

8EHQ-0294-12888

**Hoechst Celanese**

**Contains No CBI**

Department of  
Environmental, Health &  
Safety Affairs (DEHSA)

(A)

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February 1, 1994  
MRS-011-94

Document Processing Center (TS-790)  
U.S. Environmental Protection Agency  
401 M Street, S.W.  
Washington, D.C. 20460  
Attn: TSCA Section 8(e) Coordinator



INIT 02/08/94



88940000130

Dear Sir or Madam:

In accordance with the requirements of TSCA Section 8(e), Hoechst Celanese hereby submits two reports for eye irritation in the rabbit of two related materials C<sub>12</sub>-O<sub>16</sub> ethoxylated alcohol (CAS No. 68551-12-2).

Irreversible pseudopterygium was noted in 1 out of 6 animals in the no rinse group in each study. This is a rare irritant reaction.

This submission contains no confidential business information.

If any further information is required, do not hesitate to contact Dr. Michele R. Sullivan, Director, Product Stewardship at 908-231-4480.

Sincerely,

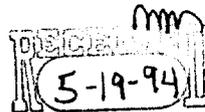
Susan Engelman  
Vice President, Environmental, Health & Safety Affairs

RUB  
2/2/94

Encl.

CERTIFIED MAIL/  
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File: Log No. 170



54 FEB -8 AM 8:17  
OFFICE OF POLLUTION  
PREVENTION AND TOXICS  
REC'D

Hoechst

98 pgs.

**A PRIMARY EYE IRRITATION STUDY IN RABBITS  
WITH C-1849**

**FINAL REPORT**

Author

Deborah A. Douds, M.S.

Study Completed on

January 5, 1994

Performing Laboratory

Springborn Laboratories, Inc. (SLS)  
Life Sciences Division  
640 North Elizabeth Street  
Spencerville, OH 45887

SLS Study No.

3206.297

Submitted to

Hoechst Celanese Corporation  
Route 202-206  
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SLS Study No. 3206.297

(2)

### COMPLIANCE STATEMENT

This study was conducted in compliance with the Good Laboratory Practice Regulations as described by the FDA (21 CFR Part 58) and the EPA (40 CFR Parts 160 and 792).



Deborah A. Douds, M.S.  
Study Director/Author  
Springborn Laboratories, Inc.

Date

1/5/94

**QUALITY ASSURANCE STATEMENT**

This study was inspected by the Quality Assurance Unit and reports were submitted to management and the study director in accordance with SLS's Standard Operating Procedures as follows:

<u>Phase</u>	<u>Date</u>
Body Weights	08/31/93
Data Audit	11/04/93
Final Report Review	01/05/94
Report to Study Director and Management	12/07/93, 01/05/94

This study was conducted in compliance with the Good Laboratory Practice Regulations as described by the FDA (21 CFR Part 58) and the EPA (40 CFR Parts 160 and 792).

Richard J. Clarke  
Richard J. Clarke, B.S.  
Quality Assurance Auditor I

Date 1-5-94

Raymond V. Karcher  
Raymond V. Karcher, B.A., LAT  
Quality Assurance Supervisor

Date 1-5-94

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### SUMMARY

The potential eye irritant and/or corrosive effects of C-1849 were evaluated on New Zealand White rabbits. Each of nine rabbits received a 0.1 ml dose of the test article in the conjunctival sac of the right eye. At 30 seconds postinstillation, both eyes of three rabbits were rinsed with physiological saline (rinsed group); no rinsing procedure was utilized on the six remaining rabbits (no rinse group). The contralateral eye of each animal remained untreated and served as a control. Test and control eyes were examined for signs of irritation for up to 28 days following dosing.

No Rinse Group: Exposure to the test article produced corneal opacity in 4/6 test eyes at the 24 hour scoring interval. The cornea injury was confirmed by positive fluorescein dye retention in 3/6 test eyes. The corneal opacity diminished during the remainder of the test period and resolved in all but one test eye by study day 7. Corneal opacity remained in 1/6 test eyes at the day 28 scoring interval. Iritis was observed in 6/6 test eyes at the 1 hour scoring interval and resolved completely in all animals by study day 21. Conjunctivitis (redness, swelling and discharge) was noted in 6/6 test eyes at the 1 hour scoring interval. The conjunctival irritation generally diminished during the remainder of the test period and resolved completely in 5/6 animals by study day 28. The conjunctival irritation remained in 1/6 test eyes at the 28 day scoring interval. Additional ocular findings included sloughing of the corneal epithelium, corneal neovascularization and corneal bulging, which were noted in 4/6, 1/6 and 1/6 test eyes, respectively. On study day 7, the bulbar conjunctivae of 1/6 test eyes extended approximately 2 mm around the entire length of the perilimbal region on the corneal surface. This finding progressed over the course of the study and was confirmed as pseudopterygium by a board certified veterinarian ophthalmologist on study day 18. The finding persisted in this animal until study termination. The cause of this finding could not be definitely determined; however, this finding has been observed in untreated animals.

Rinsed Group: Exposure to the test article produced corneal opacity in 2/3 test eyes at the 24 hour scoring interval. The corneal injury was confirmed by positive fluorescein dye retention in 1/3 test eyes. The corneal opacity diminished during the remainder of the test period and resolved in all test eyes by study day 7. Iritis was observed in 3/3 test eyes at the 1 hour scoring interval and resolved completely in all animals by the 48 hour scoring interval. Conjunctivitis (redness, swelling and discharge) was noted in 3/3 test eyes at the 1 hour scoring interval. The conjunctival irritation generally diminished during the remainder of the test period and resolved completely in all animals by study day 7. Additional ocular findings included sloughing of the corneal epithelium, which was noted in 2/3 test eyes.

Based on the no rinse group data, C-1849 is considered to be a moderate irritant to the ocular tissue of the rabbit. Based on the rinsed group data, C-1849 is considered to be a moderate irritant to the ocular tissue of the rabbit.

## I. INTRODUCTION

This study was performed to assess the irritant and/or corrosive effects of C-1849 in New Zealand White rabbits when administered by a single ocular dose. This study is intended to provide information on the potential health hazards of the test article with respect to ocular exposure. Data from this study may serve as a basis for classification and/or labeling of the test article. This study was performed at Springborn Laboratories, Inc., 553 North Broadway, Spencerville, Ohio.

## II. MATERIALS AND METHODS

### Study Dates

GLP Initiation:	August 11, 1993
In-life Initiation:	August 31, 1993
In-life Completion:	September 28, 1993

### Protocol

The study protocol and Protocol Amendment No. 1 are presented in Appendix A.

### Test Article

Sponsor I.D.:	C-1849
Lot No.:	404
Springborn I.D.:	S93.010.3206
Receipt Date:	July 19, 1993
Physical Description:	White cloudy liquid
Storage Conditions:	Room temperature
Expiration Date:	None provided

### Test Article Preparation

The test article was administered as received from the Sponsor.

The Sponsor is responsible for any necessary evaluations related to chemical composition, purity, strength, stability and other data required by 21 CFR Part 58.105, 40 CFR Parts 160.105 and 792.105.

**Animals and Animal Husbandry**

**Description:** Adult, New Zealand White rabbits were received at SLS from Mohican Valley Rabbitry, Loudonville, Ohio.

**Method of Identification:** Upon receipt, plastic ear tags displaying unique identification numbers were used to individually identify the animals. Cage cards displaying at least the study number, animal number and sex were affixed to each cage.

**Housing:** The animals were housed individually in suspended stainless steel cages. All housing and care were based on the standards recommended by the Guide for the Care and Use of Laboratory Animals [1].

**Environment:** The animal room temperature and relative humidity ranges were 64-74°F and 53-94%, respectively. Environmental control equipment was monitored and adjusted as necessary to minimize fluctuations in the animal room environment. Light timers were set to maintain a 12-hour light/12-hour dark cycle. There were ten to twelve air changes in the animal room per hour. The animal room temperature and relative humidity were recorded a minimum of once daily.

**Food:** Purina Certified Rabbit Chow #5322 was provided ad libitum to the animals throughout the study. The lot number and expiration date of each batch of diet used during the study were recorded. The feed was analyzed by the supplier for nutritional components and environmental contaminants. Dietary limitations for various environmental contaminants, including heavy metals, pesticides, polychlorinated biphenyls and total aflatoxin are set by the manufacturer. Within these limits, contaminants which may have been present were not expected to compromise the purpose of this study. Results of the dietary analyses (Certificates of Analysis) are provided by the manufacturer for each lot of diet. These are maintained by SLS.

**Water:** Municipal tap water treated by reverse osmosis or deionization (back-up system) was available to the animals ad libitum throughout the study. The purified water was supplied by an automatic watering system. Monitoring of the drinking water for contaminants was conducted by SLS and the records are available for inspection. Within generally accepted limits, contaminants which may have been present were not expected to compromise the purpose of this study.

**Quarantine:** Upon receipt, animals were examined, identified with plastic ear tags and then quarantined for a minimum of five days. However, the animals were not utilized until they had been in the SLS laboratory for a minimum of 7 days prior to study initiation.

**Animal Selection:** The animals chosen for study use were arbitrarily selected from healthy stock animals to avoid potential bias. All animals received a detailed pretest examination prior to dosing. Only healthy animals were chosen for study use. Females were nulliparous and nonpregnant.

### III. EXPERIMENTAL PROCEDURES

**Preliminary Examination:** Prior to dosing on day 0, both eyes of each animal provisionally selected for test use were examined macroscopically for ocular irritation with the aid of an auxiliary light source. In addition, the corneal surface was examined using fluorescein sodium dye. One drop of physiological saline was applied to the end of a fluorescein impregnated strip and the strip gently applied to the superior sclera of each eye. Following an approximate 15 second exposure, the eyes were thoroughly rinsed with physiological saline. The corneal surface was then examined for dye retention using a long-wave UV light source. Animals exhibiting ocular irritation, preexisting corneal injury or fluorescein dye retention (other than normal background retention) were not used on study. All animals found to be acceptable for test use were returned to their cages until dosing.

**Dosing:** A minimum of one hour after the preliminary ocular examination, the test article was instilled as follows:

Group	Concentration (%)	Amount Instilled	No. of Animals	
			Males	Females
No Rinse	100	0.1 ml	1	5
Rinsed	100	0.1 ml	1	2

The test article was instilled into the conjunctival sac of the right eye of each animal after gently pulling the lower lid away from the eye. Following instillation, the eyelids were gently held together for approximately one second in order to limit test article loss and the animal was returned to its cage. The contralateral eye remained untreated to serve as a control.

**Rinsing Procedure:** Approximately 30 seconds after instillation of the test article, the test and control eyes of three rabbits were rinsed with physiological saline (rinsed group). The remaining rabbits were not rinsed (no rinse group).

**Ocular Observations:** The eyes were macroscopically examined with the aid of an auxiliary light source for signs of irritation at 1, 24, 48 and 72 hours and up to 28 days after dosing according to the Draize Ocular Irritation Grading System presented in Appendix B of this report. Following macroscopic observations at the 24 hour scoring interval, the fluorescein examination procedure was repeated on all test and control eyes and any residual test article was gently rinsed from the eye at this time (if possible). If positive (+) fluorescein dye retention was noted at 24 hours (other than normal background retention, stippling or mechanical abrasions), a fluorescein exam was

conducted on the affected eyes at each subsequent interval until a negative (-) response was obtained. The test eye of animal #8066 was examined by a veterinarian ophthalmologist on study day 18.

**Clinical Observations:** Any unusual observations or mortality were recorded. Mortality checks were performed twice daily, in the morning and afternoon.

**Body Weights:** Individual body weights were obtained for each animal prior to dosing on study day 0.

**Scheduled Euthanasia:** Each animal was euthanized (intravenous injection of sodium pentobarbital) following its final observation interval. Gross necropsy examinations were not required for these animals.

### **Protocol Deviations**

The temperature and relative humidity of the animal room (64-74°F and 53-94%, respectively) exceeded the ranges specified in the protocol (61-70°F and 40-60%, respectively) during this study. The animal room temperature and humidity were inadvertently not recorded on 9/7/93. These occurrences are considered to have had no adverse effect on the outcome of this study.

## **IV. ANALYSIS OF DATA**

The ocular irritation score for each parameter (i.e., corneal opacity x area, iritis and conjunctival redness + swelling + discharge) was multiplied by the appropriate factor (i.e., corneal injury x 5, iritis x 5, conjunctivitis x 2) and the totals added for each animal/interval. The group mean irritation score was then calculated for each scoring interval based on the number of animals initially dosed in each group. The calculated group mean ocular irritation scores for each interval were used to classify the test article according to the Kay and Calandra Ocular Evaluation Criteria [2] presented in Appendix C of this report.

## **V. MAINTENANCE OF RAW DATA AND RECORDS**

The remaining test article was returned to the Sponsor following completion of the in-life phase of the study. All original paper data, the final report and magnetically encoded records were transferred to the SLS archives for a period of 10 years. The Sponsor will be contacted prior to final disposition of these items.

## VI. RESULTS

### Ocular Observations:

Individual Data (No Rinse Group): Table 1

Individual Data (Rinsed Group): Table 2

No Rinse Group: Exposure to the test article produced corneal opacity in 4/6 test eyes at the 24 hour scoring interval. The cornea injury was confirmed by positive fluorescein dye retention in 3/6 test eyes. The corneal opacity diminished during the remainder of the test period and resolved in all but one test eye by study day 7. Corneal opacity remained in 1/6 test eyes at the day 28 scoring interval. Iritis was observed in 6/6 test eyes at the 1 hour scoring interval and resolved completely in all animals by study day 21. Conjunctivitis (redness, swelling and discharge) was noted in 6/6 test eyes at the 1 hour scoring interval. The conjunctival irritation generally diminished during the remainder of the test period and resolved completely in 5/6 animals by study day 28. The conjunctival irritation remained in 1/6 test eyes at the 28 day scoring interval. Additional ocular findings included sloughing of the corneal epithelium, corneal neovascularization and corneal bulging, which were noted in 4/6, 1/6 and 1/6 test eyes, respectively. On study day 7, the bulbar conjunctivae of 1/6 test eyes extended approximately 2 mm around the entire length of the perilimbal region on the corneal surface. This finding progressed over the course of the study and was confirmed as pseudopterygium by a board certified veterinarian ophthalmologist on study day 18. The finding persisted in this animal until study termination. The cause of this finding could not be definitely determined; however, this finding has been observed in untreated animals.

