AD-A016 152

TOXICOLOGICAL EVALUATION OF n-HEXYL CARBORANE, CARBORANYLMETHYLETHYL SULFIDE AND CARBORANYLMETHYLPROPYL SULFIDE

Richard A. Angerhofer, et al

Army Environmental Hygiene Agency
Aberdeen Proving Ground, Maryland

May 1975

303120

TOXICOLOGICAL EVALUATION OF n-HEXYL CARBORANE, CARBORANYLMETHYLETHYL SULFIDE AND CARBORANYLMETHYLPROPYL SULFIDE

STUDY NO. 51-044-74/76
JANUARY 1974 - MAY 1975

Approved for public release; distribution unlimited.

US ARMY
ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MD 21010

45

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER: 51-044-74/76	2. GOVT ACCESSION NO.
3. RECIPIENT'S CATALOG NUMBER	
4. TITLE (and Subtitle): Toxicological Evaluation of n-Hexyl Carborane, Carboranylmethylethyl Sulfide and Carboranylmethylpropyl Sulfide	5. TYPE OF REPORT & PERIOD COVERED: Special Study Jan 74 - May 75
	6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s): RICHARD A. ANGERHOFER MAURICE H. WEEKS CONRAD R. POPE	8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS: US Army Environmental Hygiene Agency Aberdeen Proving Ground, MD 21010	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS: Commander US Army Health Services Command Fort Sam Houston, TX 78234	12. REPORT DATE
	13. NUMBER OF PAGES: 48
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)	15. SECURITY CLASS. (of this report): UNCLASSIFIED
	15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; distribution unlimited.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

n-hexyl carborane	NHC	LD50
carboranylmethylethyl sulfide	Skin irritation studies	Sensitization
carboranylmethylpropyl sulfide	Primary irritation evaluation	Studies
CMES	Nonirritating Concentrations	Prenatal
CMPS	Approximate lethal dose	Toxicity

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The relative toxicities of technical grade n-hexyl carborane (NHC), carboranylmethylethyl sulfide (CMES) and carboranylmethylpropyl sulfide (CMPS) were investigated using rats, guinea pigs, rabbits and dogs. Each compound produced primary irritation when applied to the intact and abraded skin of rabbits. Data indicated little acute toxic hazard would be expected from acute accidental ingestion. Acute vapor and aerosol inhalation exposures of animals resulted experimentally in no deleterious effect from the three compounds. Respiratory irritation with some minimal lung damage and transient eye effects occurred in

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

Block 19. Keywords:

Physiological Studies
Acute Inhalation Vapor Exposures
Acute Inhalation Aerosol Exposures
Subchronic Inhalation Aerosol Exposures
In Vitro Mutagenic Evaluation
Parenteral Administration Studies

Block 20. Abstract:

dogs and rats as a result of repeated exposures to aerosols of NHC for 6 hours per day, 5 days per week for 6 weeks at concentrations of 77 and 245 mg/M^3. NHC and CMPS appeared to be nonmutagenic on the basis of microbial assays, while CMES appeared to be weakly mutagenic.

DEPARTMENT OF THE ARMY
U S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

HSE-LT/WP

15 OCT 1975

TOXICOLOGICAL EVALUATION OF n-HEXYL CARBORANE, CARBORANYLMETHYLETHYL SULFIDE AND CARBORANYLMETHYLPROPYL SULFIDE

STUDY NO. 51-044-74/76
JANUARY 1974 - MAY 1975

ABSTRACT

The relative toxicities of technical grade n-hexyl carborane (NHC), carboranylmethylethyl sulfide (CMES), and carboranylmethylpropyl sulfide (CMPS) were investigated using rats, guinea pigs, rabbits and dogs. Each compound produced primary irritation when applied to the intact and abraded skin of rabbits. Data indicate little acute toxic hazard would be expected from acute accidental ingestion. Acute vapor and aerosol inhalation exposures of animals resulted experimentally in no deleterious effect from the three compounds. Respiratory irritation with some minimal lung damage and transient eye effects occurred in dogs and rats as a result of repeated exposures to aerosols of NHC for 6 hours per day, 5 days per week for 6 weeks at concentrations of 77 and 245 mg/M^3. NHC and CMPS appeared to be nonmutagenic on the basis of microbial assays, while CMES appeared to be weakly mutagenic.

It was recommended that personnel potentially exposed to NHC or CMPS wear protective gloves, coveralls and goggles. Medical surveillance of workers involved in handling these materials should take cognizance of the potential for irritation of the respiratory tract, skin and eyes. Human exposure to CMES should be prevented until carcinogenic risk has been determined by appropriate techniques.

Approved for public release; distribution unlimited.

DEPARTMENT OF THE ARMY
U S. ARMY ENVIRONMENTAL HYG'ENE AGENCY
ABERDEEN PROVING GROUND. MARYLAND 21010

HSE-LT/WP

TOXICOLOGICAL EVALUATION OF N-HEXYL CARBORANE, CARBORANYLMETHYLETHYL SULFIDE AND CARBORANYLMETHYLPROPYL SULFIDE*

STUDY NO. 51-044-74/76
JANUARY 1974 - MAY 1975

1. REFERENCES.

a. Letter, DASG-HCH-O, Office of The Surgeon General, 29 January 1974, subject: Toxicological Evaluation.

b. Letter, AMSMI-RKC, US Army Missile Command, Redstone Arsenal, AL, 19 March 1974, to this Agency.

c. Letter, AMSMI-O, US Army Missile Command, 16 August 1972, subject: Toxicological Evaluation.

d. Letter, AMSMI-O, US Army Missile Command, 28 March 1974, subject: Toxicological Evaluation.

2. PURPOSE. The purpose of this study was to acquire information concerning the toxicity in animals of n-hexyl carborane (NHC), carboranylmethylethyl sulfide (CMES) and carboranylmethylpropyl sulfide (CMPS). This information provides a basis for advising on possible hazards associated with the manufacture of these compounds and safety precautions to be observed in their handling (reference para 1c).

3. BACKGROUND.

a. The United States Army Missile Command is considering using NHC, CMES and CMPS as components in the Army's solid fuel system (reference para 1d). These materials have been synthesized in the laboratory and pilot plants. Propellants prepared from these compounds are processed or mixed at about 140 - 145°F. As presently used in the laboratory and small scale facilities, operating procedures require well ventilated areas with throughput air and with the operator wearing rubber gloves when handling the technical grade carboranes or the carborane containing propellants. If production facilities are expanded, an increased exposure potential will exist. Industrial hygiene and engineering procedures are needed that are based on some knowledge of the toxicology of these compounds in order to control any potential hazards associated with their manufacture and processing into solid fuels.

---

* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals." US Department of Health, Education and Welfare Publication No. (NIH) 74-23, revised 1972 - second printing 1974.

b. A literature search using the data base of the National Library of Medicine and a limited survey of various industrial and governmental laboratories revealed no data on the toxicity of the three subject carboranes.

c. NHC, CMES and CMPS were obtained through Redstone Arsenal, Alabama, from the manufacturer, Olin Corporation, Stamford, CT. NHC is a clear liquid with a musty, acrid odor. The lot numbers of NHC used were H-13179 and H-13166. CMES and CMPS are slightly cloudy liquids having pungent oily odors. The lot numbers used in the tests were H-12722 for CMES and H-12736-2 for CMPS. The three compounds are soluble in organic solvents, such as hexane and acetone, but not soluble in water.

4. SUMMARY OF FINDINGS. The relative toxicity of technical grade NHC, CMES and CMPS was investigated by this Agency using rats, guinea pigs, rabbits and dogs. The three carboranes were found to be primary skin irritants with CMES producing the least severe reaction. The highest nonirritating concentration to the skin was 0.1 percent for each compound. Data indicate that NHC is practically nontoxic when administered orally to rats and that CMES and CMPS are moderately toxic. The intravenous approximate lethal doses (ALD) in rabbits were 150, 320, and 320 mg/kg for NHC, CMES and CMPS, respectively. The three compounds are classified as only slightly toxic when administered dermally to rabbits with NHC being the least toxic. None of the three carboranes caused skin sensitization reactions in guinea pigs. Physiological changes in dogs following intravenous administration of high doses of NHC suggest that the lung may be the major target organ affected. Histologic examination of organs following parenteral administration of NHC, CMPS and CMES to rabbits showed that these compounds caused severe pulmonary edema and hemorrhage in the lower respiratory tract. No prenatal toxicity was observed when NHC was administered orally or by inhalation to pregnant albino rats. Acute 1- and 4-hour aerosol exposures and single 8-hour saturated vapor exposures of the three compounds to rats resulted experimentally in no deleterious effect. Respiratory irritation, with some minimal lung damage and transient eye effects, occurred in rats and dogs as a result of repeated exposures to aerosols of NHC 6 hours per day, 5 days per week for 6 weeks at concentrations of 77 and 245 mg/M^3. In vitro mutagenic studies in microbial assays showed NHC and CMPS to be nonmutagenic on the assays performed while CMES was weakly mutagenic. Definitions of selected terms and abbreviations used in this report are found in Appendix A. Statistical significance in this report has been selected at the .01 level of probability. Infrared spectra of the technical grade compounds are found in Appendix B. A detailed tabular presentation of toxicity data follows:

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
SKIN IRRITATION STUDIES		
Rabbits		
Primary Irritation Evaluation		
Single 24-hour application of NHC, CMES, and CMPS to intact and abraded skin of New Zealand White rabbits.		
0.5 ml technical grade NHC was applied to each of six rabbits.	Very slight edema and very slight erythema of intact and abraded skin were present 24 hours after application. Severe edema and severe erythema were seen after 72 hours. Seven days after application severe edema and severe erythema persisted as well as necrosis and eschar formation. Individual erythema and edema scores ranged from 1 to 4 with modes of 1 and 4, respectively (ref Appendix C).	NHC must be regarded as a primary skin irritant to man with a potential for causing tissue destruction. Personnel should wear skin and eye protection and exercise extreme caution when handling this material.
0.5 ml technical grade CMES was applied to each of six rabbits.	Very slight edema and very slight erythema of intact and abraded skin were present 24 hours after application. Well defined erythema and slight edema were seen after 72 hours. Seven days after application severe erythema and severe edema were observed as well as necrosis and eschar formation. Individual erythema and edema scores of intact skin ranged from 1 to 2 with modes of 1 and 2 and erythema and edema scores of abraded skin ranged from 1 to 4 with a mode of 1 (ref Appendix C).	CMES must be regarded as a primary skin irritant to man with a potential for causing tissue destruction. Extreme caution must be exercised when handling this compound and personnel should wear skin and eye protection.

