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89-890000159

ATTN: 8(e) Coordinator

Dear Sir or Madam:

With regard to:

TSCA Section 8(e) Submission on: Organofunctional Silane A-1100
Submitted by: Union Carbide Corporation
Submission Date: March 24, 1989

As a follow-up to the above-noted submission by Union Carbide Corporation, the following report is attached:

"Silane A-1100: Acute Toxicity and Primary Irritancy Studies", Bushy Run Research Center, Project Report 52-43, April 18, 1989.

In the attached report the term "BUSINESS CONFIDENTIAL" is entered on the first page. This precautionary statement was for internal use at the time of issuance of the report. It is hereby waived for purposes of the needs of the Agency in assessing health and safety information. You are advised, however, that the publication rights to the contained information are the property of Union Carbide Corporation.

Please communicate through my office (203/794-5230) if there are any questions concerning this report.

Very truly yours,

William C. Kuryla
Assistant Director
Product Safety

WCK/ama
Attachment

2154Y



BUSHY RUN RESEARCH CENTER

R.D. 4, Mellon Road, Export, Pennsylvania 15632

Telephone (412) 733-5200
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PROJECT REPORT 52-43

TITLE: Silane A-1100
Acute Toxicity and Primary Irritancy Studies

AUTHORS: R. C. Myers
S. M. Christopher

SPONSOR: W. F. Gorham
Specialty Chemicals Division
Union Carbide Corporation

DATE: April 18, 1989



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Project Report 52-43
BRRC Number 88-15-11008
18 Pages
April 18, 1989

Silane A-1100

Acute Toxicity and Primary Irritancy Studies

Sponsor: Specialty Chemicals Division
Union Carbide Corporation

* * * * *

SUMMARY

Peroral, Rat (Fasted)

Males: LD50 = 2.83 ml/kg; sample dosed as received.
Females: LD50 = 1.57 ml/kg; sample dosed as received.
Significant kidney pathology observed.

Percutaneous, Rabbit

Males: LD50 = 4.29 ml/kg; sample dosed as received.
Females: LD50 = 4.29 ml/kg; sample dosed as received.
Significant kidney pathology observed.

Inhalation, Rat; Substantially Saturated Vapor (Static)

Males: 6.0 hours killed 0 of 5 (signs noted).
Females: 6.0 hours killed 0 of 5 (signs noted).

Skin Irritation, Rabbit (4-hr occluded)

Minor to moderate erythema on 6 of 6 rabbits, minor to severe edema on 6, necrosis on 4, ecchymosis on one, ulceration on one, fissuring on 4, desquamation on 6, alopecia on 6 from 0.5 ml; irritation (especially desquamation and alopecia) persisted through 14 days.

Corrosive by D.O.T. definition.

Eye Irritation, Rabbit

Severe corneal injury in all 6 eyes (including irregularly-shaped corneas and/or vascularization), iritis in 6, severe conjunctival irritation (with necrosis) and a pus-like ocular discharge in 6 from 0.1 ml; severe irritation persisted through 7 days. Minor to severe corneal injury in 6 of 6 eyes (with irregularly-shaped corneas and vascularization in 3), iritis in 6, severe conjunctival irritation (with necrosis) in 6 with a purulent ocular discharge in 5 from 0.005 ml; one dead at 20 days from unknown causes; 3 healed at 21 days.

INTERPRETATION

Silane A-1100 was moderately toxic following its administration by single peroral intubation and following single cutaneous application. A single static inhalation exposure to substantially saturated vapor produced no deaths but signs of inhalation toxicity included hypoactivity, coordination loss and loss of righting reflexes. A 4-hour application to covered rabbit skin resulted in moderate to severe irritation. Instillation of 0.1 ml and 0.005 ml of sample into rabbit eyes produced severe irritation.

Because of clinical signs seen in animals following the cutaneous toxicity study (blood in the urogenital/rectal areas), suspected target tissues were identified and subjected to microscopic examination. A notable finding was the occurrence of acute tubular necrosis in the kidney cortex from both the peroral (rat) and percutaneous (rabbit) tests.

SAMPLE

Quantity: One quart

Submitted By: J. J. Behen/
C. R. Thrash

Date Received: August 22, 1988

Division: Specialty Chemicals
Tarrytown, NY

Identification: Lot #0123CC073088;
UCC 3209F

UCC Charge No.: 500-566-496500

Description: Clear, non-viscous
liquid.

BPRC Sample No.: 51-366

Approximately 20 ml of the remaining sample will be retained for at least 2 years following issuance of this report.

Post-testing analysis confirmed the presence of A-1100 at a concentration of 96.1%, ethanol at 2.7% and the two-silicon siloxane at 1.1%. See Appendix 1 for detailed analysis.

PROCEDURES

Descriptions of the test procedures are included in the attached standard test procedures section (Appendix 2). The sample was dosed as received for all tests.

RESULTS

Results of the peroral, percutaneous, inhalation and skin irritation tests are given in Tables 1 through 4, respectively. Eye test results are presented in Tables 5 and 6 with a summary appearing in Table 7.

The LD50 for male rats receiving peroral doses of Silane A-1100 was 2.83 ml/kg; that for females was 1.57 ml/kg. Signs of toxicity included sluggishness, lacrimation, kyphosis, an unkempt appearance, piloerection (in one), yellow stains on the periurogenital fur (positive for blood by HEMASTIX®), red crust on the perinasal and/or periorcular fur, brown stain on the periurogenital fur, closed eye lids in one, emaciation (in one) and diarrhea. Deaths occurred at one to 4 days. Survivors recovered at 2 to 9 days. Necropsy of victims revealed dark red or mottled lungs, dark red or white stomachs (glandular portion), yellow intestines, stomachs and intestines filled with gas and/or yellow to brown liquid, discolored kidneys (dark red, brown or mottled) and one mottled dark red spleen. There were no remarkable gross lesions evident in survivors.

The kidneys and urinary bladders from 2 to 3 rats (males and/or females) at dosages of 4.0 and 2.0 ml/kg were saved and examined histologically. Detailed results appear in Appendix 3 (Pathology Report) and Appendix 4 ("Summary of Renal Effects"). Acute tubular necrosis (involving the cortical tubules) and mineralization of the tubular epithelium were evident for males at 4.0 ml/kg and for females at 2.0 ml/kg. Hyperplasia involving the renal tubular epithelium was apparent in one of the 2 males examined at 2.0 ml/kg. Only one rat (a male at 4.0 ml/kg) had a significant lesion in the urinary bladder - a focal area of epithelial necrosis.

By the percutaneous route, the LD50 for male and for female rabbits was 4.29 ml/kg. Local cutaneous effects included erythema, edema, ecchymoses, necrosis, desquamation, fissuring, ulceration, alopecia and scabs. Blood in the rectal and urogenital areas (verified by a BRRC pathologist) was apparent in several animals (especially at a dosage of 4.0 ml/kg). For the affected animals, blood was apparent around the anus, on the feet and under the animals cages. Hemorrhaging was also evident under the skin of animals at a dosage of 4.0 ml/kg. Some animals also had blood clots and mucous around the rectal area or on the animal cage board. Other signs of toxicity included sluggishness, salivation (in one), an unsteady gait (in 2), prostration and diarrhea (in one). Time to death ranged from one to 3 days. Survivors recovered at 2 to 4 days. Gross pathologic findings included discolored lungs (red, pink or mottled), lungs of one with dark red foci, mottled tan livers, stomachs with thick white mucous, stomachs with dark areas or hemorrhages, one stomach with black foci, tan or hemorrhaged kidneys, ureters and urethra with hemorrhages (in one), bladders filled with red liquid (one with a dark red clot) and the untreated skin of 2 stained dark red.

