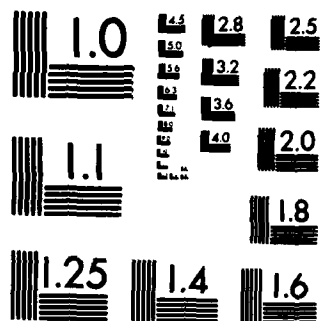






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INSTITUTE REPORT NO. 182

AD-A146 777

ACUTE DERMAL TOXICITY OF (E)-1,2,3,4-TETRAHYDRO-6-METHYL-1-(2-METHYL-1-OXO-2-BUTENYL) QUINOLINE (CHR5) IN MALE AND FEMALE RATS

CRAIG W. WHITE, DVM, CPT VC
LAWRENCE MULLEN, BS, SP5
and
THOMAS P. KELLNER, BA, SP5

TOXICOLOGY GROUP
DIVISION OF RESEARCH SUPPORT

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AUGUST 1984

Toxicology Series 73

LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129

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Acute Dermal Toxicity of (E)-1,2,3,4-Tetrahydro-6-Methyl-1-(2-Methyl-1-Oxo-2-Butenyl) Quinoline (CHR5) in Male and Female Rats (Toxicology Series 73)--White, Mullen and Kellner

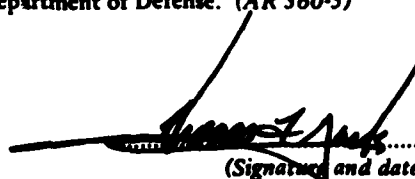
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This material has been reviewed by Letterman Army Institute of Research and there is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense. (AR 360-5)

 8 Aug 84
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18. SUPPLEMENTARY NOTES		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number)		
Acute Dermal Toxicity, Insect Repellent, Toxicology, (E) 1,2,3,4-Tetrahydro-6-Methyl-1-Oxo-2-Butenyl) Quinoline, CHR5		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number)		
The acute dermal toxicity potential of the candidate insect repellent (E)-1,2,3,4-tetrahydro-6-methyl-1-(2-methyl-1-oxo-2-butenyl) quinoline (CHR5*) was determined in male and female rats by using intact skin site application exposure for 24 hours. There were no compound related deaths at the maximum dose level (2 ml/kg) during this study. *Code Name for 1,2,3,4-Tetrahydro-6-Methyl-1-(2-Methyl-1-Oxo-2-Butenyl) Quinoline		

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ABSTRACT

The acute dermal toxicity potential of the candidate insect repellent (E)-1,2,3,4-tetrahydro-6-methyl-1-(2-methyl-1-oxo-2-butenyl) quinoline (CHR5*) was determined in male and female rats by using intact skin site application exposure for 24 hours. There were no compound related deaths at the maximum dose level (2 ml/kg) during this study.

*Code Name for 1,2,3,4-Tetrahydro-6-Methyl-1-(2-Methyl-1-Oxo-2-Butenyl) Quinoline

KEY WORDS: Acute Dermal Toxicity, Insect Repellent, Toxicology, (E)-1,2,3,4-Tetrahydro-6-Methyl-1-(2-Methyl-1-Oxo-2-Butenyl) Quinoline, CHR5

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PREFACE

TYPE REPORT: Acute Dermal Toxicity GLP Report

TESTING FACILITY: U.S. Army Medical Research and Development Command
Letterman Army Institute of Research
Presidio of San Francisco, CA 94129

SPONSOR: U.S. Army Medical Research and Development Command
Letterman Army Institute of Research
Presidio of San Francisco, CA 94129

PROJECT/WORK UNIT/APC: Development of Repellents Against Medically
Important Arthropods, 3M162770A871, WU 201,
APC, TLO6

GLP STUDY NUMBER: 82019

STUDY DIRECTOR: COL John T. Fruin, DVM, PhD, VC, Diplomate of
American College of Veterinary Preventive Medicine

PRINCIPAL INVESTIGATOR: CPT Craig W. White, DVM, VC

CO-PRINCIPAL INVESTIGATOR: SP5 Thomas P. Kellner, BS

PATHOLOGIST: MAJ Glen E. Marrs, Jr., DVM, MS, VC, Diplomate of American
College of Veterinary Pathologists

REPORT AND DATA MANAGEMENT: A copy of the final report, study protocol,
retired SOPs, raw data, analytical,
stability, and purity data of the test
compound, tissues, and an aliquot of the
test compound will be retained in the LAIR
Archives.

