TRADE SECRET

Study Title

H-25134: Oral Approximate Lethal Dose (ALD) in Rats

Laboratory Project ID: DuPont-9417

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STUDY COMPLETED ON: January 21, 2002

PERFORMING LABORATORY: E.I. du Pont de Nemours and Company
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[redacted]

CERTIFICATION

We, the undersigned, declare that this report provides an accurate evaluation of the data obtained from this study.

Reviewed by: Erica K Pia 21-Jan-2002
Erica K. Pia, B.S.
Associate Scientist
Date

Issued by Study Director: Carol Finlay 21-Jan-2002
Carol Finlay, B.A.
Staff Scientist
Date

STUDY INFORMATION

Substance Tested: [redacted]

Synonyms/Codes: [redacted]
- H-25134

[redacted]

Submitter's Notebook Number(s): [redacted]

Haskell Number: 25134

CAS Registry Number: [redacted]

Composition: [redacted]

Purity: [redacted]

Known Impurities: [redacted]

Physical Characteristics: Dark brown solid

Sponsor: E.I. du Pont de Nemours and Company
Wilmington, Delaware 19898
U.S.A.

Study Initiated/Completed: November 28, 2001 / (see report cover page)

In-Life Initiated/Completed: December 7, 2001 / January 18, 2002

STUDY PERSONNEL

Study Director: Carol Finlay, B.A.
Management: Judith C. Stadler, Ph.D., D.A.B.T.
Primary Technician: Erica K. Pia, B.S.

Toxicology Report Preparation: Lisa G. Burchfield, A.A.

Laboratory Veterinarian: William Singleton, D.V.M., A.C.L.A.M.

SUMMARY

H-25134 was administered as a single oral dose by intragastric intubation to male rats at doses of 670, 2300, 3400, 5000, 7500, and 11,000 mg/kg. Following dosing, the rats were weighed and observed for mortality and clinical signs of toxicity over a 14-day observation period.

No deaths occurred during the study. Body weight loss of approximately 2% of initial body weight occurred by the day after dosing in the rat dosed at 3400 mg/kg. The rat dosed at 5000 mg/kg exhibited diarrhea the day after dosing. Brown-stained face, perineum, and perianal were observed up to 3 days after dosing in the rat dosed at 7500 mg/kg. This rat also had body weight loss of approximately 7% of initial weight by the day after dosing. The rat dosed at 11,000 mg/kg exhibited diarrhea and brown-stained perineum up to 2 days after dosing and body weight loss of approximately 8% of initial weight the day after dosing.

Under the conditions of this study, the oral ALD for H-25134 was greater than 11,000 mg/kg of body weight. This substance is considered to be very low in toxicity (ALD greater than 5000 mg/kg) when administered as a single oral dose to male rats.

INTRODUCTION

The purpose of this test was to determine an approximate lethal dose (ALD) of H-25134 when administered as a single oral dose to male rats. The ALD was defined as the lowest dose administered which caused death either on the day of dosing or within 14 days post exposure.

MATERIALS AND METHODS

A. Test Substance

The test substance, H-25134, was supplied by the sponsor as a dark brown solid. The test substance appeared to be stable under the conditions of the study. No evidence of instability, such as a change in color or physical state, was observed.

B. Animal Husbandry

Male Crl:CD®(SD)IGS BR rats were received from Charles River Laboratories, Inc., Raleigh, North Carolina. Rats were housed singly in stainless steel, wire-mesh cages suspended above cage boards. Each rat was assigned a unique identification number which was recorded on a card affixed to the cage. The rats were tail-marked, using a water-insoluble marker, with the last 3 digits of the animal number. PMI Nutrition International, Inc. Certified Rodent LabDiet® 5002 and water were available *ad libitum*.

As specified in the Haskell Laboratory animal health and environmental monitoring program, the following procedures are performed periodically to ensure that contaminant levels are below those that would be expected to impact the scientific integrity of the study:

- Water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.
- Feed samples are analyzed for total bacterial, spore, and fungal counts.
- Samples from freshly washed cages and cage racks are analyzed to ensure adequate sanitation by the cagewashers.

Certified animal feed is used, guaranteed by the manufacturer to meet specified nutritional requirements and not to exceed stated maximum concentrations of key contaminants, including specified heavy metals, aflatoxin, chlorinated hydrocarbons, and organophosphates. The presence of these contaminants below the maximum concentration stated by the manufacturer would not be expected to impact the integrity of the study.

The animal health and environmental monitoring program is administered by the attending laboratory animal veterinarian. Evaluation of these data did not indicate any conditions that affected the validity of the study

Rats were quarantined, weighed, and observed for general health for 6 days. Animal rooms were maintained on a timer-controlled, 12-hour light/12-hour dark cycle. Environmental conditions of the rooms were targeted for a temperature of 23 ± 1°C and relative humidity of 50 ± 10%. Excursions outside these ranges were of small magnitude and/or brief duration and did not adversely affect the validity of the study.

C. Protocol

The container of test substance was heated in a 65°C water bath until the test substance was liquefied. The test substance was then stirred. The test substance was suspended in corn oil and administered to 1 rat per dose rate by intragastric intubation. The volumes administered were calculated based on the suspension concentration and body weights collected on the day of dosing. Doses administered ranged from 2300 to 11,000 mg/kg of body weight in increments of approximately 50%. Additionally, 1 rat was dosed at 670 mg/kg. The dosing day was test day 1; postexposure day 14 was test day 15. Following administration of the test substance, rats were observed for clinical signs of toxicity.

The rats were weighed and observed daily until signs of toxicity subsided, and then at least 3 times a week throughout the 14-day observation period. Observations for mortality and signs of illness, injury, or abnormal behavior were made daily throughout the study. Pathology examinations of test animals were not performed.

RESULTS AND DISCUSSION

A. Dosing and Mortality Data

No deaths occurred during the study. The dose regimen is detailed below.

Dose (mg/kg)	Volume (mL)	Suspension Concentration (mg/mL)	Initial Body Weight (g)	Mortality
670	1.4	150	313.3	No
2300	4.9	150	319.4	No
3400	4.0	250	294	No
5000	5.9[a]	250	293.3	No
7500	9.4[a]	250	314.9	No
11,000	12.4[b]	250	282.6	No

[a] Administered in 2 portions 15 minutes apart.
[b] Administered in 3 portions approximately 15 minutes apart.

B. Clinical Signs and Body Weights

Body weight loss of approximately 2% of initial body weight occurred by the day after dosing in the rat dosed at 3400 mg/kg. The rat dosed at 5000 mg/kg exhibited diarrhea the day after dosing. Brown-stained face, perineum, and perianal were observed up to 3 days after dosing in the rat dosed at 7500 mg/kg. This rat also had body weight loss of approximately 7% of initial weight by the day after dosing. The rat dosed at 11,000 mg/kg exhibited diarrhea and brown-stained perineum up to 2 days after dosing and body weight loss of approximately 8% of initial weight the day after dosing.

CONCLUSIONS

Under the conditions of this study, the oral ALD for H-25134 was greater than 11,000 mg/kg of body weight. This substance is considered to be very low in toxicity (ALD greater than 5000 mg/kg) when administered as a single oral dose to male rats.

RECORDS AND SAMPLE STORAGE

Specimens (if applicable), raw data, and the final report will be retained at Haskell Laboratory, Newark, Delaware, or at Iron Mountain Records Management, Wilmington, Delaware (formerly known as the E.I. du Pont de Nemours and Company Records Management Center.)