The kidneys, bladders and treated skin from rabbits receiving various cutaneous doses (8.0, 4.0, 2.0 and 1.0 ml/kg) of Silane A-1100 were saved and subjected to detailed histological examination. The Pathology Report (Appendix 5) and the "Summary of Renal Effects" (Appendix 6) give the detailed results. Male and female animals from the higher dosage groups (8.0 and 4.0 ml/kg) had marked acute tubular nephrosis with involvement of the convoluted tubules of the cortex. These animals also exhibited mild to moderate tubular proteinosis (also involving the cortical tubules) and interstitial nephritis. The treated skin for animals that died at the higher two dosages was acutely necrotic.

Animals surviving the 14 day period for dosages of 4.0, 2.0 and 1.0 ml/kg had little renal change. However, marked changes in the treated skin were noted, including necrosis, hyperplasia and inflammation with instances of eschar formation, acanthosis, dermatitis, dermal fibrosis and adnexal necrosis.

Histologic examination of the stomachs of a few animals revealed instances of necrosis and dissociation of gastric mucosal epithelial cells.

Exposure to a statically-generated, substantially saturated vapor produced no deaths of male or female rats during or following the 6-hr test. Hypoactivity, ataxia and a negative air righting reflex were evident during or following exposure. Animals recovered after one day. Necropsy revealed no remarkable gross lesions.

A 4-hour application of 0.5 ml of Silane A-1100 to occluded rabbit skin resulted in minor to moderate erythema on 6 of 6 rabbits and minor to severe edema on 6. After 5 hours (one hour after the contact period), ecchymosis was apparent on one animal. Necrosis was observed on 3 animals by one day and on another animal by 7 days. All 6 animals exhibited desquamation and 4 rabbits had fissuring within 7 days. There was no erythema or edema evident on any animal at 10 days. At this time ulceration was evident on one animal and alopecia was observed on most. Desquamation, alopecia and ulceration (on one) persisted through 14 days. This material is corrosive to the skin by Department of Transportation (D.O.T.) definition.

Instillation of 0.1 ml of sample into rabbit eyes resulted in severe corneal injury, iritis and severe conjunctival irritation. Within one hour each rabbit developed necrosis of the conjunctivae. By 48 hours, 6 of 6 animals had a purulent ocular discharge. All rabbits exhibited irregularly-shaped corneas (characterized by surface bulges) and 4 animals had corneal vascularization by 7 days. Because of the severe, possibly-irreversible irritation noted on each rabbit at 7 days, all rabbits were sacrificed for humane reasons at the request of the study director.

Following the instillation of 0.005 ml of sample into rabbit eyes, minor to severe corneal injury developed in 6 of 6 rabbits. All rabbits had necrosis of the conjunctivae within one hour. By 48 hours, 5 animals developed a purulent ocular discharge. Three rabbits had an irregularly-shaped cornea and vascularization within 7 days. Two animals had a normal appearance by 7 days. One of the animals died at 20 days. There was no evidence that this death was related to the treatment. A total of 3 of the remaining 5 eyes were completely healed by 21 days. The other eyes still exhibited substantial injury.

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Reviewed and Approved by:

Roy C. Myers 4-17-89
Roy C. Myers, B.S., DABT Date
Study Director

Darol E. Dodd 4/17/89
Darol E. Dodd, Ph.D., DABT Date
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Acknowledgments:

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Master Technologist

WPC/kam/1632K-1
03-29-89

Table 1

Peroral Intubation, Single Dose to Rats

Material: Silane A-1100

Sample No.: 51-366

Dosage, Dead/ Dosed Days to Death Mean Weight, $\bar{x} \pm S.D.$
ml/kg 0 Days 7 Days 14 Days

Signs of Toxicity

Gross Pathology*

Male Rats

4.00	4/5	1,2,2,2	244± 32.0	254	283	Sluggishness (marked in 2 animals), kyphosis, diarrhea, red crust on peri-nasal fur at 1 day; lacrimation in 2, piloerection in 1 at 1 day; brown stain on perigenital fur of 1 at 2 days. Survivor recovered at 3 days.	In victims, lungs of 2 mottled dark red; stomachs dark red (glandular portions); stomach of 1 filled with yellow liquid; intestines of 2 distended, filled with yellow to brown liquid; spleen of 1 mottled dark red. In survivor, nothing remarkable.
2.00	1/5	2	234± 12.3	251± 54.8	302± 34.2	Marked sluggishness in 1 at 1 day; unkempt appearance, red crust on peri-nasal and periorcular fur, diarrhea at 1 day; eyelids of 1 closed at 1 day; brown stain on perigenital fur at 2 days; emaciation of 1 at 7 days. Survivors recovered at 5 to 9 days.	In victim, lungs bright red; stomach mottled dark red (glandular portion) and filled with light brown liquid. In survivors, nothing remarkable.
1.00	0/5	-	238± 24.0	278± 173	304± 18.7	None noted.	Nothing remarkable.

(Continued)



Table 1 (Continued)

Peroral Intubation, Single Dose to Rats

Material: Silane A-1100

Sample No.: 51-366

Dosage, ml/kg	Dead/ Dosed	Days to Death	Mean Weight, $\bar{x} \pm$ S.D.			Signs of Toxicity	Gross Pathology ^a
			0 Days	7 Days	14 Days		
2.00	5/5	2,3,3,3,4	223± 6.6	-	-	Sluggishness (marked in 2 animals), unkempt appearance, red crust on periorbicular and perinasal fur, diarrhea at 1 day; lacrimation in 2 at 1 day.	Lungs bright pink; stomachs of 2 dark red or mottled (glandular portion); stomachs, intestines filled with light brown liquid; intestines of 1 yellow; kidneys dark red.
1.41	1/5	1	212± 11.2	227± 9.4	234± 6.8	Sluggishness in 2 at 4.0 hr to 1 day; brown stain on periorbicular fur, red crust on perinasal fur at 1 day; urine status on periorbicular fur (positive for blood by HEMASTIX®). Survivors recovered at 2 days.	In victim, lungs dark red; stomach white to dark red (glandular portion); intestines yellow, filled with yellow liquid. Nothing remarkable in survivors.
1.00	0/5	-	211± 9.3	231± 10.5	241± 17.0	Sluggishness in 1 at 1 day. Recovery at 2 days.	Nothing remarkable.

LD50s with 95% Confidence Limits:

Males: 2.83 (1.61 to 4.98) ml/kg; sample dosed as received.
Females: 1.57 (1.34 to 1.85) ml/kg; sample dosed as received.

LD50 Slopes:

Males: 3.89
Females: 11.2

^aSeveral kidneys and bladders were also saved and processed for microscopic evaluation. See text for results.