TEST SUBSTANCE: (E)-1,2,3,4-Tetrahydro-6-Methyl-1-(2-Methyl-1-Oxo-2-
Butenyl) Quinoline (CHR5)

INCLUSIVE STUDY DATES: 22 June 1982 - 12 July 1982

OBJECTIVE: The objective of this study is to determine the toxicity
of CHR5 when administered onto the intact skin of the rat.

ACKNOWLEDGMENTS

The authors wish to thank SSG Lance White; SP5 Florence McKinley, BS; SP5 Marlin McKinley, BS; SP4 Justo Rodriguez, BS; SP5 Evelyn Zimmerman; Carolyn Lewis, MS; and John Dacey for their assistance in performing the research. The authors also wish to thank William Riefenrath, PhD, for providing the chemical and Louis Rutledge, MS, for the background information.

SIGNATURES OF PRINCIPAL SCIENTISTS AND MANAGERS INVOLVED IN THE STUDY:

We, the undersigned, believe the study numbers 82019 described in this report to be scientifically sound and the results in this report and interpretations to be valid. The study was conducted to comply, to the best of our ability, with the Good Laboratory Practice Regulations for Non-Clinical Laboratory Studies, outlined by the Food and Drug Administration.

John T. Fruin 20 Dec 83
JOHN T. FRUIN / DATE
COL, VC
Study Director

Craig W. White 12 Nov 83
CRAIG W. WHITE / DATE
CPT, VC
Principal Investigator

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DEPARTMENT OF THE ARMY
LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129

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19 Jun 84

MEMORANDUM FOR RECORD

SUBJECT: Report of GLP Compliance

I hereby certify that in relation to LAIR GLP study 82019 the following inspections were made:

29 Jun 82

12 Jul 82

The report and raw data for this study were audited on 15 Jun 84.

Routine inspections with no adverse findings are reported quarterly, thus these inspections are also included in the 7 Jul 82 report to Management and the Study Director.

A handwritten signature in cursive script, appearing to read "Nelson R. Powers".

NELSON R. POWERS, Ph.D.
DAC
Chief, Quality Assurance Unit

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Acute Dermal Toxicity of (E)-1,2,3,4-Tetrahydro-6-Methyl-1-(2-Methyl-1-Oxo-2-Butenyl) Quinoline (CHR5) in Male and Female Rats--White et al

The goal of the insect repellent program is to develop better insect repellents for the protection of soldiers from insects and insect-borne diseases in the field. In the last several years the Division of Cutaneous Hazards, Letterman Army Institute of Research (LAIR), has tested a large number of chemical compounds, submitted by SRI International, the U.S. Department of Agriculture (USDA), and private industry, against a variety of mosquitoes, sand flies, fleas, ticks, and mites in animals and in vitro test systems. Several of these materials have shown sufficient repellent activity and persistence on the skin of animals to warrant consideration for use in lieu of, or in conjunction with, the current troop-issue insect repellent, 71.25% N,N-diethyl-m-toluamide (m-DEET) in ethanol. One of these new formulations, (E)-1,2,3,4-tetrahydro-6-methyl-1-(2-methyl-1-oxo-2-butenyl) quinoline (CHR5), appears to be more persistent than the current troop-issue repellent in efficacy tests on animals and was therefore submitted for preclinical toxicity testing.

Objective of Study

The objective of this study is to determine the acute toxicity of CHR5 when administered onto the intact skin of the rat.

Description of Test

Dermal toxicity is one of the three categories of toxicity defined by route of exposure in the Federal Hazardous Substances Act (FHSA). The albino rat is used in acute dermal toxicity studies because it is more sensitive than man, and is widely used for acute oral and parenteral studies as well as various subchronic and chronic studies (1).

