

**CODING FORMS FOR SRC INDEXING**

<b>Microfiche No.</b>		OTS0001148	
<b>New Doc ID</b>	FYI-OTS-0794-1148	<b>Old Doc ID</b>	
<b>Date Produced</b>	11/23/87	<b>Date Received</b>	07/26/94
		<b>TSCA Section</b>	FYI
<b>Submitting Organization</b>		AMOCO CORP	
<b>Contractor</b>			
<b>Document Title</b>		INITIAL SUBMISSION: LETTER FROM AMOCO CORP TO DYNAMAC CORP REGARDING PHOSPHORODITHIIC ACID ESTERS WITH ATTACHMENTS, DATED 11/23/87	
<b>Chemical Category</b>		PHOSPHORODITHIIC ACID ESTERS	

Identification No. (1)		No. of Pages		2			
Inv. No. <b>FYI-0794-1148</b>		Old Inv. No.		4			
Case No. (6)				5			
Date Forwarded (6)		Date Rec'd (6)	Cont. Code	8			
		<b>N</b>					
Check One: <input type="checkbox"/> Publication <input type="checkbox"/> Internally Generated <input type="checkbox"/> Externally Generated		Pub/Journal Name		9			
				9			
Author(s)				10			
Organ. Name				11			
Dept./Div.				12			
P.O. Box	13	Street No./Name		14			
CITY	15	STATE	16	ZIP	17	COUNTRY	18
NID No. (7)	19	D & B NO. (11)		20			
CONFESSOR				21			
Doc Type		<b>F.Y.I.</b>		22			
Doc Title				23			
Chemical Name (300 per name)		25	CAS No. (10)	24			

SANITIZED VERSION

7/26/94  
001198



NYI-94-001146  
INIT 07/26/94

**Amoco Corporation**

200 East Randolph Drive  
Chicago, Illinois 60601  
Product Safety, Toxicology and Information Systems  
Division of Environmental Affairs & Safety Department  
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Daniel M. Talsma  
Supervisor, Toxic Substances Control and Compliance

November 23, 1987



84940000222

Dr. Lou Borghi  
Dynamac Corporation  
1140 Rockville Pike  
Rockville, MD 20852

**Contains No CBI**

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NPPPT/CHMO  
94 JUL 26 PM 3:55

Dear Dr. Borghi:

In this letter, we furnish information on phosphorodithioc acid esters, which should be helpful to the TSCA Interagency Testing Committee (ITC) in their assessment of health effects and exposure. The acid esters appear on the list for the Sixth Scoring Exercise by the ITC.

A copy of this letter with the confidential information included has been sent to Dr. Robert Brink of EPA.

Production

Amoco Petroleum Additives Company, a wholly owned subsidiary of Amoco Corporation, manufactures the acid-esters at their facility in Wood River, Illinois. While the acid-esters are each described with a

are only intermediates in the manufacturing process, never leaving the plant-site in that form, except for some small samples. The acid-mixed-esters are stored only for a short time before being neutralized to the zinc salts which become the products of commerce.

The quantities of related products manufactured in 1986 are given in the attached table. (See Attachment A.) The quantities apply to that portion of the mixed-ester ascribed to the specific ester, and include the weight of zinc acquired in the process of neutralization.

Process Description

Manufacture of the acid-mixed-ester is described in the attached block diagram titled, "ZOP Acid Production." (See Attachment B.) Batches

8 0 0 8

Use

Amoco markets the products as zinc salts in blends with other components for lubrication of metallic working parts, principally in motor vehicles. The products are called petroleum additives.

Employees Exposed

At the manufacturing site in Wood River, Illinois, the following number of employees are involved with the acid-mixed-esters and zinc salts:

Workplace Concentration

Toxicity Data

In the attached Material Safety Data Sheet for "Amoco 198 Acid (Attachment C), toxicity data are noted on page 3 for this acid-mixed-ester before neutralization.

Reports are also attached for the following toxicity studies on "Amoco 198 Acid," otherwise called "Precursor of A-198."

<u>Study</u>	<u>Date</u>	<u>Attachment</u>
Primary Eye Irritation	February 2, 1984	D
Primary Dermal Irritation	March 28, 1984	E
Acute Dermal Toxicity	April 30, 1984	F
Acute Inhalation Toxicity	July 27, 1984	G
Acute Inhalation Toxicity	November 19, 1986	H

We have no data on environmental effects of the acid-mixed-esters. It is reported that aquatic effects of the zinc salt of the

acid-mixed-esters have been submitted to EPA from a so-called MARPOL group.

Insofar as the petroleum additives business is concerned, it would appear that ITC should be more interested in the zinc salts, since the acid-mixed-esters are not products of commerce.

Statement Regarding Confidentiality of This Information

This letter contains confidential information. Amoco Petroleum Additives Company claims confidentiality on behalf of itself, Amoco Corporation, and all of its affiliates which will, hereinafter, be referred to collectively as Amoco. Amoco is expressly relying on 5 U.S.C. Section 552(b)(4), 15 U.S.C. Section 2613, and the EPA regulations 40 CFR, Part 2, that this information (or any copies of summaries of it) will not be made the subject of general public disclosure. The confidentiality of the information provided herein is protected by the Fifth Amendment to the United States Constitution, which requires compensation for the taking of property. Amoco is also relying on 40 CFR, Section 2.205, and it requests that the EPA hold the contents of this letter in the strictest confidence and not disclose it to the public, unless ordered to do so by a federal court.

If any person (including any government employee who is not an employee of the EPA) should request an opportunity to inspect or copy this information or this letter, we request that we be immediately notified of the request, be furnished with a copy of all written materials pertaining to the request (including but not limited to the request), and be given sufficient advance notice of any intended release so that Amoco may, if deemed necessary or appropriate, pursue any remedies available to it. The furnishing of this information should not be deemed a general waiver of any attorney/client privilege or a waiver of any other privilege by either Amoco or any of the individuals involved. Nor should the furnishing of this information be deemed a waiver of any right that Amoco or the individuals involved may have to decline disclosure of any additional information sought by your office.

The request set forth in the preceding paragraph also applies to any memoranda, notes, transcripts, or other writings of any sort whatsoever which are made by or at the direction of any employee of the EPA (or any other government agency) and which incorporate, include, or relate to any of the matters (1) contained in any materials furnished by Amoco or its employees or agents to the EPA (or any other government agency), or (2) referred to in any conference, meeting, telephone conversation, or interview between (a) employees, former employees, representatives, agents, present or former counsel of Amoco, and (b) employees of the EPA (or any government agency).

In the event that EPA receives an FOIA request directed at this information, we will cooperate fully in defending against that request. The assertions, claims, and requests contained in this

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letter are intended to supplement the confidentiality provisions of the Toxic Substances Control Act.

General

We would appreciate receiving a copy of the non-confidential report which is submitted to the ITC on these acid-esters.

We hope this information meets your need.

Very truly yours,



DNT/BGT/dc

Enclosures

0 0 0 6

**MATERIAL SAFETY  
DATA SHEET**

AMOCO 198 ACID

**MANUFACTURER/SUPPLIER:**  
Amoco Petroleum Additives Co.  
231 South Bemiston Avenue  
Clayton, Missouri 63105  
TEL. 314/654-8000

**EMERGENCY HEALTH INFORMATION:** (800) 447-8735  
**EMERGENCY SPILL INFORMATION:** (800) 424-9300  
**OTHER PRODUCT SAFETY INFORMATION:** (314) 856-3516

**IMPORTANT COMPONENTS:** Dithiophosphoric acid.  
Degradation product, hydrogen sulfide (CAS 7783-06-4),  
ACGIH TLV 10 ppm, OSHA Ceiling 20 ppm.

**WARNING STATEMENT:** Danger! Flammable. Causes eye damage and skin burns. Harmful if swallowed. Vapor and mist harmful if inhaled. Can cause severe irritation of the mouth, throat, and esophagus. Hydrogen sulfide and other toxic vapors are given off at room temperature and more when heated.

**HMIS/NFPA CODES:**(HEALTH;3)(FLAMMABILITY;2)(REACTIVITY;1)

**APPEARANCE AND ODOR:** Clear, light-colored liquid.

**HEALTH HAZARD INFORMATION**

**EYE**

**EFFECT:** Causes eye damage.

**FIRST AID:** Immediately flush eyes with plenty of water for at least 15 minutes, then get immediate medical attention.

**PROTECTION:** Do not get in eyes. Wear chemical goggles and face shield.

**SKIN**

**EFFECT:** Causes skin burns.

**FIRST AID:** Immediately wash exposed skin with soap and water. Get prompt medical attention if irritation develops. Remove contaminated clothing, including shoes, and thoroughly clean and dry before reuse.

**PROTECTION:** Do not get on skin or clothing. Wear impervious clothing and gloves. Wear face shield.

**INHALATION**

**EFFECT:** Vapor: Mist: Harmful if inhaled.

**FIRST AID:** If adverse effects occur, remove to uncontaminated area. Give artificial respiration if not breathing. Get immediate medical attention.

**PROTECTION:** Avoid breathing vapor and/or mist. Use with adequate ventilation. If ventilation is inadequate, use supplied-air respirator approved by NIOSH/MSHA.

