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ACUTE ORAL TOXICITY (LD50) OF CHR 9 IN RATS(U)
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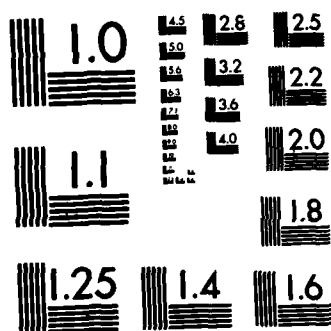
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The acute oral toxicity potential of triethylene glycol monohexyl ether (CHR9), a candidate insect repellent, was tested in male and female rats exposed to dose levels ranging from vehicle control to 10 ml/kg body weight. Animals were single dosed and observed for 14 days. Only one female rat died during the observation period. No male rats died. There are no LD50 calculation or time of death curves for this study, due to the low toxicity of this chemical. The compound is considered practically non-toxic by the criteria of the National Research Council.		

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TECHNICAL NOTE NO. 82-36TN

ACUTE ORAL TOXICITY (LD₅₀) OF CHR 9 IN RATS

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**TOXICOLOGY GROUP.
DIVISION OF RESEARCH SUPPORT**

JUNE 1982

Toxicology Series 34

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

Acute Oral Toxicity (LD₅₀) of CHR 9 in Rats - Mullen et al
Toxicology Series 34

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In conducting the research described in this report, the investigation adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care, Institute of Laboratory Animal Resources, National Research Council.

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)

John D. Marshall 18 June 82
(Signature and date)

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PREFACE

TYPE REPORT: Acute Oral Toxicity GLP Report

TESTING FACILITY: Toxicology Group, Division of Research Support,
Letterman Army Institute of Research
Presidio of San Francisco, CA 94129

SPONSOR: Division of Cutaneous Hazards
Letterman Army Institute of Research
Presidio of San Francisco, CA 94192

PROJECT/WORK UNIT/APC: Prevention of Military Disease Hazards
3M16770A871, WU 201, Development of Repellents
Against Medically Important Arthropods, APC FL07

GLP STUDY NUMBER: 81028

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

PRINCIPAL INVESTIGATOR: CPT Martha A. Hanes, DVM, VC

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

REPORT AND DATA MANAGER: Carolyn M. Lewis, MS

REPORT AND DATA MANAGEMENT: All raw data, a copy of the final report,
study protocol and retired SOPs will be
retained in the LAIR Archive

TEST SUBSTANCES: CHR 9, Triethylene glycol monohexyl ether

INCLUSIVE STUDY DATES: 23 October - 18 November 1981

OBJECTIVE: To determine the acute oral toxicity potential of CHR 9,
Triethylene glycol monohexyl ether.



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The authors wish to thank SSG Lance White, SP5 Joe Alletto, BS; SP4 Thomas Kellner, BS; Justo Rodriquez, BA; SP4 Evelyn Zimmerman, William Langley, MS; and Callie Crosby, BS, for performing the daily observations, maintaining the health care of the animals, and compiling data in a usable form.

SIGNATURES OF PRINCIPAL SCIENTISTS AND MANAGERS INVOLVED IN THE STUDY:

We, the undersigned, believe the study number 81028 described in this report to be scientifically sound and the results in this report and interpretation to be valid. The study was conducted to comply, to the best of our ability, with the Good Laboratory Practice Regulations outlined by the Food and Drug Administration.

John T. Fruin 15 Apr 82
JOHN T. FRUIN / DATE
COL, VC
Study Director

Martha A. Hanes, 15 Apr 82
MARTHA A. HANES / DATE
CPT, VC
Principal Investigator

Glen W. Hays, Jr. 8 Apr 82
GLEN W. HAYS / DATE
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Carolyn M. Lewis 8 Jan 82
CAROLYN M. LEWIS, MS / DATE
Data Manager



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

REPLY TO
ATTENTION OF:

SGRD-ULZ-QA

10 Jun 82

MEMORANDUM FOR RECORD

SUBJECT: Report of GLP Compliance

I hereby certify that in relation to LAIR GLP study 81028 the following inspections were made:

23 Oct 81 0810 hrs
23 Oct 81 1100 hrs
26 Oct 81
3 Nov 81
17 Nov 81

The report and raw data for this study were audited on 23 Apr 82.

Routine inspections with no adverse findings are reported quarterly, thus these inspections are also included in the 4 Jan 82 report to management and the Study Director.

