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TOXICITY OF PURIFIED DIGLYCIDYL
ETHER OF BISPHENOL A: RESULTS OF
PRELIMINARY STUDIES.

GLYCIDOL & ITS DERIVATIVES

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DIGLYCIDYL ETHER OF BISPHENOL A

1675-54-3

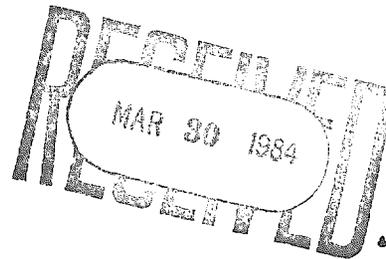
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Report No. 178

SUBMISSION OF LISTS AND COPIES OF HEALTH AND SAFETY STUDIES
Federal Register, 47:38780-38799, September 2, 1982

<u>Name of Requested Substance</u>	<u>CAS Number</u>
diglycidyl ether of bisphenol A	1675-54-3

Other Component



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SHELL TOXICOLOGY LABORATORY (TUNSTALL)

Group Research Report TLGR.0010.77

Title: Toxicity of purified diglycidyl ether of bisphenol A:
Results of preliminary studies.

Authors: J. W. Hend, D. G. Clark and A. D. Coombs.

Reviewed by: V. K. H. Brown.

Work done by: Shell Toxicology Laboratory and the Statistics
Unit of Shell Biosciences Laboratory.

Object: To carry out a preliminary toxicological
investigation of purified diglycidyl ether of
bisphenol A.

Summary:

1. Both Batch EP1 and 75/15875 of purified diglycidyl ether of bisphenol A were found to have a low order of acute toxicity by both the oral and the percutaneous routes.
2. Undiluted diglycidyl ether of bisphenol A, was found to be mildly to moderately irritant to intact and abraded rabbit skin.
3. Diglycidyl ether of bisphenol A, was found to be irritant to mouse skin following four weeks repeated application when applied as 20%, 10%, 5% and 1% w/v solutions in toluene. No skin reactions were seen with either of batch numbers 75/15875 or EP1 of purified diglycidyl ether of bisphenol A when applied as 10%, 5%, 1% and 0.5% w/v solutions in acetone to mouse skin.
4. Diglycidyl ether of bisphenol A, batch numbers 75/15875, produced moderate skin sensitization in guinea pigs.

E. Sharpe

pp D. E. STEVENSON, M.A., Ph.D., B.Sc., B.V.Sc., M.R.C.V.S.,
Director, Shell Toxicology Laboratory (Tunstall).

Date: February, 1978.

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INTRODUCTION

The two samples of diglycidyl ether of bisphenol A described in this report were obtained by removing all the light ends and certain of the heavy ends from a sample of EPIKOTE* 828.

This report describes the results from preliminary studies which have been carried out on purified diglycidyl ether of bisphenol A. It was not possible to evaluate both batch numbers 75/15875 and EP1 in every study because test material was unavailable.

* Shell Registered Trade Mark

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MATERIALS AND METHODS

Materials

The sample of purified diglycidyl ether of bisphenol A designated Batch No. 75/15875, was purified and supplied by Koninklijke/Shell Laboratorium, Amsterdam (KLSA), whilst that referred to as Pure EP1 was purified and supplied by Ciba-Geigy Ltd., Basle, Switzerland.

Animals

Species	Strain/Breed	Source
Mouse	CF1	Shell Toxicology Laboratory Breeding Unit
Rat	Wistar	Shell Toxicology Laboratory Breeding Unit.
Rabbit	New Zealand White	Ranch Rabbits, Crawley, Sussex.
Guinea-pigs	'P' strain	Shell Toxicology Laboratory Breeding Unit

EXPERIMENTAL DETAILS

Acute toxicity

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

Purified diglycidyl ether of bisphenol A was administered to Wistar rats (aged 12-14 weeks) and CF1 mice (18-25 g).

The animals were weighed and fasted overnight. The rats and mice were dosed by oesophageal intubation with purified diglycidyl ether of bisphenol A as a solution in acetone or toluene. Food and water were available ad libitum for the nine days observation period.

1.1 Single dose acute percutaneous toxicity (see Appendix II)

The method of Noakes and Sanderson⁽¹⁾ was used to determine the acute percutaneous toxicity of purified diglycidyl ether of bisphenol A to rats and mice.

