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88990000180

Re: Notice of TSCA Section 8(e) Substantial Risk Information for Cesium Acetate

Dear Sir or Madam:

Cabot is submitting this letter as notice under the Toxic Substances Control Act (TSCA) section 8(e) regarding substantial risk information. We have determined that the results of a primary skin irritation study conducted on cesium acetate (CAS No. 3396-11-0) are reportable based on the guidelines for reporting skin irritation studies contained in the U.S. EPA June 1991 Section 8(e) Reporting Guide. On April 2, 1999, a self-disclosure notice was filed with U.S. EPA Region I on Cabot's behalf by John Dubeck of Keller and Heckman, LLP; in follow-up, this section 8(e) letter is being submitted within the 60-day corrective action period.

As detailed in the enclosed submission, cesium acetate was tested in a primary skin irritation study in rabbits in accordance with EPA Pesticide Assessment Guidelines, Subdivision F (81-5) EPA Health Effects Testing Guidelines (TSCA Guideline no. 798.4470) and the OECD Guidelines for Testing of Chemicals No. 404. An aliquot of 0.5 ml undiluted cesium acetate was applied underneath a one inch by one inch gauze patch located at one intact dorsal skin area of each of six test rabbits. The patch was removed after 4 hours, and any residual test material was wiped from the test site using a moistened paper towel. Well-defined, moderate or severe erythema and edema were noted at the 1/2 - 1 hour reading. At the 24-hour reading, one of the animals continued to exhibit severe erythema and edema and also showed evidence of corrosion (i.e., necrosis). This animal was terminated for humane reasons. Two of the five remaining

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Office of Prevention, Pesticides, and Toxic Substances
U.S. Environmental Protection Agency
May 28, 1999
Page 2

animals continued to exhibit irritation at Day 7 but were completely recovered at Day 14. Blanching and desquamation were also noted in most of the animals at various times but had disappeared by Day 14. In summary, cesium acetate was categorized as corrosive based on the necrosis observed in one animal.

In an acute dermal toxicity study in rabbits conducted with the same material, similar dermal effects were reported, including: moderate to extreme erythema, slight to marked edema, mild to moderate desquamation, slight coriaceousness, necrosis, blanching, scabbing, and purple/dark brown discoloration. However, no details regarding the number of affected animals or recovery time were provided in the report. It should be noted that the test material was held in contact with the skin for a period of 24 hours, as dictated by the protocol. (Note: the LD₅₀ for cesium acetate was reported to be > 5000 mg/kg).

If you have any questions regarding this submission, please do not hesitate to contact me at 978-670-6965.

Sincerely,

D. Cooper Rees

D. Cooper Rees, Ph.D., DABT
Director of Toxicology and Corporate Toxicologist

Enclosure

cc: Rosina Toscano, U.S. EPA - Region I
John Dubeck, Esq., Keller and Heckman, LLP



REPORT FOR

**Primary Skin Irritation Study In Rabbits:
Cesium Acetate**

PROJECT NO. 96-8310-21

FOR

**Cabot Corporation
157 Concord Road
Billerica, MA 01821-7001**

January 30, 1997

BY

**HILL TOP RESEARCH, Ltd.
(formerly Hill Top Research, Inc.)
Main and Mill Streets
Miamiville, OH 45147**

A. 06

Cabot Corporation

Ref.: 96-8310-21

January 30, 1997

TITLE: Primary Skin Irritation Study in Rabbits

TEST MATERIAL: Cesium Acetate

AUTHOR: Kenneth J. Harrod, B.A.

COMPLETION DATE: May 27, 1997

PERFORMING LABORATORY: Hill Top Research, Ltd. (formerly Hill Top Research, Inc.)
Main and Mill Streets
Miamiville, OH 45147

HILL TOP PROJECT NO.: 96-8310-21

SPONSORED BY: Cabot Corporation
157 Concord Road
Billerica, MA 01821-7001

SUBMITTED BY:

DATE SUBMITTED:

EPA DATA REQUIREMENT: 81-5

Cabot Corporation

Ref.: 96-8310-21

January 30, 1997

CONFIDENTIALITY STATEMENT

Hill Top Research, Ltd. (formerly Hill Top Research, Inc.) shall not disclose information contained in this report or any other information related to the study which is the subject of this report to third parties without prior written consent of the Study Sponsor.