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
SKIN IRRITATION STUDIES		
Rabbits		
Primary Irritation Evaluation (cont) 0.5 ml technical grade CMPS was applied to each of six rabbits.	Very slight edema and very slight erythema of intact and abraded skin were present 24 hours after application. Severe erythema and slight to severe edema were seen in intact and abraded skin after 72 hours. Seven days after application severe erythema and severe edema were observed as well as necrosis and eschar formation. Individual erythema and edema scores of intact skin ranged from 1 to 2 with modes of 1 and 2 and erythema and edema scores of abraded skin ranged from 1 to 4 with a mode of 1 (ref Appendix C).	CMPS must be regarded as a primary skin irritant to man with a potential for causing tissue destruction. Extreme caution must be exercised when handling this material and personnel should wear skin and eye protection.

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
SKIN IRRITATION STUDIES (cont)		
Determination of Nonirritating Concentration of NHC		
0.01 ml of technical grade NHC applied to intact skin of five rabbits.	Slight erythema and capillary injection noted in four of five rabbits at 24 hours (ref Appendix D).	Personnel coming into contact with technical grade compound should use eye and skin protection.
0.01 ml of 10 percent (w/v) solution of NHC in acetone applied to intact skin of five rabbits.	Capillary injection noted in five of five rabbits at 24 hours.	Personnel coming into contact with this compound at this concentration should use eye and skin protection.
0.01 ml of 1.0 percent (w/v) solution of NHC in acetone applied to intact skin of five rabbits.	Slight capillary injection noted in four of five rabbits at 24 hours.	Compound at this concentration should not cause irritation to human skin, provided it is washed off immediately.
0.01 ml of 0.1 percent (w/v) solution of NHC in acetone applied to intact skin of five rabbits.	No irritation observed.	Not irritating to rabbit skin. The compound at this concentration is not expected to cause irritation to human skin.
0.01 ml of 0.01 percent (w/v) solution of NHC in acetone applied to intact skin of five rabbits.	No irritation observed.	Not irritating to rabbit skin. The compound at this concentration is not expected to cause irritation to human skin.
0.01 ml of acetone applied to intact skin of five rabbits.	No irritation observed.	Acetone itself was not irritating to rabbit skin.

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
SKIN IRRITATION STUDIES (cont)		
Determination of Nonirritating Concentration of CMES		
0.01 ml of technical grade CMES applied to intact skin of five rabbits.	Strong erythema noted in five of five rabbits at 24 hours (ref Appendix D)	Personnel coming into contact with technical grade compound should use eye and skin protection.
0.01 ml of 10 percent (w/v) solution of CMES in acetone applied to intact skin of five rabbits.	Slight erythema in three rabbits; slight capillary injection in two rabbits after 24 hours.	Personnel coming into contact with this compound at this concentration should use eye and skin protection.
0.01 ml of 1.0 percent (w/v) solution of CMES in acetone applied to intact skin of five rabbits.	Slight capillary injection noted in four of five rabbits at 24 hours.	Compound at this concentration should not cause irritation to human skin, provided it is washed off immediately.
0.01 ml of 0.1 percent (w/v) solution of CMES in acetone applied to intact skin of five rabbits.	No irritation observed.	Not irritating to rabbit skin. The compound at this concentration is not expected to cause irritation to human skin.
0.01 ml of 0.01 percent (w/v) solution of CMES in acetone applied to intact skin of five rabbits.	No irritation observed.	Not irritating to rabbit skin. The compound at this concentration is not expected to cause irritation to human skin.
0.01 ml of acetone applied to intact skin of five rabbits.	No irritation observed.	Acetone by itself was not irritating to rabbit skin.

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
SKIN IRRITATION STUDIES (cont)		
Determination of Nonirritating Concentration of CMPS.		
0.01 ml of technical grade CMPS applied to intact skin of five rabbits.	Necrosis in one rabbit, erythema and capillary injection in four rabbits noted at 24 hours. (ref Appendix D).	Personnel coming into contact with technical grade compound should use eye and skin protection.
0.01 ml of 10 percent (w/v) solution of CMPS in acetone applied to intact skin of five rabbits.	Edema in one rabbit and capillary injection in three rabbits noted at 24 hours.	Personnel coming into contact with this compound at this concentration should use eye and skin protection.
0.01 ml of 1.0 percent (w/v) solution of CMPS in acetone applied to intact skin of five rabbits.	Slight capillary injection in one of five rabbits noted at 24 hours.	Compound at this concentration should not cause irritation to human skin, provided it is washed off immediately.
0.01 ml of 0.1 percent (w/v) solution of CMPS in acetone applied to intact skin of five rabbits.	No irritation observed.	Not irritating to rabbit skin. The compound at this concentration is not expected to cause irritation to human skin.
0.01 ml of 0.01 percent (w/v) solution of CMPS in acetone applied to intact skin of five rabbits.	No irritation observed.	Not irritating to rabbit skin. The compound at this concentration is not expected to cause irritation to human skin.
0.01 ml of acetone applied to intact skin of five rabbits.	No irritation observed.	Acetone by itself was not irritating to rabbit skin.

To: Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
APPROXIMATE LETHAL DOSE		
NHC		
Intraperitoneal		
Rat (male) Propylene glycol diluent	ALD - 1900 mg/kg All sublethal dosages tested, 112-446 mg/kg, caused some degree of decreased locomotor activity.	
Oral		
Rat (male) Propylene glycol diluent	ALL - > 9700 mg/kg	Presents little lethal hazard from acute ingestion.
Rat (female) Propylene glycol diluent	ALD - > 9700 mg/kg	
Intravenous		
Rabbit (male)	ALD - 150 mg/kg Lethal dosages caused lethargy, convulsions, and bloody discharge from nose. Necropsies revealed excess fluid around brain of animals which had died.	

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
APPROXIMATE LETHAL DOSE		
CMES		
Oral		
Rat (male) Propylene glycol diluent	ALD - 3900 mg/kg Signs before death were decreased activity, salivation, tremors and convulsions.	Presents little lethal hazard from acute ingestion.
Rat (female) Propylene glycol diluent	ALD - 850 mg/kg Signs before death were decreased activity, salivation, tremors and convulsions.	Female rats seem to be more sensitive than male rats to lethal effects of CMES. Sex may influence action of compound.
Intravenous		
Rabbit (male)	ALD - 320 mg/kg Signs before death were bloody discharge from nose and convulsions. Necropsies performed 14 days after dosing revealed no gross changes.	

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
APPROXIMATE LETHAL DOSE		
CMPS		
Oral		
Rat (male) Propylene glycol diluent	ALD - 1900 mg/kg Signs before death were decreased activity, salivation, tremors and convulsions.	Presents little lethal hazard from acute ingestion.
Rat (female) Propylene glycol diluent	ALD - 1900 mg/kg Signs before death were decreased activity, salivation, tremors and convulsions.	
Intravenous		
Rabbit (male)	ALD - 320 mg/kg Signs before death were bloody discharge from nose and convulsions. Necropsies performed 14 days after dosing revealed no gross changes.	

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
LD-50 ORAL Rats (male)		
CMES Six rats per dosage level propylene glycol diluent	LD50 - 2085 mg/kg (1851-2348 mg/kg)* Death occurred at dosages of 1585 mg/kg and higher as well as signs of decreased activity, discharge from eyes and nose, salivation, tremors and convulsions. Necropsy of surviving rats after 14 days revealed no gross abnormalities.	CMES and CMPS are classified as moderately toxic compounds. Parameters of classification found in Appendix E.
CMPS Six rats per dosage level propylene glycol diluent	LD50-3440 mg/kg (2800-4230 mg/kg)* Death occurred at dosages of 2000 mg/kg and higher as well as signs of decreased activity, discharge from eyes and nose, salivation, tremors and convulsions. Necropsy of surviving rats after 14 days revealed no gross abnormalities.	

* 95 percent confidence limits.

Tox Study No. 53-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
LD-50 DERMAL		
Rabbits (male) NHC		
Four rabbits per dosage level - technical grade material.	LD-50 > 10 ml/kg No deaths at dosage levels up to 10 ml/kg. Signs involved only severe primary skin irritation. Necropsy of surviving rabbits after 14 days revealed no gross abnormalities.	Presents little lethal hazard from acute accidental contact. Causes local skin damage and NHC should be prevented from coming in contact with the skin and if accidentally exposed should be washed off immediately. Dermally, NHC can be classified as a slightly toxic compound. Parameters of classification are found in Appendix E.
CMES		
Four rabbits per dosage level - technical grade material	LD-50 3.89 ml/kg (0.9 - 16.0 mg/kg)* Deaths occurred at dosage levels of 3 and 10 ml/kg at 1 to 7 days after dosing as well as signs of decreased activity. Mild to severe primary skin irritation was noted at all dosage levels.	Compound causes skin damage and should be prevented from coming in contact with the skin and if accidentally exposed should be washed off immediately. Dermally, CMES is classified as a slightly toxic compound. Parameters of classification are found in Appendix E.
CMPS		
Four rabbits per dosage level - technical grade material.	LD-50 3.16 ml/kg (1.6-6.4 mg/kg)* Deaths occurred at 3 and 10 ml/kg dosage levels 4 to 5 days after application. No other systemic signs were observed. Mild to severe primary skin irritation was noted at all dosage levels.	Compound causes skin damage and should be prevented from coming in contact with the skin and if accidentally exposed should be washed off immediately. Dermally, CMPS is classified as a slightly toxic compound. Parameters of classification are found in Apperdix E.

* 95 percent confidence limits

Tox Study No. 52-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
SENSITIZATION STUDIES		
Guinea Pigs (Male)		
Intradermal injections of 0.1 ml of suspension (w/v) of NHC, CMES, CMPS or dinitrochlorobenzene (DNCB) in a mixture containing one volume of propylene glycol and 29 volumes of normal saline.		
10 test guinea pigs receiving and challenged with an overt irritant concentration of a 1.0 percent suspension of NHC.	Challenge dose of test compounds (first intradermal injection) at concentrations of 1.0 and 0.1 percent for NHC and 0.1 percent for CMES and CMPS produced no greater response than did prior sensitizing doses.	Test compounds NHC, CMES and CMPS did not sensitize guinea pigs and would not be expected to produce a sensitization reaction in humans.
10 test guinea pigs receiving and challenged with threshold irritant concentration of a 0.1 percent suspension of NHC.		
10 test guinea pigs receiving and challenged with threshold irritant concentration of a 0.1 percent suspension of CMES.		
10 test guinea pigs receiving and challenged with threshold irritant concentration of a 0.1 percent suspension of CMPS.		
10 positive control guinea pigs receiving and challenged with a 0.1 percent suspension of DNCB.		
25 cage control guinea pigs: five each receiving test compound without prior sensitizing doses; five receiving challenge dose of DNCB without prior sensitizing dose.		

