Study Title

Approximate Lethal Dose (ALD) of H-21333 in Rats

Laboratory Project ID

Haskell Laboratory Report No. 649-95

Author

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Study Completed On

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Performing Laboratory

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in compliance with EPA TSCA Good Laboratory Practice Standards (40 CFR 792) with the following exceptions:

1. The dosing preparations used in the study were not analyzed for stability, homogeneity, or accuracy of concentration. The procedures used by trained staff to prepare the dosing preparations ensured:

   - the accuracy of concentration because the test substance was weighed on an analytical balance accurate to 3 decimal places and the vehicle in which it was suspended was accurately measured in a flask graduated in 1 mL increments,
   - homogeneity because the mixture was stirred prior to dosing and while portions were removed for dose administration, and
   - stability because the time between dose preparation and administration was kept to a minimum (less than 1 hour).

2. H-21333 did not undergo GLP analysis to determine purity.

The deviations did not affect the validity of the study.

Submitter: E. I. du Pont de Nemours and Company

Sponsor: DuPont Specialty Chemicals
E. I. du Pont de Nemours and Company

Study Director: Tracy A. Filliben 1/23/96
Tracy A. Filliben
Toxicology Associate

GENERAL INFORMATION

Substance Tested:	[redacted]
Synonyms/Codes:	[redacted]
Physical Form:	Off white solid
Composition:	[redacted]
Contaminants:	[redacted]
Purity:	[redacted]
Submitter's Notebook No.:	[redacted]
CAS Registry No.:	[redacted]
Sponsor:	DuPont Specialty Chemicals E. I. du Pont de Nemours and Company Wilmington, Delaware
Study Initiated - Completed:	8/8/95 - 1/23/96
In Life Phase Initiated - Completed:	8/9/95 - 8/28/95

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SUMMARY

H-21333 was administered as a single oral dose by intragastric intubation to male rats. Rats were found dead up to 7 days after dosing. Clinical signs of toxicity were observed in lethally and nonlethally dosed animals. Under the conditions of this test, the ALD was 2300 mg/kg of body weight. This substance is considered to be slightly toxic (ALD 500 - 5000 mg/kg) when administered as a single oral dose.

Work by: M. Scott Karr

M. Scott Karr
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Reviewed and Approved for Issue: Tracy A. Filliben 1/23/96

Tracy A. Filliben
Study Director

TAF/lmp/alw

QUALITY ASSURANCE DOCUMENTATION

(H-21333)

Date(s) of Inspection:

Conduct - 8/9/95

Records, Report(s) - 1/22,23/96

Date(s) Findings Reported to:

Study Director - 1/23/96

Management - > 1/23/96

Reported by: Ronald B. Macturk — 1/23/96

Ronald B. Macturk
Quality Assurance Auditor

Date

INTRODUCTION

The purpose of this test was to determine an approximate lethal dose of H-21333 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. Animal Husbandry

Male Crl:CD®BR rats, approximately 7 weeks old, were received from Charles River Breeding Laboratories, Raleigh, North Carolina. Rats were housed singly in suspended, stainless steel, wire-mesh cages. 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. Purina Certified Rodent Chow® #5002 and water were available ad libitum.

Haskell Laboratory has an animal health monitoring program. This program is monitored and administered by the Laboratory Veterinarian. Water samples are periodically analyzed for total bacterial counts and for the presence of coliforms, lead, and other contaminants. Additionally, samples from freshly washed cages and cage racks are periodically analyzed to assure adequate sanitation by the cagewashers. Data from this program are maintained separately from study records. Animal feed is certified by the manufacturer to meet specified nutritional requirements and to be free of a list of specified contaminants. On the basis of these analyses, there is no evidence suggesting that contaminants were present in the feed or water in amounts which may have interfered with the results of this study.

Rats were quarantined, weighed, and observed for general health for approximately one week prior to testing. 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°C ± 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.

B. Protocol

The test substance was suspended in deionized water and administered to 1 rat per dose rate by intragastric intubation. In the absence of visible evidence to the contrary, the test substance was assumed to be

stable under the conditions of administration. Dose rates administered ranged from 450 to 3400 mg/kg of body weight in increments of approximately 50%. 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.

Surviving 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 were made daily throughout the study. Pathological examinations of test animals were not performed.

C. Records Retention

All raw data and the final report will be stored in the archives of Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours and Company, Newark, Delaware or in the DuPont Records Management Center, Wilmington, Delaware.

RESULTS

A. Dosage and Mortality Data

The dosage regimen and the mortality resulting over the 15-day test period are detailed below. The lowest dose of H-21333 which resulted in the death of a test animal was 2300 mg/kg. Rats were found dead up to 7 days after dosing.

Dosage (mg/kg)	Dose Volume (mL)	Suspension Concentration (mg/mL)	Initial Body Weight (g)	Mortality
450	0.55	200	243	No
670	1.2	150	264	No
1000	1.3	200	250	No
1500	1.9	200	247	No
2300	3.9	150	257	Yes
3400	4.2	200	246	Yes

B. Clinical Signs

Nonlethal Doses

The rats dosed at 450, 670, 1000, and 1500 mg/kg exhibited continuous weight losses of up to approximately 26% of initial body weight 2,3,or 6 days after dosing. Clinical signs observed in these rats included ruffled fur, lethargic behavior, hunched over posture, wet perineum, or alopecia of the underbody. Most clinical signs of toxicity had subsided by 7 days after dosing.

Lethal doses

The rat dosed at 2300 mg/kg exhibited a weight loss of approximately 39% of initial body weight by 6 days after dosing and was found dead by 7 days after dosing. The rat dosed at 3400 mg/kg exhibited a weight loss of approximately 22% of initial body weight by 3 days after dosing and was found dead by 4 days after dosing. Clinical signs of toxicity observed in these rats included lethargic behavior, ruffled fur, hunched over posture, or dry red nasal or ocular discharge.

CONCLUSION

Under the conditions of this study, the ALD for H-21333 was 2300 mg/kg of body weight. This substance is considered to be slightly toxic (ALD 500 - 5000 mg/kg) when administered as a single oral dose to male rats.