MB Research Laboratories

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Study Title	:	Acute Dermal Irritation/Corrosion in Rabbits
Test Article	:	NAT-9152, Lot# 6820913
Author	:	Blair Yasso, B.S., Study Director
Study Completed On	:	26 Nov 2013
Performing Laboratory	:	MB Research Laboratories 1765 Wentz Road P.O. Box 178 Spinnerstown, PA 18968
MB Research Project #	:	MB 13-21992.03
MB Research Protocol #	:	2130-05
Sponsor	:	Toda America, Inc. 4750 W. Dickman Road Battle Creek, MI 49037
Citation	:	Blair Yasso, B.S. (2013) Unpublished Report by MB Research Laboratories

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GOOD LABORATORY PRACTICES COMPLIANCE STATEMENT

This study was conducted in accordance with the Good Laboratory Practices of the EPA, 40 CFR 160 and 792, FDA 21 CFR 58 and as specified in Principles on Good Laboratory Practices, published by the Organization for Economic Cooperation & Development (OECD), 1997, with the following exception:

Test article characterization information, provided by the Sponsor, was not complete. See Appendix A for information that was provided. The effect of the lack of full test article characterization information cannot be fully assessed.

STUDY DIRECTOR:

26 NOV 2013

Blair Yasso, B.S. Date
MB RESEARCH LABORATORIES

PROJECT NUMBER : MB 13-21992.03
TEST ARTICLE : NAT-9152, Lot# 6820913
SPONSOR : TODA AMERICA, INC.
TITLE : Acute Dermal Irritation/Corrosion in Rabbits
PROTOCOL # : 2130-05

A B S T R A C T

Objective: To determine the irritant or corrosive effects, if any, of a test article when applied to the skin of a rabbit. This study was designed to comply with the standards set forth in OECD Guideline for Testing of Chemicals, Number 404 Acute Dermal Irritation/Corrosion.

Method Synopsis: Since the test article was not expected to produce severe irritation or corrosion, three healthy New Zealand White rabbits (2 males - 1 female) were dosed dermally with NAT-9152, Lot# 6820913. The test article (0.5 g) was applied dermally to one intact site per rabbit and wrapped with a semi-occlusive dressing. The test article was kept in contact with the skin for 4 hours at which time the wrappings were removed. Erythema and edema were scored at 1, 24, 48 and 72 hours. The skin was also evaluated for ulceration and necrosis or any evidence of tissue destruction at these time periods. Animals were observed for mortality, toxicological and pharmacological effects at each dermal observation period. Body weights were recorded pretest and at termination.

Summary:

Erythema and edema were absent at 1 hour and test article staining was observed. At 24 hours, erythema was absent to very slight and edema was absent; pale areas and test article staining were observed. Erythema was absent to very slight and edema was absent at 48 hours. Erythema and edema were absent at 72 hours.

There were no abnormal physical signs observed.

All three animals' body weight remained the same by study termination.

Conclusion: NAT-9152, Lot# 6820913 is not a dermal irritant.

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OBJECTIVE

To determine the irritant or corrosive effects, if any, of a test article when applied to the skin of a rabbit. This study was designed to comply with the standards set forth in OECD Guideline for Testing of Chemicals, Number 404 Acute Dermal Irritation/Corrosion.

TEST ARTICLE

Label Identity	:	NAT-9152, Lot# 6820913
Test Article Characterization	:	See Appendix A for Test Article Characterization.
Stability	:	Not supplied by the Sponsor.
Supplied by	:	Toda America, Inc.
Date Received	:	07 Aug 2013
Storage	:	Room temperature and humidity
Description	:	Black powder
Sample Preparation	:	The test article was individually weighed and moistened with 0.5 ml of distilled water to form a pasty consistency.

TEST DATES

Study Initiation	(date protocol signed)	:	20 Aug 2013
Experimental Start Date	(1st exposure to test substance)	:	20 Aug 2013
Experimental Term Date	(last date data collected)	:	23 Aug 2013
Draft Report Submitted	(if applicable)	:	08 Oct 2013
Final Report Signed	(study completion)	:	26 Nov 2013

EXPERIMENTAL DESIGN

Test Animals

Animals were received from Covance Research Products Inc., Denver, PA on 07 Aug 2013. Following an acclimation period of at least five days, three healthy New Zealand White rabbits (2 males - 1 female) were selected from a larger group without conscious bias.

The animals were born on 19 Jan 2013 and 16 Feb 2013. The pretest body weight range was 3.0 - 3.1 kg.

The animals were identified by cage notation and a uniquely numbered metal eartag and individually housed in suspended cages. Absorbent paper bedding was placed beneath the cages and changed at least three times per week. Fresh PMI Rabbit Chow (Diet #5321) was provided daily. Water was available *ad libitum*. The animal room, reserved exclusively for rabbits on acute tests, was temperature controlled, had a 12-hour light/dark cycle, and was kept clean and vermin free.

EXPERIMENTAL DESIGN (continued)

Site Preparation

Approximately 24 hours prior to application of the test article, the dorsal area of the trunk of each animal was clipped free of hair. Only animals with healthy intact skin were used. Each dose site was approximately 6 cm^2.