Cabot Corporation

Ref.: 96-8310-21

January 30, 1997

COMPLIANCE STATEMENT

All aspects of this study, as defined in the Protocol, were conducted in accordance with Good Laboratory Practice Standards (40 CFR).

HILL TOP RESEARCH, Ltd.
(formerly Hill Top Research, Inc.)



Kenneth J. Harrod, B.A.
Study Director
Acute Toxicology

SPONSOR

Howard Marks, Ph.D.
Consulting Toxicologist
for Cabot Corporation

SUBMITTER

Howard Marks, Ph.D.
Consulting Toxicologist
for Cabot Corporation

Cabot Corporation

Ref.: 96-8310-21

January 30, 1997

HILL TOP RESEARCH, Ltd.
(formerly Hill Top Research, Inc.)

IMPORTANT NOTICE

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

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REPORT APPROVAL

Report Prepared by:

HILL TOP RESEARCH, Ltd.
(formerly Hill Top Research, Inc.)


Ruth Triplett 5-27-97
Department Secretary
Acute Toxicology

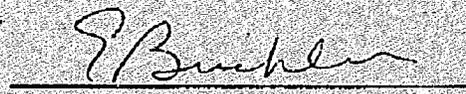
Report Approved by:

HILL TOP RESEARCH, Ltd.
(formerly Hill Top Research, Inc.)


Kenneth J. Harrod, B.A.
Study Director
Acute Toxicology

Report issued by:

HILL TOP RESEARCH, Ltd.
(formerly Hill Top Research, Inc.)


Edwin V. Buehler, Ph.D.
Vice President, Scientific Affairs
Acute Toxicology 5-27-97

CONTRIBUTORS

The following members of Hill Top Research, Ltd. (formerly Hill Top Research, Inc.) contributed to the conduct and reporting of Project No. 96-8310-21:

<u>Name</u>	<u>Title</u>	<u>Function</u>
E. Buehler, Ph.D.	Vice President, Scientific Affairs Director of Toxicology	Director of Toxicology
J. Kreuzmann, B.A.	Branch Manager II	Manager, Toxicology
T. Morris, B.S.	Department Manager	Manager, Toxicology
L. Goble	Office Manager	Report Supervisor Office Management
E. Darks, B.S.	Study Manager	Conduct of Study
K. Harrod, B.A.	Study Coordinator	Study Director Conduct of Study
M. Watson	Study Coordinator	Conduct of Study
M. Cole, A.S.	Technician II	Conduct of Study
J. Croley, B.S.	Technician II	Conduct of Study
V. Banks	Technician I	Conduct of Study
M. Marshall	Technician I	Conduct of Study
R. Triplett	Department Secretary	Report Preparation

SUMMARY/CONCLUSIONS

The primary skin irritancy of undiluted Cesium Acetate was evaluated in compliance with the conditions specified in the regulation for the enforcement of the Federal Insecticide, Fungicide, and Rodenticide Act (40 CFR), the Toxic Substances Control Act (40 CFR), and the OECD Guidelines.

A 0.5 ml amount of undiluted Cesium Acetate was applied to a single intact application site on the backs of six New Zealand White rabbits for an approximate four hour exposure period. The application sites were scored for each rabbit approximately ½ - 1 hour and 24 hours after removal of the patches and any residual test material. Due to the observation of corrosion (necrosis) at the treatment site of animal #6, observation of this animal was terminated following the 24 hour reading for humane reasons. All remaining animals (#1-5) were scored approximately 48 and 72 hours after removal. Animals #1-5, which exhibited irritation at the 72 hour reading, were held and examined for a Day 7 reading in order to establish reversibility of irritation in these animals. Animals #1 and 3, which continued to exhibit irritation at the Day 7 reading, were held and examined for a Day 14 reading in order to further evaluate the reversibility of irritation in these animals.

At the ½ - 1 hour reading, animals exhibited well defined to moderate to severe erythema and moderate to severe edema. At the 24 hour reading, a single animal exhibited severe erythema and severe edema. Evidence of corrosion (areas of necrosis) was observed at this scoring interval on the single animal. The remaining animals exhibited well defined erythema and very slight to moderate edema. At the 72 hour reading, animals maintained on the test exhibited very slight to well defined erythema and no to slight edema. Full recovery was observed in all animals maintained on the test by the Day 14 reading. Additional changes noted in the coloration and/or texture of the skin of the animals included blanching, purple discoloration, and desquamation.

