PRODUCT SAFETY LABORATORIES

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PRODUCT

Citrex

STUDY TITLE

Primary Skin Irritation Study in Rabbits

DATA REQUIREMENT

U.S. EPA Health Effects Test Guidelines, OPPTS 870.2500 (1998)

AUTHOR

Daniel J. Merkel, B.S.

STUDY COMPLETED ON

June 13, 2005

PERFORMING LABORATORY

Product Safety Laboratories

2394 Highway 130

Dayton, New Jersey 08810

LABORATORY STUDY NUMBER

16826

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STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA 10 (d) (1) (A), (B) or (C).

Company: **CITREX INC.**

Company Agent: _____ Name _____ Title

_____ Signature _____ Date

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Company: **CITREX INC.**

Company Agent: Fernando Tamames (Name) President (Title)

(Signature) 2/7/06 (Date)

PSL PRODUCT SAFETY LABORATORIES

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

Citrex

This study meets the requirements of 40 CFR Part 160: U.S. EPA (FIFRA) with the following exception: Specific information related to the stability, characterization, identity and verification of the test substance concentration as received and tested is the responsibility of the study Sponsor (see Test Substance section).

Study Director: _____
Daniel J. Merkel, B.S.
Product Safety Laboratories

6/13/05
Date

Submitter: _____
Signature Fernando Tamames

2/7/06
Date

Sponsor: _____
Signature Fernando Tamames

2/7/06
Date

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QUALITY ASSURANCE STATEMENT

The Product Safety Laboratories' Quality Assurance Unit reviewed this study for adherence to PSL's Standard Operating Procedures, the study protocol, and all applicable GLP standards. This final report was found to be an accurate representation of the work conducted. Records of QA findings are kept on file. The summary below provides verification of statements made in the final report section that addresses Quality Assurance audits.

QA activities for this study:

QA Activity	Date Conducted	Date Findings Reported To Study Director And Management
Protocol review	1/26/04[1]; 3/28/05	1/26/04; 3/28/05
In-process inspection: *48 hour scoring*	2/10/05	3/28/05
Raw data audit	3/28/05	3/28/05
Draft report review	3/28/05	3/28/05
Final report review	6/13/05	6/13/05

Annamarie LaPorte
Quality Assurance Auditor
Product Safety Laboratories

[1] PSL's "generic" protocol used for this study was reviewed by the Quality Assurance group on this date.

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PRIMARY SKIN IRRITATION STUDY IN RABBITS

PROTOCOL NO.:	P326
AGENCY:	EPA (FIFRA)
STUDY NUMBER:	16826
SPONSOR:	CITREX INC. 1394 Coral Way Miami, Florida 33145
TEST SUBSTANCE IDENTIFICATION:	Citrex (see Section 8, Amendment #1) Lot #1742
TEST SUBSTANCE DESCRIPTION:	Yellow liquid with a slight citric odor
DATE RECEIVED:	December 16, 2004
PSL REFERENCE NO.:	041216-2D
STUDY INITIATION DATE:	January 20, 2005
DATES OF TEST:	February 8 - 11, 2005
NOTEBOOK NO.:	04-114: pages 127-127A, 128-138

1. PURPOSE

To provide information on the skin irritation likely to arise from a single topical exposure to Citrex.

2. SUMMARY

A primary skin irritation test was conducted with rabbits to determine the potential for Citrex to produce irritation after a single topical application. Under the conditions of this study, the test substance is classified as slightly irritating to the skin.

Five-tenths of a milliliter of the test substance was applied to the skin of three healthy rabbits for 4 hours. Following exposure, dermal irritation was evaluated by the method of Draize *et al.*[1] (see Table 3).

[1] Draize, J.H., Woodward, G. and Calvery, H.O. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J. Pharmacol. Exp. Ther.* 1944; 82:377-390.

There was no edema observed at any treated site during this study. One hour after patch removal, all three treated sites exhibited very slight erythema. The overall incidence and severity of irritation decreased thereafter. Although desquamation was noted at all three dose sites, all animals were free of erythema and edema within 72 hours.

The incidence, severity and reversibility of irritation are detailed below:

	Incidence of Irritation	
Time After Patch Removal	**Erythema**	**Edema**
1 hour	3/3	0/3
24 hours	1/3	0/3
48 hours	1/3	0/3
72 hours	0/3	0/3

Time After Patch Removal	Severity of Irritation – Mean Score
1 hour	1.0
24 hours	0.3
48 hours	0.3
72 hours	0

The Primary Dermal Irritation Index (PDII) calculated for this test substance was 0.4.

