Acute Oral Toxicity Screen

with T-3421

in Albino Rats

Experiment No.: 0883AR0287

Conducted At: Safety Evaluation Laboratory
Riker Laboratories, Inc.
St. Paul, Minnesota

Dates Conducted: August 2, 1983 to September 7, 1983

Conducted By: D. M. Markoe, Jr. 12/30/83
D. M. Markoe, Jr., BS Date
Toxicologist
Study Director

Reviewed By: Karen D. O'Malley 1/12/84
K. D. O'Malley, BS Date
Senior Toxicologist
Acute Toxicology

K. L. Ebbens 1/17/84
K. L. Ebbens, BS Date
Supervisor, Toxicology Testing

dc:
M. T. Case
D. D. Griffith
W. C. McCormick

Summary

The acute oral toxicity screen with T-3421 was conducted from August 2, 1983 to September 7, 1983 at Riker Laboratories, Inc., St. Paul, Minnesota using male and female albino rats ranging in body weight from 191-258 grams. The test article was administered by gastric intubation at dosage levels of 5,000, 2,000, 500 and 200 mg/kg body weight with mortalities of 10/10, 10/10, 10/10 and 2/10 noted respectively from one hour to six days post dose administration. The untoward behavioral reactions which occurred during the 14 day observation period generally consisted of hypoactivity, lethargy, prostration, diarrhea and unkempt appearance with the onset occurring from 1-30 minutes to day four post dose administration. Clonic convulsions were noted in two animals prior to death, trancient alopecia was noted in two animals while dyspnea and salivation were noted in one animal during the study. All reactions subsided by day eleven or death precluded recovery. Body weight gains were noted in animals which survived the study period. Necropsies performed at termination of the study revealed no visible lesions while hyperemic or hemorrhagic lungs and/or hemorrhagic intestinal tract generally were noted in the animals which died during the conduct of the study. The acute oral LD50 of T-3421 is greater than 200 mg/kg and less than 500 mg/kg in male and female albino rats.

Introduction

The objective of this study was to determine the acute oral LD50 of T-3421 in albino rats. This study was conducted in accordance with the Food and Drug Administration's Good Laboratory Practice Regulation of 1978. 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 stock cages in temperature and humidity controlled rooms and permitted a standard laboratory diet[b] plus water ad libitum except during the 16 hour period immediately prior to gastric intubation when food was withheld.

Five male and five female rats were administered the test material at preselected dosage levels. The doses were administered at a constant volume of 10 ml/kg directly into the stomachs of the rats using a hypodermic syringe equipped with an intubation needle.

After gastric administration of the test material, 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] King Labs, Oregon, WI
[b] Ralston Purina Laboratory Chow, Ralston Purina, St. Louis, MO

TABLE 1
ACUTE ORAL TOXICITY STUDY - ALBINO RATS
with T-3421
Mortality, Necropsy 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
5000	M	3R3553	208	(Day 6)	-	5/5	100
		3R3554	210	(Day 2)	-		
		3R3555	197	(Day 6)	-		
		3R3556	219	(1 Hour)	-		
		3R3557	214	(Day 6)	-		
5000	F	3R3573	191	(1 Hour)	-	5/5	100
		3R3574	207	(1 Hour)	-		
		3R3575	207	(1 Hour)	-		
		3R3576	192	(1 Hour)	-		
		3R3577	209	(Day 1)	-		
2000	M	3R3558	195	(Day 6)	-	5/5	100
		3R3559	207	(Day 6)	-		
		3R3560	209	(Day 6)	-		
		3R3561	217	(Day 6)	-		
		3R3562	207	(Day 2)	-		
2000	F	3R3578	199	(Day 6)	-	5/5	100
		3R3579	218	(1 Hour)	-		
		3R3580	201	(1 Hour)	-		
		3R3581	205	(Day 1)	-		
		3R3582	203	(1 Hour)	-		
500	M	3R4070	210	(Day 3)	-	5/5	100
		3R4071	212	(Day 4)	-		
		3R4072	213	(Day 6)	-		
		3R4073	217	(Day 5)	-		
		3R4074	216	(Day 4)	-		
500	F	3R4106	204	(Day 6)	-	5/5	100
		3R4107	200	(Day 4)	-		
		3R4108	205	(Day 5)	-		
		3R4109	221	(Day 3)	-		
		3R4110	198	(Day 4)	-		

TABLE 1 (concluded)

ACUTE ORAL TOXICITY STUDY - ALBINO RATS

with T-3421

Mortality, Necropsy 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
200	M	3R4075	251	(Day 6)	-	1/5	20
		3R4076	236	274	297		
		3R4077	253	303	336		
		3R4078	258	302	345		
		3R4079	248	249	297		
200	F	3R4111	220	230	243	1/5	20
		3R4112	212	242	242		
		3R4113	217	236	236		
		3R4114	238	253	257		
		3R4115	225	(Day 5)	-		

Note: Figures in parenthesis indicate time of death

[a] Test article administered as a suspension in water.
The approximate oral LD50 is greater than 200 mg/kg and less than 500 mg/kg in fasted male and female albino rats.

