

Contact allergy to epoxy (meth)acrylates

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Background: Contact allergy to epoxy (meth)acrylates, 2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy)phenyl]propane (bis-GMA), 2,2-bis[4-(2-hydroxy-3-acryloxypropoxy)phenyl]propane (bis-GA), 2,2-bis[4-(methacryloxyethoxy)phenyl]propane (bis-EMA), 2,2-bis[4-(methacryloxy)phenyl]propane (bis-MA), and glycidyl methacrylate (GMA) is often manifested together with contact allergy to diglycidyl ether of bisphenol A (DGEBA) epoxy resin.

Objective: To analyse patterns of concomitant allergic reactions to the five epoxy (meth)acrylates in relation to exposure.

Methods: We reviewed the 1994–2008 patch test files at the Finnish Institute of Occupational Health (FIOH) for reactions to the five epoxy (meth)acrylates, and examined the patients' medical records for exposure.

Results: Twenty-four patients had an allergic reaction to at least one of the studied epoxy (meth)acrylates, but specific exposure was found only in five patients: two bis-GMA allergies from dental products, two bis-GA allergies from UV-curable printing inks, and one bis-GA allergy from an anaerobic glue. Only 25% of the patients were negative to DGEBA epoxy resin.

Conclusions: The great majority of allergic patch test reactions to bis-GMA, bis-GA, GMA and bis-EMA were not associated with specific exposure, and cross-allergy to DGEBA epoxy resin remained a probable explanation. However, independent reactions to bis-GA indicated specific exposure. Anaerobic sealants may induce sensitization not only to aliphatic (meth)acrylates but also to aromatic bis-GA.

Key words: anaerobic glue; bis-EMA; bis-GA; bis-GMA; bis-MA; DGEBA epoxy resin; epoxy-reactive diluents; GMA; occupational; patch test. © John Wiley & Sons A/S, 2009.

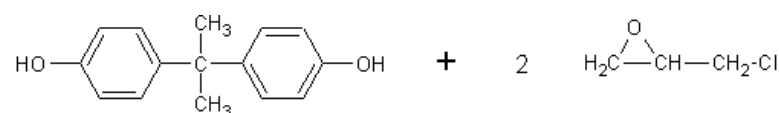
Conflicts of interest: The authors have declared no conflicts.

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In polymeric chemistry, diglycidyl ether of bisphenol A (DGEBA) epoxy resin and its raw materials, bisphenol A and epichlorohydrin (Fig. 1), can be combined with acrylates and methacrylates. In the 1960s, the first epoxy (meth)acrylate, 2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy)phenyl]propane (bis-GMA; named also bisphenol A diglycidyl methacrylate or epoxy dimethacrylate; CAS 1565-94-2; Fig. 2) was developed for dental composite resins. It is manufactured by reacting DGEBA with methacrylic acid or bisphenol A with glycidyl methacrylate (GMA) (1). 2,2-bis[4-(2-hydroxy-3-acryloxypropoxy)phenyl]propane (bis-GA; named also epoxy diacrylate or epoxy acrylate; CAS 37625-93-3) is the corresponding diacrylate. 2,2-bis

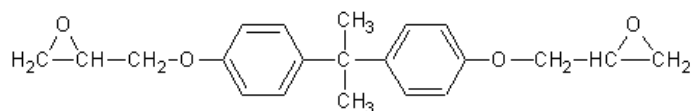
[4-(methacryloxyethoxy)phenyl]propane (bis-EMA; CAS 24448-20-2) and 2,2-bis[4-(methacryloxy)phenyl]propane (bis-MA; CAS 3253-39-2) have been developed as substitutes for bis-GMA. These four compounds are often presented under the heading 'epoxy acrylates' although they do not contain epoxy groups. GMA (CAS 106-91-2) is a smaller compound that contains, in addition to a reactive methacrylate group, one reactive epoxy group. In the present study, the five compounds are called epoxy (meth)acrylates.

Allergic reactions to bis-GMA, bis-EMA and bis-GA often appear together (2) and in connection with contact allergy to DGEBA epoxy resin (2, 3). At the Finnish Institute of Occupational Health (FIOH),

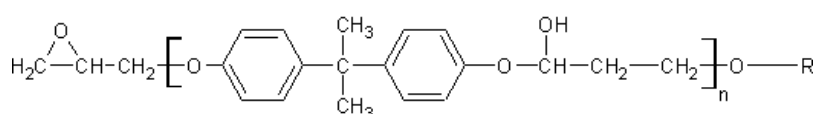


Bisphenol A

Epichlorohydrin

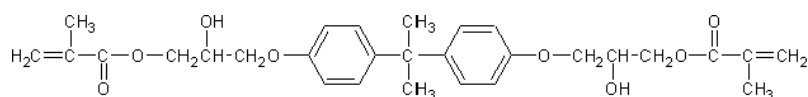


Diglycidyl ether of bisphenol A (DGEBA)

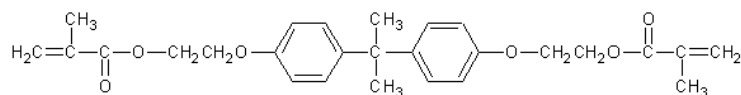


DGEBA epoxy resin

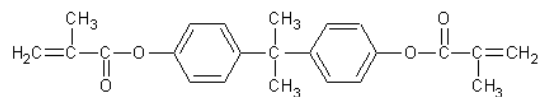
Fig. 1. The chemical structure of diglycidyl ether of bisphenol A (DGEBA) epoxy resin and its raw materials.



