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A REPORT PREPARED

MICROFILM

FOR

DYNAMIT NOBEL

---o0o---

SIX SILANE SAMPLES

ACUTE TOXICITY INVESTIGATIONS

1976 - I0065 - 1167 - 30

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INTRODUCTION

Six silane samples were provided for acute toxicity evaluation by means of the following methods:

- a) Acute oral toxicity to rats.
- b) Draize skin test.
- c) Draize eye test.

The test materials were as follows.

- 1) Gamma - Aminopropyltriethoxysilane (AMEO)
- 2) Gamma - Glycidyloxypropyltrimethoxysilane (GLYMO)
- 3) Gamma - Methacryloxypropyltrimethoxysilane (MEMO)
- 4) Gamma - Mercaptopropyltrimethoxysilane (MTMO)
- 5) Vinyltrimethoxysilane (VTMO)
- 6) Vinyl tris (beta - methoxyethoxy) silane (VTMOEO).

a) ACUTE ORAL TOXICITY TO RATSMATERIALS AND METHOD1) Experimental Animals

Wistar rats of both sexes weighing 200 ± 2 g were used for these investigations. The animals were housed in grid floor cages under artificial lighting with a 12 hour photoperiod and with the ambient temperature themostatically maintained at $22 \pm 2^{\circ}\text{C}$.

Throughout the observation period of these experiments all animals were segregated in cages according to sex and dosage group.

2) Preparation and Administration of test materials

In order to facilitate oral administration, each test material was diluted or suspended as necessary in a suitable dose vehicle (for details of vehicle and concentration used for each assay see Tables of Results).

Prior to administration, all animals were fasted overnight (water allowed ad libitum) and provided their normal diet subsequent to dosing. Oral administration was by gavage using a metal cannula.

3) LD50 Determinations

A preliminary range-finding trial was conducted for each test material in order to determine the range of acute oral toxicity of each compound. These animals were observed immediately after administration and then at daily intervals for a period of 7 days ; any deaths or signs of toxicity were recorded.

On the basis of the results of these preliminary trials, further doses were administered to larger groups of animals in order to determine the median lethal oral dose (LD50) more precisely, or to demonstrate that this value is greater than 5000 mg/kg or 5.0 ml/kg. (This dose is generally accepted as the upper limit used to differentiate toxic and non-toxic substances administered by this route to rats). For these trials groups of 10 animals (5 male and 5 female) were used for each dose level. All animals were observed at daily intervals over a period of 14 days after dosing, and signs of toxicity and incidence of mortality were recorded.

From these latter results the LD50 together with its 95% confidence limits of each test material was calculated by the method of Litchfield, J.T. and Wilcoxon, F. (1949) J. Pharm Exp Therap. 96, 99.

RESULTS

Full results are given in Tables 1 - 6.

These give details of the dosing vehicle and concentrations employed together with the type, onset and duration of any signs of toxicity.

b) DRAIZE SKIN TESTS

Materials and Methods

These tests were performed as laid down in the F.D.A. Handbook, Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, F.D.A. (1959) p.47.

Four New Zealand White rabbits were used for each sample. Their backs were shaved with electric clippers and one side of each back abraded with a suitable abrading tool. A 0.5 ml sample of the test material was applied to areas of both intact and abraded skin. These areas were then occluded by means of one inch gauze pads secured with adhesive tape and further occluded with a 'Stockinette' sleeve covering the entire trunk of the animal.

After twenty-four hours the patches were removed and the resultant reactions in both intact and abraded skin evaluated according to the Draize scale (See Table 7). Further readings were made at 72 hours, the final score being the combined averages for the readings on intact and abraded skin at 24 and 72 hours. This average is referred to as the Primary Irritation Index.

RESULTS

Full results are given in Tables 8 - 13.

With the exception of the samples of AMEO and MEMO, these materials were found to be non-irritant or almost non-irritant under the conditions of these experiments.

The sample of MEMO was found to be slightly irritant, eliciting slight to moderate erythema on all animals after 24 hours. No significant differences were observed between the reactions evoked on intact and abraded skin. The Primary Irritation Index was calculated to be 1.19, this material is therefore classified as a mild primary irritant.

In marked contrast, the sample of AMEO was observed to cause severe dermal irritation. Moderate to severe erythema accompanied by oedema was observed on all animals after 24 hours exposure.

These reactions tended to be more severe on abraded skin and became more pronounced, leading to induration and eschar formation, after 72 hours. The Primary Irritation Index was calculated to be 6.5, this material is therefore classified as a severe primary irritant.

c) DRAIZE EYE TESTS

Materials and Methods

These tests were modified versions of that laid down in the F.D.A. Handbook Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, 1959 p.49.

Six adult New Zealand white rabbits were used for each test material. A 0.1 ml sample of each of the test materials instilled into one eye of each rabbit, the contralateral eye remaining untreated as a control. In three rabbits the treated eye remained unwashed, and in three rabbits the treated eyes were washed with 20 ml lukewarm water 4 seconds after instillation. Readings were made at 1, 2, 3, 4 and 7 days to assess the irritant effects on various parts of the eyes. These assessments were made according to the Draize scale (See Table 14).

RESULTS

Full results are given in Tables 15 - 20.

With the exception of the compound AMEO, each test material elicited only very mild ocular irritation in those animals in which the treated eye remained unwashed. This irritation was confined to slight erythema and oedema of the conjunctival membranes which in general did not persist beyond 48 hours after instillation. At no time was the cornea or iris of any animal affected.

The sample of AMEO produced severe ocular irritation in all animals, including those in which the treated eye was washed following instillation. Maximum scores were recorded for all parameters and in view of the severity of these reactions and the obvious permanent damage which would result from this insult all animals were sacrificed after 24 hours.

SUMMARY

None of these compounds was found to be especially toxic systemically when administered by gavage to Wistar rats, in fact three compounds (GLYMO MEMO and VTMO) can be classified as non-toxic by this route since the LD50 of each has been demonstrated to be greater than 5.0 ml/kg. The most toxic sample in this respect was MTMO with an LD50 value of 1.83 ml/kg.

