AR226-0294

Acute Oral Toxicity Screen

with T-2574CoC

in Albino Rats

Experiment No.: 0979AR0037

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

Dates Conducted: August 6, 1979 to September 6, 1979

Conducted By: D. M. Markoe, Jr. 9/19/79
D. M. Markoe, Jr. Date
Laboratory Technician

K. L. Ebbens 9/26/79
K. L. Ebbens, BS Date
Senior Toxicologist
Study Director

dc: M. T. Case
K. L. Ebbens (2)
F. D. Griffith
W. C. McCormick

Summary

An acute oral toxicity screen with T-2574CoC was conducted from August 6, 1979 to September 6, 1979 at Riker Laboratories, Inc., St. Paul, Minnesota using male and female albino rats ranging in body weight from 203 to 300 grams. The test article was administered by gastric intubation at dosage levels of 5,000 and 1,000 mg/kg body weight with mortalities of 10/10 and 0/10 noted respectively. The untoward behavioral reactions which occurred during the study generally consisted of diarrhea, hypoactivity, lethargy, urinary incontinence and unkempt appearance with the onset of the reactions occurring from two hours to seven days post dose administration. All reactions subsided by day seven or death precluded recovery. Autolysis precluded gross tissue evaluation of the animals from the 5,000 mg/kg dose group with the exception of one male which had hemorrhagic lungs while necropsy of the animals from the 1,000 mg/kg dose group revealed no visible lesions. The approximate oral LD50 of T-2574CoC is between 5,000 and 1,000 mg/kg in fasted male and female albino rats.

Introduction

The objective of this study[a] was to approximate the acute oral LD50 of T-2574CoC in fasted male and female albino rats. The study was initiated at Riker Laboratories, Inc., St. Paul, Minnesota on August 6, 1979 and completed on September 6, 1979. The raw data generated by the Study Director and final report are stored in the conducting laboratory's archives.

[a] Riker Toxicity Experiment No.: 0979AR0037, Test Method 605A

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 the 16 - 20 hour period immediately prior to gastric intubation when food was withheld.

The rats were administered the test article at two dosage levels. All doses were administered at a constant volume of 20 ml/kg 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, day one, seven and final body weights, mortalities (Table 1) and adverse reactions (Table 2) were recorde 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, technical personnel involved in the study, composition characteristics, and Quality Assurance statement are contained in Appendices I-IV.

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

TABLE 1

ACUTE ORAL TOXICITY SCREEN - ALBINO RATS

with T-2574CoC

Mortality, Necropsy and Body Weight Data

Dose [a] (mg/kg)	Sex	Animal Number	Individual Body Weights (g) Test Day Number: 0	1	7	14	Number Dead / Number Tested	Percent Dead
5,000	M	9R11167	288	- (5 Days) -			5/5	100
		9R11168	250	-	- (8 Days)			
		9R11169	300	- (6 Days) -				
		9R11170	287	- (7 Days) -				
		9R11171	281	- (7 Days) -				
	F	9R10266	220	- (5 Days) -			5/5	100
		9R10267	224	- (3 Days) -				
		9R10268	261	- (7 Days) -				
		9R10269	244	- (6 Days) -				
		9R10270	264	- (4 Days) -				
1,000	M	9R12376	231	239	273	302	0/5	0
		9R12377	216	218	196	250		
		9R12378	203	221	219	266		
		9R12379	224	245	273	305		
		9R12380	239	256	280	317		
	F	9R12408	223	240	250	244	0/5	0
		9R12409	208	226	213	224		
		9R12410	214	232	221	232		
		9R12411	216	227	238	230		
		9R12412	214	229	233	241		

Note: Figures in parentheses indicate time of death

The acute oral LD50 appears to be less than 5,000 mg/kg and greater than 1,000 mg/kg in fasted male and female albino rats.

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

Necropsy Findings:
Autolysis precluded gross tissue evaluation of all animals from the 5,000 mg/kg dose group with the exception of one male which had hemorrhagic lungs. Necropsy of the animals from the 1,000 mg/kg dose group revealed no visible lesions.

