Olin

ENVIRONMENTAL HYGIENE AND TOXICOLOGY DEPARTMENT

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Document Control Officer (WH-557)
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Office of Toxic Substances
Environmental Protection Agency
401 M Street, NW
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ORIGINAL

Dear Gentlemen:

RE: SECTION 8(e) NOTICE OF SUBSTANTIAL RISK - TEST REPORT
FLUOROTRIETHOXYSILANE (FTES) CAS #358-60-1

As per our memo dated 6/17/96, a copy of the final report for MB 96-4955.02 Acute Dermal Toxicity in Rabbits/LD_{50} in Rabbits with Fluorotriethoxysilane is being sent to you for inclusion with our 8(e) submission.

Sincerely yours,

Steven J. Barbee, Ph.D., D.A.B.T., C.I.H.
Associate Director, Environmental Hygiene & Toxicology

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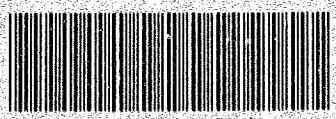

PROJECT NUMBER : MB 96-4955.02

TEST ARTICLE : FTES

SPONSOR : OLIN CORPORATION

TITLE : ACUTE DERMAL TOXICITY IN RABBITS/LD_{50} IN RABBITS

PROTOCOL # : 197-03 R/A

ABSTRACT

Method Synopsis - Five healthy male and five healthy female New Zealand Albino rabbits were dosed dermally with FTES at an initial dose of 2000 mg/kg of body weight. Although compound related mortality occurred, only two additional groups of five males and five females/group were dosed as indicated below. The test article was kept in contact with the skin for 24 hours. Dermal responses were recorded on days 1, 7 and 14. Animals were observed for toxicity and pharmacological effects at 1, 2 and 4 hours post dose and once daily for 14 days. All animals were observed twice a day for mortality. Body weights were recorded pretest, weekly and at death or termination in the survivors. All animals were examined for gross pathology. Abnormal tissues were preserved in 10% buffered formalin for possible future microscopic examination.

Summary - Mortality response to the three dermal applications was:

Dose mg/kg	# Animals M/F	# Dead M/F
1000	5/5	0/0
2000	5/5	2/2
2500	5/5	1/0

The deaths occurred by day 12 and were preceded by physical signs of emaciation, lethargy, ataxia, diarrhea, soiling of the anogenital area, few feces, yellow nasal discharge, ptosis, dyspnea, mucoid diarrhea and lack of mobility due to the severity of the dermal reactions. Necropsy of the dead animals revealed abnormalities of the treated skin, spleen, liver, kidneys, gall bladder and gastrointestinal tract, as well as emaciation, soiling of the anogenital area and yellow staining of the nose/mouth area.

Physical signs noted in survivors included lethargy, diarrhea, soiling of the anogenital area, few feces, ptosis, emaciation, yellow nasal discharge, mucoid diarrhea and lack of mobility due to the severity of the dermal reactions. Additionally, red staining was noted in the bedding under one survivor dosed at 2500 mg/kg for one day only.

Instances of weight loss were noted in survivors of all doses. Draize dermal scores, well defined to severe on day 1 were severe on days 7 and 14. Additionally, instances of moderate to severe eschar and necrosis were noted in survivors on days 7 and 14 and were considered indicative of injuries in depth.

Necropsy of the survivors revealed treated skin abnormalities which extended into the underlying musculature. Other abnormalities noted in survivors included emaciation, soiling of the anogenital area, as well as liver, kidney and intestinal anbormalities.

Conclusion - The LD 50 is greater than 2000 mg/kg of body weight. The deaths noted during the study as well as the instances of weight loss and abnormal physical signs were apparently due to the severity of the dermal reactions rather than to any systemic toxic effect of the test article.

Final report:

Approved by : 19 Jun 96
Daniel R. Cerven, M.S.
Study Director

Reviewed by : 6/18/96
Oscar M. Moreno, Ph.D.
Management

GOOD LABORATORY PRACTICES

This study was conducted in accordance with the Good Laboratory Practices as specified in The Testing of Chemicals, published by the Organization for Economic Cooperation and Development (OECD), 1982.

Daniel R. Cerven, M.S. 27 May 96 Date
Study Director

QUALITY ASSURANCE EVALUATION

The Quality Assurance Unit (QAU) has reviewed this report and determined that it accurately describes the methods and standard operating procedures used, and that the results contained herein accurately and fully reflect the raw data from this study.

