ORIGINAL

TSCA NON-CONFIDENTIAL BUSINESS INFORMATION

DOCUMENT DESCRIPTION	DOCUMENT CONTROL NUMBER	DATE RECEIVED
8EHQ-92-12853	89110000316	5/18/11

COMMENTS: COMMUN S (DECLASS)

DOES NOT CONTAIN CBI

335477

FOIA for Petroleum Distillate--BP responsive document
Scott Sherlock to: Burge, Farley 05/03/2011 03:25 PM

Farley

Many thanks for your response and your help in facilitating BP's agreement to declassify the TSCA 8(e) submission of August 25, 1992 (non-CBI excerpt attached)

We expect to direct the document, in its entirety, to the FOIA requestor no sooner than Thursday, May 5th and then later place it in the public files soon thereafter.

[Untitled].pdf

Again many thanks for your cooperation.

Scott M. Sherlock, Attorney Advisor
Environmental Assistance Division
Office of Pollution Prevention and Toxics
202.564-8257 (telephone)
202.564-8251 (facsimile)
sherlock.scott@epa.gov (e-mail)

"Burge, Farley" **Scott, BP does not object to the release of the st...** 05/02/2011 04:59:51 PM

From: "Burge, Farley" <Farley.Burge@bp.com>
To: Scott Sherlock/DC/USEPA/US@EPA
Date: 05/02/2011 04:59 PM
Subject: RE: FOIA for Petroleum Distillate

Scott,

BP does not object to the release of the studies referenced in the letter to the FOIA requestor, to the extent BP has or has ever had standing to make/waive such an objection. Our review of our records indicates that BP does not manufacture either of the substances in question and has not done so for 10 years or so. Please let me know if you have any questions. Thank you.

Farley Burge
Attorney - HSSE
BP Legal
501 Westlake Park Blvd.
Houston, Texas 77079
281.366.2415 (Direct)
713.715.9606 (Cell)
Farley.Burge@bp.com

CONTAINS NO CBI

-----Original Message-----

BP CHEMICALS

BP Chemicals Inc.
200 Public Square
Cleveland, Ohio 44114-2375
(216) 586-4141

TSCA CONFIDENTIAL BUSINESS INFORMATION
92 AUG 28 PM 1:45

Certified Mail
Return Receipt Requested

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8EHQ-92-12853
INIT C 08/28/92

Document Processing Center (TS-790)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, S. W.
Washington, DC 20460

Attn: TSCA Section 8(e) Coordinator (CAP Agreement)

Re: EPA ID No. 8ECAP-0009

Dear Sir or Madam:

BP Chemicals, Inc. submits the attached study pursuant to the terms of the TSCA Section 8(e) Compliance Audit Program (CAP) and the BP America CAP Agreement:

DECLASSIFIED PER EMAIL OF 5/2/11 BUNGE FAMILEY ATTORNEY BP TO SCOTT SHERLOCK USEPA

Study Identification

Primary Skin Irritation Study in Rabbits of CPS&T No. 89-003; Laboratory Project No. 89-3807-21 (B); Final Report dated October 16, 1989.

and

Primary Eye Irritation Study in Rabbits of CPS&T No. 89-003; Laboratory Project No. 89-3807-21 (C); Final Report dated October 16, 1989.

Identity of Tested Chemical Substance/Mixture and CAS Number (if known)

CPS&T No. 89-003 contains[1]:

[2-Propenoic acid, homopolymer, sodium salt; (CAS No. 9003-04-7)]

[Distillates, petroleum, hydrotreated light; (CAS No. 64742-47-8)]

[Benzenesulfonic acid, dodecyl-, compd. with 2-propanamine (1:1); (CAS No. 26264-05-1)]

TSCA CONFIDENTIAL BUSINESS INFORMATION

[1] Information contained in brackets [ ] is declared as Confidential Business Information.

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[Sulfuric acid monododecyl ester sodium salt; (CAS No. 151-21-3)] [2]

and, a purchased proprietary surfactant package for which we could not obtain chemical composition from the manufacturer.

Summary of Results

Skin Irritancy in Rabbits

The primary skin irritancy of CPS&T No. 89-003, undiluted and as a 3% w/v formulation in deionized water, was evaluated in rabbits. Changes in the coloration and/or texture of the skin exposed to the undiluted material included necrosis, open bleeding, and scabbing. Based upon these results the undiluted test material is classified as a skin corrosive and as a primary skin irritant.

No changes occurred in the skin exposed to the 3% formulation.

Eye Irritancy in Rabbits

The primary ocular irritancy of CPS&T No. 89-003, undiluted and as a 3% w/v formulation in deionized water, was evaluated in rabbits. The eyes of all rabbits exposed to the undiluted material showed moderate to severe corneal, iridal, and conjunctival changes. Based upon these results, the undiluted material is classified as an ocular irritant. No evidence of corrosivity was noted.

No remarkable changes occurred in the eyes exposed to the 3% formulation.

BP Chemicals includes warnings about the hazards defined in this study on product labels and Material Safety Data Sheets for CPS&T No. 89-003.

Previous PMN or 8(e) Submissions by BPA: EPA Document Control Number(s)

None.

CONTAINS NO CBI

---

[2] Information contained in brackets [ ] is declared as Confidential Business Information.

Submitted by:

Richard B. Stalzer
Manager, Health, Safety and
Environmental Quality
BP Chemicals, Inc.
216-586-5311

August 25, 1992

Date

Primary Skin Irritation Study in Rabbits

of: CPS & T No. 89-003

for: B.P. America, Inc.

Hill Top Biolabs Project No. 89-3807-21 (B)

Report Issue Date: 10.16.89

Report Issued by:

HILL TOP BIOLABS, INC.

Edwin V. Buehler, Ph.D.
Vice President, Scientific Affairs
Director of Toxicology

B.P. America, Inc.

Ref.: 89-3807-21 (B)

September 6, 1989

COMPLIANCE STATEMENT

This study was conducted in accordance with Good Laboratory Practice Standards (21 CFR 58).

HILL TOP BIOLABS, INC.

James J. Kreuzmann, B.A. 10.16.89
Study Director, Acute Toxicology

B.P. America, Inc.

Ref.: 89-3807-21 (B) September 6, 1989

HILL TOP BIOLABS, INC.

IMPORTANT NOTICE

Hill Top Biolabs, Inc., submits this report with the understanding that no portion of it will be used for advertising or promotion without obtaining our prior written consent to the specific proposed use. When such use is desired we will be glad to assist in the preparation of mutually acceptable excerpts or summaries.

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APPENDICES

B.P. America, Inc.

Ref.: 89-3807-21 (B)

September 6, 1989

REPORT APPROVAL

Report Prepared by:

HILL TOP BIOLABS, INC.

Lisa G. Goble
Report Writer,
Acute Toxicology
10-6-89

Project Monitor:

HILL TOP BIOLABS, INC.

