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ACUTE TOXICITY, SKIN IRRITANCY AND SKIN SENSITIZATION OF THE DIGLYCIDYL ETHER OF 1,4-BUTANE DIOL

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GLYCIDOL & ITS DERIVATIVES		999999994	
OXIRANE, 2,2'-[1,4-BUTANEDIYLBIS(OXYMETHYLENE)]BIS-		2425-79-8	

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THIS DOCUMENT HAS BEEN DECLASSIFIED PER LETTER FROM CIBA-GEIGY DATED MARCH 1, 1984. (SEE LAST SIX FRAMES OF FICHE (FICHE SET).

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CAS 2425-79-8

ACUTE TOXICITY, SKIN IRRITANCY AND SKIN SENSITIZATION

OF THE DIGLYCIDYL ETHER OF 1,4-BUTANE DIOL

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ACUTE TOXICITY, SKIN IRRITANCY AND SKIN SENSITIZATION OF THE DIGLYCIDYL ETHER OF 1,4-BUTANE DIOL

SUMMARY

The acute toxicity of the diglycidyl ether of 1,4-butane diol has been examined and the acute oral and percutaneous LD_{50} values determined. The skin irritancy and skin sensitization potentials have been determined for this material.

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INTRODUCTION

At a meeting between Ciba-Geigy and Shell[1] the details of a toxicological evaluation of various resins, to be carried out by Shell Toxicology Laboratory (Tunstall), were discussed. It was agreed that Shell Toxicology Laboratory (Tunstall) would carry out the following tests on the diglycidyl ether of 1,4-butane diol.

1. Acute oral toxicity.
2. Acute percutaneous toxicity.
3. Skin irritation.
4. Skin sensitisation.

The purpose of this report is to describe the methods which have been used to carry out the evaluation and also present the data from the experiments.

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MATERIALS AND METHODS

Materials

The sample of diglycidyl ether of 1,4-butane diol was supplied to Shell Toxicology Laboratory (Tunstall) by Ciba-Geigy Ltd., Basle, Switzerland.

Animals

Species	Strain	Source
Mouse	CFT	Shell Toxicology Laboratory (Tunstall) Breeding Unit.
Rat	Wistar	Shell Toxicology Laboratory (Tunstall) Breeding Unit.
Rabbit	New Zealand White	Goleside Ltd., Northchurch, Berkhampstead, Herts.
Guinea-pig	'P' Strain	Shell Toxicology Laboratory (Tunstall) Breeding Unit.

Experimental details

1. Single dose acute oral toxicity (See Appendix I)

Diglycidyl ether of 1,4-butane diol was administered to Wistar rats (aged 12-14 weeks) and CFT mice (18-25 g).

The animals were weighed and fasted overnight. The rats and mice were dosed by oesophageal intubation with diglycidyl ether of 1,4-butane diol as a solution in acetone or toluene. Food and water were available *ad libitum* for the nine day observation period.

2. Single dose acute percutaneous toxicity (See Appendix II)

The method of Monkman and Sanderson[1] was used to determine the acute percutaneous toxicity of diglycidyl ether of 1,4-butane diol to rats and mice.

3. Primary skin irritation (See Appendix III)

Rabbits

The degree of primary irritation caused by diglycidyl ether of 1,4-butane diol was assessed according to the method described by Draize[2].

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Mice

The degree of primary irritancy caused by repeated applications of diglycidyl ether of 1,4-butane diol was investigated in male and female mice. Two studies of four weeks duration were carried out, the first using toluene as the solvent and the second using acetone.

Both studies were carried out using CFI mice (bred under specific pathogen-free conditions at Shell Toxicology Laboratory (Tunstall), housed individually in polypropylene cages and provided with water and cubed diet (Spratts Laboratory Diet Number 1 supplied by Spratts Ltd., Barking, Essex) ad libitum. All mice were six weeks old when first dosed.

In both studies a range of dose levels were examined using five animals per dose level.

