

Contact allergy to reactive diluents and related aliphatic epoxy resins

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Summary

Background. Diglycidyl ether of bisphenol A resin (DGEBA-R) is the most common sensitizer in epoxy systems, but a minority of patients also develop contact allergy to reactive diluents.

Objectives. To analyse the frequency and clinical relevance of allergic reactions to different epoxy reactive diluents and related aliphatic epoxy resins.

Methods. Test files (January 1991 to June 2014) were screened, and the clinical records of patients with allergic reactions were analysed for occupation, concomitant allergic reactions, and exposure.

Results. A total of 67 patients reacted to at least one of the compounds. The largest numbers of allergic reactions were to phenyl glycidyl ether (PGE; $n = 41$), 1,4-butanediol diglycidyl ether (BDDGE; $n = 34$), and *p*-tert-butylphenyl glycidyl ether (PTBPGE; $n = 19$). Ten of the patients did not have contact allergy to DGEBA-R. The reactions of 5 of these were related to the use of BDDGE-containing products. We found no significant exposure to PGE or PTBPGE in patients sensitized to them, but some of the patients had used cresyl glycidyl ether-containing products.

Conclusions. Allergic reactions to reactive diluents and related aliphatic epoxy resins usually occurred together with reactions to DGEBA-R. BDDGE was the clinically most significant compound, and was the sole cause of occupational allergic contact dermatitis in 3 patients.

Key words: 1,4-butanediol diglycidyl ether; cresyl glycidyl ether; cycloaliphatic epoxy resins; phenyl glycidyl ether; *p*-tert-butylphenyl glycidyl ether.

Chemicals in epoxy resin systems are among the most common causes of occupational allergic contact dermatitis. Approximately 75% of the epoxy resins currently used worldwide are derived from diglycidyl ether of bisphenol A (DGEBA; CAS no. 1675-54-3) (1). DGEBA resin

(DGEBA-R) is also the most significant sensitizer in epoxy resin systems, but contact allergies to other epoxy resins, hardeners and modifiers such as diluents also occur. Epoxy reactive diluents are used to lower viscosity in order to improve the handling and wetting characteristics of epoxy resin systems. Reactive diluents have epoxy functionality, and become part of the cured network of epoxy polymer (1). Reactive diluents are generally glycidyl ethers, sometimes glycidyl esters, of aliphatic or aromatic structure (Figs 1–3). Concomitant sensitization to reactive diluents and DGEBA-R is rather common, but isolated contact allergy to reactive diluents is rare (2, 3).

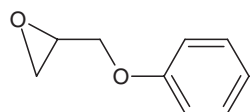
Diluents with several epoxy groups can be used as resins in some epoxy systems. Thus, the distinction between reactive diluents and resins is not always clear.

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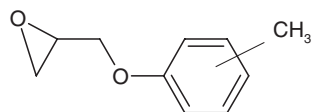
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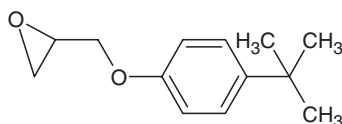
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Phenyl glycidyl ether (PGE);
CAS no. 122-60-1



Cresyl glycidyl ether (CGE);
CAS no. 26447-14-3



p-tert. butyl phenyl glycidyl ether
(PTBPGE); CAS no. 3101-60-8

Fig. 1. Chemical structures of aromatic monoglycidyl ethers (reactive diluents).

For this reason, we decided to analyse related aliphatic epoxy resins together with reactive diluents. In addition, co-sensitization occurs between the two groups (4). The aliphatic epoxy resins of the present study include both cycloaliphatic compounds and non-cyclic aliphatic resins (Fig. 4).

Contact allergy to epoxy compounds has been an area of special interest at the Finnish Institute of Occupational Health (FIOH) (5), and our patients exposed to epoxy products are tested with an epoxy patch test series comprising not only commercial test substances but also many in-house test substances. We have recently published our results on epoxy hardeners (6) and bisphenol F epoxy resin (7). The aim of the present study was

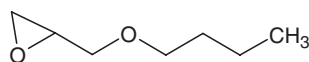
to retrospectively describe FIOH patients with allergic reactions to reactive diluents and structurally related aliphatic [non-DGEBA/diglycidyl ether of bisphenol F (DGEBF)] epoxy resins from the last two decades.

Methods

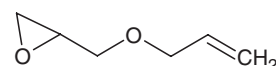
We performed the patch tests with Finn Chambers® (SmartPractice™, Phoenix, AZ, USA) according to International Contact Dermatitis Research Group recommendations. We read the tests two or three times: on D2, D3, and D4, on D2, D3, and D6, or on D2 and D5, depending on the day of application. We asked patients to inform us whether they had noticed new reactions after the final reading. All patch tested patients at the FIOH have a suspected occupational skin disease. They come from all parts of Finland.