Apart from the compound AMEO these materials exhibited only marginal dermal and ocular irritation in rabbits. The compound AMEO however, was found to be extremely irritant to both the skin and eyes of rabbits.

A further comparison of these compounds is given in Table 21.

TABLE 1

Gamma - Aminopropyltriethoxysilane - ACUTE ORAL TOXICITY DETERMINATIONSPECIES : RATVEHICLE : DISTILLED WATERRANGE-FINDER TRIAL

Dose ml/kg	Concentration of Test Material	Deaths By Day				
		1	2	3	4	7
5.0	As Supplied	2/2	2/2	2/2	2/2	2/2
2.5	20%	0/2	0/2	0/2	0/2	0/2
1.0	20%	0/2	0/2	0/2	0/2	0/2
0.5	20%	0/2	0/2	0/2	0/2	0/2

FINAL ASSAY

Dose ml/kg	Concentration of Test Material	Deaths by Day						Percentage Mortality
		1	2	3	4	7	14	
5.0	As Supplied	5/10	7/10	9/10	10/10	10/10	10/10	100
4.5	As Supplied	8/10	9/10	9/10	9/10	9/10	9/10	90
3.9	20%	4/10	5/10	7/10	7/10	7/10	7/10	70
3.1	20%	1/10	1/10	1/10	1/10	1/10	1/10	10
2.5	20%	0/10	0/10	0/10	0/10	0/10	0/10	0

SIGNS OF TOXICITY : Salivation, ataxia and lethargy followed by tonic and clonic convulsions within 1 hour of administration at high dose levels. 50% of deaths occurred within 1 hour at the highest dose level. Survivors at 24 hours exhibited severe diarrhoea and diuresis and further deaths occurred up to 72 hours after administration.

LD50 VALUE : 3.65 (3.26 - 4.09) ml/kg.

TABLE 2

Gamma - Glycidyoxypropyltrimethoxysilane - ACUTE ORAL TOXICITY DETERMINATIONSPECIES : RATVEHICLE : COTTON SEED OILRANGE-FINDER TRIAL

Dose ml/kg	Concentration of Test Material	Deaths by Day				
		1	2	3	4	7
5.0	As Supplied	0/2	0/2	0/2	0/2	0/2
2.5	20%	0/2	0/2	0/2	0/2	0/2
1.0	20%	0/2	0/2	0/2	0/2	0/2
0.5	20%	0/2	0/2	0/2	0/2	0/2

FINAL ASSAY

Dose ml/kg	Concentration of Test Material	Deaths by Day						Percentage Mortality
		1	2	3	4	7	14	
12.6	As Supplied	5/10	8/10	8/10	8/10	8/10	8/10	80
10.0	As Supplied	7/10	7/10	7/10	7/10	7/10	7/10	70
6.3	As Supplied	3/10	3/10	3/10	3/10	3/10	3/10	30
5.0	As Supplied	3/10	3/10	3/10	3/10	3/10	3/10	30
3.9	As Supplied	1/10	1/10	1/10	1/10	1/10	1/10	10

SIGNS OF TOXICITY : Piloerection and lethargy within 1 hour of administration, followed by coma and death. All deaths occurred within 48 hours of administration and all survivors were generally asymptomatic after this time.

LD50 VALUE : 7.50 (6.00 - 9.37) ml/kg.

TABLE 3

Gamma - Methacryloxypropyltrimethoxysilane - ACUTE ORAL TOXICITY DETERMINATIONSPECIES : RATVEHICLE : COTTON SEED OILRANGE-FINDER TRIAL

Dose ml/kg	Concentration of Test Material	Deaths by Day				
		1	2	3	4	7
5.0	As Supplied	0/2	0/2	0/2	0/2	0/2
2.5	20%	0/2	0/2	0/2	0/2	0/2
1.0	20%	0/2	0/2	0/2	0/2	0/2
0.5	20%	0/2	0/2	0/2	0/2	0/2

FINAL ASSAY

Dose ml/kg	Concentration of Test Material	Deaths by Day						Percentage Mortality
		1	2	3	4	7	14	
5.0	As Supplied	0/10	0/10	0/10	0/10	0/10	0/10	0

SIGNS OF TOXICITY : NONELD50 VALUE : Exceeds 5.0 ml/kg.

TABLE 4

Gamma - Mercaptopropyltrimethoxysilane - ACUTE ORAL TOXICITY DETERMINATION

SPECIES : RAT

VEHICLE : COTTON SEED OIL

RANGE-FINDER TRIAL

Dose ml/kg	Concentration of Test Material	Deaths by Day				
		1	2	3	4	7
5.0	As Supplied	2/2	2/2	2/2	2/2	2/2
2.5	20%	1/2	1/2	1/2	1/2	1/2
1.0	20%	0/2	0/2	0/2	0/2	0/2
0.5	20%	0/2	0/2	0/2	0/2	0/2

FINAL ASSAY

Dose ml/kg	Concentration of Test Material	Deaths by Day						Percentage Mortality
		1	2	3	4	7	14	
2.5	20%	9/10	10/10	10/10	10/10	10/10	10/10	100
2.0	20%	6/10	6/10	7/10	7/10	7/10	7/10	70
1.6	20%	0/10	1/10	2/10	2/10	2/10	2/10	20
1.0	20%	0/10	0/10	0/10	0/10	0/10	0/10	0

SIGNS OF TOXICITY : Piloerection, excessive salivation, lethargy and ataxia within 1 hour of administration followed by diuresis after 24 hours. Deaths occurred up to 72 hours after administration, survivors were generally asymptomatic at this time.

LD50 VALUE : 1.83 (1.67 - 2.03) ml/kg.

