA 7-2a AR 335-15

TO:

FROM: Badger Army Ammunition Plant, Baraboo, Wisconsin 53913

DATE: 10 August 1984

DA LOT NUMBER: 50/50 blend of lots BAJ-47670 and BAJ-47671

COMPOSITION NUMBER: WC 844 for Cartridge 5.56 mm, BALL, M193

MFG AT: Badger Army Ammunition Plant

PACKED AMOUNT: LB

CONTRACT NUMBER: DAAA09-73-C-0004

SPECIFICATION NUMBER: MIL-P-3984E w/Amendment 4 and Drawing No. C10542743 Rev. C

NITROCELLULOSE

ACCEPTED BLEND NUMBERS	NITROGEN CONTENT	KI STARCH(65.5°C)	STABILITY (134.5°C)
Nitrocellulose (NC) extracted from excessed Single Base Propellant.	MAX %	MIN	MIN
	MIN %	MIN	MIN
	AVG %	MIN	MIN
NC complied with MIL-N-244A			EXPLOSION HR

MANUFACTURE OF PROPELLANT

_____POUNDS SOLVENT PER POUND NC/DRY WEIGHT INGREDIENTS CONSISTING OF _____ POUNDS ALCOHOL AND _____ POUNDS _____ PER 100 POUNDS SOLVENT. PERCENTAGE REMIX TO WHOLE _____.

TEMPERATURE FROM	TEMPERATURE TO	PROCESS–SOLVENT RECOVERY AND DRYING	TIME DAYS	TIME HOURS

PROPELLANT COMPOSITION / TESTS OF FINISHED PROPELLANT / STABILITY AND PHYSICAL TESTS

CONSTITUENT	% FORMULA	% TOLERANCE	% MEASURED		FORMULA	ACTUAL
Nitroglycerin			10.235	HEAT TEST 120°	Min 60 min	65 min.*
Dinitrotoluene			0.685	No Explosion (HRS)	Min 5	5+*
Diphenylamine			1.105	FORM OF PROPELLANT		
Dibutylphthalate			5.255	Dust&Foreign Mat.		0.02
Nitrocellulose			83.23	Graphite		0.075
Total Volatiles			1.045	Grav. Density		1.008
Moisture and Volatiles			0.895	Nitrogen		13.075
Residual Solvent			0.49			
Calcium Carbonate			0.09			
Sodium Sulfate			0.12			

CLOSED BOMB	LOT NUMBER	TEMP °F	RELATIVE QUICKNESS	RELATIVE FORCE
TEST				
STANDARD			100.00%	100.00%

PROPELLANT DIMENSIONS (INCHES)	SPEC	DIE	FINISHED	MEAN VARIATION IN % OF MEAN DIMENSIONS: SPEC	ACTUAL
LENGTH (L)					
DIAMETER (D)					
PERF DIA (d)					

REMARKS

WEB DIFFERENCE /STD DEV IN % OF WEB AVERAGE

L.D

D.d

SAMPLED

TEST FINISHED

OFFERED

DESCRIPTION SHEETS FORWARDED

TYPE OF PACKING CONTAINER

REMARKS: Tested 29 February 1984.

SIGNATURE OF CONTRACTOR'S REPRESENTATIVE

SIGNATURE OF GOVERNMENT QUALITY ASSURANCE REPRESENTATIVE

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: 3.41 to 4.25 kg

Identification procedures: Ear tag

Pretest conditioning:

1. Quarantine from 25 January - 7 February 1985
2. Animal were close-clipped and examined 24 hours before dosing.

Justification: Laboratory rabbits are a proven sensitive animal model for dermal irritation.

Appendix C: HISTORICAL LISTING OF STUDY EVENTS

Date	Event
24 Jan 85	Rabbits arrived at LAIP and were examined and caged.
25 Jan 85	Animals were tattooed, weighed, and placed under a 2-week quarantine. One rabbit (85F038) was submitted to necropsy for quality control.
24 Jan - 7 Feb 85	Animals were checked daily by DACS personnel.
1 Feb 85	Animals were weighed.
7 Feb 85	All rabbits were treated with Canex® and mineral oil in their ears to prevent ear mites. Rabbits were removed from quarantine after being certified healthy by DACS Staff Veterinarian.
8 Feb 85	Animals were weighed.
8 - 12 Feb 85	Animals were checked daily.
12 Feb 85	Animals were close-clipped and areas marked.
13 Feb 85	Animals were weighed. Test substance was applied for 4 hours. Patches were removed and sites scored within 30-60 minutes.
14 - 27 Feb 85	Animals were observed daily.
14 - 16 Feb 85	Areas were scored at 24, 48, and 72 hours after exposure.
20 Feb 85	Animals were weighed.
27 Feb 85	Animals were weighed and submitted for necropsy, skin tissues were collected for microscopic evaluation.