JOHN C. JOHNSON
CPT, MS
Quality Assurance Officer

ACUTE ORAL TOXICITY (LD₅₀) OF CHR 9 IN RATS-- Mullen 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, bugs, 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. The Division of Cutaneous Hazards has also evaluated a number of new formulations of m-DEET prepared at LAIR or submitted by private industry. Several of these new formulations have been more persistent than the current troop-issue repellent in tests on animals.

Toxicity Testing Repellent Program

It is now planned to test the best of the new compounds and formulations on human volunteers to confirm the results that have been obtained in the in vitro and animal tests and to evaluate their performance under conditions of actual use. Before this can be done, it is necessary to obtain certain toxicity data on each compound or formulation to insure that it is safe for application to the skin. The toxicity tests required for registration of a new insect repellent are prescribed by the Environmental Protection Agency (EPA). The basic animal toxicity tests required for experimental use of the new compounds and formulations on human volunteers are prescribed by the LAIR and USAMRDC Human Use Committees. An acute oral toxicity (LD₅₀) test is one of the animal toxicity tests for CHR 9 requested by the Division of Cutaneous Hazards so that the formulation could be considered for human testing. If adverse toxicity data are obtained with the animal tests, the formulation will be eliminated from consideration, and the prospective tests on human volunteers will not be carried out. The toxicity testing program thereby serves as both a safety factor and secondary screen in the repellent development scheme.

Objective of Study

The objective of this study was to determine the acute oral toxicity potential of triethylene glycol monohexyl ether in rats.

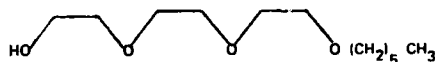
METHODS

Test Substance

1. Chemical Name: Triethylene glycol monohexyl ether

Chemical Abstract Service Registry No.: 25961-89-1

Molecular structure: $C_{12}H_{26}O_4$



Molecular weight: 234

pH: Neutral in water

Physical state: Liquid

Boiling point: 122° C at 0.5 mm of Hg

Compound density: Refractive Index $n^D = 1.44245$ at 23° C

Stability: Stable at room temperature

Contaminants: Impurities: triethylene glycol and
hexyl bromide < 4%

Manufacturer: SRI International, 333 Ravenswood Ave.
Menlo Park, CA 94025

Manufacturer Lot No: S-10581-12-2, 23 February 1973

Purity: > 96%

Animal Data

Species: Rat (Rattus norvegicus)

Strain: Sprague Dawley

Source: Timco Breeding Laboratories, 305 Almeda-Geroa Rd.
Houston, Texas 77047

Sex: Male and Female

Age: 6 weeks at receipt

Method of Randomization: TOXSYS^R Animal Allocation Program

Animals in Each Group: 14 animals, 7 males and 7 females
per group; total, 4 groups, ie, 56 animals

Condition of Animals at Start of Study: Normal

Body Weight Range: 128-193 g at receipt
Males, 209-277 g; Females 185-224 g at dosing

Identification Procedures: Ear tag (SOP-OP-ARG-1)

Pretest Conditioning:

A. Quarantine from 23 October to 2 November 1982

B. Predose - acclimated with 1 cc water daily from
26-30 October and 2 November 1981.

Justification: The Sprague Dawley rat is a proven sensitive
mammalian model for oral LD₅₀ determination.

Environmental Conditions

Caging: Number/cage = 1; Type cage used = stainless steel,
wire mesh bottom, battery type, no bedding.

Diet: Certified Ralston Purina Rodent Diet 5002 ad lib.

Water: Central line to cage battery

Temperature: 75 $\pm$ 2 F (24 $\pm$ 1) C

Humidity: $44 \pm 5\%$

Photoperiod: 0600 - 2000 hr/day (14 hr of light).

Dosing

CHR 9 was removed from refrigerated storage bottles and placed in 20 ml scintillation vials and warmed to between 38 to 42 C to avoid rapid cooling of the animals stomach. Three dose levels (5.01 ml/kg, 7.08 ml/kg and 10 ml/kg) were given to both male and female rats (Table 1). The dose for each animal was calculated based on the animal's weight, the dose level desired and the concentration of the dosing solution. The total volume was adjusted with corn oil to deliver 2.6 ml of total volume per male rat and 2.4 ml per female rat.