In conclusion, undiluted Cesium Formate is classified in FIFRA Toxicity Category I based on the response observed following dermal administration.

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METHODS (See Appendix 1 for Protocol and Supplemental Instructions)

Study Identification

Hill Top Project Number: 96-8310-21

Reference Code

96-8310-21/CABC 2-4-2/06-10-96/ORIGINAL

Testing Facility

Hill Top Research, Ltd. (formerly Hill Top Research, Inc.)

Main and Mill Streets

Miamiville, Ohio 45147

Phone: (513) 831-3114

Fax: (513) 831-1217

Sponsor

Cabot Corporation

157 Concord Road

Billerica, MA 01821-7001

Data Retention

All records that would be required to reconstruct the study and demonstrate adherence to the Protocol will be maintained. Following completion of the study, the original raw data and the original of the final report will be maintained indefinitely in Hill Top's commercial off-site records storage facility in the form of hard copy to comply with EPA record keeping regulations. The testing facility will retain a copy of these study records in the form of microfilm.

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Study Dates

Project Initiation Date:	December 26, 1996
Experimental Start Date:	January 14, 1997
Experimental Termination Date:	January 28, 1997
Project Completion Date:	May 27, 1997

Purpose

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

Applicable Regulations

This study was conducted according to the Good Laboratory Practice Standards of the EPA's Federal Insecticide, Fungicide, and Rodenticide Act (40 CFR, Part 160). The study was designed to satisfy EPA Pesticide Assessment Guidelines, Subdivision F (81-5) EPA Health Effects Testing Guidelines (TSCA Guideline No. 798.4470) and the OECD Guidelines for Testing of Chemicals (404). This study was placed on the master schedule of EPA regulated studies.

Quality Assurance

The Protocol, study conduct, and the final report were audited by the Quality Assurance Unit in accordance with applicable Standard Operating Procedures (SOPs).

Test Material

Identification:	Cesium Acetate
Lot Number:	2378-221
Physical Description:	A cloudy liquid
Storage Conditions:	Room temperature

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January 30, 1997

Test Material Purity and Stability

The Sponsor assumes responsibility for purity and stability determinations (including under test conditions). Information on composition and method of synthesis was held by the Sponsor. Analyses of test material for concentration, solubility, homogeneity, and stability were not done by Hill Top Research, Ltd. (formerly Hill Top Research, Inc.).

Test Material Disposition

The test material container was weighed when received at the testing facility, and a record of all test material use was maintained. Test material was stored in the original container.

Unused test material was returned at the termination of the study to the Sponsor. The test material was packed in a suitable container to maintain the temperature conditions specified by Sponsor during transit plus an adequate margin of safety for any transit delays.

Test System Justification

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

Test Animals

Naive, young adult New Zealand White rabbits (three males and three females) weighing 2.426 to 2.966 kg were used. The animals were purchased from a U.S.D.A. licensed supplier.

Animal Supplier

Myrtle's Rabbitry Incorporated
4678 Bethesda Road
Thompson Station, Tennessee 37179

Number of Animals

Six animals.

Housing and Animal Care

All animals were acclimated to the laboratory for at least five days before being used. Animals were housed singly in wire mesh suspension cages and were supplied Teklad Hi-Fiber Rabbit Diet and tap water ad libitum during both acclimation and test periods. The animal room was maintained on a 12-hour light/12-hour dark cycle and at a temperature of 61-72°F and a relative humidity of 30-70%. There were no contaminants in either the feed or the water that were expected to affect the outcome of this study.

Animal Selection

The animals were randomly caged according to Standard Operating Procedures.

Animal Identification

A cage card and ear tag were used to identify each rabbit.

Preparation of Test Animals

On the day prior to test material administration, the application sites were prepared by clipping the hair from the dorsal surface of the trunk using an electric clipper. The treatment sites were inspected for interfering lesions, irritation, or defects that would preclude the use of any of the animals.

Test Material Administration

The test material was administered at a dose of 0.5 ml. The test material was applied under an approximate one inch by one inch gauze patch, two layers thick, at one intact skin area on each of the six test rabbits. The application sites were rotated to minimize bias due to site-to-site variation. Each patch was held in place with adhesive tape. After application of the patches, the trunk of each rabbit was wrapped with rubber dental dam which was secured with staples. An outer layer of gauze was then wrapped around the trunk of each animal and secured with tape. Each animal was fitted with an Elizabethan collar to prevent wrapping and patch removal. Following approximately 4 hours of exposure, the restraining device, wrapping, and patches were removed. Test sites were wiped free of residual test material using a paper towel moistened with tap water.