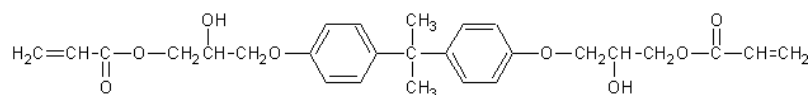
2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy)-phenyl]propane (bis-GMA)



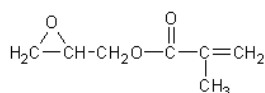
2,2-bis[4-(methacryloxyethoxy)phenyl]propane (bis-EMA)



2,2-bis[4-(methacryloxy)phenyl]propane (bis-MA)



2,2-bis[4-(2-hydroxy-3-acryloxypropoxy)phenyl]propane (bis-GA; epoxy diacrylate)



Glycidyl methacrylate (GMA)

Fig. 2. The chemical structures of the studied epoxy (meth)acrylates.

Table 1. Patients with allergic reactions to at least one epoxy (meth)acrylate, their occupation, allergic patch test reactions and exposure to epoxy (meth)acrylates, epoxy resin, aliphatic (meth)acrylates, epoxy-reactive diluents and diagnosis

Patch test reactions												
No.	Occupation	bis-GMA	bis-GA	bis-EMA	bis-MA	GMA	Epoxy resin	Epoxy-reactive diluents	Aliphatic (meth)acrylates (only +/+/+/+/+)	Exposure	Diagnosis	
1	Assembler of hydraulic devices	–	+	–	NT	–	–	NT	HPMA +	Anaerobic retainer: HPMA and bis-GA 8% ^a (Table 3)	OACD from HPMA and bis-GA in an anaerobic retainer (glue)	
2	Advertisement worker, silk printing	–	+	–	NT	–	–	NT	DEGDA +	UV-curable silk print primer: bis-GA 13.5%, urethane acrylate resins and other acrylates ^a (see Case Report 2)	OACD from bis-GA and DEGDA in a UV-curable silk print primer	
3	Silk-screen printer Patient 2 in (2)	–	++	–	–	NT	–	NT	TPGDA++, TREGDA++, PEA++, EA+, DEGDA ++	UV curing overprint varnish (UV lacquer): TPGDA 20–50% and epoxy acrylate (CAS 37625-93-3; bis-GA) 30–60% ^b	OACD from TPGDA and bis-GA in a UV curing overprint varnish	
4	Dentist Patient 8 in (4)	+	+	+	NT	–	++	NT	–	Dental composite resins: bis-GMA ^b	OACD from bis-GMA in dental composite resins	
5	Cleaner (Dental patient) Patient 8 in (2); Patient 1 in (5); (6); (7)	+++	+++	+++	??	–	+++	–	MMA++, HEMA+ + +, HPMA++, EGDMA+ + +, TREGDMA+ +, EA+ +, BA+ +, EEA+ + +, PEA+ + +, BUDA+ + +, HDDA+ + +, DEGDA+ + +, DPGDA+ + +, TPGDA+ +, PETA+ +, al-UDA+	Dental composite resins: bis-GMA and methacrylates Temporary crown: modified bis EMA ^c	Epoxy resin allergy diagnosed 13 years earlier ACD from dental epoxy (meth)acrylates	

Table 1. (Continued)

Patch test reactions											
No.	Occupation	bis-GMA	bis-GA	bis-EMA	bis-MA	GMA	Epoxy resin	Epoxy-reactive diluents	Aliphatic (meth)acrylates (only +/+/+/+/++)	Exposure	Diagnosis
6	Dentist Patient 4 in (4)	-	-	-	-	+	-	NT	HEMA++, HPMA++, EGDMA++, MMA+, EMA+, EA+	Dental products: 2-HEMA, TREGDMA, bis-GMA, UEDMA ^b Structured nail products: EMA, HPMA, TREGDMA, ECA, isobutylMA ^c Anaerobic sealant: methacrylates, no GMA ^a	OACD from methacrylates in dental restorative products OACD from methacrylates in structured nails
7	Manicurist	-	-	++	NT	+	-	NT	EA+, EMA+, HPMA++, BUDMA+, EGDMA++, MMA+, THFMA+		
8	Plumber Patient 4 in (8)	-	-	-	-	+	-	NT	HEMA++, HPMA++, EGDMA++, EMA+, TREGDMA++, BUDMA++, THFMA++, UEDMA+, TREGDA+++, DEGDA++		OACD from methacrylates in a pipe sealant
9	Machinist-assembler Patient 3 in (8)	-	-	?+	-	+	++	NT	HEMA+++, HPMA+++, EGDMA+++, TREGDMA+++, BUDMA+++, MMA+, THFMA+++, TREGDA+++, DEGDA+++, HDDA+++, PEA+++, BUDA+++, EA+	Exposure to an epoxy glue and methacrylates in anaerobic sealants	OACD from epoxy resin in a glue and methacrylates in anaerobic sealants
10	Construction worker, ex-printer	-	-	-	-	++	+	PGE++BDDGE++ TREGDA+, BUDA+, DEGDA+	TREGDA+, BUDA+, DEGDA+	Epoxy resin in a concrete injection product Polyglycol diacrylate 25% ^b in a UV-curable overprint lacquer in previous printing work	OACD from epoxy resin, occupational contact allergy to acrylate compounds in previous printing work