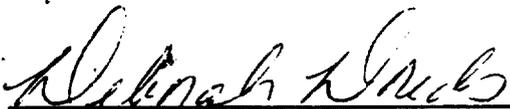
Normal background positive fluorescein dye retention was observed in 1/6 test eyes (stippling). This finding was not considered significant. No corneal opacity, iritis or conjunctivitis was observed in the control eyes.

Rinsed Group: Exposure to the test article produced corneal opacity in 2/3 test eyes at the 24 hour scoring interval. The corneal injury was confirmed by positive fluorescein dye retention in 1/3 test eyes. The corneal opacity diminished during the remainder of the test period and resolved in all test eyes by study day 7. Iritis was observed in 3/3 test eyes at the 1 hour scoring interval and resolved completely in all animals by the 48 hour scoring interval. Conjunctivitis (redness, swelling and discharge) was noted in 3/3 test eyes at the 1 hour scoring interval. The conjunctival irritation generally diminished during the remainder of the test period and resolved completely in all animals by study day 7. Additional ocular findings included sloughing of the corneal epithelium, which was noted in 2/3 test eyes.

Normal background positive fluorescein dye retention was observed in 1/3 test eyes (mechanical abrasion). This finding was not considered significant. No corneal opacity, iritis or conjunctivitis was observed in the control eyes.

**VII. CONCLUSION**

Based on the no rinse group data, C-1849 is considered to be a moderate irritant to the ocular tissue of the rabbit. Based on the rinsed group data, C-1849 is considered to be a moderate irritant to the ocular tissue of the rabbit.



Deborah A. Douds, M.S.  
Study Director

Date 1/5/94

**VIII. REPORT REVIEW**



Kimberly L. Bonnette, M.S., LATG  
Toxicologist

Date 1/5/94



Rusty E. Rush, M.S., LAT  
Manager of Acute Toxicology  
and Special Studies

Date 1-5-94

**IX. REFERENCES**

1. Guide for the Care and Use of Laboratory Animals, DHHS Publication No. (NIH) 86-23, 1985.
2. Kay, J.H. and Calandra, J.C., Interpretation of Eye Irritation Tests, Journal of the Society of Cosmetic Chemists, 13:281-289, 1962.

TABLE 1  
 A PRIMARY EYE IRRITATION STUDY IN RABBITS  
 INDIVIDUAL OCULAR IRRITATION SCORES  
 (NO RINSE GROUP)

Animal No./Sex Body Weight (kg)	Scoring Interval	Cornea			Iris		Conjunctivae			Total	Fluorescein Exam and Comments (See Appendix D for Key to Codes)		
		O	A	Ox5	I	Ix5	R	S	D		(R+S+D)/2	Test Eye	Control Eye
8106/F 2.930	1 Hour	0	0	0	1	5	2	2	2	12	17		
	24 Hours	0	0	0	1	5	2	2	1	10	15		[-]
	48 Hours	0	0	0	0	0	2	1	0	6	6		[-]
	72 Hours	0	0	0	0	0	2	1	0	6	6		[-]
7 Days	0	0	0	0	0	0	0	0	0	0			
8108/F 2.664	1 Hour	0	0	0	1	5	2	2	2	12	17		
	24 Hours	0	0	0	1	5	2	2	0	8	13		[-]
	48 Hours	0	0	0	0	0	2	2	0	8	8		
	72 Hours	0	0	0	0	0	2	1	0	6	6		
	7 Days	0	0	0	0	0	0	1	0	2	2		
10 Days	0	0	0	0	0	0	0	0	0	0			
8074/M 2.848	1 Hour	0	0	0	1	5	2	2	3	14	19		
	24 Hours	2	3	30	1	5	2	2	3	14	49		SCE
	48 Hours	2	3	30	1	5	2	2	3	14	49		[+] SCE,FAO
	72 Hours	2	2	20	1	5	3	2	2	14	39		[+] SCE,FAO
	7 Days	0	0	0	0	0	2	1	0	6	6		[-]
	10 Days	0	0	0	0	0	1	1	0	4	4		HL:ARE
14 Days	0	0	0	0	0	0	0	0	0	0		HL:ARE	

TABLE 1  
A PRIMARY EYE IRRITATION STUDY IN RABBITS  
INDIVIDUAL OCULAR IRRITATION SCORES  
(NO RINSE GROUP)

SLS STUDY NO.: 3206.297  
CLIENT: HOECHST CELANESE

Animal No./Sex Body Weight* (kg)	Scoring Interval	Cornea		Iris		Conjunctivae			Total	Fluorescein Exam and Comments (See Appendix D for Key to Codes)			
		O	A	Ox5	I	Ix5	R	S		D	Test Eye	Control Eye	
8066/F*	1 Hour	0	0	0	1	5	1	2	2	10	15	SCE	
3.151	24 Hours	1	1	5	1	5	2	2	1	10	20	[-] SCE	[-]
	48 Hours	0	0	0	0	0	2	2	0	8	8		
	72 Hours	0	0	0	0	0	2	2	0	8	8		
	7 Days	0	0	0	0	0	2	1	0	6	6	BCS	
	10 Days	0	0	0	0	0	1	1	0	4	4	BCE5	
	14 Days	0	0	0	b	-	1	1	0	4	d	BCE5	
	21 Days	0	0	0	b	-	1	1	0	4	d	BCE5	
	28 Days	0	0	0	c	-	1	1	0	4	d	BCP	
8042/F	1 Hour	0	0	0	1	5	1	2	3	12	17	SCE	
2.952	24 Hours	2	1	10	1	5	2	2	2*	12	27	[+] SCE,FAO	[-]
	48 Hours	2	1	10	1	5	2	2	1	10	25	[+] SCE,FAO	
	72 Hours	1	1	5	1	5	2	1	0	6	16	[+] FAO	
	7 Days	0	0	0	0	0	1	1	0	4	4	[-]	
	10 Days	0	0	0	0	0	1	0	0	2	2		
	14 Days	0	0	0	0	0	0	0	0	0	0		

\*Study day 18, finding by veterinarian ophthalmologist: pseudopterygium OD - proliferation of conjunctiva over cornea; not adherent; globe normal behind lesion.

\*Unable to score iris due to observation of BCE5.

\*Unable to score iris due to observation of BCP.

\*Unable to calculate total score due to the inability to examine the iris.

TABLE 1  
A PRIMARY EYE IRRITATION STUDY IN RABBITS  
INDIVIDUAL OCULAR IRRITATION SCORES  
(NO RINSE GROUP)

SLS STUDY NO.: 3206.297  
CLIENT: HOECHST CELANESE

Animal No./Sex Body Weight (kg)	Scoring Interval	Cornea		Iris		Conjunctivae			Total	Fluorescein Exam and Comments (See Appendix D for Key to Codes)				
		O	A	Ox	Ax5	I	Ix5	R		S	D	(R+S+D)/2	Test Eye	Control Eye
8055/F	1 Hour	0	0	0	0	1	5	2	2	3	14	19	SCE	
2.856	24 Hours	2	4	40	40	1	5	2	2	2	12	57	[+] SCE,FAO	[-]
	48 Hours	2	4	40	40	1	5	2	2	2	12	57	[+] SCE,FAO	
	72 Hours	2	3	30	30	1	5	3	2	2	14	49	[+] SCE,FAO	
	7 Days	2	2	20	20	1	5	3	2	2	14	39	[+] SCE,FAO	
	10 Days	2	2	20	20	1	5	2	2	2	12	37	[+] SCE,FAO,VAS-2	
	14 Days	2	1	10	10	1	5	2	2	1	10	25	[+] SCE,FAO, VAS-2,CB	
	21 Days	1	1	5	5	0	0	0	1	0	2	7	[+] FAO,VAS-1,ST	
	28 Days	1	1	5	5	0	0	0	0	0	0	5	[-] VAS-1	

(16)

Group Mean Irritation Scores	
1 Hour	17.33
24 Hours	30.17
48 Hours	25.50
72 Hours	20.67
7 Days	9.50
10 Days	7.83
14 Days	5.00*
21 Days	1.40*
28 Days	1.00*

\*Mean score based on five animals. Animal #8066 was excluded due to the inability to examine the iris.

TABLE 2  
 A PRIMARY EYE IRRITATION STUDY IN RABBITS  
 INDIVIDUAL OCULAR IRRITATION SCORES  
 (RINSED GROUP)

Animal No./Sex Body Weight (kg)	Scoring Interval	Cornea		Iris		Conjunctivae			Total	Fluorescein Exam and Comments (See Appendix D for Key to Codes)					
		O	A	Ox	Ax5	I	Ix5	R		S	D	(R+S+D)2	Test Eye	Control Eye	
8115/M 2.757	1 Hour	0	0	0	0	1	5	2	2	2	2	12	17		
	24 Hours	1	1	5	0	0	0	2	2	0	0	8	13		[-]
	48 Hours	0	0	0	0	0	0	2	1	0	0	6	6		[-]
	72 Hours	0	0	0	0	0	0	2	1	0	0	6	6		
	7 Days	0	0	0	0	0	0	0	0	0	0	0	0		
8155/F 2.977	1 Hour	0	0	0	0	1	5	2	2	1	1	10	15	SCE	
	24 Hours	2	2	20	1	5	2	2	2	1	1	10	35	[+] SCE,FAO	[-]
	48 Hours	2	1	10	0	0	0	2	1	0	0	6	16	[+] SCE,FAO	
	72 Hours	1	1	5	0	0	0	2	1	0	0	6	11	[-]	
	7 Days	0	0	0	0	0	0	0	0	0	0	0	0		
8151/F 2.560	1 Hour	0	0	0	0	1	5	2	2	2	2	12	17	SCE	
	24 Hours	0	0	0	0	0	0	2	2	0	0	8	8	[+] SCE,MI	[-]
	48 Hours	0	0	0	0	0	0	2	1	0	0	6	6		
	72 Hours	0	0	0	0	0	0	1	1	0	0	4	4		
	7 Days	0	0	0	0	0	0	0	0	0	0	0	0		

Group Mean Irritation Scores

1 Hour	-	16.33
24 Hours	-	18.67
48 Hours	-	9.33
72 Hours	-	7.00
7 Days	-	0.00

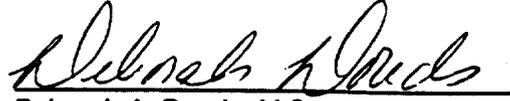
TABLE 3  
A PRIMARY EYE IRRITATION STUDY IN RABBITS  
INDIVIDUAL CLINICAL OBSERVATIONS  
(POSITIVE FINDINGS)

SLS STUDY NO.: 3206.297  
CLIENT: HOECHST CELANESE

Group	Animal No./Sex	Clinical Observations
No Rinse Group	8108/F	Animal excessively pawed test eye following dosing

(18)

AMENDED PAGE



Deborah A. Douds, M.S.  
Study Director

Date 4/10/94

**APPENDIX A**

**Protocol and Amendment**

APR 3 1993

**A PRIMARY EYE IRRITATION STUDY IN RABBITS WITH C-1849**

**Springborn Study No. 3206.297**

**Springborn Laboratories, Inc. (SLS)  
Life Sciences Division  
640 North Elizabeth Street  
Spencerville, Ohio 45887**

**Deborah A. Douds, M.S.  
Study Director**

**For**

**Hoechst Celanese Corporation  
Route 202-206  
P.O. Box 2500  
Somerville, NJ 08876-1258**

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**I. PURPOSE**

To assess the irritant and/or corrosive effects of a test article in rabbits when administered by a single ocular dose. This study is intended to provide information on the potential health hazards of the test article with respect to ocular exposure. Data from this study may serve as a basis for classification and/or labeling of the test article.

**II. SPONSOR**

Hoechst Celanese Corporation  
Route 202-206  
P.O. Box 2500  
Somerville, NJ 08876-1258

**III. SPONSOR'S REPRESENTATIVE**

Richard E. Ouellette, Ph.D., DABT  
Phone: (908) 231-3943  
Fax: (909) 231-4554

**IV. TESTING LOCATION**

Springborn Laboratories, Inc.  
Life Sciences Division  
553 North Broadway  
Spencerville, OH 45887  
Phone: (419) 647-4196  
FAX: (419) 647-6458

**V. SPRINGBORN PERSONNEL RESPONSIBILITIES**

Deborah A. Douds, M.S.  
Study Director/Associate Toxicologist

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Manager of Pathology

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Supervisor of Gross & Fetal Pathology

Anita M. Bosau  
Director of Quality Assurance

Raymond V. Karcher, B.A., LAT  
Quality Assurance Supervisor

VI. PROPOSED STUDY SCHEDULE

- A. Initiation of In-life Phase: August 1993
- B. Completion of In-life Phase: August 1993
- C. Audited Report Date: Ten weeks after in-life completion

**VII. TEST ARTICLE IDENTIFICATION****A. Sponsor's Identification**

C-1849

**B. SLS Test Article Identification Number**

S93.010.3206

**C. Characteristics**

The Sponsor is responsible for any necessary evaluations related to chemical composition, purity, strength, stability and other data required by 21 CFR Part 58.105, 40 CFR Parts 160.105 and 792.105. Any special storage conditions for the test article will be supplied by the Sponsor.

**D. Handling Precautions**

Safety data regarding the test article should be provided by the Sponsor (Material Safety Data Sheet or equivalent, if available). Technical personnel should review this information prior to handling the test article. In addition, any special handling precautions will be provided by the Sponsor/Study Director.

**E. Method of Test Article Preparation**

Liquids, gels and pastes are generally administered as received from the Sponsor. Solids and powders are generally ground and sieved prior to test use. This may be accomplished by grinding the material in a mortar and pestle and passing the material through a No. 40 mesh sieve. The weight of processed test article that occupies a volume of 0.1 ml will be determined by measuring a convenient volume (at least 2 ml) of the powder in a suitable volumetric container. The powder will be gently compacted by tapping the measuring container. The test article dose per eye will then be calculated (weight equivalent of 0.1 ml, not to exceed 100 mg). The test article will be prepared and/or dispensed fresh on the day of dosing. The method of preparation will be documented in the raw data and presented in the final report. Test articles with a pH of  $\leq 2$  or  $\geq 11.5$  may not need to be tested due to their potential corrosive properties unless authorized by the Sponsor.

