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ALLERGENICITY OF EPOXY RESINS IN THE GUINEA PIG

Arnar Thorgeirsson and Sigfrid Fregert

From the Department of Dermatology, Section of Occupational Dermatology, University of Lund, Lund, Sweden

Abstract. The sensitizing capacity of epoxy resins of diglycidylether–Bisphenol A type was investigated using the "guinea pig maximization test". One isolated resin had a molecular weight (MW) of 340, which is the lowest among this type of epoxy resin. The other resins were mixtures with different MWs. Their distribution is not known, but only their average MW. The low molecular weight resin sensitized all of the animals and can be classified as an extreme allergen. The sensitizing capacity decreased in inverse proportion to the increase in the average MW of the resin mixtures. The cross-testing also indicated that the resin mixtures with higher average MW contained enough of the low MW resin (MW 340) to render this resin a sensitizer. Bisphenol A did not sensitize the animals at all but epichlorhydrin sensitized 60 %. It is evident that in order to formulate hypoallergenic epoxy resins it will be necessary to achieve sensitization of animals with isolated resins of varying molecular weight.

Key words: Contact sensitization; Guinea pig maximization test; Epoxy resins; Epichlorhydrin; Bisphenol A

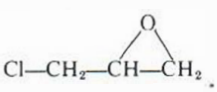
Since the early 1950ies many reports on occupational allergic contact dermatitis from epoxy compounds have been published (1, 2, 4, 5, 7, 10, 13, 15, 17, 18, 23). The main sensitizers in uncured epoxy compounds are the resins, reactive diluents and hardeners (curing agents).

By means of the "guinea pig maximization test" (11, 12), the high sensitizing capacity of some reactive diluents has been demonstrated in a previous work (21). Several sensitization studies have been made on guinea pigs with epoxy resins (6, 12, 14, 22). According to clinical experience, the low molecular resins cause allergic contact dermatitis more often than do the high molecular ones (1, 14). No investigations appear to have been carried out to illustrate any correlation between the size of the molecule and the sensitizing capacity.

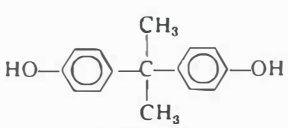
The aim of the present work was to study, by means of the guinea pig maximization test (GPM-test), if there is any correlation between molecular weight (MW) of epoxy resins of diglycidylether–Bisphenol A type and the sensitization capacity.

Chemistry of epoxy resins

The commonest types of epoxy resin are those formed by combining epichlorhydrin and 2,2-*bis*(*p*-hydroxyphenyl)propan (=Bisphenol A) (15, 16, 19, 20).



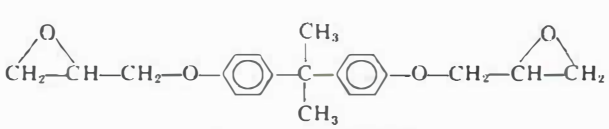
Epichlorhydrin



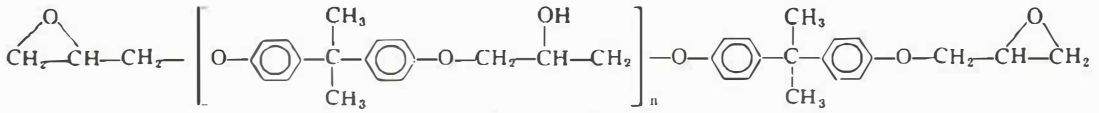
Bisphenol A

The smallest molecule of this type of epoxy resin has a MW of 340.

By varying the proportions of epichlorhydrin and bisphenol A during processing, varying amounts of low and high molecular resins can be formed in a mixture.



Epoxy resin, MW 340



Epoxy resin

The repeated part [ ]$_n$ has a MW of 284. Thus, the MWs are 340(n=0), 624(n=1), 908(n=2) etc. The resins with a MW of 908 and more are solid and those of lower MW are liquid or semi-solid. Epoxy resins with a MW up to about 10000 (n~35) are available commercially. The 'equivalent weight' is half the MW, as the molecule contains two reactive epoxide groups. All marketed epoxy resins are mixtures of resins with different MWs. In commercial data sheets the average molecular or equivalent weight is given but not the distribution of the resins of differing molecular size.

