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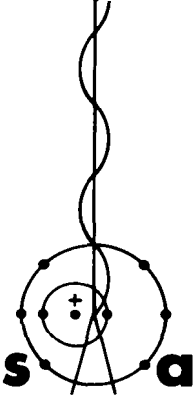

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A PRELIMINARY TOXICOLOGICAL STUDY OF SILASTIC 386 CATALYST

by

D. M. Smith, G. A. Drake, L. M. Holland, D. E. Jackson,

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ABSTRACT

The calculated acute oral LD_{50}^{30} values for Silastic 386 catalyst were 1225 mg/kg in mice and 4350 mg/kg in rats. According to classical guidelines, the compound would be slightly to moderately toxic in both species. Skin application studies in the rabbit demonstrated the compound to be mildly irritating. The eye irritation study disclosed the compound to be a severe irritant causing conjunctivitis, photophobia, corneal edema, corneal ulceration, anterior uveitis, and keratitis. The sensitization study in the guinea pig did not show Silastic 386 catalyst to be deleterious in this regard.

I. INTRODUCTION

As part of the Mammalian Biology Group's (H-4) applied toxicology program, Silastic 386 catalyst was examined to define its toxic properties with the following tests: (1) acute oral toxicity; (2) primary skin irritation; (3) skin sensitization; and (4) eye conjunctival instillation. Silastic 386 catalyst is composed largely of stannous octoate, and the cured Silastic 386 is used as a foam elastomer cushioning agent.

II. EXPERIMENTAL PROCEDURES

A. Source of Material

The test material Silastic 386 catalyst (Dow-Corning Corporation, Midland, Michigan) was supplied in 200-mℓ samples by Group WX-3 of the LASL Design Engineering Division. The material was stored at 25°C in a glass container sealed in a plastic bag.

B. Single-Dose Acute Oral Toxicity (LD_{50}^{30} Days)

1. Rats. Twenty young adult (107-day-old) Sprague-Dawley male rats, weighing 240 to 260 g, were used in each of 6 test groups. The compound was administered intragastrically in graded doses to ether-sedated, fasted rats as a suspension in corn oil using a ball-tipped needle and syringe. Because of its innocuous properties, this vehicle was used to suspend the stannous octoate catalyst.

After treatment, all animals were observed daily for 30 days for aberrant physiological and behavioral responses. We initially conducted range-finding studies at various dose levels to identify the range of toxicity[1,2] with 5 animals per level. The data are on file in the Mammalian Biology Group at the Los Alamos Scientific Laboratory as Compound H-4-#5.

2. Mice. The procedure for single-dose oral-toxicity determination in mice was the same as for rats. Twenty young adult CD-1 mice, weighing 28 to 34 g, were used in each of 4 test groups. As with rats, all animals were observed daily for 30 days after treatment for abnormal physiological and behavioral responses.

C. Long-Term Oral Toxicity

1. Mice. Thirty young CD-1 mice, weighing 23 to 28 g, were given a single LD_{25} dose of Silastic 386 catalyst and will be observed until death. Pathophysiological observations, including gross and microscopic necropsy examinations, will then be made.

2. Rats. Thirty young Sprague-Dawley rats, weighing 260 to 340 g, were given a single LD_{25} dose of Silastic 386 catalyst as in the mouse test above.

D. Multiple Oral Doses

Thirty young CD-1 mice, weighing 24 to 30 g, were given an LD_{10} dose of Silastic 386 catalyst daily on 5 consecutive days. These animals will be observed until death when pathophysiological results, including gross and microscopic necropsy examinations, will be made.

E. Primary Skin Irritation

The Draize test[3] was used to assess primary skin irritation properties. Six New Zealand white rabbits, weighing 2.5 to 3.5 kg each, were used. The back of each rabbit was clipped free of hair using Oster electric clippers (Oster Corporation, Racine, Wisconsin) with a #40 blade 24 h before application of the compound. Two sites were superficially abraded and two left unabraded. The compound was applied in 0.5-mℓ quantities to each location. The test sites were covered with a gauze pad, and the entire back was covered with an adhesive plastic surgical drape and overwrapped with a linen cloth. The wraps were removed 24 h later, and each test site was scored visually for erythema and edema. Readings were recorded for 24, 48, and 72 h. A primary irritation score was calculated for the 24- and 72-h readings.