In the first study using toluene solvent, diglycidyl ether of 1,4-butane diol was administered as 20%, 10% 5%, 1%, 0.5% and 0.25% w/v solutions. A further dose group of five male and five female mice received toluene solvent only. In the second study using acetone solvent, diglycidyl ether of 1,4-butane diol was administered as 20%, 10%, 5%, 1%, 0.5%, 0.2%, and 0.1% w/v solutions. Two further dose groups were added to this experiment. One received acetone solvent only and the mice in the other group were shaved and left untreated.

In both studies a randomised block design was used. Each animal was dosed twice and shaved once a week for a period of four weeks. All test solutions and solvents were applied by measuring 0.2 ml onto the shaved dorsal surface of the mouse from a glass syringe.

All animals were observed continuously throughout the study for any signs of irritancy.

4. Skin sensitisation (See Appendix IV)

The method of Beuhler[3] was used to assess the skin sensitizing potential of diglycidyl ether of 1,4-butane diol.

The concentrations of diglycidyl ether of 1,4-butane diol used for induction and challenge are tabulated below:-

Concentration % w/w of test material in soft paraffin B.P.

Sample	Topical induction	Topical challenge
Diglycidyl ether of 1,4-butane diol.	1	0.5

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RESULTS AND DISCUSSION

1. Acute oral toxicity (See Table 1)

The single dose acute oral LD_{50} values of diglycidyl ether of 1,4-butane diol when dosed as 20% w/v solutions in toluene and acetone were found to be as follows:-

Compound	Rat LD_{50} mg/kg	Mouse LD_{50} mg/kg	
	Toluene	Toluene	Acetone
Diglycidyl ether of 1,4-butane diol	>300	>400	>400

2. Acute percutaneous toxicity (See Table 2)

The single dose acute percutaneous LD_{50} values of diglycidyl ether of 1,4-butane diol when dosed as 20% w/v solutions in toluene and acetone were found to be as follows:-

Compound	Rat LD_{50} mg/kg		Mouse LD_{50} mg/kg	
	Toluene	Acetone	Toluene	Acetone
Diglycidyl ether of 1,4-butane diol	>800	>800	>800	>800

3. Primary skin irritation

Rabbits (See Tables 3-5)

One 24 hour application of "undiluted" diglycidyl ether of 1,4-butane diol to intact and abraded occluded rabbit skin caused severe irritation resulting in black necrotic patches.

A 24 hour application of a 20% w/v solution of diglycidyl ether of 1,4-butane diol in toluene caused severe irritation to abraded and intact occluded rabbit skin. An escher was observed in two males and the skin of all rabbits was hardened by day 7.

The toluene blank was moderately irritant to intact rabbit skin.

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A 20% w/v solution of diglycidyl ether of 1,4-butane diol in acetone caused moderate to severe skin irritation to intact and abraded occluded rabbit skin. An eschar was observed in two males. One female rabbit became very lethargic and had difficulty in breathing within 5 hours of being wrapped; the adhesive bandage was therefore removed to allow the animal to recover. This animal was subsequently sacrificed after 24 hours due to its poor clinical condition and the severity of the skin reaction.

The acetone blank caused a mild transient skin irritation in the male rabbit and practically no irritation in the female.

Mice

After one application of 20% w/v diglycidyl ether of 1,4-butane diol in toluene five out of five males and one out of five females were found dead. Three of the remaining top dose females died one day after the second application had been given and the fifth top dose female died three days after the second application. One male was found dead two days after being treated once with 0.2 ml 10% w/v diglycidyl ether of 1,4-butane diol in toluene. After one weeks exposure to 10% w/v diglycidyl ether of 1,4-butane diol in toluene, four of the remaining males had brown dorsal crusts of dead skin. After two weeks exposure to 10% w/v diglycidyl ether of 1,4-butane diol in toluene only one male was left surviving. Although this animal survived to the end of the study it still exhibited a brown dorsal crust of dead skin (see Photograph 1). No deaths were seen in female mice treated with 10% w/v diglycidyl ether of 1,4-butane diol in toluene but after four weeks exposure all animals showed brown crusts or scabs (see Photograph 2). At 5% w/v both male and female mice were seen to exhibit eschar as with those animals treated at 10% and 20% w/v diglycidyl ether of 1,4-butane diol in toluene. Eschar and hyperaemia were seen in male mice at 1%, 0.5% and 0.25% w/v but in female mice only hyperaemia was noticed at these dose levels. The reappearance of hair growth was seen in both male and female mice in the 1%, 0.5% and 0.25% w/v levels after four weeks exposure to diglycidyl ether of 1,4-butane diol. At 5% w/v some hair growth was observed but not in all animals and at 10% and 20% w/v no hair growth was observed.

