CODING FORMS FOR SRC INDEXING

Microfiche No.		
OTS0000901G5		
New Doc ID	Old Doc ID	
OTS FYI-0892-0901		
Date Produced	Date Received	TSCA Section
12/03/85	08/24/92	FYI
Submitting Organization		
PHILLIPS PETROLEUM CO		
Contractor		
HAZLETON LABORATORIES		
Document Title		
TOXICOLOGICAL INVESTIGATION OF API 83-09 (STRAIGHT RUN KEROSINE)		
Chemical Category		
API 83-09 (STRAIGHT RUN KEROSINE)		

Contains No CBI

90165

Toxicology Read File

2926

American Petroleum Institute
1220 L Street, Northwest
Washington, D.C. 20005
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Health and Environmental
Sciences Department

API HESD Res Publ:

32-32858

ACUTE ORAL TOXICITY STUDY IN RATS
ACUTE DERMAL TOXICITY STUDY IN RABBITS
PRIMARY DERMAL IRRITATION STUDY IN RABBITS
PRIMARY EYE IRRITATION STUDY IN RABBITS
DERMAL SENSITIZATION STUDY IN GUINEA PIGS

API 83-09
STRAIGHT RUN KEROSINE
(CAS 8008-20-6)

STUDY CONDUCTED UNDER CONTRACT PS-45 BY:

Hazleton Laboratories America, Inc.
Madison WI.

December 1985

An equal opportunity employer

American Petroleum Institute
1220 L Street, Northwest
Washington, D.C. 20005
202-682-8000

American Petroleum Institute
Health and Environmental Sciences Department

QUALITY ASSURANCE STATEMENT

Study Title: Acute Oral Toxicity, Aucte Dermal Toxicity, Primary Dermal Irritation, Primary Eye Irritation, Dermal Sensitization Study of API 83-09

Testing Facility Number: HLA 40602086

API Product Safety Number: PS-45

This study was reviewed by API Quality Assurance personnel on the dates indicated below for compliance with applicable Good Laboratory Practice regulations.

Copies of reports by API Quality Assurance personnel are available upon written request to the Director of the Health and Environmental Sciences Department of the American Petroleum Institute or his designee.

Date(s) of Inspection/Review	Type of Inspection
May 22, 1985	Review of Raw Data and Draft Final Report (Oral Tox, Dermal Tox, Primate Dermal, Eye)
June 11, 1985	Review of Raw Data and Draft Final Report (Dermal Sensitization)
December 2, 1985	Acceptance of Final Report

Kenneth L. Bristol
Kenneth L. Bristol
Quality Assurance Associate

12-3-85
Date

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HAZLETON LABORATORIES AMERICA, INC

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ABSTRACT

Test material (83-09) was evaluated for acute oral toxicity in rats; acute dermal toxicity, primary skin irritation and primary eye irritation in rabbits; and dermal sensitization in guinea pigs. The results of this testing are as follows.

API 83-09

- Estimated Oral LD_{50} in Rats - Male and Female - greater than 5.0 g/kg of body weight
- Estimated Dermal LD_{50} in Rabbits - Male and Female - greater than 2.0 g/kg of body weight
- Primary Dermal Irritation Index - 5.5
- Primary Eye Irritation Scores:

	1 Hour	24 Hours	48 Hours	72 Hours	7 Days
Group I (unwashed)	0.7	0.0	0.0	0.0	0.0
Group II (washed)	2.0	0.0	0.0	0.0	0.0

- Dermal Sensitization - Is not considered to be a skin sensitizer in guinea pigs when tested by the closed patch technique.

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SPONSOR: AMERICAN PETROLEUM INSTITUTE
WASHINGTON DC 20005

STUDY NO.: 40602086
REPORTED: 03/22/85

SAMPLE: API NO. 83-09

ENCLOSED: TEST MATERIAL DATA SHEET - PAGE 2
ACUTE ORAL TOXICITY - PAGES 3 TO 7
ACUTE DERMAL TOXICITY - PAGES 8 TO 12
PRIMARY DERMAL IRRITATION - PAGES 13 TO 16
PRIMARY EYE IRRITATION - PAGES 17 TO 21
DERMAL SENSITIZATION - PAGES 22 TO 33
QUALITY ASSURANCE STATEMENT - 34 AND 35
SCORDING SCALES APPENDIX

SUMMARY OF RESULTS

ORAL LD50 - MALE AND FEMALE, GREATER THAN 5.0 G/KG OF BODY WEIGHT
DERMAL LD50 - MALE AND FEMALE - GREATER THAN 2.0 G/KG OF BODY WEIGHT
PRIMARY DERMAL IRRITATION INDEX = 5.5
PRIMARY EYE IRRITATION SCORES:

	1 HOUR	24 HOUR	48 HOUR	72 HOUR	7 DAYS
GROUP I (UNWASHED)	0.7	0.0	0.0	0.0	0.0
GROUP II (WASHED)	2.0	0.0	0.0	0.0	0.0

DERMAL SENSITIZATION - IS NOT CONSIDERED TO BE A SKIN SENSITIZER IN GUINEA PIGS WHEN TESTED BY THE CLOSED PATCH TECHNIQUE

SIGNED: Wayne A. Madison
WAYNE A. MADISON
STUDY DIRECTOR, ACUTE TOXICOLOGY

11/26/85
DATE

SUPERVISORY PERSONNEL INVOLVED IN THE STUDY: STEVEN M. GLAZA
TECHNICAL SUPERVISOR

BY AND FOR HAZLETON LABORATORIES AMERICA, INC.

A COPY OF THE FINAL REPORT AND ALL RAW DATA FROM THIS STUDY ARE RETAINED IN THE ARCHIVES OF HAZLETON LABORATORIES AMERICA, INC., MADISON, WISCONSIN.

Generic Refinery Stream 13 - 1 stream selected*

Straight Run Kerosine [*8008-20-6] F000-0753

A complex combination of hydrocarbons produced by the distillation of crude oil. It consists of hydrocarbons having carbon numbers predominantly in the range of C_9 through C_{16} and boiling in the range of approximately 150°C to 290°C (320°F to 554°F).