Table 2

Cutaneous Application, Single Dose to Rabbits

Material: Silane A-1100

Sample No.: 51-366

Dosage, Dead/ Dosed Days to Death* 0 Days 7 Days 14 Days Mean Weight, g ± S.D. Skin Irritation Signs of Toxicity Gross Pathology

Male Rabbits

8.0	5/5	1,1,1,2,2	2405± 134	-	-	Erythema, edema, necrosis, ecchymosis at 1 day.	Sluggishness in 1 at 1 day; prostration in 1 at 1 day; substantial hemorrhaging around the urogenital area (of 1) or rectal area (of 2)** at 1 day; red periturogenital wetness on 1 at death; salivation in 1 at death.	Lungs of 2 bright red and/or mottled; livers mottled tan; stomachs of 2 with thick white mucous; stomach of 1 hemorrhaged; kidneys of 2 tan; kidney of 1 hemorrhaged; urinary bladder of 2 red liquid-filled.
4.0	2/5	2,3	2562± 158	2213± 144	2382± 150	Erythema at 1 day persisting on 2 at 14 days; edema at 1 to 7 days or death; ecchymosis at 1 day; necrosis at 1 to 14 days or death; fissuring at 7 days; desquamation, scabs, ulcerations at 7 to 14 days; alopecia at 14 days.	In victims, sluggishness and unsteady gait at 1 day; mucous around rectal area of 1 at 1 day; mucous and blood clots under cage of 1 at 2 days. In survivors, sluggishness at 1 day; substantial hemorrhaging** around the rectal area of 2 at 1 day; blood clots under cage of 2 at 2 days. Survivors recovered at 2 to 3 days.	In victims, lungs of 1 dark red; stomach of 1 with dark areas; stomach of 1 with black foci; kidneys of 1 hemorrhaged; bladder of 1 with a dark red clot; liver of 1 mottled tan. In survivors, lungs with dark red foci or mottling.

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Date

(Continued)

Table 2 (Continued)

Cutaneous Application, Single Dose to Rabbits

Material: Silane A-110u

Sample No.: 51-366

Dosage, Dead/ Dosed Days to Death* Mean Weight, g ± S.D. 0 Days 7 Days 14 Days Skin Irritation Signs of Toxicity Gross Pathology

Male Rabbits

2.0	0/5 -	2660± 195	2597± 195	2774± 158	Ecchymosis at 1 day; erythema, necrosis at 1 to 14 days; edema at 1 to 7 days; fissuring at 7 days, persisting on 1 at 14 days; desquamation, scabs, alopecia at 7 to 14 days; ulceration at 14 days.	Substantial hemorrhag- ing** around rectal area of 1 at 1 day. Recovery at 4 days.	Lungs of 2 dark red or pink.
1.0	0/5 -	2480± 152	2575± 94	2808± 121	Ecchymosis at 1 day; edema at 1 to 7 days; erythema at 1 day, persisting on 2 at 14 days; necrosis at 1 to 14 days; fissuring on 2 at 7 days; desquama- tion at 7 to 14 days; ulcerations on 2 at 14 days; alopecia at 7 to 14 days; scabs at 14 days.	Substantial hemorrhag- ing** around rectal area of 1 at 1 day. Recovery at 2 days.	Nothing remarkable.

Female Rabbits

8.0	5/5 2,2,2,2,2	2416± 73	-	-	Erythema, edema, necrosis, ecchymosis at 1 day to death.	Sluggishness at 1 day; prostration in 2, unsteady gait in 1 at 1 day; clear discharge on perinatal fur of 1 at 2 days.	Lungs mottled red and/or pink; livers of 2 mottled tan; stomachs with thick white mucous; kidneys of 1 tan.
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(Continued)

Table 2. (Continued)

Cutaneous Application, Single Dose to Rabbits

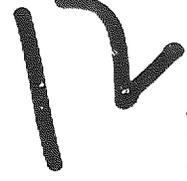
Material: Silane A-1100

Sample No.: 51-366

Dosage, Dead/ Days to Mean Weight, g ± S.D. ml/kg. Dosed Death* 0 Days 7 Days 14 Days Skin Irritation Signs of Toxicity Gross Pathology

Female Rabbits

4.0	2/5	2,3	2804± 138	2269± 306	2587± 211	Erythema, ecchymosis at 1 day; edema at 1 day persisting on 2 at 7 days; necrosis at 1 to 14 days or death; desquamation, ulcerations at 7 to 14 days; fisting on 2 at 7 days; scabs, alopecia at 14 days.	In victims, sluggishness and substantial hemorrhaging** around rectal and vaginal area at 1 day; unsteady gait and diarrhea (in 1) at 2 days. In survivors, sluggishness and substantial hemorrhaging** around rectal area at 1 day; free blood and blood clots under cage at 2 days; emaciation of 1 at 7 days. Recovery of 2 survivors at 3 days.	In victims, lungs of 1 bright red; stomach of 1 with small round areas adhered to walls; kidneys hemorrhaged; urinary bladders of 2 filled with red liquid; ureters, urethra of 1 hemorrhaged. In survivors, lungs dark red or mottled.
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2.0	0/5	-	2388± 192	2390± 313	2565± 327	Erythema, ecchymosis at 1 day; edema at 1 to 7 days; necrosis at 1 to 14 days; desquamation, fissuring at 7 to 14 days; scabs, alopecia at 14 days; ulceration on 1 at 14 days.	Substantial hemorrhaging** from the rectal area of 2 at 1 day; sluggishness in 1 at 1 day; blood under cage of 1 at 7 days. Recovery of 1 at 4 days.	Nothing remarkable.
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(Continued)

Table 2 (Continued)

Cutaneous Application, Single Dose to Rabbits

Material: Silane A-1100

Sample No.: 51-366

Dosage, Dead/ Dosed Days to Death* Mean Weight, g ± S.D. 14 Days Skin Irritation Signs of Toxicity Gross Pathology

Female Rabbits

Dosage, ml/kg	Dead/ Dosed	Days to Death*	Mean Weight, g ± S.D.	14 Days	Skin Irritation	Signs of Toxicity	Gross Pathology
1.0	0/5	-	2515± 222	2603± 235	2806± 280	Ecchymosis at 1 day; erythema at 1 day, persisting on 2 at 14 days; edema at 1 to 7 days; necrosis at 1 to 14 days; fissuring on 2 at 7 to 14 days; desquamation, scabs, alopecia at 14 days; ulcerations on 1 at 14 days.	Diarrhea in 1 at 1 day. Recovery at 2 days. Nothing remarkable.

LD50s with 95% Confidence Limits:

Males: 4.29 (2.90 to 6.34) ml/kg; sample dosed as received.

Females: 4.29 (2.90 to 6.34) ml/kg; sample dosed as received.

LD50 Slopes:

Males: 4.96

Females: 4.96

*Days to death expressed as days after the beginning of the contact period.

**A substantial amount of free blood was found around the anus, on the feet and under the cage. Kidneys and urinary bladders were saved for pathologic examination. See text for results.

WPC/kam/1632K-1

01-04-89

Table 3

Inhalation of Substantially Saturated Vapor, Single Exposure to Rats; Static Conditions at 25°C

Material: Silane A-1100*

Sample No.: 51-366

Dead/ Days to Mean Weight, g ± S.D.
Dosed Death 0 Days 7 Days 14 Days Signs of Toxicity Gross Pathology

Male Rats

6.0 hr	0/5	-	265± 7.4	285± 10.9	305± 12.5	Hypoactivity within 3 hr; ataxia within 3.5 hr; negative air righting reflex upon removal. Recovery after 1 day.	Nothing remarkable.
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Female Rats

6.0 hr	0/5	-	238± 10.9	238± 13.8	243± 14.1	Hypoactivity within 3 hr; ataxia within 3.5 hr; negative air righting reflex upon removal. Recovery after 1 day.	Nothing remarkable.
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LT50's:

Males: 6.0 hours of exposure killed 0 of 5.
Females: 6.0 hours of exposure killed 0 of 5.

