PRODUCT SAFETY LABORATORIES

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PRODUCT

Citrex

STUDY TITLE

Acute Oral Toxicity Up And Down Procedure In Rats

DATA REQUIREMENT

U.S. EPA Health Effects Test Guidelines, OPPTS 870.1100 (2002)

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

16851

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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: Fernando Lamarmes (Name) President (Title)

Signature

2/7/06 (Date)

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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 Tamarres

2/7/06
Date

Sponsor:

Signature Fernando Tamarres

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: *Day 1 in-life observations (Animal #519)*	1/28/05	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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ACUTE ORAL TOXICITY UP AND DOWN PROCEDURE IN RATS

PROTOCOL NO.:	P320.UDP
AGENCY:	EPA (FIFRA)
STUDY NUMBER:	16851
SPONSOR:	CITREX INC. 1394 Coral Way Miami, Florida 33145
TEST SUBSTANCE IDENTIFICATION:	Citrex 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 21, 2005
DATES OF TEST:	January 27 - February 11, 2005
NOTEBOOK NO.:	04-114: pages 30-30A, 31-42

1. PURPOSE

To provide information on health hazards likely to arise from a short-term exposure to Citrex by the oral route.

2. SUMMARY

An acute oral toxicity test (Up and Down Procedure) was conducted with rats to determine the potential for Citrex to produce toxicity from a single dose via the oral route. Under the conditions of this study, the acute oral LD_{50} of the test substance is greater than 5,000 mg/kg of body weight in female rats.

An initial limit dose of 5,000 mg/kg was administered to one healthy female rat by oral gavage. Due to the absence of mortality in this animal, two additional females received the same dose level. Since these animals survived, no additional animals were tested. Females were selected for the test because they are frequently more sensitive to the toxicity of test compounds than males. All animals were observed for mortality, signs of gross toxicity, and behavioral changes at least once daily for 14 days

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after dosing. Body weights were recorded prior to administration and again on Days 7 and 14 (termination) after dosing. Necropsies were performed on all animals at terminal sacrifice.

All animals survived, gained body weight, and appeared active and healthy during the study. There were no signs of gross toxicity, adverse pharmacologic effects, or abnormal behavior. No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

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 administered 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): 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: Female, nulliparous and non-pregnant.

3.B.3 Species/Strain: Rat/Sprague-Dawley derived, albino.

3.B.4 Age/Body weight: Young adult (10 weeks)/195-205 grams at experimental start.

3.B.5 Source: Received from Ace Animals, Inc., Boyertown, PA on January 4, 2005.

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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: 13 or 14 days

4.A.5 Food: Purina Rodent Chow #5012

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 rat on receipt and a stainless steel ear tag bearing this number was attached to the rat. This number, together with a sequential animal number assigned to study number 16851, constituted unique identification.

5. PROCEDURE

A. Selection of Animals

Prior to each dosing, experimentally naive rats were fasted overnight by removing the feed from their cages. During the fasting period, the rats were examined for health and weighed (initial). Three healthy female rats were selected for test.

B. Dose Calculations

Individual doses were calculated based on the initial body weights, taking into account the specific gravity (determined by PSL) of the test substance.

C. Dosing

The test substance was administered using a stainless steel ball-tipped gavage needle attached to an appropriate syringe. Following administration, each animal was returned to its designated cage. Feed was replaced approximately 3-4 hours after dosing.

Individual animals were dosed as follows:

Dosing Sequence	Animal No.	Dose Level (mg/kg)	Short-Term Outcome	Long-Term Outcome
1	519	5,000	S	S
2	571		S	S
3	572		S	S

S – Survival

D. Body Weights

Individual body weights of the animals were recorded prior to test substance administration (initial) and again on Days 7 and 14 (termination) after dosing.

E. Cage-Side Observations

The animals were observed for mortality, signs of gross toxicity, and behavioral changes during the first several hours post-dosing and at least once daily thereafter for 14 days after dosing. Observations included gross evaluation of skin and fur, eyes and mucous membranes, respiratory, circulatory, autonomic and central nervous systems, somatomotor activity and behavior pattern. Particular attention was directed to observation of tremors, convulsions, salivation, diarrhea, and coma.

F. Necropsy

All rats were euthanized via CO_2 inhalation at the end of the 14-day observation period. Gross necropsies were performed on all animals. Tissues and organs of the thoracic and abdominal cavities were examined.

6. STUDY CONDUCT

This study was conducted at Product Safety Laboratories, 725 Cranbury Road, East Brunswick, New Jersey 08816. The primary technician for this study was Jacek Ochalski, D.V.M. This study was conducted to comply with the Good Laboratory Practice (GLP) regulations as defined in:

- 40 CFR 160: U.S. EPA GLP Standards: Pesticide Programs (FIFRA)

and in accordance with:

- U.S. EPA Health Effects Test Guidelines, OPPTS 870.1100 (2002)

7. QUALITY ASSURANCE

The final report was audited for agreement with the raw data records and for compliance with the protocol, Product Safety Laboratories Standard Operating Procedures and appropriate Good Laboratory Practice Standards. Dates of inspections and audits performed during the study and the dates of reporting of the inspection and audit findings to the Study Director and Facility Management are presented in the Quality Assurance Statement.

8. AMENDMENT TO THE PROTOCOL

At the request of the Sponsor, the Composition section of the protocol was changed from

Active ingredient = Ascorbic acid 0.0017803%

to

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%

9. DEVIATIONS FROM FINAL PROTOCOL

None.

10. FINAL REPORT AND RECORDS TO BE MAINTAINED

The original, signed final report will be forwarded to the Sponsor. A copy of this signed report, together with the protocol and all raw data generated at Product Safety Laboratories, is maintained in the Product Safety Laboratories Archives. PSL will maintain these records for a period of at least five years. After this time, the Sponsor will be offered the opportunity to take possession of the records or will be charged an archiving fee for continued archiving by PSL.

11. RESULTS

Individual body weights and doses are presented in Table 1. Individual cage-side and necropsy observations are presented in Tables 2 and 3, respectively.

All animals survived, gained body weight and appeared active and healthy during the study. There were no signs of gross toxicity, adverse pharmacologic effects, or abnormal behavior. No gross

abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

12. CONCLUSION

Under the conditions of this study, the acute oral LD_{50} of Citrex is greater than 5,000 milligrams per kilogram of body weight in female rats.

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SIGNATURES

Citrex

We, the undersigned, declare that the methods, results and data contained in this report faithfully reflect the procedures used and raw data collected during the study.

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

6/13/05
Date

Gary Wnorowski, B.A., M.B.A.
President
Product Safety Laboratories

6/13/05
Date

TABLE 1: INDIVIDUAL BODY WEIGHTS AND DOSES

Animal No.	Sex	Dose Level (mg/kg)	Body Weight (g)			Dose[1]
			Initial	Day 7	Day 14	ml
519	F	5,000	205	221	249	1.0
571	F		184	201	243	0.94
572	F		195	212	248	0.99

[1] The test substance was administered as received. Specific Gravity - 0.980 g/ml.

TABLE 2: INDIVIDUAL CAGE-SIDE OBSERVATIONS

Animal Number	Findings	Day of Occurrence
FEMALES		
5,000 mg/kg Dose Level		
519, 571, 572	Active and healthy	0-14

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TABLE 3: INDIVIDUAL NECROPSY OBSERVATIONS

Animal Number	Tissue	Findings
FEMALES		
5,000 mg/kg Dose Level		
519, 571, 572	All tissues and organs	No gross abnormalities