Sample Designation	Range of Company Data*	Physical Data Actual #83-09
Company		
API		
Other_____		
Tests		
Gravity, °API	40.1-47.4	43.0
Sulfur, Wt.%	0.02-0.73	0.47
Nitrogen, ppm	1-16	5.4
Flash, °F	120-165†	144
Pour Pt., °F	-15 - -55	-55
Freeze Pt., °F	-41	---
Cloud Pt., °F	---	
Aniline Pt., °F	152.6	
Viscosity, 40°C cST	1.31-1.67	
RVP, lbs	0.2	
Color	0.5§ - +29§§	
Cetane Index	---	
Distillation, °F (ASTM D-86 Equiv)		
IBP	258-399	238
10%	360-389	327
50%	406-440	405
90%	460-510	475
95%	476-524	490
EP	512-557	520
P, %	---	---
O, %	1.0-2.5	2.5
N, %	---	---
A, %	14.6-20.5	15.5
Saturates, %	77.0-85.4	82

†TC
*10 specifications from 7 major companies; data tight no target spec per se.
§ASTM
§§Saybolt

ACUTE ORAL TOXICITY

Objective: To determine the acute oral toxicity produced when a test material is administered by the oral route (gavage) to rats.

Test Material: 83-09

Physical Description of Test Material: Clear, pale-yellow liquid

Purity and Stability of Test Material: Sponsor assumes responsibility for purity and stability determinations.

Test Animal: Young adult male and female albino rats (approximately 7 weeks of age) of the Sprague-Dawley strain were procured and maintained in group cages in temperature- and humidity-controlled rooms with a 12-hour light/12-hour dark lighting cycle. The animals were provided continuous access to Purina Certified Rodent Chow® #5002 and water, and held for an acclimation period of at least 14 days.

Animals were chosen at random from the acclimated animals and they weighed between 303 and 336 g for males and between 204 and 217 g for females prior to fasting. Five male and five female albino rats were used for a single dosage level of 5.0 g/kg. Food and water were available ad libitum throughout the study period except for an overnight period prior to test material administration when food, but not water, was withheld. Following fasting the animals weighed between 276 and 301 g for males and between 190 and 204 g for females. Test animals were individually housed and identified by animal number and corresponding ear tag.

Reason for Species Selection: The rat is the animal classically used due to its small size, ready availability, and large amount of background data.

Administration of Test Material: An individual dose was calculated for each animal based upon its fasted body weight and administered undiluted by gavage.

The dose volume of the test material was 6.25 mL/kg of body weight based upon the average bulk density of 0.80 g/mL.

Observations: The animals were observed for clinical signs and mortality at hourly intervals during the first 6 hours after test material administration. The animals were observed twice daily thereafter for 14 days for clinical signs and mortality.

Body weights were taken before fasting, just prior to test material administration, and at 7 and 14 days following test material administration.

Pathology: At study termination all animals were euthanatized with an overexposure of carbon dioxide, subjected to a gross necropsy examination, and abnormalities were recorded.

SUMMARY

Test Animal: Albino rats - Sprague-Dawley strain
Source: Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts
Date Animals Received: 04/17/84
Date Test Started: 05/03/84 Date Test Completed: 05/17/84

Temperature and Humidity of Animal Room: 22° to 23°C
38% to 50% relative humidity

Route of Administration: Oral gavage

Estimated Oral LD50: Male - greater than 5.0 g/kg of body weight
Female - greater than 5.0 g/kg of body weight

Dose Level (g/kg)	Average Body Weights (g)				Mortality (Number Dead/Number Dosed)
	Pre-fast	Initial	Day 7	Terminal	
			Male		
5.0	320	293	334	374	0/5
			Female		
5.0	210	196	222	235	0/5

Comments: Clinical signs seen during the study included: hypoactivity, ataxia, prostration, soft stool, lacrimation, yellow-stained abdomen and/or urogenital region, and hair loss on abdomen and/or urogenital region. In addition, one male rat was discovered with its teeth caught in the cage on Day 14 and exhibited nasal discharge, gasping, and missing teeth.

Deviation from the Protocol: The rats were fasted overnight for a period of approximately 19 hours prior to test material administration rather than 16 to 18 hours as stated in the protocol.

Water purified by reverse osmosis, not tap water, was available *ad libitum* to the animals.

These deviations are not considered to have had an effect on the validity of the study.

STUDY NUMBER 40602086
API 83-09

Acute Oral Toxicity
Summary of Clinical Signs (Number of Animals Affected)

Dose Level: 5.0 g/kg

Observation	Hours						Days													
	1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Males																				
Appeared normal	3	3	3	1	1	1	0	0	2	3	4	4	4	3	3	3	3	4	4	3
Hypoactivity	2	2	2	4	4	4	5	5	3	2	0	0	0	0	0	0	0	0	0	0
Yellow-stained abdomen	0	0	0	1	1	1	4	4	0	0	0	0	0	0	0	0	0	0	0	0
Soft stool	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ataxia	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Prostration	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Hair loss on abdomen	0	0	0	0	0	0	0	0	0	0	1	1	1	2	2	2	2	1	1	1
Nasal discharge	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Gasping	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Missing teeth	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Females																				
Appeared normal	3	3	3	4	5	5	1	2	3	3	3	3	1	1	2	2	2	2	2	2
Hypoactivity	2	2	2	1	0	0	4	2	1	1	1	1	0	0	0	0	0	0	0	0
Lacrimation	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Yellow-stained abdomen	0	0	0	0	0	0	2	1	1	1	1	1	0	0	0	0	0	0	0	0
Yellow-stained urogenital area	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0
Hair loss on abdomen urogenital area	0	0	0	0	0	0	0	0	0	0	0	0	4	4	3	3	3	3	3	3

PATHOLOGY

Animal Number	Sex	Test Day Died	Test Day Sacrificed	Necropsy Comments
		5.0 g/kg of Body Weight - Date Dosed: May 3, 1984		
C16043	M	-	14	No visible lesions.
C16044	M	-	14	No visible lesions.
C16045	M	-	14	Muzzle broken (cage injury); lungs - mottled dark red and red; stomach - contents stained dark red.
C16046	M	-	14	No visible lesions.
C16047	M	-	14	No visible lesions.
C16081	F	-	14	No visible lesions.
C16082	F	-	14	No visible lesions.
C16083	F	-	14	No visible lesions.
C16084	F	-	14	No visible lesions.
C16086	F	-	14	No visible lesions.

Acute Dermal Toxicity

Objective: To assess the systemic toxicity and relative skin irritancy of a test material when applied to the skin.

Test Material: 83-09

Physical Description of Test Material: Clear, pale-yellow liquid

Purity and Stability of Test Material: Sponsor assumes responsibility for purity and stability determinations.

Test Animal: Young adult male and female rabbits of the New Zealand White strain (approximately 14 weeks of age) were procured and maintained individually in screen-bottom cages in temperature- and humidity-controlled rooms with a 12-hour light, 12-hour dark lighting cycle. The animals were provided continuous access to Purina Certified Rabbit Chow® #5322 and water, and held for an acclimation period of at least 14 days.