**VIII. TEST SYSTEM****A. Justification of Test System**

1. The rabbit is the preferred species for primary eye irritation testing by various U.S. and International regulatory agencies.
2. The New Zealand White rabbit has been shown to be sensitive to the irritant/corrosive effects of a variety of drugs and chemicals. Therefore, this species and strain is a reasonable alternative to larger mammals for primary eye irritation testing of drugs and chemicals for human safety assessment.
3. The New Zealand White rabbit has been used extensively for eye irritation testing. Thus, data from this study may be compared and contrasted to other studies performed in New Zealand White rabbits.
4. Historical information concerning New Zealand White rabbits is available at SLS and in the published literature.
5. Healthy, outbred New Zealand White rabbits may be obtained from reliable, USDA approved and regulated suppliers.
6. The laboratory rabbit may be safely handled and manipulated by trained technical personnel.

**B. Justification of Route of Exposure and Number of Animals**

1. Ocular administration of the test substance was selected since this is a potential route of human exposure.
2. Since New Zealand White rabbits have no pigment and have an easily accessible ocular area, substances may be accurately instilled and any resulting effects easily observed.
3. The number of animals used on this study will be consistent with the guidelines published by a number of U.S. and International regulatory agencies including EPA-FIFRA, EPA-TSCA, FDA, CPSC-FHSA, DOT, IMO, EEC, OECD, MAFF and MOHW.

**C. Description****1. Species**

Rabbit

**2. Strain**

New Zealand White

**3. Source**

Mohican Valley Rabbitry or another USDA approved supplier

**4. Age and Body Weight Range**

Adult, approximately 2.0 to 3.5 kg (prior to dosing on day 0)

**5. Number and Sex**

3 rabbit test (males and/or females)

6 rabbit test (males and/or females)

9 rabbit test (males and/or females)

**D. Method of Identification**

Plastic ear tags displaying unique identification numbers will be used to individually identify the animals. Cage cards displaying at least the study number, animal number, and sex will be affixed to each cage.

**IX. ANIMAL HUSBANDRY AND EXPERIMENTAL DESIGN****A. Animal Housing****1. Housing**

The animals will be housed individually in suspended stainless steel cages. All housing and care will conform to the standards recommended by the Guide for the Care and Use of Laboratory Animals [1].

## 2. Environment

The environmental conditions in the animal room will be controlled. The desired animal room temperature and relative humidity ranges are 61-70°F and 40-60%, respectively. Environmental control equipment will be monitored and adjusted as necessary to minimize fluctuations in the animal room environment. Light timers will be set to maintain a 12-hour light/12-hour dark cycle. There will be ten to twelve air changes in the animal room per hour. The animal room temperature and relative humidity will be recorded a minimum of once daily.

## 3. Food

Purina Certified Rabbit Chow #5322 will be provided ad libitum to the animals throughout the study. The lot number and expiration date of each batch of diet used during the study will be recorded. The feed is analyzed by the supplier for nutritional components and environmental contaminants. Dietary limitations for various environmental contaminants, including heavy metals, pesticides, polychlorinated biphenyls and total aflatoxin are set by the manufacturer. Within these limits, contaminants which may be present are not expected to compromise the purpose of this study. Results of the dietary analyses (Certificates of Analysis) are provided by the manufacturer for each lot of diet. These will be maintained by the testing laboratory.

## 4. Water

Municipal tap water treated by reverse osmosis or deionization (back-up system) will be available to the animals ad libitum throughout the study. The purified water will be supplied by an automatic watering system. Monitoring of the drinking water for contaminants will be conducted by the testing laboratory and the records will be available for inspection. Within generally accepted limits, contaminants which may be present are not expected to compromise the purpose of this study.

## B. Quarantine

Upon receipt, the animals will be examined, identified with plastic ear tags, and then quarantined for a minimum of 5 days. However, the animals will not be utilized until they have been in the SLS laboratory for a minimum of 7 days prior to study initiation.

**C. Animal Selection**

The animals chosen for study use will be arbitrarily selected from healthy stock animals to avoid potential bias. All animals will receive a detailed pretest examination prior to dosing. Only healthy animals will be chosen for study use. Females will be nulliparous and nonpregnant.

**D. Experimental Design [2]**

The Sponsor may select the following options:

- 3 rabbit test (No Rinse Procedure)
- 6 rabbit test (No Rinse Procedure)
- 6 rabbit test (Rinse and No Rinse Procedure)
- 9 rabbit test (Rinse and No Rinse Procedure)

**X. EXPERIMENTAL PROCEDURES****A. Preliminary Examination**

On day 0 prior to dosing, both eyes of each animal provisionally selected for test use will be examined macroscopically for ocular irritation with the aid of an auxiliary light source. In addition, the corneal surface will be examined using fluorescein sodium dye. One drop of physiological saline will be applied to the end of a fluorescein impregnated strip and the strip gently applied to the superior sclera of each eye. Following an approximate 15 second exposure, the eyes will be thoroughly rinsed with physiological saline. The corneal surface will then be examined for dye retention under a long-wave UV light source. Animals exhibiting ocular irritation, preexisting corneal injury or fluorescein dye retention (other than normal background retention) will not be used on study. All animals found to be acceptable for test use will be returned to their cages until dosing.

**B. Dosing**

A minimum of one hour after preliminary ocular examination, the test article will be instilled into the conjunctival sac of the right eye of each animal after gently pulling the lower lid away from the eye. Liquids, gels and pastes will

be administered at a volume of 0.1 ml. Solids and powders will be administered at a weight equivalent to 0.1 ml volume, not to exceed 0.1 g. Following instillation, the eyelids will be gently held together for approximately one second in order to limit test article loss and the animal returned to its cage. The contralateral eye will remain untreated to serve as a control. Following dosing, the Study Director will be notified by the technician if severe local reactions occur or if the animals exhibit overt clinical indications of pain/distress immediately postdose. If such is noted, the Sponsor will be contacted to see if the animals should be humanely euthanized.

C. Rinsing Procedure

If a rinsed group is included in this study, approximately 2 to 3 minutes after instillation of the test article, the test and control eyes of three rabbits will be rinsed with 0.9% physiological saline to remove the test article (rinsed group). The remaining rabbits will not be rinsed (no rinse group).

D. Body Weights

Individual body weights will be obtained for each animal prior to dosing on study day 0.

E. Ocular Observations

The eyes will be macroscopically examined with the aid of an auxiliary light source for signs of irritation at 1, 24, 48 and 72 hours after dosing according to the Draize Ocular Irritation Grading System presented in Protocol Appendix A. At the discretion of the study director, a biomicroscopic slit-lamp may be utilized to further examine and clarify ocular lesions. Following macroscopic observations at the 24 hour scoring interval, the fluorescein examination procedure will be repeated on all test and control eyes and any residual test article should be gently rinsed from the eye at this time (if possible) using 0.9% physiological saline. If positive (+) fluorescein dye retention is noted at 24 hours (other than normal background retention, stippling or mechanical abrasions), a fluorescein exam will be conducted on the affected eyes at each subsequent interval until a negative (-) response is obtained. If there is no evidence of treatment related ocular irritation at the 72 hour scoring interval, the study will be terminated. If ocular irritation persists in any test eye, the observation period may be extended for the affected animals (scored on days 7, 10, 14 and 21). Animals requiring an extended observation period will remain on test (up to and including 21 days

post-dose) until the irritation has resolved, permanent injury is evident or the Study Director/Sponsor determines that additional scoring intervals are unnecessary.

**F. Clinical Observations**

Any unusual observations and mortality will be recorded. Mortality checks will be performed twice daily, in the morning and afternoon.

**G. Unscheduled Deaths**

Any animals dying during the study period will be necropsied. Body cavities (cranial, thoracic, abdominal and pelvic) will be opened and examined. No tissues will be retained.

**H. Scheduled Euthanasia**

Each surviving animal will be euthanized by intravenous injection of sodium pentobarbital following its final observation interval. A gross necropsy examination will not be required for surviving animals.

**XI. DATA REPORTING**

Two copies of the final report (one bound and one unbound) and one 3½" diskette containing the final report will be submitted to the Sponsor. The final report will include all information necessary to provide a complete and accurate description and evaluation of the experimental procedures and results.

The report will include at least the following information and data:

- Table of Contents
- Regulatory Compliance
- Summary
- Introduction
- Experimental Design and Test Procedures
- Presentation and Discussion of Results
- Conclusion
- References
- Data Tables
- Protocol and Amendments
- SLS Personnel Responsibilities

**XII. ANALYSIS OF DATA**

For each group, the ocular irritation score for each parameter (i.e., corneal opacity x area, iritis and conjunctival redness + swelling + discharge) will be multiplied by the appropriate factor (i.e., corneal injury x 5, iritis x 5, conjunctivitis x 2) and the totals added for each animal/interval. The group mean irritation score will then be calculated for each scoring interval based on the number of animals initially dosed in each group. If an animal dies during the study, the total animals in that group will be reduced (by the number of animals dead) for each subsequent scoring interval for the purpose of calculating the mean ocular irritation score for each interval. The calculated group mean ocular irritation scores for each interval will be used to classify the test article according to the Kay and Calandra Ocular Evaluation Criteria presented in Protocol Appendix B [3].

**XIII. MAINTENANCE OF RAW DATA, RECORDS AND SPECIMENS**

All original data, magnetically encoded records, specimens and reports from this study are the property of the Sponsor. These materials shall be available at SLS to facilitate auditing of the study during its progress and prior to acceptance of the final report. The remaining test article(s) will be returned to the Sponsor following completion of the in-life phase of the study. Where necessary, the Sponsor will be responsible for maintaining a retention sample of the test article. All original paper data, the final report, magnetically encoded records, and any specimens will be transferred to the SLS archives for a period of 10 years. The Sponsor will be contacted prior to the final disposition of these items.

**XIV. REGULATORY COMPLIANCE**

This study may be submitted to and will be performed in general compliance with EPA-TSCA guidelines; the principles of the Good Laboratory Practice regulations as described by the FDA (21 CFR Part 58) and EPA (40 CFR Parts 160 and 792). Changes may be made in this protocol prior to, during, and/or following study completion. A protocol amendment will be prepared for such changes and will be signed by the Study Director, SLS Quality Assurance Unit and the Sponsor. The Sponsor shall be notified as soon as practical whenever an event occurs that is unexpected and may have an effect on the study.

**XV. QUALITY ASSURANCE**

The study will be inspected once during the in-life phase by the Springborn Laboratories, Inc., Life Sciences Division's Quality Assurance Unit to assure compliance with Good Laboratory Practice regulations, SLS's Standard Operating Procedures and for conformance with the protocol and protocol amendments. The final report will be audited prior to submission to the Sponsor to ensure that it completely and accurately describes the test procedures and results of the study.

**XVI. USDA ANIMAL WELFARE COMPLIANCE STATEMENT**

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (9 CFR) and the Public Health Service Policy on Humane Care and Use of Laboratory Animals (OPRR, NIH, 1986). Wherever possible, procedures used in this study have been designed to avoid or minimize discomfort, distress and pain to animals. All methods are described in this study protocol or in written laboratory standard operating procedures. These procedures are based on the most currently available technologies concerning proper laboratory animal use and management. This protocol has been reviewed and approved by Springborn Laboratories, Inc. Institutional Animal Care and Use Committee (IACUC) for a maximum of 12 animals.

This study is being conducted to evaluate potential irritant effects of the test article and potential reversibility of such effects. Following dosing, the Study Director will be notified by the technician if severe local reactions occur or if the animals exhibit overt clinical indications of pain/distress immediately postdose. If severe reactions are noted, the Sponsor will be contacted to see if the animals should be humanely euthanized. In the event that the Sponsor cannot be contacted, the Study Director and/or Facility Veterinarian may decide to humanely euthanize the animals. The ocular tissue will not be anesthetized prior to or following dosing since inhibition of the blink and/or tear response may elevate the irritation response. In addition, the anesthetic agents may interact with the test article and thereby alter the ocular response. Methods of euthanasia used during this study are in conformance with the above referenced regulations and the American Veterinary Medical Association Panel on Euthanasia (JAVMA, 1993).

**XVII. PROTOCOL APPROVAL**

The Sponsor's signature below documents for the Study Director that there are no acceptable non-animal alternatives for this study, the study does not unnecessarily duplicate previous studies and that the study is needed for regulatory purposes and/or human safety assessment.

*Deborah A. Douds*  
Deborah A. Douds, M.S.  
Study Director (SLS)

Date 8/11/93

*Richard E. Ouellette*  
Richard E. Ouellette, Ph.D., DABT  
Sponsor's Representative  
(Principal Investigator)

Date 8/16/93

*Christophe W. Wilson*  
Raymond V. Karcher, B.A., LAT  
Quality Assurance Unit (SLS)

Date 8/11/93

*Patricia K. Jenkins*  
Patricia K. Jenkins, A.A.S., LATG  
IACUC Representative (SLS)

Date 8-12-93

**XVIII. REFERENCES**

1. Guide for the Care and Use of Laboratory Animals, DHHS Publication No. (NIH) 86-23, 1985.
2. Draize, J.H., Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, The Association of Food and Drug Officials of the United States, 46-59, 1959.
3. Kay, J.H. and Calandra, J.C., Interpretation of Eye Irritation Tests, Journal of the Society of Cosmetic Chemists, 13:281-289, 1962.

**PROTOCOL APPENDIX A**  
**OCULAR IRRITATION GRADING SYSTEM**  
**(DRAIZE)**

<u>CORNEA</u>	<u>Score</u>
<b>(O) Opacity--degree of density (area most dense taken for reading)</b>	
No ulceration or opacity . . . . .	0
Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible . . . . .	1*
Easily discernible translucent area, details of iris slightly obscured . . . . .	2*
Nacreous (opalescent) area, no details of iris visible, size of pupil barely discernible . . . . .	3*
Opaque cornea, iris not discernible through opacity . . . . .	4*

<b>(A) Area of cornea involved (total area exhibiting any opacity, regardless of degree)</b>	
No ulceration or opacity . . . . .	0
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

Cornea Score = O x A x 5                      Total Maximum = 80

**IRIS**

<b>(I) Iritis</b>	
Normal . . . . .	0
Markedly deepened rugae (folds above normal), congestion, swelling, moderate circumcorneal hyperemia or injection, any or all of these or combination of any thereof, iris is still reacting to light (sluggish reaction is positive) . . . . .	1*
No reaction to light, hemorrhage, gross destruction (any or all of these) . . . . .	2*

Iris Score = I x 5                      Total Maximum = 10

\* = Positive effect.