Observations

The application sites were scored for each rabbit approximately 1/2 - 1 hour and 24 hours after removal of the patches and any residual test material. Due to the observation of corrosion (necrosis) at the treatment site of animal #6, observation of this animal was terminated following the 24 hour reading for humane reasons. All remaining animals (#1-5) were scored approximately 48 and 72 hours after removal. Animals #1-5, which exhibited irritation at the 72 hour reading, were held and examined for a Day 7 reading in order to establish reversibility of irritation in these animals. Animals #1 and 3, which continued to exhibit irritation at the Day 7 reading were held and examined for a Day 14 reading in order to further evaluate the reversibility of irritation in these animals. All scoring was conducted using the Draize Method described below:

EVALUATION OF DERMAL IRRITATION

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

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

Edema Formation (most severely affected area graded):

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

Any other notable responses were documented.

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

1. Erythema and eschar formation, intact skin, 1/2 - 1 hour.
2. Erythema and eschar formation, intact skin, 24 hours.
3. Edema, intact skin, 1/2 - 1 hour.
4. Edema, intact skin, 24 hours.

Due to the termination of scoring of animal #6 following the 24 hour reading, the skin grades for animals #1-5 only were totaled and averaged for each of the following categories:

5. Erythema and eschar formation, intact skin, 48 hours.
6. Erythema and eschar formation, intact skin, 72 hours.
7. Edema, intact skin, 48 hours.
8. Edema, intact skin, 72 hours.

Interpretation

The test material was categorized in accordance with 40 CFR 156, Proposed as described below:

1. Category I - Corrosive (tissue destruction dermis and/or scarring)
2. Category II - Severe irritation at 72 hours (severe erythema or edema)
3. Category III - Moderate irritation at 72 hours (moderate erythema)
4. Category IV - Mild or slight or no irritation at 72 hours (no irritation or slight erythema)

Body Weights

Body weights were measured for each animal on the day of dosing.

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RESULTS

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

The results of the application of undiluted Cesium Acetate to intact skin areas of New Zealand White rabbits are summarized in Table 1.

At the ½ - 1 hour reading, animals exhibited well defined to moderate to severe erythema and moderate to severe edema. At the 24 hour reading, a single animal exhibited severe erythema and severe edema. Evidence of corrosion (areas of necrosis) was observed at this scoring interval on the single animal. The remaining animals exhibited well defined erythema and very slight to moderate edema. At the 72 hour reading, animals maintained on the test exhibited very slight to well defined erythema and no to slight edema. Full recovery was observed in all animals maintained on the test by the Day 14 reading. Additional changes noted in the coloration and/or texture of the skin of the animals included blanching, purple discoloration, and desquamation.

PROTOCOL DEVIATIONS

The Protocol was followed without deviation.

REFERENCE

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

Table 1
Primary Skin Irritation in Rabbits Following a
4 Hour Dermal Application of Undiluted Cesium Acetate

Skin Condition	Reading	Score for each Rabbit ^a						Total Score	Average Score
		No. 1 -28 ♂ 2755 g	No. 2 -29 ♂ 2653 g	No. 3 -30 ♂ 2436 g	No. 4 -37 ♀ 2966 g	No. 5 -42 ♀ 2443 g	No. 6 -46 ♀ 2426 g		
Erythema and Eschar Formation									
	Site	A	B	C	D	A	B		
Intact	½ - 1 hr	2L	2L	2L	2L	2L	3LP	13	2.17
	24 hr	2R	2	2R	2	2	4RN	14	2.33
	48 hr	2R	1	2R	2	1	NA	8	1.60
	72 hr	1R	1	2R	1	1	NA	6	1.20
	Day 7	1S	0S	1S	0	0	NA	2	0.40
	Day 14	0	ND	0	ND	ND	NA	0	0.00
Edema Formation									
	Site	A	B	C	D	A	B		
Intact	½ - 1 hr	4	3	4	3	3	4	21	3.50
	24 hr	2	1	3	2	2	4	14	2.33
	48 hr	2	1	3	1	1	NA	8	1.60
	72 hr	2	1	2	1	0	NA	6	1.20
	Day 7	1	0	1	0	0	NA	2	0.40
	Day 14	0	ND	0	ND	ND	NA	0	0.00
Primary Irritation Index (PII) = W									

^aScoring key is presented on Page 14 of this report.