TABLE 5

Gamma - Vinyltrimethoxysilane - ACUTE ORAL TOXICITY DETERMINATIONSPECIED : RATVEHICLE : COTTON SEED OILRANGE-FINDER TRIAL

Dose ml/kg	Concentration of Test Material	Deaths by Day				
		1	2	3	4	7
5.0	As Supplied	0/2	0/2	0/2	0/2	0/2
2.5	20%	0/2	0/2	0/2	0/2	0/2
1.0	20%	0/2	0/2	0/2	0/2	0/2
0.5	20%	0/2	0/2	0/2	0/2	0/2

FINAL ASSAY

Dose ml/kg	Concentration of Test Material	Deaths by Day						Percentage Mortality
		1	2	3	4	7	14	
10.0	As Supplied	2/10	4/10	7/10	7/10	7/10	7/10	70
7.9	As Supplied	1/10	3/10	5/10	5/10	5/10	5/10	50
6.3	As Supplied	1/10	1/10	1/10	2/10	2/10	2/10	20
5.0	As Supplied	0/10	0/10	1/10	1/10	1/10	1/10	10
3.9	As Supplied	0/10	0/10	0/10	0/10	0/10	0/10	0

SIGNS OF TOXICITY : Lethargy, diuresis and diarrhoea within 6 hours of administration followed by blood staining around mouth and nostrils at 24 hours. Deaths occurred up to 96 hours after administration, survivors were generally asymptomatic after one week.

LD50 VALUE : 8.20 (6.83 - 9.84) ml/kg.

TABLE 6

Vinyl tris (beta-methoxyethoxy) silane - ACUTE ORAL TOXICITY DETERMINATION

SPECIES : RAT

VEHICLE : COTTON SEED OIL

RANGE-FINDER TRIAL

Dose ml/kg	Concentration of Test Material	Deaths by Day				
		1	2	3	4	7
5.0	As Supplied	2/2	2/2	2/2	2/2	2/2
2.5	20%	0/2	0/2	0/2	0/2	0/2
1.0	20%	0/2	0/2	0/2	0/2	0/2
0.5	20%	0/2	0/2	0/2	0/2	0/2

FINAL ASSAY

Dose ml/kg	Concentration of Test Material	Deaths by Day						Percentage Mortality
		1	2	3	4	7	14	
5.0	As Supplied	2/10	6/10	10/10	10/10	10/10	10/10	100
3.9	20%	4/10	8/10	8/10	9/10	9/10	9/10	90
2.5	20%	0/10	4/10	6/10	7/10	7/10	7/10	70
2.0	20%	3/10	3/10	3/10	3/10	3/10	3/10	30
1.6	20%	0/10	1/10	2/10	2/10	2/10	2/10	20
1.0	20%	0/10	0/10	0/10	0/10	0/10	0/10	0

SIGNS OF TOXICITY : Piloerection and lethargy within 6 hours of administration, followed by excessive salivation, sweating, diuresis, diarrhoea and blood staining around mouth and nostrils. Deaths occurred up to 96 hours after administration and survivors were asymptomatic after 4 days.

LD50 VALUE : 2.30 (1.92 - 2.76) ml/kg.

TABLE 6

Vinyl tris (beta-methoxyethoxy) silane - ACUTE ORAL TOXICITY DETERMINATION

SPECIES : RAT

VEHICLE : COTTON SEED OIL

RANGE-FINDER TRIAL

Dose ml/kg	Concentration of Test Material	Deaths by Day				
		1	2	3	4	7
5.0	As Supplied	2/2	2/2	2/2	2/2	2/2
2.5	20%	0/2	0/2	0/2	0/2	0/2
1.0	20%	0/2	0/2	0/2	0/2	0/2
0.5	20%	0/2	0/2	0/2	0/2	0/2

FINAL ASSAY

Dose ml/kg	Concentration of Test Material	Deaths by Day						Percentage Mortality
		1	2	3	4	7	14	
5.0	As Supplied	2/10	6/10	10/10	10/10	10/10	10/10	100
3.9	20%	4/10	8/10	8/10	9/10	9/10	9/10	90
2.5	20%	0/10	4/10	6/10	7/10	7/10	7/10	70
2.0	20%	3/10	3/10	3/10	3/10	3/10	3/10	30
1.6	20%	0/10	1/10	2/10	2/10	2/10	2/10	20
1.0	20%	0/10	0/10	0/10	0/10	0/10	0/10	0

SIGNS OF TOXICITY : Piloerection and lethargy within 6 hours of administration, followed by excessive salivation, sweating, diuresis, diarrhoea and blood staining around mouth and nostrils. Deaths occurred up to 96 hours after administration and survivors were asymptomatic after 4 days.

LD50 VALUE : 2.30 (1.92 - 2.76) ml/kg.

TABLE 7

DRAIZE SKIN IRRITATION SCORING SYSTEM

(1)	<u>Erythema and Eschar Formation:</u>	
	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
		—
	Total possible erythema score:	4
(2)	<u>Edema Formation:</u>	
	No edema	0
	Very slight edema (barely perceptible)	1
	Slight edema (edges of area well defined definite raising)	2
	Moderate edema (raised approximately 1mm)	3
	Severe edema (raised more 1mm and extending beyond area of exposure)	4
		—
	Total possible edema score:	4

TABLE 8

Gamma-Aminopropyltriethoxysilane - DRAIZE SKIN TEST

RABBIT NUMBER	TIME (HOURS)	INTACT		ABRADED	
		E	0	E	0
1	24	3	2	4	3
	72	3	4	4	4
2	24	3	2	4	3
	72	2	3	4	4
3	24	3	2	4	3
	72	4	3	4	3
4	24	3	1	4	3
	72	4	3	4	4

PRIMARY IRRITATION INDEX : 6.50

TABLE 9

Gamma-Glycidyloxypropyltrimethoxysilane - DRAIZE SKIN TEST

RABBIT NUMBER	TIME (HOURS)	INTACT		ABRADED	
		E	O	E	O
5	24	0	0	0	0
	72	0	0	0	0
6	24	1	0	0	0
	72	0	0	0	0
7	24	0	0	0	0
	72	0	0	0	0
8	24	0	0	0	0
	72	0	0	0	0