After two weeks application of toluene solvent only male and female CFI mice exhibited severe irritancy (see Photographs 3 and 4). By the end of the study the degree of irritancy had decreased and hair growth had recommenced (see Photographs 5 and 6).

After two applications of 20% w/v diglycidyl ether of 1,4-butane diol in acetone five out of five males and three out of five females were either found dead or sacrificed for humanitarian reasons. The two remaining female mice were sent to pathology individually six days and nine days respectively after the start of the experiment. After two weeks exposure to 10% w/v diglycidyl ether of 1,4-butane diol in acetone one male and two female mice had been found dead or sacrificed on humanitarian grounds. The remaining male and female mice treated with 10% w/v diglycidyl ether of 1,4-butane diol exhibited dorsal crusts of brown skin,

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scabs and hyperaemia from day seven to the end of the week study (see Photographs 7 and 8). No mortality was recorded in male and female mice treated with 5% w/v diglycidyl ether of 1,4-butane diol in acetone for four weeks. However after two doses brown crusts were present in both sexes and from ten days after the start of the experiment all animals exhibited escher and hyperaemia to the end of the study (see Photographs 9 and 10). No skin irritation was seen in male or female mice treated with 1%, 0.5%, 0.2% and 0.1% w/v diglycidyl ether of 1,4-butane diol in acetone. No skin irritation was evident in male or female mice treated with acetone solvent alone (see Photographs 11 and 12).

From the results obtained it is possible to estimate the maximum tolerated dose for diglycidyl ether of 1,4-butane diol in toluene as 0.25% w/v or less and in acetone as 1% w/v.

4. Skin sensitization (Table 6)

Using the Beuhler procedure for detecting skin sensitizers, 12 out of 20 test animals previously exposed to diglycidyl ether of 1,4-butane diol showed skin reactions to a challenge treatment. In view of the number of animals responding and the severity of the responses, diglycidyl ether of 1,4-butane diol was considered to be a moderate skin sensitiser.

CONCLUSIONS

Diglycidyl ether of 1,4-butane diol has a low order of acute toxicity by both oral and percutaneous routes when administered as a 10% w/v solution.

Diglycidyl ether of 1,4-butane diol was found to be severely irritant to occluded rabbit skin when applied undiluted or as a 20% w/v solution in toluene or acetone.

Diglycidyl ether of 1,4-butane diol was found to be acutely toxic when applied percutaneously, as a 20% w/v solution in toluene or acetone to male and female mice, as a 10% w/v solution in toluene to male mice and as a 10% w/v solution in acetone to male and female mice. When applied to mouse skin as 5%, 1%, 0.5% and 0.25% w/v solutions in toluene, diglycidyl ether of 1,4-butane diol was found to be severely irritant. Severe irritation was observed in male and female mice treated with 5% w/v diglycidyl ether of 1,4-butane diol in acetone. No skin reactions were seen with 1%, 0.5%, 0.2% and 0.1% w/v solutions of diglycidyl ether of 1,4-butane diol in acetone.

Diglycidyl ether of 1,4-butane diol was found to cause skin sensitization in guinea-pigs.

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Director, Shell Toxicology Laboratory (Tunstall)

Date: November, 1977.

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REFERENCES

1. Discussion on toxicity of Epoxy compounds.
Minutes of a meeting between Shell and Ciba-Geigy held in London, 12th November, 1975.

2. Noakes, D. N. and Sanderson, D. M. (1969).
A method for determining the dermal toxicity of pesticides.
Br. J. industr. Med., 26, 59-64.