The QAU inspected the scoring, systemic observation and body weight phase of the study on 3/20/96, audited the raw data on 5/06/96, and audited the report on 5/22/96. QAU findings were reported to management and the Study Director on 5/23/96.

Bonnie W. Cerven, Director 5/23/96 Date
Quality Assurance Unit

TITLE OF REPORT : ACUTE DERMAL TOXICITY IN RABBITS/LD $_{50}$ IN RABBITS

PROTOCOL NUMBER: 197-03 R/A

OBJECTIVE : To determine the potential for toxicity of the test article when applied dermally. This study was designed to comply with the standards set forth by OECD Guidelines for Testing Chemicals, Number 402, adopted February 24, 1987.

TEST ARTICLE

Source : OLIN CORPORATION
Date Received : 2/29/96

Test Article Label : FTES

Storage : The test article was stored at room temperature and humidity.

Test Article Description : Clear liquid

Specific Gravity : 0.98

Sample Preparation : The test article was used as received.

TEST ANIMALS

Animals were received from Ace Animals on 2/06 and 3/12/96. Following a quarantine period of at least one week, fifteen healthy male and fifteen healthy female New Zealand Albino rabbits were randomly assigned to this test from a larger group.

The animals were born the weeks of 10/22/95 through 12/31/95. The pretest weight range was 2.1 - 2.9 kg for males and 2.0 - 2.7 kg for females. The animals were identified by cage notation and a uniquely numbered metal eartag. The animals were housed 1/cage in suspended wire mesh cages. Bedding was placed beneath the cages and changed at least three times/week. Fresh Purina Rabbit Chow (Diet #5321) was provided daily. Water was available ad libitum.

The animal room, reserved exclusively for rabbits on acute tests, was temperature controlled, had a 12 hour dark/light cycle and was kept clean and vermin free.

TEST DATES

Study Initiation	(Date Protocol Signed)	:	3/01/96
Experimental Start	(1st Exposure to Test Substance)	:	3/06/96
Experimental Term	(Last date data collected)	:	4/04/96
Draft Report Submitted	(If applicable)	:	5/23/96
Study Completion	(Submission of Final Report)	:	6/19/96

SITE PREPARATION

Approximately 24 hours prior to application of the test article, the dorsal area of the trunk of each animal was clipped free of hair. The prepared site was approximately 10% of the body surface and remained intact.

EXPERIMENTAL DESIGN

The test article was used as received and dosed on an mg/kg basis. The dose was based on the sample weight as calculated from the specific gravity. The test article was measured by syringe and applied to the test site on top of a four layered surgical gauze patch measuring 4 x 6 inches. Gentle pressure was applied to the gauze to aid the distribution of the test article over the area. The torso was wrapped with plastic which was secured with non-irritating tape. At 24 hours, the patches were removed. Any residual test article was gently washed off with distilled water prior to dermal observations.

TYPE AND FREQUENCY OF OBSERVATIONS

In Vivo - The test sites were scored for dermal irritation at 24 hours post dose and on days 7 and 14 using the numerical Draize scale. Additional signs were described.

The animals were observed 1, 2 and 4 hours post dose and once daily for 14 days for toxicity and pharmacological effects. The animals were observed twice daily for 14 days for mortality.

Body weights were recorded pretest, weekly and at death or termination.

Post Mortem - At study termination, all survivors were humanely sacrificed using CO_2. All animals were examined for gross pathology. Abnormal tissues were preserved in 10% buffered formalin for possible future microscopic examination.

ANALYSIS OF DATA

An estimate of the LD_{50} was made based on mortality occurring during the study.

RETENTION OF DATA

The raw data is filed at MB Research by project number. The final report is filed at MB Research by sponsor name and MB project number.

The test article will be returned to the sponsor following submission of the report. The preserved tissues are stored at MB Research by sponsor name and MB project number. The sponsor will be contacted for final disposition following submission of the report.

AMENDMENT TO THE PROTOCOL

Although compound related mortality occurred, only two additional groups of five males and five females/group were dosed per sponsor's instructions to the study director.

RESULTS

1. LD 50:

The LD 50 is greater than 2000 mg/kg of body weight.