Eight animals, identified by animal number and corresponding ear tag, were chosen at random from the acclimated animals, treated, and maintained during the observation period as specified for the acclimation period. Four male and four female rabbits weighing between 2,302 and 2,644 g were used for a single dosage level of 2.0 g/kg. Approximately 18 hours before test material application, the hair was removed from the back of each rabbit with an electric clipper. The shaved area constituted approximately 10% of the total body surface area. Just prior to test material administration, abraded areas of two male and two female rabbits were prepared by making longitudinal epidermal abrasions over the area of exposure. The abrasions were sufficiently deep to penetrate the stratum corneum but not deep enough to penetrate to the dermal layer and cause bleeding.

Reasons for Species Selection: The New Zealand White albino rabbit has been the animal of choice due to the amount of background information on this species.

Preparation of Test Material: The sample was dosed as received. An individual dose at a level of 2.0 g/kg was weighed out for each animal based upon its body weight at study initiation.

Treatment: The prepared backs of the animals received a single test material application. The area of application was wrapped with an eight-ply gauze bandage and overwrapped with Saran Wrap® and Elastoplast® tape. Twenty-four hours later the bandages were removed and the backs wiped

clean with wet disposable towels (not washed) as thoroughly as possible without irritating the skin. Collars were used to restrain the test animals during the 24-hour exposure period to prevent oral ingestion of the test material.

Observations: The rabbits were observed for clinical signs and mortality hourly for the first 6 hours after dosing, then daily for dermal irritation and twice daily for clinical signs and mortality for a period of 14 days. Body weights were taken just prior to administration, at 7 days, and at study termination.

Pathology: At study termination, all animals were euthanatized with an overexposure of carbon dioxide, subjected to a gross necropsy examination, and all abnormalities were recorded.

STUDY NUMBER 40602086
API 83-09

SUMMARY

Test Animal: Albino rabbits - New Zealand White
Source: Hazleton Dutchland, Inc., Denver, Pennsylvania
Date Animals Received: 04/11/84
Date Test Started: 04/26/84 Date Test Completed: 05/10/84

Temperature and Humidity of Animal Room: 20° to 23°C
42% to 74% relative humidity

Method of Administration: Dermal application

Estimated Dermal LD50: Male - Greater than 2.0 g/kg of body weight
Female - Greater than 2.0 g/kg of body weight

Dose Level (g/kg)	Average Body Weights (g) Initial	Day 7	Terminal	Mortality (Number Dead/Number Dosed)
		Male		
2.0 (Intact)	2,555	2,481	2,662	0/2
2.0 (Abraded)	2,542	2,221	2,403	0/2
		Female		
2.0 (Intact)	2,515	2,513	2,755	0/2
2.0 (Abraded)	2,341	2,359	2,543	0/2

Comments: Clinical signs observed during the study period included hypoactivity and diarrhea. Dermal irritation seen during the study ranged from slight to severe for erythema and edema, from slight to marked for atonia, desquamation and fissuring, and from slight to moderate for coriaceousness. Other dermal irritation observed included subcutaneous hemorrhage, blanching, and scab formation.

Deviations from the Protocol: Four animals had an initial body weight that was less than the 2.5-kg limit stated in the protocol.

During the study period the relative humidity of the animal room ranged from 42% to 74% rather than 30% to 70% as stated in the protocol.

These deviations are not considered to have had an effect on the validicy of this study.

STUDY NUMBER 40602086
API 83-09

Acute Dermal Toxicity
Summary of Clinical Signs
(Number of Animals Affected)

Dose Level: 2.0 g/kg

Observation	Hours						Days													
	1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Males																				
Appeared normal	4	4	4	4	4	4	0	2	2	2	3	4	4	4	4	4	4	4	4	4
Hypoactivity	0	0	0	0	0	0	4	2	2	2	1	0	0	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Females																				
Appeared normal	4	4	4	4	4	4	2	2	4	4	4	4	4	4	4	4	4	4	4	4
Hypoactivity	0	0	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0

STUDY NUMBER 40602086
API 83-09

PATHOLOGY

Animal Number	Sex	Test Day Died	Test Day Sacrificed	Necropsy Comments
2.0 g/kg of Body Weight - Date Dosed: April 26, 1984				
F04268	M	-	14	Skin of test site thickened.
F04251	M	-	14	Skin of test site thickened and crusty.
F04252	M	-	14	Skin of test site thickened.
F04257	M	-	14	Skin of test site thickened and crusty.
F04261	F	-	14	Skin of test site thickened and crusted.
F04255	F	-	14	No visible lesions.
F04271	F	-	14	Skin of test site thickened and crusted.
F04259	F	-	14	Skin of test site thickened and crusted.

STUDY NUMBER 40602086
API 83-09

Primary Dermal Irritation

Objective: To determine the relative level of primary skin irritation of a test material on rabbits under occluded conditions.

Test Material: 83-09

Physical Description of Test Material: Clear, pale-yellow liquid

Purity and Stability of Test Material: Sponsor assumes responsibility for purity and stability determinations.

Test Animal: Young adult rabbits of the New Zealand White strain (approximately 14 weeks of age) were procured and maintained individually in screen-bottom cages in temperature- and humidity-controlled rooms with a 12-hour light, 12-hour dark lighting cycle. The animals were provided continuous access to Purina Certified Rabbit Chow® #5322 and water, and held for an acclimation period of at least 14 days.

Six male acclimated animals, identified by animal number and corresponding ear tag, were chosen at random for the test based upon health and a body weight range of 2.3 to 2.8 kg, treated, and maintained during the observation period as specified for the acclimation period. Approximately 24 hours prior to exposure, the hair was clipped from the back and flanks of each animal. Just prior to test material administration, abraded areas were prepared by making crisscross epidermal abrasions over the area of exposure. The abrasions were sufficiently deep to penetrate the stratum corneum but not deep enough to penetrate to the dermal layer and cause bleeding.

Reasons for Species Selection: Historically, the New Zealand White albino rabbit has been the animal of choice for evaluating the effect of chemicals on the skin.

Preparation of Test Material: The sample was dosed as received. The pH was not determined.

Treatment: The test material was applied to two areas on each rabbit, one abraded area and one intact area, in the amount of 0.5 mL per area. The test site on the left side was abraded for three rabbits and the test site on the right side was abraded for the remaining three rabbits. The treated areas were each covered with a 2.5-cm x 2.5-cm gauze patch (two single layers thick), secured with paper tape and overwrapped with Saran Wrap® and Elastoplast® tape to maintain the test material in contact with the skin and decrease the rate of evaporation. Collars were used to restrain the animals during the 24-hour exposure period to prevent oral ingestion of the test material.