3. Draize, J. H., (1959).
'Dermal Toxicity' in 'Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics'.
Association of Food and Drug officials in the United States of America.

4. Beuhler, E. V. (1965).
Delayed contact hypersensitivity in guinea-pigs.
Arch. Dermatol. 91, 171-177.

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Table 1 - Acute oral mortality data

Species	Route	Vehicle and Concentration % w/v
Wistar rat	Oral	Digylcidyl ether of 1,4-butane diol (ex Ciba Geigy) 20% w/v in tolvene

Dosage mg/kg	Daily Mortality (Days 1-10) 1 M	1 F	2 M	2 F	3 M	3 F	4 M	4 F	5 M	5 F	6 M	6 F	7 M	7 F	8 M	8 F	9 M	9 F	10 M	10 F	Cumulative Mortality M	F	Total
500																					0/4	0/4	0/8
500																					0/4	0/4	0/8

Species	Route	Vehicle and Concentration % w/v
CFI Mice	Oral	Diglycidyl ether of 1,4-butane diol (ex Ciba Geigy) 20% w/v in tolvene

Dosage mg/kg	Daily Mortality (Days 1-10) 1 M	1 F	2 M	2 F	3 M	3 F	4 M	4 F	5 M	5 F	6 M	6 F	7 M	7 F	8 M	8 F	9 M	9 F	10 M	10 F	Cumulative Mortality M	F	Total
200																					0/4	0/4	0/8
400			1																		1/4	0/4	1/8

Species	Route	Vehicle and Concentration % w/v
CFI Mice	Oral	Diglycidyl ether of 1,4-butane diol (ex Ciba Geigy) 20% w/v in acetone

Dosage mg/kg	Daily Mortality (Days 1-10) 1 M	1 F	2 M	2 F	3 M	3 F	4 M	4 F	5 M	5 F	6 M	6 F	7 M	7 F	8 M	8 F	9 M	9 F	10 M	10 F	Cumulative Mortality M	F	Total
100						1															0/4	1/4	1/8
200			1																		1/4	0/4	1/8
400																					0/4	0/4	0/8

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Table 2 - Acute percutaneous mortality data

Species	Route	Vehicle and Concentration % w/v
Wistar rat	Percutaneous	Diglycidyl ether of 1,4-butane diol (ex Ciba Geigy) 20% w/v in toluene

Dosage mg/kg	Daily Mortality (Days 1-10) 1 M	1 F	2 M	2 F	3 M	3 F	4 M	4 F	5 M	5 F	6 M	6 F	7 M	7 F	8 M	8 F	9 M	9 F	10 M	10 F	Cumulative Mortality M	F	Total
800																					0/4	0/4	0/8
400																					0/4	0/4	0/8

Species	Route	Vehicle and Concentration % w/v
Wistar rat	Percutaneous	Diglycidyl ether of 1,4-butane diol (ex Ciba Geigy) 20% w/v in acetone

Dosage mg/kg	Daily Mortality (Days 1-10) 1 M	1 F	2 M	2 F	3 M	3 F	4 M	4 F	5 M	5 F	6 M	6 F	7 M	7 F	8 M	8 F	9 M	9 F	10 M	10 F	Cumulative Mortality M	F	Total
800																					0/4	0/4	0/8

Species	Route	Vehicle and Concentration % w/v
CFI Mice	Percutaneous	Diglycidyl ether of 1,4-butane diol (ex Ciba Geigy) 10% w/v in toluene

Dosage mg/kg	Daily Mortality (Days 1-10) 1 M	1 F	2 M	2 F	3 M	3 F	4 M	4 F	5 M	5 F	6 M	6 F	7 M	7 F	8 M	8 F	9 M	9 F	10 M	10 F	Cumulative Mortality M	F	Total
200																					0/4	0/4	0/8
400																					0/4	0/4	0/8
800																					0/4	0/4	0/8

Species	Route	Vehicle and Concentration % w/v
CFI Mice	Percutaneous	Diglycidyl ether of 1,4-butane diol (ex Ciba Geigy) 20% w/v in acetone