Necropsy

Necropsy of the animals which survived the observation period revealed no visible lesions while necropsy of those animals which died during the conduct of the study generally had hyperemic or hemorrhagic lungs. Hemorrhagic small intestine was noted at the 500 mg/kg dose level and one animal from the 200 mg/kg dose group. One incidence of mottled liver was noted at the 5,000 mg/kg level.

TABLE 2

ACUTE ORAL TOXICITY SCREEN - ALBINO RATS

with T-3421

Summary of Reactions

Dose mg/kg	Reactions / Sex	Observation Periods: Number Affected/Number Dosed — Minutes: 1-30	60	120	Days: 1	2	3	4	5	6	7	8	9	10	11	12	13	14
5000	M																	
	Hypoactivity		2/5	0/4		3/3	3/3	-	-	*								
	Lethargy	2/5	3/5	4/4	4/4	0/3												
	Salivation	1/5	0/5															
	Dyspnea		1/5	0/4														
	Diarrhea				4/4	3/3	3/3	-	-	*								
	Unkempt Appearance					3/3	3/3	-	-	*								
5000	F																	
	Hypoactivity	1/5	0/3															
	Lethargy	4/5	1/3	0/1														
	Prostration		2/3	1/1	*													
2000	M																	
	Hypoactivity		2/5	2/5	5/5	4/4	4/4	-	-	*								
	Lethargy	3/5	3/5	1/5	0/5													
	Prostration			2/5	0/5													
	Diarrhea				5/5	4/4	4/4	-	-	*								
	Unkempt Appearance					4/4	4/4	-	-	*								
2000	F																	
	Hypoactivity	2/5	1/2	0/2	1/1	1/1	1/1	-	-	*								
	Lethargy	3/5	1/2	0/2														
	Prostration			2/2	0/1													
	Diarrhea				1/1	1/1	1/1	-	-	*								
	Unkempt Appearance					1/1	1/1	-	-	*								

TABLE 2 (concluded)

ACUTE ORAL TOXICITY SCREEN - ALBINO RATS

with T-3421

Summary of Reactions

Dose mg/kg	Sex / Reactions	Observation Periods: Minutes 1-30	Minutes 60	Minutes 120	Days 1	2	3	4	5	6	7	8	9	10	11	12	13	14
	Number Affected/Number Dosed																	
500	M																	
	Hypoactivity							2/3	1/1	*								
	Convulsions (clonic)							1/3	0/1									
500	Hypoactivity							3/3	2/2	*								
	Ataxia						1/4	0/3										
200	M																	
	Convulsions (clonic)								1/5	0/4								
200	F																	
	Alopecia											2/4	2/4	–	2/4	0/4		

Key:
Blank indicates no significant reactions
- observations inadvertenly missed over weekend
* Total Death

Riker Experiment No.: [illegible]

APPENDIX I

7.

PROTOCOL

TEST: Acute Oral Toxicity Scan

SPONSOR: 3M Commercial Chemical Division

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

TEST ARTICLE: T-7401

CONTROL ARTICLE: None

PROPOSED STARTING/COMPLETION DATE OF TEST: 5/31 - 6/13

TEST SYSTEM: Albino Rat (CD)

SOURCE: King Lab, Oregon, WI

Sex: M/F
Number: 5
Weight Range: 200 - 300 gm

OBJECTIVE: The objective of this test will be to characterize the acute oral toxicity of the test article in albino rats. Rat 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 5,000 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 administration of the test article, 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. The acute medial lethal dose (LD_{50}) of the test article will be calculated, if possible, using a probit analysis method at the end of the observation period. 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.

RECEIVED
JUN 13 1983
SAFETY EVALUATION

W. C. McCormick 6-7-83
Sponsor Date

[signature] 6/9/83
Study Director Date

3MA10020004

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

1. Weekend observation for August 6 and 7 were inadvertently missed and on September 3rd.

D. M. Markoe, Jr. — Study Director — 10/5/83 — Date

2. Due to a delay in study conduct the proposed completion date should be amended to 1/84.

D. M. Markoe, Jr. — Study Director — 12/29/83 — 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

Test and/or Control Article Characterization

for KTZ-15 (CC#34-4)
T-3421

1. The identity strength, uniformity, composition, purity or other pertinent characterizations of the test and/or control substances have been determined and documented as of 25 May 83

2. The method of synthesis or origin of the test and control substances, including their amount and the method of bioassay (if applicable) is documented.

yes V no ____

3. The stability of the test and/or control substances have been determined or will be determined as of 25 Jun 83 or end of Test

The above information and documentation are located in the sponsor's records.

D. Parker 5/25/83
Sponsor Date

cc L.D. Winter 236-2B
W.C. McCormick 220-2E
W.H. Pearlman 223-65E
D. Parker 236-1

APPENDIX IV

QUALITY ASSURANCE STATEMENT

Acute Toxicology Laboratory Studies

Study No.: 0783AR0227

This short term study was audited by Compliance Audit, and the final report examined against the raw data on January 25, 1984. The results of the audit were reported to the study director and to management on January 25, 1984.

In addition to the data audit, different significant phases for studies underway in the Acute Toxicology Laboratory are inspected weekly on a recurring cycle, and the facilities are examined by Compliance Audit on a three month schedule.

Compliance Audit

Date January 25, 1984

3MA10020008