**PROTOCOL APPENDIX A--Continued**  
**OCULAR IRRITATION GRADING SYSTEM**  
**(DRAIZE)**

<u>CONJUNCTIVAE</u>	<u>Score</u>
<b>(R) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)</b>	
Blood vessels normal .....	0
Some blood vessels definitely hyperemic (injected) above normal (slight erythema) .....	1
Diffuse, crimson color, individual vessels not easily discernible (moderate erythema) .....	2*
Diffuse beefy red (marked erythema) .....	3*
<b>(S) Swelling (lids and/or nictating membrane)</b>	
No swelling .....	0
Any swelling above normal (includes nictitating membrane, slightly swollen) .....	1
Obvious swelling with partial eversion of lids .....	2*
Swelling with lids about half closed .....	3*
Swelling with lids more than half closed .....	4*
<b>(D) Discharge</b>	
No discharge .....	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals) .....	1
Discharge with moistening of the lids and hairs just adjacent to lids .....	2
Discharge with moistening of the lids and hairs and considerable area around the eye .....	3

Conjunctival Score = (R + S + D) x 2      Total Maximum = 20

\* = Positive effect.

**PROTOCOL APPENDIX B**  
**OCULAR EVALUATION CRITERIA**  
 (Kay and Calandra)

Maximum mean score (days 0-3)	Maximum mean score	Persistence of Individual Scores	Descriptive Rating and Class
0.00 - 0.49	24 hours = 0		Non-Irritating 1
	24 hours > 0		Practically Non-Irritating 2
0.50 - 2.49	24 hours = 0		Non-Irritating 1
	24 hours > 0		Practically Non-Irritating 2
2.50 - 14.99	48 hours = 0		Slight Irritant 3
	48 hours > 0		Mild Irritant 4
15.00 - 24.99	72 hours = 0		Mild Irritant 4
	72 hours > 0		Moderate Irritant 5
25.00 - 49.99	7 day ≤ 20	> half of day 7 scores ≤ 10	Moderate Irritant 5
		> half of day 7 scores > 10, but no score > 20	Moderate Irritant 5
		> half of day 7 scores > 10, and any score > 20	Severe Irritant 6
	7 day > 20		Severe Irritant 6
50.00 - 79.99	7 day ≤ 40	> half of day 7 scores ≤ 30	Severe Irritant 6
		> half of day 7 scores > 30, but no score > 60	Severe Irritant 6
		> half of day 7 scores > 30, and any score > 60	Very Severe Irritant 7
	7 day > 40		Very Severe Irritant 7
80.00 - 99.99	7 day ≤ 80	> half of day 7 scores ≤ 60	Very Severe Irritant 7
		> half of day 7 scores > 60, but no score > 100	Very Severe Irritant 7
		> half of day 7 scores > 60, and any score > 100	Extremely Severe Irritant 8
	7 day > 80		Extremely Severe Irritant 8
100.00 - 110.00	7 day ≤ 80		Very Severe Irritant 7
	7 day > 80		Extremely Severe Irritant 8

**A PRIMARY EYE IRRITATION STUDY IN RABBITS  
WITH C-1849**

**PROTOCOL AMENDMENT  
NO. 1**

SLS STUDY NO. 3206.297

PAGE 1 OF 2

TEST ARTICLE C-1849

1) PART TO BE CHANGED/REVISED: X.C. EXPERIMENTAL PROCEDURES

**CHANGE/REVISION:** The test and control eyes of the rabbits in the rinsed group were rinsed approximately 30 seconds postinstillation as opposed to 2 to 3 minutes as stated in the protocol.

**REASON FOR CHANGE/REVISION:** Sponsor's request.

2) PART TO BE CHANGED/REVISED: X.E. EXPERIMENTAL PROCEDURES

**CHANGE/REVISION:** The test eye of animal number 8066/F was examined on study day 18 by Dr. Wilkie, a veterinarian ophthalmologist.

**REASON FOR CHANGE/REVISION:** The Sponsor requested this animal be examined due to the finding of bulbar conjunctivae extends approximately 5 mm around entire length of perilimbal region on corneal surface.



**APPENDIX B**

**Ocular Irritation Grading System**

OCULAR IRRITATION GRADING SYSTEM  
(DRAIZE)

CORNEA

Score

(O)	Opacity--degree of density (area most dense taken for reading)	
	No ulceration or opacity . . . . .	0
	Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible . . . . .	1*
	Easily discernible translucent area, details of iris slightly obscured . . . . .	2*
	Opalescent (nacreous) area, no details of iris visible, size of pupil barely discernible . . . . .	3*
	Opaque cornea, iris not discernible through opacity . . . . .	4*
(A)	Area of cornea involved (total area exhibiting any opacity, regardless of degree)	
	No ulceration or opacity . . . . .	0
	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

Cornea Score = O x A x 5      Total Maximum = 80

IRIS

(I)	Iritis	
	Normal . . . . .	0
	Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris is still reacting to light (sluggish reaction is positive) . . . . .	1*
	No reaction to light, hemorrhage, gross destruction (any or all of these) . . . . .	2*

Iris Score = I x 5      Total Maximum = 10

\* = Positive effect.

OCULAR IRRITATION GRADING SYSTEM  
(DRAIZE)

<u>CONJUNCTIVAE</u>	<u>Score</u>
(R) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)	
Blood vessels normal .....	0
Blood vessels definitely injected (hyperemic) above normal (slight erythema) .....	1
More diffuse, deeper crimson red, individual vessels not easily discernible (moderate erythema) .....	2*
Diffuse beefy red (marked erythema) .....	3*
(S) Swelling	
No swelling .....	0
Any swelling above normal (includes nictitating membrane, slightly swollen) .....	1
Obvious swelling with partial eversion of lids .....	2*
Swelling with lids about half closed .....	3*
Swelling with lids more than half closed .....	4*
(D) 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 lids and hairs just adjacent to lids .....	2
Discharge with moistening of lids and hairs and considerable area around the eye .....	3

Conjunctival Score = (R + S + D)x2                      Total Maximum = 20

\* = Positive effect.

**APPENDIX C**

**Ocular Evaluation Criteria**

**OCULAR EVALUATION CRITERIA**  
(Kay and Caiandra)

Maximum mean score (days 0-3)	Maximum mean score	Persistence of Individual Scores	Descriptive Rating and Class
0.00 - 0.49	24 hours = 0		Non-Irritating 1
	24 hours > 0		Practically Non-Irritating 2
0.50 - 2.49	24 hours = 0		Non-Irritating 1
	24 hours > 0		Practically Non-Irritating 2
2.50 - 14.99	48 hours = 0		Slight Irritant 3
	48 hours > 0		Mild Irritant 4
15.00 - 24.99	72 hours = 0		Mild Irritant 4
	72 hours > 0		Moderate Irritant 5
25.00 - 49.99	7 day ≤ 20	> half of day 7 scores ≤ 10	Moderate Irritant 5
		> half of day 7 scores > 10, but no score > 20	Moderate Irritant 5
		> half of day 7 scores > 10, and any score > 20	Severe Irritant 6
	7 day > 20		Severe Irritant 6
50.00 - 79.99	7 day ≤ 40	> half of day 7 scores ≤ 30	Severe Irritant 6
		> half of day 7 scores > 30, but no score > 60	Severe Irritant 6
		> half of day 7 scores > 30, and any score > 60	Very Severe Irritant 7
	7 day > 40		Very Severe Irritant 7
80.00 - 99.99	7 day ≤ 80	> half of day 7 scores ≤ 60	Very Severe Irritant 7
		> half of day 7 scores > 60, but no score > 100	Very Severe Irritant 7
		> half of day 7 scores > 60, and any score > 100	Extremely Severe Irritant 8
	7 day > 80		Extremely Severe Irritant 8
100.00 - 110.00	7 day ≤ 80		Very Severe Irritant 7
	7 day > 80		Extremely Severe Irritant 8

**APPENDIX D**

**Key to Codes**

**APPENDIX E**

**SLS Personnel Responsibilities**

### **SLS PERSONNEL RESPONSIBILITIES**

<b>Deborah A. Douds, M.S.</b>	<b>Study Director/Associate Toxicologist</b>
<b>Rusty E. Rush, M.S., LAT</b>	<b>Alternate Contact/ Manager of Acute Toxicology and Special Studies</b>
<b>Malcolm Blair, Ph.D.</b>	<b>Director of Research</b>
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**A PRIMARY EYE IRRITATION STUDY IN RABBITS  
WITH C-1850**

**FINAL REPORT**

Author

Todd N. Merriman, A.S., LATG

Study Completed on

December 23, 1993

Performing Laboratory

Springborn Laboratories, Inc. (SLS)  
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SLS Study No.

3206.300

Submitted to

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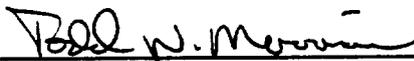
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SLS Study No. 3206.300

(2)

### COMPLIANCE STATEMENT

This study was conducted in compliance with the Good Laboratory Practice Regulations as described by the FDA (21 CFR Part 58) and the EPA (40 CFR Parts 160 and 792).



\_\_\_\_\_  
Todd N. Merriman, A.S., LATG  
Study Director/Author  
Springborn Laboratories, Inc.

Date 12/23/93

**QUALITY ASSURANCE STATEMENT**

This study was inspected by the Quality Assurance Unit and reports were submitted to management and the study director in accordance with SLS's Standard Operating Procedures as follows:

<u>Phase</u>	<u>Date</u>
Room/Environmental Conditions	09/02/93
Data Audit	11/03/93
Final Report Review	12/23/93
Report to Study Director and Management	12/23/93

This study was conducted in compliance with the Good Laboratory Practice Regulations as described by the FDA (21 CFR Part 58) and the EPA (40 CFR Parts 160 and 792).

Richard J. Clarke  
Richard J. Clarke, B.S.  
Quality Assurance Auditor I

Date 12-23-93

Raymond V. Karcher  
Raymond V. Karcher, B.A., LAT  
Quality Assurance Supervisor

Date 12-23-93

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### SUMMARY

The potential eye irritant and/or corrosive effects of C-1850 were evaluated on New Zealand White rabbits. Each of nine rabbits received a 0.1 ml dose of the test article in the conjunctival sac of the right eye. At 30 seconds postinstillation, both eyes of three rabbits were rinsed with physiological saline (rinsed group); no rinsing procedure was utilized on the six remaining rabbits (no rinse group). The contralateral eye of each animal remained untreated and served as a control. Test and control eyes were examined for signs of irritation for up to 28 days following dosing.

No Rinse Group: Exposure to the test article produced corneal opacity in 5/6 test eyes by the 24 hour scoring interval which was confirmed at this interval by positive fluorescein dye retention. The corneal opacity diminished during the remainder of the test period and resolved in 4/6 test eyes by study day 7. Corneal opacity was still observed in 1/6 test eyes at the day 28 scoring interval. Iritis was observed in 5/6 test eyes at the 1 hour scoring interval. The remaining animal in this group was observed with iritis at the 24 hour scoring interval. The iritis resolved completely in all animals by study day 21. Conjunctivitis (redness, swelling and discharge) was noted in 6/6 test eyes at the 1 hour scoring interval. The conjunctival irritation generally diminished during the remainder of the test period and resolved completely in 4/6 animals by study day 21. Additional ocular findings included sloughing of the corneal epithelium, slight dulling of normal luster of cornea and corneal neovascularization, which were noted in 5/6, 5/6 and 1/6 test eyes, respectively. On study day 7, 1/6 animals was observed to have the bulbar conjunctivae extending approximately 5 mm around the entire length of the perilimbal region of the corneal surface. This finding progressed over the course of the study and was confirmed as pseudopterygium by a board certified veterinarian ophthalmologist on study day 18. The finding persisted in this animal until study termination. The cause of this finding could not be definitely determined, however, this finding has been observed in untreated animals.

Rinsed Group: Exposure to the test article produced corneal opacity in 3/3 test eyes at the 1 hour scoring interval. The corneal injury was confirmed by positive fluorescein dye retention at the 24 hour scoring interval. The corneal opacity diminished in 1/3 test eyes during the remainder of the test period and resolved completely by study day 7. In the remaining 2/3 test eyes the corneal opacity degree of density remained consistent, but the area of opacity diminished over the remainder of the test period. The corneal opacity in these two animals did not resolve by study termination (day 28). Iritis was observed in 3/3 test eyes at the 1 hour scoring interval and resolved completely in all animals by study day 28. Conjunctivitis (redness, swelling and discharge) was noted in 3/3 test eyes at the 1 hour scoring interval. The conjunctival irritation generally diminished during the remainder of the test period and resolved completely in 2/3 animals by study day 21. Additional ocular findings included sloughing of the corneal epithelium, slight dulling of normal luster of cornea and corneal neovascularization, which were noted in 3/3, 2/3 and 2/3 test eyes, respectively.

SLS Study No. 3206.300

(7)

Based on the no rinse group data, C-1850 is considered to be a moderate irritant to the ocular tissue of the rabbit. Based on the rinsed group data, C-1850 is considered to be a severe irritant to the ocular tissue of the rabbit.

## I. INTRODUCTION

This study was performed to assess the irritant and/or corrosive effects of C-1850 in New Zealand White rabbits when administered by a single ocular dose. This study is intended to provide information on the potential health hazards of the test article with respect to ocular exposure. Data from this study may serve as a basis for classification and/or labeling of the test article. This study was performed at Springborn Laboratories, Inc., 553 North Broadway, Spencerville, Ohio.

## II. MATERIALS AND METHODS

### Study Dates

GLP Initiation:	August 25, 1993
In-life Initiation:	August 31, 1993
In-life Completion:	September 28, 1993

### Protocol

The study protocol and Protocol Amendment No. 1 are presented in Appendix A.