PRIMARY IRRITATION INDEX : 0.06

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TABLE 10

Gamma-Methacryloxypropyltrimethoxysilane - DRAIZE SKIN TEST

RABBIT NUMBER	TIME (HOURS)	INTACT		ABRADED	
		E	O	E	O
9	24	2	0	2	0
	72	2	1	2	0
10	24	1	0	1	0
	72	0	0	0	0
11	24	1	0	1	0
	72	2	0	2	0
12	24	1	0	1	0
	72	0	0	0	0

PRIMARY IRRITATION INDEX : 1.19

TABLE 11

Gamma-Mercaptopropyltrimethoxysilane - DRAIZE SKIN TEST

RABBIT NUMBER	TIME (HOURS)	INTACT		ABRADED	
		E	0	E	0
13	24	1	0	1	0
	72	0	0	0	0
14	24	0	0	0	0
	72	0	0	0	0
15	24	0	0	0	0
	72	0	0	0	0
16	24	0	0	1	0
	72	0	0	0	0

PRIMARY IRRITATION INDEX : 0.19

TABLE 12

Vinyltrimethoxysilane - DRAIZE SKIN TEST

RABBIT NUMBER	TIME (HOURS)	INTACT		ABRADED	
		E	0	E	0
17	24	0	0	0	0
	72	0	0	0	0
18	24	0	0	0	0
	72	0	0	0	0
19	24	0	0	0	0
	72	0	0	0	0
20	24	0	0	0	0
	72	0	0	0	0

PRIMARY IRRITATION INDEX : 0.00

TABLE 13

Vinyl tris (beta-methoxyethoxy) silane - DRAIZE SKIN TEST

RABBIT NUMBER	TIME (HOURS)	INTACT		ABRADED	
		E	O	E	O
21	24	0	0	1	0
	72	1	0	1	0
22	24	0	0	0	0
	72	0	0	0	0
23	24	0	0	0	0
	72	0	0	0	0
24	24	0	0	0	0
	72	0	0	0	0

PRIMARY IRRITATION INDEX : 0.19

TABLE 14

DRAIZE SYSTEM FOR SCORING OCULAR LESIONS1. CORNEA

- A. Opacity-degree of density (area most dense for reading) :
- | | |
|--|---|
| No opacity | 0 |
| Scattered or diffuse area, details of iris clearly visible | 1 |
| Easily discernible translucent areas, details of iris slightly obscured | 2 |
| Opalescent areas, no details of iris visible, size of pupil 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 quarters | 3 |
| Greater than three quarters, up to whole area | 4 |

A x B x 5

Total maximum = 80

2. IRIS

- A. Values :
- | | |
|--|---|
| Normal | 0 |
| Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reaction is positive) | 1 |
| No reaction to light, haemorrhage, gross destruction (any or all of these) | 2 |

A x 5

Total maximum = 10

TABLE 14 (Cont'd)

DRAIZE SYSTEM FOR SCORING OCULAR LESIONS3. CONJUNCTIVAE

A. Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris):

Vessels normal 0

Vessels definitely injected above normal 1

More diffuse, deeper crimson red, individual vessels not easily discernible 2

Diffuse, beefy red 3

B. Chemosis:

No swelling 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. Discharge:

No discharge 0

Any amount different from normal (does not include small amounts observed in inner canthus of normal animals). 1

Discharge with moistening of the lids and hairs just adjacent to lids 2

Discharge with moistening of the lids and hairs, and considerable area around the eye 3

Score (A + B + C) x 2

Total maximum = 20

TABLE 15

Gamma-Aminopropyltriethoxysilane - EYE TEST

Rb No.	Time (days)	Cornea			Conjunctivae			Cn.	Ir.	Cj.	Total
		A	B	Iris	A	B	C				
UNWASHED 25	1	4	4	?	3	4	3	80	?	20	100
	2	ANIMAL SACRIFICED AFTER 24 HOURS									
	3	ANIMAL SACRIFICED AFTER 24 HOURS									
	4	ANIMAL SACRIFICED AFTER 24 HOURS									
	7	ANIMAL SACRIFICED AFTER 24 HOURS									
26	1	4	4	?	3	4	3	80	?	20	100
	2	ANIMAL SACRIFICED AFTER 24 HOURS									
	3	ANIMAL SACRIFICED AFTER 24 HOURS									
	4	ANIMAL SACRIFICED AFTER 24 HOURS									
	7	ANIMAL SACRIFICED AFTER 24 HOURS									
27	1	3	4	?	3	4	3	60	?	20	80
	2	ANIMAL SACRIFICED AFTER 24 HOURS									
	3	ANIMAL SACRIFICED AFTER 24 HOURS									
	4	ANIMAL SACRIFICED AFTER 24 HOURS									
	7	ANIMAL SACRIFICED AFTER 24 HOURS									
WASHED 4 secs. 28	1	4	4	?	3	4	3	80	?	20	100
	2	ANIMAL SACRIFICED AFTER 24 HOURS									
	3	ANIMAL SACRIFICED AFTER 24 HOURS									
	4	ANIMAL SACRIFICED AFTER 24 HOURS									
	7	ANIMAL SACRIFICED AFTER 24 HOURS									
29	1	4	4	?	3	4	3	80	?	20	100
	2	ANIMAL SACRIFICED AFTER 24 HOURS									
	3	ANIMAL SACRIFICED AFTER 24 HOURS									
	4	ANIMAL SACRIFICED AFTER 24 HOURS									
	7	ANIMAL SACRIFICED AFTER 24 HOURS									
30	1	4	4	?	3	4	3	80	?	20	100
	2	ANIMAL SACRIFICED AFTER 24 HOURS									
	3	ANIMAL SACRIFICED AFTER 24 HOURS									
	4	ANIMAL SACRIFICED AFTER 24 HOURS									
	7	ANIMAL SACRIFICED AFTER 24 HOURS									

TABLE 21

Summary of acute toxicological investigations

Compound	Acute oral toxicity (ml/kg)	Primary Irritation Index	Total Score for Eye Irritation
AMEO	3.65 (3.26 - 4.09)	6.50	Maximum scores obtained
GLYMO	> 5.0	0.06	42
MEMO	> 5.0	1.19	14
NTMO	1.83 (1.65 - 2.03)	0.19	16
VTMO	> 5.0	0.00	28
VTMOEO	2.30 (1.92 - 2.76)	0.19	10

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87-1900186 A(5)

Industrial **BIO-TEST** Laboratories, Inc.