Observations: After the 24 hours of exposure, the patches were removed and the test material was wiped with wet disposable paper towels from the area as thoroughly as possible without irritating the skin. The degree of erythema and edema was recorded according to the Draize[1] technique. A second reading was taken at 72 hours to determine the primary dermal irritation index for the sample. Because irritation was present at 72 hours, observations were repeated at 96 hours, and at 7 and 14 days. Body weights were taken just prior to test material application and at weekly intervals during the study.

Pathology: At study termination, all animals were euthanatized with an overexposure of carbon dioxide and discarded.

SUMMARY

Test Animal: Albino rabbits - New Zealand White
Source: Hazleton Dutchland, Inc., Denver, Pennsylvania
Date Animals Received: 04/24/84
Date Test Started: 05/10/84 Date Test Completed: 05/24/84

Temperature and Humidity of Animal Room: 20° to 25°C
58% to 65% relative humidity

Primary Dermal Irritation Score*

Observation Period	Erythema		Edema		Total Dermal Irritation Scores
	Intact	Abraded	Intact	Abraded	
24 Hours	2.5	2.8	2.8	3.2	5.7
72 Hours	2.8	3.0	2.3	2.2	5.2
96 Hours	2.8	3.0	2.7	2.5	5.5
7 Days	2.3	2.3	2.0	2.2	4.4
14 Days	0.3	0.7	0.0	0.0	0.5

Primary dermal irritation index:** 5.5

Average Body Weights (g)

Initial	Day 7	Day 14
2,616	2,712	2,922

*The primary dermal irritation score is the sum of the irritation scores for each site divided by the number of animals at each observation period.
**The primary dermal irritation index is the sum of the 24- and 72-hour total dermal irritation scores divided by two and rounded to the nearest tenth.

Comments: This test material produced moderate to severe levels of irritation to the skin of rabbits as a result of a 24-hour exposure. Blanching was seen within the test sites of two animals at 24 and 72 hours and of three animals at 96 hours. Subcutaneous hemorrhaging within the test sites was exhibited by two animals at 96 hours. No sign of systemic toxicity was seen during the study.

Deviations from the Protocol: One animal had an initial body weight that was less than the 2.5 kg limit that was stated in the protocol.

During the study period the temperature of the animal room ranged from 20° to 25°C rather than 19° to 23°C as stated in the protocol.

These deviations are not considered to have had an effect on the validity of this study.

Table 1

Individual Dermal Irritation Scores

Animal Number		Erythema Score					Edema Score				
		Hours			Days		Hours			Days	
		24	72	96	7	14	24	72	96	7	14
FO4423	Intact	2	3	3	2	1	2	2	2	2	0
	Abraded	2	3	3	2	1	3	2	3	3	0
FO4473	Intact	3	3	4	2	0	4	4	4	3	0
	Abraded	3	3	4	3	1	4	4	4	3	0
FO4495	Intact	2	3	3	2	0	1	2	3	1	0
	Abraded	4	4	3	2	1	3	2	2	2	0
FO4465	Intact	3	3	2	2	0	4	3	2	2	0
	Abraded	3	3	2	2	0	4	2	2	1	0
FO4466	Intact	2	3	3	3	0	2	2	3	2	0
	Abraded	2	3	4	2	0	1	2	2	2	0
FO4459	Intact	3	2	2	3	1	4	1	2	2	0
	Abraded	3	2	2	3	1	4	1	2	2	0

STUDY NUMBER 40602086
API 83-09

Primary Eye Irritation

Objective: To determine the level of irritation produced following a single exposure of a test material to one eye of albino rabbits.

Test Material: 83-09

Physical Description of Test Material: Clear, pale-yellow liquid

Purity and Stability of Test Material: Sponsor assumes responsibility for purity and stability determinations.

Test Animal: Young adult rabbits of the New Zealand White strain (approximately 14 weeks of age) were procured and maintained individually in screen-bottom cages in temperature- and humidity-controlled rooms with a 12-hour light, 12-hour dark lighting cycle. The animals were provided continuous access to Purina Certified Rabbit Chow® #5322 and water, and held for an acclimation period of at least 14 days.

Nine acclimated rabbits, identified by animal number and corresponding ear tag, were chosen at random for the test based upon health and a body weight range of 2.0 to 2.4 kg. The eyes were examined approximately 24 hours prior to test material administration using sodium fluorescein dye procedures. Only those animals with no sign of ocular irritation or injury were used. The animals were divided into two groups, Group I consisting of six rabbits and Group II consisting of three rabbits.

Reason for Species Selection: The New Zealand White albino rabbit is the accepted animal for this study based upon its large orbit and nonpigmented iris.

Preparation of Test Material: The sample was dosed as received. The pH was not determined.

Treatment: Each rabbit received 0.1 mL of the liquid test material dripped onto the corneal surface above the everted lower lid of one eye, with the contralateral eye serving as the untreated control. The upper and lower lids were gently held together for 1 second to prevent loss of material before releasing. Group II animals had the treated and control eye flushed for 1 minute with lukewarm water starting 20 to 30 seconds after test material instillation. The eyes of the rabbits in Group I remained unflushed.

STUDY NUMBER 40602086
API 83-09

Observations: Readings of ocular lesions in the treated eyes of both groups were made at 1, 24, 48, and 72 hours and at 7 days after treatment. At the 72-hour and 7-day readings, sodium fluorescein was used to aid in revealing possible corneal injury. Grading and scoring of irritation was performed using the Draize[1] technique. Body weights were taken just prior to test material administration and at study termination.

Pathology: At study termination, all animals were euthanatized with an overexposure of carbon dioxide and discarded.

SUMMARY

Test Animal: Albino rabbits - New Zealand White
Source: Hazleton Dutchland, Inc., Denver, Pennsylvania
Date Animals Received: 04/24/84
Date Test Started: 05/09/84 Date Test Completed: 05/16/84
Temperature and Humidity of Animal Room: 21° to 25°C
58% to 64% relative humidity

Primary Eye Irritation Score*

Observation Period	Group I (Unwashed Eyes) Six Rabbit Mean	Group II (Washed Eyes) Three Rabbit Mean
1 Hour	0.7	2.0
24 Hours	0.0	0.0
48 Hours	0.0	0.0
72 Hours	0.0	0.0
7 Days	0.0	0.0

*The primary eye irritation score is the total eye irritation score for all the animals, divided by the number of animals in each group (six or three) at each observation period (i.e., average irritation score).