Kenneth J. Harrod 10-9-89
Kenneth J. Harrod, B.A.
Senior Technician,
Acute Toxicology

Report Approved by:

HILL TOP BIOLABS, INC.

for James J. Kreuzmann, B.A.
Study Director,
Acute Toxicology
10.16.89

CONTRIBUTORS

The following members of Hill Top Biolabs, Inc., contributed to the conduct and reporting of Project No. 89-3807-21 (B):

Name	Title	Function
E. Buehler, Ph.D.	Vice President, Scientific Affairs Director of Toxicology	Manager, Toxicology
J. Kreuzmann, B.A.	Director of Technical Services	Study Director, Conduct of Study
B. Lynn, A.S.	Assistant Study Director	Conduct of Study
S. Coffey, B.S.	Research Supervisor	Conduct of Study
D. Schumann, B.S.	Research Supervisor	Conduct of Study
M. Watson	Research Assistant	Conduct of Study
T. Morris, B.S.	Research Assistant	Conduct of Study
K. Harrod, B.A.	Senior Technician	Project Monitor, Conduct of Study
D. Shuster, B.S.	Technician	Conduct of Study
M. LeQuire, A.S.	Technician	Conduct of Study
T. Gastineau	Lead Animal Care Technician	Conduct of Study
P. Nardini	Animal Caretaker	Conduct of Study
V. Wiggins	Animal Caretaker	Conduct of Study
L. Adams	Animal Caretaker	Conduct of Study
L. Goble	Report Writer	Report Preparation

GENERAL INFORMATION

Project No.:	89-3807-21 (B)
Test/Protocol No.:	Primary Skin Irritation Study in Rabbits 1-3-1/2-10-88/REV 4
Testing Facility:	Hill Top Biolabs, Inc. Main and Mill Streets Miamiville, OH 45147
Sponsor:	B.P. America, Inc. 200 Public Square Cleveland, OH 44114-2375
Sample Identification:	CPS & T No. 89-003
Date Sample Received:	June 30, 1989
Source of Animals:	Clerco Research Farm
Date Study Initiated:	July 13, 1989
Date Project Started:	July 18, 1989
Date Project Completed:	July 21, 1989

SAMPLE CHARACTERIZATION AND STABILITY

The sponsor has assumed responsibility for test substance derivation, characterization, and stability testing.

The test material, CPS & T No. 89-003, was an opaque beige liquid. Two test material aliquots were received and were stored at room temperature throughout the study in semi-clear nalgene bottles with lids. The partially used test material aliquot was disposed of following the completion of testing. The unused test material aliquot was returned to the sponsor following the completion of testing.

DATA RETENTION

The raw data and the original of the final report will be on file at the testing facility for a period of not less than two years. Permanent records will be in the form of microfilm.

SUMMARY/CONCLUSIONS

The primary skin irritancy of CPS & T No. 89-003, undiluted and as a 3% w/v formulation in deionized water, was evaluated in compliance with the conditions specified in the regulation for the enforcement of the Federal Hazardous Substances Act (16 CFR 1500).

The Primary Irritation Index (PII), based on erythema and edema responses to the undiluted test material, was found to be 6.0.

The Primary Irritation Index (PII), based on erythema and edema responses to the test material as a 3% formulation, was found to be 3.4.

Critical changes in the coloration and/or texture of the skin exposed to the undiluted test material included necrosis, open bleeding, and scabbing. These and any other changes may be found in the raw data in Appendix 2.

No changes in the coloration or texture of the skin exposed to the test material as a 3% formulation were noted.

Evidence of corrosion (necrosis) was found in response to the undiluted test material.

No evidence of corrosion (necrosis) was found in response to the test material as a 3% formulation.

The test material, when applied undiluted, is classified as a primary irritant and as a corrosive by dermal application.

The test material, when applied as a 3% w/v formulation in deionized water, is not classified as a primary irritant or as a corrosive by dermal application.

METHODS (See Appendix 1 for Protocol and Supplemental Instructions)

This standardized procedure was conducted according to the general conditions of the protocol and specifically as designated on the Project Instruction Sheet and Supplemental Instructions, as applicable. As such, it satisfies the criteria established by the Federal Hazardous Substances Act (16 CFR 1500).

Young adult, New Zealand White rabbits (three males and three females) were used in this study. Each animal received 0.5 ml of undiluted test material under a 1" x 1" gauze square. The same six animals received 0.5 ml of test material administered as a 3% w/v formulation in deionized water under a 1" x 1" gauze square. Both concentrations of test material were each applied to one intact and one abraded skin site.

The values for each rabbit were totaled and averaged for each of the following categories for each concentration:

1. Erythema and eschar formation, intact skin, 24 hours.
2. Erythema and eschar formation, abraded skin, 24 hours.
3. Erythema and eschar formation, intact skin, 72 hours.
4. Erythema and eschar formation, abraded skin, 72 hours.
5. Edema, intact skin, 24 hours.
6. Edema, abraded skin, 24 hours
7. Edema, intact skin, 72 hours
8. Edema, abraded skin, 72 hours.

The eight average scores from above for each concentration were added together and the results divided by four to obtain the Primary Irritation Index (PII). A corrosive test material is one which causes destruction or irreversible damage to tissue, while a primary irritant is one which gives a PII of five or more on a scale of 0-8.

RESULTS

The report as constituted presents all the important observations that are critical to the interpretation of the test.

The results of the 24-hour application of each concentration of CPS & T No. 89-003 to intact and abraded skin areas are summarized in Tables 1 and 2. Raw data may be found in Appendix 2.

PROTOCOL DEVIATIONS

The protocol was followed without deviation.

REFERENCE

Draize, J. H. (1959). Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics. Association of Food and Drug Officials of the United States. Austin, Texas.

Table 1

Primary Skin Irritation in Rabbits Following a 24-Hour Dermal Application of Undiluted CPS & T No. 89-003

Skin Condition	Observation Time	Score for each Rabbit[a] No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	Total Score	Average Score
Erythema Formation									
	Site	**A**	**B**	**C**	**D**	**A**	**B**		
Intact	24 hrs	3ELP	2EP	3ELP	3EHLP	3EHLP	3EHLP	17	2.83
	72 hrs	2CHNPR	2BCHNPR	2CLNPR	2HNLPR	1ACHNPR	2HNLPR	11	1.83
	Site	**B**	**C**	**D**	**A**	**B**	**C**		
Abraded	24 hrs	3ELPS	2EHP	3EP	3EHLP	3EHLP	3EHLP	17	2.83
	72 hrs	2CHNPR	2BCHNPR	2CLNPR	2BHNOPR	2CHLNOPR	2HLNPR	12	2.00
Edema Formation									
	Site	**A**	**B**	**C**	**D**	**A**	**B**		
Intact	24 hrs	4	2	4	4	4	3	21	3.50
	72 hrs	3	3	4	4	4	4	22	3.67
	Site	**B**	**C**	**D**	**A**	**B**	**C**		
Abraded	24 hrs	3	3	4	4	4	4	22	3.67
	72 hrs	2	3	4	4	4	4	21	3.50
				Primary Irritation Index (PII)				6.0	

[a]Scoring key appended to report.

A = Footnote inadvertently not recorded and not recoverable.
B = Areas of dark brown and dark red discoloration on site.
C = Site coriaceousness.
E = Entire site appears to be covered with blanching which is moist and appears to be sloughing.
H = Hair on site.
L = Light brown discoloration on site.
N = Entire site appears necrotic.
O = Small area of open bleeding on edge of site.
P = Erythema taken at perimeter.
R = Entire site covered with scabbing.
S = Small scab on abrasion.

Table 2

Primary Skin Irritation in Rabbits Following a 24-Hour Dermal Application of CPS & T No. 89-003 as a 3% w/v Formulation in Deionized Water

Skin Condition	Observation Time	Score for each Rabbit[a] No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	Total Score	Average Score
		Erythema Formation							
	Site	**C**	**D**	**A**	**B**	**C**	**D**		
Intact	24 hrs	2	3H	3	3H	3H	3H	17	2.83
	72 hrs	1H	1H	2	1H	2H	1H	8	1.33
	Site	**D**	**A**	**B**	**C**	**D**	**A**		
Abraded	24 hrs	2	3H	3	3H	3H	3H	17	2.83
	72 hrs	1H	1H	2	2H	2H	1H	9	1.50
		Edema Formation							
	Site	**C**	**D**	**A**	**B**	**C**	**D**		
Intact	24 hrs	2	2	2	3	3	2	14	2.33
	72 hrs	0	0	0	0	0	0	0	0.00
	Site	**D**	**A**	**B**	**C**	**D**	**A**		
Abraded	24 hrs	2	2	2	4	3	2	15	2.50
	72 hrs	0	1	0	0	0	0	1	0.17
		Primary Irritation Index (PII)						3.4	

[a]Scoring key appended to report.

H = Hair on site.

B.P. America, Inc.