F. Eye Irritation

Six New Zealand white rabbits, weighing 2.5 to 3.5 kg, were used in this facet of the study. Both rabbit eyes were checked for abnormalities before instillation. The compound (0.1 mℓ) was instilled into the conjunctival envelope of the left eye of each rabbit; the right eye served as a control. Two of the rabbits had the compound washed from the eye 30 s after instillation with 0.15 M NaCl, 2 at 5 min after instillation, and 2 did not have the compound washed from the eye. Each eye was graded for ocular lesions at 1 and 4 h on the day of application and again at 24, 48, and 72 h postapplication. Of particular interest was determination of whether the cornea, iris, and conjunctivae became inflamed. The procedure and grading system were taken from the Draize test.

G. Skin Sensitization

Six female guinea pigs, weighing 326 to 503 g, were used in the treatment group. The animals were housed individually and fed commercial laboratory stock diets ad libitum supplemented daily by lettuce and cabbage. The test compound was diluted to a concentration of 0.1% with corn oil and was administered in a series of 10 "sensitizing" injections into the lower back and flanks of the guinea pigs. The test sites were clipped free of hair before each injection. Injections were made randomly over the test area on Sunday, Tuesday, and Thursday with a 1-mℓ tuberculin syringe fitted with a 25-gauge needle. The volume of the first injection was 0.05 mℓ, and the other 9 were each 0.1 mℓ. At 24 h after injection, the reaction was scored for redness, height, and diameter. Redness and height were scored as described by Landsteiner and Jacobs;[4] the diameters of the reactions were measured in millimeters using a micrometer caliper. At 2 wk after administration of the tenth sensitizing injection, the lower back and flanks of each guinea pig were clipped free of hair, and a challenge injection of 0.05 mℓ was administered. The reaction of each animal was graded 24 h later and compared with the results from the sensitizing injections.

III. RESULTS AND DISCUSSION

A. Single-Dose Acute Oral Toxicity (LD_{50}^{30} Days)

1. Rats. Oral toxicity data for Silastic 386 catalyst in corn oil are given in Fig. 1 and are summarized in Table I. Within 1 h after recovery from the anesthesia, the animals that died became somnolent, with coma and death ensuing. The behavioral and physiological responses of survivors after administration appeared normal except for one animal that "wasted" away until death at 21 days after administration of the material. The LD_{50}^{30} was 4350 mg/kg, with 95% confidence limits of 3800 to 4990 mg/kg. These least-squares parameters and their standard deviations were calculated with a LASL computer program (LSMFT).

2. Mice. Oral toxicity data for Silastic 386 catalyst in corn oil for mice are given in Fig. 2 and are summarized in Table II using computer output as above. Within 30 min after recovery from

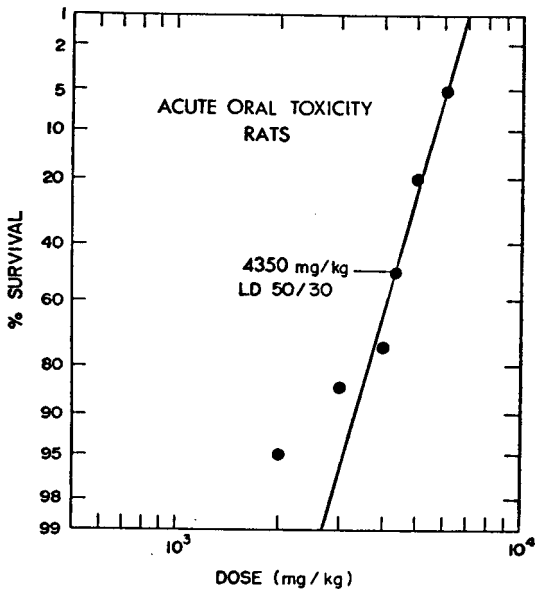

Fig. 1. Acute oral toxicity of Silastic 386 catalyst in Sprague-Dawley rats.