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
PRENATAL TOXICITY STUDIES Rats		
NHC, CMES, CBPS, sodium salicylate, corn oil and propylene glycol were administered orally each to groups of 20 to 30 rats daily from day 6 through day 16 of gestation. Day 0 of gestation was counted as the day sperm was found in the vaginal smear. The females were sacrificed on day 20 of gestation by intracardiac injection of sodium pentobarbital. The reproductive tracts were exposed by laparotomy, and the corpora lutea, implantation sites and resorption sites were recorded. The fetuses were removed, examined for gross abnormalities and the sex and weight of each fetus recorded. All grossly abnormal fetuses and 50 percent of the apparently normal fetuses were further studied as Bouin-fixed, freehand sections for soft tissue abnormalities or after alizarin red S staining for skeletal malformations. Daily oral dosages were: 100 mg/kg NHC 1000 mg/kg NHC 200 mg/kg sodium salicylate (positive control) 1 ml/kg corn oil	Fetuses from NHC treated females showed no difference in fetal resorptions or male/female sex ratios nor gross normality of the fetus, fetal skeleton or soft tissue from solvent controls. Significantly, lower average fetal weights were observed in NHC and salicylate treated rats, also salicylate treated rats showed fetuses with exposed vertebral columns. No other fetal abnormalities were observed in any fetus. No maternal deaths occurred during the test in the solvent control or NHC-treated, however, 2 in the salicylated-treated died prior to termination of the test. Fetuses from CMES-treated females showed no difference in fetal resorption or male/female sex ratio nor gross normality of the fetus, fetal skeleton or soft tissue from solvent controls. Significantly lower average fetal weights were observed in CMES-treated females. No other fetal abnormalities were observed in any fetus. All females treated with 240 mg/kg/day and 13 out of 22 treated with 120 mg/kg/day died during the dosing period. However, the weight gain of the surviving females was not significantly different from solvent controls.	N-hexyl carborane administered to pregnant rats during gestation by intragastric intubation does not appear to present any significant hazard to the developing fetus. Carboranylmethylethyl sulfide administered to pregnant rats during gestation by intragastric intubation does not appear to present any significant hazard to the developing fetus.

Tox Study No. 51-044-74/76, Jan 71 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
PRENATAL TOXICITY STUDIES (cont) Rats 60 mg/kg CMES 120 mg/kg CMES 240 mg/kg CMES 1 ml/kg corn oil 190 mg/kg CMPS 380 mg/kg CMPS 1 ml/kg propylene glycol	Fetuses from CMPS-treated females showed no difference in male/female sex ratios, nor gross normality of the fetus, fetal skeleton and soft tissue from solvent controls. However, the fetuses showed significantly lower average fetal weights and an increase in the number of fetal resorptions. No other fetal abnormalities were observed in any fetus. All females receiving 380 mg/kg/day and 17 out of 30 receiving 190 mg/kg/day died during the dosing period. Maternal weight gain of the surviving females were significantly lower from solvent control.	Carboranylmethylpropyl sulfide administered to pregnant rats during gestation appears to have the potential for possible embryotoxin. Additional finite studies would be necessary to clearly delineate this toxic property or action to estimate its overall hazard potential to humans.

Tox Study No. 1-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
PHYSIOLOGICAL STUDIES		
Dogs		
Studies were made to determine the physiological effects of N-hexyl carborane (NHC in dogs following intravenous) administration.		
One beagle was given NHC, 25 mg/kg, at 30-minute intervals for a total dose of 200 mg/kg. Heart rate, blood pressure, respiration rate and electrocardiogram (EKG) were recorded. Arterial blood was taken every 30 minutes for blood gas analysis and for red and white blood cell counts, hematocrit and mean cell volume.	Signs included bradycardia, lowering of blood pressure, increased respiration rate (decreased tidal volume), increase in the PCO_2 and a decrease in PO_2 and pH. There was no significant change in the white or red blood cell count nor in the hematocrit or mean cell volume. Necropsy revealed massive pulmonary edema and hemorrhage with capillary destruction.	Findings suggest that the lung is the primary target organ for lethal effects observed with this compound.
One beagle was given NHC, 50 mg/kg, at 30-minute intervals for a total dose of 100 mg/kg. Heart rate, blood pressure, respiration rate and EKG were recorded.	Signs included bradycardia, lowering of blood pressure, increased respiration rate (decreased tidal volume) and increase in height of R and T wave of EKG. The animal died 26 minutes after the second injection of 50 mg/kg. Necropsy revealed pulmonary damage discussed above.	Findings suggest that the lung is the target organ for the lethal effects observed with this compound.
One beagle was given NHC, 50 mg/kg, at 30-minute intervals for a total dose of 200 mg/kg. Heart rate, blood pressure, respiratory rate and depth, EKG and cerebrospinal fluid pressure were recorded. Arterial and venous blood was sampled for blood gas analysis.	Signs included bradycardia, lowering of blood pressure, increased respiratory rate (decreased tidal volume), increase in arterial PCO_2 and a decrease in PO_2 and PH. Cerebrospinal fluid pressure was normal for two hours and showed an increase only when the animal was in its terminal stage.	Findings suggest that the lung is the target organ for the lethal effect observed with this compound.
One beagle was given NHC, 50 mg/kg, at 30-minute intervals for a total dose of 200 mg/kg. Heart rate, blood pressure, respiration rate and depth and EKG were recorded. Arterial and venous blood was sampled for blood gas analysis.	Signs included bradycardia, lowering of blood pressure, increased respiration rate (decreased tidal volume), increased in arterial PCO_2 and a decrease in PO_2 and pH. Responses to injected epinephrine and nikethamide remained normal.	Findings suggest that the compound causes pulmonary edema and hemmorhage when given by the intravenous route. Findings suggest the lung as target organ.

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
ACUTE INHALATION VAPOR EXPOSURES SINGLE 8-HOUR SATURATED VAPOR EXPOSURES		
Rats		
Groups of six male rats each were exposed to saturated vapors of NHC, CMES, and CMPS. Dispersion bubbler was held at 24°C.	Nominal chamber concentrations were: NHC - 0.0 mg/l CMES - 0.104 mg/l CMPS - 0.104 mg/l	NHC has a very low volatility and should present no hazard at room temperature due to the inhalation of vapors.
Control groups of six male rats each were exposed to chamber air only.	Animals from all groups showed no signs of toxicity during exposure and for 14 days thereafter. Body weight gain and organ to body weight ratios of the exposed rats were not significantly different.	Vapors of CMES and CMPS at low concentrations and room temperature present little potential hazard from acute inhalation exposure.
Groups of six male rats each were: exposed to saturated vapors of NHC, CMES, and CMPS. Dispersion bubblers were held at 65°C.	Nominal chamber concentrations were NHC - 0.104 mg/l CMES - 0.521 mg/l CMPS - 0.416 mg/l	Vapors of NHC, CMES and CMPS present little potential hazard from acute inhalation exposure.
Control groups of six male rats each were exposed to chamber air only.	Animals from all groups showed no signs of toxicity during exposure and for 14 days thereafter. Body weight gain and organ to body weight ratios of exposed rats compared to control rats were not significantly different.	Vapor exposure at room temperature for NHC, CMES and CMPS over this period of time resulted experimentally in no deleterious effect.
	No chemically induced histopathological lesions were observed in the brain, heart, nasal turbinates, liver, spleen, kidneys or testes of rats exposed to NHC, CMES and CMPS vapors. Emphysema was observed in the lungs of five of six rats exposed to CMES at 65°C and in the lungs of three of five rats exposed to NHC at 66°C. Emphysema was not observed in the six rats exposed to CMPS at 65°C. No chemically induced histopathological lesions were observed in the lungs of rats exposed to NHC, CMES and CMPS vapors at 24°C.	Vapor exposure at 65°C for CMES and NHC over this period of time produced emphysema. Vapor exposure at 65°C for CMPS over this period of time resulted experimentally in no deleterious effect.

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
ACUTE INHALATION AEROSOL EXPOSURES SINGLE 1-HOUR EXPOSURE Rats		
Groups of 10 male rats each were exposed to aerosols of NHC, CMES and CMPS. A Dautrebande D_{30} aerosol generator was used to disperse each compound at 24°C.	Nominal chamber concentrations were: NHC - 2.02 mg/l CMES - 2.08 mg/l CMPS - 2.08 mg/l	Aerosol exposure at noted concentrations of NHC, CMES and CMPS over this period of time resulted experimentally in no deleterious effect.
A control group for each compound of five males was exposed to chamber air only.	Animals from all groups were quiet during exposure. No signs were seen post exposure and no deaths. No significant changes were observed in body weight between control and exposed groups of animals over a 14-day post exposure period. At necropsy, there were no gross lesions attributable to the inhalation of any of the test substances. No chemically induced histopathologic changes were noted in the brain, nasal turbinates, lung, heart, liver, kidney, spleen or testes of rats exposed to acute 1-hour aerosol exposures to NHC, CMES and CMPS.	

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
ACUTE INHALATION AEROSOL EXPOSURES *SINGLE 4-HOUR EXPOSURE* Rats		
Groups of 10 male rats each were exposed to aerosols of NHC, CMES and CMPS at two different concentrations each. A Dautrebande D_{30} aerosol generator was used to disperse each compound at 24°.	Average compound concentration for Exposure #1 NHC - 1.35 mg/l CMES - 0.87 mg/l CMPS - 0.86 mg/l Exposure #2 NHC - 2.19 mg/l CMES - 1.91 mg/l CMPS - 1.48 mg/l	Aerosol exposures at noted concentrations of NHC over this period of time resulted experimentally in no deleterious effect. This compound should present little potential hazard from acute inhalation aerosol exposure.
Control groups of five male rats were exposed to chamber air only.	Animals from all groups were quiet during exposure and showed no signs of toxicity during exposure and for 14 days thereafter. Body weight gain and organ to body weight ratios of exposed rats compared to control rats were not significantly different.	Aerosol exposures at noted concentrations of CMES and CMPS over this period of time resulted experimentally in potentiating the appearance of chronic respiratory disease in the test rats.
Exposure concentrations were based upon analysis of chamber atmospheric samples collected during each exposure using in-line midget impingers, each containing 10 ml n-hexane. Samples were analyzed for each specific compound by means of gas chromatography (ref Appendix F).	No chemically induced histopathological lesions were observed in the brain, heart, trachea, liver, spleen, kidneys or testes of rats exposed to NHC, CMES and CMPS aerosols. Histological differences were not observed between groups of lungs from controls and the two aerosol levels of NHC. Histologically, pneumonitis was present in 4 of 10 test rats and in 0 of 5 controls for CMPS at 0.86 mg/l. Histologically, pneumonitis was present in 3 of 10 test rats and 1 of 5 controls for CMPS at 1.48 mg/l. Histologically, pneumonitis was present in 3 of 10 test rats and in 1 of 5 controls for CMES at 0.87 mg/l. Histologically, pneumonitis was present in 3 of 20 test rats and in 0 of 4 controls for CMES at 1.91 mg/l.	