Ref.: 89-3807-21 (B)

September 6, 1989

QUALITY ASSURANCE STATEMENT

Date of Inspection	Date Findings Reported to Study Director	Date Findings Reported to Management
7/18/89	7/24/89	7/24/89
7/19/89	7/24/89	7/24/89

Report	Date Reviewed
Final	10/5/89

Debra McMillan-Ash
Auditor, Quality Assurance

10-16-89
Date

Ralph Anderson
Director of Quality Assurance and Regulatory Affairs

10/16/89
Date

B.P. America, Inc.

Ref.: 89-3807-21 (B)

September 6, 1989

Appendix 1

Copies of Protocol and Supplemental Instructions

(Total Number of Pages - 9)

PROJECT INSTRUCTION SHEET

TYPE OF PROJECT: Acute Oral Toxicity - Limit Primary Skin Irritation Primary Eye Irritation Delayed Contact Hypersensitivity	**DATE:** 7-12-89	**PROJECT NO.:** 89-3807-21 **PAGE NO.:**
	BY: B.J. Lynn, A.S. **SUPERVISOR:** J.J. Kreuzmann, B.A.	
CLIENT: B.P. America, Inc.		**BUDGET QUOTE:** A = $2,798.00 D = $4,570.00
CLIENT'S REPRESENTATIVE: Dale Marino		**CODE:** BPAM
CLIENT'S P.O. NO: 0008904090	**BILLING INSTRUCTIONS:** Bill through Project No. 89-3807-21 on a 40/60 plus basis	

SAMPLES AND DESCRIPTIONS	LOT NO.	DATE RECEIVED
CPS&T No. 89-003	NA	June 30, 1989

PROJECT INSTRUCTIONS: **Authorized by:** Dale Marino
Letter of: 6-13-89 **Verbally on:** 7-12-89 **Project Monitor:** K. Harrod, B.A.

STATEMENT OF PROTOCOL

1. Proposed Start Date: July 17, 1989
2. Report Date: October 16, 1989
3. HTB Study Director: James J. Kreuzmann, B.A.
4. Sponsor: B.P. America, Inc.
   200 Public Square
   Cleveland, OH 44114-2375
5. Protocol Modifications:

A. The sponsor has agreed to assume responsibility for all aspects of test material stability under the conditions of this testing program.

B. Two primary skin and eye irritation studies will be run on this test material. One of each test type will be done on the undiluted test material. The second of each test type will be done on a 3% w/v formulation in deionized water.

C. There is no Appendix B for this DCH protocol. Appendix A suffices for all available skin sites.

Protocol Modifications A - C have been discussed with and agreed upon by Dale Marino of B.P. America, Inc., on July 12, 1989.

Verbal results to Dale Marino of B.P. America, Inc., at (216) 586-4431.

PROJECT INSTRUCTIONS - Run the following studies in strict accordance with the referenced protocols and any above indicated protocol modifications as applicable.

Test Types	Reference Code	Study Cost	Study Code
Acute Oral Toxicity - Limit	1-1-1	$522.00	
(2) Primary Skin Irritations	1-3-1	$588.00/each	160
(2) Primary Eye Irritations	1-4-1	$550.00/each	
Delayed Contact Hypersensitivity	4-1-1	$4,570.00	250

This acute oral toxicity limit test will be dosed at 5.0 g/kg.

The 25 mm Hill Top Chamber with a volume of 0.3 ml will be used for this DCH study.

A vehicle of deionized water will be used for both induction and primary challenge phases of testing.

Formulations for this DCH study will be done w/v.

APPROVED BY:

Edwin V. Buehler, Ph.D.
Director of Toxicology 7-13-89

James J. Kreuzmann, B.A.
Study Director 7-13-89

PREPARED BY: BJL	TYPED BY: lg

Regulated: X FDA ___ EPA ___ Other
Non-Regulated: ___ QA Audited: In-Life: X Report: X

89-3807-21
PM

PROTOCOL
PRIMARY SKIN IRRITATION STUDY
IN RABBITS (FHSA 16 CFR 1500)

PURPOSE

This study is designed to assess the potential of a test article to cause irritation after a topical application to the skin of New Zealand White rabbits.

The general protocol is to be supplemented with specific details as provided by a Project Instruction Sheet and other information as necessary.

APPLICABLE REGULATION

Federal Hazardous Substances Labeling Act (16 CFR 1500).

TESTING FACILITY

Hill Top Biolabs, Inc.
Miamiville, Ohio 45147 (513) 831-3114

PROPOSED STARTING DATE

Established after receipt of test material and the approved study protocol, and will be specified in the Project Instruction Sheet.

TEST SYSTEM JUSTIFICATION

The rabbit is the animal model of choice. The test system is designated by federal regulations since it has been used historically for this type of study and will allow the data to be compared to that of other compounds.

TEST ANIMAL

Young adult, New Zealand White rabbits of either sex from an approved U.S.D.A. supplier will be used. The supplier and date of arrival will be documented.

NUMBER OF ANIMALS

Six animals

HOUSING AND ANIMAL CARE

Animals will be acclimated to the laboratory for at least one day before being used. Animals will be housed singly in suspension cages with wire mesh floors and will be fed PURINA LABORATORY RABBIT CHOW (or other comparable diet) and tap water ad libitum. The animals will be maintained on a 12-hour light/12-hour dark cycle.

ANIMAL IDENTIFICATION

Cage cards and individual ear tags will be used to identify each rabbit.

PREPARATION OF TEST ANIMALS

Prior to dosing the application sites will be prepared by clipping the hair from the dorsal area of the rabbits. Abraded areas will be prepared by making minor epidermal incisions with a hypodermic needle. The abrasions will be sufficiently deep to penetrate the stratum corneum but not deep enough to produce bleeding.

ADMINISTRATION OF TEST ARTICLE

If the test article is a liquid, 0.5 ml of the test article will generally be used. If a semi-solid, 0.5 g of the test article will generally be used. If the material is a solid, the test article will be moistened with an appropriate solvent (e.g. physiological saline).

The test material may be applied (0.5 ml or 0.5 g) either to or under a one-inch by one-inch surgical gauze patch, two layers thick, to an intact skin area and to an abraded skin area on each of the six test rabbits. The application sites will be rotated to minimize bias due to site-to-site variation.

Each patch will be held in place with adhesive tape. After application of the patches, the trunk of each rabbit will be wrapped with rubber dental dam which will be secured with staples. An outer layer of gauze and tape will be placed around the trunk of each animal. Each animal will be fitted with an appropriate restraining device to deter removal of the wrapping. After approximately 24 hours, the rabbits will be released from restraint and the wrapping and patches will be removed. Test sites may be wiped free of residual test material by a gentle sponging using a towel moistened with water or other appropriate solvent.

OBSERVATIONS

The application sites will be scored for each rabbit either immediately prior to or following the removal of residual test material as practical (an approximate 24-hour reading) and again two days later (an approximate 72-hour reading) according to the Draize scale given in Appendix I. The skin will also be observed for evidence of tissue destruction or other changes not included in Appendix I.

OBSERVATIONS (Cont.)

The skin grades for each rabbit will be totaled and averaged for each of the following categories:

1. Erythema and eschar formation, intact skin, 24 hours.
2. Erythema and eschar formation, abraded skin, 24 hours.
3. Erythema and eschar formation, intact skin, 72 hours.
4. Erythema and eschar formation, abraded skin, 72 hours.
5. Edema, intact skin, 24 hours.
6. Edema, abraded skin, 24 hours.
7. Edema, intact skin, 72 hours.
8. Edema, abraded skin, 72 hours.

The eight average scores from above will be added together and the results divided by four to obtain the Primary Irritation Index (PII). A primary irritant is one which gives a PII of five or more while a corrosive material is one which causes destruction or irreversible damage to tissue.

The times of dose application, 24-hour reading, and 72-hour reading will be documented as will the corresponding irritation scores. When injury is noted, the nature of the injury will be documented (e.g., necrosis). Any other changes from the normal texture or color of skin will also be documented.

REPORT

The report will include (but may not be limited to) identification of the animals and test procedure, protocol deviations if any, a description of the test material (including date of receipt, color, and form), solvent (if any), dosage, description of irritative effects, primary irritation index, and summary. The report will include the classification of the test material, if applicable.