Primary skin irritation

2. Rabbits (see Appendix III)

The degree of primary irritancy caused by diglycidyl ether of bisphenol A was assessed according to the method described by Draize⁽²⁾.

2.1 Mice

The degree of primary irritancy caused by repeated applications of diglycidyl ether of bisphenol A 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. In both studies a range of dose levels were examined using five animals per dose level.

The studies were carried out using CF1 mice (bred under specific pathogen-free conditions at Shell Toxicology Laboratory Breeding Unit) housed individually in polypropylene cages and provided with water and cubed diet (Spratts Laboratory Diet No. 1, supplied by Spiller-Spratts Ltd., Barking, Essex) ad libitum. All mice were six weeks old when first dosed.

In the first study using toluene solvent, the diglycidyl ether of bisphenol A, batch number 75/15875, was administered as 20%, 10%, 5% and 1% w/v solutions together with a further dose group of five male and five female mice exposed to toluene solvent only. In the second study using acetone solvent, two samples of the diglycidyl ether of bisphenol A, batch number 75/15875 (as purified by KSLA) and EP1 (as purified by Ciba-Geigy) were tested as 10%, 5%, 1% and 0.5% w/v solutions. Two further 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 weekly 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 irritation.

Skin sensitization (see Appendix IV)

The method of Beuhler⁽³⁾ was used to assess the sensitizing potential of the diglycidyl ether of bisphenol A.

In the one experiment performed, three topical inductions of 51.4% w/w diglycidyl ether of bisphenol A, (batch number 75/15875), in soft paraffin BP were challenged by one application of 25% w/v in soft paraffin BP.

RESULTS AND DISCUSSION

Acute oral toxicity (Tables 1 and 2)

The single dose acute oral LD₅₀ of diglycidyl ether of bisphenol A, batch number 75/15875 and EP1, when dosed as 20% w/v solution 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 bisphenol A				
Batch No. 75/15875	>1000	>1000	>500	>800
Batch No. EP1	>500	>500	>500	>500

Acute percutaneous toxicity (Tables 3 and 4)

The single dose acute percutaneous LD₅₀ of diglycidyl ether of bisphenol A batch numbers 75/15875 and EP1, 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 bisphenol A				
Batch No. 75/15875	>1600	>800	>1600	>1600
Batch No. EP1	>1600	>800	>1600	>1600

Primary skin irritation

2.1 Rabbits (Table 5)

One 24 hour application of undiluted diglycidyl ether of bisphenol A, batch number 75/15875 to both abraded and intact occluded rabbit skin was found to cause mild transient erythema and oedema with the exception of one female that showed moderate irritation.

2.2 Mice

In the first study male and female CF1 mice exhibited severe irritancy after two weeks application of toluene solvent only. By the end of the study the degree of irritancy had decreased and hair growth had recommenced. Diglycidyl ether of bisphenol A, batch number 75/15875 produced skin irritation after 2 weeks exposure when applied as 20%, 10%, 5% and 1% w/v solutions in toluene. After four weeks application of diglycidyl ether of bisphenol A in toluene at all test concentrations no hair growth was apparent and signs of irritation were still present.

In the second study using acetone solvent, no skin irritation was seen at 10%, 5%, 1%, 0.5% w/v with either batch number 75/15875 or batch number EPl of diglycidyl ether of bisphenol A.

From the available data it is possible to estimate the maximum tolerated dose (MTD) for diglycidyl ether of bisphenol A, batch number 75/15875, in toluene as 1% w/v or less and for batch numbers 75/15875 and EPl in acetone as 10% w/v or greater.

Skin sensitization (Table 6)

Undiluted diglycidyl ether of bisphenol A, batch number 75/15875, was shown to be a moderate skin sensitizer when tested according to the Beuhler technique.

CONCLUSIONS

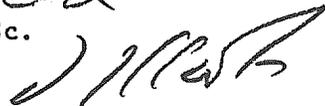
Diglycidyl ether of bisphenol A dissolved in either acetone or toluene was found to have a low order of acute toxicity by both oral and percutaneous routes.

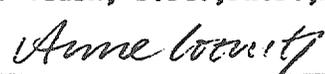
Application of undiluted diglycidyl ether of bisphenol A, batch No. 75/15875, to intact and abraded rabbit skin caused mild to moderate skin irritation.