Table 1. (Continued)

Patch test reactions												
No.	Occupation	bis-GMA	bis-GA	bis-EMA	bis-MA	GMA	Epoxy resin	Epoxy-reactive diluents	Aliphatic (meth)acrylates (only +/+/+/+)	Exposure	Diagnosis	
11	Warehouse worker	-	-	-	-	+	++	PGE+++ CGE++	-	Epoxy glue: PGE 0.038%, phenol novolac glycidyl ether 52%, epoxy resin 2% ^a Methacrylate glues: MMA ^b	OACD from novolac epoxy resin, epoxy resin and reactive diluents	
12	Assembler in a foundry Patient 9 in (8)	-	-	-	NT	++	++ ^d	PGE++ BDDGE+ CGE++	EMA++, HEMA++++, HPMA+++, MMA+, EGDMA++++, TREGDMA++, THFMA+, DMAEMA+ Methacrylate series NT	Anaerobic sealants, ECA instant adhesive, various epoxy resins (hexanediol diglycidyl ether 2.5–10% in one) No present exposure to epoxy compounds, acrylates or epoxy (meth)acrylates Previously seaming material for swimming pools (epoxy compounds)	OACD from epoxy compounds and methacrylates	
13	Bricklayer	-	-	NT	NT	+	++	PGE++ BDDGE++			Occupational contact allergy to epoxy compounds	
14	Renovation worker	+	++	NT	NT	+	++	PGE+ BDDGE+ CGE?+	Methacrylate series NT	Epoxy primer, coating and repair mass for floors: Epoxy resin, alkyl glycidyl ether Fixing and seaming putty: epoxy resins and CGE Analysis: no bis-GMA	OACD from epoxy resin and epoxy-reactive diluents OACD from epoxy compounds in a fixing and seaming putty	
15	Bricklayer	+	?+	-	NT	++	++	PGE++ BDDGE++ p-tert-butyl-PGE+	-			

Table 1. (Continued)

		Patch test reactions										Exposure	Diagnosis
		Aliphatic (meth)acrylates (only +/+ +/+ +/+ +/+)											
No.	Occupation	bis-GMA	bis-GA	bis-EMA	bis-MA	GMA	Epoxy resin	Epoxy-reactive dilutents					
16	Floor layer Patient 11 in (2)	++	++	++	-	NT	++ +	PGE++	-		Epoxy in floor coatings, no known exposure to epoxy (meth)acrylates	OACD from epoxy compounds	
17	Sales manager, ex-foreman in a plastic company	++	++	NT	-	NT	++ +	-	TREGDA-, MMA-, BUDMA-, ECA-, Others NT	Past exposure to epoxy resin No present exposure to epoxy resin, acrylates or epoxy (meth)acrylates	OACD from epoxy resin diagnosed 16 years earlier		
18	Patient 10 in (2) Construction supervisor	++	++	NT	-	NT	++ +	PGE+ + + CGE+ + n-BGE+ + BDDGE+ +,	TREGDA-, MMA-, ECA- Others NT	Past exposure to epoxy resins in a plastic factory and in a concrete factory No known exposure to epoxy (meth)acrylates	OACD from epoxy resin diagnosed 2 years earlier		
19	Painter	+	+	NT	NT	-	++ +	BDDGE?+	Methacrylate series NT	Epoxy paint	OACD from epoxy compounds in paints		
20	Assembler of hydraulic devices Patient 2 in (8)	I + II ++	I ?+ II ++	-	-	-	++	-	TREGDMA+ +, HEMA+, EGDMA+, TREGDA +	Anaerobic sealants Epoxy paints	OACD from methacrylates in anaerobic sealants and epoxy compounds in paints		
21	Painter	NT	+	NT	NT	-	++	p-tert-butyl- PGE ++	Methacrylate series NT	Epoxy paints	OACD from epoxy compounds in paints		
22	Floor layer	++	++	NT	NT	-	positive ^d	-	Methacrylate series NT	Epoxy coatings	Previously diagnosed OACD from epoxy compounds		