2. MORTALITY:

Dose Level mg/kg	# Treated M/F	# Dead M/F
1000	5/5	0/0
2000	5/5	2/2
2500	5/5	1/0

3. BODY WEIGHTS AND DOSE VOLUME:

@ 1000 mg/kg:

Eartag # & Sex	Dose Volume cc	Weights - kg 0	7	14
E4487-M	2.6	2.5	2.7	2.7
E4888-M	2.6	2.5	2.4	2.4
E4489-M	2.6	2.5	2.4	2.5
E4490-M	2.1	2.1	2.1	2.1
E4492-M	2.4	2.4	2.4	2.4
MEAN		2.4	2.4	2.4
S.D.		0.2	0.2	0.2
E4529-F	2.4	2.4	2.4	2.4
E4530-F	2.1	2.1	2.1	2.1
E4531-F	2.0	2.0	2.1	2.1
E4532-F	2.0	2.0	2.1	2.1
E4533-F	2.0	2.0	2.0	1.7
MEAN		2.1	2.1	2.1
S.D.		0.2	0.2	0.2

3. BODY WEIGHTS AND DOSE VOLUME (cont'd):

@ 2000 mg/kg:

Eartag # & Sex	Dose Volume cc	Weights - kg 0	7	14
E4169-M	5.1	2.5		
E4174-M	5.1	2.5	2.1	2.4
E4178-M	5.9	2.9	2.7	2.9
E4179-M	5.1	2.5	2.2	2.5
E4184-M	5.3	2.6	1.8	
MEAN		2.6	2.2	2.6
S.D.		0.2	0.4	0.3
E4219-F	4.5	2.2		
E4224-F	4.9	2.4	2.6	2.8
E4228-F	5.5	2.7		
E4229-F	5.3	2.6	2.5	2.6
E4230-F	4.9	2.4	2.2	2.5
MEAN		2.5	2.4	2.6
S.D.		0.2	0.2	0.2

@ 2500 mg/kg:

E4482-M	6.6	2.6	2.0	2.0
E4491-M	5.9	2.3		
E4494-M	5.6	2.2	1.7	1.7
E4495-M	6.1	2.4	2.1	2.2
E4496-M	6.4	2.5	1.7	2.1
MEAN		2.4	1.9	2.0
S.D.		0.2	0.2	0.2
E4534-F	6.4	2.5	2.3	2.3
E4536-F	5.9	2.3	2.1	2.1
E4537-F	6.4	2.5	2.3	2.2
E4539-F	6.4	2.5	2.3	2.3
E4540-F	6.4	2.5	2.4	2.4
MEAN		2.5	2.3	2.3
S.D.		0.1	0.1	0.1

No entry indicates animal died prior to observation.

3a. DERMAL REACTIONS:

@ 1000 mg/kg:

Eartag # & Sex	1 R	1 E	7 R	7 E	14 R	14 E	% Remaining
E4487-M	1bcd	2	>4m,bcd	2	>4m,bc	2	<10
E4888-M	2abcd	2	>4s,bcd	2	>4s,bcd	2	<10
E4489-M	2abcd	2	>4s,bcd	2	>4s,bcd	2	<10
E4490-M	1abcd	3	>4ms,bcd	2	>4ms,bcd	2	<10
E4492-M	2abcd	3	>4s,bcd	2	>4s,bcd	2	<10
E4529-F	1bcd	2	>4m,bcd	2	>4m,bcd	2	<10
E4530-F	2bcd	2	4bcd	1	4bcdf	1	<10
E4531-F	3abcd	3	>4s,bcd	2	>4s,bcd	2	<10
E4532-F	1bcd	2	>4ms,bcd	2	>4s,bcd	2	<10
E4533-F	2bcda	2	4bcd	1	>4m,bcd	1	<10

@ 2000 mg/kg:

E4169-M	2abcd	3	DEAD DAY 7				10
E4174-M	1abcd	2	>4s,c	1	>4s	1	10
E4178-M	3abcd	2	>4s,abc	2	>4s,abc	1	10
E4179-M	1abcd	2	>4n,abc	2	>4n,abc	1	10
E4161-M	1abcd	3	>4s,abc	1	DEAD DAY 12		10
E4219-F	2abcd	2	DEAD DAY 3				10
E4224-F	2abcd	2	>4s,abc	2	>4n,abc	1	10
E4228-F	3abcd	3	DEAD DAY 2				10
E4229-F	1abcd	2	>4s,abc	1	>4n,abc	1	10
E4230-F	2abcd	3	>4s,abc	2	>4n,abc	1	10

CODE: R = erythema (redness)
E = edema
a = yellow areas
b = brown areas
c = black areas
d = skin feels dry to touch
f = flaking skin
>4ms = moderate to severe eschar
>4s = severe eschar
>4m = moderate eschar
>4n = necrosis
% Remaining = a visual estimate of the amount of material remaining on the skin, gauze and occlusive binding at 24 hours, after the occlusive binding was removed.