Average Body Weights (g)

	Initiation	Termination
Group I	2,176	2,369
Group II	2,147	2,366

Comments: A pain response (vocalization) was elicited from one animal following instillation of the test material. No corneal or iridal irritation was seen during the study. All irritation had cleared by the 24-hour observation. No sign of systemic toxicity was observed during the study.

Deviations from the Protocol: All animals had an initial body weight that was less than the 2.5 kg limit that was stated in the protocol.

During the study period the temperature of the animal room ranged from 21° to 25°C rather than 19° to 23°C as stated in the protocol.

These deviations are not considered to have had an effect on the validity of this study.

STUDY NUMBER 40602086
API 83-09

Table 1

Individual Eye Irritation Scores

Animal Number	Observation Period	Cornea A	Cornea B	Score A x B x 5	Iris A	Score A x 5	Conjunctivae A	Conjunctivae B	Conjunctivae C	Score (A + B + C)2
				Group I - Unwashed						
F04468	1 Hour	0	0	0	0	0	0	0	0	0
	24 Hours	0	0	0	0	0	0	0	0	0
	48 Hours	0	0	0	0	0	0	0	0	0
	72 Hours	0	0	0	0	0	0	0	0	0
	7 Days	0	0	0	0	0	0	0	0	0
F04469	1 Hour	0	0	0	0	0	0	0	0	0
	24 Hours	0	0	0	0	0	0	0	0	0
	48 Hours	0	0	0	0	0	0	0	0	0
	72 Hours	0	0	0	0	0	0	0	0	0
	7 Days	0	0	0	0	0	0	0	0	0
F04470	1 Hour	0	0	0	0	0	0	0	0	0
	24 Hours	0	0	0	0	0	0	0	0	0
	48 Hours	0	0	0	0	0	0	0	0	0
	72 Hours	0	0	0	0	0	0	0	0	0
	7 Days	0	0	0	0	0	0	0	0	0
F04471	1 Hour	0	0	0	0	0	0	0	0	0
	24 Hours	0	0	0	0	0	0	0	0	0
	48 Hours	0	0	0	0	0	0	0	0	0
	72 Hours	0	0	0	0	0	0	0	0	0
	7 Days	0	0	0	0	0	0	0	0	0
F04410	1 Hour	0	0	0	0	0	0	0	0	0
	24 Hours	0	0	0	0	0	0	0	0	0
	48 Hours	0	0	0	0	0	0	0	0	0
	72 Hours	0	0	0	0	0	0	0	0	0
	7 Days	0	0	0	0	0	0	0	0	0
F04424	1 Hour	0	0	0	0	0	1	1	0	4
	24 Hours	0	0	0	0	0	0	0	0	0
	48 Hours	0	0	0	0	0	0	0	0	0
	72 Hours	0	0	0	0	0	0	0	0	0
	7 Days	0	0	0	0	0	0	0	0	0

Table 1 (Continued)

Individual Eye Irritation Scores

Animal Number	Observation Period	Cornea A	Cornea B	Score A x B x 5	Iris A	Score A x 5	Conjunctivae A	Conjunctivae B	Conjunctivae C	Score (A + B + C)2
				Group II - Washed						
F04474	1 Hour	0	0	0	0	0	0	0	0	0
	24 Hours	0	0	0	0	0	0	0	0	0
	48 Hours	0	0	0	0	0	0	0	0	0
	72 Hours	0	0	0	0	0	0	0	0	0
	7 Days	0	0	0	0	0	0	0	0	0
F04345	1 Hour	0	0	0	0	0	0	1	0	2
	24 Hours	0	0	0	0	0	0	0	0	0
	48 Hours	0	0	0	0	0	0	0	0	0
	72 Hours	0	0	0	0	0	0	0	0	0
	7 Days	0	0	0	0	0	0	0	0	0
F04475	1 Hour	0	0	0	0	0	1	1	0	4
	24 Hours	0	0	0	0	0	0	0	0	0
	48 Hours	0	0	0	0	0	0	0	0	0
	72 Hours	0	0	0	0	0	0	0	0	0
	7 Days	0	0	0	0	0	0	0	0	0

Dermal Sensitization

Objective: To determine the delayed contact hypersensitivity potential of 83-07 in guinea pigs.

Test Material: 83-09

Physical Description: Clear, pale yellow liquid

Purity and Stability of Test Material: Sponsor assumes responsibility for purity and stability determinations.

Test Animal: Young adult male albino guinea pigs of the Hartley strain (approximately 5 to 6 weeks of age) were procured from Hazleton Dutchland, Inc., Denver, Pennsylvania, maintained in individual cages in temperature- and humidity-controlled rooms with a 12-hour light/12-hour dark lighting cycle, provided continuous access to Purina Certified Guinea Pig Chow #5026 and water, and held for an acclimation period of at least 14 days.

Seventy-six acclimated animals, identified by individual animal number and corresponding ear tag, were chosen at random for this study based upon health and body weight. The animals, weighing between 354 and 518 g, were divided into six groups consisting of a treated group of 10 guinea pigs, a naive control group of 10 guinea pigs, a vehicle control group of 10 guinea pigs, a positive control group of 20 guinea pigs, a naive positive control group of 20 guinea pigs, and a dose-range group of six guinea pigs. The positive and naive positive control groups were common to API-sponsored Study Nos. 40602084, 40602085, and 40602086. Purina Certified Guinea Pig Chow #5026 and water were available ad libitum throughout the study period. There were no known components or contaminants in the diet or water which could be expected to interfere with this study.

Reason for Species Selection: The guinea pig is an acceptable model for skin sensitization studies.

Preparation of Test Material: A range-finding study consisting of six guinea pigs was utilized with each animal receiving two concentrations of test material. The sample was initally administered undiluted and at concentrations of 25%, 50%, and 75% v/v in paraffin oil. Each animal was dosed with two concentrations of the test material. Because of the irritation seen at the 25% v/v level, additional levels of 10% and 1% v/v were needed to determine the irritation threshold of the test material. The 1% and 10% v/v dilutions resulted in no dermal irritation. Very slight dermal irritation resulted from one of the two applications of the 25% v/v dilution, with the other application producing no response. The 50% v/v applications produced very slight initiation responses, the 75% v/v

application produced a very slight to well-defined response, and the undiluted test material produced moderate to severe responses. Based upon these results, the test material was administered as a 75% v/v dilution (a mild to moderately irritating concentration) in paraffin oil for the sensitizing phase and as a 10% v/v dilution (believed to be the highest nonirritating concentration) in paraffin oil for the challenge dose.