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ORIGINAL REPORT

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REPORT TO

DOW CORNING CORPORATION

TOXICITY STUDIES ON

TX - 27

Z-6040, Lot 22

1963-I0065 - 1167-2

REPORT TO
DOW CORNING CORPORATION
TOXICITY STUDIES ON
TX - 27
DOW CORNING® Z-6040 silane

I. Introduction

A sample identified as TX - 27 was received from Dow Corning Corporation for toxicological evaluation. The following toxicity studies were conducted:

Acute Oral Toxicity - Albino Rats
Acute Vapor Inhalation Toxicity - Albino Rats
Acute Percutaneous Toxicity - Albino Rabbit
Eye Irritation Test - Albino Rabbits
Skin Irritation Test - Albino Rabbits

II. Procedures

A. Acute Oral Toxicity - Albino Rats

Healthy, young albino rats of the Sprague-Dawley strain with an average body weight of approximately 110 grams were used as test animals. The rats were divided into groups of four animals each for dosing purposes.

All animals used were kept under observation for 14 days.

prior to experimental use, during which period they were checked for general physical well-being and homogeneity. The animals were housed individually in stock cages and permitted a standard laboratory rat diet* plus water ad libitum until 16 hours immediately prior to oral intubation.

On the morning of the first test day, after a 16-hour fast (water permitted), the selected dose groups of four rats each (two male and two female) were intubated with previously calculated doses of the undiluted test material. All doses were administered directly into the stomachs of the rats using a hypodermic syringe equipped with a ball-pointed intubating needle.

Following oral administration of the test material, the rats were returned to their stock cages and observed for the succeeding 14 days.

At the end of the observation period, all data were collected and arrangements were made to calculate the acute oral mean lethal dose (LD_{50}) of the test material using the techniques of Weil**, Thompson***, and Thompson and Weil****.

*Rockland Rat Diet, Rockland Farms, New City, New York

**Weil, Carrol S.: Tables for Convenient Calculation of Median-Effective Dose (LD_{50} or ED_{50}) and Instructions in Their Use. Biometrics, Sept. 1952

***Thompson, William R.: Use of Moving Averages and Interpolation to Estimate Median-Effective Dose. Bact. Rev., Nov. 1947.

****Thompson, William R. and Weil, Carrol S.: On the Construction of Tables for Moving Average Interpolation. Biometrics, March, 1952.

B. Acute Vapor Inhalation Toxicity - Albino Rats

Young, adult albino rats of the Sprague-Dawley strain with an average body weight of 250 grams were employed as test animals. All animals used were kept under observation for five days prior to experimental use, during which period they were checked for general physical well-being and homogeneity. The animals were housed individually in stock cages and permitted a standard laboratory rat diet* plus water ad libitum. The test animals were not fasted prior to the inhalation exposure.

Three groups of four rats each (two male and two female) were utilized in the study of the test material. The inhalation experiment was conducted in a multiple inhalation chamber designed for simultaneous exposure to atmospheres saturated and fractionally saturated with vapors of the test material. The test was designed to run for a four-hour period. At the end of the exposure period the rats were returned to their stock cages and observed for the succeeding 14 days. At the end of the 14-day observation period all surviving animals were sacrificed for gross pathologic examinations.

An outline of the test conditions is presented in Table 1.

* See footnote * page 2

TABLE I

TEST MATERIAL: TX -27

Acute Vapor Inhalation Toxicity - Albino Rats

Outline of Test Conditions

Group Number	Number of Animals Tested Per Chamber	Exposure Time (Hours)	Air Delivery Rate (L/min)	Approximate Average Concentration (mg/L)	Degree of Saturation
I	4	4	1	2.7	Saturated
II	4	4	1	1.4	1/2
III	4	4	1	0.7	1/4

TABLE I

TEST MATERIAL: TX -27

Acute Vapor Inhalation Toxicity - Albino Rats

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II	4	4	1	1.4	1/2
III	4	4	1	0.7	1/4

C. Acute Percutaneous Toxicity - Albino Rabbits

Young adult, New Zealand strain albino rabbits with an average body weight of 2.5 kilograms were employed as test animals. All rabbits had been maintained under observation in the laboratory for seven days prior to testing. During the pre-test period the animals were examined with respect to their general health and suitability as test animals. The rabbits were housed in individual stainless steel cages and maintained on a standard laboratory rabbit ration*. Food and water were permitted ad libitum.

Twenty-four hours prior to the percutaneous applications, the backs of the rabbits were shaved free of hair with electric clippers. The shaved area on each animal constituted about ten per cent of the total body surface area. The animals were then returned to their stock cages to await testing on the following day. The 24-hour waiting period allowed recovery of the stratum corneum from the disturbance which accompanied the close-clipping procedure and also permitted healing of any microscopic abrasions possibly produced during the process.

On the testing day, the rabbits received skin applications of the undiluted test material at several selected dose levels. Each dose level consisted of four rabbits (two male and two female). After each application, the exposure site was covered by wrapping the trunk of the animal with an impervious plastic sheeting which was securely taped in place. This

* Rockland Rabbit Diet, Rockland Farms, New City, New York

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plastic wrap insured intimate contact of epidermis and test material.

The test material remained in contact with the skin for 24 hours. Behavioral reactions were observed and recorded during the contact period, after which the plastic sheeting was removed from each test rabbit. The exposure sites were examined for local reactions and the animals returned to their stock cages. Observations for mortality, local reactions, and behavioral abnormalities were continued for a total of 14 days following the skin applications.