All animals received a single dose on 3 November 1981. A 18 gauge 3 inch gastric gavage needle (Popper and Sons, Inc., New Hyde Park, N.Y.) was used to administer the chemical by gastric intubation. This was performed without sedation or anesthesia of animals.

In the approximate lethal dose study the compound was diluted with corn oil to deliver a constant amount to the animal. In an effort to decrease variability, corn oil was added to the compound during this study. Corn oil has been used historically in LD₅₀ studies as a carrier for water insoluble compounds.

Observations

Animals were checked daily during the quarantine period. During the course of the study, animals were observed at 0730 and 1530 for the first week and at 0730 for the remaining week for clinical signs of toxicity. Findings are reported later in this report.

Statistical Methods

Because the Bliss Probit analysis is dependent on three data points, and only one animal died, the LD₅₀ and slope could not be determined.

Duration of Study

Animals were quarantined for 9 days. The study continued for 15 days after dosing.

Historical Listing of Study Events

23 Oct 81	45 male and 45 female rats arrived at LAIR. They were sexed, observed for illness, ear tagged and housed in the GLP Suite.
23 Oct 81	Rats were submitted to pathology for quality control.
26-30 Oct and 2 Nov 81	Rats predosed with 1 cc water.
2 Nov 81	Rats out of quarantine, weighed, observed for illness and randomized into groups.
3 Nov 81	Rats were weighed and dosed according to group.
3 - 10 Nov 81	Clinical signs recorded at 0730 and 1530 hr daily.
23,25,30 Oct & 2,3,6,10* 13,17,18 Nov 81	Animals were weighed. * (females only)
11 - 18 Nov 81	Clinical signs were recorded at 0730 hr daily.
16 Nov 81	Feed removed from males.
17 Nov 81	Feed removed from females, males sacrificed, gross pathological observations performed and recorded.
18 Nov 81	Females sacrificed, gross pathological observations performed.

Changes to Original Objectives and Procedures

1. Animals were not fasted. The protocol requested feed to be removed the afternoon before dosing. Due to technician error, feed was removed approximately 0600 hours the day of dosing.

2. Misdosed animals that were sent to necropsy had ingesta in their stomachs. Two male animals received 0.1 ml more volume than the rest of the animals due to the low toxicity of the chemical and the unexpected higher weights (see 1 above). One of two animals was a misdose and was eliminated from further consideration. Due to the large amount (>2 ml/animal) of material administered to each animal, 4 animals were misdosed. One male died 24 hours after misdosing with signs of a central nervous system disorder. One female died 5.5 hours after dosing. One male and one female remained alive after misdosing.

3. On 6 November 1981, several rats were noted to have lost weight or failed to gain the expected 15 ± 5 grams of body weight per day. To check for dose responsiveness of the weight loss, the mean weight per dose group for each weighing day was calculated and graphed. For each dose group, male and females, the mean weight per dose group increased between 3 November and 6 November 1981 (Figures 1 and 2). The affected animals were then considered to be water deprived, and the tips of the automatic waterers were loosened to permit a continuous flow of water.

4. Animals were not observed on the afternoon of 8 November 1981 due to a technician error. Since animals were still showing signs of toxicity, the missed observation probably affected the clinical signs tabulation.

5. LD₅₀ determinations, line slopes and death curves could not be produced from the results of this study (1).

6. Relative humidity was up to 80% for 5 hours on 24 October and 7.5 hours on 7 November 1981 due to steam outage. This is not expected to have any effect.

7. CPT Martha Hanes replaced MAJ Glen Marrs as Principal Investigator when a family emergency occurred before the study was initiated.