3. MATERIALS

A. Test Substance

The test substance, identified as Citrex, Lot #1742, was received on December 16, 2004 and was further identified with PSL Reference Number 041216-2D. The test substance was a yellow liquid with a slight citric odor and was stored at room temperature. The sample was applied as received. Documentation of the methods of synthesis, fabrication, or derivation of the test substance is retained at Siatag, Barcelona, Spain.

The following information related to the characterization of the test substance was provided by the Sponsor:

Composition (see Section 8, Amendment #2): Ascorbic Acid - 0.017803% (active ingredient)
Citric Acid – 0.03%
Lactic Acid – 0.04%
Sodium Chloride – 0.01%
Ammonium Propionate – 0.01%
Vegetable Glycerin – 0.88%

pH: 2.84 (tap water).

Solubility: Soluble in water.

Stability: Test substance was expected to be stable for the duration of testing.

Expiration Date: Not applicable.

B. Animals

3.B.1 Number of Animals: 3

3.B.2 Sex: 2 Males and 1 Female. The female assigned to test was nulliparous and non-pregnant.

3.B.3 Species/Strain: Rabbit/New Zealand albino.

3.B.4 Age: Young adult.

3.B.5 Source: Received from Robinson Services, Inc. Clemmons, NC on February 2, 2005.

4. METHODS

A. Husbandry

4.A.1 Housing: The animals were singly housed in suspended stainless steel caging with mesh floors which conform to the size recommendations in the most recent *Guide for the Care and Use of Laboratory Animals DHEW (NIH)*. Litter paper was placed beneath the cage and was changed at least three times per week.

4.A.2 Animal Room Temperature Range: 20-22°C

4.A.3 Photoperiod: 12-hour light/dark cycle

4.A.4 Acclimation Period: 6 days

4.A.5 Food: Pelleted Purina Rabbit Chow #5326

4.A.6 Water: Filtered tap water was supplied *ad-libitum* by an automatic water dispensing system.

4.A.7 Contaminants: There were no known contaminants reasonably expected to be found in the food or water at levels which would have interfered with the results of this study. Analyses of the food and water are conducted at least once a year and the records are kept on file at Product Safety Laboratories.

B. Identification

4.B.1 Cage: Each cage was identified with a cage card indicating at least the study number and identification and sex of the animal.

4.B.2 Animal: A number was allocated to each rabbit on receipt and a stainless steel ear tag bearing this number was attached to the animal. This number, together with a sequential animal number assigned to study 16826, constituted unique identification.

5. PROCEDURE

A. Preparation and Selection of Animals

On the day before application, a group of animals was prepared by clipping (Oster model #A5-small) the dorsal area and the trunk. On the day of dosing, but prior to application, the animals were examined for health and the skin checked for any abnormalities. Three healthy animals without pre-existing skin irritation were selected for test.

B. Application of Test Substance

Five-tenths of a milliliter of the test substance was applied to one 6 cm^2 intact dose site on each animal and covered with a 1-inch x 1-inch, 4-ply gauze pad. The pad and entire trunk of each animal were then wrapped with semi-occlusive 3-inch Micropore tape to avoid dislocation of the pad. Elizabethan collars were placed on each rabbit and they were returned to their designated cages.

After 4 hours of exposure to the test substance, the pads and collars were removed and the test sites were gently cleansed of any residual test substance.

C. Evaluation of Test Sites

Individual dose sites were scored according to the Draize scoring system[1] (see Table 3) at approximately 1, 24, 48, and 72 hours after patch removal.

The classification of irritancy was obtained by adding the average erythema and edema scores for the 1, 24, 48, and 72-hour scoring intervals and dividing by the number of evaluation intervals (4).

The resulting Primary Dermal Irritation Index (PDII) was classified as follows:

PDII	Classification
0	Non-irritating
> 0 - 2.0	Slightly irritating
2.1 - 5.0	Moderately irritating
> 5.0	Severely irritating

D. Cage-Side Observations

The animals were observed for signs of gross toxicity and behavioral changes at least once daily during the test period. Observations included gross evaluation of skin and fur, eyes and mucous

[1] Draize, J.H., Woodward, G. and Calvery, H.O. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J. Pharmacol. Exp. Ther.* 1944; 82:377-390.