NOTICE

This study will be run according to good laboratory practices. If it becomes necessary to make changes on the approved protocol, the revisions and reasons for change will be documented, reported to the sponsor and will become part of the permanent file for that study. Similarly the sponsor will be notified as soon as is practical whenever an event occurs that is unexpected and may have an effect on the validity of the study.

DATA RETENTION

All records that would be required to reconstruct the study and demonstrate adherence to the protocol will be maintained. The raw data and the original of the final report will be on file at the testing facility for a period of not less than two years. Permanent records will be in the form of microfilm. Unused test articles will be destroyed, unless requested otherwise.

REFERENCE

Draize, J. H. (1959). In
Appraisal of Chemicals in Foods, Drugs and Cosmetics. Association of Food and Drug Officials of the United States. Austin, Texas.

REFERENCE CODE

1-3-1/2-10-88/REV 4 (VOIDS REV 3)

89-3807-21

Primary Skin Irritation

APPROVAL FORM P10

Protocol Approval Form
TOXICOLOGY DIVISION
Hill Top Biolabs, Inc.

Protocol Title	Reference Code
Primary Skin Irritation Study in Rabbits (FHSA 16 CFR 1500)	1-3-1/2-10-88/REV 4 (VOIDS 3)

Protocol Approved By (Hill Top Biolabs, Inc.):

3-14-89
Date

Edwin V. Buehler, Ph.D.
Vice President, Scientific Affairs
Director of Toxicology

Protocol Approved By (Sponsor):

( ) Approved without modification

( ) Approved with modification

Supplemental Information Form Attached - Yes ( ) No ( )

4/19/89
Date

Signed

Date

BP AMERICA
Client Company

200 PUBLIC SQUARE (7-480-K)
CLEVELAND OHIO 44114-2375
Address

Primary Skin Irritation

APPENDIX I

EVALUATION OF DERMAL IRRITATION

Erythema and Eschar Formation (most severely affected area graded):

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 (most severely affected area graded):

No edema 0

Very slight edema (barely perceptible) 1

Slight edema (edges of area will-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

89-3807-21
P04

HILL TOP BIOLABS, INC.

TOXICOLOGY
SIGNATURE/INITIALS OF EMPLOYEES

Edwin V. Buehler, Ph.D.
Vice President, Scientific Affairs
Director of Toxicology

B. J. Lynn, A.S.
Assistant Study Director

Susan R. Coffey, B.S.
Research Supervisor

Teresa D. Morris, B.S.
Research Assistant

Tammy Gastineau
Lead Animal Care Technician

Patti Nardini
Animal Caretaker

Lisa Goble
Report Writer

Kathleen A. Reinhardt, B.S.
Report Writer

Kenneth J. Harrod, B.A.
Senior Technician

Deborah D. Schumann, B.S.
Research Supervisor

James J. Kreuzmann, B.A.
Director of Technical Services

Douglas R. Shuster, B.S.
Technician

Sandra F. Leukering
Head of Client Services

Marna Watson
Research Assistant

Deborah K. Lewis
Report Coordinator

Sandra L. Webster
Report Writer

June 26, 1989

HILL TOP BIOLABS, INC.

89-3807-21

P25

TOXICOLOGY
SIGNATURE/INITIALS OF EMPLOYEES

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Lisa Adams
Animal Caretaker

B S Lynn BSL
B. J. Lynn, A.S.
Assistant Study Director

E Buehler EB
Edwin V. Buehler, Ph.D.
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Director of Toxicology

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Animal Caretaker

DKL
Deborah K. Lewis DKL
Deborah K. Lewis
Report Coordinator

Revised - July 26, 1989

B.P. America, Inc.

Ref.: 89-3807-21 (B)

September 6, 1989

Appendix 2

Copies of Raw Data

(Total Number of Pages - 6)

Project No.: 89-3807-21

Page No.: 32

EXPLAINING RAW DATA ENTRY ERRORS

When a raw data entry error is made it is necessary to explain the error. In order to speed-up the process, conserve notebook space, and add some consistency throughout the organization to these explanations, the following numeral listing has been developed:

1. Misspelled
2. Mathematical error
3. Wrong entry (date, sample no., word, etc.)
4. Transposition or sequencing error
5. Transcription error
6. Procedural change
7. Wrong conclusion
8. Illegible entry
9. Unnecessary entry
10. Footnoted explanation
11. Additional comment
12. Duplicate page (copied for microfilming purposes)

Each time an error is made it will be initialed, dated, and one of the above numbers will be placed next to the initials and circled.

PRIMARY SKIN IRRITATION TEST

FORM 1

PROJECT NO. 89-3807-21

PAGE NO. 39

Compound: CPS&T No. 89-003 Start: 7-18-89 Finish: 7-21-89

Concentration: undiluted Solvent: NA Dose: 0.5ml applied under a 1"x1" gauze square

Dosed With: 2.5cc syringe Dosed By: Tom/DS Sample Preparation: NA

Sheet Prepared By: TOM Time of: Dosing: 2:34 pm 24 hrs: 2:38pm 72 hrs: 2:31 pm

Animal Supplier: CR Animal Arrival Date: 7-12-89 Room No.: 01

For footnote explanations sk page 43. KJH 8-28-89

Rabbit Number and Sex	#1 953 ♂	#2 958 ♂	#3 959 ♂	#4 977 ♀	#5 978 ♀	#6 979 ♀

ERYTHEMA AND ESCHAR FORMATION

Intact Skin (1989)		Site A	Site B	Site C	Site D	Site A	Site B	IT.	Total	Avg.
7-19	24 hr.	3 LP E	2 E P	3 LP E	3 EH LP	3 EH LP	3 EH LP	MW DS	17	2.83
7-21	72 hr.	2 EH RN	2 PH BR	3 CP RN LH	2 PH R	Ø	2 PH CR	MW DS	11	1.83
Abraded Skin		**Site B**	**Site C**	**Site D**	**Site A**	**Site B**	**Site C**	**IT.**	**Total**	**Avg.**
7-19	24 hr.	3 SP LE	2 HP E	3 P E	3 EH P	3 EH LP	3 EH LP	MW DS	17	2.83
7-21	72 hr.	2 PN CR H	2 PH BR	2 CP LH	N OPH 2 R	2 LPH CR	2 NRH LP	MW DS	12	2.00

EDEMA FORMATION

Intact Skin (1989)		Site A	Site B	Site C	Site D	Site A	Site B	IT.	Total	Avg.
7-19	24 hr.	4	2	4	4	4	3	MW DS	21	3.50
7-21	72 hr.	3	3	4	4	4	4	MW DS	22	3.67
Abraded Skin		**Site B**	**Site C**	**Site D**	**Site A**	**Site B**	**Site C**	**IT.**	**Total**	**Avg.**
7-19	24 hr.	3	3	4	4	4	4	MW DS	22	3.67
7-21	72 hr.	~~3~~ 2	3	4	4	4	4	MW DS	21	3.50
		③ MW 7-21-89						TOTAL	23.83	

PRIMARY IRRITATION SCORE = 6.0 KJH 7-24-89

SITE KEY: Head (A C / B D) Tail

Footnotes:

Checked By: KJH 7-24-89

Project No.: 89-3807-21

Page No.: 40

Checked by: KTH 7-24-89

	Yes	No	NA
Animals shaved per protocol on 7-17-89	T X		
Animals abraded per protocol	T X		
Animals dosed per protocol	T X		
Animals wrapped per protocol	T X		
Animals restrained per protocol collars	T X		
Sites wiped prior to scoring	M X		
Sites wiped after scoring		M X	

Notes: T=TDM 7.18.89 M=MW 7.19.89

Studies rabbits were on previously: 1- NA 2- NA

3- NA 4- NA 5- NA 6- NA

Animals judged satisfactory for re-use:

NA ✓ Yes _____ Signature: _____ Date: _____

PRIMARY SKIN IRRITATION TEST

FORM 2

PROJECT NO. 89-3807-01

PAGE NO. 41

Compound: CPS & T No. 89-003 Start: 7-18-89 Finish: 7-21-89

Concentration: 3% w/v Solvent: Deionized Water Dose: a 1" x 1" gauze square 0.5ml applied under

③TDN 3889 3.0

Dosed With: 2.5cc Syringe Dosed By: TDM/DS Sample Preparation: see sample prep sheet

Sheet Prepared By: TDM Time of: Dosing: 2:34 pm 24 hrs: 2:38pm 72 hrs: 2:31 p.m

Animal Supplier: CR Animal Arrival Date: 7-12-89 Room No.: 01

For footnote explanations see page 43. KTH 8-28-89

Rabbit Number and Sex	#1 953 ♂	#2 958 ♂	#3 959 ♂	#4 977 ♀	#5 978 ♀	#6 979 ♀

ERYTHEMA AND ESCHAR FORMATION

Intact Skin (1989)		Site C	Site D	Site A	Site B	Site C	Site D	IT.	Total	Avg.
7-19	24 hr.	2	3 H	3	3 H	3 H	3 H	MW DS	17	2.83
7-21	72 hr.	1 H	1 H	2	1 H	2 H	1 H	MW DS	8	1.33
Abraded Skin		**Site D**	**Site A**	**Site B**	**Site C**	**Site D**	**Site A**	**IT.**	**Total**	**Avg.**
7-19	24 hr.	2	3 H	3	3 H	3 H	3 H	MW DS	17	2.83
7-21	72 hr.	1 H	1 H	2	2 H	2 H	1 H	MW DS	9	1.50

EDEMA FORMATION

Intact Skin (1989)		Site C	Site D	Site A	Site B	Site C	Site D	IT.	Total	Avg.
7-19	24 hr.	2	2	2	3	3	2	MW DS	14	2.33
7-21	72 hr.	0	0	0	0	0	0	MW DS	0	0.00
Abraded Skin		**Site D**	**Site A**	**Site B**	**Site C**	**Site D**	**Site A**	**IT.**	**Total**	**Avg.**
7-19	24 hr.	2	2	2	4	3	2	MW DS	15	2.50
7-21	72 hr.	0	1	0	0	0	0	MW DS	1	0.17
								TOTAL	13.49	

PRIMARY IRRITATION SCORE = 3.4 KTH 7-24-89

SITE KEY

Head
A C
B D
Tail

Footnotes:

Checked By: KTH 7-24-89

Project No.: 89-3807-21

Page No.: 42

Checked by: KDH 7-24-89

	Yes	No	NA
Animals shaved per protocol (T) DM 7-17-89	X		
Animals abraded per protocol (T)	X		
Animals dosed per protocol (T)	X		
Animals wrapped per protocol (T)	X		
Animals restrained per protocol (T) ADDED	X		
Sites wiped prior to scoring (M)	X		
Sites wiped after scoring (M)		X	

Notes: T=TDM 7-18-89 M=MW 7-19-89

Studies rabbits were on previously: 1- NA 2- NA

3- NA 4- NA 5- NA 6- NA

Animals judged satisfactory for re-use:

NA ✓ Yes _____ Signature: _____ Date: _____

Footnote Explanation Sheet

Project Number	89.3807-21
Page Number	43

P = Erythema taken at perimeter.

E = Entire site appears to be covered with blanching which is moist and appears to be sloughing.

S = Small scab or abrasion.

H = Hair on site.

L = Light brown discoloration on site.

all above footnotes mw 7-15-89

③ mw 7.21.89
R = ~~Erosion~~ Entire site covered with scabbing. mw 7-21-89

C = Site coloration. mw 7-21-89

B = Areas of dark brown & dark red discoloration on site. mw 7.21.89

③
Q = Error mw 7-21-89

O = small area of open bleeding on edge of site mw 7.21.89

N = Entire site appears necrotic. mw 7-21-89

A = Footnote inadvertently not recorded & irrecoverable

mw added 9-13-89

Primary Eye Irritation Study in Rabbits

of: CPS & T No. 89-003

for: B.P. America, Inc.

Hill Top Biolabs Project No. 89-3807-21 (C)

Report Issue Date: 10.16.89

Report Issued by:

HILL TOP BIOLABS, INC.

Edwin V. Buehler, Ph.D.
Vice President, Scientific Affairs
Director of Toxicology

B.P. America, Inc.

Ref.: 89-3807-21 (C) September 6, 1989

COMPLIANCE STATEMENT

This study was conducted in accordance with Good Laboratory Practice Standards (21 CFR 58).

HILL TOP BIOLABS, INC.

for James J. Kreuzmann, B.A. 10.16.89
Study Director, Acute Toxicology

HILL TOP BIOLABS, INC.

IMPORTANT NOTICE

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B.P. America, Inc.

Ref.: 89-3807-21 (C)

September 6, 1989

REPORT APPROVAL

Report Prepared by:

HILL TOP BIOLABS, INC.

Lisa G. Goble
Report Writer,
Acute Toxicology
10-6-89

Project Monitor:

HILL TOP BIOLABS, INC.

Kenneth J. Harrod 10-9-89
Kenneth J. Harrod, B.A.
Senior Technician,
Acute Toxicology

Report Approved by:

HILL TOP BIOLABS, INC.

James J. Kreuzmann, B.A.
Study Director,
Acute Toxicology
10.16.89

CONTRIBUTORS

The following members of Hill Top Biolabs, Inc., contributed to the conduct and reporting of Project No. 89-3807-21 (B):

Name	Title	Function
E. Buehler, Ph.D.	Vice President, Scientific Affairs Director of Toxicology	Manager, Toxicology
J. Kreuzmann, B.A.	Director of Technical Services	Study Director, Conduct of Study
B. Lynn, A.S.	Assistant Study Director	Conduct of Study
S. Coffey, B.S.	Research Supervisor	Conduct of Study
D. Schumann, B.S.	Research Supervisor	Conduct of Study
M. Watson	Research Assistant	Conduct of Study
T. Morris, B.S.	Research Assistant	Conduct of Study
K. Harrod, B.A.	Senior Technician	Project Monitor, Conduct of Study
D. Shuster, B.S.	Technician	Conduct of Study
M. LeQuire, A.S.	Technician	Conduct of Study
T. Gastineau	Lead Animal Care Technician	Conduct of Study
P. Nardini	Animal Caretaker	Conduct of Study
V. Wiggins	Animal Caretaker	Conduct of Study
L. Adams	Animal Caretaker	Conduct of Study
L. Goble	Report Writer	Report Preparation

GENERAL INFORMATION

Project No.:	89-3807-21 (C)
Test/Protocol No.:	Primary Eye Irritation Study in Rabbits 1-4-1/2-5-88/REV 4
Testing Facility:	Hill Top Biolabs, Inc. Main and Mill Streets Miamiville, OH 45147
Sponsor:	B.P. America, Inc. 200 Public Square Cleveland, OH 44114-2375
Sample Identification:	CPS & T No. 89-003
Date Sample Received:	June 30, 1989
Source of Animals:	Clerco Research Farm
Date Study Initiated:	July 13, 1989
Date Project Started:	July 17, 1989
Date Project Completed:	July 20, 1989

SAMPLE CHARACTERIZATION AND STABILITY

The sponsor has assumed responsibility for test substance derivation, characterization, and stability testing.

The test material, CPS & T No. 89-003, was an opaque beige liquid. Two test material aliquots were received and were stored at room temperature throughout the study in semi-clear nalgene bottles with lids. The partially used test material aliquot was disposed of following the completion of testing. The unused test material aliquot was returned to the sponsor following the completion of testing.

DATA RETENTION

The raw data and the original of the final report will be on file at the testing facility for a period of not less than two years. Permanent records will be in the form of microfilm.

SUMMARY/CONCLUSIONS

The primary ocular irritancy of CPS & T No. 89-003, undiluted and as a 3% w/v formulation in deionized water, was evaluated in compliance with the conditions specified in the regulation for the enforcement of the Federal Hazardous Substances Act (16 CFR 1500).