Reactive diluents and related aliphatic epoxy resins have been mostly tested in a special epoxy compound series, but phenyl glycidyl ether (PGE; CAS no. 122-60-1), cresyl glycidyl ether (CGE; CAS no. 26447-14-3) and butyl glycidyl ether (BGE; CAS no. 2426-08-6) were included in a plastic and glues series and not in the epoxy series for 6 years. The test substances and their providers and concentrations have varied over the years, and are shown in Table 1. The chemical structures of the studied compounds are shown in Figs 1–4. In addition, some patients were tested with the same chemicals outside the routine test series, for example when investigating components of their own products. These patients are not included in Table 1, but one of them is mentioned in the text below.

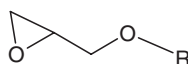
We screened the test files from January 1991 to June 2014 for allergic reactions to reactive diluents and related aliphatic epoxy resins. We included all patients with an allergic reaction (+/++/+++) to at least one of the compounds. The patients' clinical records were analysed for occupation, symptoms, safety data sheets (SDSs), results



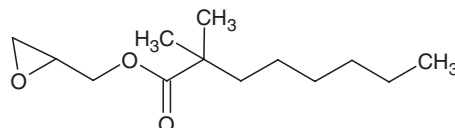
n-Butyl glycidyl ether
(BGE); CAS no. 2426-08-6



Allyl glycidyl ether;
CAS no. 106-92-3

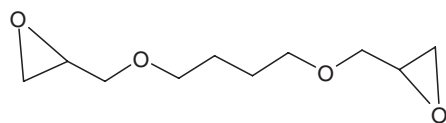


Alkyl (C12-C14) glycidyl ether;
Epoxide 8; CAS no. 68609-97-2

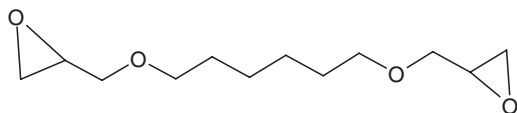


Glycidyl ester of neodecanoic acid;
Cardura E 10; CAS no. 26761-45-5

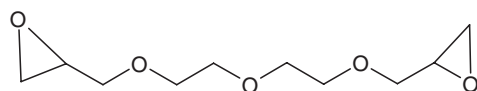
Fig. 2. Chemical structures of aliphatic monoglycidyl ethers (reactive diluents). In some compounds, an example of a common trade name is given.



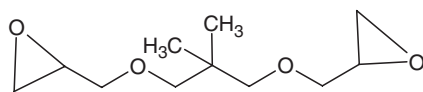
1,4-Butanediol diglycidyl ether (BDDGE);
CAS no. 2425-79-8



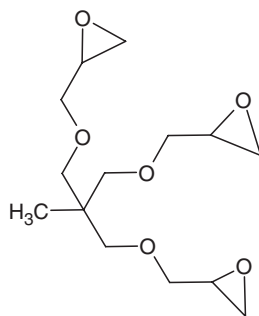
1,5-Hexanediol diglycidyl ether (HDDGE;
Grilonit RV 1812); CAS no. 16096-31-4



Diethylene glycol diglycidyl ether (DEGDGE;
DEG diluent); CAS no. 39443-66-8 or 4206-61-5



Neopentyl glycol diglycidyl ether (NPGDGE;
Grilonit RV 1815); CAS no. 17557-23-2



Trimethylolpropane triglycidylether (TMPTGE);
CAS no. 30499-70-8

Fig. 3. Chemical structures of aliphatic diglycidyl and triglycidyl ethers (reactive diluents). In some compounds, an example of a common trade name is given.

of the chemical analyses of their own products, patch test reactions to their own products, and diagnosis.

For chemical analyses, we dissolved samples of the patients' own epoxy products (usually resin parts of the epoxy products used at the workplace) in acetone. We determined acetone-soluble epoxy compounds by gas chromatography with mass spectrometry (MS) detection. Glycidyl ethers and esters were identified

by comparing their mass spectra with the mass spectra of standards and the mass spectra in the Wiley MS-library. We used standards of known purity for quantification.

The epoxy products containing reactive diluents and related aliphatic epoxy resins on the market in Finland were gathered from the Finnish Product Register of Chemicals, which is maintained by the Finnish Safety and Chemicals Agency. A chemical that is on the market or in use in Finland and poses a risk to health or to the environment must be notified to the Finnish Product Register of Chemicals; however, the coverage of the register is not complete, because some producers/importers might neglect to notify their products. We obtained information on the products from the register according to substance by CAS numbers.