Dosage mg/kg	Daily Mortality (Days 1-10) 1 M	1 F	2 M	2 F	3 M	3 F	4 M	4 F	5 M	5 F	6 M	6 F	7 M	7 F	8 M	8 F	9 M	9 F	10 M	10 F	Cumulative Mortality M	F	Total
800																					0/4	0/4	0/8

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Table 3 - Primary irritation of occluded rabbit skin after a single application of diglycidyl ether of 1,4-butane diol, undiluted

Animal No.	Sex		Response	24 hours	48 hours	72 hours	7 days
4762	F	Non-abraded patch	Erythema	4	4	4	4
			Oedema	2-3	2-3	2-3	4
4763	F	Abraded patch	Erythema	4	4	4	4
			Oedema	2-3	2-3	2-3	4
4764	F	Non-abraded patch	Erythema	2	2-3	2-3	2-3
			Oedema	1-2	1-2	1-2	2-3
4765	F	Abraded patch	Erythema	4	4	4	4
			Oedema	3-4	3-4	3-4	4
4766	M	Non-abraded patch	Erythema	4	4	4	4
			Oedema	3	3	3	3-4
4767	M	Abraded patch	Erythema	4	4	4	4
			Oedema	3-4	3	3	4
4768	M	Non-abraded patch	Erythema	4	4	4	4
			Oedema	3-4	3	3	3-4
4769	M	Abraded patch	Erythema	4	3-4	3-4	4
			Oedema	3-4	3-4	3-4	3-4

Scale: Readings 0 = No erythema to 4 = Beet redness
Readings 0 = No oedema to 4 = Severe oedema

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Table 4 - Primary irritation of occluded rabbit skin after a single application of 20% w/v diglycidyl ether of 1,4-butane diol in toluene

Animal No.	Sex		Response	24 hours	48 hours	72 hours	7 days
4789	F	Non-abraded patch	Erythema	4	4	4	4
			Oedema	3-4	4	4	4
4790	F	Abraded patch	Erythema	4	Animal sacrificed at 24 h		
			Oedema	4	Animal sacrificed at 24 h		
4791	F	Non-abraded patch	Erythema	4	4	3-4	3
			Oedema	4	3	3	2-3
4792*	F	Abraded patch	Erythema	2	2	2	2
			Oedema	2-3	2	2	1-2
4793	M	Non-abraded patch	Erythema	4	4	4	4
			Oedema	3-4	3-4	4	4
4794	M	Abraded patch	Erythema	2-3	2	2	1-2
			Oedema	3-4	2	1-2	1
4795	M	Non-abraded patch	Erythema	4	4	4	4
			Oedema	4	3-4	3-4	4
4796*	M	Abraded patch	Erythema	2	2	1-2	1-2
			Oedema	2-3	2-3	2	1

Scale: Readings 0 = No erythema to 4 = Best redness
Readings 0 = No oedema to 4 = Severe oedema

* Animals treated with toluene solvent only.

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Table 3 - Primary irritation of occluded rabbit skin after a single application of 20% w/v diglycidyl ether of 1,4-butane diol in acetone

Animal No.	Sex		Response	24 hours	48 hours	72 hours	7 days
4789	F	Non-abraded patch	Erythema	2	2	2	2
			Oedema	1-2	2	2	1-2
4790	F	Abraded patch	Erythema	4	Animal sacrificed at 24 h		
			Oedema	3-4	Animal sacrificed at 24 h		
4791	F	Non-abraded patch	Erythema	4	2	2	1-2
			Oedema	3-4	2-3	2	1-2
4792*	F	Abraded patch	Erythema	0-1	0	0	0
			Oedema	0	0	0	0
4793	M	Non-abraded patch	Erythema	4	4	4	3-4
			Oedema	4	3-4	3-4	3
4794	M	Abraded patch	Erythema	2-3	2-3	2-3	3-4
			Oedema	3	2-3	2	0-1
4795	M	Non-abraded patch	Erythema	3	2-3	2	0-1
			Oedema	2-3	2	2	0
4796*	M	Abraded patch	Erythema	1	0-1	0	0
			Oedema	1-2	1	0	0