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HEALTH HAZARD INFORMATION - CONTINUED

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## INGESTION

EFFECT: Can cause severe irritation of the mouth, throat and esophagus.  
FIRST AID: If swallowed, drink plenty of water, do NOT induce vomiting. Get immediate medical attention.

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FIRE AND EXPLOSION INFORMATION

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FLASHPOINT: 80°F, (27°C) ASTM D56  
EXTINGUISHING MEDIA: Agents approved for Class B hazards (e.g., dry chemical, carbon dioxide, halogenated agents, foam, steam) or water fog.  
UNUSUAL FIRE AND EXPLOSION HAZARDS: Flammable liquid. Vapor may explode if ignited in enclosed area.  
PRECAUTIONS: Keep away from ignition sources (e.g., heat, sparks and open flames). Use with adequate ventilation. Keep container closed. Toxic vapors are given off when heated.

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REACTIVITY INFORMATION

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DANGEROUS REACTIONS: None identified.  
HAZARDOUS DECOMPOSITION: None. Decomposes to highly toxic hydrogen sulfide, sulfur dioxide and mercaptans.  
STABILITY: Hydrogen sulfide and other toxic vapors are given off at room temperature and more when heated.

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CHEMICAL AND PHYSICAL PROPERTIES

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SOLUBILITY IN WATER: Negligible, below 0.1%.  
SPECIFIC GRAVITY (WATER = 1): 0.96  
VISCOSITY: 10 cSt @ 40°C.

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**STORAGE AND ENVIRONMENTAL PROTECTION**

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- STORAGE REQUIREMENTS:** Store in flammable liquids storage area. Store away from heat, ignition sources, and open flame in accordance with applicable federal, state, or local regulations. Keep container closed.
- SPILLS AND LEAKS:** Remove or shut off all sources of ignition. Remove mechanically or contain on an absorbent material. Keep out of sewers and waterways.
- WASTE DISPOSAL:** Disposal must be in accordance with applicable federal, state, or local regulations. Residues and spilled material are hazardous waste due to ignitability. Residues and spilled material are hazardous waste due to corrosivity. Enclosed-controlled incineration is recommended unless directed otherwise by applicable ordinances.
- EMPTY CONTAINERS:** The container for this product can present explosion or fire hazards, even when emptied! To avoid risk of injury, do not cut, puncture or weld on or near this container. Since the emptied containers retain product residue, follow label warnings even after container is emptied.

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**TOXICOLOGICAL INFORMATION**

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**EYE:** Irritation score (day 1) 78.5/110 (rabbit).

**SKIN:** Irritation score 8.0/8.0 (rabbit). Dermal LD50 is greater than 2 g/kg (rabbits).

**INHALATION:** In a 4-hour inhalation study, the test material was heated to 66.1°C. The estimated nominal concentration was 0.69 to 1.03 mg/l (maximum attainable concentration under these experimental conditions). One rat out of ten died. Clinical observations during exposure included convulsions, severe salivation, increased respiratory rate, and breathing difficulties. In a separate 4-hour study, the test material was heated to 100°C. The nominal concentration was 0.198 mg/l. No rats died during the study.

Hydrogen sulfide is a component of the toxic vapors given off by this product. If concentrations above 600 ppm, brief exposures (minutes) to H<sub>2</sub>S can be lethal. At these concentrations, H<sub>2</sub>S may not be detected by smell. At low concentrations, it is a respiratory irritant.

It is important that proper hygiene and personal protection precautions be followed when using this product so as to avoid a possible health risk to humans.

No component of this product is identified as a carcinogen by NTP, IARC or OSHA.

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**REGULATORY INFORMATION**

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**OSHA HAZARD COMMUNICATION STANDARD:** Flammable liquid. Corrosive. Toxic.

**DOT PROPER SHIPPING NAME (BULK, LAND):** Flammable Liquid, Corrosive, N.O.S. (contains hydrogen sulfide), UN2924, RQ.

## ISSUE INFORMATION

BY:



Stephen A. Elbert  
Mgr., Product Safety & Toxicology

ISSUED: November 13, 1987  
SUPERSEDES: May 04, 1987

This material safety data sheet and the information it contains is offered to you in good faith as accurate. We have reviewed any information contained in this data sheet which we received from sources outside our company. We believe that information to be correct but cannot guarantee its accuracy or completeness. Health and safety precautions in this data sheet may not be adequate for all individuals and/or situations. It is the user's obligation to evaluate and use this product safely and to comply with all applicable laws and regulations. No statement made in this data sheet shall be construed as a permission or recommendation for the use of any product in a manner that might infringe existing patents. No warranty is made, either express or implied.

**PRIMARY EYE IRRITATION STUDY OF  
DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) IN RABBITS  
Study No. 699  
Test Article No. 230**

**SUMMARY**

DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) was instilled undiluted at a dose of 0.1 ml into one eye of each of six rabbits, with the other eye serving as an untreated control. The treated eye of each rabbit was scored for irritation at 1, 2, 3, 4, 7, 14, and 21 days following test article instillation. The control eye was used for comparison.

The maximum irritation score of 78.5/110.0 was obtained 1 day after administration of the test article. Complete recovery from all signs of ocular irritation was not evident in any rabbit by the final scoring interval.

During the study, all rabbits exhibited a positive reaction to the test article. Therefore, DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) was judged to be a primary eye irritant as defined by the Federal Hazardous Substances Labeling Act.

**STUDY PARTICIPANTS:**

Vladislava S. Rac, D.V.M., M.S., Study Pathologist

Christopher Lord, Technician

Calvin Reaves, Animal Care

This report was prepared by Marcia Reckers.

*Marcia Reckers* 2/2/84  
Marcia Reckers, B.S. Date  
Study Director  
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*Nabil S. Hatoum* 2/2/84  
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Josephine M. Reed, M.M., M.S. Date  
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PRIMARY EYE IRRITATION STUDY OF  
DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) IN RABBITS

I. INTRODUCTION

The purpose of this study was to determine the primary eye irritation potential of DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) in rabbits.

II. MATERIALS AND METHODS

a. Test Article: DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) (identification no. 5507-146) was received November 2, 1985. The test article was a black liquid with a viscosity similar to gasoline. It was received in a glass jar and stored at room temperature (approximately 22°C).

b. Dosage Formulation: The test article was instilled undiluted.

c. Animals: New Zealand albino rabbits were purchased from Hazelton Dutchland Laboratories, Denver, PA, for use in this study. Upon arrival (10/25/83), the rabbits were held in quarantine for approximately 2 weeks and examined carefully to insure their health and suitability as test subjects. Rabbits selected for the study were identified by a unique numbered metal tag inserted through the pinna of the right ear and by a cage card.

d. Food and Water: Purina Lab Rabbit Chow HF #5326 (Ralston Purina Co., St. Louis, MO) and water supplied from a reverse-osmosis purifier by an automatic watering system were available *ad libitum*.

e. Environment: The rabbits were housed individually in stainless steel cages measuring 61.0 x 45.5 x 42.0 cm. Poly pads (12 ply, Shepherd Specialty Papers, Inc., Kalamazoo, MI) were placed in the pan below the stainless steel mesh floor of each animal cage to absorb liquids. Air conditioned animal rooms were maintained at approximately 22°C and 40% relative humidity. Fluorescent lighting was provided for 12 hours followed by 12 hours of darkness.

f. Methods:

1. Animals: Rabbits used on test were selected at random and assigned to a single group of three males and three females.
2. Preparation: Three days prior to study initiation, the rabbits were examined for general health and for corneal lesions with the aid of 2%

0 0 1 3

sodium fluorescein (Aldrich Chemicals, Milwaukee, WI) and ultraviolet light. Rabbits found at that time to have any ocular lesions were excluded from the study. However, one rabbit was excluded from the study just prior to dosing due to apparent ocular irritation. Its replacement was grossly examined without the aid of 2% sodium fluorescein.

3. Dosing: On the day of study initiation (11/7/83), 0.1 ml of the undiluted test article was instilled into the everted lower lid of the right eye of each rabbit. The lids of the treated eyes were held closed for 1-3 seconds following the instillation of the test article. The other eye was left untreated.
4. Observations: All rabbits were observed daily for mortality and morbidity.
5. Body Weights: The rabbits were weighed immediately prior to dosing.
6. Ocular Examinations: The treated eye of each test rabbit was examined 1, 2, 3, 4, 7, 14, and 21 days following test article instillation. At each interval, ocular lesions were scored according to the method of Draize (Appendix I). The cornea was observed for appearance and extent of opacity with the aid of 2% sodium fluorescein and ultraviolet light; the iris for congestion, swelling, circumcorneal injection, and reaction to light; and the conjunctiva for erythema, chemosis, and discharge.
7. Animal Disposition: After the final observation (11/28/83), the rabbits were sacrificed by anesthetic overdose and discarded without necropsy.

g. Evaluation: The scores were tabulated by interval and scoring category. Mean scores per category were calculated, multiplied by the appropriate weighting factors and summed.