L = Site appears blanched.

P = Purple discoloration on site.

R = Areas of blanching on site.

N = Areas of necrosis on site.

NA = Not applicable. Due to the necrosis observed at the treatment site of animal #6, scoring of this animal was terminated following the 24 hour reading.

S = Desquamation on site.

W = PII unable to be calculated due to termination of animal #6.

ND = No data. All irritation cleared at previous reading.

QUALITY ASSURANCE STATEMENT

This study was inspected in accordance with the SOP's of Hill Top Research, Ltd. (formerly Hill Top Research, Inc.). QA findings derived from the inspection(s) during the conduct of the study and from the inspection of the final report are documented and have been reported to the appropriate personnel.

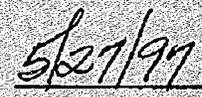
Date of Inspection	Date Findings Reported to Study Director	Date Findings Reported to Management
January 13, 1997	January 27, 1997	January 28, 1997

Protocol	Date Reviewed
Final	December 27, 1996

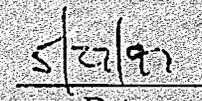
Report	Date Reviewed
Draft	February 4, 1997
Final	May 27, 1997

Reviewed by:


Quality Assurance Auditor


Date


Ralph Anderson, B.S.
Director of Quality Assurance


Date

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Cabot Corporation

Ref.: 96-8310-21

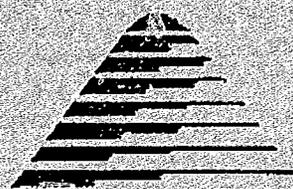
January 30, 1997

Appendix 1

Copy of Protocol and Supplemental Instructions

(Total Number of Pages - 11)

96-8310-21
P3



PROTOCOL

PRIMARY SKIN IRRITATION STUDY IN RABBITS

Study Identification

Hill Top Project Number: 96-8310-21

Reference Code

96-8310-21/CABC 2-4-2/06-10-96/ORIGINAL

Testing Facility

Hill Top Research, Inc.
Main and Mill Streets
Miamiville, OH 45147
Phone: (513) 831-3114
Fax: (513) 831-1217

Sponsor

Cabot Corporation
157 Concord Road
Billerica, MA 01821-7001

Sponsor's Representative

Mr. Howard Marks
Phone: (508) 670-6978
Fax: (508) 670-6955

Study Director

Kenneth J. Harrod, B.A.

Primary Skin Irritation Study in Rabbits

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Data Retention

All records that would be required to reconstruct the study and demonstrate adherence to the Protocol will be maintained. Following completion of the study, the original raw data and the original of the final report will be maintained indefinitely in Hill Top's commercial off-site records storage facility in the form of hard copy to comply with EPA record keeping regulations. The testing facility will retain a copy of these study records in the form of microfilm.

Proposed Study Dates

Proposed Experimental Start Date: January 14, 1997

Proposed Experimental Termination Date: January 17, 1997

Proposed Draft Report Date: January 31, 1997

Purpose

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

Institutional Animal Care and Use Committee

Any subsequent modification of this method which is believed will significantly increase the stress to the animals involved will be presented to the Chairman of Hill Top's Institutional Animal Care and Use Committee or a designate for deliberation.

No analgesics may be given to the animals participating on this study without the express approval of the Study Director and the Sponsor. If approved, administration would be as defined by SOP'S 21-ANIC-14-0560F and 21-ANIC-14-0570A. A decision to euthanize animals prior to the completion of the standard observation period can be determined by the Study Director and the Sponsor.

The Sponsor, to the best of their knowledge, assures that this project is not an unnecessary duplication of previous experiments and that no feasible alternative test methodology is available. The Director of Toxicology at Hill Top Research, Inc., after an extensive and continuing literature review, also has determined that there are no validated alternatives to this method and concurs with the Society of Toxicology Position Paper (Fund. Appl. Toxicol. [1989] 13, 621-623).

Applicable Regulations

This study will be conducted according to the Good Laboratory Practice Standards of the EPA's Federal Insecticide, Fungicide, and Rodenticide Act (40 CFR, Part 160). The study is designed to satisfy EPA Pesticide Assessment Guidelines, Subdivision F (81-5) EPA Health Effects Testing Guidelines (TSCA Guideline No. 798.4470) and the OECD Guidelines for Testing of Chemicals (404). This study will be placed on the master schedule of regulated studies.