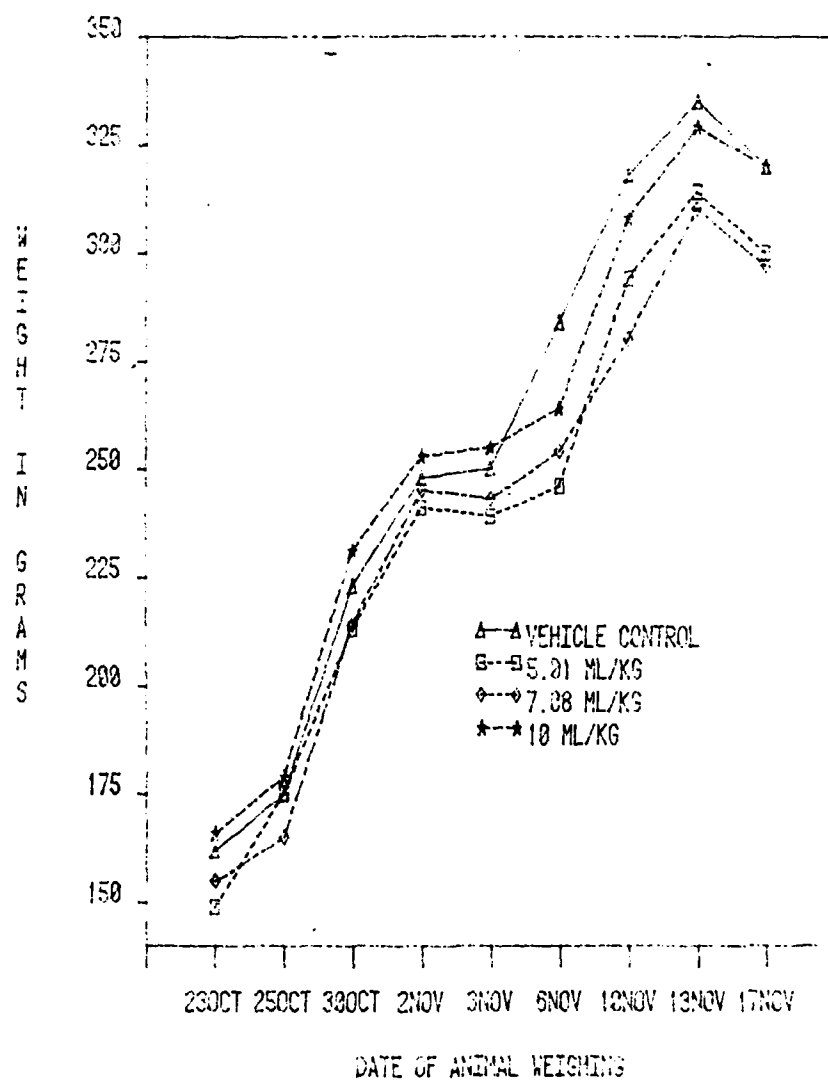


Figure 1: Weight Graph for Male Rats Exposed to CHR 9 on 3 November 1981 (GLP Study 81028).