3a. DERMAL REACTIONS:

@ 2500 mg/kg:

Eartag # & Sex	1 R	1 E	7 R	7 E	14 R	14 E	% Remaining
E4482-M	4abcd	2	>4n,abcd	2	>4n,abc	2	10
E4491-M	>4m,abcd	3	DEAD DAY 5				10
E4494-M	2abcd	2	>4n,abcd	2	>4n,abc	2	10
E4495-M	2abcd	2	>4ms,bcd	2	>4n,abc	2	10
E4496-M	3abcd	2	>4n,bcd	2	>4n,abc	2	10
E4534-F	4abcd	2	>4n,bcd	2	>4n,abc	2	10
E4536-F	3abcd	3	>4n,abcd	2	>4n,abc	2	10
E4537-F	3abcd	2	>4n,bcd	2	>4n,abc	2	10
E4539-F	2abcd	2	>4n,bcd	2	>4n,abc	2	10
E4540-F	3abcd	3	>4n,bcd	2	>4n,abc	2	10

CODE: R = erythema (redness)
E = edema
a = yellow areas
b = brown areas
c = black areas
d = skin feels dry to touch
>4ms = moderate to severe eschar
>4m = moderate eschar
>4n = necrosis
% Remaining = a visual estimate of the amount of material remaining on the skin, gauze and occlusive binding at 24 hours, after the occlusive binding was removed.

TOXICITY CODE

B = lethargy

D = diarrhea

E = ataxia

M = dyspnea

Q = ptosis

T = soiling of the anogenital area

W = appears emaciated

X = few feces

Y = yellow nasal discharge

Z = dead

1 = lack of mobility due to severe dermal reactions

2 = mucoid diarrhea

3 = red staining in bedding pan

4. TOXICITY:

@ 1000 mg/kg

TIME : PERIOD:	E4487-M	E4488-M	E4489-M	E4490-M	E4492-M	E4529-F	E4530-F	E4531-F	E4532-F	E4533-F
HOUR 1										
HOUR 2										
HOUR 4										
DAY 1			B		D		B	D		
DAY 2			B,D	B,D	B,D		B	B,D	B	B
DAY 3					D		B	B		
DAY 4										
DAY 5										
DAY 6										
DAY 7										
DAY 8										
DAY 9										
DAY 10										
DAY 11										
DAY 12										D
DAY 13										D
DAY 14										D,T

NO ENTRY INDICATES ANIMALS APPEARED NORMAL.

TOXICITY CODE ON PAGE -11-

4. TOXICITY:

@ 2000 mg/kg

TIME : PERIOD:	E4169-M	E4174-M	E4178-M	E4179-M	E4184-M	E4219-F	E4224-F	E4228-F	E4229-F	E4230-F
HOUR 1										
HOUR 2										
HOUR 4										
DAY 1										
DAY 2	*	1	1	1	1	1	1	1,Z	1	1
DAY 3	1	1	1	1	1	Z	1		1	1
DAY 4	1	1	1	1	1		1		1	1
DAY 5	X,1	1	1	1	D,1		1		1	1
DAY 6	X,1	1	1	1	1,2		1		1	1
DAY 7	Z	1	D,1	1	W,B,D,X,1,2		1		1	1
DAY 8		1	D,1	1	W,B,D,X,1		1		1	1
DAY 9		1	D,1	1	W,B,D,X,1		1		1	1
DAY 10		1	D,1	1	W,B,D,X,Y,T, Q,1		1		1	1
DAY 11		1	1	1	W,B,E,D,T,X, Y,Q,M,1		1		1	1
DAY 12		1	1	1	Z		1		1	1
DAY 13		1	1	1			1		1	1
DAY 14		1	1	1			1		1	1

NO ENTRY INDICATES ANIMALS APPEARED NORMAL.