According to the Federal Hazardous Substances Labeling Act, a compound is considered a primary eye irritant if at least four of the the six rabbits exhibit a positive reaction. A rabbit is considered to exhibit a positive reaction if, at any observation period, the test article produces ulceration or opacity of the cornea (any cornea score greater than 0), inflammation or slight circumcorneal injection of blood vessels of the iris (any iris score greater than 0), any obvious conjunctival swelling with partial eversion of the lids (a chemosis score of 2 or greater), or conjunctival erythema of diffuse crimson red with individual vessels not easily discernible (an erythema score of 2 or greater).

### III. RESULTS

a. Mortality: No deaths were observed during the study. However, one male rabbit had severe ocular irritation and was euthanized on the 14th day of the study following consultation with the Sponsor.

b. Body Weights: The weight range for rabbits used in this study was 2.4 to 2.9 kg.

c. Ocular Lesions: The individual irritation scores (Appendix II) were tabulated in Table 1. The treated eyes of all rabbits had severe ocular irritation (corneal opacity, damage to iris and conjunctival irritation) at the first 4 scoring intervals. By the 7th day, recovery from corneal opacity was evident in three rabbits. However, lackluster/pitting and/or pannus formation (Appendix III) were noted in four rabbits at this time. One male rabbit had severe ocular irritation through the 14th day following dosing and was therefore euthanized prior to the termination of the study. Although complete recovery from all signs of ocular irritation was not evident in any rabbit, the five remaining rabbits showed no sign of corneal opacity and the iris of three rabbits appeared normal by the final scoring interval.

### IV. EVALUATION

Primary Irritation Score: The primary eye irritation scores are shown in Table 1. During the course of the study all of the rabbits exhibited a positive reaction. Therefore, DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) is a primary eye irritant as defined by the Federal Hazardous Substances Labeling Act.

### V. QUALITY ASSURANCE

Laboratory operations were inspected on November 9, 1983 by Josephine M. Reed. The final draft report was audited on January 27, 1984 by Josephine M. Reed. The study was found to be in compliance with ITRI Life Sciences Quality Assurance criteria. Original data generated during this study are maintained in the ITRI Life Sciences Archives as specified by standard operating procedures.

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VI. TABLES

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TABLE 1  
SUMMATION OF EYE IRRITATION SCORES

STUDY NO. : 699		TEST ARTICLE NO. : 230		DOSE: 0.1ML			
		RABBIT NUMBER					
		818	819	820	804	822	823
I. CORNEA							
-----							
	DAYS FOLLOWING INSTILLATION						
DENSITY OF OPACITY(A)	1	40	30	30	30	20	45
AREA OF OPACITY(B)	2	40	30	30	30	20	30
	3	10	45	30	30	5	40
FORMULA: I=AxBx5	4	10	10	40	20	5	40
	7	0	0	30	20	0	20
	14	0	0	30	5	0	0
	21	0	0	-	0	0	0
II. IRIS							
-----							
FORMULA: II=AxD	1	5	5	10	10	5	5
	2	5	5	5	5	5	5
	3	5	5	5	5	5	5
	4	5	5	5	5	5	5
	7	5	5	5	5	5	5
	14	5	0	10	5	0	5
	21	5	0	-	0	0	5
III. CONJUNCTIVA							
-----							
ERYTHEMA(A)	1	20	20	20	16	20	20
CHEMOSIS(B)	2	20	20	20	20	20	20
DISCHARGE(C)	3	20	20	20	18	18	20
	4	20	20	18	16	12	20
	7	14	14	20	20	10	18
FORMULA III=(A+B+C)x2	14	6	8	20	20	5	10
	21	5	10	-	8	4	12

LD1002499

TABLE I (cont'd)  
SUMMATION OF EYE IRRITATION SCORES

STUDY NO. : 699

TEST ARTICLE NO. : 230

DOSE: 0.1ML

TOTAL EYE IRRITATION SCORES

RABBIT NUMBER

FORMULA:  $TS = \sum I_i$

DAYS FOLLOWING  
INSTILLATION

	818	819	820	354	822	823
1	55	85	110	85	55	70
2	65	85	85	85	45	55
3	35	70	85	53	28	65
4	35	35	63	41	22	65
7	19	19	85	45	15	43
14	11	8	110	30	6	15
21	11	10	-	8	4	17

MEAN TOTAL EYE IRRITATION SCORE/DAY

TS

FORMULA:  $TS = \text{SUM OF } TS/6$

1	78.5
2	65.0
3	56.0
4	43.5
7	37.7
14	30.0
21	10.0*

\*FORMULA:  $TS = \text{SUM OF } TS/5$

VII. APPENDICES

APPENDIX I

SCALE FOR SCORING OCULAR LESIONS\*

<b>1. Cornea</b>		
<b>A. Opacity-degree of density (area most dense taken for reading)</b>		
No opacity		0
Scattered or diffuse area, details of iris clearly visible		1
Easily discernible translucent areas, details of iris slightly obscured		2
Opaque areas, no details of iris visible, size of pupil barely discernible		3
Opaque, iris invisible		4
<b>B. Area of cornea involved</b>		
One quarter (or less) but not zero		1
Greater than one quarter, but less than three quarters		2
Greater than half, but less than three quarters		3
Greater than three quarters, up to whole area		4
Score equals A x B x 5	Total Maximum =	80
<b>2. Iris</b>		
<b>A. Values</b>		
Normal		0
Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light, (sluggish reaction is positive)		1
No reaction to light, hemorrhage, gross destruction (any or all of these)		2
Score equals A x 5	Total Maximum =	10
<b>3. Conjunctivae</b>		
<b>A. Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)</b>		
Vessels normal		0
Vessels definitely injected above normal		1
More diffuse, deeper crimson red, individual vessels not easily discernible		2
Diffuse beefy red		3
<b>B. Chemosis</b>		
No swelling		0
Any swelling above normal (includes nictitating membrane)		1
Obvious swelling with partial eversion of lids		2
Swelling with lids about half closed		3
Swelling with lids about half closed to completely closed		4
<b>C. Discharge</b>		
No discharge		0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)		1
Discharge with moistening of the lids and hairs just adjacent to lids		2
Discharge with moistening of the lids and hairs, and considerable area around the eye		3
Score equals (A+B+C) x 2	Total Maximum =	20

The maximum score is the sum of all scores obtained for the cornea, iris, and conjunctivae. Total maximum score possible =110

\*Draize, J.H., Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, Assoc. Food and Drug Officials of the U.S., Austin, TX, 1959.

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APPENDIX II

INDIVIDUAL EYE IRRITATION SCORES

CORNEA (A=DENSITY OF OPACITY, B=AREA OF OPACITY)

ANIMAL NUMBER	SEX	DAY 1		DAY 2		DAY 3		DAY 4		DAY 7		DAY 14		DAY 21	
		A	B	A	B	A	B	A	B	A	B	A	B	A	B
010	N	2	4	2	4	2	1	2	1	0	0	0	0	0	0
019	N	3	4	3	4	3	3	2	1	0	0	0	0	0	0
020	N	4	4	3	4	3	4	2	4	3	4	4	4	4	4
054	F	3	4	2	3	2	3	2	2	2	2	1	1	0	0
072	F	2	3	2	2	1	1	1	1	0	0	0	0	0	0
073	F	3	3	2	3	2	4	2	4	2	2	0	0	0	0

IRIS(A)

ANIMAL NUMBER	SEX	DAY 1		DAY 2		DAY 3		DAY 4		DAY 7		DAY 14		DAY 21	
		A	B	A	B	A	B	A	B	A	B	A	B	A	B
018	N	1	1	1	1	1	1	1	1	1	1	1	1	1	1
019	N	1	1	1	1	1	1	1	1	1	1	0	0	0	0
020	N	2	2	1	1	1	1	1	1	1	2	2	1	0	0
054	F	2	2	1	1	1	1	1	1	1	1	1	0	0	0
072	F	1	1	1	1	1	1	1	1	1	1	0	0	0	0
073	F	1	1	1	1	1	1	1	1	1	1	1	1	1	1

CONJUNCTIVA (A=ERYTHEMA, B=CHEMOSIS, C=DISCHARGE)

ANIMAL NUMBER	SEX	DAY 1			DAY 2			DAY 3			DAY 4			DAY 7			DAY 14			DAY 21			
		A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	
010	N	3	4	3	3	4	3	3	4	3	3	4	3	3	4	0	1	2	0	1	2	0	0
019	N	3	4	3	3	4	3	3	4	3	3	4	3	3	4	0	1	3	0	2	3	0	1
020	N	3	4	3	3	4	3	3	4	3	3	4	2	3	4	3	3	4	3	3	4	3	1
054	F	3	4	1	3	4	3	3	4	2	3	4	1	3	4	3	3	4	3	3	4	3	1
072	F	3	4	3	3	4	3	3	4	2	2	4	0	1	2	0	1	2	0	1	2	0	0
073	F	3	4	3	3	4	3	3	4	3	3	4	3	3	4	2	3	4	3	3	4	3	1

**APPENDIX III**

**DESCRIPTION OF INDIVIDUAL OCULAR LESIONS**

<b><u>ANIMAL NUMBER</u></b>	<b>Day:</b>	<b><u>7</u></b>	<b><u>14</u></b>	<b><u>21</u></b>
818		-	-	-
819		Scab around eye Lackluster/pitting	-	-
820		Pannus formation Lackluster/pitting	Pannus formation	
854		Lackluster/pitting	-	-
822		-	-	-
823		Pannus formation Lackluster/pitting	Corneal bulging	Lackluster/pitting

0 0 2 2

**PRIMARY DERMAL IRRITATION STUDY OF  
DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) IN RABBITS**  
Study No. 700  
Test Article No. 230

**SUMMARY**

DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) was applied at a dose of 0.5 ml to each of two abraded and two non-abraded test sites on the shaved backs of six rabbits. All test sites were examined for signs of dermal irritation (edema, erythema and/or eschar formation) at 1, 3, 7, 14, and 21 days following test article application.