### Test Article

Sponsor I.D.:	C-1850
Lot No.:	None provided
Springborn I.D.:	S93.011.3206
Receipt Date:	August 5, 1993
Physical Description:	White cloudy liquid
Storage Conditions:	Room temperature
Expiration Date:	None provided

### Test Article Preparation

The test article was administered as received from the Sponsor.

The Sponsor is responsible for any necessary evaluations related to chemical composition, purity, strength, stability and other data required by 21 CFR Part 58.105, 40 CFR Parts 160.105 and 792.105.

### **Animals and Animal Husbandry**

**Description:** Adult, New Zealand White rabbits were received at SLS from Mohican Valley Rabbitry, Loudonville, Ohio.

**Method of Identification:** Upon receipt, plastic ear tags displaying unique identification numbers were used to individually identify the animals. Cage cards displaying at least the study number, animal number and sex were affixed to each cage.

**Housing:** The animals were housed individually in suspended stainless steel cages. All housing and care were based on the standards recommended by the Guide for the Care and Use of Laboratory Animals [1].

**Environment:** The animal room temperature and relative humidity ranges were 64-74°F and 53-94%, respectively. Environmental control equipment was monitored and adjusted as necessary to minimize fluctuations in the animal room environment. Light timers were set to maintain a 12-hour light/12-hour dark cycle. There were ten to twelve air changes in the animal room per hour. The animal room temperature and relative humidity were recorded a minimum of once daily.

**Food:** Purina Certified Rabbit Chow #5322 was provided ad libitum to the animals throughout the study. The lot number and expiration date of each batch of diet used during the study were recorded. The feed was analyzed by the supplier for nutritional components and environmental contaminants. Dietary limitations for various environmental contaminants, including heavy metals, pesticides, polychlorinated biphenyls and total aflatoxin are set by the manufacturer. Within these limits, contaminants which may have been present were not expected to compromise the purpose of this study. Results of the dietary analyses (Certificates of Analysis) are provided by the manufacturer for each lot of diet. These are maintained by SLS.

**Water:** Municipal tap water treated by reverse osmosis or deionization (back-up system) was available to the animals ad libitum throughout the study. The purified water was supplied by an automatic watering system. Monitoring of the drinking water for contaminants was conducted by SLS and the records are available for inspection. Within generally accepted limits, contaminants which may have been present were not expected to compromise the purpose of this study.

**Quarantine:** Upon receipt, animals were examined, identified with plastic ear tags and then quarantined for a minimum of five days. However, the animals were not placed on study until each animal received at least seven days of acclimation.

**Animal Selection:** The animals chosen for study use were arbitrarily selected from healthy stock animals to avoid potential bias. All animals received a detailed pretest examination prior to dosing. Only healthy animals were chosen for study use. Females were nulliparous and nonpregnant.

### III. EXPERIMENTAL PROCEDURES

Preliminary Examination: Prior to dosing on day 0, both eyes of each animal provisionally selected for test use were examined macroscopically for ocular irritation with the aid of an auxiliary light source. In addition, the corneal surface was examined using fluorescein sodium dye. One drop of physiological saline was applied to the end of a fluorescein impregnated strip and the strip gently applied to the superior sclera of each eye. Following an approximate 15 second exposure, the eyes were thoroughly rinsed with physiological saline. The corneal surface was then examined for dye retention using a long-wave UV light source. Animals exhibiting ocular irritation, preexisting corneal injury or fluorescein dye retention (other than normal background retention) were not used on study. All animals found to be acceptable for test use were returned to their cages until dosing.

Dosing: A minimum of one hour after the preliminary ocular examination, the test article was instilled as follows:

Group	Concentration (%)	Amount Instilled	No. of Animals	
			Males	Females
No Rinse	100	0.1 ml	5	1
Rinsed	100	0.1 ml	0	3

The test article was instilled into the conjunctival sac of the right eye of each animal after gently pulling the lower lid away from the eye. Following instillation, the eyelids were gently held together for approximately one second in order to limit test article loss and the animal was returned to its cage. The contralateral eye remained untreated to serve as a control.

Rinsing Procedure: Approximately 30 seconds after instillation of the test article, the test and control eyes of three rabbits were rinsed with physiological saline (rinsed group). The remaining rabbits were not rinsed (no rinse group).

Ocular Observations: The eyes were macroscopically examined with the aid of an auxiliary light source for signs of irritation at 1, 24, 48 and 72 hours and up to 28 days after dosing according to the Draize Ocular Irritation Grading System presented in Appendix B of this report. Following macroscopic observations at the 24 hour scoring interval, the fluorescein examination procedure was repeated on all test and control eyes and any residual test article was gently rinsed from the eye at this time (if possible). If positive (+) fluorescein dye retention was noted at 24 hours (other than normal background retention, stippling or mechanical abrasions), a fluorescein exam was

conducted on the affected eyes at each subsequent interval until a negative (-) response was obtained. The test eye of animal 8171/M was examined by a veterinarian ophthalmologist on study day 18.

Clinical Observations: Any unusual observations or mortality were recorded. Mortality checks were performed twice daily, in the morning and afternoon.

Body Weights: Individual body weights were obtained for each animal prior to dosing on study day 0.

Scheduled Euthanasia: Each animal was euthanized (intravenous injection of sodium pentobarbital) following its final observation interval. Gross necropsy examinations were not required for these animals.

#### **Protocol Deviations**

The temperature and relative humidity of the animal room (64-74°F and 53-94%, respectively) exceeded the ranges specified in the protocol (61-70°F and 40-60%, respectively) during this study. The animal room temperature and relative humidity were inadvertently not recorded on 9/7/93. These occurrences are considered to have had no adverse effect on the outcome of this study.

#### **IV. ANALYSIS OF DATA**

The ocular irritation score for each parameter (i.e., corneal opacity x area, iritis and conjunctival redness + swelling + discharge) was multiplied by the appropriate factor (i.e., corneal injury x 5, iritis x 5, conjunctivitis x 2) and the totals added for each animal/interval. The group mean irritation score was then calculated for each scoring interval based on the number of animals initially dosed in each group. The calculated group mean ocular irritation scores for each interval were used to classify the test article according to the Kay and Calandra Ocular Evaluation Criteria [2] presented in Appendix C of this report.

#### **V. MAINTENANCE OF RAW DATA AND RECORDS**

The remaining test article was returned to the Sponsor following completion of the in-life phase of the study. All original paper data, the final report and magnetically encoded records were transferred to the SLS archives for a period of 10 years. The Sponsor will be contacted prior to final disposition of these items.

## VI. RESULTS

### Ocular Observations:

Individual Data (No Rinse Group): Table 1

Individual Data (Rinsed Group): Table 2

No Rinse Group: Exposure to the test article produced corneal opacity in 5/6 test eyes by the 24 hour scoring interval which was confirmed at this interval by positive fluorescein dye retention. The corneal opacity diminished during the remainder of the test period and resolved in 4/6 test eyes by study day 7. Corneal opacity was still observed in 1/6 test eyes at the day 28 scoring interval. Iritis was observed in 5/6 test eyes at the 1 hour scoring interval. The remaining animal in this group was observed with iritis at the 24 hour scoring interval. The iritis resolved completely in all animals by study day 21. Conjunctivitis (redness, swelling and discharge) was noted in 6/6 test eyes at the 1 hour scoring interval. The conjunctival irritation generally diminished during the remainder of the test period and resolved completely in 4/6 animals by study day 21. Additional ocular findings included sloughing of the corneal epithelium, slight dulling of normal luster of cornea and corneal neovascularization, which were noted in 5/6, 5/6 and 1/6 test eyes, respectively. On study day 7, 1/6 animals was observed to have the bulbar conjunctivae extending approximately 5 mm around the entire length of the perilimbal region of the corneal surface. This finding progressed over the course of the study and was confirmed as pseudopterygium by a board certified veterinarian ophthalmologist on study day 18. The finding persisted in this animal until study termination. The cause of this finding could not be definitely determined, however, this finding has been observed in untreated animals.

Normal background positive fluorescein dye retention was observed in 2/6 test eyes (stippling). These findings were not considered significant. No corneal opacity, iritis or conjunctivitis was observed in the control eyes.

Rinsed Group: Exposure to the test article produced corneal opacity in 3/3 test eyes at the 1 hour scoring interval. The corneal injury was confirmed by positive fluorescein dye retention at the 24 hour scoring interval. The corneal opacity diminished in 1/3 test eyes during the remainder of the test period and resolved completely by study day 7. In the remaining 2/3 test eyes the corneal opacity degree of density remained consistent, but the area of opacity diminished over the remainder of the test period. The corneal opacity in these two animals did not resolve by study termination (day 28). Iritis was observed in 3/3 test eyes at the 1 hour scoring interval and resolved completely in all animals by study day 28. Conjunctivitis (redness, swelling and discharge) was noted in 3/3 test eyes at the 1 hour scoring interval. The conjunctival irritation generally diminished during the remainder of the test period and resolved completely in 2/3 animals by study day 21. Additional ocular findings included sloughing of the corneal epithelium, slight dulling of

normal luster of cornea and corneal neovascularization, which were noted in 3/3, 2/3 and 2/3 test eyes, respectively.

No corneal opacity, iritis or conjunctivitis was observed in the control eyes.

**VII. CONCLUSION**

Based on the no rinse group data, C-1850 is considered to be a moderate irritant to the ocular tissue of the rabbit. Based on the rinsed group data, C-1850 is considered to be a severe irritant to the ocular tissue of the rabbit.

  
\_\_\_\_\_  
Todd N. Merriman, A.S., LATG  
Study Director

Date 12/23/93

**VIII. REPORT REVIEW**

  
\_\_\_\_\_  
Deborah A. Douds, M.S.  
Toxicologist

Date 12/23/93

  
\_\_\_\_\_  
Malcolm Blair, Ph.D.  
Director of Research

Date 12/23/93

IX. **REFERENCES**

1. Guide for the Care and Use of Laboratory Animals, DHHS Publication No. (NIH) 86-23, 1985.
2. Kay, J.H. and Calandra, J.C., Interpretation of Eye Irritation Tests, Journal of the Society of Cosmetic Chemists, 13:281-289, 1962.

TABLE 1  
PRIMARY EYE IRRITATION STUDY IN RABBITS  
INDIVIDUAL OCULAR IRRITATION SCORES  
(NO RINSE GROUP)

SLS STUDY NO.: 3206.300  
CLIENT: HOECHST CELANESE CORP.

Animal No./Sex Body Weight (kg)	Scoring Interval	Cornea		Iris		Conjunctivae			Total	Test Eye	Fluorescein Exam and Comments (See Appendix D for Key to Codes)	Control Eye			
		O	A	Ox	Ax5	I	Ix5	R					S	D	
8157/M 2.497	1 Hour	0	0	0	0	1	5	2	2	3	14	19	SCE,SDL		
	24 Hours	2	4	40	40	1	5	2	2	2	12	57	[+] SCE,FAO		[-]
	48 Hours	2	4	40	40	1	5	2	2	2	12	57	[+] SCE,FAO		
	72 Hours	2	4	40	40	1	5	2	2	1	10	55	[+] SCE,FAG		
	7 Days	2	2	20	20	1	5	2	2	1	10	35	[+] FAO,VAS-1		
	10 Days	2	1	10	10	1	5	2	2	1	10	25	[+] FAO,VAS-2		
	14 Days	3	1	15	15	1	5	2	2	1	10	30	[+] FAO,VAS-2		
	21 Days	2	1	10	10	0	0	1	1	0	4	14	[+] FAO,ST		
28 Days	2	1	10	10	0	0	0	1	0	2	12	[+] FAO			
8158/M 2.272	1 Hour	0	0	0	0	0	0	2	1	2	10	10	[+] FAO		[-]
	24 Hours	2	1	10	10	1	5	2	2	1	10	25	[-]		
	48 Hours	0	0	0	0	0	0	2	1	0	6	6			
	72 Hours	0	0	0	0	0	0	2	1	0	6	6			
	7 Days	0	0	0	0	0	0	1	1	0	4	4			
	10 Days	0	0	0	0	0	0	1	1	0	4	4			
14 Days	0	0	0	0	0	0	0	0	0	0	0				
8165/M 2.466	1 Hour	1	2	10	10	1	5	2	2	2	12	27	SCE,SDL		
	24 Hours	2	4	40	40	1	5	2	2	2	12	57	[+] SCE,FAO		[-]
	48 Hours	2	3	30	30	1	5	2	2	0	8	43	[+] SCE,FAO		
	72 Hours	2	1	10	10	0	0	2	1	0	6	16	[+] FAO		
	7 Days	0	0	0	0	0	0	2	1	0	6	6	[-]		
	10 Days	0	0	0	0	0	0	1	1	0	4	4			
14 Days	0	0	0	0	0	0	0	0	0	0	0				

SLS STUDY NO.: 3206.300  
 CLIENT: HOECHST CELANESE CORP.

TABLE 1  
 PRIMARY EYE IRRITATION STUDY IN RABBITS  
 INDIVIDUAL OCULAR IRRITATION SCORES  
 (NO RINSE GROUP)

PAGE 2

Animal No./Sex Body Weight (kg)	Scoring Interval	Cornea		Iris		Conjunctivae			Total	Fluorescein Exam and Comments (See Appendix D for Key to Codes)		
		O	A	Ox	Ax5	I	Ix5	R		S	D	(R+S+D)/2
8166/M	1 Hour	0	0	0	1	5	2	2	2	12	SCE,SDL	
2.415	24 Hours	0	0	0	0	0	2	2	0	8	[-]	[-]
	48 Hours	0	0	0	0	0	2	2	0	8		
	72 Hours	0	0	0	0	0	2	2	0	8		
	7 Days	0	0	0	0	0	1	1	0	4		
	10 Days	0	0	0	0	0	1	1	0	4		
	14 Days	0	0	0	0	0	1	0	0	2		
	21 Days	0	0	0	0	0	0	0	0	0		
8171/M <sup>a</sup>	1 Hour	1	3	15	1	5	2	2	2	12	SCE,SDL	
2.392	24 Hours	2	4	40	1	5	2	2	2	12	[+] SCE,FAO	[-]
	48 Hours	2	2	20	1	5	2	2	2	12	[+] SCE,FAO	
	72 Hours	2	1	10	1	5	2	2	0	8	[+] SCE,FAO,ST	
	7 Days	0	0	0	0	0	2	2	0	8	[-] BCS	
	10 Days	0	0	0	b	-	2	1	0	6	BCE7	
	14 Days	0	0	0	c	-	1	1	0	4	BCP	
	21 Days	0	0	0	c	-	1	1	0	4	BCP	
	28 Days	0	0	0	c	-	1	1	0	4	BCP	

<sup>a</sup>Study day 18, finding by veterinarian ophthalmologist: pseudopterygium OD - proliferation of conjunctiva over cornea; not adherent; globe normal behind lesion.