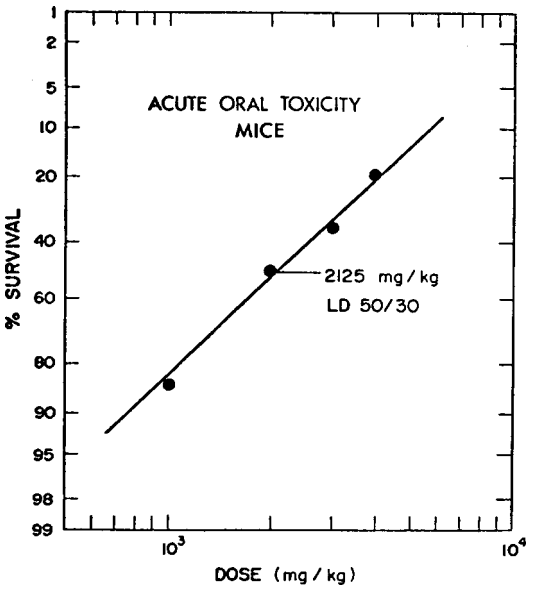

Fig. 2. Acute oral toxicity of Silastic 386 catalyst in CD-1 mice.

TABLE I

ACUTE ORAL TOXICITY OF SILASTIC 386 CATALYST TO FASTED SPRAGUE-DAWLEY RATS

Dose (mg/kg)	Number of Survivors / Number of Treated	Time of Death (h)	LD_{50}^{30} Days (mg/kg)
2000	19/20	4-24	
3000	17/20	4-500[a]	4350
4000	15/20	4-24	(3800-4990)[b]
5000	4/20	4-24	
6000	1/20	4-24	

[a]One animal recovered from a deep sleep in 2 days but quit eating and wasted away.

[b]At the 95% confidence limit.

TABLE II

ACUTE ORAL TOXICITY OF SILASTIC 386 CATALYST TO FASTED CD-1 MICE

Dose (mg/kg)	Number of Survivors / Number of Treated	Time of Death (h)	LD_{50}^{30} Days (mg/kg)
1000	17/20	4-24	
2000	10/20	2-24	2125
3000	7/20	2-24	(1835-2470)[a]
4000	4/20	2-24	

[a]At the 95% confidence limit.

the anesthesia, the animals that eventually died appeared to be in a somnolent state that progressed to coma and death. The behavioral and physiological responses of survivors after administration appeared normal. The LD_{50}^{30} was 2125 mg/kg, with 95% confidence limits of 1835 to 2470 mg/kg.

B. Primary Skin Irritation

Silastic 386 catalyst caused slight edema in 4 of the 6 treated rabbits at the 24-h reading. All 6 rabbits developed erythema in 24 h. At 72 h, 5 of the 6 rabbits still had erythema, but none demonstrated edema. The total primary irritation score for Silastic 386 catalyst was 1.03.

C. Eye Irritation

Table III summarizes eye irritation responses for Silastic 386 catalyst in the 3 treated groups. This compound caused irritation in the conjunctivae, iris, and corneal tissues, with no differences observed between the treatment groups. All treated rabbit eyes developed chemosis, vascular injection, acute conjunctivitis, corneal edema, and opacity within 1 h. The same changes were seen at the 4-h observation. At 24 h, 1 rabbit eye was almost

swollen shut (blepharitis), and all rabbits had severe keratitis with ulceration, corneal edema, and opacity with a thick white (mucopurulent) discharge. All treated eyes were swollen shut at 48 h. At this time, the eyes were washed with Dacriose (Cooper Laboratories, Inc., San German, Puerto Rico) to facilitate examination and scoring. The eyes were characterized by acute conjunctivitis, keratitis, corneal opacity, and edema. The treated eyes were swollen shut at 72 h. After washing with Dacriose, a large amount of mucopurulent exudate was flushed from each treated eye. The eyes had normal pupillary response to light but exhibited corneal opacity, severe chemosis, keratoconjunctivitis, and corneal edema.

After 4 days, all treated rabbit eyes remained inflamed. One animal from the "no wash" group was sacrificed and the eye enucleated for a histopathological evaluation. The other 5 rabbits were treated topically once a day with Neosone (Upjohn, Kalamazoo, Michigan). After 2 wk of treatment with Neosome, all treated eyes still had corneal opacity, some redness, keratitis, and chemosis. These rabbits were sacrificed for pathological evaluation.