Dosing

The test article was individually weighed, 0.5 g per site and moistened with 0.5 ml of distilled water to form a pasty consistency. The test article was applied over a 2 x 3 cm gauze patch. Gentle pressure was applied to aid in the distribution of the test article over the prepared site. The patch was secured with non-irritating tape. The torso was covered with a piece of porous dressing (semi-occlusive) large enough to cover the dose site with at least 5 cm square to spare on all sides of the gauze patch. Porous, non-irritating tape was used to encircle the trunk of the animal. The test article was kept in contact with the skin for 4 hours at which time the wrappings and patches were removed. Distilled water was used to gently wash the dose sites after the exposure period, prior to scoring for dermal reactions. Test article staining was noted at 1 and 24 hours.

Type and Frequency of Observations

The test sites were scored for dermal irritation at 1, 24, 48 and 72 hours. Erythema and edema were scored according to the numerical Draize technique below. The skin was also evaluated for ulceration and necrosis or any evidence of tissue destruction. Additional signs were described.

Erythema	
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 (injuries in depth)	4

Edema	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well-defined by definite raising)	2
Moderate edema (raised approximately 1.0 mm)	3
Severe edema (raised more than 1.0 mm, extending beyond the area of exposure)	4

EXPERIMENTAL DESIGN (continued)

Type and Frequency of Observations (continued)

Body weights were recorded pretest and at termination.

Animals were observed for mortality, toxicological and pharmacological effects at each dermal observation period. All animals were humanely sacrificed using CO_2 following study termination.

Analysis of Data

Dermal Irritation is the production of reversible damage to the skin following application of a test substance for up to 4 hours.

Dermal Corrosion is the production of irreversible damage to the skin following exposure to the test substance for up to 4 hours.

Retention of Data

Upon signing the final report, all raw data, supporting documentation and reports are submitted to the Archivist by the Study Director. The raw data is filed at MB Research by project number. The final report is filed at MB Research by Sponsor name and MB project number.

All data generated during the conduct of this study are archived at MB Research for at least ten years from the date of the final report. The Sponsor will be contacted in writing to determine final disposition of the records. If the Sponsor fails to respond within 90 days, the archived material will be promptly discarded.

Any remaining test article will be discarded following submission of the report.

Amendment to the Protocol

At the request of the Sponsor, the test article will be discarded following submission of the report.

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RESULTS and DISCUSSION

1. **Dermal Observations (Table 1)**

   Erythema and edema were absent at 1 hour and test article staining was observed. At 24 hours, erythema was absent to very slight and edema was absent; pale areas and test article staining were observed. Erythema was absent to very slight and edema was absent at 48 hours. Erythema and edema were absent at 72 hours.

2. **Systemic Observations and Body Weights (Table 1)**

   There were no abnormal physical signs observed.

   All three animals' body weight remained the same by study termination.

CONCLUSION

NAT-9152, Lot# 6820913 is not a dermal irritant.

FINAL REPORT

Approved by:

26 NOV 2013

Blair Yasso, B.S. Date
Study Director

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Table 1: Dermal Observations, Body Weights and Systemic Observations

Rabbit Eartag:		H6540	H6532	H6533
Sex:		F	M	M
Pretest Body Weight - kg:		3.0	3.1	3.1
Terminal Body Weight - kg:		3.0	3.1	3.1
Time after patch removal:				
1 Hour -	Erythema	0,t	0,t	0,t
	Edema	0	0	0
Systemic Observations		A	A	A
24 Hour -	Erythema	0,t,p	1	0,t
	Edema	0	0	0
Systemic Observations		A	A	A
48 Hour -	Erythema	0	1	0
	Edema	0	0	0
Systemic Observations		A	A	A
72 Hour -	Erythema	0	0	0
	Edema	0	0	0
Systemic Observations		A	A	A

A = Appeared normal p = pale areas t = test article staining

QUALITY ASSURANCE EVALUATION

The Quality Assurance Unit has inspected a critical phase of this study, audited the raw data and the report and determined that the methods and results contained herein accurately reflect the raw data. A summary of the compliance inspections is presented below.

Date of Inspection	Phase	Performed By	Date Inspection Results Reported	
			Sty. Dir.	Mgmt.
22 Aug 2013	Scoring	Mark Coker	22 Aug 2013	22 Aug 2013
06 Sep 2013	Raw data audit	Mark Coker	06 Sep 2013	06 Sep 2013
04 Oct 2013	Draft report audit	Cynthia M. Kelsch	04 Oct 2013	26 Nov 2013
26 Nov 2013	Final report audit	Mark Coker	26 Nov 2013	26 Nov 2013

Mark A. Coker 26 Nov 13

Mark Coker, B.A. Date
Quality Assurance Unit

D-2199

August 02 2013

Analytical Report

TAI

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sign H. Okimaka sign A. Inoue

Approved	Prepared
QA manager	QA

Trade NAT-9152

Lot.No. 6820913 **Weight** 50 g

CHEMICAL ANALYSIS	
Li/(Ni+Co+Al) mole ratio	0.97
Ni mol%	81.0
Co mol%	15.1
Al mol%	3.9
Impurity	
Na(%)	≦0.01
Fe(%)	≦0.01
PHYSICAL ANALYSIS	
Surface Area(m^2/g)	0.19
Tap Density(g/ml)	2.90
Particle Size Distribution by Laser Diffraction	
D-10(μm)	8.2
D-50(μm)	15.0
D-90(μm)	26.1
CRYSTAL ANALYSIS	
	attached XRD chart