Table 1. (Continued)

Patch test reactions											
No.	Occupation	bis-GMA	bis-GA	bis-EMA	bis-MA	GMA	Epoxy resin	Epoxy-reactive diluents	Aliphatic (meth)acrylates (only +/+++/++++)	Exposure	Diagnosis
23	Operator of stone crushing mill, ex-farmer, carpenter and construction worker	-	++	-	NT	-	+	-	TREGDA++ +, DPGDA++ +, BA++ +, EA++ +, BUDA++ +, HDDA++ +, PEA++ +, EEA++ +, DEGDA++ +, TPGDA++ +, PETA++ + +, OTA 480++ + +, ar-UDA++ +, HEMA+, EGDMA++ +, TMPTA++ +	No known present work-related exposure to epoxy compounds, acrylates or epoxy (meth)acrylates	No epoxy/acrylate-related OACD
24	Packer of plastic bottles	-	++	-	NT	-	?+	-	TREGDA++ +, EA++ +, BUDA++ + +, EEA++ +, HDDA++ +, DEGDA++ + +, TPGDA++ +, ar-UDA++ + +, PEA+, TMPTA++ +, PETA++ + +, OTA 480++ +, DPGDA++ + +, HEMA++ +, HPMA++ +, EGDMA++ +	No known exposure to acrylates, epoxy (meth)acrylates or epoxy compounds	No epoxy/acrylate-related OACD

^aResult of chemical analysis,^binformation in SDS,^cinformation from the manufacturer,^dtested in a local hospital before investigations at the FIOH; -negative test result; NT, not tested; OACD, occupational allergic contact dermatitis; ACD, allergic contact dermatitis; bis-GMA, 2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy)phenyl]propane; bis-EMA, 2,2-bis[4-(methacryloxyethoxy)phenyl]propane; bis-MA, 2,2-bis[4-(methacryloxy)phenyl]propane; bis-GA, 2,2-bis[4-(2-hydroxy-3-acryloxypropoxy)phenyl]propane; 2-HEMA, 2-hydroxyethyl methacrylate; EGDMA, ethylene glycol dimethacrylate; 2-HPMA, 2-hydroxypropyl methacrylate; TREGDMA, triethylene glycol dimethacrylate; THFMA, tetrahydrofurfuryl methacrylate; EMA, ethyl methacrylate; UEDMA, urethane dimethacrylate; BUDA, 1,4-butanediol diacrylate; HDDA, 1,6-hexanediol diacrylate; EDA, diethylene glycol diacrylate; DEGDA, diethylene glycol diacrylate; GMA, glycidyl methacrylate; PETA, pentaerythritol triacrylate; ar-UDA, urethane diacrylate, aromatic; DMAEMA, N,N-dimethylaminoethyl methacrylate; PEA, phenoxethyl acrylate; TMPTA, trimethylolpropane triacrylate; PETA, pentaerythritol triacrylate; ar-UDA, urethane diacrylate, aromatic; DMAEMA, N,N-dimethylaminoethyl methacrylate; BMA, N-butyl methacrylate; EEA, ethoxyethyl acrylate; DPGDA, dipropylene glycol diacrylate; TPGDA, tripropylene glycol diacrylate; OTA 480, Oligotriacrylate 480; ECA, ethyl cyanoacrylate; PGE, phenyl glycidyl ether; BDDGE, 1,4-butanediol diglycidyl ether; CGE, cresyl glycidyl ether; MA, methacrylate

Table 2. The test substances of the epoxy (meth)acrylates, their concentrations, providers, CAS numbers, total numbers and product types in the Product Register of Chemicals

Patch test substance	Concentration	Provider	CAS number	Number of products in the register	Types of products in the register (number of each product type)
bis-GMA	2% pet.	T	1565-94-2	130	Dental care (127) Wind screen repair resin (1) Filler for motor vehicles (1) Adhesives, glues (2)
bis-GA (epoxy acrylate)	0.5% pet.	C	37625-93-3	1	UV curing overprint varnish (1)
bis-EMA	1% pet.	C	24448-20-2	22	2-component glue (4) Anaerobic or other glue (12) Dental product (3) Polyester gel coat for boats (1)
bis-MA	2% pet.	C	3253-39-2	0	—
Glycidyl methacrylate	0.1% pet.	O ^a	106-91-2	6	The chemical itself (2) 2-component structural adhesive (2) Car paint (2)

^aDiluted from Aldrich's 97% glycidyl methacrylate.

T, Trolab (Hermal, Reinbeck, Germany); C, Chemotechnique (Vellinge, Sweden); O, in-house test substance; CAS, Chemical Abstracts Service.