Results

During the study period, a total of 4445 patients were tested with the baseline series, yielding allergic reactions (+/++/+++) to DGEBA-R in 181 patients (4.1%). Seventeen patients were not tested with DGEBA-R at the FIOH because of previously diagnosed contact allergy, which increased the total number of DGEBA-R-allergic patients to 198 (4.5%). We tested the epoxy series in a total of 729 patients (16%). The plastic and glue series comprising PGE, CGE and BGE was tested in 325 patients, 215 of whom were simultaneously tested with the epoxy series. The number of tested patients and allergic reactions to each compound are shown in Table 1. A total of 67 patients were included. Sixty-six of these had allergic reactions to reactive diluents and 19 to related aliphatic epoxy resins. Concomitant reactions to several compounds were common ($n=47$; 70%). Fifty-three (79%) patients reacted to aromatic reactive diluents and 37 (55%) to aliphatic reactive diluents.

Ten (15%) patients did not have contact allergy to DGEBA-R in the baseline series. Their occupations, patch test results, exposure and diagnoses are shown in Table 2. In 3 cases, 1,4-butanediol diglycidyl ether (BDDGE; CAS no. 2425-79-8) was the sole cause of occupational allergic contact dermatitis.

Aromatic monoglycidyl ethers

Of the aromatic glycidyl ethers, PGE was positive in 41 patients, CGE in 16 patients, and *p*-tert-butylphenyl glycidyl ether (PTBPGE; CAS no. 3101-60-8) in 19 patients. The total number of patients who reacted to aromatic monoglycidyl ethers was 53. Table 3 shows

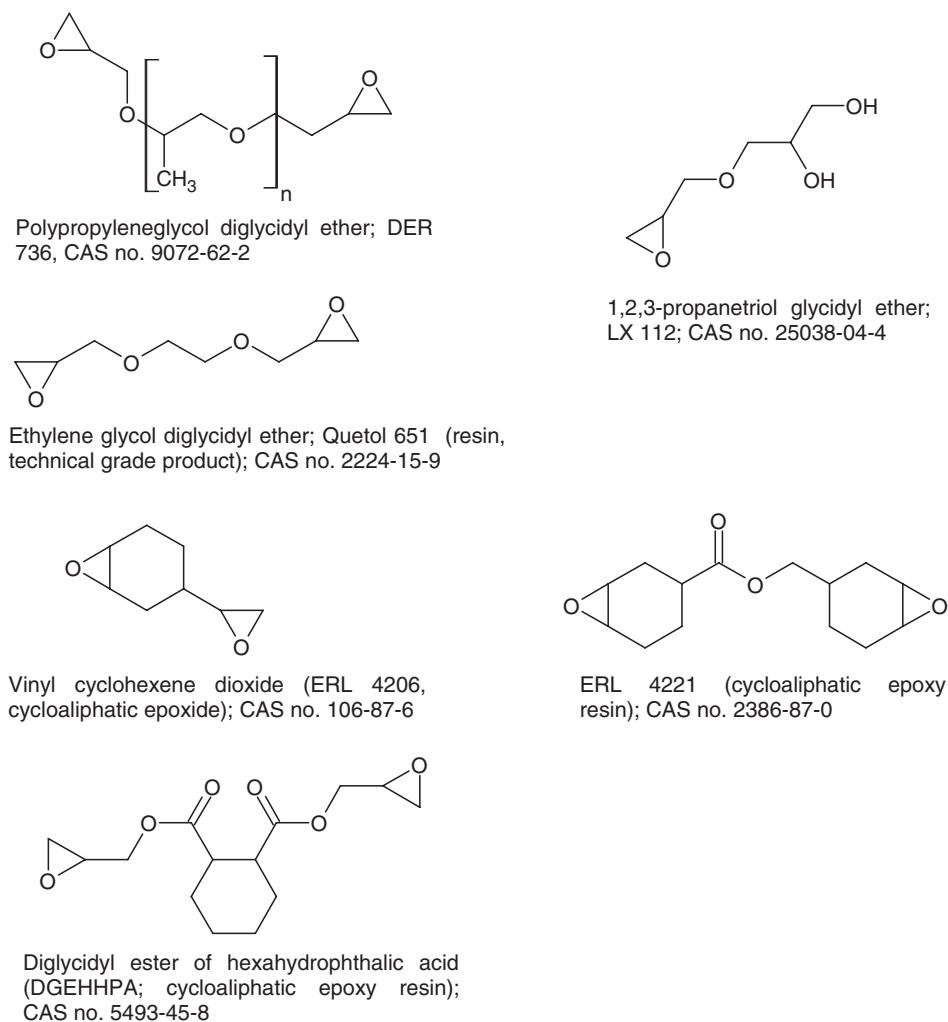


Fig. 4. Chemical structures of aliphatic epoxy resins. In some compounds, an example of a common trade name is given.