<sup>b</sup>Unable to score iris due to additional observation of BCE7.

<sup>c</sup>Unable to score iris due to additional observation of BCP.

TABLE 1  
 PRIMARY EYE IRRITATION STUDY IN RABBITS  
 INDIVIDUAL OCULAR IRRITATION SCORES  
 (NO RINSE GROUP)

SLS STUDY NO.: 3206.300  
 CLIENT: HOECHST CELANESE CORP.

Animal No./Sex Body Weight (kg)	Scoring Interval	Cornea		Iris		Conjunctivae			Total	Fluorescein Exam and Comments (See Appendix D for Key to Codes)			
		O	A	Ox	5	I	Ix	5		R	S	D	(R+S+D)/2
8200/F	1 Hour	1	3	15	1	5	2	2	2	12	32	SCE,SDL	
2.218	24 Hours	2	4	40	1	5	2	2	1	10	55	[+] SCE,FAO	[-]
	48 Hours	2	3	30	1	5	2	1	0	6	41	[+] SCE,FAO	
	72 Hours	2	2	20	1	5	2	1	0	6	31	[+] SCE,FAO	
	7 Days	0	0	0	0	0	2	1	0	6	6	[-]	
	10 Days	0	0	0	0	0	1	1	0	4	4		
	14 Days	0	0	0	0	0	1	1	0	4	4		
	21 Days	0	0	0	0	0	0	0	0	0	0		

Group Mean Irritation Scores	
1 Hour	22.83
24 Hours	43.17
48 Hours	32.00
72 Hours	23.17
7 Days	10.50
10 Days	7.83
14 Days	6.67
21 Days	3.00
28 Days	2.67

TABLE 2  
 PRIMARY EYE IRRITATION STUDY IN RABBITS  
 INDIVIDUAL OCULAR IRRITATION SCORES  
 (RINSED GROUP)

Animal No./Sex Body Weight (kg)	Scoring Interval	Cornea		Iris		Conjunctivae			Total	Fluorescein Exam and Comments (See Appendix D for Key to Codes)			
		O	A	Ox	Ax5	I	Ix5	R		S	D	(R+S+D)2	Test Eye
8201/F 2.432	1 Hour	2	4	40	1	5	2	2	2	12	57	SCE,SDL	
	24 Hours	2	4	40	1	5	2	2	1	10	55	[+] SCE,FAO	[-]
	48 Hours	2	4	40	1	5	3	2	1	12	57	[+] SCE,FAO	
	72 Hours	2	4	40	1	5	3	2	1	12	57	[+] SCE,FAO	
	7 Days	2	4	40	1	5	2	2	1	10	55	[+] SCE,FAO,VAS-2	
	10 Days	2	4	40	1	5	3	2	1	12	57	[+] SCE,FAO,VAS-2	
	14 Days	2	3	30	1	5	3	2	1	12	47	[+] FAO,VAS-3	
	21 Days	2	3	30	1	5	2	1	0	6	41	[+] FAO,VAS-3	
	28 Days	2	2	20	0	0	1	0	0	2	22	[+] FAO,VAS-1	
	8197/F 2.406	1 Hour	2	4	40	1	5	2	2	2	12	57	SCE,SDL
24 Hours	2	4	40	1	5	2	2	2	12	57	[+] SCE,FAO	[-]	
48 Hours	2	3	30	1	5	2	2	1	10	45	[+] SCE,FAO		
72 Hours	2	1	10	1	5	2	2	0	8	23	[+] FAO		
7 Days	2	1	10	0	0	2	1	0	6	16	[+] FAO,VAS-1		
10 Days	2	1	10	0	0	2	1	0	6	16	[+] FAO,VAS-1		
14 Days	2	1	10	0	0	1	0	0	2	12	[+] FAO		
21 Days	2 <sup>a</sup>	1 <sup>a</sup>	10	0	0	0	0	0	0	10	[+] FAO		
28 Days	2 <sup>a</sup>	1 <sup>a</sup>	10	0	0	0	0	0	0	10	[+] FAO		

<sup>a</sup>Corneal mineralization with dimensions of approximately 2 mm x 4 mm at approximately 4 to 6 o'clock.

TABLE 2  
 PRIMARY EYE IRRITATION STUDY IN RABBITS  
 INDIVIDUAL OCULAR IRRITATION SCORES  
 (RINSED GROUP)

SLS STUDY NO.: 3206.300  
 CLIENT: HOECHST CELANESE CORP.

Animal No./Sex Body Weight (kg)	Scoring Interval	Cornea		Iris		Conjunctivae			Total	Fluorescein Exam and Comments (See Appendix D for Key to Codes)			
		O	A	Ox	Ax5	R	S	D		(R+S+D)/2	Test Eye	Control Eye	
8193/F	1 Hour	2	4	40	1	5	2	2	2	12	57	SCE	
2.214	24 Hours	2	4	40	1	5	2	1	1	8	53	[+] SCE,FAO	[-]
	48 Hours	2	4	40	1	5	2	1	1	8	53	[+] SCE,FAO	
	72 Hours	2	3	30	1	5	2	1	0	6	41	[+] SCE,FAO	
	7 Days	0	0	0	0	0	1	1	0	4	4	[-]	
	10 Days	0	0	0	0	0	1	1	0	4	4		
	14 Days	0	0	0	0	0	1	0	0	2	2		
	21 Days	0	0	0	0	0	0	0	0	0	0		

Group Mean Irritation Scores	
1 Hour	57.00
24 Hours	55.00
48 Hours	51.67
72 Hours	40.33
7 Days	25.00
10 Days	25.67
14 Days	20.33
21 Days	17.00
28 Days	10.67

SLS STUDY NO.: 3206.300  
CLIENT: HOECHST CELANESE CORP.

TABLE 3  
PRIMARY EYE IRRITATION STUDY IN RABBITS  
INDIVIDUAL CLINICAL OBSERVATIONS  
(POSITIVE FINDINGS)

PAGE 1

Group	Animal No./Sex	Clinical Observations
No Rinse Group	8157/M	Animal excessively pawed test eye following dosing
		Animal exhibited excessive squinting of test eye following dosing
	8165/M	Animal exhibited excessive squinting of test eye following dosing
	8166/M	Animal excessively pawed test eye following dosing
	8171/M	Animal exhibited excessive squinting of test eye following dosing
	8200/F	Animal exhibited excessive squinting of test eye following dosing
Rinsed Group	8197/F	Animal excessively pawed test eye following dosing
		Animal exhibited excessive squinting of test eye following dosing

**APPENDIX A**

**Protocol and Amendment**

**A PRIMARY EYE IRRITATION STUDY IN RABBITS WITH C-1850**

Springborn Study No. 3206.300

Springborn Laboratories, Inc. (SLS)  
Life Sciences Division  
640 North Elizabeth Street  
Spencerville, Ohio 45887

Todd N. Merriman, A.S., LAT  
Study Director

For

Hoechst Celanese Corporation  
Route 202-206  
P.O. Box 2500  
Somerville, NJ 08876-1258

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I. PURPOSE

To assess the irritant and/or corrosive effects of a test article in rabbits when administered by a single ocular dose. This study is intended to provide information on the potential health hazards of the test article with respect to ocular exposure. Data from this study may serve as a basis for classification and/or labeling of the test article.

II. SPONSOR

Hoechst Celanese Corporation  
Route 202-206  
P.O. Box 2500  
Somerville, NJ 08876-1258

III. SPONSOR'S REPRESENTATIVE

Richard E. Ouellette, Ph.D., DABT  
Phone: (908) 231-3943  
Fax: (908) 231-4554

IV. TESTING LOCATION

Springborn Laboratories, Inc.  
Life Sciences Division  
553 North Broadway  
Spencerville, OH 45887  
Phone: (419) 647-4196  
FAX: (419) 647-6458

V. SPRINGBORN PERSONNEL RESPONSIBILITIES

Todd N. Merriman, A.S., LAT  
Study Director/Associate Toxicologist

Rusty E. Rush, M.S., LAT  
Alternate Contact/Manager of Acute Toxicology and Special Studies

Malcolm Blair, Ph.D.  
Director of Research

Joseph C. Siglin, M.S., DABT  
Associate Director of Toxicology

Kimberly L. Bonnette, M.S., LATG  
Toxicologist

Deborah A. Douds, M.S.  
Associate Toxicologist

Patricia K. Jenkins, AAS, LATG  
Acute Toxicology Supervisor

Pamela S. Smith, ALAT  
Unit Leader

Delores P. Knippen  
Pharmacy Supervisor

Cynthia J. Ziegra, VMD, Ph.D.  
Manager of Pathology

Steven H. Magness, B.S., LATG  
Supervisor of Gross & Fetal Pathology

Anita M. Bosau  
Director of Quality Assurance

Raymond V. Karcher, B.A., LAT  
Quality Assurance Supervisor

VI. PROPOSED STUDY SCHEDULE

A. Initiation of In-life Phase: August 1993

B. Completion of In-life Phase: September 1993

C. Audited Report Date: Ten weeks following in-life completion

**VII. TEST ARTICLE IDENTIFICATION****A. Sponsor's Identification**

C-1850

**B. SLS Test Article Identification Number**

S93.011.3206

**C. Characteristics**

The Sponsor is responsible for any necessary evaluations related to chemical composition, purity, strength, stability and other data required by 21 CFR Part 58.105, 40 CFR Parts 160.105 and 792.105. Any special storage conditions for the test article will be supplied by the Sponsor.

**D. Handling Precautions**

Safety data regarding the test article should be provided by the Sponsor (Material Safety Data Sheet or equivalent, if available). Technical personnel should review this information prior to handling the test article. In addition, any special handling precautions will be provided by the Sponsor/Study Director.

**E. Method of Test Article Preparation**

Liquids, gels and pastes are generally administered as received from the Sponsor. Solids and powders are generally ground and sieved prior to test use. This may be accomplished by grinding the material in a mortar and pestle and passing the material through a No. 40 mesh sieve. The weight of processed test article that occupies a volume of 0.1 ml will be determined by measuring a convenient volume (at least 2 ml) of the powder in a suitable volumetric container. The powder will be gently compacted by tapping the measuring container. The test article dose per eye will then be calculated (weight equivalent of 0.1 ml, not to exceed 100 mg). The test article will be prepared and/or dispensed fresh on the day of dosing. The method of preparation will be documented in the raw data and presented in the final report. Test articles with a pH of  $\leq 2$  or  $\geq 11.5$  may not need to be tested due to their potential corrosive properties unless authorized by the Sponsor.

**VIII. TEST SYSTEM****A. Justification of Test System**

1. The rabbit is the preferred species for primary eye irritation testing by various U.S. and International regulatory agencies.
2. The New Zealand White rabbit has been shown to be sensitive to the irritant/corrosive effects of a variety of drugs and chemicals. Therefore, this species and strain is a reasonable alternative to larger mammals for primary eye irritation testing of drugs and chemicals for human safety assessment.
3. The New Zealand White rabbit has been used extensively for eye irritation testing. Thus, data from this study may be compared and contrasted to other studies performed in New Zealand White rabbits.
4. Historical information concerning New Zealand White rabbits is available at SLS and in the published literature.
5. Healthy, outbred New Zealand White rabbits may be obtained from reliable, USDA approved and regulated suppliers.
6. The laboratory rabbit may be safely handled and manipulated by trained technical personnel.

**B. Justification of Route of Exposure and Number of Animals**

1. Ocular administration of the test substance was selected since this is a potential route of human exposure.
2. Since New Zealand White rabbits have no pigment and have an easily accessible ocular area, substances may be accurately instilled and any resulting effects easily observed.
3. The number of animals used on this study will be consistent with the guidelines published by a number of U.S. and International regulatory agencies including EPA-FIFRA, EPA-TSCA, FDA, CPSC-FHSA, DOT, IMO, EEC, OECD, MAFF and MOHW.

C. Description

1. Species

Rabbit

2. Strain

New Zealand White

3. Source

Mohican Valley Rabbitry or another USDA approved supplier

4. Age and Body Weight Range

Adult, approximately 2.0 to 3.5 kg (prior to dosing on day 0)

5. Number and Sex

3 rabbit test (males and/or females)

6 rabbit test (males and/or females)

9 rabbit test (males and/or females)

D. Method of Identification

Plastic ear tags displaying unique identification numbers will be used to individually identify the animals. Cage cards displaying at least the study number, animal number, and sex will be affixed to each cage.

IX. ANIMAL HUSBANDRY AND EXPERIMENTAL DESIGN

A. Animal Housing

1. Housing

The animals will be housed individually in suspended stainless steel cages. All housing and care will conform to the standards recommended by the Guide for the Care and Use of Laboratory Animals [1].

## 2. Environment

The environmental conditions in the animal room will be controlled. The desired animal room temperature and relative humidity ranges are 61-70°F and 40-60%, respectively. Environmental control equipment will be monitored and adjusted as necessary to minimize fluctuations in the animal room environment. Light timers will be set to maintain a 12-hour light/12-hour dark cycle. There will be ten to twelve air changes in the animal room per hour. The animal room temperature and relative humidity will be recorded a minimum of once daily.

## 3. Food

Purina Certified Rabbit Chow #5322 will be provided ad libitum to the animals throughout the study. The lot number and expiration date of each batch of diet used during the study will be recorded. The feed is analyzed by the supplier for nutritional components and environmental contaminants. Dietary limitations for various environmental contaminants, including heavy metals, pesticides, polychlorinated biphenyls and total aflatoxin are set by the manufacturer. Within these limits, contaminants which may be present are not expected to compromise the purpose of this study. Results of the dietary analyses (Certificates of Analysis) are provided by the manufacturer for each lot of diet. These will be maintained by the testing laboratory.