Table 3. Allergic patch test reactions to epoxy (meth)acrylates in patients with contact allergy to DGEBA epoxy resin

	Number of patients tested	Allergic reactions <i>N</i> (%)
bis-GA	105	11 (10)
bis-GMA	100	10 (10)
bis-EMA	41	3 (7)
bis-MA	29	0 (0)
Glycidyl methacrylate	85	7 (8)

the above-mentioned five epoxy (meth)acrylates have been tested in the 'methacrylate/acrylate' and 'epoxy' series, and we wanted to analyse the patterns of concomitant patch test reactions and relate them to exposure. We also searched the products that contained the studied chemicals in the Product Register of Chemicals to get an impression of their current use in Finland. In the present series, 10 patients have been described in detail or included in larger patient series reported from FIOH (all the references are given in Table 1). We also describe in detail two cases of occupational bis-GA allergy, one from UV-cured overprint primer and another from anaerobic sealant, a source of sensitization which to our knowledge has not been described previously.

Patients and Methods

We screened our patch test files from September 1994 to May 2008 for allergic reactions to bis-GMA, bis-EMA, bis-MA, bis-GA and GMA. The test methods have been described earlier (4). The patch test preparations are presented in Table 2. The compounds have been tested in our 'methacrylate/acrylate' and 'epoxy' series in varying combinations during the study period.

All the patients with an allergic reaction (+/+/-+++) to at least one of the above-mentioned

Table 4. The patch test reactions, information on the safety data sheets and results of chemical analyses of two anaerobic sealants of Patient no. 1 who on routine patch tests reacted to bis-GA (+), 2-HPMA (+), 2-HEMA (?+) and EGDMA (?+)

	Anaerobic retainer	Anaerobic thread locker
Patch test reaction to the glue	2% +, 0.67% +, 0.2% ?+	2% +, 0.67% ?+, 0.2% ?+
Information in the safety data sheet	HPMA 50–100% ^a	N,N-dimethyl-p-toluidine <1% Cumene hydroperoxide 1–3% (no mention of acrylates)
Chemical analysis	HPMA 56%, HEMA 0.12%, bis-GA 8%	2-HEMA 0.14% HPMA 0.01% DEGDMA 3.6% TREGDMA 14.1% TETEGDMA 15.3% penta EGDMA 6.9% hexa EGDMA 3.2%

2-HEMA, 2-hydroxyethyl methacrylate; HPMA, 2-hydroxypropyl methacrylate; DEGDMA, diethylene glycol dimethacrylate; TREGDMA, triethylene glycol dimethacrylate; TETEGDMA, tetraethylene glycol dimethacrylate; EGDMA, ethylene glycol dimethacrylate; bis-GA, 2,2-bis[4-(2-hydroxy-3-acryloxypropoxy)phenyl]-propane

substances were included in the study. We analysed their clinical records for occupation, symptoms, diagnosis, safety data sheets, results of the chemical analyses of the products used by the patients, patch test reactions to other (meth)acrylates, the standard DGEBA epoxy resin and epoxy-reactive diluents.

During the study period, the baseline series was tested in 2904 patients, of whom 521 were tested with the 'methacrylate/acrylate' series, 461 with the 'epoxy' series, and 138 patients were tested with both the 'methacrylate/acrylate' and 'epoxy' series.

The product samples were dissolved in acetone, and the chemical analyses of mono- and

dimethacrylates were performed by gas chromatography with a mass selective detector at FIOH (Turku) as previously described (9). Bis-GA was analysed by liquid chromatography with UV-detection (9).

We searched the five epoxy (meth)acrylates by their CAS numbers in the Product Register of Chemicals [National Supervisory Authority for Welfare and Health (Valvira), Tampere, Finland, http://www.valvira.fi/en/chemicals/product_register_of_chemicals] and recorded the product types and the number of each product type.

Results

A total of 24 patients had an allergic reaction to at least one of the five studied compounds. The results of the patch tests, data on exposure, and diagnoses are given in Table 1. Specific exposure to the studied compounds was found in the first five patients, of whom Patients 1 and 2 have not been reported previously.

During the study period, we investigated 123 patients with contact allergy to DGEBA epoxy resin. The frequencies of positive reactions to the studied epoxy (meth)acrylates in this subgroup are given in Table 3. Of the 123 epoxy allergic patients, 18 were not tested with any of the compounds and 23% of those who were tested reacted to at least one of the studied compounds (24/105). The proportion of epoxy allergic patients reacting to bis-GMA, bis-EMA, bis-MA or bis-GA was 16% (17/105).

Case Reports

Patient no. 1

A 56-year-old assembler of hydraulic devices had used anaerobic sealants for years without any skin problems. Soon after starting to use two new anaerobic products, he developed dermatitis on his hands, wrists and face. The symptoms subsided and disappeared during a sick leave and did not reappear. The company discontinued the use of the two new products and reintroduced Loctite™ glues. In patch tests, the patient reacted to bis-GA (+), 2-hydroxypropyl methacrylate (2-HPMA; +), 2-hydroxyethyl methacrylate (2-HEMA; ?+), and ethylene glycol dimethacrylate (EGDMA; ?+). Because the safety data sheets did not mention bis-GA, the glues were analysed. The results are given in Table 4. With regard to the face symptoms, airborne origin cannot be excluded, but transfer via hands is an alternative explanation.