Edema, erythema and/or eschar formation were observed within the test sites of all rabbits at all scoring intervals. In addition, necrosis was evident 1, 3 and 7 days following test article application. Although severe erythema and/or eschar formation persisted throughout the study, a decrease in the severity of edema was noted in the majority of rabbits at the final scoring interval.

The Primary Dermal Irritation Score was 8.0/8.0. Therefore, DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) was judged to be a primary dermal irritant as defined by the Federal Hazardous Substances Labeling Act.

**STUDY PARTICIPANTS:**

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PRIMARY DERMAL IRRITATION STUDY OF  
DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) IN RABBITS

I. INTRODUCTION

The purpose of this study was to determine the primary dermal irritancy of DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) in rabbits.

II. MATERIALS AND METHODS

a. Test Article: DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198, identification no. 5507-146) was received November 2, 1983. The test article was a black liquid with a viscosity similar to gasoline. It was received in a glass jar and stored at room temperature (approximately 22°C).

b. Dosage Formulation: The test article was applied undiluted.

c. Animals: New Zealand albino rabbits were purchased from Hazelton Dutchland Laboratories, Denver, PA for use in this study. Upon arrival (11/8/83), the rabbits were held in quarantine for approximately 1 week and examined carefully to insure their health and suitability as test subjects. Rabbits selected for the study were identified by a unique numbered metal tag inserted through the pinna of the right ear and by a cage card.

d. Food and Water: Purina Lab Rabbit Chow HF #5326 (Ralston Purina Co., St. Louis, MO) and water supplied from a reverse-osmosis purifier by an automatic watering system were available *ad libitum*.

e. Environment: The rabbits were housed individually in stainless steel cages measuring 61.0 x 45.5 x 42.0 cm. Poly pads (12 ply, Shepherd Specialty Papers, Inc., Kalamazoo, MI) were placed in the pan below the stainless steel mesh floor of each animal cage to absorb liquids. Air conditioned animal rooms were maintained at approximately 22°C and 40% relative humidity. Fluorescent lighting was provided for 12 hours followed by 12 hours of darkness.

f. Methods:

1. Animals: Rabbits used on test were selected at random and assigned to a single group of four males and two females.
2. Skin Preparation: Approximately 24 hours prior to study initiation, fur was clipped from an area approximately 240 cm<sup>2</sup> on the back of each

rabbit, and the skin was examined for abnormalities. Rabbits found at that time to have significant skin abnormalities were excluded from the study. Immediately prior to dosing, four test sites (2.5 x 2.5 cm each), two on either side of the midline, were designated in the clipped area on the back of each rabbit. The test sites on the right side were abraded in a pattern with a hypodermic needle so as to penetrate the stratum corneum but not the dermis. The test sites on the left side were left intact.

3. Dosing: A 0.5 ml quantity of the test article was applied to each of the four test sites on November 15, 1983 and was covered with a 2.5 x 2.5 cm adhesive dressing (Coverlet<sup>R</sup>, Beiersdorf Inc., S. Norwalk, CN). The mid-section of the rabbit was wrapped in a lint-free cloth towel (Fisher Scientific) and elastic adhesive bandage (Elastoplast<sup>R</sup>, Beiersdorf Inc., S. Norwalk, CN), which prevented removal of the test article while allowing the rabbit free movement.

All wrapping materials and adhesive dressings were removed 24 hours after application, and the application sites were rinsed with a 0.9% sodium chloride solution and towel dried.

4. Observations: All rabbits were observed daily for mortality and morbidity.
5. Body Weights: The rabbits were weighed immediately prior to dosing.
6. Skin Examinations: Each test site was scored for irritation according to the method of Draize (Appendix I). The test sites were examined and scored 1, 3, 7, 14, and 21 days after application for edema, erythema and/or eschar formation.
7. Animal Disposition: After the final observation (12/6/83), the rabbits were sacrificed by anesthetic overdose and discarded without necropsy.

g. Evaluation: The scores obtained at each observation interval after test article application were weighted by the frequency of their occurrence. Only the weighted scores of day 1 and 3 were added and the sum divided by four to yield the Primary Dermal Irritation Score.

The test sites were examined 7, 14, and 21 days after application of the test material to determine the reversibility of the test article-induced dermal changes.

According to the Federal Hazardous Substances Labeling Act (38 FR 27012, Sept. 27, 1973; 38 FR 30105, Nov. 1, 1973), a score of 5.0 or greater out of a possible 8.0 defines the test article as a primary dermal irritant.

### III. RESULTS

- a. Mortality: No deaths were observed during the study.
- b. Body Weights: The weight range for rabbits used in this study was 2.6 to 3.0 kg.
- c. Skin Effects: The individual irritation scores were tabulated in Table I. Severe dermal irritation (edema, erythema and/or eschar formation) was observed within the test sites of all rabbits at all scoring intervals. In addition, all test sites were necrotic 1, 3 and 7 days following application of the test article. Although severe erythema and/or eschar formation persisted throughout the study, a decrease in the severity of edema was noted in the majority of rabbits at the final scoring interval.

### IV. EVALUATION

The calculations for the Primary Dermal Irritation Score are presented in Table 2. The Primary Dermal Irritation Score for this test article is 8.0. Therefore, DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) is a primary dermal irritant as defined by the Federal Hazardous Substances Labeling Act.

### V. QUALITY ASSURANCE

Laboratory operations were inspected on November 16 and December 1, 1983 by Josephine M. Reed. The raw data and final draft report were audited on March 9, 1984 by Josephine M. Reed. The study was found to be in compliance with ITRI Life Sciences Quality Assurance criteria. Original data generated during this study are maintained by the ITRI Life Sciences Archives as specified by standard operating procedures.

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VI. TABLES

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**TABLE 1**  
**Incidence and Summation of Responses**

Study Number: 700    Test Article Number: 230    Dose: 0.5 ml/site    Application sites = 12

SKIN REACTION: SKIN CONDITION:	<u>ERYTHEMA &amp;/OR ESCHAR</u>		<u>EDEMA</u>	
	<u>ABRADED</u>	<u>INTACT</u>	<u>ABRADED</u>	<u>INTACT</u>
SCORES 1 DAY FOLLOWING APPLICATION	0	0	0	0
	1	0	0	0
	2	0	0	0
	3	0	0	0
	4	12/12	12/12	12/12
SUMMATIONS:		48/12	48/12	48/12
SCORES 3 DAYS FOLLOWING APPLICATION	0	0	0	0
	1	0	0	0
	2	0	0	0
	3	0	0	0
	4	12/12	12/12	12/12
SUMMATIONS:		48/12	48/12	48/12

**TABLE 1 (cont.)**  
**Incidence and Summation of Responses**

**Study Number: 700    Test Article Number: 230    Dose: 0.5 ml/site    Application sites = 12**

SKIN REACTION: SKIN CONDITION:	<u>ERYTHEMA &amp;/OR ESCHAR</u>		<u>EDEMA</u>	
	<u>ABRADED</u>	<u>INTACT</u>	<u>ABRADED</u>	<u>INTACT</u>
0	0	0	0	0
1	0	0	0	0
<b>SCORES</b>	2	0	0	0
<b>7 DAYS</b>	3	0	0	0
<b>FOLLOWING</b>	4	12/12	12/12	12/12
<b>APPLICATION</b>				
<b>SUMMATIONS:</b>	48/12	48/12	48/12	48/12
0	0	0	0	0
1	0	0	0	0
<b>SCORES</b>	2	0	2/12	2/12
<b>14 DAYS</b>	3	0	10/12	10/12
<b>FOLLOWING</b>	4	12/12	0	0
<b>APPLICATION</b>				
<b>SUMMATIONS:</b>	48/12	48/12	34/12	34/12

**TABLE 1 (cont.)  
Incidence and Summation of Responses**

**Study Number: 700    Test Article Number: 230    Dose: 0.5 ml/site    Application sites = 12**

SKIN REACTION: SKIN CONDITION:	<u>ERYTHEMA &amp;/OR ESCHAR</u>		<u>EDEMA</u>	
	<u>ABRADED</u>	<u>INTACT</u>	<u>ABRADED</u>	<u>INTACT</u>
0	0	0	0	0
1	0	0	0	0
2	0	0	8/12	6/12
3	0	0	2/12	4/12
4	12/12	12/12	2/12	2/12
<b>SUMMATIONS:</b>	<b>48/12</b>	<b>48/12</b>	<b>30/12</b>	<b>32/12</b>