The animal's dorsal and lateral sections are close-clipped so that no less than 10% of the body surface area is available for application of material (2). The maximum quantity of liquid test substance applied is 2 ml/kg. The test dose must remain in contact with the skin throughout the 24-hour exposure period. For materials of anticipated low toxicity, an initial range-finding dose of 2 g/kg of body weight applied to five or more animals of each sex is sufficient to demonstrate a lack of appreciable dermal toxicity. At the end of

White--2

the exposure periods, any residual material is gently removed with a gauze compress and the animal is examined daily for signs of systemic toxicity and localized dermal reaction. After the 14-day observation period, animals are sacrificed, a gross necropsy performed, and two sections of the exposed skin are processed for histopathology (1).

Study Conduct

This study was performed according to LAIR SOP OP-STX-30 (3).

MATERIALS

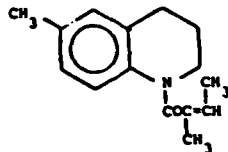
Test Substance

Chemical name: (E)-1,2,3,4-Tetrahydro-6-Methyl-1-(2-Methyl-1-Oxo-2-Butenyl) Quinoline

Code name: CHR5, USDA AI3-36166

CAS: Unknown

Molecular structure:



Empirical formula: $C_{15}H_{19}NO$

Other test substance information was provided by Starks Associates and is presented in Appendix A.

Vehicle

No vehicles were used in this study.

Animal Data

Twenty male and twenty female albino Sprague-Dawley rats were received on 22 June 1982 from Bantin-Kingman, Fremont, CA 94076. On 23 June 1982 the rats weight ranged from 119 to 171 g; all were in good general health. The male rats were born on 19 May 1982, and the female rats were born on 15 May 1982. The rats were ear tagged according to LAIR SOP OP-ARG-1.

Husbandry

Rats were caged individually in stainless steel wire mesh cages with automatic flushes. The diet consisted of Certified Purina Rodent

Chow Diet #5002 (Ralston Purina Company, Checkerboard Square, St. Louis, MO 63188) ad libitum; water was provided by automatic lick dispensers connected to a central line. The animal room temperature was maintained at 18 ± 1.5 C. The relative humidity in the animal room ranged from 70 to 85%, except for brief unavoidable spikes up to 100%, during the daily cage cleanings. The photoperiod was 15 hours of light per day.

METHODS

Group Assignment/Acclimation:

Ten male and ten female rats were assigned to each of two study groups. Group Number 1 was the dose group and Group Number 2 was the negative control group. The animals were assigned to this study using the Beckman TOXSYS Animal Allocation Program (LAIR SOP OP-ISC-24). The rats were acclimated for seven days at LAIR before dosing. Animal observations were conducted daily for clinical signs, dermal toxicity and mortality.

Dose Levels

The test was conducted as a limit test (SOP-OP-STX-30) wherein 10 males and 10 females were assigned to the treatment group and received a dose of 2 ml/kg of CHR5. A negative control group of 10 males and 10 females was also tested. The dosing material remained in contact with the skin for 24 hours. If a test is conducted at this dose level and no compound related mortality occurs, then a full study using 3 dose levels is not necessary (4). All animals were dosed on 29 June 1982.

Dose volume was administered to each animal according to weight (range 0.34 to 0.41 ml of undiluted test compound).

Compound Preparation

The compound tested is an oily powder at room temperature but liquifies at about 39 C. The compound was heated to 45 C and dosage was measured volumetrically to provide a dosage rate of 2.0 ml/kg.

Chemical Analysis of Dosing Material

Chemical analyses of CHR5 are given in Appendix A. Starks Associates provided the compound for testing and included analytical data to verify identity and purity of CHR5.

Test Procedures

The skin of the rats was not abraded for the limit test as recommended in the SOP because the objective of this study was to access dermal toxicity on intact skin. The test material was

administered to the close-clipped skin of the rat with a needleless syringe at the appropriate dose volume. The dorsal and abdominal areas were not covered with wrapping material, as the rats displayed no interest or annoyance in the test compound application sites. The rats were observed and clinical signs recorded within six hours of administration of the test substance. Historical listing of study events appears in Appendix B.

Observations

The rats did not lick the CHR5 probably because of the extreme unpleasant odor characteristic of the compound. After 24 hours of exposure the residual test substance was removed from the skin by wiping with gauze pads and observation of the animal and application site were made. Animals were weighed every 3-4 days during the study test period. Observations were recorded daily. At the end of the 2-week period, animals were anesthetized with sodium pentobarbital, sacrificed by exsanguination from severed axillary vessels and necropsies were performed. The skin was examined microscopically.