Scale: Readings 0 = No erythema to 4 = Beet redness
Readings 0 = No oedema to 4 = Severe oedema

* Animals treated with acetone solvent only

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Table 6 - Skin sensitization reaction in guinea-pigs exposed to diglycidyl ether of 1,4-butane diol

Animal number	Sex	Skin response after challenge procedure		
		Immediate	24 hours	48 hours
Treated				
1	Male	0	0	0
2	Male	0-1	0	0
3	Male	0	0	0
4	Male	0-1	0	0
5	Male	0	0	0
1	Female	0-1	0	0
2	Female	0	0	0
3	Female	0	0	0
4	Female	1	0	0
5	Female	0	0	0
6	Male	0	0	0
7	Male	3	0	0
8	Male	1	0	0
9	Male	1	0	0
10	Male	0-1	0	0
6	Female	0-1	0	0
7	Female	1-2	0	0
8	Female	1-2	0	0
9	Female	1	0	0
10	Female	0	0	0
Control				
1	Male	0	0	0
2	Male	0	0	0
3	Male	0	0	0
4	Male	0	0	0
5	Male	0	0	0
1	Female	0	0	0
2	Female	0	0	0
3	Female	0	0	0
4	Female	0	0	0
5	Female	0	0	0

Three topical inductions with 1% w/v diglycidyl ether of 1,4-butane diol in soft paraffin B.P.

Topical challenge of 0.5% w/v diglycidyl ether of 1,4-butane diol in soft paraffin B.P.

Key: 0 = No skin reaction. 1 = Slight skin reaction.
2 = Moderate skin reaction. 3 = Severe skin reaction.

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APPENDIX II

ACUTE PERCUTANEOUS TOXICITY

The method used was the same as that described by Noakes and Sanderson for pesticides.

Four rats of each sex, aged 12-13 weeks, were used at each dose level. The test material was placed onto the shorn dorso-lumbar skin and bandaged into contact with the skin using an impermeable dressing of aluminium foil and waterproof plaster. The rats were housed individually over the 24 hours exposure period during which time the animals were deprived of food but allowed water ad libitum.

After 24 hours the dressings were removed and the exposed area was washed with a tepid dilute detergent solution. The rats were then housed in cages of four of one sex and observed for signs of intoxication during the following 9 days.

Noakes, D. N. and Sanderson, D. M., (1969).
A method for determining toxicity of pesticides.
Br. J. industr. Med., 26, 59-64.

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APPENDIX III

PRIMARY IRRITATION OF THE SKIN

The method used was that described by Draize.

Primary irritation of the abraded and intact skin of each of four male and four female rabbits was measured. The dorsal hair between the shoulders and the hindquarters was closely shorn by means of electric clippers. A 2 x 2 cm area of the shorn skin was abraded using a fine hypodermic needle. Injuries were deep enough to disturb the stratum corneum but not sufficiently deep to cause bleeding. 2 x 2 cm lint patches were applied to the abraded and intact skin and 0.5 ml test material was applied to each. The patches were covered by an occlusive polyethylene film which was secured in position by means of an elastic adhesive bandage (3" Poroplast). The patches were left in place for 24 hours.

Reactions were assessed visually for the degree of erythema and oedema as shown in the table below. Seven days after the application of the test material a final visual assessment was made.

No erythema	=	0	No oedema	=	0
Pale pink	=	1	Soft skin	=	1
Redness	=	2	Oedema	=	2
Severe redness	=	3	More definite oedema	=	3
Beet redness	=	4	Severe oedema	=	4

Draize, J. H., (1969).
'Dermal Toxicity' in "Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics".
Association of Food and Drug Officials of the United States of America.

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APPENDIX IV

SKIN SENSITIZATION

The Beuhler method was used to assess the skin sensitizing potential of the test material.

A preliminary screen was carried out to determine the concentrations of test material to be used for the topical inductions and topical challenge. Two male and two female guinea-pigs were used for each test concentration.

Groups of ten male and ten female guinea-pigs were used for the test and a further five males and five females as controls.