At the end of the observation period, all data were collected and arrangements made to calculate the acute percutaneous mean lethal dose (LD₅₀) of the test material using the techniques of Weil*, Thompson**, and Thompson and Weil***.

* See footnote **, page 2

** See footnote ***, page 2

*** See footnote ****, page 2

D. Eye Irritation Test - Albino Rabbits

A group of five albino rabbits was used to evaluate the eye irritating properties of TX-27. Young adult, New Zealand strain animals were selected for the test.

The test method employed was patterned after that of Draize et al*. Exactly 0.1 ml of undiluted test material was instilled into the conjunctival sac of the right eye of each test rabbit in a group of five animals. The left eye of each animal served as a scoring control.

One, 24, 48, 72, 96 hours, and 7 days following the initial instillations, the cornea, iris, and palpebral conjunctiva were examined individually and graded for irritation and injury according to a standard scoring system*. The maximum possible score at any one examination and scoring period is 110 points which indicates maximal irritation and damage to all three ocular tissues. Zero score indicates no irritation whatever.

After the completion of the test, the scores were analyzed and a descriptive eye irritation rating was assigned to the test material. The criteria used for assignment of the descriptive rating were the frequency, the extent, and the persistence of irritation or damage which occurred to the three ocular tissues. In the classification system used, special emphasis was placed upon irritation or damage to

* "Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes", Draize, John H., Woodard, Geoffrey, and Calvery, Herbert O., J. Pharm. & Exp. Ther., 82, 4, December 1944.

the cornea. Correspondingly less stress was placed upon conjunctival and iridial effects.

The descriptive rating assigned was one of the following, each of which characterizes a particular level of ophthalmic irritation and damage:

Non-Irritating
Practically Non-Irritating
Minimally Irritating
Mildly Irritating
Moderately Irritating
Severely Irritating
Extremely Irritating
Maximally Irritating

E. Skin Irritation Test - Albino Rabbits

Four albino rabbits were used in the evaluation of primary skin irritating properties of TX - 27. The test procedure employed was modeled after that of Draize et al.*

Prior to the application of the test material, the hair was clipped from the backs and flanks of each of the four rabbits. Two test sites located at the midline of the back approximately ten centimeters apart were selected on each rabbit. One of the two sites selected was abraded by making four epidermal incisions, two perpendicular to the other two while the other skin site remained intact.

The test material was applied undiluted to the skin of the prepared exposure sites on each of four rabbits. Applications were in the form of square gauze patches, 2.5 cm on a side, containing 0.5 ml of undiluted test material. These were affixed directly over the skin test sites and secured in place by means of thin strips of adhesive tape.

In the above manner, the test material was evaluated for primary irritation on each of four rabbits, a total of eight sites (four intact and four abraded) being employed.

Following the patch applications, the entire trunk of each test animal was wrapped in an impervious plastic sheeting. This helped to hold the patches in position and retarded evaporation during the 24-hour exposure period.

* See footnote page 7

At the end of 24 hours, the plastic wrappings and patches were removed. The skin sites were then individually examined and scored separately for both erythema and edema on a graded scale of 0 to 4. After 72 hours had elapsed, the sites were re-examined and rescored.

In evaluating the average irritation present, scores for individual intact and abraded sites were recorded separately for each of the two scoring time intervals. The mean scores for the 24- and 72-hour grading periods were then averaged to obtain separate mean irritation grades for both intact and abraded skin. Finally, the latter two means were averaged to give a combined average irritation score. The scoring criteria for erythema and edema are shown in Table II.

TABLE II

Scoring Criteria for Skin Reactions

<u>Erythema and Eschar Formation</u>	
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
Total Possible Erythema Score	4
<u>Edema Formation</u>	
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (area raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4
Total Possible Edema Score	4
Total Possible Primary Irritation Score	8

III. Results

A. Acute Oral Toxicity - Albino Rats

1. Mortality

The mortality data are presented in Table III and are illustrated graphically in Figure 1.

TABLE III

TEST MATERIAL: TX - 27

Acute Oral Toxicity - Albino Rats

Mortality Data

Dose g/kg	Concentration Administered	Number Dead	Number Tested	Per Cent Dead
4.6	undiluted	0	4	0
6.8	undiluted	0	4	0
10.2	undiluted	4	4	100
15.4	undiluted	4	4	100