Changes/Deviation

The dose level was delivered at 2 ml/kg rather than 2 g/kg since the test substance was applied as a liquid. The test compound was heated to 45 C rather than the 47 C stated in the protocol amendment.

RESULTS

Clinical Observations

During the course of the study, observations were split into two major categories: systemic which apply to the general health of the animal, and dermal which relate to skin exposure.

Systemic. No clinical systemic signs were noted that were interpreted as signs of toxicity attributable to the test compound.

Dermal. The only sign related to dermal toxicity was very slight erythema, seen in 3 of 10 CHR5-dosed males and 1 of 10 CHR5-dosed females. Erythema was observed on 30 June 1982 at the 24 hour post-dosing observation for each affected rat. The erythema occurred on the back and involved a maximum of 5% of the close-clipped exposure area.

Pathological Observations

The gross necropsy and skin histopathology results revealed no indications that CHR5 exerted any systemic or local pathology at the 2.0 ml/kg dose level (Appendix C).

DISCUSSION

The acute dermal toxicity test revealed that CHR5 did not cause clinical signs of systemic toxicity at 2 ml/kg when applied to approximately 10% of the body surface of rats. CHR5 caused no inflammatory response in skin samples examined microscopically 14 days after exposure. The acute dermal toxicity test evaluates the potential for systemic toxic effects of a given substance. Rats are an appropriate animal model for this test as they are generally more sensitive to the dermal effects of a test compound than is man (1).

CONCLUSION

CHR5 causes minimal irritation to the close-clipped, intact skin of rats exposed for a 24-hour period and observed for two weeks.

RECOMMENDATION

CHR5 should undergo additional preclinical toxicity testing dependent on efficacy results of subsequent studies.

REFERENCES

1. Committee for the Revision of NAS Publication 1138. Committee on Toxicology, National Research Council. Principles and procedures for evaluating the toxicity of household substances. Prepared for the Consumer Product Safety Commission. Washington, DC: National Academy of Sciences, 1977.
2. Association of Food and Drug Officials of U.S. Appraisal of the safety of chemicals in foods, drugs and cosmetics (4th printing). 1959.
3. Letterman Army Institute of Research Standard Operating Procedure OP-STX-30. Letterman Army Institute of Research, Presidio of San Francisco, CA 94129, 29 Nov 82: 1-9.
4. Environmental Protection Agency. Good Laboratory Practices proposed regulations (40 CFR 770,771,772) and preamble as published in the Federal Register, 22 Aug 78, 9 May 79, 26 Jul and 18 Apr 80, (45 FR26373).

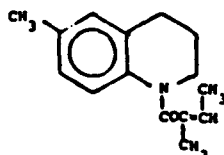
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APPENDICES

CHEMICAL DATA

Chemical Name: (E)-1,2,3,4-Tetrahydro-6-Methyl-1-(2-Methyl-1-Oxo-2-Butenyl) Quinoline (CHR5)

Chemical structure:



Empirical formula: $C_{15}H_{19}NO$

Molecular weight: 229

pH: Non Aqueous

Physical state: White crystalline solid

Melting point: 37-37.5 C

Compound density: Unknown

Compound refractory index: Unknown

Compound stability: Unknown but presumed to be stable at room temperature

Purity: Unknown

Contaminants: Unknown

Manufacturer Lot No: 0205

Manufacturer: Starks Associates, Inc.
1280 Niagara Street
Buffalo, New York 14213

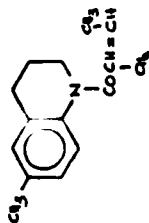
Published Toxicity Data: No toxicity data on this compound has been published.