*Sample changed overnight from a clear liquid to a milky white liquid with a white plastic-like surface coating.

WPC/kam/1632K-1
01-05-88

14

Table 4

Primary Skin Irritation - Rabbit

Material: Silane A-1100 Sample No.: 51-366 Conditions: 0.5 ml dosed

| Date: 09-19-88 |
|------------------------|------------------------|------------------------|------------------------|------------------------|
| Rabbit No:
88-23677 | Rabbit No:
88-23682 | Rabbit No:
88-23683 | Rabbit No:
88-23694 | Rabbit No:
88-23704 |
| Sex: Male | Sex: Male | Sex: Male | Sex: Female | Sex: Female |
| | | | | Rabbit No:
88-23705 |
| | | | | Sex: Female |

Erythema & Eschar Formation

Time (After Initiation of Contact):	Score	Mean Score						
5 hours	3	2	2	1	1	1	3	2.0
1 day	2	2	1	1	1	1	2	1.5
2 days	2	2	1	1	1	1	2	1.5
3 days	2	2	1	1	1	1	2	1.5
7 days	0	0	0	0	0	0	0	0.0
10 days	0	0	0	0	0	0	0	0.0
14 days	0	0	0	0	0	0	0	0.0

Edema Formation

Time:	Score	Mean Score						
5 hours	4	4	2	1	2	2	3	2.7
1 day	2	2	1	1	1	1	2	1.5
2 days	2	2	1	1	1	1	2	1.5
3 days	2	2	1	1	1	1	2	1.5
7 days	1	0	0	0	0	0	1	0.3
10 days	0	0	0	0	0	0	0	0.0
14 days	0	0	0	0	0	0	0	0.0

Other Irritation or Effects

Time:	Effect	Effect	Effect	Effect	Effect	Effect	Effect
5 hours	N	EC	None	None	None	N	N
1 day	N	N	None	None	None	N	N
2 days	N	N	None	None	None	N	N
3 days	N	N	D	D	D	N	N
7 days	N,D,S	D,AL	D,F	D,F	N,D,F	N,D,F	N,D,F
10 days	N,D,AL,U	D,AL	D,AL	D,AL	N,D,F	N,D,AL,F	N,D,AL,F
14 days	D,AL,U	D,AL	D,AL	D,AL	D,AL	D,AL	D,AL

Specific Effects/Remarks: AL = alopecia; D = desquamation; N = necrosis; S = scab formation; F = fissuring; U = ulceration

Table 5

Primary Eye Irritation-Rabbit

Material: Silane A-1100 Sample No.: 51-366 Amount: 0.1 ml

Rabbit No:	88-23889	88-23890	88-23896	88-22218	88-22219	88-22220	
Sex/Eye Dosed	Male/R	Male/L	Male/R	Female/L	Female/R	Female/L	
Date Dosed	09-20-88	09-20-88	09-20-88	09-20-88	09-20-88	09-20-88	
Scores/Effects at 1 hr							Mean
Cornea: Opacity	1	4	3	2	2	4	2.7
Area	4	3	2	4	4	3	3.3
Iris: Inflamm.	1	*	1	1	1	1	*
Conjunct: Redness	2	2	2	2	2	2	2.0
Chemosis	1	1	2	2	2	2	1.7
Discharge	3	3	3	3	3	3	3.0

Other Effects/Remarks: Necrosis of the conjunctivae and/or nictitating membrane.

Scores/Effects at 4 hr							Mean
Cornea: Opacity	2	4	3	2	2	4	2.8
Area	2	3	2	2	4	3	2.7
Iris: Inflamm.	1	*	1	1	1	1	*
Conjunct: Redness	2	2	2	2	2	2	2.0
Chemosis	2	2	2	2	2	2	2.0
Discharge	3	3	3	3	3	3	3.0

Other Effects/Remarks: Necrosis of the conjunctivae and/or nictitating membrane.

Scores/Effects at 24 hr							Mean
Cornea: Opacity	2	4	3	2	2	2	2.5
Area	2	2	2	2	3	2	2.2
Iris: Inflamm.	1	1	1	1	1	1	1.0
Conjunct: Redness	2	2	2	3	2	2	2.2
Chemosis	1	2	2	1	2	2	1.7
Discharge	3	3	3	3	3	3	3.0
Fluorescein Exam.	100%	100%	100%	100%	100%	100%	100%

Other Effects/Remarks: Necrosis of the conjunctivae and/or nictitating membrane; Rabbits 23890, 22219 and 22220 with a pus-like ocular discharge.

Scores/Effects at 48 hr							Mean
Cornea: Opacity	2	4	3	2	4	2	2.8
Area	2	2	2	2	3	2	2.2
Iris: Inflamm.	1	1	1	1	1	1	1.0
Conjunct: Redness	2	2	2	2	3	3	2.3
Chemosis	1	1	2	1	2	2	1.5
Discharge	3	3	3	2	3	3	2.8
Fluorescein Exam.	90%	95%	50%	90%	60%	95%	80%

Other Effects/Remarks: Necrosis of the conjunctivae and nictitating membrane; pus-like ocular discharge.

(Continued)

Table 5 (Continued)

Primary Eye Irritation-Rabbit

Material: Silane A-1100 Sample No.: 51-366 Amount: 0.1 ml

Rabbit No:	88-23889	88-23890	88-23896	88-22218	88-22219	88-22220	
Sex/Eye Dosed	Male/R	Male/L	Male/R	Female/L	Female/R	Female/L	
Date Dosed	09-20-88	09-20-88	09-20-88	09-20-88	09-20-88	09-20-88	
Scores/Effects at 72 hr							Mean
Cornea: Opacity	3	4	3	2	4	2	3.0
Area	2	3	2	3	3	2	2.5
Iris: Inflamm.	1	1	1	1	*	1	*
Conjunct: Redness	2	3	2	2	3	2	2.3
Chemosis	1	2	2	1	2	2	1.7
Discharge	2	3	3	2	3	3	2.7
Fluorescein Exam.	40%	50%	40%	80%	10%	20%	40%

Other Effects/Remarks: Necrosis of the conjunctivae and nictitating membrane.

Scores/Effects at 7 days							Mean
Cornea: Opacity	4	4	4	4	4	2	3.7
Area	4	4	4	4	4	2	3.7
Iris: Inflamm.	*	*	*	*	*	0	*
Conjunct: Redness	1	2	1	2	2	1	1.5
Chemosis	1	1	1	1	2	1	1.2
Discharge	1	2	1	2	3	1	1.7
Fluorescein Exam.	10%	50%	20%	0%	10%	0%	15%

Other Effects/Remarks: Necrosis of the conjunctivae and nictitating membrane; an irregularly-shaped cornea; Rabbits 23890, 23896, 22218 and 22220 with corneal vascularization. Each rabbit was euthanized at 7 days for humane reasons.

*Scoring impossible because of corneal opacity or an irregular corneal shape.