## 4. Water

Municipal tap water treated by reverse osmosis or deionization (back-up system) will be available to the animals ad libitum throughout the study. The purified water will be supplied by an automatic watering system. Monitoring of the drinking water for contaminants will be conducted by the testing laboratory and the records will be available for inspection. Within generally accepted limits, contaminants which may be present are not expected to compromise the purpose of this study.

## B. Quarantine

Upon receipt, the animals will be examined, identified with plastic ear tags, and then quarantined for a minimum of 5 days. However, the animals will not be utilized until they have been in the SLS laboratory for a minimum of 7 days prior to study initiation.

**C. Animal Selection**

The animals chosen for study use will be arbitrarily selected from healthy stock animals to avoid potential bias. All animals will receive a detailed pretest examination prior to dosing. Only healthy animals will be chosen for study use. Females will be nulliparous and nonpregnant.

**D. Experimental Design [2]**

The Sponsor may select the following options:

3 rabbit test (No Rinse Procedure)

6 rabbit test (No Rinse Procedure)

6 rabbit test (Rinse and No Rinse Procedure)

9 rabbit test (Rinse and No Rinse Procedure)

**X. EXPERIMENTAL PROCEDURES****A. Preliminary Examination**

On day 0 prior to dosing, both eyes of each animal provisionally selected for test use will be examined macroscopically for ocular irritation with the aid of an auxiliary light source. In addition, the corneal surface will be examined using fluorescein sodium dye. One drop of physiological saline will be applied to the end of a fluorescein impregnated strip and the strip gently applied to the superior sclera of each eye. Following an approximate 15 second exposure, the eyes will be thoroughly rinsed with physiological saline. The corneal surface will then be examined for dye retention under a long-wave UV light source. Animals exhibiting ocular irritation, preexisting corneal injury or fluorescein dye retention (other than normal background retention) will not be used on study. All animals found to be acceptable for test use will be returned to their cages until dosing.

**B. Dosing**

A minimum of one hour after preliminary ocular examination, the test article will be instilled into the conjunctival sac of the right eye of each animal after gently pulling the lower lid away from the eye. Liquids, gels and pastes will

be administered at a volume of 0.1 ml. Solids and powders will be administered at a weight equivalent to 0.1 ml volume, not to exceed 0.1 g. Following instillation, the eyelids will be gently held together for approximately one second in order to limit test article loss and the animal returned to its cage. The contralateral eye will remain untreated to serve as a control. Following dosing, the Study Director will be notified by the technician if severe local reactions occur or if the animals exhibit overt clinical indications of pain/distress immediately postdose. If such is noted, the Sponsor will be contacted to see if the animals should be humanely euthanized.

C. Rinsing Procedure

If a rinsed group is included in this study, approximately 2 to 3 minutes after instillation of the test article, the test and control eyes of three rabbits will be rinsed with 0.9% physiological saline to remove the test article (rinsed group). The remaining rabbits will not be rinsed (no rinse group).

D. Body Weights

Individual body weights will be obtained for each animal prior to dosing on study day 0.

E. Ocular Observations

The eyes will be macroscopically examined with the aid of an auxiliary light source for signs of irritation at 1, 24, 48 and 72 hours after dosing according to the Draize Ocular Irritation Grading System presented in Protocol Appendix A. At the discretion of the study director, a biomicroscopic slit-lamp may be utilized to further examine and clarify ocular lesions. Following macroscopic observations at the 24 hour scoring interval, the fluorescein examination procedure will be repeated on all test and control eyes and any residual test article should be gently rinsed from the eye at this time (if possible) using 0.9% physiological saline. If positive (+) fluorescein dye retention is noted at 24 hours (other than normal background retention, stippling or mechanical abrasions), a fluorescein exam will be conducted on the affected eyes at each subsequent interval until a negative (-) response is obtained. If there is no evidence of treatment related ocular irritation at the 72 hour scoring interval, the study will be terminated. If ocular irritation persists in any test eye, the observation period may be extended for the affected animals (scored on days 7, 10, 14 and 21). Animals requiring an extended observation period will remain on test (up to and including 21 days

post-dose) until the irritation has resolved, permanent injury is evident or the Study Director/Sponsor determines that additional scoring intervals are unnecessary.

F. Clinical Observations

Any unusual observations and mortality will be recorded. Mortality checks will be performed twice daily, in the morning and afternoon.

G. Unscheduled Deaths

Any animals dying during the study period will be necropsied. Body cavities (cranial, thoracic, abdominal and pelvic) will be opened and examined. No tissues will be retained.

H. Scheduled Euthanasia

Each surviving animal will be euthanized by intravenous injection of sodium pentobarbital following its final observation interval. A gross necropsy examination will not be required for surviving animals.

XI. DATA REPORTING

Two copies of the final report (one bound and one unbound) and one 3½" diskette containing the final report will be submitted to the Sponsor. The final report will include all information necessary to provide a complete and accurate description and evaluation of the experimental procedures and results.

The report will include at least the following information and data:

- Table of Contents
- Regulatory Compliance
- Summary
- Introduction
- Experimental Design and Test Procedures
- Presentation and Discussion of Results
- Conclusion
- References
- Data Tables
- Protocol and Amendments
- SLS Personnel Responsibilities

## **XII. ANALYSIS OF DATA**

For each group, the ocular irritation score for each parameter (i.e., corneal opacity x area, iritis and conjunctival redness + swelling + discharge) will be multiplied by the appropriate factor (i.e., corneal injury x 5, iritis x 5, conjunctivitis x 2) and the totals added for each animal/interval. The group mean irritation score will then be calculated for each scoring interval based on the number of animals initially dosed in each group. If an animal dies during the study, the total animals in that group will be reduced (by the number of animals dead) for each subsequent scoring interval for the purpose of calculating the mean ocular irritation score for each interval. The calculated group mean ocular irritation scores for each interval will be used to classify the test article according to the Kay and Calandra Ocular Evaluation Criteria presented in Protocol Appendix B [3].

## **XIII. MAINTENANCE OF RAW DATA, RECORDS AND SPECIMENS**

All original data, magnetically encoded records, specimens and reports from this study are the property of the Sponsor. These materials shall be available at SLS to facilitate auditing of the study during its progress and prior to acceptance of the final report. The remaining test article(s) will be returned to the Sponsor following completion of the in-life phase of the study. Where necessary, the Sponsor will be responsible for maintaining a retention sample of the test article. All original paper data, the final report, magnetically encoded records, and any specimens will be transferred to the SLS archives for a period of 10 years. The Sponsor will be contacted prior to the final disposition of these items.

## **XIV. REGULATORY COMPLIANCE**

This study may be submitted to and will be performed in general compliance with EPA-TSCA guidelines; the principles of the Good Laboratory Practice regulations as described by the FDA (21 CFR Part 58) and EPA (40 CFR Parts 160 and 792). Changes may be made in this protocol prior to, during, and/or following study completion. A protocol amendment will be prepared for such changes and will be signed by the Study Director, SLS Quality Assurance Unit and the Sponsor. The Sponsor shall be notified as soon as practical whenever an event occurs that is unexpected and may have an effect on the study.

**XV. QUALITY ASSURANCE**

The study will be inspected at least once during the in-life phase by the Springborn Laboratories, Inc., Life Sciences Division's Quality Assurance Unit to assure compliance with Good Laboratory Practice regulations, SLS's Standard Operating Procedures and for conformance with the protocol and protocol amendments. The final report will be audited prior to submission to the Sponsor to ensure that it completely and accurately describes the test procedures and results of the study.

**XVI. USDA ANIMAL WELFARE COMPLIANCE STATEMENT**

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (9 CFR) and the Public Health Service Policy on Humane Care and Use of Laboratory Animals (OPRR, NIH, 1986). Wherever possible, procedures used in this study have been designed to avoid or minimize discomfort, distress and pain to animals. All methods are described in this study protocol or in written laboratory standard operating procedures. These procedures are based on the most currently available technologies concerning proper laboratory animal use and management. This protocol has been reviewed and approved by Springborn Laboratories, Inc. Institutional Animal Care and Use Committee (IACUC) for a maximum of 12 animals.

This study is being conducted to evaluate potential irritant effects of the test article and potential reversibility of such effects. Following dosing, the Study Director will be notified by the technician if severe local reactions occur or if the animals exhibit overt clinical indications of pain/distress immediately postdose. If severe reactions are noted, the Sponsor will be contacted to see if the animals should be humanely euthanized. In the event that the Sponsor cannot be contacted, the Study Director and/or Facility Veterinarian may decide to humanely euthanize the animals. The ocular tissue will not be anesthetized prior to or following dosing since inhibition of the blink and/or tear response may elevate the irritation response. In addition, the anesthetic agents may interact with the test article and thereby alter the ocular response. Methods of euthanasia used during this study are in conformance with the above referenced regulations and the American Veterinary Medical Association Panel on Euthanasia (JAVMA, 1993).

**XVII. PROTOCOL APPROVAL**

The Sponsor's signature below documents for the Study Director that there are no acceptable non-animal alternatives for this study, the study does not unnecessarily duplicate previous studies and that the study is needed for regulatory purposes and/or human safety assessment.

Todd N. Merriman  
Todd N. Merriman, A.S., LAT  
Study Director (SLS)

Date 8/25/93

Raymond V. Karcher  
Raymond V. Karcher, B.A., LAT  
Quality Assurance Unit (SLS)

Date 8-25-93

Richard E. Ouellette  
Richard E. Ouellette, Ph.D., DABT  
Sponsor's Representative  
(Principal Investigator)

Date 8/30/93

Patricia K. Jenkins  
Patricia K. Jenkins, A.A.S., LATG  
IACUC Representative (SLS)

Date 8/25/93

**XVIII. REFERENCES**

1. Guide for the Care and Use of Laboratory Animals, DHHS Publication No. (NIH) 86-23, 1985.
2. Draize, J.H., Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, The Association of Food and Drug Officials of the United States, 46-59, 1959.
3. Kay, J.H. and Calandra, J.C., Interpretation of Eye Irritation Tests, Journal of the Society of Cosmetic Chemists, 13:281-289, 1962.

PROTOCOL APPENDIX A  
OCULAR IRRITATION GRADING SYSTEM  
(DRAIZE)

Score

CORNEA

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

No ulceration or opacity . . . . .	0
Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible . . . . .	1*
Easily discernible translucent area, details of iris slightly obscured . . . . .	2*
Nacreous (opalescent) area, no details of iris visible, size of pupil barely discernible . . . . .	3*
Opaque cornea, iris not discernible through opacity . . . . .	4*

(A) Area of cornea involved (total area exhibiting any opacity, regardless of degree)

No ulceration or opacity . . . . .	0
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

Cornea Score = O x A x 5

Total Maximum = 80

IRIS

(I) Iritis

Normal . . . . .	0
Markedly deepened rugae (folds above normal), congestion, swelling, moderate circumcorneal hyperemia or injection, any or all of these or combination of any thereof, iris is still reacting to light (sluggish reaction is positive) . . . . .	1*
No reaction to light, hemorrhage, gross destruction (any or all of these) . . . . .	2*

Iris Score = I x 5

Total Maximum = 10

\* = Positive effect.

**PROTOCOL APPENDIX A--Continued**  
**OCULAR IRRITATION GRADING SYSTEM**  
**(DRAIZE)**

<u>CONJUNCTIVAE</u>	<u>Score</u>
<b>(R) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)</b>	
Blood vessels normal .....	0
Some blood vessels definitely hyperemic (injected) above normal (slight erythema) .....	1
Diffuse, crimson color, individual vessels not easily discernible (moderate erythema) .....	2*
Diffuse beefy red (marked erythema) .....	3*
<b>(S) Swelling (lids and/or nictating membrane)</b>	
No swelling .....	0
Any swelling above normal (includes nictitating membrane, slightly swollen) .....	1
Obvious swelling with partial eversion of lids .....	2*
Swelling with lids about half closed .....	3*
Swelling with lids more than half closed .....	4*
<b>(D) Discharge</b>	
No discharge .....	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals) .....	1
Discharge with moistening of the lids and hairs just adjacent to lids .....	2
Discharge with moistening of the lids and hairs and considerable area around the eye .....	3

Conjunctival Score = (R + S + D) x 2      Total Maximum = 20

\* = Positive effect.

**PROTOCOL APPENDIX B**  
**OCULAR EVALUATION CRITERIA**  
 (Kay and Calandra)

Maximum mean score (days 0-3)	Maximum mean score	Persistence of Individual Scores	Descriptive Rating and Class
0.00 - 0.49	24 hours = 0		Non-Irritating 1
	24 hours > 0		Practically Non-Irritating 2
0.50 - 2.49	24 hours = 0		Non-Irritating 1
	24 hours > 0		Practically Non-Irritating 2
2.50 - 14.99	48 hours = 0		Slight Irritant 3
	48 hours > 0		Mild Irritant 4
15.00 - 24.99	72 hours = 0		Mild Irritant 4
	72 hours > 0		Moderate Irritant 5
25.00 - 49.99	7 day ≤ 20	> half of day 7 scores ≤ 10	Moderate Irritant 5
		> half of day 7 scores > 10, but no score > 20	Moderate Irritant 5
		> half of day 7 scores > 10, and any score > 20	Severe Irritant 6
	7 day > 20		Severe Irritant 6
50.00 - 79.99	7 day ≤ 40	> half of day 7 scores ≤ 30	Severe Irritant 6
		> half of day 7 scores > 30, but no score > 60	Severe Irritant 6
		> half of day 7 scores > 30, and any score > 60	Very Severe Irritant 7
	7 day > 40		Very Severe Irritant 7
80.00 - 99.99	7 day ≤ 80	> half of day 7 scores ≤ 60	Very Severe Irritant 7
		> half of day 7 scores > 60, but no score > 100	Very Severe Irritant 7
		> half of day 7 scores > 60, and any score > 100	Extremely Severe Irritant 8
	7 day > 80		Extremely Severe Irritant 8
100.00 - 110.00	7 day ≤ 80		Very Severe Irritant 7
	7 day > 80		Extremely Severe Irritant 8

**A PRIMARY EYE IRRITATION STUDY IN RABBITS  
WITH C-1850**

**PROTOCOL AMENDMENT  
NO. 1**

DEC 10 1993

SLS STUDY NO. 3206.300 PAGE 1 OF 1

TEST ARTICLE C-1850

1) PART TO BE CHANGED/REVISED: X.C. EXPERIMENTAL PROCEDURES

CHANGE/REVISION: The test and control eyes of the rabbits in the rinsed group were rinsed approximately 30 seconds postinstillation as opposed to 2 to 3 minutes as stated in the protocol.