Other information: Unknown

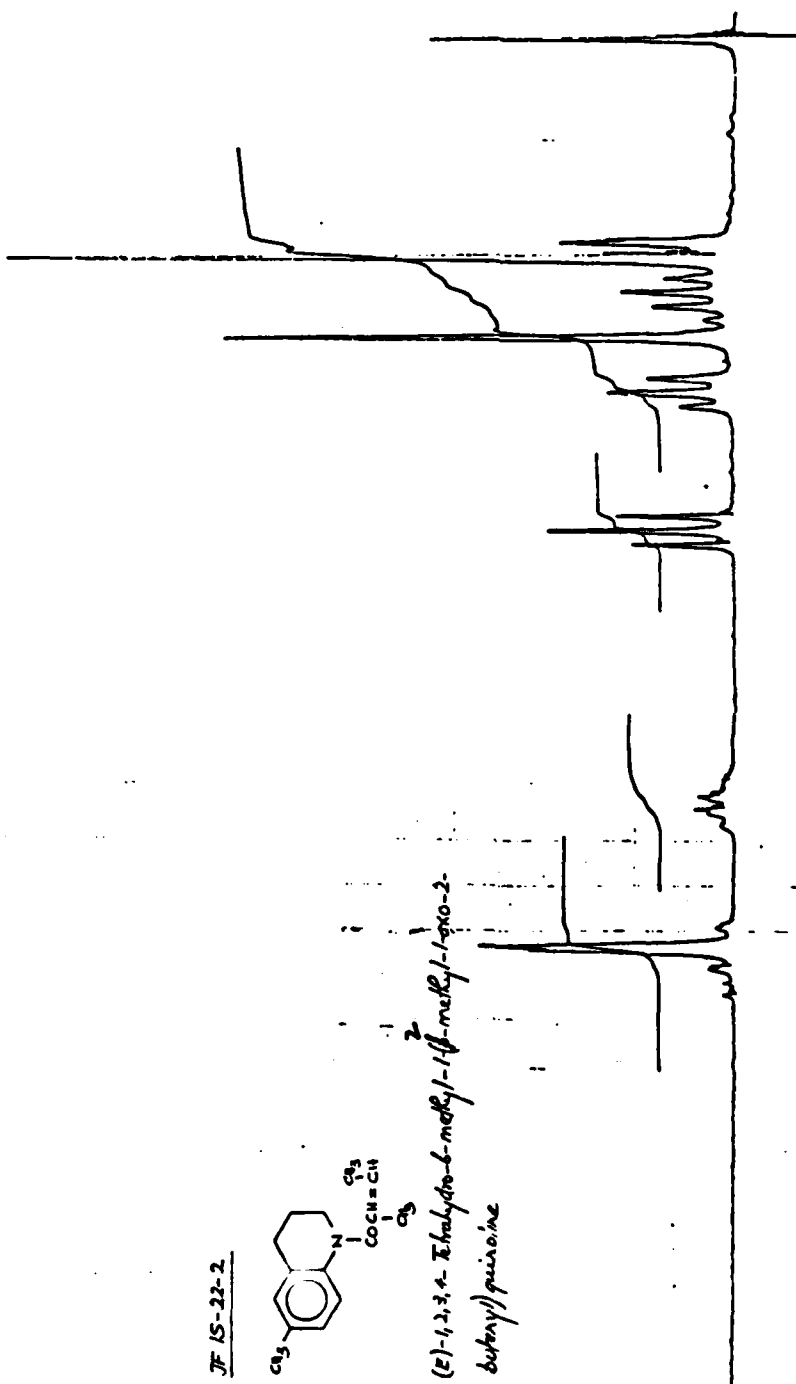
DATA SHEET FOR COMPOUNDS											
GR. NO. WR250018AA			SUBMITTER Starks Associates, Inc. 1280 Niagara Street Buffalo, New York 14213					SUBMITTER KEY NO. 0205			
DATE SHIPPED		DAY 15	MO 2	YR 82	DATE RECEIVED		DAY 17	MO 2	YR 82	DATE ACKNOWLEDGED	
NAME OF COMPOUND (E)-1,2,3,4-Tetrahydro-6-methyl-1-(3-methyl-1-oxo-2-butenyl)quinoline					0530						
STRUCTURE ST E 2.5 BK16177											
MOL. FORMULA $C_{15}H_{19}NO$			MOL. WT. 229.324			ANALYSES					
APPEARANCE white crystalline solid						ELEMENT		CALCULATED		FOUND	
QUANTITY 1061 g		CODE NO. JF15-22-2				C		78.56		78.90	
NOTESBOOK REF. JF15-22-2		PREPARED BY J. F. Novotny				H		8.35		8.52	
TEST SYSTEM						N		6.11		6.00	
						S					
B.P.		M.P.		REFRACT. INDEX							
		37-37.5°									
attached spectrum											
attached spectrum											
CHROMATOGRAPHY*Homogeneous (Baker precoated T.C. plates, glass support 5 cm x 10 cm, 0.25 mm silica gel 60 F-254; detection - ultraviolet light).						LITERATURE 1. The compound is unknown to the chemical literature.					