Acute Oral LD₅₀ = 8.4 g/kg

Standard Deviation of LD₅₀ = ± 0.4 g/kg

Acute Oral LD₁ = 7.3 g/kg

Acute Oral LD₉₉ = 9.6 g/kg

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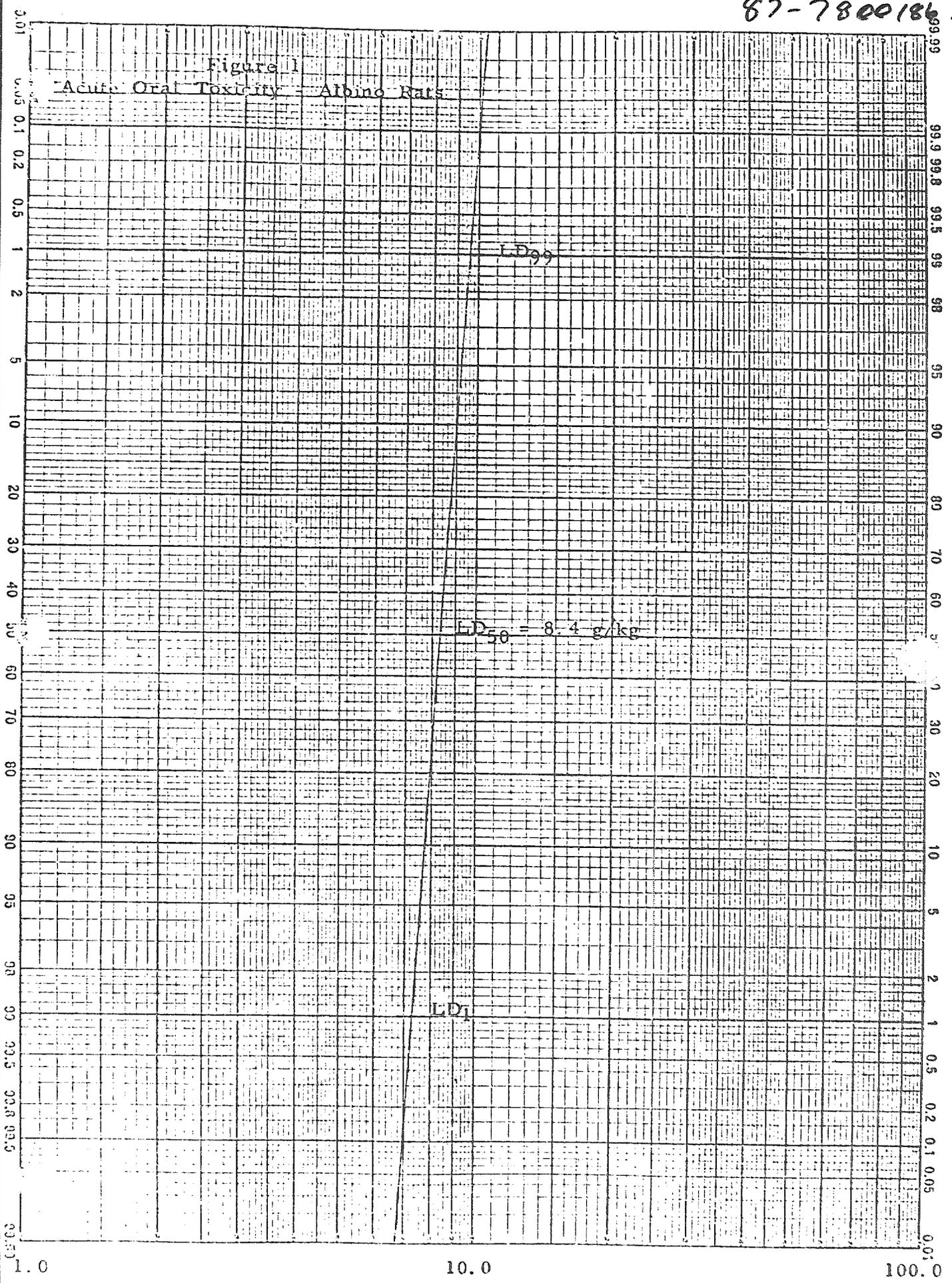


Figure 1
Acute Oral Toxicity - Albino Rats

Dose, g/kg

1.0 10.0 100.0

2. Reactions

Rats in all dose groups exhibited slight to moderate ataxia approximately two minutes after dosing. The ataxia lasted five to ten minutes and was followed by moderate to severe sedation. In addition, animals in the 10.2 and 15.4 g/kg dose groups displayed muscular weakness and hyperpnea approximately ten minutes after administration of the test material. The reactions persisted 24 hours or until death intervened. Deaths occurred 20 minutes to 18 hours after oral gavage.

Necropsy of animals which died during the study and animals sacrificed at the conclusion of the 14-day observation period did not disclose any significant gross pathologic alterations in any of the tissues and organs examined.

B. Acute Vapor Inhalation Toxicity - Albino Rats

No deaths or untoward behavioral reactions were noted among rats exposed for four hours to atmospheres saturated or fractionally saturated with vapors of the test material.

Necropsy of animals sacrificed at the conclusion of the 14-day observation period did not reveal any significant gross pathologic alterations in any of the tissues and organs examined.

C. Acute Percutaneous Toxicity - Albino Rabbits

1. Mortality

The mortality data are presented in Table IV and are illustrated graphically in Figure 2.

TABLE IV

TEST MATERIAL: TX - 27

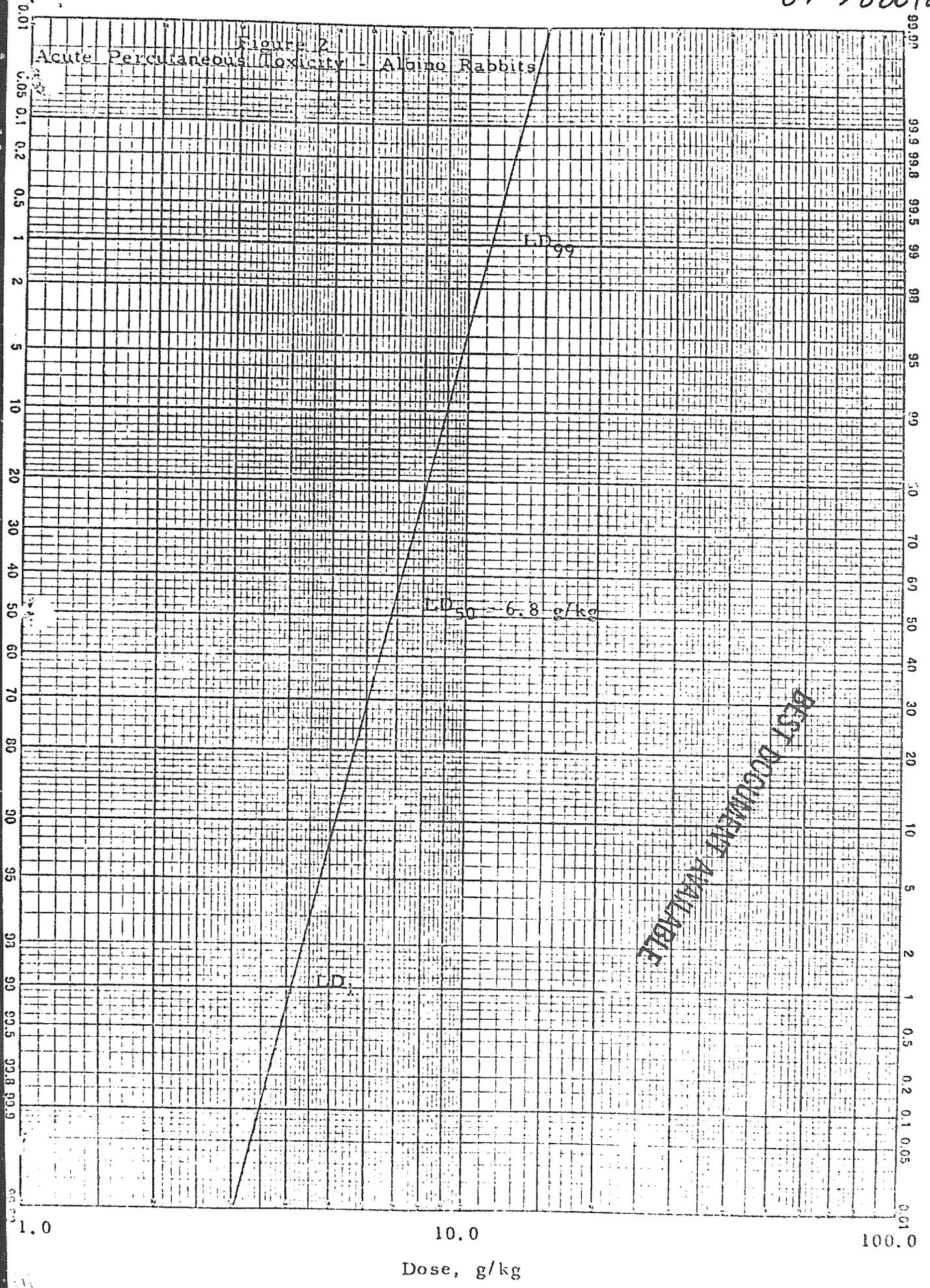
Acute Percutaneous Toxicity - Albino Rabbits