An area 5 x 5 cm was closely shaved on the left flank of each test animal, by means of an electric razor. 0.5 ml of the test material at a concentration producing slight irritation was applied to a 4 x 4 cm patch of Whatman No. 3 MM filter paper and the patch was then placed over the shaved area. This was covered by overlapping impermeable plastic adhesive (5 cm Blenderm) which in turn was firmly secured by an elastic adhesive bandage (3" Foroplast). This dressing was left in place for 24 hours. Treatments were repeated once weekly for 3 weeks. Two weeks after the last exposure, all test and control animals were challenged in the same manner with duplicate closed patches on the right flank using a non-irritant concentration of the material. The animals were examined for a sensitization reaction 24 and 48 hours after removal of the patches. Three hours before the 24 hour reading the test sites were closely shaved with an electric razor.

Beuhler, E. V. (1965).
Delayed contact hypersensitivity in guinea-pigs.
Arch. Dermatol. 91, 171-177.

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A male mouse after 4 weeks exposure to 10% w/v diglycidyl ether of 1,4—butane diol in toluene

2

A female mouse after 4 weeks exposure to 10% w/v diglycidyl ether of 1,4—butane diol in toluene

3

A male mouse after 2 weeks exposure to toluene solvent alone

4

A female mouse after 2 weeks exposure to toluene solvent alone

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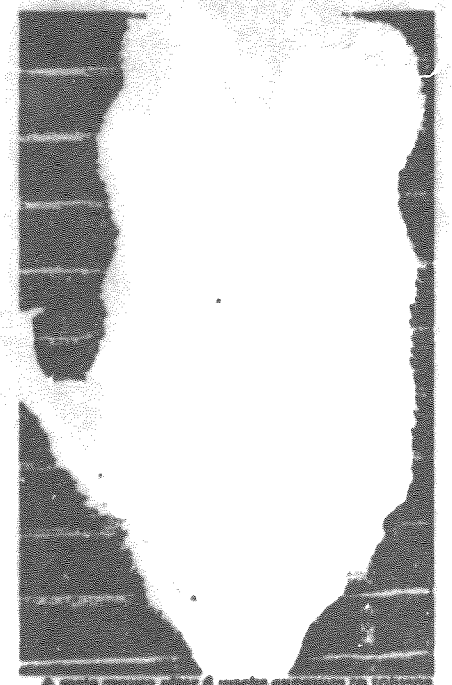

5 A male mouse after 4 weeks exposure to toluene solvent alone

6 A female mouse after 4 weeks exposure to toluene solvent alone

7 A male mouse after 4 weeks exposure to 10% w/v diglycidyl ether of 1,4—butane diol in acetone

8 A female mouse after 4 weeks exposure to 10% w/v diglycidyl ether of 1,4—butane diol in acetone

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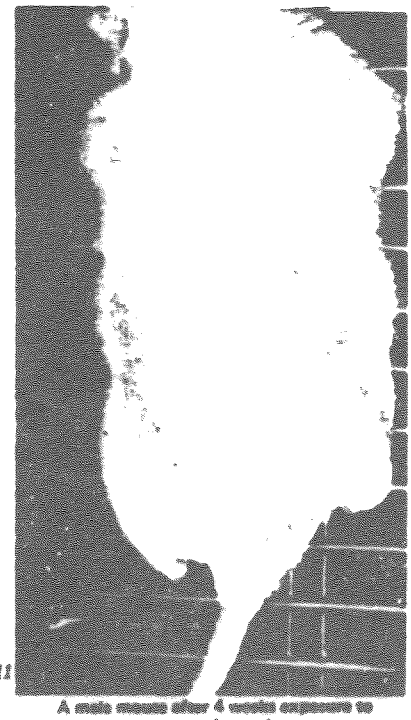
9 A male mouse after 4 weeks exposure to 5% w/v diglycidyl ether of 1,4—butane diol in acetone

10 A female mouse after 4 weeks exposure to 5% w/v diglycidyl ether of 1,4—butane diol



11 A male mouse after 4 weeks exposure to acetone solvent alone

12 A female mouse after 4 weeks exposure to acetone solvent alone