MATERIAL AND METHODS

The methods were principally the same as in our previous work (21) and were in accordance with the original description of the GPM-test (11, 12).

Animals. Albino female guinea pigs of Hartley strain, weighing 300–400 g, were used. Twenty animals were exposed to each resin, and 15 to Bisphenol A and epichlorhydrin. Twenty or 15 animals respectively served as controls in each series.

Chemicals. The chemicals were commercial products supplied by The Swedish Plastics Federation. The epoxy resins used were mixtures of resins of various average molecular weights (MWs) (Table I). They were all of diglycidylether–Bisphenol A type. One sample contained the isolated resin with the lowest possible MW, 340 (Furnished by CIBA-GEIGY). Bisphenol A (UCAR) and epichlorhydrin (Eastman, Kodak) were also included in the study.

Sensitization concentrations. Topical irritancy of the chemicals dissolved in acetone, methylethylketone (MEK), or ethanol, was studied by 24-hour occluded patch testing. A 5% concentration in acetone (w/v) of the lowest MW resins was found to be suitable for inducing sensitivity. Equimolar concentrations of the resins with higher MWs were used as previously recommended for other sensitizers which are chemically related (9). The resin with an average MW of 1 850 was dissolved in methylethylketone. The most suitable concentration for sensitization with Bisphenol A was found to be 5% in acetone (w/v) and for epichlorhydrin 5% in ethanol (w/v). The same concentrations and vehicles were used for intradermal and topical sensitization.

Induction of sensitivity. The animals were sensitized in a two-stage procedure: intradermal injections and topical application. Three intradermal injections of the following mixtures were made on each side in a row in the shoulder region:

1. 0.1 ml complete Freund's adjuvant (Difco Lab., Mich.) blended with an equal amount of water.
2. 0.1 ml of the respective substance in appropriate vehicle and concentration (Table I).
3. 0.1 ml of a mixture containing the substance in the vehicle and an equal amount of complete Freund's adjuvant. The final concentration of the substance is given in Table I.

One week after the first phase of sensitization, the topical application, in the same concentration as in the intradermal injection, was performed as a 48-hour occluded patch test in the shoulder region.

Challenge. Two weeks after the second stage of sensitization a 24-hour occluded patch test (Al-test, Imeco, Astra Agency) was performed on the flank. The test concentrations of the resins were a fifth of those used for sensitization (Table I). Bisphenol A was tested in a concentration of 1% in acetone, and epichlorhydrin 1% in ethanol. Only evident redness and/or swelling was regarded as an allergic response. The reactions were judged by each author independently.

Cross-testing. Simultaneous with the challenge, the other substances were also applied on the animals as patch tests.

Controls. At the same time as the sensitized animals

Table I. *Concentrations of epoxy resins for sensitization and challenge*

Epoxy resins MW	Vehicle	Sensitization		Challenge (% w/v)
		Intradermal (% w/v)	Topical (% w/v)	
340	Acetone	5.0	5.0	1.0
350	Acetone	5.0	5.0	1.0
480	Acetone	7.0	7.0	1.4
900	Acetone	12.9	12.9	2.6
1 280	Acetone	18.3	18.3	3.7
1 850	MEK	26.4	26.4	5.3

Table II. *Challenge reactions in animals sensitized to epoxy resins of various molecular weights (MW)*
20 animals in each series

Epoxy resin MW	Reacting animals	
	Number	Per cent
340	20	100
350	20	100
480	17	85
900	11	55
1 280	6	30
1 850	0	0
Controls	0	0

Table III. *Sensitization to Bisphenol A and epichlorhydrin*
15 animals in each series

Substance	Vehicle	Reacting animals	
		Number	Per cent
Bisphenol A	Acetone	0	0
Epichlorhydrin	Ethanol	9	60
Controls		0	0

in each series were challenged, control animals were also tested with the same substances in the same concentrations. These animals had not been previously injected with Freund's adjuvant or acetone.