Treatment: Just prior to each application the hair was removed from the back of each animal with electric clippers. The test material was applied to one area on each animal by placing 0.4 mL of test material on an adhesive pad (Hilltop Chamber, 25-mm diameter) and placing the pad on the test site on the left anterior quadrant (right anterior quadrant for challenge dose) of each animal. The patch was then covered with a strip of dental dam and overwrapped with Elastoplast tape. After 6 hours of exposure, the patches and wrappings were removed and the test sites were wiped with wet disposable paper towels.

The vehicle control, paraffin oil, was administered undiluted with a dosage volume of 0.4 mL for the sensitizing phase of the study. The study method used for the vehicle control group was the same as that of the test group.

The positive control, 2,4-dinitrochlorobenzene, was administered at a concentration of 0.3% w/v in 80% aqueous ethanol, with a dosage volume of 0.4 mL for the sensitizing phase. The study method used for the positive control group was the same as that of the test and vehicle control groups. The positive control suspensions used for the sensitizing and challenge phases of the study were prepared fresh, just prior to each application.

The animals received one application per week for 3 weeks for a total of three applications. Due to the moderate to severe irritation present in the test site of the test and positive control animals, the third sensitizing dose was applied to a test site slightly posterior to the initial site.

Two weeks following the administration of the third sensitizing dose, a challenge dose of 0.4 mL of a 1% v/v mixture of test material in paraffin oil was administered to the test group in the same manner as during the sensitizing phase of the study. At this time, the animals in the naive control group were also dosed with the test material mixture in the same manner as the test group. The vehicle control group animals were dosed with 0.4 mL of undiluted paraffin oil. For the positive control group and naive (previously untreated) positive control group, the animals were dosed with 0.4 mL of a 0.1% w/v suspension of 2,4-dinitro- chlorobenzene in acetone. A previously untreated test site was used for the challenge application on each animal.

Approximately 3 hours prior to the 24-hour examination following the dose range and challenge applications, the test site on each animal was depilated by applying Neet depilatory for 20 minutes, which was then washed off with lukewarm water.

Observations: The application sites were read and scored for erythema and edema at 24 and 48 hours following each application according to the Draize[1] technique. Reactions to the challenge dose were read and scored at 24 and 48 hours, as was done following the sensitizing applications. The animals were observed for general behavior and appearance once daily during the entire study period. Body weights were taken at study initiation, at weekly intervals during the study, and at study termination.

0 0 2 9

STUDY NO. 40602086
API 83-09

Pathology: Animals that died on study were subjected to a gross necropsy examination. Surviving animals at study termination were sacrificed and discarded.

Evaluation of Challenge Responses: Determination of sensitization was based upon reactions to the challenge dose. Grades of 1 or greater in the test animals indicate evidence of sensitization, provided grades of less than 1 are seen in the naive control animals. If grades of 1 or greater are noted in the naive control animals, then the reactions of test animals that exceed the most severe naive control reaction are considered sensitization reactions.

STUDY NO. 40602086
API 83-09

Test Animal: Albino guinea pigs - Hartley strain
Source: Hazleton Dutchland, Inc., Denver, Pennsylvania
Date Animals Received: 10/23 and 11/06/84
Date Test Started: 11/07/84 Date Test Completed: 12/12/84
Temperature and Humidity of Animal Room: 21° to 25°C
42% to 66% relative humidity

Summary of Skin Reactions*
Test Material: 83-09

Animal Number	Sensitizing Phase Three Applications (75% v/v) Erythema Average	Erythema (High)	Edema Average	Edema (High)	Challenge Phase Single Application (10% v/v) Erythema Average	Erythema (High)	Edema Average	Edema (High)
			Test Group					
E02871	1.3	(2)	0.5	(2)	0.0	(0)	0.0	(0)
E02872	1.2	(2)	0.7	(2)	0.0	(0)	0.0	(0)
E02873	1.7	(2)	0.8	(2)	0.0	(0)	0.0	(0)
E02874	1.8	(3)	1.2	(3)	0.0	(0)	0.0	(0)
E02875	1.3	(2)	0.8	(2)	0.0	(0)	0.0	(0)
E02876**	-	-	-	-	-	-	-	-
E02877	1.5	(3)	1.0	(2)	0.0	(0)	0.0	(0)
E02883	1.3	(2)	1.2	(3)	0.0	(0)	0.0	(0)
E02880	1.8	(3)	1.3	(3)	0.0	(0)	0.0	(0)
E02942	1.7	(3)	1.5	(3)	0.0	(0)	0.0	(0)

*The average erythema and edema value is the mean of the Draize scores for the six observations (sensitizing treatment) or two observations (challenge treatment) of the application site for each animal. The high reading is the largest score recorded for the respective animal during that phase of the study.

**Animal died on Study Day 9.

Summary of Skin Reactions (Continued)*

Animal Number	Challenge Phase Single Application (10% v/v) Erythema Average	Erythema (High)	Edema Average	Edema (High)
Naive Control Group				
E02881	0.0	(0)	0.0	(0)
E02882	0.0	(0)	0.0	(0)
E02879	1.0	(1)	0.0	(0)
E02884	0.0	(0)	0.0	(0)
E02885	0.0	(0)	0.0	(0)
E02886	0.5	(1)	0.0	(0)
E02887	0.0	(0)	0.0	(0)
E02888	0.0	(0)	0.0	(0)
E02889	0.0	(0)	0.0	(0)
E02890	0.0	(0)	0.0	(0)

Animal Number	Sensitizing Phase Three Applications (Undiluted) Erythema Average	Erythema (High)	Edema Average	Edema (High)	Challenge Phase Single Application (Undiluted) Erythema Average	Erythema (High)	Edema Average	Edema (High)
Vehicle Control Group (Paraffin Oil)								
E02891	0.0	(0)	0.0	(0)	0.0	(0)	0.0	(0)
E02892	0.0	(0)	0.0	(0)	0.0	(0)	0.0	(0)
E02893	0.0	(0)	0.0	(0)	0.0	(0)	0.0	(0)
E02894	0.0	(0)	0.0	(0)	0.0	(0)	0.0	(0)
E02895	0.0	(0)	0.0	(0)	0.0	(0)	0.0	(0)
E02896	0.0	(0)	0.0	(0)	0.0	(0)	0.0	(0)
E02897	0.0	(0)	0.0	(0)	0.0	(0)	0.0	(0)
E02898	0.0	(0)	0.0	(0)	0.0	(0)	0.0	(0)
E02899	0.0	(0)	0.0	(0)	0.0	(0)	0.0	(0)
E02900	0.0	(0)	0.0	(0)	0.5	(1)	0.0	(0)

*The average erythema and edema value is the mean of the Draize scores for the six observations (sensitizing treatment) or two observations (challenge treatment) of the application site for each animal. The high reading is the largest score recorded for the respective animal during that phase of the study.