TABLE 2

ACUTE ORAL TOXICITY SCREEN - ALBINO RATS

with T-2574CoC

Summary of Reactions

Dose (mg/kg)	Sex	Reaction	Number Affected / Number Dosed	Time of Onset Following Dose Administration [a]	Cessation of Reaction Following Dose Administration [b]	Time of Death Following Dose
5,000	M	Hypoactivity	5/5	2 Hours	7 Days	5 - 8 Days
		Lethargy	1/5	7 Days	Until Death	
		Salivation	1/5	7 Days	Until Death	
		Unkempt Appearance	5/5	2 Days	Until Death	
		Urinary Incontinence	5/5	1 Day	6 Days	
5,000	F	Alopecia	1/5	5 Days	Until Death	3 - 7 Days
		Ataxia	1/5	4 Days	Until Death	
		Emaciation	1/5	4 Days	Until Death	
		Hypoactivity	5/5	2 Hours	6 Days	
		Lethargy	3/5	4 Days	Until Death	
		Unkempt Appearance	5/5	2 Days	5 Days	
		Urinary Incontinence	5/5	1 Day	4 Days	
1,000	M	Diarrhea	2/5	1 Hour	1 Day	----------
		Hypoactivity	1/5	1 Day	2 Days	
		Unkempt Appearance	5/5	1 Day	6 Days	
1,000	F	Diarrhea	2/5	1 Hour	1 Day	----------
		Unkempt Appearance	5/5	1 Day	6 Days	

[a] Time indicates when first animal in the dose group exhibits the reaction
[b] Time indicates when no animal in the dose group exhibits the reaction

Riker Experiment No.: 0979AR003

APPENDIX I
PROTOCOL

5.

TEST: Acute Oral Toxicity - Single Dose

SPONSOR: 3M Company Commercial Chemical Division

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

TEST ARTICLE: T-2574 CoC

CONTROL ARTICLE: none

PROPOSED STARTING/COMPLETION DATE OF TEST: 8-79 / 10-79

TEST SYSTEM AND SOURCE: Charles River Breeding Laboratory, Rats

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

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 a card affixed to the outside of the cage. A single dosage of 5,000 d mg/kg will be administered to each animal. 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.[c] 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 and the final report will be stored in the Riker Laboratories Archives, St. Paul, Minnesota.

[a] Purina Laboratory Chow, Ralston Purina, St. Louis, Missouri

[b] Animals will be fasted for ≈ 16 hours prior to dosing

[c] Day 1 and Day 7 body weights will be taken.

[d] If necessary to further characterize the toxicity, additional dose levels will be administered.

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JUL 20 1979

Safety Evaluation

William C. McCormick 7/18/79
Sponsor Date

K D O'Malley 7/25/79
Study Director Date

1. Due to the nature of the test material (solid) it was dosed as a suspension in cottonseed oil at a constant volume of 20 ml/kg body weight.

Study Director 5/13/79 Date

2. 5000 mg/kg Day one body weights were errantly omitted as well as the day seven body weight for the animal which was alive on that day. Dosed 9/19/79

Study Director 9/19-79 Date

3. _____

Study Director Date

4. _____

Study Director Date

5. _____

Study Director Date

6. _____

Study Director Date

7. _____

Study Director Date

8. _____

Study Director Date

APPENDIX I (concluded)

Amendment to Protocol

Note to the File

As of September 1, 1979, K. L. Ebbens has replaced K. D. O'Malley as Study Director.

K. L. Ebbens

APPENDIX II

Technical Personnel Involved in the Study

Name	Function
D. M. Markoe, Jr.,	Acute Biocompatibility Laboratory Technician
K. D. O'Malley, BS	Advanced Toxicologist Technical Writer
K. L. Ebbens, BS	Senior Toxicologist Study Director
G. C. Pecore	Coordinator 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 regulated by the Good Laboratory Practice Act of 1978 and therefore a statement signed and prepared by the Quality Assurance group is not applicable. This study was, however, audited by the Quality Assurance group.

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