The eyes of all of the six rabbits exposed to the undiluted test material were found to show evidence of positive corneal, iris, and conjunctival changes.

None of the eyes of the six rabbits exposed to the test material as a 3% formulation were found to show evidence of positive corneal, iris, or conjunctival changes.

Maximum total irritation scores in individual animals exposed to the undiluted test material ranged from 23 to 39.

Maximum total irritation scores in individual animals exposed to the test material as a 3% formulation ranged from 0 to 2.

Any changes noted to the eyes themselves, in response to either test material concentration, may be found in the raw data in Appendix 2.

No evidence of corrosion was noted in response to either test material concentration.

The test material, when applied undiluted, is classified as an irritant by ocular application

The test material, when applied as a 3% w/v formulation in deionized water, is not classified as an irritant by ocular application.

METHODS (See Appendix 1 for Protocol and Supplemental Instructions)

This standardized procedure was conducted according to the general conditions of the protocol and specifically as designated on the Project Instruction Sheet and Supplemental Instructions, as applicable. As such, it satisfies the criteria established by the Federal Hazardous Substances Act (16 CFR 1500).

Young adult, New Zealand White rabbits (six males and six females) were used in this study. The test material, either undiluted or as a 3% w/v formulation in deionized water, was appropriately applied at a dose of 0.1 ml to one eye of each animal.

An animal will be considered as exhibiting a positive response if it satisfies one of the following conditions:

1. Exhibiting scores of grade 1 or more in corneal opacity,
2. Exhibiting scores of grade 1 or more in iris changes,
3. Exhibiting scores of grade 2 or more for conjunctival erythema,
4. Exhibiting scores of grade 2 or more for conjunctival edema.

The test material was then classified according to the following criteria:

1. Positive scores in 4 to 6 rabbits = irritant;
2. Positive scores in 2 to 3 rabbits = indeterminate (additional testing required for classification); and
3. Positive scores in 0 to 1 animals = nonirritant.

The test material is considered corrosive if it produces in-depth destruction of living tissue.

RESULTS

The report as constituted presents all the important observations that are critical to the interpretation of the test.

The results of the application of each concentration of CPS & T No. 89-003 to the eyes of New Zealand White rabbits are summarized in Tables 1 and 2. Raw data may be found in Appendix 2.

PROTOCOL DEVIATIONS

The protocol was followed without deviation.

REFERENCE

Draize, J. H. (1959). Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics. Association of Food and Drug Officials of the United States. Austin, Texas.

Table 1

Primary Eye Irritation in Rabbits Following an Ocular Application of Undiluted CPS & T No. 89-003

Animal Number	Time	Cornea[a] A	Cornea[a] B	Iris	Conjunctiva[a] C	Conjunctiva[a] D	Conjunctiva[a] E	Total[bc] Score
1-956	24 hr	1	3	1	2B	3	2	34
	48 hr	1	2	1	2BL	2	2	27
	72 hr	1	1	0	1LT	2	0	11
2-957	24 hr	1	4	1	2BL	4	1	39
	48 hr	1	4	1	2BL	2	0	33
	72 hr	1	3	1	1T	2	0	26
3-954	24 hr	1	3	1	2BL	3	1	32
	48 hr	1	2	1	2BL	3	0	25
	72 hr	1	1	0	1LT	2	0	11
4-962	24 hr	1	3	1	2B	3	1	32
	48 hr	1	1	1	2	2	0	18
	72 hr	1	1	1	2T	1	0	16
5-963	24 hr	1	2	1	2BL	2	0	23
	48 hr	1	2	0	2L	2	0	18
	72 hr	1	1	0	2T	2	0	13
6-965	24 hr	1	2	1	2BL	3	1	27
	48 hr	1	2	0	2L	2	0	18
	72 hr	1	1	0	2T	1	0	11

[a] A = Degree of Opacity; B = Area Affected; C = Erythema; D = Swelling; and E = Discharge.

[b] Scoring key appended to report.

[c] Total Score is the sum of the following three sub-totals, with a maximum score of 110:

1. Degree of opacity x area involved x 5
2. Iris score x 5
3. (Sum of scores for erythema, swelling, and discharge) x 2

B = Blistered appearance to conjunctiva.

L = Blanched appearance to conjunctiva.

T = Thickened appearance to conjunctiva.

Table 2

Primary Eye Irritation in Rabbits Following an Ocular Application of CPS & T No. 89-003 as a 3% w/v Formulation in Deionized Water

Animal Number	Time	Cornea[a]		Iris	Conjunctiva[a]			Total[bc] Score
		A	B		C	D	E	
7-960	24 hr	0	0	0	0	0	0	0
	48 hr	0	0	0	0	0	0	0
	72 hr	0	0	0	0	0	0	0
8-961	24 hr	0	0	0	0	0	0	0
	48 hr	0	0	0	0	0	0	0
	72 hr	0	0	0	0	0	0	0
9-955	24 hr	0	0	0	0	0	0	0
	48 hr	0	0	0	0	0	0	0
	72 hr	0	0	0	0	0	0	0
10-966	24 hr	0	0	0	1	0	0	2
	48 hr	0	0	0	1	0	0	2
	72 hr	0	0	0	0	0	0	0
11-967	24 hr	0	0	0	0	0	0	0
	48 hr	0	0	0	0	0	0	0
	72 hr	0	0	0	0	0	0	0
12-968	24 hr	0	0	0	0	0	0	0
	48 hr	0	0	0	0	0	0	0
	72 hr	0	0	0	0	0	0	0

[a] A = Degree of Opacity; B = Area Affected; C = Erythema; D = Swelling; and E = Discharge.

[b] Scoring key appended to report.

[c] Total Score is the sum of the following three sub-totals, with a maximum score of 110:

1. Degree of opacity x area involved x 5
2. Iris score x 5
3. (Sum of scores for erythema, swelling, and discharge) x 2

B.P. America, Inc.

Ref.: 89-3807-21 (C)

September 6, 1989

QUALITY ASSURANCE STATEMENT

Date of Inspection	Date Findings Reported to Study Director	Date Findings Reported to Management
7/17/89	7/19/89	7/19/89
7/20/89	7/24/89	7/24/89

Report	Date Reviewed
Final	10/5/89

Debra McMillan-Ash
Auditor, Quality Assurance

10-16-89
Date

Ralph Anderson
Director of Quality Assurance and Regulatory Affairs

10/16/89
Date

B.P. America, Inc.

Ref.: 89-3807-21 (C)

September 6, 1989

Appendix 1

Copies of Protocol and Supplemental Instructions

(Total Number of Pages - 10)

PROJECT INSTRUCTION SHEET

TYPE OF PROJECT: Acute Oral Toxicity - Limit Primary Skin Irritation Primary Eye Irritation Delayed Contact Hypersensitivity	**DATE:** 7-12-89	**PROJECT NO.:** 89-3807-21 **PAGE NO.:**
	BY: B.J. Lynn, A.S. **SUPERVISOR:** J.J. Kreuzmann, B.A.	
CLIENT: B.P. America, Inc.		**BUDGET QUOTE:** A = $2,798.00 D = $4,570.00
CLIENT'S REPRESENTATIVE: Dale Marino		**CODE:** BPAM
CLIENT'S P.O. NO: 0008904090	**BILLING INSTRUCTIONS:** Bill through Project No. 89-3807-21 on a 40/60 plus basis	

SAMPLES AND DESCRIPTIONS	LOT NO.	DATE RECEIVED
CPS&T No. 89-003	NA	June 30, 1989

PROJECT INSTRUCTIONS: Authorized by: Dale Marino
Letter of: 6-13-89 **Verbally on:** 7-12-89 **Project Monitor:** K. Harrod, B.A.