Furthermore, one series of 20 animals were injected with "complete Freund's adjuvant" and acetone of the same volume and in the same way as in the animals in the experimental groups but without epoxy resin. After one week the animals were exposed to the 48-hour occlusive patch test with acetone in the shoulder region. Finally, 2 weeks later, they were patch tested with all the resins used in this study and with acetone for 24 hours in the same way as for the animals in the experimental groups.

RESULTS

The test results for the resins are set out in Table II.

All the 20 animals exposed to epoxy resin with a MW of 340 and to that with an average MW of 350 became sensitized. Of 20 animals, 17 reacted to the resin having an average MW of 480, 11 to that of 900, and 6 to that of 1 280. None reacted to the resin with an average MW of 1 850.

Bisphenol A gave no reaction in the 15 animals exposed. Epichlorhydrin sensitized 9 of 15 animals (Table III).

There were no reactions in the control animals (Tables II and III). On cross-testing, the three low MW resins elicited reactions in most animals. The three high MW resins gave few reactions (Table IV).

The animals sensitized to resins did not react to bisphenol A or epichlorhydrin nor did animals sensitized to bisphenol A or epichlorhydrin react to resins.

DISCUSSION

The epoxy resin with a MW of 340 sensitized all the animals. Thus, it can be classified as an extreme (grade IV) sensitizer (12). This resin was the only one in the present study that was in isolated form. Of the Bisphenol A-type resins, it is the one with the smallest possible MW. The mixture of resins with an average MW of 350 also sensitized all of the animals. The major constituent in this resin mixture is probably that with a MW of 340. Resins with increasing average MW given in equimolar concentrations elicited a decreasing number of positive tests in the animals. The resin with the highest average MW (1850) gave no reaction on challenge.

Bisphenol A did not sensitize at all in the GPM-

Table IV. *Cross reactions in animals sensitized to epoxy resins of various molecular weights (MW)*
20 animals in each series

Epoxy resin used for sensitization (MW)	Number of cross-reactions to epoxy resins (MW)					
	340	350	480	900	1 280	1 850
340		20	20	0	0	0
350	15		16	6	2	0
480	19	19		10	8	0
900	18	19	17		8	0
1 280	18	18	18	9		
1 850	13	13	11	1	0	

test. Yet it has been reported that this chemical may give reactions in persons sensitized to epoxy compounds (3, 8).

Epichlorhydrin sensitized 60% of the animals and can be classified as a moderate (grade III) sensitizer (12). It has been reported that it may give reactions in persons sensitized to epoxy compounds (2, 10). In this study the animals sensitized to epoxy resins did not react to epichlorhydrin nor did animals sensitized to epichlorhydrin or bisphenol A react to resins.

Irrespective of the MW of the resin used for sensitization, the three low molecular weight resins gave a high cross-reaction rate and the three high MW resins gave a low cross reaction rate (Tables II and IV). For example, the animals sensitized to resin 1850 showed no reactions on challenge with this resin (Table II) but more than half of the animals reacted to the three low MW resins (Table IV).

It is probable that the resin of MW 340 is present in all the mixtures but in smaller proportions in those with the highest MW. It is possible that these small amounts are sufficient to induce sensitivity when injected intradermally but are not sufficient to elicit reactions in the epicutaneous challenge test.

The possible sensitization capacity of the isolated resins with MWs of 624 and 908 etc. has not been investigated. Such an investigation is required in order to establish if it is possible to produce hypoallergenic epoxy resin mixtures in the future. Until now only one resin (MW 340) is available in isolated form. At present, an attempt to isolate resins with other MWs is in progress.

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S. Fregert, M.D.
Section of Occupational Dermatology
University Hospital
S-221 85 Lund
Sweden