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
SUBCHRONIC INHALATION AEROSOL EXPOSURES		
NHC		
Groups of male rats and male dogs were exposed to aerosols of NHC, 6 hours per day, 5 days per week for 6 weeks. NHC was aerosolized by use of a Laskin generator for a low concentration chamber (77 mg/M^3). A high concentration chamber (245 mg/M^3) was also run using a Spraying Systems Aerosol Nozzle #1650 for compound dispersion. Chamber air samples for both concentrations were aralyzed by gas chromatography (ref Appendix F). All animals used in these experiments were observed during a preliminary period. Cont ol groups exposed to chamber air were matched with each treatment group in respect to number, age, sex and body weight. Animals were weighed weekly and observed daily for general appearance and behavior. Periodic clinical and hematological examinations were made on dogs for pre-exposure control values and during the course of the experimental period. Dogs were sacrificed and necropsied at the end of 6 weeks while 10 rats were necropsied at 3 weeks and 6 weeks of the exposure period. One group of 10 exposed and 10 controls was held for 4 weeks post exposure before necropsy. The following organs were removed at necropsy and processed for histopathological examination: brain, pituitary eyes, nasal turbinates, thyroid, heart, trachea, esophagus, stomach, small and large intestines, pancreas, liver, kidneys, adrenals, testes, prostate, skeletal muscle and bone.		

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
SUBCHRONIC INHALATION AEROSOL EXPOSURES (Cont)		
NHC		
Three male beagle dogs and 30 male albino rats exposed to either 77 mg/M^3 or 245 mg/M^3 of NHC. Three male beagle dogs and 30 male albino rats similarly exposed to air only (chamber controls). Exposures lasted 6 hours per day, 5 days per week for 6 weeks.	Dogs and rats exposed to aerosols of NHC (77 or 245 mg/M^3) showed gasping and excessive preening during each exposure in the first week. These signs disappeared overnight. No clinically significant changes were found in the following blood parameters measured in dogs: erythrocyte and plasma cholinesterase, alkaline phosphatase, blood urea nitrogen, hematocrit, erythrocyte count and mean cell volume. No significant organ to body weight changes between test and control rats were noted. No chemically induced gross or histopathological lesions were observed except in lung tissue sections of dogs. Lungs of NHC-exposed dogs showed areas of interstitial pneumonitis, indicative of developing emphysema. Control dog lungs were clear.	Subchronic exposures to aerosols of NHC may produce transitory respiratory irritation and such exposures may result in progressive pulmonary damage.

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
SUBCHRONIC INHALATION AEROSOL EXPOSURES (Cont)		
NHC		
Prenatal Toxicity Study Group NHC exposed (77 mg/M^3) A group of 10 pregnant rats was exposed to NHC (77 mg/M^3) for 6 hours a day from days 6-10 and 13-17 of gestation (day 0 is day sperm was found in a vaginal smear). A group of 10 pregnant chamber controls was treated in the same manner. NHC exposed (245 mg/M^3) A group of 10 pregnant rats was exposed to NHC (245 mg/M^3) for 6 hours a day from days 6-10 and 13-17 of gestation. A group of 10 pregnant chamber controls was treated in the same manner.	Observations made on fetal resorptions, fetal male and female sex ratio and gross normality of the fetus showed NHC exposed to be no different from the chamber controls. These observations hold true for both exposure concentrations.	n-hexyl carborane inhaled by pregnant rats during gestation does not appear to present any significant hazard to the developing fetus at concentrations of 77 and 245 mg/M^3.

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
SUBCHRONIC INHALATION AEROSOL STUDIES		
NHC Aerosol (high and low concentrations)		
Behavioral Toxicity Study Group		
NHC exposed (77 mg/M^3) A group of six pretrained rats was exposed to NHC, 77µg/l, 6 hours per day, 5 days per week for 7 exposure days. Animals were given water for 1 hour only each day as water was the reward for stimulus response. Responses were tested pre-exposure and after days 1 and 7 of exposure. A group of six chamber controls was treated in the same manner.	No significant change in response to stimulus was noted between baseline rate of response and post exposure rate of response of control and exposed animals.	NHC presents no hazard to the behavior of trained rats exposed at a concentration of 77 mg/M^3.
NHC exposed (245 mg/M^3) A group of six pretrained rats was exposed to NHC, 77µg/l, 6 hours per day, 5 days per week for 30 exposure days. Animals were given water for 1 hour only each day as water was the reward for stimulus response. Responses were tested pre-exposure and after 30 days exposure. A group of six chamber controls was treated in the same manner.	An increase in response to stimulus was observed at 30 days in the exposed group. The chamber controls showed no consistent rise or fall in individual rates of responding.	NHC aerosols of a concentration of 245 mg/M^3 may cause an increase in thirst in rats.

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
IN VITRO MUTAGENIC EVALUATION* MICROORGANISMS		
One strain of yeast, saccharomyces (D4) and three strains of Salmonella typhimurium (TA-1535, TA-1537 and TA-1538) were used in evaluating the mutagenic potential of NHC, CMES and CMPS. Tissue homogenates of liver, lung and testes from rat, mouse and monkey were used as the activators in the activation system, and no tissues were added to the non-activated system. Positive and solvent controls were included. All plates were incubated at 37°C for 4 days and then scored for chromosomal changes.	NHC - The results of the nonactivation assays were negative. In the activation studies, the initial run with strain TA-1535 indicated substantial mutagenic activity. Repeat tests were conducted, but could not confirm the mutagenicity. The reasons for this first abnormal response were not apparent.	This compound appeared to be nonmutagenic on the assays performed.
	CMES - The results of the nonactivation assays were negative. The results of the activation studies indicate that, except for Salmonella typhimurium TA-1535 all other indicator strains are negative. A consistent, weak response was obtained in tests when CMES was activated by exposure to liver tissues of rats, mice and monkeys.	This compound appeared to be weakly mutagenic for indicator strain TA-1535 in activation assays. Further work to clarify mutagenic potential of this compound is necessary.
	CMPS - The results of the nonactivation and activation studies were negative.	This compound appeared to be nonmutagenic in the assays performed.

* Work contracted to Litton Bionetics, Kensington, Maryland (LBI Project #2512).

Tox Study No. 52-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
PARENTERAL ADMINISTRATION STUDIES		
Rabbits		
Sixteen male New Zealand White rabbits were used to determine histologically the location of parenterally administered NHC, CMES and CMPS. The test compounds were administered to the rabbits, signs were allowed to develop, the animals were euthanized and frozen sections of lung, liver, kidney and spleen were stained with Oil Red O. Prior to the experiment, it was determined that Oil Red O would stain the carborane materials.		
NHC		
Two rabbits served as controls and required no compound.	Histological lesions were not present in the Oil Red O treated frozen tissue sections of lung, spleen, kidney or liver.	Parenterally administered NHC in rabbits is capable of causing death via lower respiratory tract damage by destroying the integrity of the alveolar capillary wall.
Two rabbits served as solvent controls. One received an intravenous injection of mineral oil, 300 mg/kg. One received an intraperitoneal injection of mineral oil, 1000 mg/kg.	The frozen tissue sections of lungs from mineral oil treated rabbits contained Oil Red O positive droplets in capillaries that often distended the walls of these vessels Alveolar edema was also present.	
Two rabbits received an intravenous injection of NHC, 300 mg/kg. Two rabbits received an intraperitoneal injection of NHC, 1000 mg/kg.	The frozen tissue section of lung from all NHC treated rabbits had diffuse areas of venule and capillary congestion. The alveoli contained Oil Red O positive droplets and were surrounded by edematous and hemorrhagic areas. The Oil Red O positive material was present in the vascular channels of the spleen and in the veins of the kidney. Lesions were not observed in the frozen sections of liver. There was no evidence of fat embolism.	

Tox Study No. 51-044-74/76, Jan 74 - May 75

TABULAR PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
PARENTERAL ADMINISTRATION STUDIES (cont)		
Rabbits		
CMES		
Two rabbits received an intravenous injection of CMES, 320 mg/kg.	The frozen tissue sections of lung from all CMES tested rabbits had diffuse areas of venule and capillary congestion. The alveoli contained Oil Red O positive droplets and were surrounded by areas of edema and hemorrhage. These lesions were similar to but of less severity than those observed for NHC. There was no evidence of fat embolism.	Parenterally administered CMES in rabbits is capable of causing death via lower respiratory tract damage by destroying the integrity of the capillary wall.
Two rabbits received an intraperitoneal injection of CMES, 320 mg/kg.		
CMPS		
Two rabbits received an intravenous injection of CMPS, 320 mg/kg.	The frozen tissue sections of lung from all CMPS treated rabbits had diffuse areas of venule and capillary congestion surrounded by areas of edema and hemorrhage. These lesions were similar to but of less severity than those observed for NHC. There was no evidence of fat embolism.	Parenterally administered CMPS in rabbits is capable of causing death via lower respiratory tract damage by destroying the integrity of the capillary wall.
Two rabbits received an intraperitoneal injection of CMPS, 320 mg/kg.		

5. DISCUSSION.

a. Animal data from skin irritation studies indicate that technical grade NHC, CMES and CMPS should be handled with caution, using skin and eye protective equipment. Any of the compounds coming into contact with unprotected skin or eyes should be removed immediately.

b. Animal exposures to vapor concentrations of 100 mg/M^3 NHC, 500 mg/M^3 CMES and 400 mg/M^3 CMPS, suggest little acute hazard to man from short single exposures at these concentrations. NHC appears to have the lowest vapor pressure of the three compounds and should present the least potential inhalation hazard.

c. Subchronic (6 week) exposures of rats and dogs to aerosols of NHC at concentrations of 77 mg/M^3 and 245 mg/M^3 caused signs of eye discomfort and respiratory irritation with some minimal lung damage, but no significant changes in hematology or blood chemistry. These findings show that the major health hazard to be expected to man from daily inhalation of NHC at these concentrations would probably be eye and respiratory tract irritation.

d. At the present time, good industrial practices would indicate that mechanical control of vapors and aerosols of the carborane compounds in the working area would be necessary to contain and prevent possible exposure hazards to man. While environmental levels have not been established for airborne concentrations of NHC, the most likely processes requiring control are those in which fogs or mists are evolved or where hot solutions of NHC are employed.

e. Physiological data from dogs receiving NHC intravenously show that anoxia is the primary cause of death. This is probably due to an accumulation of the compound in the alveolar capillary structures causing a mechanical obstruction of the oxygen transfer system.