REASON FOR CHANGE/REVISION: Sponsor's request.

2) PART TO BE CHANGED/REVISED: X.E. EXPERIMENTAL PROCEDURES

CHANGE/REVISION: The test eye of animal number 8171/M was examined on study day 18 by Dr. Wilkie, a Veterinarian Ophthalmologist.

REASON FOR CHANGE/REVISION: The Sponsor requested this animal be examined by a Veterinarian Ophthalmologist due to the animal's findings observed on study day 7.

3) PART TO BE CHANGED/REVISED: X.E. EXPERIMENTAL PROCEDURES

CHANGE/REVISION: The observation period was extended to study day 28 for the affected animals.

REASON FOR CHANGE/REVISION: Sponsor's request.

Todd N. Merriman  
Todd N. Merriman, A.S., LATG  
Study Director (SLS)

Date 11/29/93

Richard E. Ouellette  
Richard E. Ouellette, Ph.D., DABT  
Sponsor's Representative

Date 12/1/93

Raymond V. Karcher  
Raymond V. Karcher, B.A., LAT  
Quality Assurance Unit (SLS)

Date 11-23-93

SLS Study No. 3206.300

(41)

**APPENDIX B**

**Ocular Irritation Grading System**

OCULAR IRRITATION GRADING SYSTEM  
(DRAIZE)

CORNEA

Score

(O)	Opacity--degree of density (area most dense taken for reading)	
	No ulceration or opacity . . . . .	0
	Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible . . . . .	1*
	Easily discernible translucent area, details of iris slightly obscured . . . . .	2*
	Opalescent (nacreous) area, no details of iris visible, size of pupil barely discernible . . . . .	3*
	Opaque cornea, iris not discernible through opacity . . . . .	4*
(A)	Area of cornea involved (total area exhibiting any opacity, regardless of degree)	
	No ulceration or opacity . . . . .	0
	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

Cornea Score = O x A x 5                  Total Maximum = 80

IRIS

(I)	Iritis	
	Normal . . . . .	0
	Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris is still reacting to light (sluggish reaction is positive) . . . . .	1*
	No reaction to light, hemorrhage, gross destruction (any or all of these) . . . . .	2*

Iris Score = I x 5                  Total Maximum = 10

\* = Positive effect.

OCULAR IRRITATION GRADING SYSTEM  
(DRAIZE)

CONJUNCTIVAEScore

(R)	Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)	
	Blood vessels normal . . . . .	0
	Blood vessels definitely injected (hyperemic) above normal (slight erythema) . . . . .	1
	More diffuse, deeper crimson red, individual vessels not easily discernible (moderate erythema) . . . . .	2*
	Diffuse beefy red (marked erythema) . . . . .	3*
(S)	Swelling	
	No swelling . . . . .	0
	Any swelling above normal (includes nictitating membrane, slightly swollen) . . . . .	1
	Obvious swelling with partial eversion of lids . . . . .	2*
	Swelling with lids about half closed . . . . .	3*
	Swelling with lids more than half closed . . . . .	4*
(D)	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 lids and hairs just adjacent to lids . . . . .	2
	Discharge with moistening of lids and hairs and considerable area around the eye . . . . .	3

Conjunctival Score = (R + S + D)x2

Total Maximum = 20

\* = Positive effect.

**APPENDIX C**

**Ocular Evaluation Criteria**

**OCULAR EVALUATION CRITERIA**  
(Kay and Calandra)

Maximum mean score (days 0-3)	Maximum mean score	Persistence of Individual Scores	Descriptive Rating and Class
0.00 - 0.49	24 hours = 0		Non-Irritating 1
	24 hours > 0		Practically Non-Irritating 2
0.50 - 2.49	24 hours = 0		Non-irritating 1
	24 hours > 0		Practically Non-Irritating 2
2.50 - 14.99	48 hours = 0		Slight Irritant 3
	48 hours > 0		Mild Irritant 4
15.00 - 24.99	72 hours = 0		Mild Irritant 4
	72 hours > 0		Moderate Irritant 5
25.00 - 49.99	7 day ≤ 20	> half of day 7 scores ≤ 10	Moderate Irritant 5
		> half of day 7 scores > 10, but no score > 20	Moderate Irritant 5
		> half of day 7 scores > 10, and any score > 20	Severe Irritant 6
	7 day > 20		Severe Irritant 6
50.00 - 79.99	7 day ≤ 40	> half of day 7 scores ≤ 30	Severe Irritant 6
		> half of day 7 scores > 30, but no score > 60	Severe Irritant 6
		> half of day 7 scores > 30, and any score > 60	Very Severe Irritant 7
	7 day > 40		Very Severe Irritant 7
80.00 - 99.99	7 day ≤ 80	> half of day 7 scores ≤ 60	Very Severe Irritant 7
		> half of day 7 scores > 60, but no score > 100	Very Severe Irritant 7
		> half of day 7 scores > 60, and any score > 100	Extremely Severe Irritant 8
	7 day > 80		Extremely Severe Irritant 8
100.00 - 110.00	7 day ≤ 80		Very Severe Irritant 7
	7 day > 80		Extremely Severe Irritant 8

**APPENDIX D**

**Key to Codes**

KEY TO CODESCORNEAL NEOVASCULARIZATION CODES

Minimal:	Total area of vascularized corneal tissue is $\leq$ 10% of corneal surface	VAS-1
Mild:	Total area of vascularized corneal tissue is $>$ 10% but $\leq$ 25% of corneal surface	VAS-2
Moderate:	Total area of vascularized corneal tissue is $>$ 25% but $\leq$ 50% of corneal surface	VAS-3
Extensive:	Total area of vascularized corneal tissue is $>$ 50% of corneal surface	VAS-4

STANDARD OCULAR CODES

Fluorescein exam indicates apparent mechanical abrasion to cornea -	MI
Fluorescein exam indicates stippling on cornea -	ST
Fluorescein exam indicates desquamation of cornea -	DES
Fluorescein retention associated with opacity -	FAO
Fluorescein retention associated with former area of opacity -	FAF
Sloughing of corneal epithelium -	SCE
Corneal bulging -	CB
Slight dulling of normal luster of cornea -	SDL
Raised area on cornea -	RAC
Test article present in eye -	TAE
Bulbar conjunctivae extends over entire corneal surface excluding a 2 mm opening over pupil -	BCP
Bulbar conjunctivae extends approximately 7 mm around entire length of perilimbal region on corneal surface -	BCE7
Bulbar conjunctivae extends approximately 5 mm around entire length of perilimbal region on corneal surface -	BCS

OTHER OCULAR CODES

Negative fluorescein dye retention -	[-]
Positive fluorescein dye retention -	[+]

**APPENDIX E**

**SLS Personnel Responsibilities**

**SLS PERSONNEL RESPONSIBILITIES**

Todd N. Merriman, A.S., LATG	Study Director/Associate Toxicologist
Rusty E. Rush, M.S., LAT	Alternate Contact/Manager of Acute Toxicology and Special Studies
Malcolm Blair, Ph.D.	Director of Research
Joseph C. Siglin, M.S., DABT	Associate Director of Toxicology
Kimberly L. Bonnette, M.S., LATG	Toxicologist
Deborah A. Douds, M.S.	Associate Toxicologist
Patricia K. Jenkins, AAS, LATG	Acute Toxicology Supervisor
Pamela S. Smith, ALAT	Unit Leader
Delores P. Knippen	Pharmacy Supervisor
Cynthia J. Ziegra, VMD, Ph.D., Diplomate, A.C.V.P.	Director of Pathology
David A. Wilkie, DVM, M.S., Diplomate, A.C.V.P.O.	Consultant Veterinarian Ophthalmologist
Steven H. Magness, B.S., LATG	Gross and Fetal Pathology Supervisor
Arita M. Bosau	Director of Quality Assurance
Raymond V. Karcher, B.A., LAT	Quality Assurance Supervisor



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OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

DEC 01 1994

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requesta".

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Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

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Attn: TSCA Section 8(e) Coordinator  
Office of Pollution Prevention and Toxics  
Environmental Protection Agency  
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

*Terry R. O'Bryan*  
Terry R. O'Bryan  
Risk Analysis Branch

Enclosure

12888 A



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### Triage of 8(e) Submissions

Date sent to triage: DEC 14 1994

NON-CAP

CAP

Submission number: 12888A

TSCA Inventory:

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N

D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO

AQUATO

Group 2 - Ernie Falko (1 copy total)

ATOX

SBTOX

SEN

w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

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entire document: 0 1 2 pages 1

pages 1, TAB

Notes: 2-sided

Contractor reviewer: FOR

Date: 11/1/94

CECATS/TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: Submission # BEHQ: 0294-12888 SEQ. A

TYPE: (INT) SUPP FLWP  
 SUBMITTER NAME: Hoechst Celanese Corporation

INFORMATION REQUESTED: FLY P. DATE: \_\_\_\_\_  
 0501 NO INFO REQUESTED  
 0502 INFO REQUESTED (TECII)  
 0503 INFO REQUESTED (VOL. ACTIONS)  
 0504 INFO REQUESTED (REPORTING RATIONAL/P)  
 DISPOSITION:  
 0505 REFER TO CHEMICAL SCREENING  
 0506 CAP NOTICE

0507 VOLUNTARY ACTIONS:  
 0401 NO ACTION REPORTED  
 0402 STUDIES PLANNED IN THE FUTURE  
 0403 NOTIFICATION IN WORK IN PROGRESS  
 0404 LABELS/ASSETS CHANGES  
 0405 PROCESS/ANDI INC. CHANGES  
 0406 APP/USE DISCONTINUED  
 0407 PRODUCTION DISCONTINUED  
 0408 CONFIDENTIAL

SUB. DATE: 02/01/94 OTR DATE: 02/08/94 CSRAD DATE: 05/19/94

CHEMICAL NAME: \_\_\_\_\_  
 CASE: 68551-17-1

INFORMATION TYPE:	P.F.C.	INFORMATION TYPE:	P.F.C.	INFORMATION TYPE:	P.F.C.
0201 ONCO (HUMAN)	01 02 04	0216 EPICLIN	01 02 04	0241 IMMUNO (ANIMAL)	01 02 04
0202 ONCO (ANIMAL)	01 02 04	0217 HUMAN EXPOS (PROD CONTAM)	01 02 04	0242 IMMUNO (HUMAN)	01 02 04
0203 CELL TRANS (IN VITRO)	01 02 04	0218 HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243 CHEM/PHYS PROP	01 02 04
0204 MUTA (IN VITRO)	01 02 04	0219 HUMAN EXPOS (MONITORING)	01 02 04	0244 CLASTO (IN VITRO)	01 02 04
0205 MUTA (IN VIVO)	01 02 04	0220 BCOVAQUA TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	0221 ENV. OCCUREL/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0207 REPRO/TERATO (ANIMAL)	01 02 04	0222 EMER INCI OF ENV CONTAM	01 02 04	0247 DNA DAMAGE/REPAIR	01 02 04
0208 NEURO (HUMAN)	01 02 04	0223 RESPONSE REQUEST DELAY	01 02 04	0248 PROD/USE/PROC	01 02 04
0209 NEURO (ANIMAL)	01 02 04	0224 PROD/COMP/CHEM ID	01 02 04	0251 MSDS	01 02 04
0210 ACUTE TOX (HUMAN)	01 02 04	0225 REPORTING RATIONALE	01 02 04	0259 OTHER	01 02 04
0211 CHR. TOX (HUMAN)	01 02 04	0226 CONFIDENTIAL	01 02 04		
0212 ACUTE TOX (ANIMAL)	01 02 04	0227 ALLERG (HUMAN)	01 02 04		
0213 SUB ACUTE TOX (ANIMAL)	01 02 04	0228 ALLERG (ANIMAL)	01 02 04		
0214 SUB CHRONIC TOX (ANIMAL)	01 02 04	0229 METAB/PHARMACO (ANIMAL)	01 02 04		
0215 CHRONIC TOX (ANIMAL)	01 02 04	0230 METAB/PHARMACO (HUMAN)	01 02 04		

TRACE DATA	NON-CELL INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN	USE	PRODUCTION
<u>YES</u>	NO (CONTINUE)	YES (DROP/REFER)	<u>RST</u>	LOW		
NO	NO (CONTINUE)	NO (CONTINUE)		<u>MED</u>		
IN PROGRESS	REFER			HIGH		

0294-12888 Non-Cap

0 0 0 >

<ID NUMBER>

8(e)-12888A >

<TOX CONCERN>

M >

<COMMENT>

C-1850: EYE IRRITATION IN RABBITS IS OF MODERATE CONCERN. 24-HOUR IRRITATION SCORE FOR THE GROUP (3 ANIMALS) WITH RINSE 30 SEC AFTER APPLICATION WAS 55.00; FOR THE NO-RINSE GROUP (6 ANIMALS), SCORE WAS 43.17. OPACITY, IRITIS, AND CONJUNCTIVITIS WERE SEEN IN BOTH GROUPS, WITH ONE INSTANCE OF PSEUDOPTERYGIUM IN THE NO-RINSE GROUP. EYE IRRITATION IN RABBITS WITH A SIMILAR COMPOUND, C-1849, IS OF MODERATE CONCERN. 24-HOUR IRRITATION SCORE FOR THE GROUP (3 ANIMALS) WITH RINSE 30 SEC AFTER APPLICATION WAS 18.67; FOR THE NO-RINSE GROUP (6 ANIMALS), SCORE WAS 30.17. OPACITY, IRITIS, AND CONJUNCTIVITIS WERE SEEN IN BOTH GROUPS, WITH ONE INSTANCE OF PSEUDOPTERYGIUM IN THE NO-RINSE GROUP. \$\$\$ -CPSS- 0406951403