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Primary Skin Irritation Study in Rabbits**Quality Assurance**

The Protocol, study conduct, and the final report will be audited by the Quality Assurance Unit in accordance with applicable Standard Operating Procedures (SOPs).

Test Material

Identification: Cesium Acetate
Lot Number: 2378-221
Physical Description: A cloudy liquid
Storage Conditions: Room Temperature

Test Material Purity and Stability

The Sponsor assumes responsibility for purity and stability determinations (including under test conditions). Information on composition and method of synthesis will be held by the Sponsor. Analyses of test material/vehicle for concentration, solubility, homogeneity, and stability will not be done by Hill Top Research, Inc.

Test Material Disposition

The test material container(s) will be weighed when received at the testing facility, and a record of all test material use will be maintained. Test material will be stored in the original container(s).

Unused test material will be returned at the termination of the study to the Sponsor. The test material(s) shall be packed in a suitable container to maintain the temperature conditions specified by Sponsor during transit plus an adequate margin of safety for any transit delays.

General safety precautions as required by the laboratory's policies and procedures will be followed. The Sponsor will supply basic toxicity data on the test materials to be used in this study. However, the toxicity of test materials is often not well characterized, and the contractor should be conservative in setting safety procedures.

Test System Justification

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

Test Animals

Naive young adult New Zealand White rabbits of either sex weighing 2.0 to 3.0 kg will be used. Animals which fall outside of this range may be used at the discretion of the Study Director. The animals will be purchased from a U.S.D.A. licensed supplier.

Primary Skin Irritation Study in Rabbits

Animal Supplier

Myrtle's Rabbitry Incorporated
4678 Bethesda Road
Thompson Station, TN 37179

Number of Animals

Six animals.

Housing and Animal Care

All animals will be acclimated to the laboratory for at least five days before being used. Animals will be housed singly in wire mesh suspension cages and will be supplied Teklad Hi-Fiber Rabbit Diet and tap water ad libitum during both acclimation and test periods. The animal room will be maintained on a 12-hour light/12-hour dark cycle and at a temperature of 61-72°F and a relative humidity of 30-70%. Slight variations from these ranges will not result in a Protocol deviation. There are no contaminants in either the feed or the water that would be expected to affect the outcome of this study.

Animal Selection

The animals will be randomly caged according to Standard Operating Procedures.

Animal Identification

A cage card and ear tag will be used to identify each rabbit.

Preparation of Test Animals

On the day prior to test material administration, the application sites will be prepared by clipping the hair from the dorsal surface of the trunk using an electric clipper. The treatment sites will be inspected for interfering lesions, irritation, or defects that would preclude the use of any of the animals. Animals will be reclipped as needed throughout the study.

Test Material Administration

The test material will be administered undiluted at a dose of 0.5 ml. The test material will be applied under an approximate one inch by one inch gauze patch, two layers thick, at one intact skin area on each of the six test rabbits. The application sites will be rotated to minimize bias due to site-to-site variation. Each patch will be held in place with adhesive tape. After application of the patches, the trunk of each rabbit will be wrapped with rubber dental dam which will be secured with staples. An outer layer of gauze will then be wrapped around the trunk of each animal and secured with tape. Each animal will be fitted with an Elizabethan collar to prevent wrapping and patch removal. Following approximately 4 hours of exposure, the restraining device, wrapping, and patches will be removed. Test sites may be wiped free of residual test material by a gentle sponging using a towel moistened with tap water.

Primary Skin Irritation Study in Rabbits

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Observations

The application sites will be scored for each rabbit approximately 1/2 - 1 hour, 24 hours, 48 hours, and 72 hours, after removal of the patches and any residual test material using the Draize method described below:

EVALUATION OF DERMAL IRRITATION

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

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

Edema Formation (most severely affected area graded):

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

Additional observations may be made on a per animal basis, as required by the Sponsor, to establish reversibility of irritation (Days 7 and 14). Any other notable responses will be documented.

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

1. Erythema and eschar formation, intact skin, 1/2 - 1 hour.
2. Erythema and eschar formation, intact skin, 24 hours.
3. Erythema and eschar formation, intact skin, 48 hours.
4. Erythema and eschar formation, intact skin, 72 hours.
5. Edema, intact skin, 1/2 - 1 hour.
6. Edema, intact skin, 24 hours.
7. Edema, intact skin, 48 hours.
8. Edema, intact skin, 72 hours.