Patient no. 2

Patient no. 2 was 33-year-old advertisement worker who developed work-related hand dermatitis. He was involved in silk printing of textiles and plastic materials. On patch testing he reacted to bis-GA (+), diethyleneglycol diacrylate (DEGDA; +) and his UV-curable overprint primer (photo emulsion; 10% ++, 3.2% +, 1% + in pet.). The manufacturer informed us that the primer contains 13.5% monomer-free diacrylate ester of bisphenol A epoxy resin (bis-GA) and 7.5% aromatic urethane acrylate resin, which contains 0.2–2% 2-hydroxyethyl acrylate (2-HEA; CAS 818-61-1). The primer was analysed at FIOH and found to contain 0.48% 2-HEA, 0.24% ethylene glycol-based acrylates, 2.9% propoxy-based acrylates deriving from oligoacrylate 480, and 0.05% other aliphatic diacrylates. Bis-GA or other epoxy (meth)acrylates were not analysed. We concluded that the patient had developed occupational allergic contact dermatitis from the bis-GA and DEGDA in his silk print photo emulsion.

Discussion

The present material comprises 24 patients with at least one allergic reaction to bis-GMA, bis-GA, bis-EMA or GMA. Only six (25%) of the patients were negative to DGEBA epoxy resin. Bis-GA was positive in majority of the patients (15), followed by GMA and bis-GMA (10 patients, both). Bis-EMA was positive in only four patients, but the numbers are not comparable because all the patients were not tested with all the five compounds (Tables 1 and 3). In a previous study from the USA investigating patients with known epoxy resin allergy, bis-GMA gave slightly more reactions than did bis-GA. In line with our results, the reactions to bis-EMA were not so common as reactions to bis-GMA and bis-GA (10). In the present study, 7–10% of the DGEBA epoxy-resin-allergic patients reacted to bis-GMA, bis-GA, bis-EMA and GMA (Table 3). In the North American study, the corresponding figures for bis-GMA and bis-GA were somewhat higher (17% and 15%, respectively) and for bis-EMA about the same (10%) (10).

Bis-GA

The nomenclature of bis-GA (CAS 37625-93-3) may cause confusion because the term 'epoxy acrylate' is used for this compound (e.g. Chemoteknik's test substance and the safety data sheet of Patient no. 3 in Table 1) and for the whole group of the epoxy (meth)acrylates, which are the subjects of the present study.

In the previous literature, UV-cured printing inks have been found to be an important source of bis-GA sensitization (2, 11–14), and bis-GA in the production of UV-cured paints has sensitized one patient (15). In these cases, specific exposure to bis-GA had led to specific sensitization without allergy to DGEBA epoxy resin (or bis-GMA). Our two previously unpublished cases follow the same pattern (Patients 1 and 2, Table 1). In the literature, there are, nevertheless, many bis-GA-positive cases without shown specific exposure, but these patients usually have allergic reactions to DGEBA epoxy resin and bis-GMA (2, 10). In the present series, the bis-GA-positive cases without shown specific exposure are similar: most of these patients had clearly been exposed to epoxy resin products, but not to acrylates or epoxy (meth)acrylates.

Bis-GA is formed when DGEBA epoxy resin monomer is esterified with two acrylic acids on both glycidyl ends of the molecule. Bis-GMA is the corresponding dimethacrylate of DGEBA. Animals sensitized to bis-GA have not reacted to bis-GMA or DGEBA epoxy resin (16). Similarly, our three patients with specific exposure to bis-GA did not react to bis-GMA or DGEBA epoxy resin. The animal experiment has not been performed the other way round with DGEBA epoxy resin. The human data suggest that the results might be different in a reverse test.

Patient no. 1 developed dermatitis while using anaerobic sealants and in patch tests he reacted to 2-HPMA and bis-GA. Because he did not react to DGEBA epoxy resin in the baseline series, we suspected that he had had specific exposure to bis-GA. In the chemical analysis, this compound was detected in one of his sealants at an 8% concentration. Anaerobic glues are usually based on polyethylene glycol dimethacrylate, and they often contain some 2-HPMA and 2-HEMA. To our knowledge, there are no previous reports of bis-GA allergy from anaerobic sealants. In past analyses of various products at FIOH, a trace amount of bis-GA (0.32%) was detected in an adhesive that also contained tetrahydrofurfuryl methacrylate (THFMA) and DGEBA epoxy resin (17). This case clearly indicates that when a patient has a solitary reaction to bis-GA without reactions to DGEBA epoxy resin or other epoxy (meth)acrylates, specific exposure is probable and can be proven by analysing the patch-test-positive products that the patient has handled.

Bis-GMA

Bis-GMA was introduced as a component of dental composite resin in the 1960s. Since then, it has been widely used in products used by dentists (18)

and appears also in denture materials (4, 19), artificial nail preparations (3, 20, 21) and in printing work (22). In the Finnish Product Register of Chemicals, it was also found in some adhesives, in a wind screen repair resin and a filler of motor vehicles.