6. CONCLUSION. Evaluation of toxicity data on rabbits, rats, guinea pigs and dogs indicates that with appropriate safety precautions, technical grade NHC, CMES and CMPS should present little acute toxic hazard to man. NHC appears to be the least toxic of the three compounds studied. NHC and CMPS appear to be nonmutagenic on the basis of microbial assays, where CMES appeared to be weakly mutagenic.

7. RECOMMENDATIONS.

a. Human exposure to CMES should be prevented until its genetic hazard has been determined by appropriate techniques.

b. Personnel potentially exposed to the technical grade liquids of NHC or CMPS must wear coveralls, and skin and eye protective devices.

c. Medical surveillance of workers involved with these compounds should take cognizance of the potential for irritation of the skin, eyes and respiratory tract.

d. Inhalation exposure to vapors and aerosols of NHC, CMES and CMPS should be controlled by implementation of good industrial hygiene ventilation programs. Local exhaust ventilation may be required in operations where fogs and mists are evolved or where hot solutions are used.

e. Personnel with respiratory disorders should avoid direct exposure to airborne concentrations of NHC, CMES and CMPS.

f. The recommendation given in previous guidance (reference paragraph 1c) relevant to the procedures and precautions associated with the use of NHC and CMPS based upon the parent compound, decaborane, do not seem necessary based upon the present toxicological data generated by this Agency.

Richard A. Angerhofer
RICHARD A. ANGERHOFER
Biologist
Toxicology Division

Conrad R. Pope
CONRAD R. POPE
MAJ, VC
Veterinary Pathologist
Toxicology Division

MAURICE H. WEEKS
Pharmacologist
Toxicology Division

APPROVED:

Conrad R. Pope
ARTHUR H. MC CREESH, Ph.D.
Chief, Toxicology Division

Charles R. Ritchey
CHARLES R. RITCHEY
LTC, MSC
Director, Laboratory Services

APPENDIX A

GLOSSARY OF RECURRING DEFINITIONS, ABBREVIATIONS AND SYMBOLS USED BY THE TOXICOLOGY DIVISION, USAEHA

Definitions of medical terms and abbreviations used in this report are in agreement with the New Gould Medical Dictionary, Second Edition, published by the Blakiston Division of McGraw-Hill Book Company, Inc. Statistical terms and abbreviations are in agreement with those found in J. Maxwell Little's, An Introduction to the Experimental Method, 1961, Burgess Publishing Company, Minneapolis, Minn. The following terms and abbreviations are either not found in the above references or have been modified to fit the special purposes of this report. Some of the items have been included below for special emphasis.

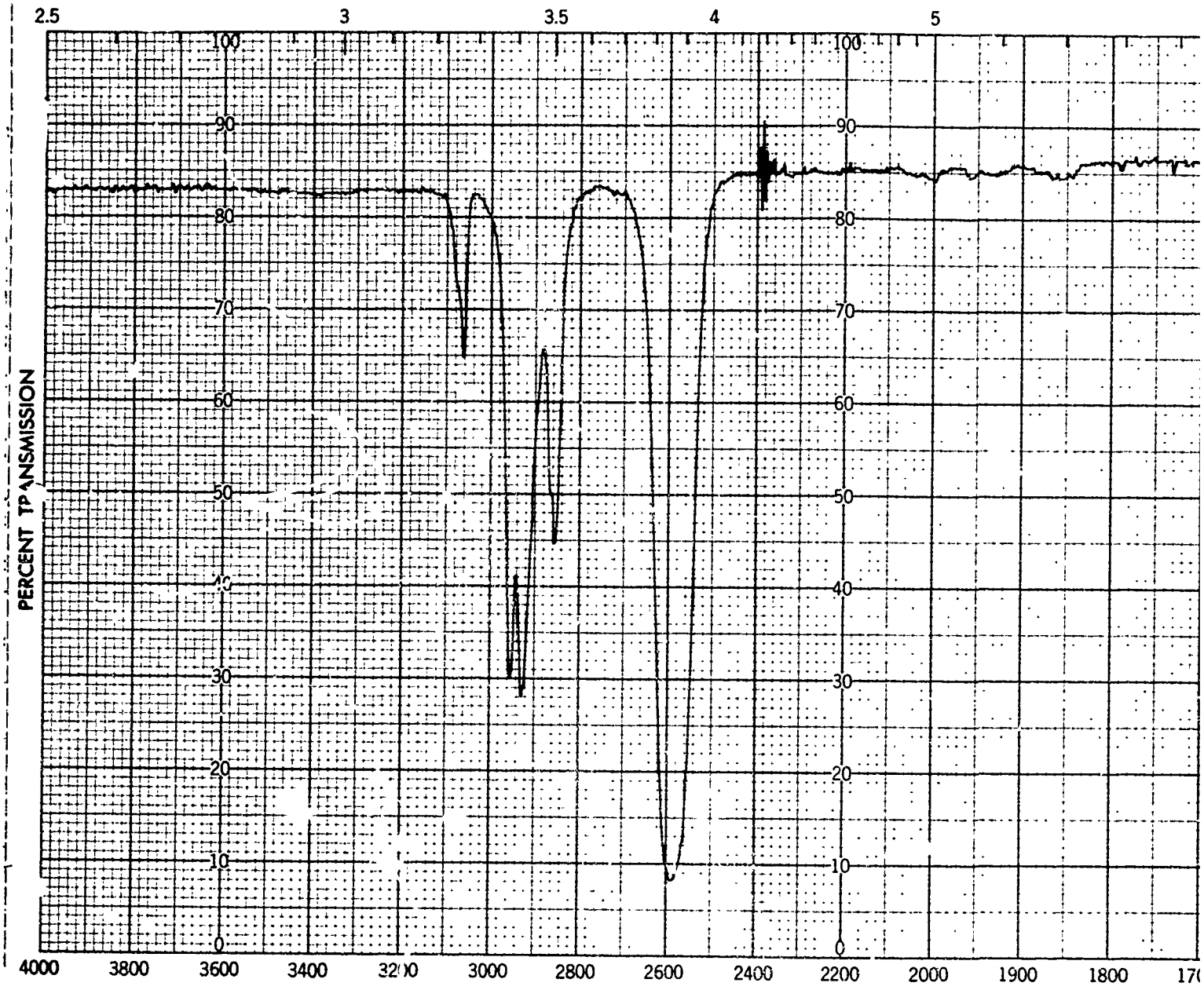
DEFINITIONS

WORD	DEFINITION
Acute Exposure	One exposure to exogenous test material for no longer than 24 hours. Animals are normally observed for 14 days after exposure.
Approximate Lethal Dose	In range finding the first dose of the lowest series of three ascending doses (each being 50% higher in concentration than the previous) all of which produce fatalities.
Hazard Evaluation	A study performed to estimate the degree of danger associated with the use of a material under specified conditions of use.
Primary Irritation	A local inflammatory reaction of the skin, produced by a compound, which does not produce destruction or irreversible change at the site of contact.
Skin Sensitizer	A compound which produces an allergic dermatitis under the conditions of test.
Subchronic Exposure	Repeated daily or constant exposure to a test material for no longer than 59 days or less than 2 days. Post observation period will vary.
Technical Grade Compound	As produced by the manufacturers of their commercial compound; definition dependent upon manufacturers criteria.

ABBREVIATIONS

ABBREVIATION	MEANING
ALD	approximate lethal dose
BUN	blood urea nitrogen
ChE	cholinesterase
CMES	carboranylmethylethyl sulfide
CMPS	carboranylmethylpropyl sulfide
>	is greater than
LD_{50}	median lethal dose
µg/l	micrograms per liter
NHC	n-hexyl carborane