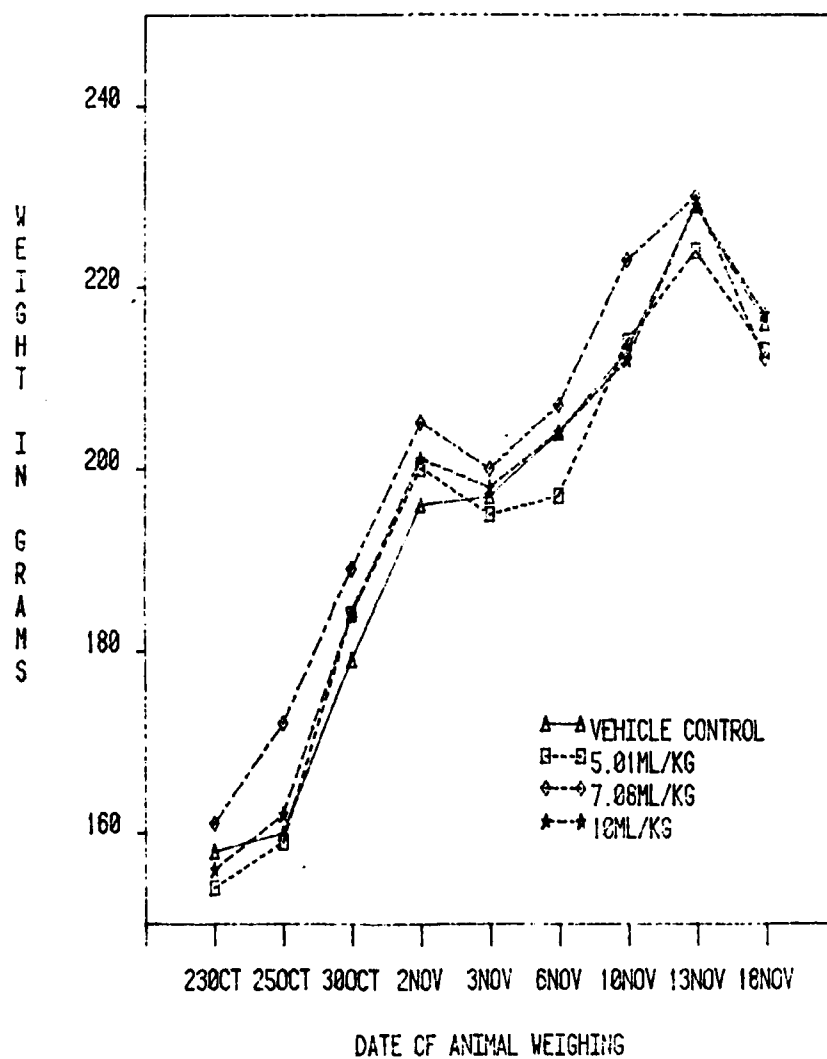


Figure 2: Weight Graph for Female Rats Exposed to CHR 9 on 3 November 1981 (GLP Study 81028).

RESULTS

Mortality

Table 1 lists the compound related deaths by group.

TABLE 1
Compound Related Deaths by Group

Group	Dose Level	Sex	Compound Related Death/ Number in Group
1	Vehicle Control	Male	0/7
		Female	0/7
2	5.01 ml/kg	Male	0/6 ^b
		Female	0/7
3	7.08 ml/kg	Male	0/7
		Female	0/6 ^a
4	10 ml/kg	Male	0/6 ^a
		Female	1/6 ^b

^a Animals eliminated because of misdosing, D8100667 (Group 4) and D8100678 (Group 3), these probably did not receive full dose volume, and survived the 14 day period.

^b Animals eliminated because of misdosing and probable trauma were: D8100671 (Group 2), died 24 hours after dosing and showed signs of Central Nervous System disorder; and D8100711 (Group 4) died 5 1/2 hours after dosing after it had been found collapsed at 1505 hours on 3 November 1981.

* * * * *

The time of death for the one female rat that died from Group 4 (10 ml/kg) was less than 48 hours after dosing.

Clinical Observation

The first week, animals were observed for clinical signs twice a day. They were observed in and out of their cages, and upon replacement into their cages, for signs of toxicity or altered function. At the termination of the two-week observation period the data were summarized by hand. Males and females were treated as separate test systems for compilation of data.

Males

Clinical signs were summarized for male rats exposed to CHR 9. There were four dose groups, including a vehicle control. No compound related deaths occurred in any of the dose groups for males.

Respiratory changes were noted in some rats in each group except Group 1 (vehicle control). One of 6 animals in Group 2 (5.0 ml/kg) showed an increase of respiration depth and a decrease in respiration rate that lasted for 4 1/2 days. In Group 3 (7.08 ml/kg), four animals experienced slight transient respiratory changes. Two out of six males in dose Group 4 (10 ml/kg) experienced slight respiratory rate and depth changes of a maximum of 1 1/2 days duration.

Sound production was noted with a high degree of frequency in dose groups 2, 3 and 4 i.e. 3 of 6, 4 of 7, and 3 of 6 animals respectively, for 6 to 72 hours after dosing, a few persisting to 120 hours. Slight piloerection was also quite prevalent, occurring in 3 of 6 (Group 2), 3 of 7 (Group 3) and 4 of 6 (Group 4) animals. Slight inactivity was noted in all four groups, occurring in 1 of 7, 3 of 6, 3 of 7, 1 of 6 rats, Groups 1 through 4 respectively. Slight humpback (hunched over) was noted in 2 of 6 rats in Group 2 and 3 of 7 in Group 3 dose group.

Harderian secretions and other glandular secretions were recorded as "red material" or "stain" and were moderate to marked in a few animals in each group. Yellow and orange stains, located perianally and ventrally, and assumed to be urinary or fecal excrement (with or without metabolic by products of the test compound) were seen in all dose groups. This represents, perhaps, a lethargy on the part of the exposed animals to undergo normal grooming behavior, and possibly the compound stained the rat hair.

Females

The only compound related death occurred approximately 48 hours after dosing; the one death occurred in the female 10 ml/kg dose group. Sound production was noted in the 5.01, 7.08 and 10 ml/kg dose groups with a frequency of 2 of 7, 3 of 6 and 3 of 6 animals, respectively. Slight piloerection and development of a slight to moderate rough coat was noted in Groups 2, 3 and 4. Two of six females in Group 3 and 2 of 6 in Group 4 assumed humpback posture. Animals in all four groups were excited, including two from the vehicle control group. Moderate accumulations of red material in the

head area were noted for animals in Groups 2, 3, and 4. This was probably increased harderian secretions. Yellow material and stains in the perianal and ventral area were noted with a frequency of 1 of 7, 3 of 7, 3 of 6 and 4 of 6 rats in Groups 1, 2, 3 and 4.