Table 6

Primary Eye Irritation-Rabbit

Material: Silane A-1100 Sample No.: 51-366 Amount: 0.005 ml

Rabbit No:	88-23867	88-23868	88-23897	88-23898	88-23900	88-23903	
Sex/Eye Dosed	Male/R	Male/L	Female/R	Female/L	Female/R	Female/L	
Date Dosed	09-27-88	09-27-88	09-27-88	09-27-88	09-27-88	09-27-88	
Scores/Effects at 1 hr							Mean
Cornea: Opacity	2	2	2	1	2	1	1.7
Area	3	2	2	2	2	2	2.2
Iris: Inflamm.	1	1	1	1	1	1	1.0
Conjunct: Redness	2	2	2	2	2	2	2.0
Chemosis	1	1	1	1	2	2	1.3
Discharge	2	3	2	3	3	3	2.7

Other Effects/Remarks: Necrosis of the conjunctivae and nictitating membrane.

Scores/Effects at 4 hr							Mean
Cornea: Opacity	2	2	2	1	2	1	1.7
Area	3	2	2	1	2	2	2.0
Iris: Inflamm.	1	1	1	1	1	1	1.0
Conjunct: Redness	2	2	2	2	2	2	2.0
Chemosis	1	1	1	1	2	2	1.3
Discharge	2	3	3	3	3	3	2.8

Other Effects/Remarks: Necrosis of the conjunctivae and nictitating membrane.

Scores/Effects at 24 hr							Mean
Cornea: Opacity	2	2	1	1	2	1	1.5
Area	3	1	2	1	2	3	2.0
Iris: Inflamm.	1	1	1	1	1	1	1.0
Conjunct: Redness	2	2	2	2	2	2	2.0
Chemosis	1	1	1	1	1	1	1.0
Discharge	2	2	3	2	3	2	2.3
Fluorescein Exam.	100%	100%	95%	85%	100%	95%	96%

Other Effects/Remarks: Necrosis of the conjunctivae and nictitating membrane; Rabbits 23897 and 23900 with a pus-like ocular discharge.

Scores/Effects at 48 hr							Mean
Cornea: Opacity	2	1	2	1	2	1	1.5
Area	3	2	2	1	3	2	2.2
Iris: Inflamm.	1	1	1	1	1	1	1.0
Conjunct: Redness	2	2	2	2	2	2	2.0
Chemosis	1	1	1	1	1	1	1.0
Discharge	2	1	3	2	2	2	2.0
Fluorescein Exam.	95%	40%	40%	50%	60%	80%	61%

Other Effects/Remarks: Necrosis of the conjunctivae and nictitating membrane; Rabbits 23867, 23868, 23900, 23898 and 23897 with a pus-like ocular discharge.

(Continued)

Table 6 (Continued)

Primary Eye Irritation-Rabbit

Material: Silane A-1100 Sample No.: 51-366 Amount: 0.005 ml

Rabbit No:	88-23867	88-23868	88-23897	88-23898	88-23900	88-23903	
Sex/Eye Dosed	Male/R	Male/L	Female/R	Female/L	Female/R	Female/L	
Date Dosed	09-27-88	09-27-88	09-27-88	09-27-88	09-27-88	09-27-88	
Scores/Effects at 72 hr							Mean
Cornea: Opacity	2	1	0	0	2	1	1.0
Area	4	2	0	0	3	2	1.8
Iris: Inflamm.	1	1	1	1	1	1	1.0
Conjunct: Redness	2	1	2	1	2	1	1.5
Chemosis	1	0	1	0	1	1	0.7
Discharge	1	1	2	1	1	1	1.2
Fluorescein Exam.	20%	0%	10%	5%	15%	40%	15%

Other Effects/Remarks: Rabbits 23897, 23898 and 23900 with necrosis of the conjunctivae and nictitating membrane and with a pus-like ocular discharge.

Scores/Effects at 7 days							Mean
Cornea: Opacity	3	0	0	0	3	1	1.2
Area	4	0	0	0	4	2	1.7
Iris: Inflamm.	1	0	0	0	1	1	0.5
Conjunct: Redness	1	0	1	0	1	1	0.7
Chemosis	0	0	0	0	0	0	0.0
Discharge	1	0	1	0	1	1	0.7
Fluorescein Exam.	5%	0%	0%	0%	0%	5%	2%

Other Effects/Remarks: Rabbits 23867, 23900 and 23903 with necrosis of the conjunctivae and nictitating membrane, corneal vascularization and an irregularly-shaped cornea.

Scores/Effects at 14 days							Mean
Cornea: Opacity	*	0	0	0	2	0	*
Area	*	0	0	0	2	0	*
Iris: Inflamm.	*	0	0	0	0	0	*
Conjunct: Redness	0	0	0	0	0	0	0.0
Chemosis	0	0	0	0	0	0	0.0
Discharge	0	0	0	0	0	0	0.0
Fluorescein Exam.	0%	0%	0%	0%	0%	0%	-

Other Effects/Remarks: Rabbits 23867 and 23900 with corneal vascularization and an irregularly-shaped cornea.

Scores/Effects at 21 days							Mean
Cornea: Opacity	2	-	0	0	1	0	0.6
Area	2	-	0	0	1	0	0.6
Iris: Inflamm.	0	-	0	0	0	0	0.0
Conjunct: Redness	0	-	0	0	0	0	0.0
Chemosis	0	-	0	0	0	0	0.0
Discharge	0	-	0	0	0	0	0.0
Fluorescein Exam.	0%	-	0%	0%	0%	0%	0%

Other Effects/Remarks: Rabbits 23867 with corneal vascularization; Rabbits 23868 found dead at 20 days (death probably not dose-related).

*Scoring impossible because of vascularization or an irregular corneal shape.

Table 7

Summary of Eye Scores

Material: Silane A-1100

Sample No: 51-366

OBSERVATION	OBSERVATION TIMES							
	1 Hr	4 Hr	24 Hr	48 Hr	72 Hr	7 Days	14 Days	21 Days
CORNEA								
Opacity:	1 to 4	2 to 4	2 to 4	2 to 4	2 to 4	2 to 4	2 to 4	2 to 4
Mean	2.7	2.8	2.5	2.8	3.0	3.0	3.7	3.7
Area:	2 to 4	2 to 4	2 to 3	2 to 3	2 to 3	2 to 3	2 to 4	2 to 4
Mean	3.3	2.7	2.2	2.2	2.5	2.5	3.7	3.7
IRIS								
Injury:	*	*	All 1	All 1	*	*	*	*
Mean	*	*	1.0	1.0	*	*	*	*
CONJUNCTIVAE								
Redness:	All 2	All 2	2 to 3	2 to 3	2 to 3	2 to 3	1 to 2	1 to 2
Mean	2.0	2.0	2.2	2.3	2.3	2.3	1.5	1.5
Chemosis:	1 to 2	All 2	1 to 2	1 to 2	1 to 2	1 to 2	1 to 2	1 to 2
Mean	1.7	2.0	1.7	1.5	1.7	1.7	1.2	1.2
Discharge:	All 3	All 3	All 3	2 to 3	2 to 3	2 to 3	1 to 3	1 to 3
Mean	3.0	3.0	3.0	2.8	2.7	2.7	1.7	1.7
CORNEA								
Opacity:	1 to 2	1 to 2	1 to 2	1 to 2	0 to 2	0 to 2	0 to 2	0 to 2
Mean	1.7	1.7	1.5	1.5	1.0	1.0	1.2	0.6
Area:	2 to 3	1 to 3	1 to 3	1 to 3	0 to 4	0 to 4	0 to 2	0 to 2
Mean	2.2	2.0	2.0	2.2	1.8	1.8	1.7	0.6
IRIS								
Injury:	All 1	All 1	All 1	All 1	All 1	0 to 1	All 0	All 0
Mean	1.0	1.0	1.0	1.0	1.0	0.5	0.0	0.0
CONJUNCTIVAE								
Redness:	All 2	All 2	All 2	All 2	1 to 2	0 to 1	All 0	All 0
Mean	2.0	2.0	2.0	2.0	1.5	0.7	0.0	0.0
Chemosis:	1 to 2	1 to 2	All 1	All 1	0 to 1	All 0	All 0	All 0
Mean	1.3	1.3	1.0	1.0	0.7	0.0	0.0	0.0
Discharge:	2 to 3	2 to 3	2 to 3	1 to 3	1 to 2	0 to 1	All 0	All 0
Mean	2.7	2.8	2.3	2.0	1.2	0.7	0.0	0.0

