Acute Oral Toxicity Screen

with T-3494

in Albino Rats

Experiment No.:	0884AR0013
Conducted At:	Safety Evaluation Laboratory Riker Laboratories, Inc. St. Paul, Minnesota
Dates Conducted:	January 19, 1984 to February 2, 1984
Conducted By:	D. M. Markoe, Jr., BS — 2/23/84 (Date) Toxicologist Study Director
Reviewed By:	K. D. O'Malley, BS — 3/13/84 (Date) Senior Toxicologist Acute Toxicology

dc: M. T. Case
K. L. Ebbens
F. D. Griffith
W. C. McCormick

Summary

The acute oral toxicity screen with T-3494 was conducted from January 19, 1984 to February 2, 1984 at Riker Laboratories, Inc., St. Paul, Minnesota using male and female albino rats ranging in body weight from 190-236 grams. The test article was administered by gastric intubation at a dosage level of 5,000 mg/kg body weight with no mortalities noted during the 14 day observation period. Diarrhea was noted on day one and subsided by the day four observation. This response, however, would be expected using cottonseed oil as the vehicle at a constant volume of 20 ml/kg. Body weight gains were noted in all animals at the end of the study. Necropsies performed at termination of the study revealed no visible lesions. The approximate oral LD50 of T-3494 is greater than 5,000 mg/kg in fasted male and female albino rats.

Introduction

The objective of this study was to determine the acute oral LD50 of T-3494 in fasted albino rats. This study is not regulated by the Food and Drug Administration's Good Laboratory Practice Regulation of 1978, although the standard operating procedures of this laboratory adhere to the general principles of this regulation. The raw data generated by the Study Director and the final report are stored in the conducting laboratory's archives.

Method and Results

Young albino rats[a] were used in this test. All animals were held under quarantine for several days prior to testing with only animals which appeared to be in good health and suitable as test animals at the initiation of the study used. The rats were housed in suspended, wire-mesh cages in temperature and humidity controlled rooms and permitted a standard laboratory diet[b] plus water ad libitum except during a 16-20 hour period immediately prior to gastric intubation when food was withheld.

The rats were administered the test material at a single dosage level. All doses were administered at a constant volume of 20 ml/kg directly into the stomachs of the rats using a hypodermic syringe equipped with a ball-tipped intubating needle[c].

After gastric administration of the test article, the rats were returned to their cages and observed for the following 14 days. Initial, seven day and final body weights, mortalities (Table 1) and adverse reactions (Table 2) were recorded. A necropsy was conducted on all animals that died during the study as well as those euthanatized at the end of the 14 day observation period (Table 1). The protocol, principal personnel involved in the study, composition characteristics and Quality Assurance statement are contained in Appendices I - IV.

[a] Charles River Breeding Laboratories, Inc., Wilmington, MA
[b] Ralston Purina Laboratory Chow, Ralston Purina, St. Louis, MO
[c] Popper and Sons, Inc., New Hyde Park, NY

TABLE 1

ACUTE ORAL TOXICITY SCREEN - ALBINO RATS

with T-3494

Mortality, Necropsy, Adverse Reactions and Body Weight Data

Dose[a] (mg/kg)	Sex	Animal Number	Individual Body Weights (g) Test Day Number: 0	7	14	Number Dead / Number Tested	Percent Dead
5,000	M	4R411	231	285	317	0/5	0
		4R412	234	297	339		
		4R413	216	263	288		
		4R414	213	268	303		
		4R415	236	285	323		
5,000	F	4R432	207	251	265	0/5	0
		4R433	191	216	232		
		4R434	190	224	218		
		4R435	205	241	255		
		4R436	199	234	251		

[a] The test article was administered as a suspension in cottonseed oil.

The acute oral LD50 is greater than 5,000 mg/kg in fasted male and female rats.

Necropsy

Necropsies performed upon termination of the study revealed no visible lesions.