The eight average scores from above will be added together and the results divided by four to obtain the Primary Irritation Index (PII).

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Interpretation

The test material will be categorized in accordance with 40 CFR 156. Proposed as described below:

1. Category I - Corrosive (tissue destruction dermis and/or scarring)
2. Category II - Severe irritation at 72 hours (severe erythema or edema)
3. Category III - Moderate irritation at 72 hours (moderate erythema)
4. Category IV - Mild or slight or no irritation at 72 hours (no irritation or slight erythema)

Body Weights

Body weights will be measured for each animal on the day of dosing.

Report

A draft report will be issued and will include but not necessarily be limited to the following:

The study objectives and procedures;

Identification of the test system;

Identification of the test material, its descriptions, and appropriate characteristics;

Concentration of the test material and, if appropriate, the diluent used;

The dose level incorporated in the study;

Initial body weights;

Critical observations directly related to the interpretation of the test;

Justifiable conclusions drawn from the study;

Appropriate classification of the test material;

No statistical analysis will be conducted for the evaluation of data.

Notice

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

Reference

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

Primary Skin Irritation Study in Rabbits

pg

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PROTOCOL APPROVAL FORM

Toxicology Division
Hill Top Research, Inc.

<u>Protocol Title</u>	<u>Reference Code</u>
Primary Skin Irritation Study in Rabbits	96-8310-21/CABC 2-4-2/ 06-10-96/ORIGINAL

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


 Kenneth J. Harrod, B.A.
 Study Director

12-26-96
 Date

Protocol Approved By (Sponsor):


 Mr. Howard Marks
 Sponsor's Representative

HOWARD MARKS, Ph.D.
CONSULTING TOXICOLOGIST
FOR CABOT CORPORATION

2 JAN 97
 Date

Cabot Corporation
 Sponsor's Name

157 Concord Road
 Billerica, MA 01821-7001
 Sponsor's Address

PROJECT NO.:	96-8310-21
PAGE NO.:	1b

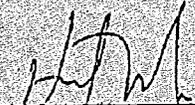
SUPPLEMENTAL INSTRUCTIONS	
TYPE OF PROJECT: Primary Skin Irritation Study In Rabbits	DATE: February 3, 1997
SPONSOR/ ADDRESS: Cabot Corporation 157 Concord Road Billerica, MA 01821-7001	CLIENT CODE: CABC
CONTACT: Howard Marks, Ph.D.	LETTER OF: NA
SPONSOR'S P.O. NO.: NA	VERBALLY ON: January 16, 1997
SAMPLE(S): Cesium Acetate	
<p>NEW INSTRUCTIONS:</p> <p>REGARDING; Termination of animal</p> <p><u>PROTOCOL AMENDMENT NO. 1</u></p> <p>Due to the observation of corrosion (necrosis) at the treatment site of animal #6-46, observation of this animal will be terminated following the 24 hour reading for humane reasons.</p> <p>The Sponsor's contact (indicated above) has authorized the instructions contained in this document verbally on January 16, 1997.</p>	
 Kenneth J. Harted, B.A. Study Director	 HOWARD MARKS, Ph.D. CONSULTING TOXICOLOGIST FOR C. BOT CORPORATION Howard Marks, Ph.D. Sponsor's Representative
2-3-97	10 FEB 97

PREPARED BY:	KJH	TYPED BY:	kjh
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EPA REGULATED (with In-Life and Report Audits)

NOTE: Please sign and date this form and return the original to the testing facility. Failure to sign this form will result in an incomplete study record.