SCORES  
21 DAYS  
FOLLOWING  
APPLICATION

**TABLE 2**  
**Primary Skin Irritation Score**

**Study Number: 799 Test Article Number: 230 Dose: 0.5 ml/site Application sites = 12**

SKIN REACTION:	<u>ERYTHEMA &amp;/OR ESCHAR</u>		<u>EDEMA</u>	
	<u>ABRADED</u>	<u>INTACT</u>	<u>ABRADED</u>	<u>INTACT</u>
<b>1 DAY FOLLOWING APPLICATION</b>	48/12	48/12	48/12	48/12
			<b>SUBTOTAL A</b>	<b>192/12</b>
<b>3 DAYS FOLLOWING APPLICATION</b>	48/12	48/12	48/12	48/12
			<b>SUBTOTAL B</b>	<b>192/12</b>

---

**SUBTOTAL A + SUBTOTAL B = TOTAL SCORE**

**192/12 + 192/12 = 384/12**

**TOTAL SCORE / 4 = PRIMARY SKIN IRRITATION SCORE**

**384/12 / 4 = 8.0**

0 0 3 2

**VII. APPENDICES**

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## APPENDIX I

### SCALE FOR SCORING SKIN LESIONS\*

#### 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 (injuries in depth)	4

##### **Edema formation:**

No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1.0 mm)	3
Severe edema (raised more than 1.0 mm extending beyond the area of exposure)	4

The mean scores for erythema and/or eschar formation for intact skin at 24 and 72 hours are added to the values for abraded skin at 24 and 72 hours. Similarly, the values for edema formation at 24 hours and 72 hours for the intact and abraded skin will be summed. The primary irritation score is the total of the eight values divided by four. A primary irritant is one which results in a score of five or more as tested by this method.

\*Draize, J.H., Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics, Assoc. Food and Drug Officials of the U.S., Austin, Texas, 1959.

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APPENDIX II

INDIVIDUAL SKIN IRRITATION SCORES

Study Number 700

Test Article Number 230

Day 1 Scoring:

<u>Animal Number</u>	<u>Sex</u>	<u>Erythema and/or Eschar</u>		<u>Edema</u>	
		<u>Abraded</u>	<u>Intact</u>	<u>Abraded</u>	<u>Intact</u>
867	M	4.4	4.4	4.4	4.4
868	M	4.4	4.4	4.4	4.4
869	M	4.4	4.4	4.4	4.4
870	M	4.4	4.4	4.4	4.4
871	F	4.4	4.4	4.4	4.4
872	F	4.4	4.4	4.4	4.4

All test sites white/green (necrosis)

Day 3 Scoring:

<u>Animal Number</u>	<u>Sex</u>	<u>Erythema and/or Eschar</u>		<u>Edema</u>	
		<u>Abraded</u>	<u>Intact</u>	<u>Abraded</u>	<u>Intact</u>
867	M	4.4	4.4	4.4	4.4
868	M	4.4	4.4	4.4	4.4
869	M	4.4	4.4	4.4	4.4
870	M	4.4	4.4	4.4	4.4
871	F	4.4	4.4	4.4	4.4
872	F	4.4	4.4	4.4	4.4

All test sites necrotic

Day 7 Scoring:

<u>Animal Number</u>	<u>Sex</u>	<u>Erythema and/or Eschar</u>		<u>Edema</u>	
		<u>Abraded</u>	<u>Intact</u>	<u>Abraded</u>	<u>Intact</u>
867	M	4.4	4.4	4.4	4.4
868	M	4.4	4.4	4.4	4.4
869	M	4.4	4.4	4.4	4.4
870	M	4.4	4.4	4.4	4.4
871	F	4.4	4.4	4.4	4.4
872	F	4.4	4.4	4.4	4.4

All test sites necrotic

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APPENDIX II (cont'd)

INDIVIDUAL SKIN IRRITATION SCORES

Study Number 700

Test Article Number 250

Day 14 Scoring:

Animal Number	Sex	Erythema and/or Eschar		Edema	
		Abraded	Intact	Abraded	Intact
867	M	4.4	4.4	3.3	3.3
868	M	4.4	4.4	2.2	2.2
869	M	4.4	4.4	3.3	3.3
870	M	4.4	4.4	3.3	3.3
871	F	4.4	4.4	3.3	3.3
872	F	4.4	4.4	3.3	3.3

Day 21 Scoring:

Animal Number	Sex	Erythema and/or Eschar		Edema	
		Abraded	Intact	Abraded	Intact
867	M	4.4	4.4	2.2	3.3
868	M	4.4	4.4	4.4	4.4
869	M	4.4	4.4	3.3	3.3
870	M	4.4	4.4	2.2	2.2
871	F	4.4	4.4	2.2	2.2
872	F	4.4	4.4	2.2	2.2

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ACUTE DERMAL TOXICITY STUDY OF  
DIALKYL DITHIOPHOSPHORIC ACID  
(PRECURSOR OF A-198) IN RABBITS

Study No. 701  
Test Article No. 230

## SUMMARY

DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) was applied at a dose of 2 g/kg to the abraded shaved backs of five male and five female rabbits. The test article was left in contact with the skin for 24 hours and then removed. The rabbits were observed during this time and for 14 days thereafter.

No rabbits died during the study. Therefore, the acute median lethal dermal dose is estimated to be greater than 2 g/kg.

The clinical signs observed following test article administration included motor incoordination, decreased motor activity, loss of righting reflex, and cyanosis. Recovery from most of these signs was evident by the 3rd day. Dermal irritation (edema, necrosis and/or ulceration) was also noted in all rabbits following unwrapping and persisted through the final observation. Gross necropsy findings consisted of pitted kidneys in one female rabbit. Findings in the remaining rabbits were within normal limits.

## STUDY PARTICIPANTS:

Vladislava S. Rac, D.V.M., M.S., Study Pathologist  
Christopher Lord, Technician  
Calvin Reaves, Animal Care  
This report was prepared by Marcia Reckers

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ACUTE DERMAL TOXICITY STUDY OF  
DIALKYL DITHIOPHOSPHORIC ACID  
(PRECURSOR OF A-198) IN RABBITS

I. INTRODUCTION

The purpose of this study was to determine the acute dermal toxicity of DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) in rabbits.

II. MATERIALS AND METHODS

a. Test Article: DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198), identification no. 5507-146, was received November 2, 1983. The test article was a black liquid with a viscosity similar to gasoline. It was received in a glass jar and stored at room temperature (approximately 22°C).

b. Dosage Formulation: The test article was applied undiluted. Doses were applied by weight but measured by volume, the equivalency being determined by the density of the material (calculated as 0.9991 g/ml).

c. Animals: New Zealand albino rabbits were purchased from Hazelton Ditchland Laboratories, Denver, PA, for use in this study. Upon arrival (11/22/83), the rabbits were held in quarantine for approximately 3 weeks and examined carefully to insure their health and suitability as test subjects. Rabbits selected for the study were identified by a unique numbered metal tag inserted through the pinna of the right ear and by a cage card.

d. Food and Water: Purina Lab Rabbit Chow HF #5326 (Ralston Purina Co., St. Louis, MO) and water supplied from a reverse-osmosis purifier by an automatic watering system were available *ad libitum*.

e. Environment: The rabbits were housed individually in stainless steel cages measuring 61.0 x 45.5 x 42.0 cm. Poly pads (12 ply, Shepherd Specialty Papers, Kalamazoo, MI) were placed in the pan below the stainless steel mesh floor of each animal cage to absorb liquids. Air conditioned animal rooms were maintained at approximately 22°C and 40% relative humidity. Fluorescent lighting was provided for 12 hours followed by 12 hours of darkness.

**f. Methods:**

1. **Animals:** Rabbits used on test were selected at random and assigned to a single group of five males and five females.
2. **Skin Preparation:** Approximately 24 hours prior to study initiation, fur was clipped from an area of approximately 240 cm<sup>2</sup> on the back of each rabbit and the skin was examined for abnormalities. Immediately prior to dosing, the back of each rabbit was abraded in a pattern with a hypodermic needle so as to penetrate the stratum corneum, but not the dermis.
3. **Dosing:** Two grams of test article per kilogram of body weight were applied uniformly to the abraded site on the back of each rabbit on December 13, 1983, and were covered with a 12.8 x 23.0 cm surgical dressing (Surgipad<sup>R</sup>, J & J Products, New Brunswick, NJ). The pad was covered by plastic film and then secured by lint-free cloth toweling (Fisher Scientific) and elastic adhesive bandage (Elastoplast<sup>R</sup>, Beiersdorf Inc., S. Norwalk, CN), which prevented removal of the test article while allowing the rabbit free movement.

The wrappings were removed after 24 hours, and the application site was rinsed using 0.9% sodium chloride solution then towel dried.

4. **Observations:** All test rabbits were observed approximately 1-1/2, 3, and 4 hours after dosing and at least once per day for 14 days after removal of the wrappings.
5. **Body Weights:** All test animals were weighed immediately prior to dosing and the weights used for dosage calculations.
6. **Necropsies:** All rabbits were sacrificed at the end of the observation period (12/28/83) by anesthetic overdose and necropsied.