Adverse Reactions

Diarrhea was noted in all animals on days one through three, inclusive.

Riker Experiment No.: 0804.R0013

4.

APPENDIX I

PROTOCOL

TEST: Acute Oral Toxicity

SPONSOR: 3M Commercial Chemicals Division

CONDUCTED BY: **Safety Evaluation Laboratory, Riker Laboratories, Inc., St. Paul, Minnesota**

TEST ARTICLE: T-3494

CONTROL ARTICLE: NONE

PROPOSED STARTING/COMPLETION DATE OF TEST: 12/83 - 3/84

TEST SYSTEM: ALBINO RATS, CD

SOURCE: CHARLSE RIVER; WILLMINGTON, MASS.

Sex: M,F
Number: 5,5
Weight Range: 200-300 grams

OBJECTIVE: The objective of this test will be to characterize the acute oral toxicity of the test article in albino Rats. Rats were selected as a test system for reproducibility of response, historical use, ease in handling and general availability.

METHOD: The animals will be housed in stainless steel suspended wire mesh cages in temperature and humidity controlled rooms during both the quarantine and test periods, with food[a] and water offered *ad libitum*[b]. Each animal will be identified by color coding, according to the laboratory's standard operating procedure, which will correspond to the animal numbers on a card affixed to the outside of the cage. A single dosage of 5000 mg/kg will be administered each animal, however, if this dosage level does not adequately characterize the toxicity of the test article, additional animals will be administered the test article at supplemental dosage levels. Any additional dosage levels will be documented and filed with this protocol. The test article will be administered to the animals in the form received from the sponsor after which the animals will be returned to their cages and observed for any untoward behavioral reactions for the following 14 days. Initial and final body weights will be recorded. A gross necropsy which will include, but not be limited to; heart, lungs, liver, kidneys and general gastrointestinal tract will be conducted on all animals which die during the conduct of the test as well as the animals surviving the test period. Any gross abnormalities which are observed during the conduct of the necropsy will be recorded with specific mention to the organ and/or site observed. All raw data generated by the study director and the final report will be stored in the Riker Laboratories' Archive, St. Paul, Minnesota.

[a] Purina Laboratory Chow, Ralston Purina, St. Louis, Missouri
[b] FOOD WILL BE WITHHELD FOR A 16-20 HOUR PERIOD PRIOR TO DOSING.

DEC 07 1983

W.C. McCormick 12/6/83
Sponsor Date

D.L. [illegible] 12/
Study Director

Riker Experiment No.: 0884AR0013

APPENDIX I (concluded)
Deviations and/or Amendments to Protocol

1. The weight range is extended to 190-300 gm to expidite the study.

D. M. Marbet 1/19/84
Study Director Date

2. _____

Study Director Date

3. _____

Study Director Date

4. _____

Study Director Date

5. _____

Study Director Date

APPENDIX II

Principal Participating Personnel Involved in the Study

Name	Function
D. M. Markoe, Jr., BS	Toxicologist Study Director
K. L. Ebbens, BS	Supervisor Toxicology Testing
K. D. O'Malley, BS	Senior Toxicologist Acute Toxicology
G. C. Pecore	Supervisor Animal Laboratory

APPENDIX III

Composition Characteristics

This study is not regulated by the Good Laboratory Practice Act of 1978 and therefore information pertaining to composition characteristics is not applicable for inclusion in this study.

APPENDIX IV

Quality Assurance Statement

This study is not officially regulated by the Good Laboratory Practice Regulation of 1978, and therefore a statement signed and prepared by the Compliance Audit department is not applicable.

The standard operating procedures of this laboratory does adhere to the general principles of this regulation. The Compliance Audit department does inspect different significant phases for studies underway in the Acute Toxicology Laboratory on a recurring cycle, and the facilities are examined on a three month schedule. In addition a select number of Research & Development studies are routinely picked at random from the Archives by the Compliance Audit department for review.