STABILITY (Check Where Applicable)						SOLUBILITY (Check Where Applicable)					
STABLE UNSTABLE ACID ☐ 56 ☐ OTHER ☐ 60 ☐ BASE ☐ 57 ☐ ☐ 61 ☐ HEAT ☐ 58 ☐ ☐ 62 ☐ LIGHT ☐ 59 ☐ ☐ 63 ☐			STABLE UNSTABLE 1 2 1 2			SOLUBILITY (Check Where Applicable) WATER 64 ☐ ☐ ☐ CHLOROFORM 70 ☐ ☐ ☐ ACID 65 ☐ ☐ ☐ ETHER 71 ☐ ☐ ☐ BASE 66 ☐ ☐ ☐ PET. ETHER 72 ☐ ☐ ☐ METHANOL 67 ☐ ☐ ☐ BENZENE 73 ☐ ☐ ☐ ETHANOL 68 ☐ ☐ ☐ 74 ☐ ☐ ☐ ACETONE 69 ☐ ☐ ☐ 75 ☐ ☐ ☐					
HYGROSCOPIC YES ☐ NO ☒ 63											
EQUATIONS INDICATING SYNTHETIC ROUTE											
a. $\text{CH}_3\text{CH}=\text{CHCOCH}_2\text{Br} + \text{HCO}_2\text{H} + (\text{CH}_3)_3\text{N} \rightarrow$ b. $\text{R} + \text{HCl} \rightarrow$ c. $\text{R} + \text{H}_2\text{O} \rightarrow$ d. $\text{R} + \text{R} \rightarrow$ PRIORITY 1 FEB 19 1982											
REMARKS: * 1. Ether; $R_f=0.83$ 2. Ethyl acetate; $R_f=0.64$ 3. Methylene chloride; $R_f=0.30$, elongated spot NMR - See attached spectrum Solvent of recrystallization - ether											
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(E)-1,2,3,4-tetrahydro-6-methyl-1-((E)-methyl-1-oxo-2-methyl-1-prop-1-en-1-yl)pyrrolidine