**III. RESULTS**

- a. **Mortality:** No deaths were observed during the study.
- b. **Body Weights:** The weight range for rabbits used in this study was 2.6 to 3.0 kg.

c. Daily Observations: The clinical signs observed in all rabbits following test article administration consisted of cyanosis and a decrease in motor activity. Other symptoms included motor incoordination in the majority of rabbits, and loss of righting reflex in four rabbits. Recovery from most of these signs occurred by the 3rd day. Following unwrapping, necrosis and edema were observed within the application sites of all rabbits and ulceration was present in eight rabbits. Dermal irritation persisted in all rabbits through the final observation.

d. Gross Pathology: Gross necropsy findings consisted of pitted kidneys in one female rabbit. Findings in the remaining rabbits were within normal limits.

#### IV. EVALUATION

Based on the results of this study, the acute median lethal dermal dose ( $LD_{50}$ ) for DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) is estimated to be greater than 2 g/kg.

#### V. QUALITY ASSURANCE

Laboratory operations were inspected on December 22, 1983 by Josephine M. Reed. The final draft report was audited on April 3, 1984 by Josephine M. Reed. The study was found to be in compliance with IITRI Life Sciences Quality Assurance criteria. Original data generated during this study are maintained in the IITRI Life Sciences Archives as specified by standard operating procedures.

VI. TABLE

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TABLE I  
SUMMARY OF CLINICAL OBSERVATIONS  
(5 rabbits/sex)

Observation:	Incidence	
	Males	Females
Motor incoordination	4	5
Decreased motor activity	5	5
Loss of righting reflex	3	1
Cyanosis	5	5
Skin (application site):		
Necrosis	5	5
Edema	5	5
Ulceration	4	4

**ACUTE INHALATION TOXICITY STUDY OF  
DIALKYL DITHIOPHOSPHORIC ACID  
(PRECURSOR OF A-198) IN RATS  
Study No. 702DR  
Test Article No. 230**

**SUMMARY**

DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) was administered as a vapor by inhalation to two groups, each consisting of 5 male and 5 female Sprague-Dawley rats. Each group was exposed for 4 hours to the vapors given off from a single, but separate batch of the test article. In the first group (Group I) the test article was preheated to 66.1°C before the start of the exposure, whereas in the second group (Group II) the test article was heated from room temperature to 66.0°C during the exposure. The estimated nominal concentrations for Group I and Group II were 0.69 - 1.03 mg/l and 0.17 - 0.51 mg/l, respectively. All surviving rats were observed for 14 days following the exposure.

One female rat from Group I died during the exposure and no deaths occurred in the second group, therefore, the 4-hour acute inhalation median lethal concentration (LC<sub>50</sub>) of DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-198) in male and female rats was estimated to be greater than the maximum attainable concentration achieved under the conditions of this study.

Clinical observations noted during the exposure included convulsions, severe salivation, increased respiratory rate, breathing difficulty, and death. Clinical observations noted in rats immediately following exposure included discolored facial fur, salivation, red nasal discharge, and dyspnea. The majority of rats from both groups returned to normal on the day following the exposure and remained normal for the remainder of the observation period.

At necropsy, the rat which died during the exposure had red, edematous lungs, and gas-filled intestines. Gross necropsy findings in some rats which survived to the end of the observation period included red or mottled lungs, red and/or brown lung foci, and tan kidneys. However, necropsy findings in the majority of rats were within normal limits.

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**ACUTE INHALATION TOXICITY STUDY OF  
DIALKYL DITHIOPHOSPHORIC ACID  
(PRECURSOR OF A-100) IN RATS**

**I. INTRODUCTION**

The purpose of this study was to determine the acute inhalation toxicity of DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-100) in rats.

**II. MATERIALS AND METHODS**

a. Test Article: DIALKYL DITHIOPHOSPHORIC ACID (PRECURSOR OF A-100), identification no. 5507-146, was received November 2, 1983. The test article was a black liquid with a viscosity similar to water and was stored in the original container at room temperature (approximately 22°C).

b. Test Atmosphere Generation: The generating system used is described in Appendix 1.

c. Animals: Male and female Sprague-Dawley rats weighing approximately 135 g were purchased from Charles River Breeding Labs Inc., Portage, MI, for use in this study. Upon arrival (11/2/83), all rats were held in quarantine for 2 weeks and examined carefully to insure their health and suitability as test subjects. Rats selected for the study were identified by a unique numbered metal tag inserted through the pinna of the right ear and by a cage card.

d. Food and Water: Purina Rodent Chow 5001 (Ralston Purina Company, St. Louis, MO) and water supplied from a reverse-osmosis purifier by an automatic watering system were available ad libitum except during the exposure period.

e. Environments: During the quarantine period and the post-exposure observation period, the rats were housed individually in suspended stainless steel cages measuring 18.4 x 16.5 x 15.9 cm. Deotized animal cage boards (Shepherd Specialty Papers, Kalamazoo, MI) were provided beneath the suspended cages. Air conditioned animal rooms were maintained at approximately 22°C and 40% relative humidity. Fluorescent lighting was provided automatically for 12 hours followed by 12 hours of darkness. During the inhalation exposure, the rats were housed individually in perforated metal exposure cages measuring 23 x 8 x 8 cm.

**f. Methods**

1. Assignment to Groups: Rats were randomly selected for testing and assigned to two groups of five males and five females each. There was no control group.

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2. **Exposure:** The exposures were conducted using two groups of rats. In the first group (Group I), the test article was preheated to 66.1°C before the start of the exposure, whereas in the second group (Group II) the test article was heated from room temperature (approximately 22°C) to 66.0°C during the exposure. The exposure was performed on November 17, 1983 for Group I and November 18, 1983 for Group II. Each group was exposed for 4 hours to the highest concentration attainable under the experimental conditions used. At the end of the 4-hour period, the generator was disconnected from the chamber and the chamber was allowed approximately 20 minutes to flush out before the animals were removed.
3. **Test Atmosphere Monitoring:** The nominal concentration of the test article in the exposure atmosphere was determined by dividing the quantity of the test article consumed by the volume of air passed through the chamber during the 4-hour exposure period. Chamber temperature and humidity were monitored during the exposure.
4. **Daily Observations:** All surviving test animals from each group were observed during and several times following the exposure, and at least once per day for the balance of the 14-day observation period.
5. **Body Weights:** All test rats were weighed immediately prior to the exposure.
6. **Necropsies:** A necropsy was immediately performed on the rat which died during the study. All rats which survived to the end of the observation period (12/1/83 and 12/2/83 for Groups I and II, respectively) were sacrificed by an anesthetic overdose and necropsied.

### III. RESULTS:

- a. **Mortality:** One female rat from Group I died during the exposure. No other deaths occurred during the study.
- b. **Chamber Concentration:** The test article temperature ranged from 66.1°C to 66.3°C for Group I, and from room temperature (approximately 22°C) to 66.0°C for Group II. It took approximately one hour for the test article to reach the desired temperature causing the rats to be exposed at the desired temperature for approximately three hours. The chamber flow for both groups was 24.5 liter/min. The flask containing the test article was weighed prior to being placed in the oil bath and reweighed at the

end of the exposure after the outside surface was washed twice with acetone and dried. The difference between the pre- and post-exposure weight of the flask was 5.0 g for Group I and 2.0 g for Group II. Since the reproducibility of the balance used was  $\pm 1.0$  gram (2.5 g pre-weight plus 0.5 g post-weight), it is estimated that the weight loss ranged from 1 to 3 grams for Group I and from 1 to 3 grams for Group II. The resultant nominal concentration range for Group I and Group II was 0.60 - 1.83 mg/l and 0.17 - 0.51 mg/l, respectively.

c. Chamber Conditions: The average temperature for both exposure groups was 24°C. The average relative humidity for Group I and Group II was 63% and 74%, respectively.

d. Daily Observations: Clinical observations noted in both groups during the exposures included convulsions, severe salivation, increased respiratory rate, and breathing difficulty. The observations appeared sooner in Group I than in Group II, however, the rats began to recover by the end of the exposure in both groups. Discolored facial fur and rales were also observed in rats from both groups immediately following the exposure, and approximately two hours post-exposure. Clinical signs noted in Group I only following the exposure included salivation, red nasal discharge or redness around the nose, breathing difficulty, hypothermia and hyperactivity. With the exception of discolored facial fur and redness around the nose, which were noted on days one and two after the exposure, all rats returned to normal and remained so for the remainder of the 14-day observation period. A summary of clinical signs is presented in Table 4.

e. Body Weights: The mean initial body weights for male and female rats in both groups were 281 g and 199 g, respectively.

f. Gross Pathology: Gross necropsy findings in the female rat from Group I, which died in study, included dark red and edematous lungs, and gas-filled intestines. Red lung foci were observed in one rat in Group I and two rats from Group II. Mottled and red lungs, and ten kidneys were observed in Group I only. Necropsy findings in three males and three females in Group I and four males and four females in Group II were within normal limits. All necropsy findings are presented in Table 5.