PROJECT NO.:	96-8310-21
PAGE NO.:	1c

SUPPLEMENTAL INSTRUCTIONS	
TYPE OF PROJECT: Primary Skin Irritation Study In Rabbits	DATE: January 30, 1997
SPONSOR/ ADDRESS: Cabot Corporation 157 Concord Road Billerica, MA 01821-7001	CLIENT CODE: CABC
CONTACT: Howard Marks, Ph.D.	LETTER OF: NA
SPONSOR'S P.O. NO.: NA	VERBALLY ON: January 21, 1997
SAMPLE(S): Cesium Acetate	
NEW INSTRUCTIONS: REGARDING; Extension of the study PROTOCOL AMENDMENT NO. 2 At the sponsor's representative's request, animals #1-5, which exhibited irritation at the 72 hour reading, will be held and examined for a Day 7 reading in order to establish reversibility of irritation in these animals. This additional reading results in the following revision of the Proposed Experimental Termination Date and the Proposed Draft Report Date: Proposed Experimental Termination Date: January 21, 1997 Proposed Draft Report Date: January 28, 1997 The Sponsor's contact (indicated above) has authorized the instructions contained in this document verbally on January 21, 1997.	
 Kenneth J. Harrod, B.A. Study Director	 HOWARD MARKS, Ph.D. CONSULTING TOXICOLOGIST FOR CABOT CORPORATION Howard Marks, Ph.D. Sponsor's Representative
2-3-97	10 FEB 97

PREPARED BY: KJH	TYPED BY: kjh
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PROJECT NO.:	96-8310-21
PAGE NO.:	1d

SUPPLEMENTAL INSTRUCTIONS

TYPE OF PROJECT: Primary Skin Irritation Study In Rabbits	DATE: January 30, 1997
SPONSOR/ ADDRESS: Cabot Corporation 157 Concord Road Billerica, MA 01821-7001	CLIENT CODE: CABC
CONTACT: Howard Marks, Ph.D.	LETTER OF: NA
SPONSOR'S P.O. NO.: NA	VERBALLY ON: January 22, 1997
	SAMPLE(S): Cesium Acetate

NEW INSTRUCTIONS:

REGARDING: Extension of the study

PROTOCOL AMENDMENT NO. 3

At the sponsor's representative's request, animals #1 and 3, which continued to exhibit irritation at the Day 7 reading, will be held and examined for a Day 14 reading in order to further evaluate the reversibility of irritation in these animals. This additional reading results in the following revision of the Proposed Experimental Termination Date and the Proposed Draft Report Date:

Proposed Experimental Termination Date: January 28, 1997

Proposed Draft Report Date: February 4, 1997

The Sponsor's contact (indicated above) has authorized the instructions contained in this document verbally on January 22, 1997.

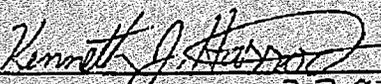
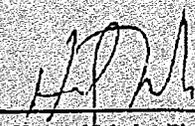
 Kenneth J. Harold, B.A. 2-3-97 Study Director	 HOWARD MARKS, Ph.D. CONSULTING TOXICOLOGIST FOR CABOT CORPORATION Howard Marks, Ph.D. 10 FEB 97 Sponsor's Representative
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PREPARED BY: KJH	TYPED BY: kjh
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PROJECT NO.:	96-8310-21
PAGE NO.:	1c

SUPPLEMENTAL INSTRUCTIONS	
TYPE OF PROJECT: Primary Skin Irritation Study In Rabbits	DATE: February 3, 1997
SPONSOR/ ADDRESS: Cabot Corporation 157 Concord Road Billerica, MA 01821-7001	CLIENT CODE: CABC
	LETTER OF: NA
	VERBALLY ON: January 30, 1997
CONTACT: Howard Marks, Ph.D.	SAMPLE(S): Cesium Acetate
SPONSOR'S P.O. NO.: NA	
<p>NEW INSTRUCTIONS:</p> <p>REGARDING: Total and average scores; Primary Irritation Index calculation</p> <p>PROTOCOL AMENDMENT NO. 4</p> <p>The Observations section of the protocol specifies that the skin grades for each rabbit will be totaled and averaged for erythema and eschar formation, and edema for each scoring interval through the 72 hour reading. However, due to the termination of scoring of animal #6 following the 24 hour reading based on observed corrosion (necrosis), the total and average scores for the 48 and 72 hour scoring intervals will be based on the scores obtained from animals #1-5 only. In addition, no Primary Irritation Index will be calculated for the test material.</p> <p>The Sponsor's contact (indicated above) has authorized the instructions contained in this document verbally on January 30, 1997.</p>	
 Kenneth J. Harford, B.A. 2-3-97 Study Director	 HOWARD MARKS, Ph.D. CONSULTING TOXICOLOGIST FOR CABOT CORPORATION Howard Marks, Ph.D. 10 FEB 97 Sponsor's Representative

PREPARED BY: KJH	TYPED BY: kjh
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NOTE: Please sign and date this form and return the original to the testing facility. Failure to sign this form will result in an incomplete study record.