Contact allergy to bis-GMA has been reported in dental workers (5, 23–29) and dental patients (6, 10, 24, 30–34), in a printer (30) and a silk-screen maker (22) and in a mechanic handling coating materials (2). The allergic reactions to bis-GMA in these studies usually occurred concomitantly with an allergic reaction to DGEBA epoxy resin. Many of the previously reported dental patients and the mechanic were reported to have been sensitized to DGEBA epoxy resin before developing symptoms from bis-GMA-containing materials (2, 6, 10, 31, 32, 34). In a German study, 6 (15%) out of 40 bis-GMA-positive patients did not react to DGEBA epoxy resin, and the only probable bis-GMA exposure was due to artificial nails in one patient (3). In the detailed descriptions of the printer (30) and one of the dental patients (33), DGEBA epoxy resin allergy was not mentioned, so it is also possible that these two patients had been sensitized to bis-GMA without co-sensitization to DGEBA epoxy resin. At FIOH, we have not seen such patients.

In the present material, all 10 bis-GMA-positive patients also reacted to DGEBA epoxy resin and bis-GA. The bis-GMA-positive cases represent 10% of 100 patients allergic to DGEBA epoxy resin during the study period who were tested with bis-GMA. In two studies from the USA (10) and Germany (3), the proportion has been somewhat higher, 17% and 18%, respectively. In the German study, Trolab's bis-GMA patch test preparation was known to contain less than 20 ppm DGEBA epoxy resin, but according to the authors it was unlikely that it would elicit positive reactions even in high-grade DGEBA-sensitized persons. The exhaustively investigated cleaner (Patient no. 5 in the present series) reacted to DGEBA resin at a concentration of 3.2 ppm, which would have explained her allergic reaction to Trolab's 2% bis-GMA preparation. She, nevertheless, reacted to the same bis-GMA diluted to a concentration of 1 ppm (5), which, in turn, cannot be explained by any impurity. Her elicitation threshold for bis-GA was also low, 10 ppm. In a recent series from Sweden, there was also a patient who reacted to 10 ppm DGEBA (35). In addition to the impurities of the test substance, impurities in the commercial bis-GMA products have presented another problem. In 1991, seven dental restorative materials were analysed at FIOH, all of which contained 100–600 ppm of DGEBA epoxy resin. In an animal study, impurities in commercial products of bis-GMA were shown to have high sensitizing

capacity, and the presence of DGEBA epoxy resin was a probable explanation for this (16). Bis-GMA *per se* had no or only low sensitizing capacity (16). In 2001, DGEBA epoxy resin oligomers were no longer detected in analyses of bis-GMA-containing dental materials at FIOH. Cross-allergy between DGEBA epoxy resin and epoxy (meth)acrylates (bis-GMA and bis-GA) has been a repeatedly proposed explanation for concomitant reactions (2, 3, 10). The results of the present study are also difficult to explain without considering cross-allergy. The vast majority of the bis-GMA patients had no known occupational exposure to bis-GMA or other epoxy (meth)acrylates. Non-occupational exposure during dental treatment could not be excluded, but the other patients, except no. 5, were occupational cases whose symptoms were not associated with dental care. The possibility that bis-GMA reactions are elicited by trace amounts of DGEBA epoxy resin in the test substance might be true in some cases, but this is not a satisfactory explanation for all of the cases. Animal sensitization studies with DGEBA epoxy resin, as proposed by Geier et al. (3), elicitation threshold studies on clinical patients, as well as product analyses might help to resolve the question.

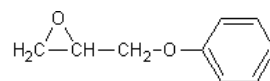
Besides its structural relation to DGEBA epoxy resin, bis-GMA is also a dimethacrylate with two reactive double bonds at both ends of the molecule. In the present material, there were two (20%) bis-GMA-positive patients who reacted to various methacrylates and were simultaneously exposed to methacrylates (Patients 5 and 20). Our figure was somewhat higher than the corresponding one in the German study, 7.5% (3). Cross-allergy to methacrylates does not explain the vast majority of the reactions to bis-GMA.

Glycidyl methacrylate

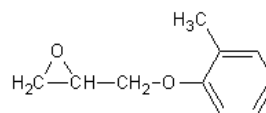
GMA was reported to cause occupational allergic contact dermatitis in a chemist who impregnated paper and textile materials to make them water and oil resistant (36), and in Sweden an allergic patch test reaction to GMA was seen in a production worker in a paint binder factory where the chemical was used (37). In the USA, three glue-related cases were positive to GMA and one of them had used an anaerobic sealant that contained GMA (38). In Spain, a worker developed occupational allergic contact dermatitis due to GMA in a liquid that was used in coating spectacle lenses (39). None of the six patients were reported to have DGEBA epoxy resin allergy. Recently, a case of chemical burn from GMA has been reported (40).