#### IV. EVALUATION

Based on the results of this study, the 4-hour acute inhalation median lethal concentration ( $LC_{50}$ ) of DIALKYL ETHIOPHOSPHORIC ACID (PRECURSOR OF A-150) in male and female rats was estimated to be greater than the maximum attainable concentration achieved under the conditions of this study.

**V. QUALITY ASSURANCE**

Laboratory operations were inspected on November 16 and 22, 1983. The final draft report was audited on January 19, 1984. Inspections and audits were performed by Josephine M. Reed. All operations were found to be in compliance with Life Sciences Quality Assurance criteria. Raw data generated during the course of the study are retained in the HTRI Life Sciences Archives as specified by standard operating procedures.

**VI. TABLES**

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TABLE 1  
Clinical Observations Noted During Exposures

<u>Observation</u>	<u>Group I</u> <u>(0.69 - 1.03 mg/l)</u>	<u>Group II</u> <u>(0.17 - 0.51 mg/l)</u>
Hyperactivity	X	—
Increased Respiratory Rate	X	—
Breathing Difficulty	X	X
Salivation	X	X
Convulsions	—	X

X = indicates a general observation noted

Note: Definitive individual observations could not be performed on animals in the chamber during the exposure.

TABLE 2

Incidence of Mortality and Clinical Observations for Group I,  
2 Hours, 4 Hours, 1 Day, and 2 Days Following Exposure  
(5 rats/sex)

<u>Observation</u>	<u>GROUP I (0.69 - 1.03 mg/l)</u>							
	<u>2 Hours</u>		<u>4 Hours</u>		<u>1 Day</u>		<u>2 Days</u>	
	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>
Death	-	1	-	-	-	-	-	-
Discolored Facial Fur	5	4	5	4	1	-	-	-
Red Nasal Discharge	3	3	-	-	-	-	-	-
Redness Around Nose	-	-	-	1	-	-	3	-
Breathing Difficulty/Rales	2	1	3	1	-	-	-	-
Salivation	2	1	-	-	-	-	-	-
Hypothermia	1	-	-	-	-	-	-	-
Discolored Paws	1	-	-	-	-	-	-	-

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TABLE 3

Incidence of Mortality and Clinical Observations for Group II,  
1.5 Hours, 3 Hours, 1 Day, and 2 Days Following Exposure  
(5 rats/sex)

<u>Observation</u>	<u>GROUP II (0.17 - 0.51 mg/l)</u>							
	<u>1.5 Hours</u>		<u>3 Hours</u>		<u>1 Day</u>		<u>2 Days</u>	
	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>
Death	-	-	-	-	-	-	-	-
Discolored Facial Fur	5	2	5	2	-	-	-	-
Breathing Difficulty/Rales	1	1	-	-	-	-	-	-

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**TABLE 4**  
**SUMMARY**  
**Incidence of Mortality and Clinical Observations**  
**Following the Exposure**  
**(5 rats/sex/group)**

<u>Observation</u>	<u>Group I</u> <u>(0.69 - 1.03 mg/l)</u>		<u>Group II</u> <u>(0.17 - 0.51 mg/l)</u>	
	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>
Death	-	1	-	-
Normal	-	-	-	2
Discolored facial fur	5	4	5	2
Salivation	2	1	-	-
Redness around nose	3	1	-	-
Red nasal discharge	3	3	-	-
Breathing difficulty/Rales	4	2	1	1
Hypothermia	1	-	-	-
Discolored paws	1	-	-	-

TABLE 5  
Incidence of Gross Necropsy Observations  
(5 rats/sex/group)

<u>Observation</u>	<u>Group I</u> (0.69 - 1.03 mg/l)		<u>Group II</u> (0.17 - 0.51 mg/l)	
	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>
Normal	3	3	4	4
Lungs:				
red/brown foci	1	-	1	1
mottled	-	1	-	-
red	-	2	-	-
edematous	-	1	-	-
Kidneys:				
tan	1	-	-	-
Intestines:				
gas-filled	-	1	-	-

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VII. APPENDICES

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APPENDIX 1

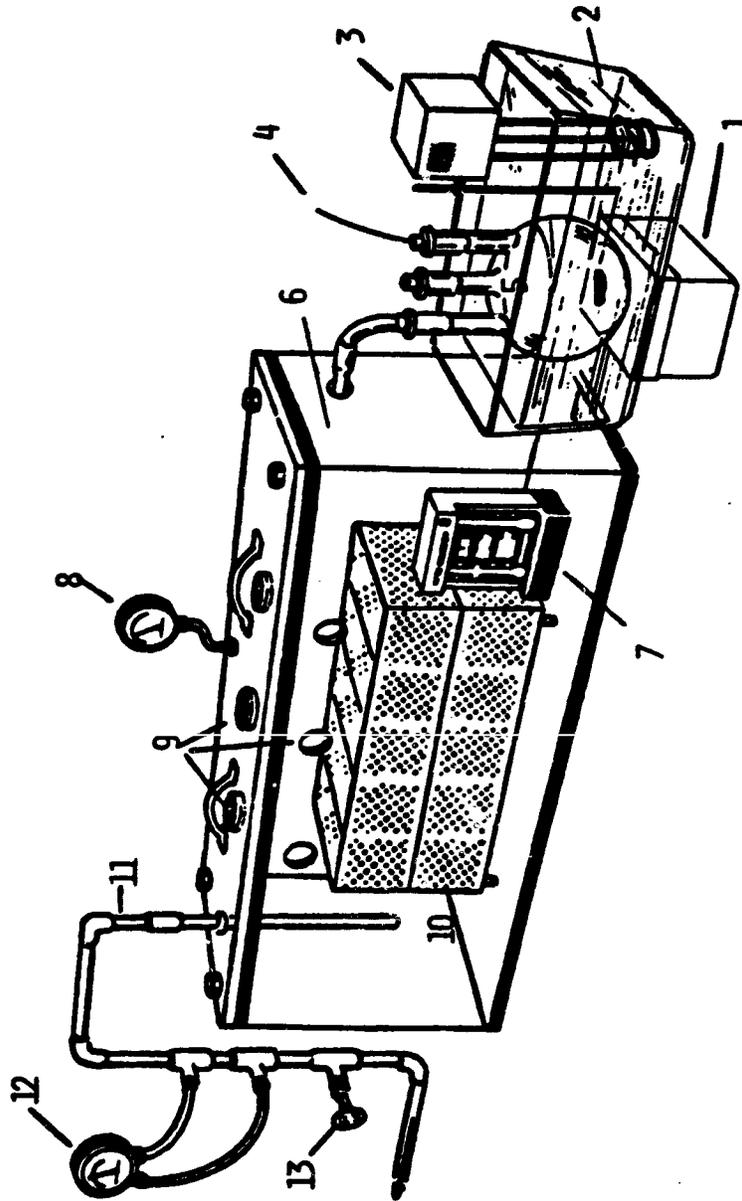
**Generating and Exposure System**

The generating system consisted of a 3-neck flask with 3000 ml capacity. The final weight of the flask containing the test article for Group I and Group II was 2869 and 3513 grams, respectively. The flask was submerged in an oil bath and the oil was heated with an immersion heater (Wheaton Model 903475, Cole Parmer Co., Chicago, IL).

The 3-neck flask was connected to the exposure chamber with all air to the chamber being drawn across the head space of the flask, carrying test article vapor into the chamber. The test article was stirred using an overhead stirrer (Wheaton Instruments, Millville, NJ) with a stainless steel stirring rod. This method of exposure atmosphere generation was recommended by the Sponsor, and is supposed to simulate possible exposure conditions.

The chamber measured 30 x 30 x 74.5 cm (70 liters) and was made of glass. The chamber top was made of Plexiglass<sup>R</sup>, and was removable to allow loading and unloading of animals. The test article vapor entered the chamber through a port near the top of one end of the chamber and exited through a pipe placed near the bottom of the chamber on the opposite end. The chamber exhaust was vented through a charcoal filter. A California-type fume hood enclosed the entire generation and exposure system.

**GENERATING AND EXPOSURE SYSTEM**



- |                      |                                |                              |
|----------------------|--------------------------------|------------------------------|
| 1- MAGNETIC STIRRER  | 6- 70-LITER EXPOSURE CHAMBER   | 11- CHAMBER EXHAUST          |
| 2- OIL BATH          | 7- HYGROMETER                  | 12- FLOW PRESSURE MAGNETELIC |
| 3- IMMERSION HEATER  | 8- CHAMBER PRESSURE MAGNETELIC | 13- FLOW VALVE               |
| 4- TEMPERATURE PROBE | 9- SAMPLE PORTS                |                              |
| 5- 3-NECK FLASK      | 10- EXPOSURE CAGES             |                              |

ACUTE INHALATION TOXICITY STUDY OF  
AMOCO 198 ACID IN RATS

Study No. 1060  
Test Article No. 230

SUMMARY

Amoco 198 Acid was heated to approximately 100°C and administered by inhalation to a group of five male and five female Sprague-Dawley rats. The rats were exposed for 4 hours to a test atmosphere concentration of 0.198 mg/l (nominal), which included a hydrogen sulfide (H<sub>2</sub>S) concentration of 74.2 ppm.