STATEMENT OF PROTOCOL

1. Proposed Start Date: July 17, 1989
2. Report Date: October 16, 1989
3. HTB Study Director: James J. Kreuzmann, B.A.
4. Sponsor: B.P. America, Inc.
   200 Public Square
   Cleveland, OH 44114-2375
5. Protocol Modifications:

A. The sponsor has agreed to assume responsibility for all aspects of test material stability under the conditions of this testing program.

B. Two primary skin and eye irritation studies will be run on this test material. One of each test type will be done on the undiluted test material. The second of each test type will be done on a 3% w/v formulation in deionized water.

C. There is no Appendix B for this DCH protocol. Appendix A suffices for all available skin sites.

Protocol Modifications A - C have been discussed with and agreed upon by Dale Marino of B.P. America, Inc., on July 12, 1989.

Verbal results to Dale Marino of B.P. America, Inc., at (216) 586-4431.

PROJECT INSTRUCTIONS - Run the following studies in strict accordance with the referenced protocols and any above indicated protocol modifications as applicable.

Test Types	Reference Code	Study Cost	Study Code
Acute Oral Toxicity - Limit	1-1-1	$522.00	
(2) Primary Skin Irritations	1-3-1	$588.00/each	160
(2) Primary Eye Irritations	1-4-1	$550.00/each	
Delayed Contact Hypersensitivity	4-1-1	$4,570.00	250

This acute oral toxicity limit test will be dosed at 5.0 g/kg.

The 25 mm Hill Top Chamber with a volume of 0.3 ml will be used for this DCH study.

A vehicle of deionized water will be used for both induction and primary challenge phases of testing.

Formulations for this DCH study will be done w/v.

APPROVED BY:

Edwin V. Buehler, Ph.D.
Director of Toxicology 7-13-89

James J. Kreuzmann, B.A.
Study Director 7-13 89

PREPARED BY: BJL	TYPED BY: lg

Regulated: X FDA ___ EPA ___ Other
Non-Regulated: ___ QA Audited: In-Life: X Report: X

PROTOCOL
EYE IRRITATION STUDY IN RABBITS -
72-HOUR OBSERVATION PERIOD (FHSA 16 CFR 1500)

PURPOSE

This study is designed to determine the irritative potential of the test article to the eyes of New Zealand White rabbits after one application without rinsing.

The general protocol is to be supplemented with specific details as provided by a Project Instruction Sheet and other information as necessary.

APPLICABLE REFERENCE

Federal Hazardous Substances Labelling Act (16 CFR 1500).

TESTING FACILITY

Hill Top Biolabs, Inc.
Miamiville, Ohio 45147 (513) 831-3114

PROPOSED STARTING DATE

Established after receipt of test material and the approved study protocol, and will be specified in the Project Instruction Sheet.

TEST SYSTEM JUSTIFICATION

The rabbit is the animal model of choice. The test system is designated by federal regulations since it has been used historically for this type of study and will allow the data to be compared to that of other compounds.

TEST ANIMALS

Young adult, New Zealand White rabbits of either sex from an approved U.S.D.A. supplier will be used. The supplier and date of arrival of the rabbits will be documented.

NUMBER OF ANIMALS

Six animals.

HOUSING AND ANIMAL CARE

Animals will be acclimated to the laboratory for at least one day before being used. Animals will be housed singly in suspension cages with wire mesh floors and will be fed PURINA LABORATORY RABBIT CHOW (or other comparable diet) and tap water ad libitum. The animals will be maintained on a 12-hour light/12-hour dark cycle.

ANIMAL IDENTIFICATION

Cage cards and individual ear tags will be used to identify each rabbit.

PREPARATION OF ANIMALS

Both eyes of each animal will be examined prior to dosing. Any eye exhibiting pre-existing defects or irritation which may compromise the validity of the study will not be used.

TEST MATERIAL ADMINISTRATION

For testing liquids, 0.1 milliliter will be used. For most solids or pastes, 100 milligrams of the test article will be used. For articles in flake, granule, powder or other particulate form, the amount that has a volume of 0.1 milliliter (after compacting as much as possible without crushing or altering the individual particles, such as by tapping the measuring container) will be used whenever this volume weighs less than 100 milligrams. In such a case, the weight of the 0.1 milliliter test dose will be recorded.

The test article will be placed in one eye of each animal by gently pulling the lower lid away from the eyeball to form a cup into which the test article is dropped. The lids will then be gently held together for approximately one second, as possible, and the animal will be released. The other eye, remaining untreated, will serve as a control. The eyes will not be rinsed following instillation of test article, but may be rinsed with U.S.P. saline, as desired, following the 24 hour reading.

OBSERVATIONS

The eyes will be examined and graded for ocular reaction approximately 24, 48, and 72 hours following dose administration according to the Draize method in Appendix I.

The material will be classified as an irritant according to the following criteria:

1. Positive scores in 4 to 6 rabbits = irritant;
2. Positive scores in 2 to 3 rabbits = indeterminate (additional testing required for classification); and
3. Positive scores in 0 to 1 animals = nonirritant.

OBSERVATIONS (Cont.)

The times of dose application, 24-hour, 48-hour, and 72-hour readings will be documented as will the corresponding irritation and scores. If any injury is noted that is not listed in the scale shown in Appendix I, the nature of the injury will be documented.

REPORT

The report will include (but may not be limited to) identification of the animals and test procedure, protocol deviations if any, a description of the test material (including date of receipt, color, and form), dosage, description of irritative effects, scores, and summary. The report will include the classification of the test material as to eye irritancy, if applicable.

NOTICE

This study will be run according to good laboratory practices. If it becomes necessary to make changes on the approved protocol, the revisions and reasons for change will be documented, reported to the sponsor and will become part of the permanent file for that study. Similarly the sponsor will be notified as soon as is practical whenever an event occurs that is unexpected and may have an effect on the validity of the study.

DATA RETENTION

All records that would be required to reconstuct the study and demonstrate adherence to the protocol will be maintained. The raw data and the original of the final report will be on file at the testing facility for a period of not less than two years. Permanent records will be in the form of microfilm. Unused test material will be destroyed, unless requested otherwise.

REFERENCE

Draize, J. H. (1959). In Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics. Association of Food and Drug Officials of the United States. Austin, Texas.

REFERENCE CODE

1-4-1/2-5-88/REV 4 (VOIDS REV 3)

SCALE FOR SCORING OCULAR LESIONS*

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 or iris slightly obscured 2**
   - Opalescent areas, no details or 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

   Score equals 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**

   Score equals A x 5 Total maximum 10

3. Conjunctivae

   A. Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)
   - 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 and partial eversion of lids 2**
   - Swelling with lids about half closed 3**
   - Swelling with lids about half closed to completely closed 4**

3. Conjunctivae (Cont.)

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 equals (A + B + C) x 2 Total maximum 20

---

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

**An animal will be considered as exhibiting a positive reaction.

89-3807-21

P17

Acute Eye Irritation APPROVAL FORM

Protocol Approval Form
TOXICOLOGY DIVISION
Hill Top Biolabs, Inc.

Protocol Title	Reference Code
Acute Eye Irritation Study in Rabbits - 72 Hour Observation Period (FHSA 16 CFR 1500)	1-4-1/2-5-88/REV 4 (VOIDS 3)

Protocol Approved By (Hill Top Biolabs, Inc.):

Edwin V. Buehler, Ph.D.
Vice President, Scientific Affairs
Director of Toxicology

3-10-89
Date

Protocol Approved By (Sponsor):

( ) Approved without modification

( ) Approved with modification

Supplemental Information Form Attached - Yes ( ) No ( )

Signed

4/19/89
Date

Signed

Date

BP AMERICA
Client Company

200 PUBLIC SQUARE (7-4801-K)
CLEVELAND, OHIO 44114-2375
Address

89-3807-21
P04

HILL TOP BIOLABS, INC.

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June 26, 1989

HILL TOP BIOLABS, INC. 89-3807-21

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B.P. America, Inc.