Gross Pathological Observations

Animals found dead in the morning were placed in the refrigerator and necropsied by the pathologist on call. Animals that died during the day were necropsied that day. Animals were not dead for more than 12 hours before they were necropsied. Necropsy was performed in accordance with SOP-OP-STX-32.

The pathologist's report appears in Appendix A.

DISCUSSION

The oral toxicity of triethylene glycol monohexyl ether (CHR 9) was tested in male and female rats (2,3,4). Signs of intoxication included increases and decreases in respiratory rates in males, sound production, piloerection, humpback and increased glandular secretion in males and females. Although clinical signs of intoxication were seen at all levels, this chemical demonstrates a very low toxicity.

CONCLUSION

CHR 9 is a relatively nontoxic compound.

RECOMMENDATION

CHR 9 could undergo continued toxicity testing for eventual human use screening, dependent on efficacy findings.

REFERENCES

1. FINNEY, D.J. Probit Analysis. (Third edition). Chapters 3 and 4. Cambridge, England: Cambridge University Press, 1971
2. INTERAGENCY REGULATORY LIAISON GROUP TESTING STANDARDS AND GUIDELINES WORK GROUP. Recommended Guideline for Acute Oral Toxicity Testing in Rodents. January 1981
3. ENVIRONMENTAL PROTECTION AGENCY Good Laboratory Practice proposed regulations (40 CFR 770, 771, 772) and preamble as published in the Federal Register, 22 Aug 78, 9 May 79, 26 Jul 79, and 18 Apr 1980 (45 FR 26373)
4. FOOD AND DRUG ADMINISTRATION Good Laboratory Practice regulations (21 CFR 58) and preamble as published in the Federal Register, 22 Aug 1978 (43 FR 5986-60025).
5. LETTERMAN ARMY INSTITUTE OF RESEARCH, Standard Operating Procedures. LAIR SOP-OP-STX-36

Gross Pathology Summary and Interpretation of GLP Study
81-028, Female Sprague-Dawley Rats.

The death of 1/6* female rats in group 4 (10.00 ml/kg) was attributed to the toxic effect of the tested compound. The death was observed 46 hours after gastric intubation with test compound. None of the female rats in group 2 (5.01 ml/kg), group 3 (7.08 ml/kg), or group 1 (controls) died prior to termination of the study.

The stomach of the rat that died was distended with gas but the rat was severely autolyzed and meaningful interpretation was impossible.

The gross findings of a small thymus and a stomach and small intestine distended with gas in 1 rat in group 3 are considered to be incidental findings that were not related to administration of the test compound.

In summary, the death of 1 rat in group 4 was the only pathologic effect that was most likely due to the single dose gastric intubation with the test compound observed in the female Sprague-Dawley rats used in this study.

Necropsies revealed no test compound related lesions in the female Sprague-Dawley rats that were killed at the termination of the study.

*Number of rats affected/Number of rats in the group.

Glen E. Marrs, Jr.

GLEN E. MARRS, DVM, MS
Diplomate, A.C.V.P.
MAJ, VC
Pathology Services Group
Division of Research Support

29 Mar 82

APPENDIX A

Gross Pathology Summary and Interpretation of GLP Study
81-028, Male Sprague-Dawley Rats.

There were no deaths in the male rats attributed to the toxic effect of the tested compound. None of the male rats in group 4 (10.00 ml/kg), group 2 (5.01 ml/kg), group 3 (7.08 ml/kg), or group 1 (controls) died prior to termination of the study.

The gross findings of dilatation of the right ventricle of the heart in 1 rat in group 2, torsion of the spermatic cord and green material in the perianal area in 1 rat in group 3, and a dilated renal pelvis in 1 rat in group 1 are considered to be incidental lesions that were not related to administration of the test compound.

Necropsies revealed no test compound related lesions in the male Sprague-Dawley rats that were killed at the termination of the study.

Glen E. Harris, Jr.

GLEN E. HARRIS, DVM, MS
Diplomate, A.C.V.P.
MAJ, VC
Pathology Services Group
Division of Research Support

29 March 1982

APPENDIX A
concluded.

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