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*Scoring impossible in some eyes because of corneal injury.
WPC/kam/1632K-1:01-05-89



excellence
through quality

March 14, 1989

R. Myers
Bushy Run Research Center
R.D. 4, Mellon Road
Export, Pennsylvania 15632

Roy:

The sample of A-189 returned for analysis has been identified as A-1100. The purity analysis on the sample when analyzed as A-1100 shows that the sample has been partially hydrolyzed as is evidenced by Ethanol at 2.7% and the two-silicon siloxane at 1.1%. The purity at 96.1% is, therefore, lower than it would have been when you received and used it.

The attached printout shows the purity and ethanol analysis of all lots produced in that time period, all with purity levels of at least 99%. The original material you received would most certainly have been one of these lots.

I would suggest that the information you collected as A-189 would be completely useful as A-1100 data.

Regards,



C. R. Thrash
Quality Assurance Manager

CRT/ksh

Attachment

cc: J. J. Behen
J. P. Hamilton
F. D. Osterholtz
J. S. Ritscher



Specialty Chemicals Division

P.O. BOX 180, SISTERSVILLE, WV 26175 (304) 652-3211

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PRODUCT: A-1100

FROM: 01JUN88 TO: 31DEC09

30065: PURITY
30155: ETHANOL

LOT NUMBER	TEST CODES: 30065	30155
1123AF061188	99.54	0.2
1123AX062988	99.55	0.18
1131CF080288	99.57	0.03
1123CU081788	99.26	0
ND. OF PTS.	4	4
MEAN	99.48	0.1025
RANGE (LOW)	99.26	0
(HIGH)	99.57	0.2
STD. DEV.	0.147196	0.1021029
MEAN - 1 SD	99.33280	0.0003971107
+ 1 SD	99.6272	0.2046029
MEAN - 2 SD	99.18561	-0.101706
+ 2 SD	99.77439	0.3067058
MEAN - 3 SD	99.03841	-0.203809
+ 3 SD	99.92159	0.4088087

13/89 08:25

31 301 6521175

UCC SISTERV. KSH

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Report 52-43

Appendix 1

Page 3 of 3

UNION CARBIDE CORP. SISTERSVILLE W.VA.

03/09/89 15:32:

AREA PERCENT TABLE

SAMPLE: A1100 .01

INST:09 VIAL:FO SER NUMBER:00

TEST :

DATE-TIME COLLECTED : 03/09/89 14:56:0

COLLECTION TIME : 22.94

DATE-TIME PROCESSED : 03/09/89 15:19:2

METHOD: 1100 / 1100

ANALYST: SA

SAMP RATE: 3.1

A1100 0123CC073088

SAMPLE WT : 1.0000

STANDARD WT : 1.0000

DILUTION FACTOR : 1.000

PK NO	GR NO	RT MINUTES	RRT MINUTES	BL	RESPONSE FACTOR	PEAK AREA	AREA WEIGHT %	COMPONENT NAME
001	1	0.376	0.377	T	0.00000	1233	10.001	AIR
002	1	0.553	0.554		0.60000	45983	2.732	ETOH
	1	1.300	1.300		1.00000			TOLUENE
003	1	3.331	3.338		1.00000	115	0.011	SIOET4
	3	5.500	5.500		1.00000			CYCLIC
	3	6.500	6.500		1.00000			CYCLIC
	2	8.000	8.000		1.00000			A1100
004	2	9.064	9.083	V	1.00000	970494	96.099	A1100
005	1	9.819	9.839		1.00000	628	0.062	CNE
	1	10.489	10.489		1.00000			C=O
006		17.840	17.877		1.00000	10658	1.055	
007		19.017	19.056		1.00000	408	0.040	

						1029519	100.000	

GROUP REPORT - A1100 .01

GP#	GROUP NAME	AREA WEIGHT %
1		2.806
2	A1100	96.099

11/10/89 returned from Bill

ATTEN ACE HANLON
THIS IS THE SAMPLE YOU REQUESTED ME TO RUN

SA
03/09/89 15:33:59

+++

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APPENDIX 2

STANDARD TEST PROCEDURES

For all tests, the animals are maintained on appropriate commercial diet and municipal water. Both are available ad libitum except during periods of fasting (rat peroral test) or manipulation. Dosage levels for the toxicity tests normally differ by a factor of 2 in a geometric series, but may differ by other constant factors if required. The maximum dosage for the peroral and percutaneous tests is 16 ml/kg. Dosages are reduced until significant signs of toxicity are not observed. LD50's and the estimated LD50 slopes are calculated by the moving average method (Thompson, 1947; Weil, 1983) and are based on a 14-day observation period. Animal weights are recorded at 0 days (before dose), 7 days and 14 days (just prior to sacrifice). At death or sacrifice, each animal is subjected to gross pathologic evaluation.

Toxicity terminology used for peroral and percutaneous LD50's includes:

<u>Term</u>	<u>LD50</u>	<u>Term</u>	<u>LD50</u>
Extremely low order	>15 ml(or g)/kg	Highly	0.05-0.5 ml(or g)/kg
Slightly	5-15 ml(or g)/kg	Seriously	0.001-0.05 ml(or g)/kg
Moderately	0.5-5 ml(or g)/kg	Dangerously	< 0.001 ml (or g)/kg

Peroral Intubation

Sprague-Dawley albino rats, weighing between 200 and 300 g, receive the test material by stomach intubation with a ball-end stainless steel needle. The sample is injected through the needle by means of a syringe and doses are varied by adjusting the volume of the test material or its dilution. The rats are fasted overnight before dosing. Five males and 5 females are included on each level used for the LD50 calculations.

Dermal Application

New Zealand White rabbits, weighing between 2.0 and 3.0 kg, are subjected to 24 hours of contact with the test material which is retained under impervious sheeting on the clipped, intact skin of the trunk. As necessary for larger doses, gauze is wrapped around the trunk over the sample to prevent leakage. Vetrap® Bandaging Tape is wrapped over the impervious sheeting and the animal is returned to its cage for the contact period. Doses are varied by adjusting the volume or weight of the test material. Solids are dosed as powders and are moistened with a sufficient amount of water or other suitable vehicle to form a paste. After the contact period, excess fluid is removed to diminish ingestion. Observations for skin reaction are made at one hour, 7 days and 14 days after the contact period. Five male and 5 females are included on each level used for the LD50 calculation.