Summary of Skin Reactions (Continued)*

Animal Number	Sensitizing Phase Three Applications (0.3% w/v) Erythema Average	Erythema (High)	Edema Average	Edema (High)	Challenge Phase Single Application (0.1% w/v) Erythema Average	Erythema (High)	Edema Average	Edema (High)
Positive Control Group (2,4-dinitrochlorobenzene)								
E02901	2.3	(4)	1.5	(3)	1.5	(2)	0.0	(0)
E02902	2.5	(4)	1.7	(4)	1.5	(2)	0.0	(0)
E02903	2.5	(4)	2.2	(4)	2.5	(3)	1.0	(1)
E02904	2.5	(4)	2.3	(4)	3.5	(4)	3.0	(3)
E02905	2.3	(4)	1.7	(3)	1.5	(2)	0.0	(0)
E02906	2.3	(4)	2.0	(4)	1.5	(2)	0.0	(0)
E02907	2.3	(4)	1.8	(4)	2.0	(2)	0.5	(1)
E02908	2.0	(3)	1.0	(3)	2.5	(3)	0.0	(0)
E02909	2.3	(4)	1.7	(4)	2.0	(2)	0.0	(0)
E02910	2.3	(4)	1.3	(3)	2.0	(2)	0.0	(0)
E02911	2.3	(4)	1.5	(3)	3.0	(3)	1.5	(2)
E02912	2.3	(4)	2.0	(4)	2.0	(2)	1.0	(1)
E02913	2.3	(4)	1.7	(4)	2.5	(3)	0.5	(1)
E02914	3.0	(4)	2.5	(4)	3.5	(4)	3.0	(3)
E02915	2.7	(4)	2.7	(4)	2.5	(3)	1.5	(2)
E02916	2.7	(4)	2.3	(4)	1.5	(2)	0.5	(1)
E02917	2.3	(4)	1.7	(3)	2.0	(2)	0.5	(1)
E02918	1.7	(4)	1.7	(4)	3.0	(3)	1.0	(1)
E02919	2.3	(4)	2.0	(4)	3.0	(4)	1.5	(2)
E02920	2.0	(4)	1.7	(4)	1.0	(1)	0.0	(0)

*The average erythema and edema value is the mean of the Draize scores for the six observations (sensitizing treatment) or two observations (challenge treatment) of the application site for each animal. The high reading is the largest score recorded for the respective animal during that phase of the study.

Summary of Skin Reactions (Continued)*

Animal Number	Challenge Phase Single Application (0.1% w/v) Erythema Average	Erythema (High)	Edema Average	Edema (High)
Naive Positive Control Group (2,4-dinitrochlorobenzene)				
E02921	0.0	(0)	0.0	(0)
E02922	0.0	(0)	0.0	(0)
E02923	0.0	(0)	0.0	(0)
E02924	0.5	(1)	0.0	(0)
E02925	0.0	(0)	0.0	(0)
E02926	0.0	(0)	0.0	(0)
E02927	0.0	(0)	0.0	(0)
E02928	1.0	(1)	0.0	(0)
E02929	0.5	(1)	0.0	(0)
E02930	0.5	(1)	0.0	(0)
E02931	0.0	(0)	0.0	(0)
E02932	0.0	(0)	0.0	(0)
E02933	0.0	(0)	0.0	(0)
E02934	0.0	(0)	0.0	(0)
E02935	0.0	(0)	0.0	(0)
E02936	0.0	(0)	0.0	(0)
E02937	0.0	(0)	0.0	(0)
E02938	0.0	(0)	0.0	(0)
E02939	0.5	(1)	0.0	(0)
E02940	0.0	(0)	0.0	(0)

*The average erythema and edema value is the mean of the Draize scores for the six observations (sensitizing treatment) or two observations (challenge treatment) of the application site for each animal. The high reading is the largest score recorded for the respective animal during that phase of the study.

Average Body Weights (g)

Initiation	Week 1	Week 2	Week 3	Week 4	Terminal
		Test Group			
419	448	524*	582*	634*	646*
		Naive Control Group			
419	465	513	569	625	617
		Vehicle Control Group			
424	458	515	563	616	614
		Positive Control Group			
436	479	524	569	623	623
		Naive Positive Control Group			
442	503	550	609	660	654

*Based on a nine-animal mean.

General Behavior and Appearance:

Clinical signs observed during the study included the following:

- Two test animals, three naive control animals, two vehicle control animals, two positive control animals, and five naive positive control animals exhibited soft stool/diarrhea sporadically throughout the study.
- One of the test animals (E02876) exhibiting soft stool/diarrhea had a weight loss of 127 g, exhibited hypoactivity and emaciation, and was found dead on Study Day 9. The gross necropsy of this animal noted the contents of the cecum to be dry and impacted.
- Two test animals, one vehicle control animal, and one positive control animal were observed to be hyperthermic to touch (feverish) on one or more days during the third week of the study.
- The vehicle control animal exhibiting hyperthermia during Week 3 also exhibited dehydration and hypoactivity on Study Day 15.
- One naive positive control animal exhibited a red ocular discharge during the last 3 days of the study.

Two test, one vehicle control, one positive control, and one naive positive control animal exhibited slight body weight losses at different intervals during the first 4 weeks of the study. One test animal, seven naive control animals, seven vehicle control animal, 13 positive control animals, and 13 naive positive control animals exhibited body weight losses of 1 to 60 g during the last 2 days of the study. These animals exhibited normal body weight gains at all other weighings. Normal body weight gains were recorded for all other animals during the study.

Summary of Skin Reactions to the Challenge Dose:

Test Group: No dermal irritation was exhibited by any animal.

Naive Control Group: Very slight erythema reactions were exhibited by two animals. The other eight animals exhibited no reaction.

Vehicle Control Group: A very slight erythema reactions were exhibited by one animal. The other nine animals exhibited no reaction.

Positive Control Group: Very slight to severe irritation was exhibited by all 20 animals. The reactions of 19 animals exceeded the highest reaction observed in the naive positive control animals.

Naive Positive Control Group: Five of the 20 animals exhibited very slight erythema reactions. The other 15 animals exhibited no reaction.

Conclusions:

Test Group: Based upon the results obtained, this test material, API 83-09, is not considered to be a skin sensitizer in guinea pigs when tested by the closed patch technique.