TOX STUDY NO. 51-044-74/76, JAN 74 - MAY 75

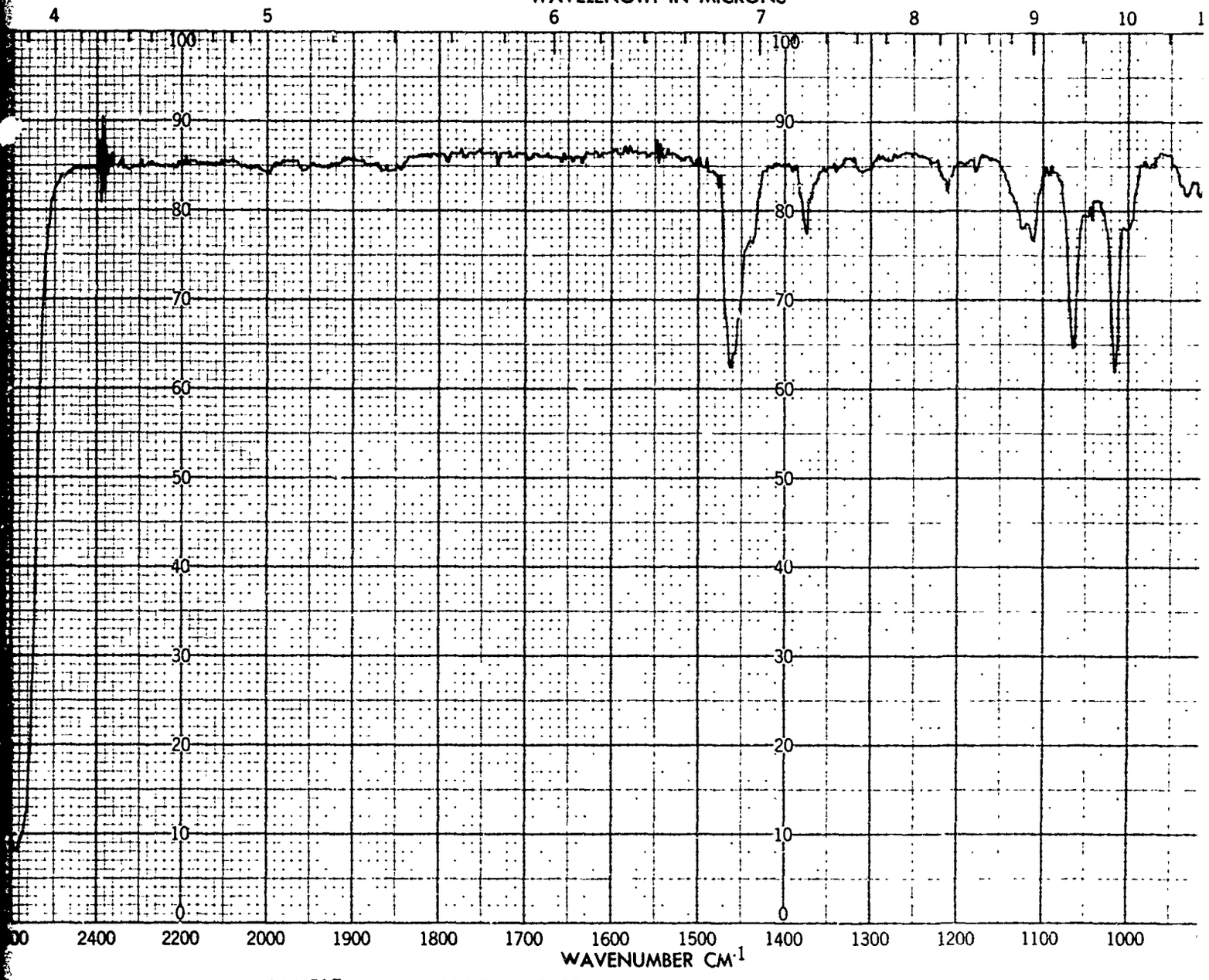


SAMPLE: N-HEXYL

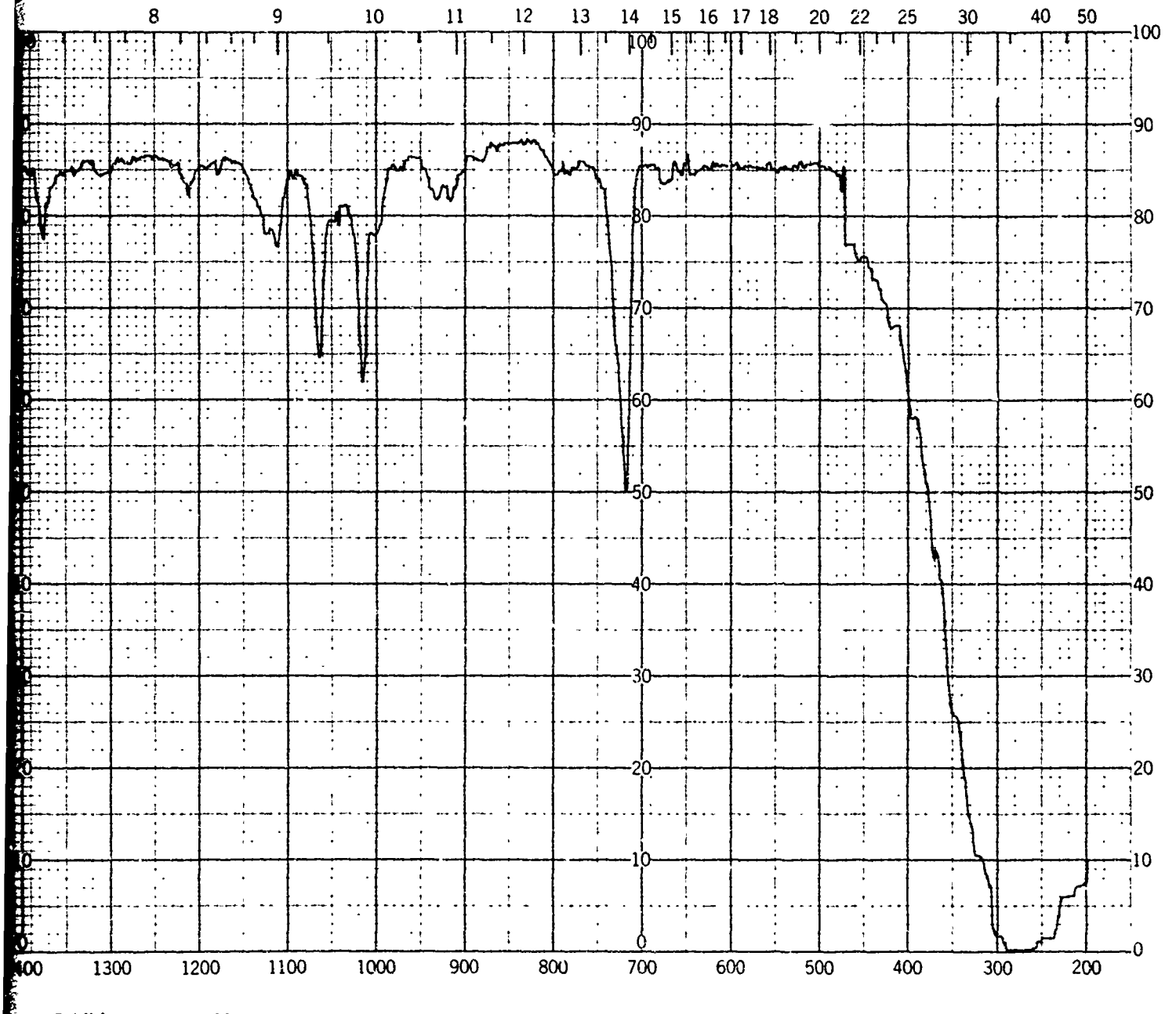
SLIT: ROUTINE

SPEED: 200 CM^{-1}

APPENDIX B
INFRARED SPECTRUM



SAMPLE:	**N-HEXYL CARBORANE**	**GAIN:**	**3%**
SLIT:	**ROUTINE**	**PERIOD:**	**2**
SPEED:	**200 CM^{-1}/MIN**	**ORDINATE:**	**0-100% T**