TABLE III

EYE IRRITATION RESPONSES IN RABBITS TREATED WITH SILASTIC 386 CATALYST[a]

	Average Irritation				
	(hours)		(days)		
Tissue Graded[b]	1	4	1	2	3
Wash at 30 s					
Cornea	40	60	70	80	80
Iris	0	0	5	5	5
Conjunctivae	12	12	18	18	18
Wash at 5 min					
Cornea	40	60	60	80	80
Iris	0	0	5	5	5
Conjunctivae	12	12	18	18	18
No Wash					
Cornea	60	60	80	80	80
Iris	0	0	5	5	5
Conjunctivae	12	12	18	18	18

[a] Two rabbits per wash condition.

[b] Maximum cornea response = 80; maximum iris response = 10; and maximum conjunctivae response = 20.

The rabbit that was sacrificed at 4 days post-exposure was from the "no wash" group. The microscope findings indicated that the right eye was normal. The cornea in the region of the limbus in the left eye was heavily infiltrated with heterophils, and an extensive zone of hemorrhage was found along the inner portion of the sclera extending from the canal of Schlemm to the ora serrata. A moderate quantity of cellular exudate was present in the filtration angle; the surface epithelium of the cornea had been destroyed, and the outer 10% of the substantia propia had swollen collagen fibers with leukocytic infiltration; no capillary proliferation was seen.

Five rabbits instilled with Silastic 386 catalyst with no wash, 30-s wash, and 5-min wash had no differences at 14 days. Pathologic evaluations indicated that the initial alteration observed was denuding of corneal epithelium, with leukocytic infiltration of the fornix of the conjunctival sac and filtration angle. The corneal epithelium had been restored over most of the surface 14 days later. The substantia propria of the cornea was infiltrated by a number of capillaries. The collagen bundles of the outer third were swollen and separated by edema fluid. No alterations were recognized in the iris or retina. The pathological alterations were considered to be of a reparable nature, with eventual recovery leaving minimal scar tissue in the cornea. Successful recovery would be dependent upon appropriate supportive therapy during recovery.

Since 0.1 mℓ of Silastic 386 catalyst caused severe eye irritation, a study to evaluate damage from smaller quantities was undertaken. Two rabbits per point were used. Quantities of 0.01, 0.025, and 0.05 mℓ were instilled in the conjunctival sac of each left eye without any washings. Table IV summarizes these data. Silastic 386 catalyst in smaller volumes than 0.1 mℓ caused less irritation to the iris, conjunctival sac, and cornea. All treated rabbit eyes developed mild chemosis, slight redness, and keratoconjunctivitis at the 1- and 4-h readings. One of the 0.01-mℓ and both of the 0.05-mℓ treated eyes developed corneal opacity at the 24-h reading. All treated rabbit eyes developed chemosis, keratitis, and corneal edema by 48 h. The 72-h readings were similar to

TABLE IV

EYE IRRITATION RESPONSES IN RABBITS TREATED WITH GRADED VOLUMES OF SILASTIC 386 CATALYST[a]

Tissue Graded[b]	Average Irritation (hours) 1	4	(days) 1	2	3
With 0.01 mℓ					
Cornea	0	2.5	20	20	10
Iris	0	0	0	0	2.5
Conjunctivae	4	6	10	14	9
With 0.025 mℓ					
Cornea	5	5	20	22.5	17.5
Iris	0	0	0	5	2.5
Conjunctivae	4	8	10	13	13
With 0.050 mℓ					
Cornea	5	5	20	25	5
Iris	0	0	0	2.5	2.5
Conjunctivae	3	4	10	15	12

[a]Two rabbits per point.

[b]Maximum cornea response = 80; maximum iris response = 10; and maximum conjunctivae response = 20.

the 24-h readings. One animal from each of these 3 groups was sacrificed at 22 days for histopathological evaluation, and 1 was saved to evaluate irritation recovery times. These results will be presented in the final report.

D. Skin Sensitization

Review of the data collected for each guinea pig in the treatment group indicates that all challenge injection reactions were within the limits of reactions recorded during the sensitizing period. The guinea pig skin sensitization study did not show Silastic 386 catalyst to be a sensitizer.

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