Inhalation Exposure

Sprague-Dawley albino rats, weighing between 200 and 300 g, are exposed to substantially saturated vapor for 6 hours. The vapor is produced by enclosing approximately 100 g of the test material in a sealed 100 to 151-liter animal chamber for approximately 18 hours (static conditions). A mixing fan

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periodically agitates the chamber atmosphere to aid in distribution of the vapor. Oxygen is added, as needed, for static exposures to maintain a chamber oxygen content of approximately 20%. If deaths occur, exposure times are varied to determine an LT50. Five males and 5 females are included for each exposure period.

Skin Irritation

Male or female New Zealand White rabbits are dosed with 0.5 ml (or 0.5 g for solids, moistened with water or other suitable vehicle). The dose is applied to the clipped, intact skin under a gauze patch and is loosely covered with impervious sheeting. Smaller amounts are given if 0.5 ml (or 0.5 g) is lethal. The test material is applied to each of 6 rabbits, which are restrained for the 4-hr contact period. Excess sample is removed after contact. Skin reaction is scored, by the method of Draize (given below), at one hour, one day, 2 days, 3 days, 7 days, and, depending on the local skin reaction, possibly 10 and 14 days after dosing.

DRAIZE SCORING SYSTEM FOR SKIN IRRITATION

<u>Evaluation of skin reactions</u>	<u>Value</u>
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 (injury 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 millimeter)-----	3
Severe edema (raised more than 1 millimeter and extending beyond the area of exposure)-----	4

Eye Irritation

Male or female New Zealand White rabbits are dosed with volumes of 0.1, 0.01 and 0.005 ml (liquid or solid). The dose is instilled into the lower conjunctival sac of one eye per animal or is placed directly on the eye. The eyelids are held together for one second. Six eyes are dosed per test volume. The eyes are scored by the attached system at one hour, approximately 4 hours, one day, 2 days, 3 days and 7 days after dosing. Additional readings are made, if necessary, at 14 and 21 days. Fluorescein (2%) staining is used to determine corneal injury before dosing and at readings after one day.

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SCALE FOR SCORING OCULAR LESIONS

Cornea:

- A. Opacity—degree of density (most dense area taken for reading)
 - No opacity----- 0
 - Scattered or diffuse area, iris details clearly visible----- 1
 - Easily discernible translucent areas, iris details slightly obscured----- 2
 - Opalescent areas, iris details not visible, pupil size barely discernible----- 3
 - Opaque, iris invisible----- 4

- B. Area of cornea involved
 - One-quarter or less, but not zero----- 1
 - Greater than one-quarter, but less than half----- 2
 - Greater than half, but less than three-quarter----- 3
 - Greater than three-quarter, up to whole area----- 4

Iris:

- A. Normal----- 0
 - Folds above normal, congestion, swelling, circumcorneal injection (any or all), iris still reacting to light----- 1
 - No reaction to light, hemorrhage, gross destruction----- 2

Conjunctivae:

- A. Vessels normal----- 0
 - Vessels definitely injected above normal----- 1
 - Diffuse, deep crimson red, individual vessels not readily discernible----- 2
 - Diffuse beefy red----- 3

- B. No chemosis----- 0
 - Any swelling above normal (includes nictitating membrane)----- 1
 - Obvious swelling with partial eversion of lids----- 2
 - Swelling with lids about half closed----- 3
 - Swelling with lids about half closed to completely closed----- 4

- C. No discharge----- 0
 - Any amount of discharge different from normal----- 1
 - Discharge with moistening of the lids and hairs adjacent to lids----- 2
 - Discharge with considerable moistening around the eyes----- 3

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APPENDIX 3

Organofunctional Silane A-1100 (51-366B)

Acute Rat Peroral Toxicity
Project No.: 88-15-11008

Anatomic Pathology Report

SUMMARY

Microscopic examination of kidneys and urinary bladders was performed on rats dosed perorally with Organofunctional Silane A-1100 at dosages of 4.0 ml/kg (males only) and 2.0 ml/kg (both males and females). The rats that died following dosage with the test material (males at 4.0 ml/kg and females at 2.0 ml/kg) all had evidence of acute necrosis of the proximal convoluted tubules in the renal cortex. The male rats dosed at 2.0 ml/kg that survived until 14 days following dosing and were then killed, had either no significant renal lesions (1 of 2), or evidence of tubular hyperplasia indicating a reparative response following necrosis.

INTRODUCTION

The objective of this limited study was to determine if the urinary tract was altered in rats that had been dosed perorally with Organofunctional Silane A-1100 in an LD₅₀ study at doses of 4.0 ml/kg and 2.0 ml/kg. Male rats dosed at 4.0 ml/kg died within 2 days of dosing and female rats dosed at 2.0 ml/kg died within 3 days of dosing.

METHODS

Kidneys and urinary bladders from 7 rats were saved in 10% neutral buffered formalin from male rats dosed at 4.0 ml/kg and 2.0 ml/kg (2 rats at each dosage level), and from 3 female rats dosed at 2.0 ml/kg. The tissues that were saved were trimmed, infiltrated and embedded in paraffin, sectioned at approximately 5 microns, and stained with hematoxylin and eosin for microscopic evaluation.

RESULTS

The kidneys from all rats that died following dosing (3 females at 2.0 ml/kg and 2 males at 4.0 ml/kg) had evidence of acute tubular necrosis involving the cortical tubules. In addition, mineralization of the tubular epithelium was seen in several of the animals.

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The kidneys from the two male rats dosed at 2.0 ml/kg that survived to Day 14 following dosing had either no significant renal lesions (1 of 2) or evidence of moderate tubular hyperplasia suggestive of earlier necrosis.

Urinary bladders were examined from all rats except one of the male rats dosed at 4.0 ml/kg. No lesions were observed in either the male or female rats dosed at 2.0 ml/kg, and the remaining male rat dosed at 4.0 ml/kg had a focal area of epithelial necrosis involving the urinary bladder.

E. H. Fowler 4-17-89
E. H. Fowler, DVM, Ph.D. Date
Diplomate, ACVP

PATH/esk/1602P-3
04-17-89

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APPENDIX 4

Summary of Renal Effects Following Single Peroral Doses to Rats

Material: Silane A-1100

Sample No.: 51-366

<u>Dosage</u> <u>ml/kg</u>	<u>Sex</u>	<u>Fate</u>	<u>No.</u> <u>Examined</u>	<u>Gross</u> <u>Appearance</u>	<u>Gross</u> <u>Pathology</u>	<u>Histopathology</u>
4.0	Male	Died (1-2 d)	2	Nothing remarkable.	Nothing remarkable.	Moderate tubular necrosis; marked kidney congestion in 1; necrosis of bladder epithelium of 1.
2.0	Male	Survived	2	Brown stain- ing of peri- urogenital fur.	Nothing remarkable.	Moderate tubular hyperplasia and mild tubular mineraliza- tion in 1.
2.0	Female	Died (3 d)	3	Nothing remarkable.	Kidneys dark red.	Moderate tubular necrosis; mild to moderate tubular mineralization in 2; moderate kidney congestion.