TOXICITY CODE ON PAGE -11-

4. TOXICITY:

@ 2500 mg/kg

TIME : PERIOD:	E4482-M	E4491-M	E4494-M	E4495-M	E4496-M	E4534-F	E4536-F	E4537-F	E4539-F	E4540-F
HOUR 1										
HOUR 2										
HOUR 4										
DAY 1					T					B
DAY 2	1	1	1	1	T,1	1	1	1	1	1
DAY 3	1	1	1	1	D,1	1	D,1	1	B,1	1
DAY 4	1	1	1	1	1	1	X,1	1	B,X,1	1
DAY 5	1	B,E,X,1,Z	X	1	X,Q	1	X,1	1	X,B,1	1
DAY 6	1		X,1	1	D,X,Q,B,1	1	1	1	B,1	1
DAY 7	1		D,X,T,B,Q,1	1	D,X,T,B,Q,1	1	1	1	B,1	1
DAY 8	1		D,X,T,B,Q, W,1	1	D,X,T,B,Q, W,1	1	1	1	B,1	1
DAY 9	1		X,T,B,Q,W,1	1	D,X,T,B,Q, W,1,3	1	1	1	1	1
DAY 10	1		X,T,B,Q,W,1	1	D,X,T,B,Q, W,1	1	1	1	1	1
DAY 11	1		X,T,B,Q,W, Y,1	1	D,X,T,B,Q, W,Y,1	1	1	1	1	1
DAY 12	1		B,D,T,X,W, Y,1	1	D,T,B,W,X, Q,1	1	1	1	1	1
DAY 13	1		D,X,B,T,W, Y,1	1	D,T,B,W,1	1	1	1	1	D,1
DAY 14	1		D,X,B,T,W, Y,1	1	D,T,B,W,1	1	1	1	1	1

NO ENTRY INDICATES ANIMALS APPEARED NORMAL.

TOXICITY CODE ON PAGE -11-

5. NECROPSY OBSERVATIONS:

@ 1000 mg/kg

	E4487-M S	E4488-M S	E4489-M S	E4490-M S	E4492-M S	E4529-F S	E4530-F S	E4531-F S	E4532-F S	E4533-F S
TREATED SKIN ABNORMALITIES**	X	X	X	X	X	X	X	X	X	X
DOSE SITE:										
damage extending to underlying musculature	X	X	X	X	X	X	X	X	X	X
ANOGENITAL AREA:										
soiled										3

CODE: S = sacrifice
X = observed
3 = pronounced or many
** = see page -9- for day 14 dermal reactions

5. NECROPSY OBSERVATIONS:

@ 2000 mg/kg

	E4169-M D	E4174-M S	E4178-M S	E4179-M S	E4184-M D	E4219-F D	E4224-F S	E4228-F D	E4229-F S	E4230-F S
TREATED SKIN ABNORMALITIES**	X	X	X	X		X	X	X	X	X
DOSE SITE:										
damage extending to underlying musculature		X	X	X			X		X	X
ANOGENITAL AREA:										
soiled					3					
EMACIATION:	3									
NOSE/MOUTH:										
stained yellow					2					
GALL BLADDER:										
larger than normal					2					
INTESTINES:										
distended with fluid					2					
pale	3				1					
SPLEEN:										
pale	3									
LIVER:										
pale margins on right lateral lobe								2		
pale	3									
pale margins						2				
KIDNEY:										
dark areas					2			2		
both, pale	2									
red areas	2									
SPLEEN:										
smaller than normal	3									

CODE: D = death S = sacrifice 1 = slight or scattered 2 = moderate or few 3 = pronounced or many X = observed

** = see page -9- for day 14 for dermal reactions

5. NECROPSY OBSERVATIONS:

@ 2500 mg/kg

	E4482-M	E4491-M	E4494-M	E4495-M	E4496-M	E4534-F	E4536-F	E4537-F	E4539-F	E4540-F
	S	D	S	S	S	S	S	S	S	S
TREATED SKIN ABNORMALITIES**	X	X	X	X	X	X	X	X	X	X
DOSE SITE:										
damage extending to underlying musculature	X	X	X	X	X	X	X	X	X	X
ANOGENITAL AREA:										
soiled					2					
EMACIATION		1	3		2					
INTESTINES:										
pale		2	2							
KIDNEYS:										
pale		2	2		1					
dark areas					2					
LIVER:										
pale margins		2								

CODE: D = death
S = sacrifice
1 = slight or scattered
2 = moderate or few
3 = pronounced or many

DRAIZE DERMAL SCORING CODE[1]

ERYTHEMA AND ESCHAR FORMATION:

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

EDEMA FORMATION:

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

[1]Draize, H. H. et al., J. Pharm. Exp. Ther. 82:377-390, 1944