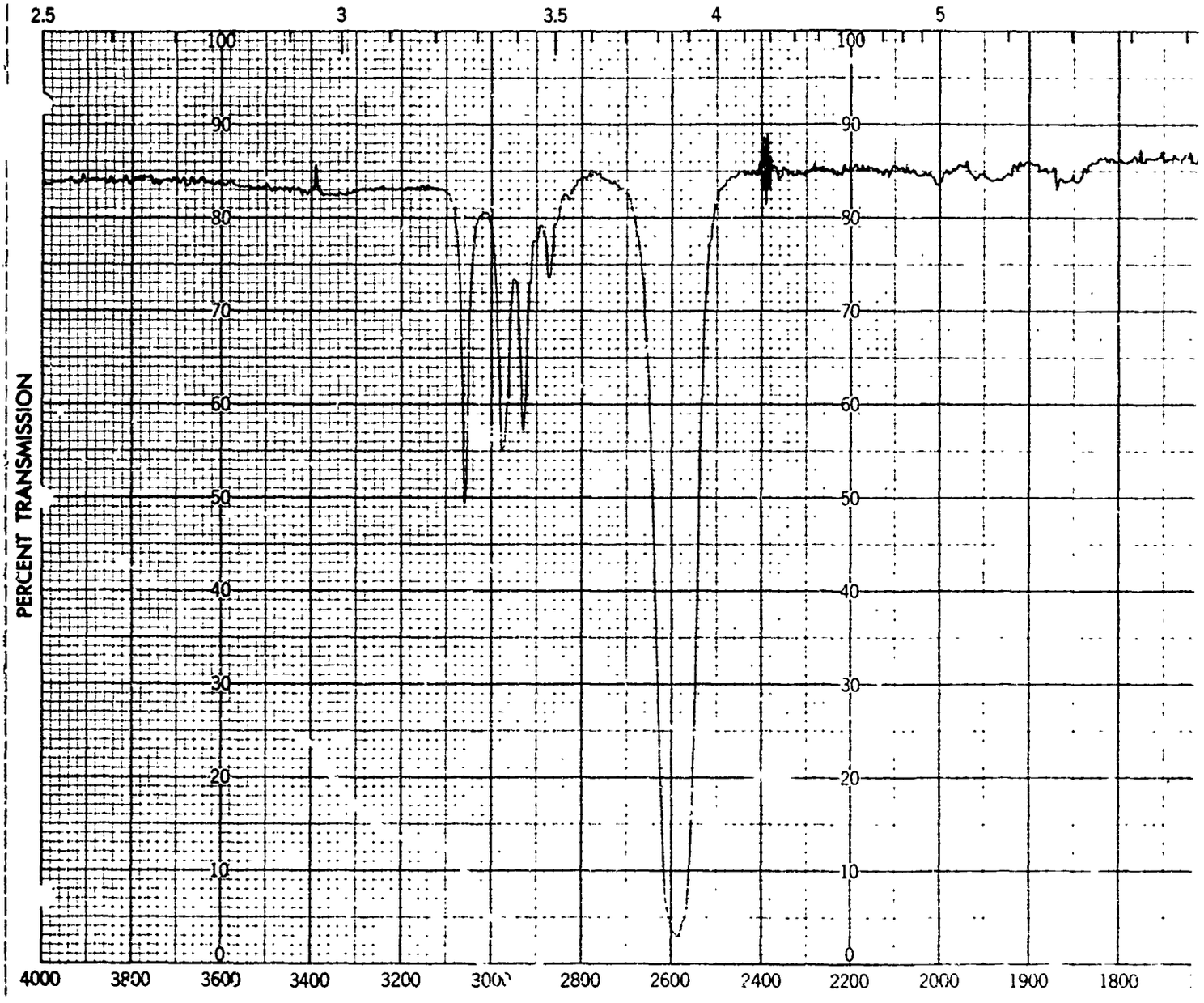


GAIN: 3%

PERIOD: 2

ORDINATE: 0-100% T

TOX STUDY NO. 51-044-74/76, JAN 74 - MAY 75

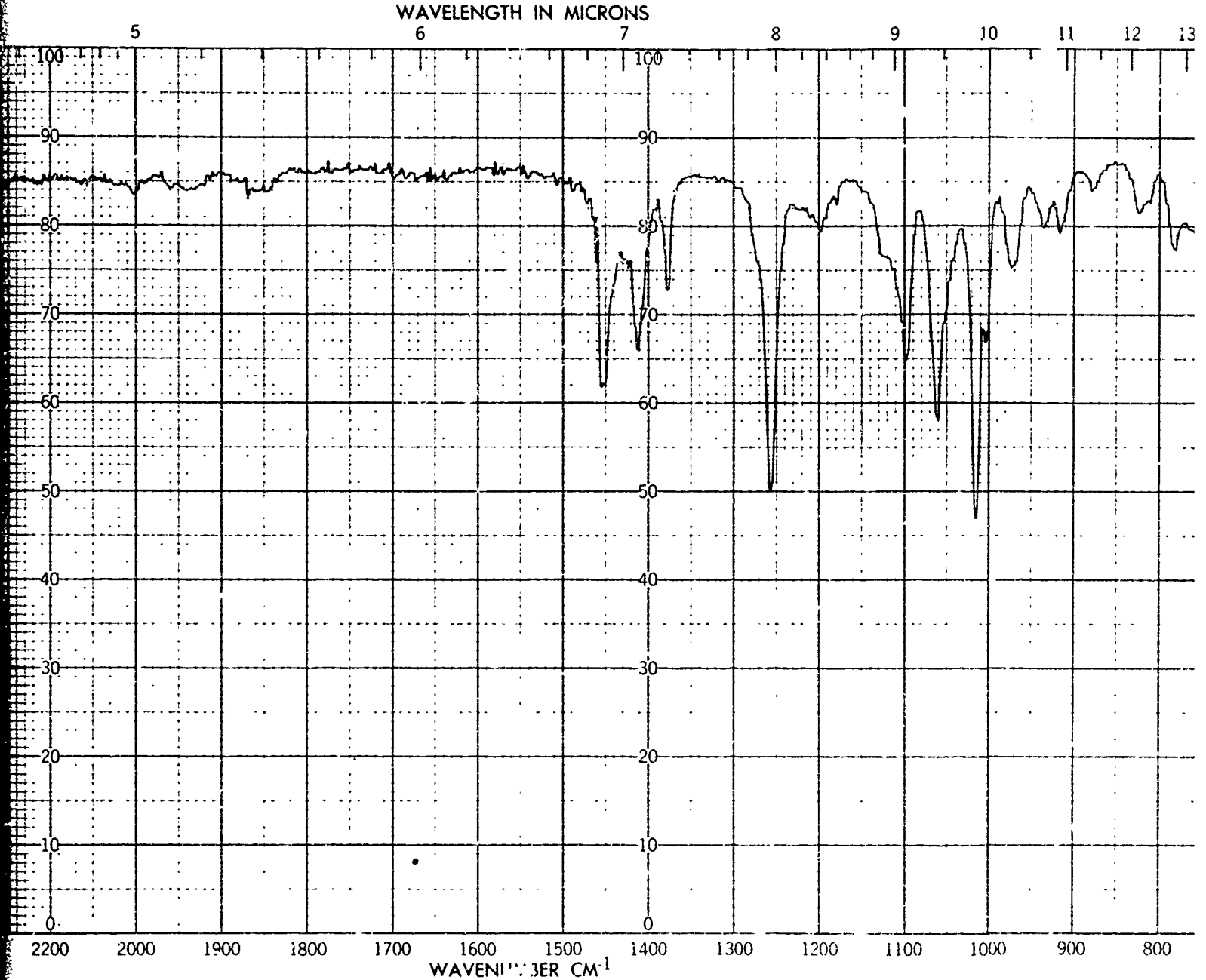


SAMPLE: CARBORANYLM

SLIT: ROUTINE

SPEED: 200 CM $^{-1}$ / MI

APPENDIX B
INFRARED SPECTRUM

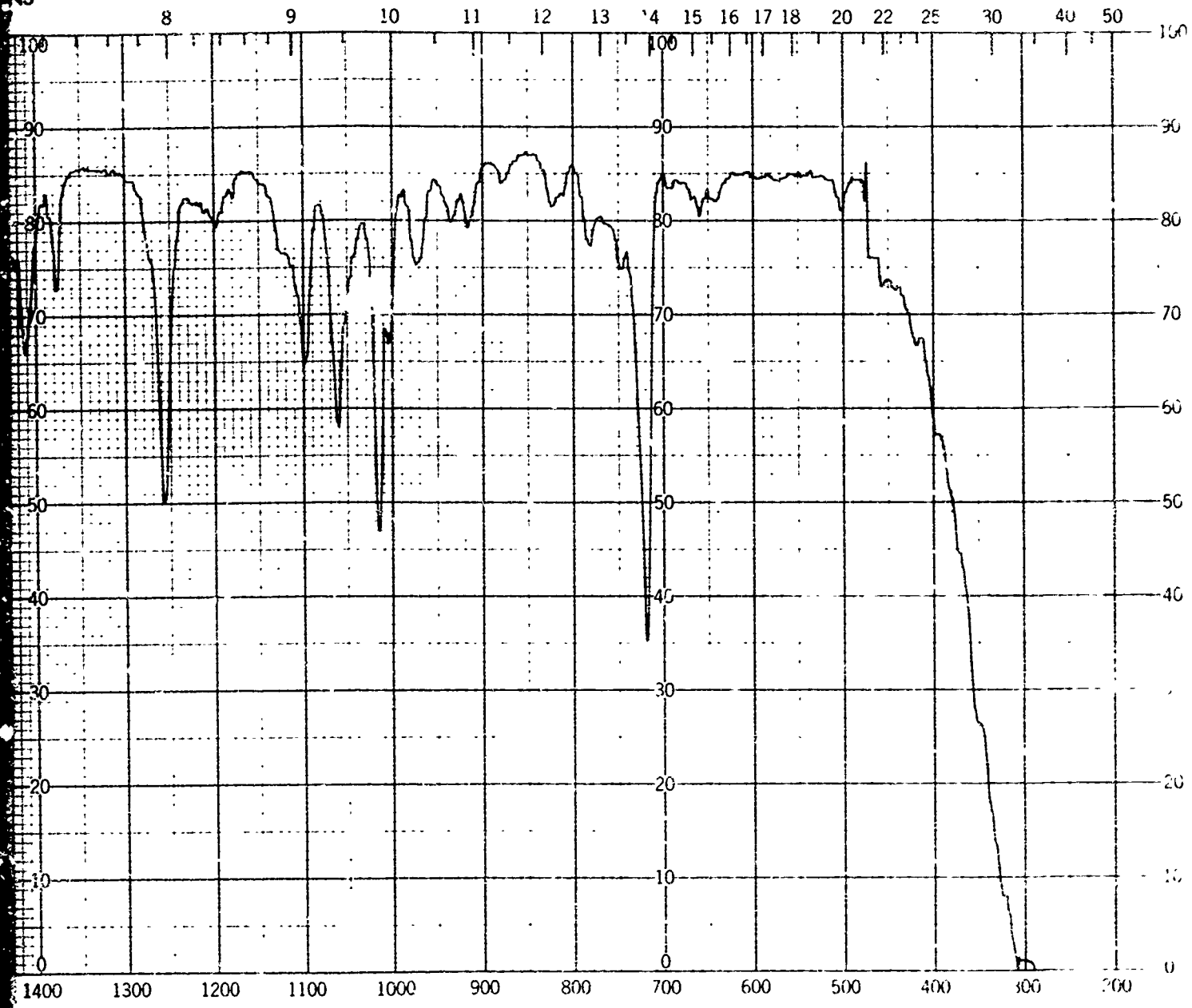


SAMPLE: CARBORANYLMETHYLETHYL SULFIDE **GAIN:** 3%

SLIT: ROUTINE **PERIOD:** 2

SPEED: 200 CM^{-1} / MIN **ORDINATE:** 0-100% T

NS

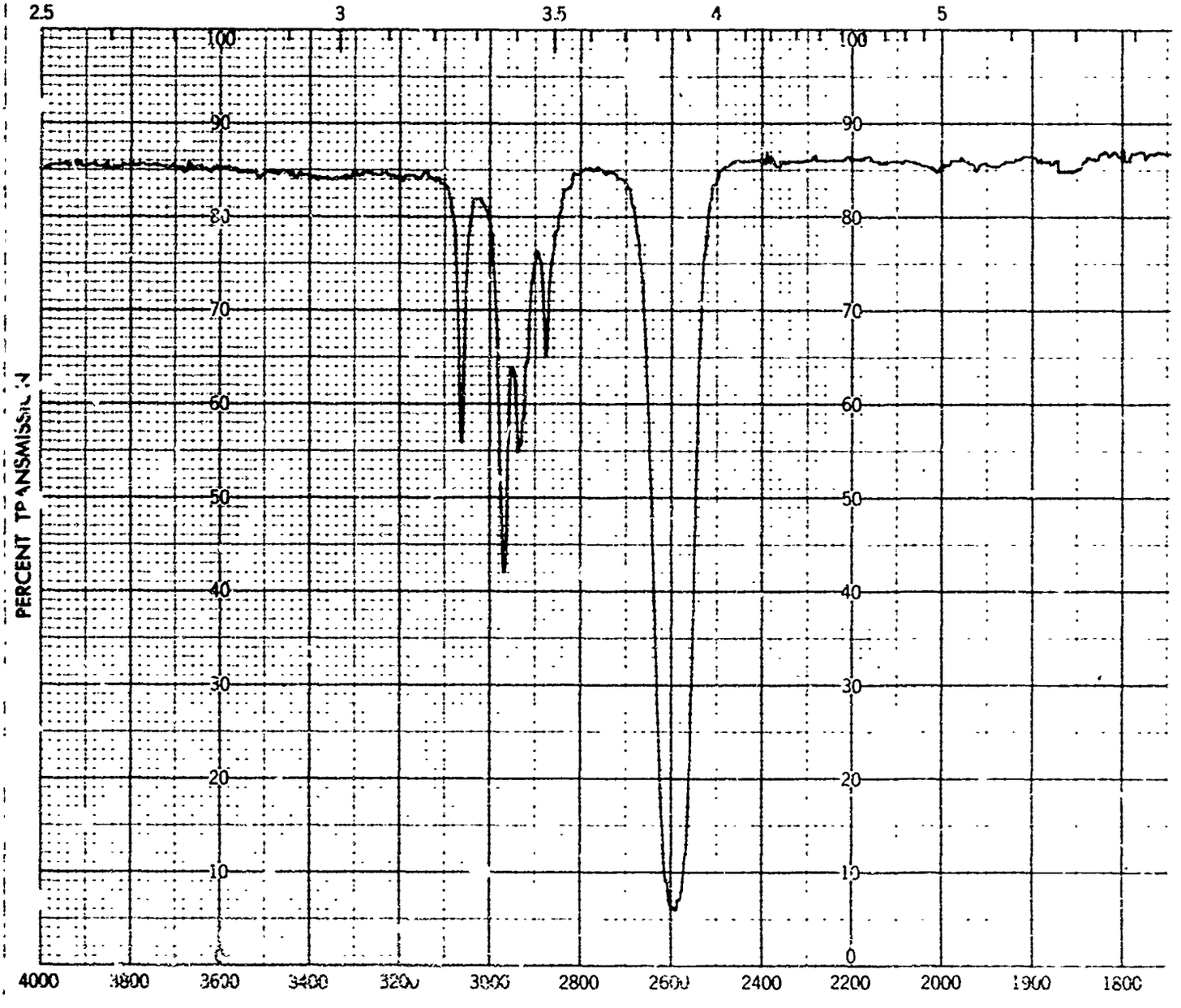


GAIN: 3%

IOD: 2

ORDINATE: 0-100% T

TOX STUDY NO. 51-044-74/76, JAN 74 - MAY 75

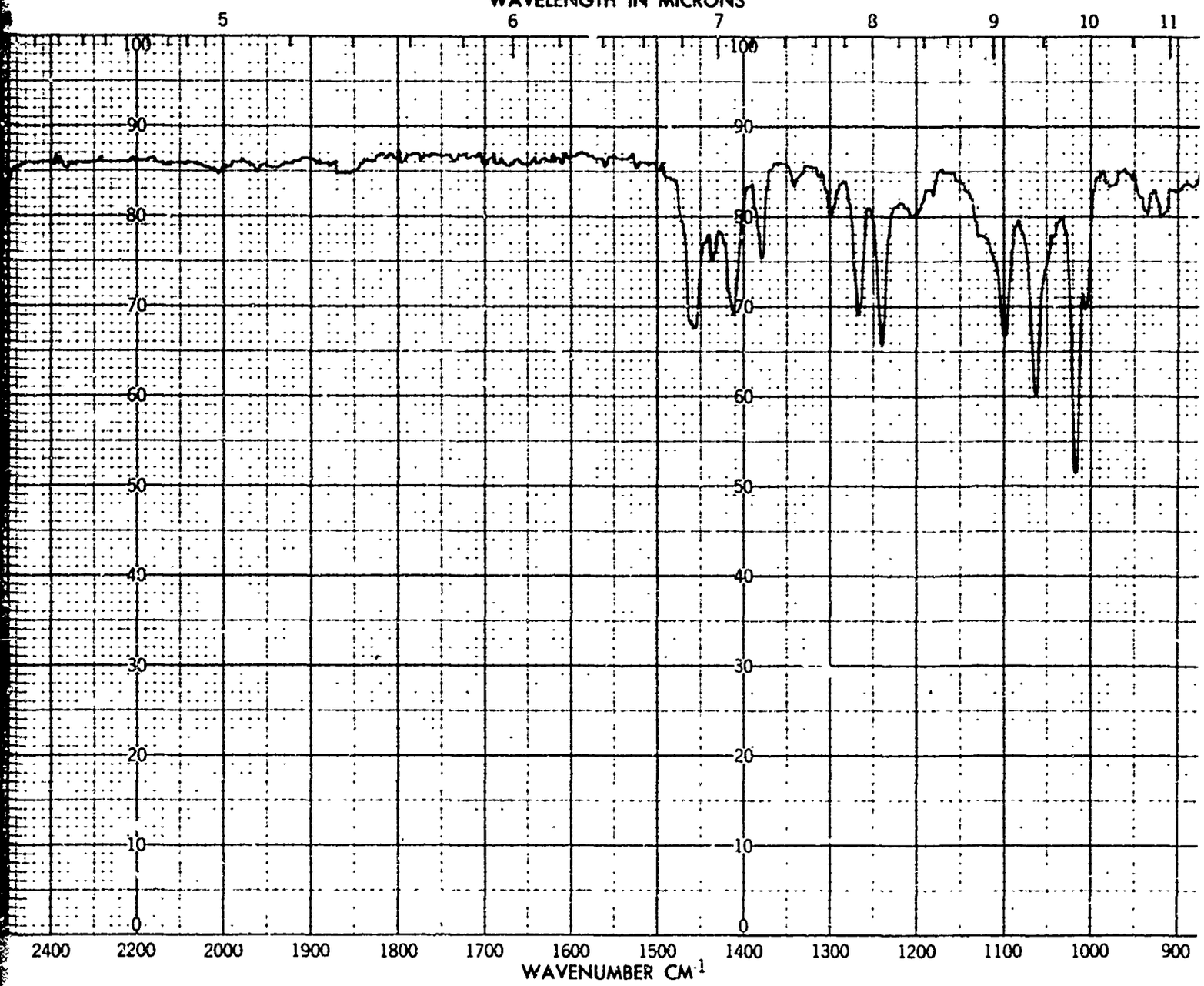


SAMPLE: CARBORANYLM

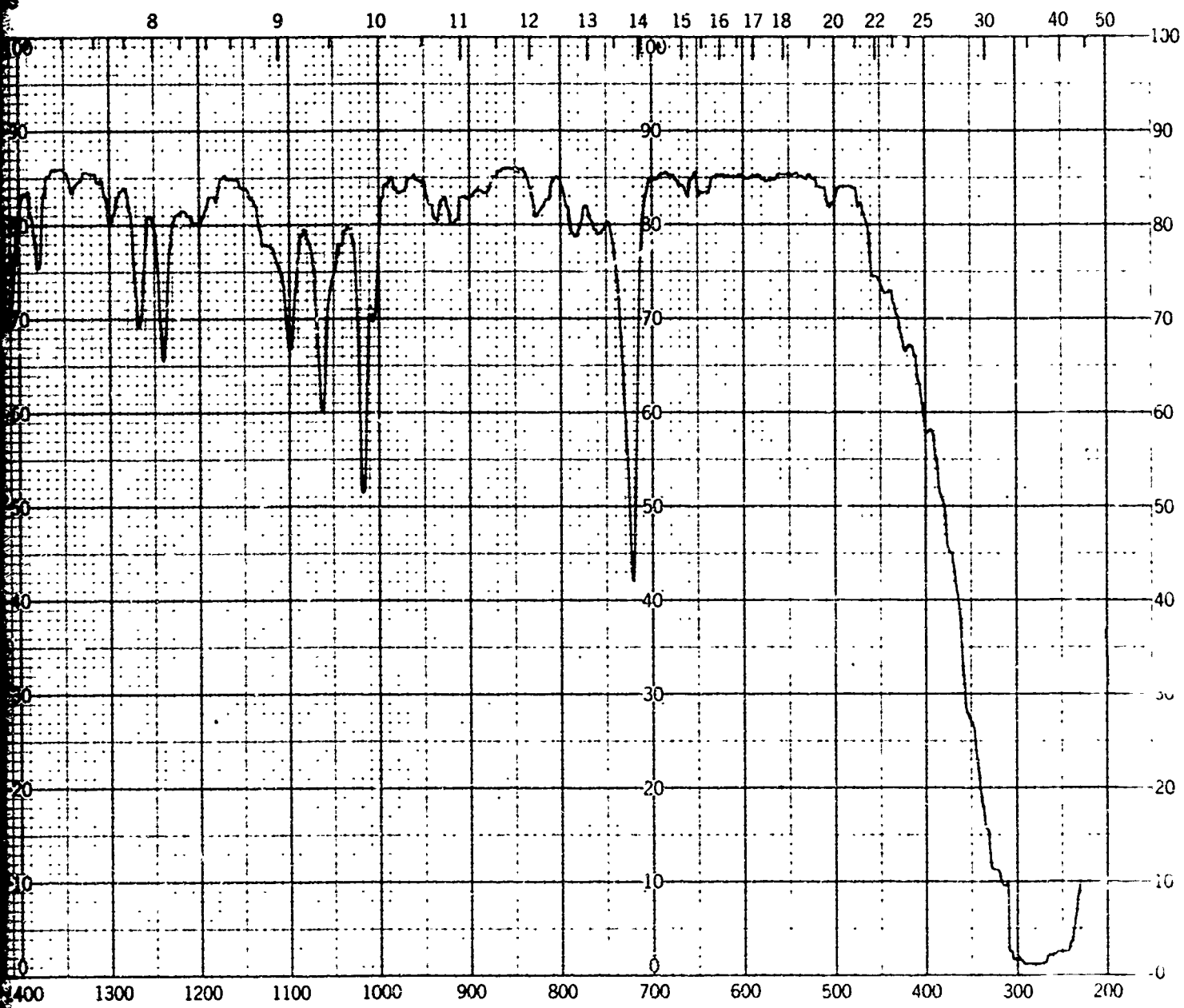
SLIT: ROUTINE

SPEED: 200 CM^{-1}/MIN

APPENDIX B
INFRARED SPECTRUM



SAMPLE:	CARBORANYLMETHYLPROPYL SULFIDE	GAIN:	3%
SLIT:	ROUTINE	PERIOD:	2
SPEED:	200 CM^{-1}/MIN	ORDINATE:	0-100% T



GAIN: 3%

PERIOD: 2

ORDINATE: 0-100% T

APPENDIX C

EVALUATION OF SKIN REACTIONS

Erythema and Eschar Formation

No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate-to-severe erythema	3
Severe erythema (beet redness to slight eschar formation)	4

Edema Formation

No edema	0
Very slight (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (edges raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4

An individual irritation score is equal to the sum of the scores for edema formation and erythema and eschar formation.

APPENDIX D

SCALE FOR NUMERICAL SCORING OF INJURY TO RABBIT SKIN WHEN DETERMINING NONIRRITATING CONCENTRATION

SKIN INJURY OBSERVATION	SCORE
No reaction	0
Slight capillary injection	1
Strong capillary injection	2
Slight erythema	3
Strong erythema	4
Slight edema	5
Strong edema	6
Slight necrosis	8
Strong necrosis	10

APPENDIX E

TABULATION OF TOXICITY DOSES*

VARIOUS ROUTES OF ADMINISTRATION

Commonly Used Terms	LD_{50} Single Oral Dose Rats	Inhalation 4-Hr Vapor Exposure Mortality 2/6 - 4/6 Rats	LD_{50} Skin Rabbits
Highly toxic	50 mg/kg or less	100 ppm or less	43 mg/kg or less