GMA is an ester of methacrylic acid and epichlorohydrin; it has a methacrylate structure at one end of the molecule and an epoxy group at the

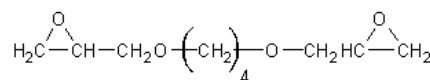
other. In the present series, 7 of the 10 patients reacting to GMA also reacted to DGEBA epoxy resin in the baseline series and had been occupationally exposed to epoxy products. All six glycidyl-methacrylate-positive patients who were tested with epoxy-reactive diluents (glycidyl ethers) displayed positive reactions to some of them. Correspondingly, only one of the seven glycidyl-methacrylate-negative patients who were tested with epoxy-reactive diluents had an allergic reaction. Thus, there was an association between allergic reactions to GMA and epoxy-reactive diluents. Our in-house 0.1% GMA test substance was analysed for



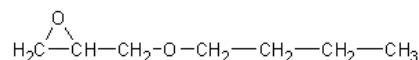
Phenyl glycidyl ether (PGE)



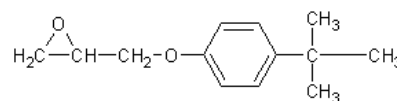
o-Cresyl glycidyl ether (CGE)



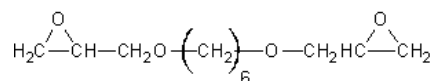
1,4-Butanediol diglycidyl ether (BDDGE)



n-Butyl glycidyl ether (BGE)



p-tert. Butyl phenyl glycidyl ether (p-tert BPGE)



1,5-Hexanediol diglycidyl ether (HDDGE)

Fig. 3. The chemical structures of epoxy-reactive diluents.

epoxy-reactive diluents and DGEBA epoxy resin with practically negative results (<50 ppm and 0.08 ppm, respectively). GMA, epoxy-reactive diluents and DGEBA monomer all share reactive epoxy groups in their glycidyl structures (Figs 1–3). Three of our glycidyl-methacrylate-positive patients were negative to DGEBA epoxy resin and had no known exposure to epoxy products. They were, nevertheless, allergic to methacrylates and had been exposed to methacrylates in dental products, artificial nail products or anaerobic sealants. Three of the DGEBA epoxy-resin-allergic patients had also used anaerobic sealants or other methacrylate glues, and two of them had methacrylate allergy concomitant with epoxy allergy. The safety data sheets and product declarations of our patients did not mention GMA and in two cases (Patients 5 and 11) patch-test-positive products were analysed for GMA with negative results. In conclusion, we did not find any specific exposure to GMA in our 10 patch-test-positive patients, so cross-allergy to either DGEBA epoxy resin/epoxy-reactive diluents or to methacrylates offers an explanation for the reactions to GMA.

Bis-EMA

In the Finnish Product Register of Chemicals, bis-EMA appears in numerous glues and in some dental products. In the literature, some cases of allergic reactions to bis-EMA are reported, many of them in dental personnel (5, 23, 41) and often with a simultaneous reaction to DGEBA epoxy resin (5, 10) and bis-GMA (5, 10, 23). However, we have not found any detailed descriptions of primary sensitization with known exposure to bis-EMA. In the previously published case of the cleaner (Patient 5), she had allergic reactions to bis-EMA before she developed symptoms from bis-EMA-containing temporary crown paste (7). In the present series, a manicurist (Patient no. 6) reacted to bis-EMA and GMA. These compounds were not mentioned in the product declarations. The reaction to bis-EMA was strong (++), and it could not be explained by DGEBA epoxy resin or bis-GMA allergy. Unfortunately, the patient's artificial nail products were not analysed for bis-EMA or GMA.

Bis-MA

In the present series, there were no reactions to bis-MA, but we ceased to test it in February 2002 for lack of allergic reactions (42). Allergic reactions to bis-MA have been reported in single dental workers from South Korea (43), the USA (28), southern Sweden (24) and Poland (41), but no data on exposure were given in these four cases. In addition,

one positive case was reported from Belgium without any details (23). In the UK, 250 patients (44), and in the USA 41 DGEBA epoxy-resin-allergic patients (10) remained negative to this substance. The search in the Finnish Chemical Register of Chemicals yielded no products containing bis-MA.

Conclusions

Allergic reactions to bis-GMA, bis-GA, GMA and bis-EMA are usually seen in patients with allergic contact dermatitis from DGEBA epoxy resin and with exposure to only epoxy resin products. Patients who were allergic to DGEBA epoxy resin (23%) reacted to some of the chemicals, most often to bis-GA (11%) and bis-GMA (10%). The majority of the reactions probably represent cross-allergy, but there are, however, some patients who are sensitized as a result of specific exposure. Especially, allergic reactions to bis-GA without concomitant DGEBA epoxy resin allergy point to specific sensitization. Glues may contain bis-EMA, bis-GMA, GMA and bis-GA. To detect contact allergy, these compounds should be tested separately in glue-associated cases, because the patients do not necessarily have concomitant allergy to DGEBA epoxy resin or acrylates.

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