Mortality Data

Dose g/kg	Concentration Administered	Number Dead	Number Tested	Per Cent Dead
4.6	undiluted	0	4	0
6.8	undiluted	3	4	75
10.2	undiluted	3	4	75
15.4	undiluted	4	4	100

Acute Percutaneous $LD_{50} = 6.8$ g/kg
Standard Deviation of $LD_{50} = \pm 0.9$ g/kg
Acute Percutaneous $LD_1 = 4.1$ g/kg
Acute Percutaneous $LD_{99} = 11.3$ g/kg

Figure 2
Acute Percutaneous Toxicity - Albino Rabbits



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Dose, g/kg

2. Reactions

Animals in all dose groups displayed mild to moderate hypoactivity approximately two to three hours following application of the test material. This hypoactivity persisted for 48 hours or until death intervened. Deaths occurred 18 to 24 hours following dermal application of the test material.

Necropsy of rabbits which died during the study and rabbits sacrificed at the end of the 14-day observation period did not reveal any significant gross pathologic alterations in any of the tissues and organs examined.

D. Eye Irritation Test - Albino Rabbits

The eye irritation scores and rating are presented in Table V.

TABLE V

TEST MATERIAL: TX - 27

Eye Irritation Test - Albino Rabbits

Tissue	Rabbit Number	1 Hour	24 Hours	48 Hours	72 Hours	96 Hours	7 Days	Maximum Possible Score
Cornea	1	0	0	0	0	0	0	80
Iris		0	0	0	0	0	0	10
Conjunctiva		2	0	0	0	0	0	20
Total		2	0	0	0	0	0	110
Cornea	2	0	0	0	0	0	0	80
Iris		5	0	0	0	0	0	10
Conjunctiva		2	0	0	0	0	0	20
Total		7	0	0	0	0	0	110
Cornea	3	5	0	0	0	0	0	80
Iris		5	0	0	0	0	0	10
Conjunctiva		2	0	0	0	0	0	20
Total		12	0	0	0	0	0	110
Cornea	4	0	0	0	0	0	0	80
Iris		5	0	0	0	0	0	10
Conjunctiva		2	0	0	0	0	0	20
Total		7	0	0	0	0	0	110
Cornea	5	0	0	0	0	0	0	80
Iris		5	0	0	0	0	0	10
Conjunctiva		2	0	0	0	0	0	20
Total		7	0	0	0	0	0	110
<u>Averages</u>								
Cornea		1.0	0.0	0.0	0.0	0.0	0.0	80
Iris		4.0	0.0	0.0	0.0	0.0	0.0	10
Conjunctiva		2.0	0.0	0.0	0.0	0.0	0.0	20
Total		7.0	0.0	0.0	0.0	0.0	0.0	110

Rating: Minimally Irritating

E. Skin Irritation Test - Albino Rabbits

The results of the skin irritation test are presented in Table VI.

IV. Summary ,A. Acute Oral Toxicity - Albino Rats

The acute oral mean lethal dose (LD₅₀) of TX - 27 for the albino rat was found to be 8.4 g/kg.

B. Acute Vapor Inhalation Toxicity - Albino Rats

No deaths were recorded among groups of albino rats exposed to atmospheres saturated and fractionally saturated with vapors of TX - 27 for a period of four hours.

C. Acute Percutaneous Toxicity - Albino Rabbits

The acute percutaneous mean lethal dose (LD₅₀) of TX - 27 for the albino rabbit was found to be 6.8 g/kg.

D. Eye Irritation Test - Albino Rabbits

When instilled into the eyes of albino rabbits, undiluted TX - 27 was found to be minimally irritating.

E. Skin Irritation Test - Albino Rabbits

When applied to intact and abraded skin of albino rabbits, undiluted TX - 27 was found to produce mild irritation.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report prepared by:

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Report approved by:

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May 24, 1963

TABLE VI

TEST MATERIAL: TX - 27

Primary Skin Irritation

Results

Number	Irritation Scores				Combined Average
	Intact Skin		Abraded Skin		
	24 Hours	72 Hours	24 Hours	72 Hours	
1	2.0	1.0	3.0	1.0	
2	2.0	2.0	3.0	3.0	
3	2.0	1.0	2.0	1.0	
4	1.0	1.0	2.0	2.0	
Mean	1.5		2.1		1.8

Primary Irritation Rating: Mildly Irritating