WPC/kam/1632K
01/09/89

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APPENDIX 5

Organofunctional Silane A-1100 (51-366B)

Acute Rabbit Percutaneous Toxicity
Project No.: 88-15-11008

Anatomic Pathology Report

SUMMARY

Male and female New Zealand White rabbits were dosed percutaneously at dosages of 8.0, 4.0, 2.0, and 1.0 ml/kg in order to determine the LD₅₀. Because of clinical findings of bloody urine on the cage floors and intensely reactive skin at the dosing site, tissues from selected rabbits were processed for microscopic observation. All rabbits that died following dosing, i.e. all males and female at 8.0 ml/kg and some of both sex at 4.0 ml/kg that were examined microscopically had marked, acute necrosis of the proximal convoluted tubules in the renal cortices with evidence of tubular proteinosis in most of the rabbits. Rabbits that survived to 14 days from the 4.0 ml/kg dosage group had only mild kidney changes. Changes in the treated skin were marked in all dosage groups, varying from acute necrotic changes in those rabbits that died, to reactive fibrosis and inflammation along with vascular changes in those rabbits that survived until the 14th day after dosing. The urinary bladders that were examined showed no consistent significant lesions.

INTRODUCTION

Rabbits dosed percutaneously in an LD₅₀ study with Organofunctional Silane A-1100 were observed clinically to have severe local reactions at the treatment site as well as bloody urine noticed on the paperboard. Tissues from the urinary system and treated skin were saved for microscopic examination from animals that died or were killed at the end of the test.

METHODS

Selected tissues from the urinary tract and treated skin were saved in 10% neutral buffered formalin for microscopic evaluation from male and female rabbits dosed percutaneously at 8.0, 4.0, 2.0 and 1.0 ml/kg with Organofunctional Silane A-1100. Rabbits were selected for further processing from each of the dosage groups of both sexes based on clinical signs, gross lesions, and whether the rabbits died or were killed at the end of the test. Two male and female rabbits were selected from each of the 8.0 and 4.0 ml/kg dosage groups, and one male and female rabbit was selected from each of the 2.0 and 1.0 ml/kg groups, none of which died during the test.

The tissues from the selected rabbits were trimmed, infiltrated and embedded in paraffin, sectioned at approximately 5 microns, stained with hematoxylin and eosin, and evaluated microscopically.

RESULTS

All male and female rabbits dosed at 8.0 ml/kg that were examined died either at Day 1 or 2 following dosing. One each of the male and female rabbits dosed at 4.0 ml/kg that were examined microscopically died on Day 3 following dosing and the other survived until the last day of study, Day 14, at which time it was sacrificed and necropsied.

Both male rabbits dosed at 8.0 ml/kg had marked acute tubular nephrosis, primarily involving the proximal convoluted tubules in the renal cortex, characterized by swelling and necrosis of the epithelial cells with sloughing of the cells into the lumina. Accompanying the nephrosis was mild to moderate tubular proteinosis, principally involving the cortical distal convoluted tubules and some of the medullary portions of the tubules. The gastric mucosal epithelium on the rabbit that died on day 2 appeared to be undergoing acute cell necrosis with disruption of the cells. The treated skin was characterized by acute epithelial cell necrosis involving the epidermis and the adnexal structures.

In the one male rabbit that died on Day 3 following dosing with 4.0 ml/kg, there was marked acute renal tubular nephrosis as described above, with moderate to marked tubular proteinosis, and mild multifocal interstitial nephritis (which was probably unrelated to the acute tubular changes). This rabbit also had dissociation of the gastric mucosal epithelial cells. The other male rabbit from this dosage group that was sacrificed on Day 14 had only occasional renal tubular epithelial cells that appeared pyknotic, possibly due to handling artifact. The treated skin in this rabbit was much more severely affected, with marked necrotic, regenerative, and inflammatory lesions including eschar formation, acanthosis, dermatitis and dermal fibrosis, and adnexal necrosis. The lungs were congested and edematous, probably due to the T61 euthanasia agent.

In the male rabbit dosed at 1.0 ml/kg, there were no significant renal lesions, but the changes in the treated skin were just as marked as those seen in the two higher dosage groups.

The results for the female rabbits were almost identical with those for the males. The rabbits that died, both from the 8.0 and 4.0 ml/kg groups had marked acute tubular nephrosis in the cortices, with evidence of tubular proteinosis, and the treated skin was acutely necrotic. Those rabbits from the three lower groups, namely 4.0, 2.0, and 1.0 ml/kg that survived until the end of the study had few renal changes, but had marked changes in the treated skin which included necrosis, hyperplasia, and inflammation. The dermal fibrosis resulting from this material was very striking. The rabbit that survived until Day 14 after dosing with 4.0 ml/kg did have evidence of previous renal tubular damage that was undergoing regenerative changes.

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Samples of urinary bladder epithelium from both male and female rabbits in the different dosage groups were essentially normal with the exception of mild autolytic changes observed in rabbits that were found dead.

In conclusion, Organofunctional Silane A-1100, when administered via the percutaneous route in NZW rabbits at concentrations employed in this study, one dose at either 8.0, 4.0, 2.0, or 1.0 ml/kg, resulted in death in all of the 8.0 ml/kg and some of the 4.0 ml/kg animals with evidence of acute renal effects, primarily necrosis in the cortical tubules, and in the rabbits that survived, the renal changes were minimal to nonexistent, but the changes in the treated skin were marked, indicating a prominent local necrotizing effect.

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04-17-89

APPENDIX 6

Summary of Renal Effects Following Single Cutaneous Doses to Rabbits

Material: Silane A-1100

Sample No.: 51-366

Dosage ml/kg	Sex	Fate	No. Examined	Gross Appearance	Gross Pathology	Histopathology
8.0	Male	Died (1-2 d)	2	Blood on anal or genital area.	Blood in bladder; hemorrhage of 1 kidney.	Marked tubular nephrosis; mild to moderate proteinosis; congestion of 1 kidney.
4.0	Male	Died (3 d)	1	Mucous and blood on rectal area and under cage.	Blood clot in bladder; kidneys hemorrhaged.	Marked tubular nephrosis; moderate to marked proteinosis; mild interstitial nephritis; marked kidney congestion.
4.0	Male	Survived	1	Blood on rectal area; free blood and clotted blood under cage.	Nothing remarkable.	Few pyknotic tubular epithelial cells; moderate tubular mineralization.
2.0	Male	Survived	1	Blood on rectal area.	Nothing remarkable.	Few pyknotic tubular epithelial cells; moderate congestion.
1.0	Male	Survivor	1	Nothing remarkable.	Nothing remarkable.	Nothing remarkable.
8.0	Female	Died (2 d)	2	Nothing remarkable.	Nothing remarkable.	Bladder with mild to marked epithelial cell degeneration and sloughing; marked to severe tubular nephrosis; moderate tubular proteinosis; moderate interstitial nephritis (in 1); moderate kidney congestion.

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(Continued)

APPENDIX 6 (Continued)

Summary of Renal Effects Following Single Cutaneous Doses to Rabbits

Material: Silane A-1100

Sample No.: 51-366

Dosage ml/kg	Sex	Fate	No. Examined	Gross Appearance	Gross Pathology	Histopathology
4.0	Female	Died (3 d)	1	Blood on rectal area; blood under cage.	Blood in bladder; kidneys hemorrhaged.	Marked tubular necrosis; tubular proteinosis; kidney congestion.
4.0	Female	Survived	1	Blood on rectal area; small amount of free blood and clotted blood under cage.	Nothing remarkable.	Mild tubular proteinosis; mild tubular epithelial cell regeneration.
2.0	Female	Survived	1	Blood on rectal area; blood under cage.	Nothing remarkable.	Nothing remarkable.
1.0	Female	Survived	1	Nothing remarkable.	Nothing remarkable.	Moderate kidney congestion.

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