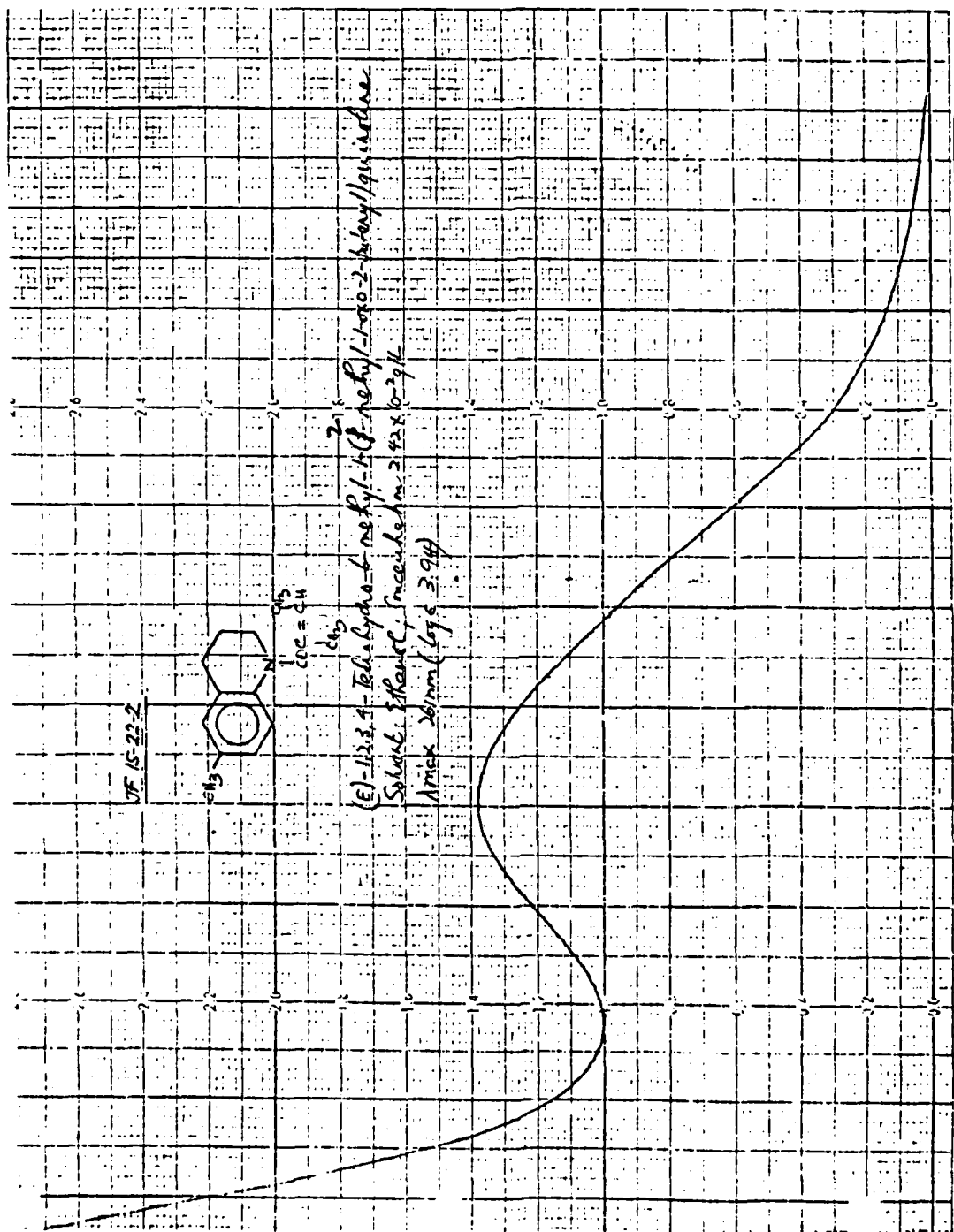


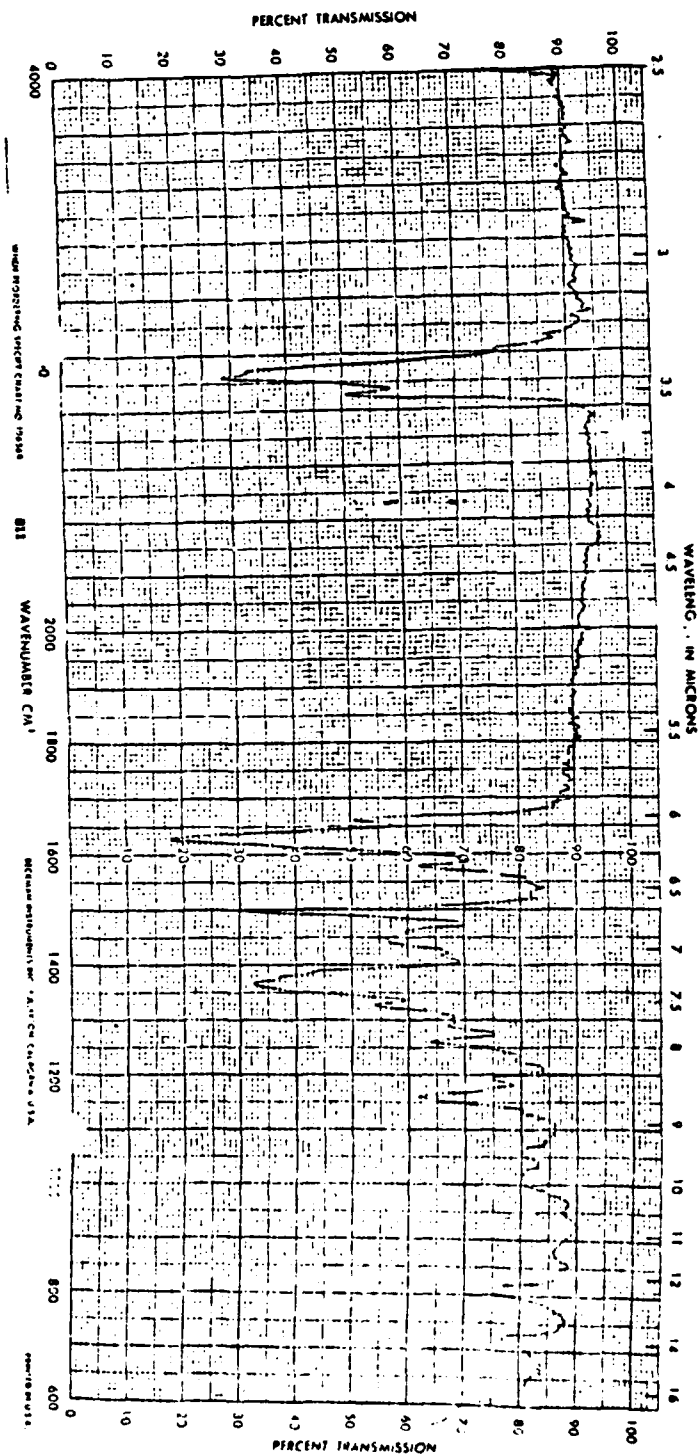
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CDCl₃