Ref.: 89-3807-21 (C)

September 6, 1989

Appendix 2

Copies of Raw Data

(Total Number of Pages - 6)

Project No.: 89-3807-21

Page No.: 32

EXPLAINING RAW DATA ENTRY ERRORS

When a raw data entry error is made it is necessary to explain the error. In order to speed-up the process, conserve notebook space, and add some consistency throughout the organization to these explanations, the following numeral listing has been developed:

1. Misspelled
2. Mathematical error
3. Wrong entry (date, sample no., word, etc.)
4. Transposition or sequencing error
5. Transcription error
6. Procedural change
7. Wrong conclusion
8. Illegible entry
9. Unnecessary entry
10. Footnoted explanation
11. Additional comment
12. Duplicate page (copied for microfilming purposes)

Each time an error is made it will be initialed, dated, and one of the above numbers will be placed next to the initials and circled.

PRIMARY EYE IRRITATION TEST

PROJECT NO. 89-3807-21

PAGE NO. 45

Compound: CPS&T No. 89-003 Start: 7-17-89 Finish: 7-20-89

Concentration: undiluted Solvent: NA Dose: 0.1ml Dosed With: 1cc syringe

Sample Preparation: NA Dosed By: KOH/MW Sheet Prep. By: KOH

Animal Supplier: Clercer Room No.: 01 Animal Arrival Date: 7-12-89

Date Prescreened: 7-17-89 Time of: Prescreen: 2:18pm Dose: 4:17pm 1 hr: NA

24 hr: 4:17pm 48 hr: 4:25pm 72 hr: 4:31pm Day 4: NA Day 7: NA

Day 10: NA Day 13: NA Day 16: NA Day 19: NA Day 21: NA

For footnote explanations see page 49. KOH 8-28-89

Rabbit Number, Sex, and Previous Studies	Eye	Date of Reading	Cornea A	Cornea B	Cornea ST	Iris	ST	Conjunctiva A	Conjunctiva B	Conjunctiva C	Conjunctiva ST	Total	IT
1- 956	RE	7-18-89	1	3	15	1	5	2^B	3	2	14	34	KOH
♂		7-19-89	1	2	10	1	5	2^B_L	2	2	12	27	KOH
NA		7-20-89	1	1	5	0	0	1^L_T	2	0	6	11	KOH
2- 957	RE	7-18-89	1	4	20	1	5	2^B_L	4	1	14	39	KOH
♂		7-19-89	1	4	20	1	5	2^B_L	2	0	8	33	KOH
NA		7-20-89	1	3	15	1	5	1^T	2	0	6	26	KOH
3- 954	RE	7-18-89	1	3	15	1	5	2^B_L	3	1	12	32	KOH
♂		7-19-89	1	2	10	1	5	2^B_L	3	0	10	25	KOH
NA		7-20-89	1	1	5	0	0	1^L_T	2	0	6	11	KOH
4- 962	RE	7-18-89	1	3	15	1	5	2^B	3	1	12	32	KOH
♀		7-19-89	1	1	5	1	5	2	2	0	8	18	KOH
NA		7-20-89	1	1	5	1	5	2^T	1	0	6	16	KOH
5- 963	RE	7-18-89	1	2	10	1	5	2^B_L	2	0	8	23	KOH
♀		7-19-89	1	2	10	0	0	2^L	2	0	8	18	KOH
NA		7-20-89	1	1	5	0	0	2^T	2	0	8	13	KOH
6- 965	RE	7-18-89	1	2	10	1	5	2^B_L	3	1	12	27	KOH
♀		7-19-89	1	2	10	0	0	2^L	2	0	8	18	KOH
NA		7-20-89	1	1	5	0	0	2^T	1	0	6	11	KOH
										Totals by		KOH 7-24-89	
Checked by: KOH 8-28-89													

Project No.: 89-3807-21

Page No.: 46

Checked By: KJH 7-24-89

Rabbit Number, Sex, and Previous Studies	Eye	Date of Reading	Cornea			Iris	ST	Conjunctiva				Total	IT
			A	B	ST			A	B	C	ST		

	Yes	No	NA
Eyes prescreened per protocol KJH 7-17-89	☑	☐	☐
Eyes rinsed KJH 7-15-89	~~☑~~	☑	
KJH 7-18-89 (3)			

	Yes	No	NA
Eyes dosed per protocol KJH 7-17-89	☑	☐	☐

Notes: _____

_____

Animals judged satisfactory for re-use:

NA ✓ Yes _____ Signature: _____ Date: _____

PRIMARY EYE IRRITATION TEST

PROJECT NO. 89-3807-21

PAGE NO. 47

Compound: CPSRT No. 89-003 Start: 7-17-89 Finish: 7-20-89

Concentration: 3.0% w/v Solvent: deionized H_2O Dose: 0.1ml Dosed With: 1.0cc syringe

Sample Preparation: see sample prep sheet Dosed By: KOH/MW Sheet Prep. By: KOH

Animal Supplier: Charles River Room No.: 01 Animal Arrival Date: 7-13-89

Date Prescreened: 7-17-89 Time of: Prescreen: 2:26pm Dose: 4:38pm 1 hr: NA

24 hr: 4:30pm 48 hr: 4:35pm 72 hr: 4:49pm Day 4: NA Day 7: NA

Day 10: NA Day 13: NA Day 16: NA Day 19: NA Day 21: NA

Rabbit Number, Sex, and Previous Studies	Eye	Date of Reading	Cornea			Iris	ST	Conjunctiva				Total	IT
			A	B	ST			A	B	C	ST		
7-960	RE	7-18-89	0	0	0	0	0	0	0	0	0	0	KOH
♂		7-19-89	0	0	0	0	0	0	0	0	0	0	KOH
NA		7-20-89	0	0	0	0	0	0	0	0	0	0	KOH
8-961	RE	7-18-89	0	0	0	0	0	0	0	0	0	0	KOH
♂		7-19-89	0	0	0	0	0	0	0	0	0	0	KOH
NA		7-20-89	0	0	0	0	0	0	0	0	0	0	KOH
9-955	RE	7-18-89	0	0	0	0	0	0	0	0	0	0	KOH
♂		7-19-89	0	0	0	0	0	0	0	0	0	0	KOH
NA		7-20-89	0	0	0	0	0	0	0	0	0	0	KOH
10-966	RE	7-18-89	0	0	0	0	0	1	0	0	2	2	KOH
♀		7-19-89	0	0	0	0	0	1	0	0	2	2	KOH
NA		7-20-89	0	0	0	0	0	0	0	0	0	0	KOH
11-967	RE	7-18-89	0	0	0	0	0	0	0	0	0	0	KOH
♀ KOH 7-19-89		~~7-19-89~~ ③	0	0	0	0	0	0	0	0	0	0	KOH
NA		7-20-89	0	0	0	0	0	0	0	0	0	0	KOH
12-968	RE	7-19-89	0	0	0	0	0	0	0	0	0	0	KOH
♀		7-19-89	0	0	0	0	0	0	0	0	0	0	KOH
NA		7-20-89	0	0	0	0	0	0	0	0	0	0	KOH
										Totals by	KOH	7-24-89	
Checked by: KOH 7-24-89													

Project No.: 89-3807-21

Page No.: 48

Checked By: KJH 7-24-89

Rabbit Number, Sex, and Previous Studies	Eye	Date of Reading	Cornea			Iris	ST	Conjunctiva				Total	IT
			A	B	ST			A	B	C	ST		

	Yes	No	NA
KJH 7-17-89 Eyes prescreened per protocol	✓		
Eyes rinsed KJH 7-18-89		✓	

	Yes	No	NA
KJH 7-17-89 Eyes dosed per protocol	✓		

Notes: _____

_____

Animals judged satisfactory for re-use:

NA _____ Yes _____ Signature: _____ Date: _____

Project Number	89-3807-21
Page Number	49

Footnote Explanation Sheet

Undiluted CPS&T No. 89-003

B= Blistered appearance to conjunctiva. KOH added 7-19-89

L= ~~Blanchey~~ Blanched appearance to conjunctiva. KOH added 7-19-89

T= Thickened appearance to conjunctiva. KOH 7-20-89