Diglycidyl ether of bisphenol A, batch number 75/15875, was found to be irritant to mouse skin when applied as 20%, 10%, 5% and 1% w/v solutions in toluene. When applied as 10%, 5%, 1%, and 0.5% w/v solutions in acetone batch numbers 75/15875 and EPl of diglycidyl ether of bisphenol A were found to be non-irritant.

Diglycidyl ether of bisphenol A batch number 75/15875 produced moderate skin sensitization in guinea pigs.


R. W. Hend, B.Sc.


D. G. Clark, B.Sc., Ph.D., M.I. Biol.



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REFERENCES

1. Noakes D.N., and Sanderson, D. M. (1969).
A method for determining the dermal toxicity of pesticides.
Br. J. industr. Med., 26, 59-64.
2. 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.
3. Beuhler, E. V. (1965).
Delayed contact hypersensitivity in guinea-pigs.
Arch. Dermatol., 91, 171-177.

Table 5 - Primary irritation of occluded rabbit skin after a single application of Diglycidyl ether of bisphenol A
Batch Number 75/15875

Animal No.	Sex		Response	24 hours	48 hours	72 hours	7 days
4120	F	Non-abraded patch	Erythema	1	0-1	0	0
			Oedema	1	0-1	0	0
4121	F	Abraded patch	Erythema	0-1	0	0	0
			Oedema	0	0	0	0
4122	F	Non-abraded patch	Erythema	1	0-1	0	0
			Oedema	0-1	0	0	0
4123	F	Abraded patch	Erythema	1-2	1-2	1-2	0-1
			Oedema	1	1-2	1	0
4124	M	Non-abraded patch	Erythema	0-1	0-1	0-1	0
			Oedema	0	0	0	0
4125	M	Abraded patch	Erythema	0-1	0-1	0-1	0
			Oedema	0-1	1	0-1	0
4126	M	Non-abraded patch	Erythema	0-1	0-1	0	0
			Oedema	0-1	0-1	0	0
4127	M	Abraded patch	Erythema	0-1	0-1	0	0
			Oedema	0-1	0-1	0	0

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

Table 6 - Skin sensitization reaction in guinea-pigs
exposed to diglycidyl ether of bisphenol A
Batch number 75/15875

Animal No.	Sex	Skin response after challenge procedure		
		Immediate	24 hours	48 hours
<u>Treated</u>				
1	Male	0	0	0
2	Male	0	0	0
3	Male	0	0	0
4	Male	0	0	0
5	Male	2	2	2
1	Female	2	2	2
2	Female	1	0	0
3	Female	3	2	2
4	Female	3	3	2
5	Female	3	2	2
6	Male	3	2	2
7	Male	0	0	0
8	Male	0	0	0
9	Male	Dead	Dead	Dead
10	Male	Dead	Dead	Dead
6	Female	0	0	0
7	Female	2	0	0
8	Female	3	2	1
9	Female	0	0	0
10	Female	2	1	1
<u>Control</u>				
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	1	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 51.4% diglycidyl ether of bisphenol A
 Batch No. 75/15875 soft paraffin B.P.
 Topical challenge of 25% w/v diglycidyl ether of bisphenol A,
 Batch No. 75/15875 soft paraffin B.P.

Key: 0 = no skin reaction 1 = slight skin reaction
 2 = moderate skin reaction 3 = severe skin reaction

(i)

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APPENDIX I

ACUTE ORAL TOXICITY

Four rats of each sex, age approximately 12 weeks, were used at each dose level. Four animals of one sex were housed in each cage. The animals were weighed, fasted overnight and the calculated dose of test material administered by intraoesophageal intubation using a ball-point needle fitted to a syringe. After dosing, food and water were available ad libitum throughout a 9 day observation period.

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(ii)

SHELL TOXICOLOGY LABORATORY (TUNSTALL)

SHELL RESEARCH LIMITED

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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(iii)

SHELL TOXICOLOGY LABORATORY (TUNSTALL)

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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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(iv)

SHELL TOXICOLOGY LABORATORY (TRESTHALL)

SHELL RESEARCH LIMITED

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 induction 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. 3MM 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" Poroplast). This dressing was left in place for 24 hours. Treatments were repeated once weekly for three 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.