Deviations from the Protocol:

During the dose-range phase of the study, six animals, rather than four, were needed to determine the irritation threshold of the test material.

Due to the density of the test material, the test material concentrations were prepared on a volume-to-volume basis rather than a weight-to-volume basis as stated in the protocol. In attempting to prepare the 75% w/v mixture, the volume that was occupied by the test material exceeded the total volume to be prepared. To maintain consistency, it was decided to prepare all test material dilutions v/v.

The guinea pigs were shaved just prior to test material administration rather than 24 hours prior as stated in the protocol. This was done to facilitate the reading of dermal reactions at 24 and 48 hours that may otherwise have been obscured by excessive hair growth.

The body weight range of the guinea pigs used in this study (350 to 552 g) differed from that stated in the protocol (350 to 550 g).

During the study period the temperature of the animal room ranged from 21° to 25°C. The protocol specified the temperature range at 22°C (±2°).

These deviations are not considered to have had an effect on the validity of this study.

STUDY NO. 40602086
API 83-09

REFERENCES

1. Draize, J.H., Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics, Published by the Association of Food and Drug Officials of the United States, pp. 46-59, (1975).

2. Buehler, E. V. and H. L. Ritz, "Planning, Conduct, and Interpretation of Guinea Pig Sensitization Patch Tests," Current Concepts in Cutaneous Toxicity, p. 28 (1980).

QUALITY ASSURANCE STATEMENT

Study No. 40602086

The report as herein attached for the above-mentioned study has been reviewed by the assigned Quality Assurance Unit of Hazleton Laboratories America, Inc. in accordance with the Good Laboratory Practice Regulations as set forth in 21 CFR 58.35 (b) (6) (7). It has been found to accurately identify and/or describe the authorized methods and standard operating procedures followed in the conduct of the study. Furthermore, the Quality Assurance Unit has conducted the following inspections of the testing facilities utilized in the conduct of this study and has submitted written reports of said inspections to the study director and/or management.

Date of Inspection	Type of Inspection	Date Issued to Management
Acute Oral Toxicity Study in Rats		
4/13/84	Protocol Review	4/13/84
5/03/84	Test Material Preparation Test Article Administration	5/03/84
3/20/85	Report Review	3/20/85
11/23/85	Report Review	11/23/85
Acute Dermal Toxicity Study in Rabbits		
4/13/84	Protocol Review	4/13/84
4/26/84	Test Article Administration	4/26/84
3/20/85	Report Review	3/20/85
11/23/85	Report Review	11/23/85
Primary Dermal Irritation Study in Rabbits		
4/13/84	Protocol Review	4/13/84
5/10/84	Test Article Administration Data Review	5/10/84
3/20/85	Report Review	3/20/85
11/23/85	Report Review	11/23/85
Primary Eye Irritation Study in Rabbits		
4/13/84	Protocol Review	4/13/84
5/11/84	Animal Observations	5/11/84
3/20/85	Report Review	3/20/85
11/23/85	Report Review	11/23/85

QAU Inspections

Study No. 40602086 (cont.)

Date of Inspection	Type of Inspection	Date Issued to Management
Dermal Sensitization Study in Guinea Pigs (Closed Patch Technique)		
10/12/84	Protocol Review	10/12/84
11/19/84	Test Article Administration	11/19/84
4/26/85	Report Review	4/26/85
11/23/85	Report Review	11/23/85

L. Lea Gough
Inspector, Quality Assurance Unit

11-26-85
Date

POOR QUALITY ORIGINAL

SCORING SCALE APPENDIX

STUDY NUMBER 40602086
API 83-09

ACUTE DERMAL TOXICITY SCORING SCALE

ERYTHEMA

0 - None
1.0 - Slight
2.0 - Moderate (well defined)
3.0 - Severe (beet red)

EDEMA

0 - None
1.0 - Slight (barely perceptible to well defined by definite raising)
2.0 - Moderate (raised approximately 1 mm)
3.0 - Severe (raised more than 1 mm)

ATONIA

0 - None
1.0 - Slight (slight impairment of elasticity)
2.0 - Moderate (slow return to normal)
3.0 - Marked (no elasticity)

DESQUAMATION

0 - None
1.0 - Slight (slight scaling)
2.0 - Moderate (scales and flakes)
3.0 - Marked (pronounced flaking with denuded areas)

CORIACEOUSNESS

0 - None
1.0 - Slight (decrease in pliability)
2.0 - Moderate (leathery texture)
3.0 - Marked (tough and brittle)

FISSURING

0 - None
1.0 - Slight (definite cracks in epidermis)
2.0 - Moderate (cracks in dermis)
3.0 - Marked (cracks with bleeding)

STUDY NUMBER 40602086
API 83-09

PRIMARY SKIN IRRITATION SCORING SCALE

(1) 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
Highest possible erythema score	4

(2) 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 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4
Highest possible edema score	4

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API 83-09

PRIMARY EYE IRRITATION SCORING SCALE

(1) Cornea

(A) Opacity - degree of density (area most dense taken for reading)

No opacity	0
Scattered or diffuse area, details of iris clearly visible	1*
Easily discernible translucent areas, details of iris slightly obscured	2*
Opalescent areas, no details of iris visible, size of pupil barely discernible	3*
Opaque, iris invisible	4*

(B) Area of cornea involved

One quarter (or less), but not zero	1
Greater than one quarter, but less than half	2
Greater than half, but less than three quarters	3
Greater than three quarters, up to whole area	4

A x B x 5 Total Maximum = 80

(2) Iris

(A) Values

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*

A x 5 Total Maximum = 10

(3) Conjunctivae

(A) Redness (refers to palpebral conjunctivae only)

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) Chemosis

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*

(C) Discharge

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 (A + B + C) x 2 Total Maximum = 20

The total score for the eye is the sum of all scores obtained for the cornea, iris, and conjunctivae.

* Starred figures indicate positive effect.

POOR QUALITY ORIGINAL

STUDY NUMBER 40602086
API 83-09

GUINEA PIG SENSITIZATION SCORING SCALE
(DRAIZE TECHNIQUE)

(1) 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
Highest possible erythema score	4

(2) 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 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4
Highest possible edema score	4

AMTEK CORP.

CERTIFICATE OF AUTHENTICITY

THIS IS TO CERTIFY that the microimages appearing on this microfiche are accurate and complete reproductions of the records of U.S. Environmental Protection Agency documents as delivered in the regular course of business for microfilming.

Data produced 6 19 97 Marcia Rubalcava

(Month) (Day) (Year) Camera Operator

Place Syracuse New York

(City) (State)