Appendix D: DERMAL IRRITATION DATA

ANIMAL NUMBER	OBSERVATION	QUADRANT* I	II	III	IV
85F018	30-60 min	0/0†	0/0	0/0	0/0
	24 hr	1/0	0/0	0/0	0/0
	48 hr#	0/0	0/0	0/0	0/0
85F019	30-60 min	0/0	0/0	1/0	1/0
	24 hr#	0/0	0/0	0/0	0/0
85F020	30-60 min#	0/0	0/0	0/0	0/0
85F021	30-60 min	1/0	0/0	0/0	0/0
	24 hr	1/0	0/0	1/0	1/0
	48 hr#	0/0	0/0	0/0	0/0
85F022	30-60 min#	0/0	0/0	0/0	0/0
85F023	30-60 min#	0/0	0/0	0/0	0/0
85F024	30-60 min	0/0	0/0	0/0	0/0
	24 hr	1/0	1/0	0/0	0/0
	48 hr#	0/0	0/0	0/0	0/0
85F025	30-60 min#	0/0	0/0	0/0	0/0

* Quadrant I=sham; II, III=treated; IV=saline

† Scores are displayed as erythema/edema

Scores were 0/0 in all quadrants for remaining observations

Appendix D (cont.): DERMAL IRRITATION DATA

SUMMARY OF PRIMARY IRRITATION TEST DATA

Animal Number	30-60 min			24 h			48 h		
	Test*	Sham	Vehicle	Test	Sham	Vehicle	Test	Sham	Vehicle
85F018	0	0	0	0	1	0	0	0	0
85F019	1	0	1	0	0	0	0	0	0
35F020	0	0	0	0	0	0	0	0	0
85F021	0	1	0	1	1	1	0	0	0
85F022	0	0	0	0	0	0	0	0	0
85F023	0	0	0	0	0	0	0	0	0
85F024	0	0	0	1	1	0	0	0	0
85F025	0	0	0	0	0	0	0	0	0
Mean	0.12	0.12	0.12	0.25	0.38	0.12	0	0	0
Net Mean Score†	0<			0			0		

*Test value is the larger of the scores in Quadrants II and III.

†Test Mean - (Greater of Sham or Vehicle Mean) = Net Mean Score

<The peak net mean score is 0; therefore, Ball Powder® is a **NON-IRRITANT**

Appendix E: PATHOLOGY REPORT

LAIR Pathology Report
GLP Study 84033
Primary Dermal Irritation Test in Rabbits (NZW-Albino)
of Ball Powder (OLIN WC 844)

History: Eight rabbits, 4 each male and female, were tested in accordance with SOP-OP-STX-34 (1 Aug 84). Tissues were submitted for histopathological evaluation.

LAIR Path #	Animal ID #	Sex	Gross Findings	Histologic Findings Skin
36955	85FØ22	male	NR (not remarkable)	NR
36956	85FØ23	male	Pinworms - cecum	NR
36957	85FØ24	male	NR	NR
36958	85FØ25	male	NR	NR
36959	85FØ21	female	Pinworms - cecum	NR
36960	85FØ18	female	Pinworms - cecum, Right lateral lobe liver green*	NR
36961	85FØ19	female	Pinworms - cecum, 3 mm focal scar, 1 each medial and left lateral liver lobes	NR
36962	85FØ20	female	Pinworms - cecum	NR

* Histologic Findings Liver #36960: There were diffuse areas of centrolobular bridging fibrosis throughout the section. Multinucleated cells often containing mineral were present within the fibrous tissue as was hemosiderin. There was piecemeal necrosis of adjacent hepatocytes along some of the borders and a few regions had almost complete loss of liver lobules.

Comments: No lesions were present that were related to the compound tested. The hepatic portal fibrosis seen in animal #85FØ18 was considered an incidental finding which preceeded the testing and was of no consequence.

LANCE O. LOLLINI, DVM
LTC, VC
Chief, Pathology Services Group

Distribution List

Commander
US Army Biomedical Research and Development Laboratory (15)
ATTN: SGRD-UBZ-C
Fort Detrick, Frederick, MD 21701-5010

Defense Technical Information Center (DTIC) (2)
ATTN: DTIC-DLA
Cameron Station
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ATTN: AHS-CDM
Fort Sam Houston, TX 78234

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ATTN: AMSCG
5001 Eisenhower Avenue
Alexandria, VA 22333

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

Dean
School of Medicine
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road
Bethesda, MD 20014

Commander
US Army Materiel Command
ATTN: AMCEN-A
5001 Eisenhower Avenue
Alexandria, VA 22333

HQDA
ATTN: DASG-PSP-E
Falls Church, VA 22041-3258

HQDA
ATTN: DAEN-RDM
20 Massachusetts, NW
Washington, D.C. 20314

CDR, US Army Toxic and Hazardous Material Agency
ATTN: DRXTH/ES
Aberdeen Proving Ground, MD 21010

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