Toxic	51-500 mg/kg	101-1,000 ppm	44-350 mg/kg
Moderatly toxic	501-5,000 mg/kg	1,001-10,000 ppm	351-2,800 mg/kg
Slightly toxic	5,001-15,000 mg/kg	10,001-100,000 ppm	2,801-22,600 mg/kg
Practically nontoxic	above 15,000 mg/kg	>100,000 ppm	above 22,600 mg/kg

* Adapted from Hodge, H.C. and Sterner, J.H. American Industrial Hygiene Association Quarterly, 10:4.93, December 1943.

APPENDIX F

CHEMICAL ANALYSES OF CHAMBER AIR SAMPLES BY GAS CHROMATOGRAPHIC METHOD AS PERFORMED BY ENVIRONMENTAL CHEMISTRY DIVISION, INDUSTRIAL HYGIENE BRANCH

Exposure air samples were collected from the chamber by means of midget impingers containing nanograde n-hexane. The contents of the impinger were transferred to a flask and the impinger washed with hexane which was then combined with the hexane used to trap the vapors. A known amount of an internal standard (heptadecane) was added to the hexane and the sample was mixed thoroughly. An aliquot of the hexane solution was then injected into a gas chromatograph. Analyses of the hexane were conducted using a Hewlett-Packard, Model 5750 gas chromatograph equipped with a flame ionization detector. The instrument was fitted with a 4 ft x 1/8 inch glass column packed with 3 percent OV-1 stationary phase on 100/120 Gas-Chrom Q®. The operating parameters were: carrier gas helium, column flow rate 20 cc/min, hydrogen gas flow to detector 55 cc/min, air flow to detector 500 cc/min, injector temperature 200°C, detector temperature 200°C, column temperatures see below.

	GC Column Temperature			
Carborane	Initial Temp. °C	Post Inj. Temp. °C	Terminal Temp. °C	Temperature Programming rate, °C/min
NHC	130	0	165	4
CMES	125	5	155	2
CMPS	130	0	165	4

Gas-Chrom Q® is a registered trademark of Applied Science Laboratories, Inc. PO Box 140, State College, PA 16801. Use of trademarked name does not imply endorsement by the US Army, but is used only to assist in identification of a specific product.