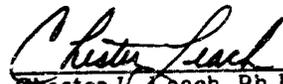
Clinical observations included lacrimation during exposure, salivation and redness/discoloration around the nose and mouth after exposure, with return to normalcy within 7 days after exposure.

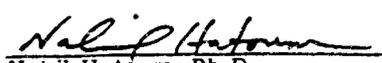
No rats died during the study. Therefore the 4-hour acute inhalation median lethal concentration (LC<sub>50</sub>) of Amoco 198 Acid in male and female rats was estimated to be greater than 0.198 mg/l (and 74.2 ppm of H<sub>2</sub>S).

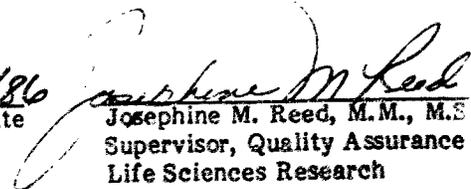
All rats gained weight during the study. Serum cholinesterase levels were unaffected by inhalation exposure to the test article. At necropsy, one female rat had gray lungs while findings in the remaining nine rats were within normal limits.

STUDY PARTICIPANTS:

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## ACUTE INHALATION TOXICITY STUDY OF AMOCO 198 ACID IN RATS

### I. INTRODUCTION

The purpose of this study was to determine the acute inhalation toxicity of Amoco 198 Acid and its effect on serum cholinesterase levels in rats.

### II. MATERIALS AND METHODS

a. Test Article: Amoco 198 Acid (identification no. 10820-21) was received May 5, 1986. The test article was a brown/olive-colored liquid. It was stored in its original container at room temperature (approximately 22°C).

b. Test Atmosphere Generation: The generating system used to produce a test atmosphere of the test article, and the H<sub>2</sub>S resulting from it, is described in Appendix 1.

c. Animals: Male and female Sprague-Dawley rats weighing approximately 135 g were purchased from Charles River Breeding Laboratories, Inc., Portage, MI, for use in this study. Upon arrival (8/20/86), all rats were held in quarantine for approximately four weeks and examined carefully to ensure their health and suitability as test subjects. Rats selected for the study were identified by a unique numbered metal tag inserted through the pinna of the right ear and by a cage card.

d. Food and Water: Purina Rodent Chow 5001 (Ralston Purina Company, St. Louis, MO) and water supplied from a reverse-osmosis purifier by an automatic watering system were available *ad libitum* except during the exposure period.

e. Environment: During the four-week quarantine and the post-exposure observation periods, the rats were housed individually in suspended stainless steel cages measuring 18.4 x 16.5 x 15.9 cm. Deotized animal cage boards (Shepherd Specialty Papers, Kalamazoo, MI) were provided beneath the suspended cages except during the exposure. Air conditioned animal rooms were maintained at approximately 22°C and 40% relative humidity. Fluorescent lighting was provided automatically for 12 hours followed by 12 hours of darkness. Rats were exposed in cages measuring 23.0 x 6.0 x 9.5 cm.

#### f. Methods:

1. Assignment to Groups: Rats were randomly selected for testing and assigned to a single group of five males and five females. There was no control group.

The rats were exposed for 4 hours to a test atmosphere containing a single batch of the test article on September 17, 1986.

**Test Atmosphere Concentration:** The nominal concentration of the test article in the atmosphere was determined by dividing the quantity of the test article consumed by the volume of air passed through the chamber during the 4-hour exposure period. The actual concentration of H<sub>2</sub>S in the exposure atmosphere was determined by injecting known volumes of the test atmosphere into a gas chromatograph (GC; Varian model 3700, Sugarland, TX), equipped with a flame photometric detector (Varian, Sugarland, TX) and calibrated with reference standards of H<sub>2</sub>S (Appendix 2).

4. **Daily Observations:** All test animals were observed during, immediately following, and approximately 2-1/2 hours after exposure, and at least once per day for the balance of the 14-day observation period.
5. **Body Weights:** All test rats were weighed immediately prior to exposure and again one week and two weeks after exposure.
6. **Serum Cholinesterase:** Blood samples were drawn via the orbital sinus from all rats approximately 18 hours before and 30 minutes following exposure and analyzed (in triplicate) for serum cholinesterase levels, using a cholinesterase reagent set (Boehringer Mannheim Diagnostics, Indianapolis, IN).
7. **Necropsies:** After the 14-day observation period (10/2/86), all surviving rats were euthanized by anesthetic overdose and subjected to a gross necropsy.

### III. RESULTS

- a. **Mortality:** No deaths occurred during the study.
- b. **Exposure Concentration:** The nominal concentration was 0.198 mg/l of test article. The time weighted average (TWA) concentration of H<sub>2</sub>S was 74.2 ppm.
- c. **Chamber Conditions:** The average chamber temperature was 23.8°C with a relative humidity range of 58 to 70%.
- d. **Daily Observations:** Lacrimation was noted in two rats during the exposure. Salivation, redness around the nose, and discoloration around the mouth were observed following the exposure (Table 1). Redness around and bulging of the right eye, caused by

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bleeding via the orbital sinus, were seen in three male and two female rats. One male rat showed no adverse signs at all during the study and all rats appeared normal by day 8.

e. Body Weight: The mean initial body weights of the male and female rats were 308 g and 215 g, respectively (Table 2). All rats gained weight during the study.

f. Serum Cholinesterase: Results of serum cholinesterase determinations are summarized in Table 3. No consistent pattern of effects on serum cholinesterase levels was apparent.

g. Gross Pathology: Gray lungs were observed in one female rat (Table 4). Necropsy findings in the other nine rats were within normal limits.

#### IV. EVALUATION

Based on the results of this study, the 4-hour acute inhalation median lethal concentration (LC<sub>50</sub>) of Amoco 198 Acid in male and female rats was estimated to be greater than 0.198 mg/L.

#### V. QUALITY ASSURANCE

Laboratory operations were inspected on September 17, 1986 by Josephine M. Reed. The final draft report was audited on November 12, 1986 by Julie McPhillips. All operations were found to be in compliance with Life Sciences Quality Assurance criteria. Raw data generated during the course of the study are retained in the ITRI Life Sciences Archives as specified by standard operating procedures.

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**VI. TABLES**

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TABLE 1  
Incidence Summary Of Clinical Observations  
(5 Rats/Sex)

<u>Observation*</u>	<u>Incidence</u>	
	<u>Males</u>	<u>Females</u>
Normal	1	0
Salivation	2	1
Redness around nose	3	5
Discoloration around mouth	1	3
Redness around eyes**	3	2
Eye bulging**	1	1

\*Lacrimation was also noted in two rats during the exposure.  
\*\*Considered to be a consequence of orbital sinus bleeding.

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**TABLE 2**  
**Summary of Body Weights**  
**(5 Rats/Sex)**

**MALES**

<u>Animal Number</u>	<u>Body Weight (g)</u>			<u>Cumulative Body Weight Change (g) (Week 2 - Week 0)</u>
	<u>Week 0</u>	<u>Week 1</u>	<u>Week 2</u>	
41	320	342	365	45
42	319	336	362	43
43	286	296	321	35
44	314	331	346	32
45	303	320	341	38
Mean	308	325	347	
S.D.*	14.2	18.1	17.8	

**FEMALES**

<u>Animal Number</u>	<u>Body Weight (g)</u>			<u>Cumulative Body Weight Change (g) (Week 2 - Week 0)</u>
	<u>Week 0</u>	<u>Week 1</u>	<u>Week 2</u>	
46	198	211	219	21
47	220	218	242	22
48	231	231	243	12
49	217	233	249	32
50	209	227	239	29
Mean	215	224	238	
S.D.	12.3	9.3	11.4	

\*S.D. = Standard Deviation

TABLE 3  
Summary of Serum Cholinesterase Analyses\*  
(5 Rats/Sex)

Serum Cholinesterase Concentration (ug/l)

MALES			
<u>Animal Number</u>	<u>Pre-Exposure</u>	<u>Post-Exposure</u>	
41	324.3 ± 14.4**	338.7 ± 4.0	
42	420.0 ± 12.0	442.0 ± 3.5	
43	354.3 ± 99.1	304.0 ± 6.0	
44	330.0 ± 3.5	332.3 ± 7.5	
45	403.3 ± 9.7	365.0 ± 3.5	
Mean ± SD of male values	366.4 ± 43.2	356.0 ± 52.5	
FEMALES			
46	1339.0 ± 10.4	1217.7 ± 11.0	
47	1741.0 ± 12.0	1542.3 ± 21.6	
48	1729.0 ± 15.9	1587.0 ± 72.5	
49	1700.7 ± 13.1	1790.0 ± 12.0	
50	1506.0 ± 15.1	1504.0 ± 20.8	
Mean ± SD of female values	1603.1 ± 175.8	1528.2 ± 205.7	

\* The pre and post-exposure values were not significantly different (t-test,  $p < 0.05$ ).

\*\* Mean ± S.D. (Standard Deviation) of 3 readings per sample.