Peak	Chemical Shift (ppm)	Integration	Assignment
1	0.9	0.05	CH ₃
2	1.2	10.10	CH ₃
3	1.5-2.5	10.10	CH ₂
4	3.1	10.10	CH
5	3.6	10.10	CH





APPENDIX A (concluded)

HISTORICAL LISTING OF STUDY EVENTS

<u>Date</u>	<u>Event</u>
22 Jun 82	Animals arrive at LAIR.
23 Jun 82	Rats observed for illness, ear tagged, weighed and caged in the GLP Suite. At least 20 males and 20 females will be assigned to the study.
24 Jun 82	Animals randomized into dose groups.
23-28 Jun 82	Animals observed once daily.
25 Jun 82	Animals weighed.
29 Jun 82	Animals weighed and dosed. Observations commence at 1200 hours. Animals were observed for clinical signs, which were recorded.
30 Jun - 11 Jul 82	Animals observed for clinical signs daily.
2,6,9 Jul 82	Animals weighed.
12 Jul 82	Animals observed for clinical signs at 0800 hours and weighed. Animals sacrificed and complete necropsies were performed with skin sampled for histopathological examination.

PATHOLOGY REPORT

GLP Study 82019

Acute Dermal Toxicity Study of CHR5 in Male and Female Sprague-Dawley Rats

History: The purpose of this study was to determine the acute dermal toxicity of (E)-1,2,3,4 - Tetrahydro-6-methyl-1-(2-methyl-1-oxo-2-butenyl) quinoline (CHR5) in male and female Sprague-Dawley rats. Two g/kg of tested material was applied to the clipped skin of rats for 24 hours. The skin of the control rats was also clipped.

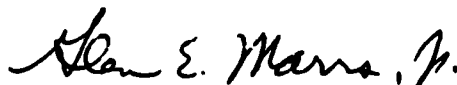
After a 13 day observation period, the rats were submitted for necropsy. They were killed by exsanguination from severed axillary vessels while under anesthesia produced by intraperitoneal injection of pentobarbital. Complete gross necropsies were performed and two specimens of skin, 1 section from each exposed area, were fixed in neutral buffered formalin, embedded in paraffin, sectioned at approximately 6 micrometers, and stained with hematoxylin and eosin for microscopic examination.

Gross necropsy findings: No gross lesions were observed in any of the male or female rats that were due to the tested compound. One of 10 male controls and 3/10 male rats dosed with 2 g/kg of CHR5 had unilateral hydronephrosis which was considered to be an incidental finding. The skin over the back of 10/10 male controls, 10/10 male rats dosed with 2g/kg of CHR5, and 5/10 female rats dosed with 2 g/kg of CHR5 was yellow-brown. Yellow-brown discoloration of the skin of the back is common in rats, especially males.

Microscopic findings: The sections of skin examined microscopically from all of the rats in this study were essentially normal.

Summary:

1. No gross lesions were observed in any of the controls or rats exposed to the CHR5 that were due to the tested compound.
2. No microscopic lesions were observed in the skin of any controls or rats that were exposed to the CHR5.



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28 February 1983

APPENDIX C

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