concomitant reactions to PGE and CGE, and to PGE and PTBPGE. In 2006, we stopped testing CGE, because almost all CGE-allergic patients also reacted to PGE, and the number of PGE-positive patients was much larger. The patients sensitized to aromatic (mono)glycidyl ethers quite commonly reacted to aliphatic glycidyl ethers, BDDGE, and/or 1,6-hexanediol diglycidyl ether (HDDGE; CAS no. 16096-31-4; Grilonit RV 1812) ($n = 19$; 36%). A large majority of the patients were allergic to DGEBA-R ($n = 50$; 94%)

PGE was not mentioned in the SDSs of the products used by the 41 patients with allergic reactions to it. In chemical analysis, two glues used in the electronic industry contained trace amounts of PGE (0.005% and 0.08%, respectively). CGE was the only aromatic glycidyl ether that was declared in the SDSs. Seven patients with allergic reactions to PGE, CGE or PTBPGE had used products

that contained CGE according to their SDSs: CGE was in the seaming products used by 4 tile setters, and in the paints and coatings used in 3 cases. In 2 cases, chemical analysis detected some CGE (0.04% and 0.05% in the above-mentioned glues used in the electronic industry, and 1.0% and 0.01% in two samples of glass fibre used in the production of sports equipment).

We started testing PTBPGE in May 2006. Since then, it has elicited allergic reactions in a relatively high number of patients (8.8% of 215 patients tested). However, we were not able to find significant exposure to PTBPGE in any of these patients. It was not mentioned in the SDSs of the products that they used. Chemical analyses were performed in 2 cases, and a trace amount of 25 ppm (0.0025%) was detected in an adhesive film used in the aircraft industry. All of the patients were allergic to DGEBA-R.

Table 1. Various reactive diluents and aliphatic (non DGEBA/DGEBF) epoxy monomers that have been tested in our routine series (epoxy compound series and plastic and glues series), providers and concentrations of the test substances, numbers of tested patients, allergic reactions for each test substance, and number of products in the Finnish Product Register of Chemicals

	Provider: concentration in petrolatum (%)	Total number of patients tested	Allergic reactions (% of patients tested)	Number of products on the Finnish market
Aromatic monoglycidyl ethers				
Phenyl glycidyl ether (PGE; CAS no. 122-60-1)	T/C: 0.25	830	41 (4.9)	0
Cresyl glycidyl ether (CGE; CAS no. 26447-14-3)	T: 0.25	647	16 (2.5)	7
<i>p</i> -tert-Butylphenyl glycidyl ether (PTBPGE; CAS no. 3101-60-8)	O: 0.25	215	19 (8.8)	26
Aliphatic monoglycidyl ethers				
Allyl glycidyl ether (CAS no. 106-92-3)*	O: 0.25	39	0	1–3 [†]
Butyl glycidyl ether (BGE; CAS no. 2426-08-6)	T: 0.25	325	3 (0.9)	0
Alkyl (C12–C14) glycidyl ether (CAS no. 68609-97-2; Epoxide® 8) [‡]	O: 0.25	39	0	144
Glycidyl ester of neodecanoic acid (CAS no. 26761-45-5; Cardura® E 10) [§]	O: 0.25	39	0	99
	O: 1	215	0	–
	Σ	254	0	–
Aliphatic diglycidyl and triglycidyl ethers				
1,4-Butanediol diglycidyl ether (BDDGE; CAS no. 2425-79-8)	O/T: 0.25	720	35 (4.9)	44
1,6-Hexanediol diglycidyl ether (HDDGE; CAS no. 16096-31-4; Grilonit® RV 1812) [¶]	O: 0.25	39	2 (5.1)	50
Diethyleneglycol diglycidyl ether (DEGDGE; CAS no. 4206-61-5)	O: 0.5	356	4 (1.1)	0
Neopentylglycol diglycidyl ether (NPGDGE; CAS no. 17557-23-2; Grilonit® RV 1815) [¶]	O: 0.25	39	1 (2.6)	5
Trimethylolpropane triglycidyl ether (TMPTGE; CAS no. 30499-70-8)	C: 0.25	79	1 (1.3)	12
Related aliphatic epoxy resins				
Polypropyleneglycol diglycidyl ether (CAS no. 9072-62-2; DER® 736) ^{**}	O: 0.5 ^{††}	726	10 (1.4)	19
Ethyleneglycol diglycidyl ether (CAS no. 2224-15-9; Quetol® 651)	O: 0.5 ^{††}	475	8 (1.7)	0
Propanetriol glycidyl ether (CAS no. 25038-04-4; LX-112® resin) ^{‡‡} mixture of diglycidyl and triglycidyl ethers of glycerol	O: 0.5 ^{††}	203	2 (1.0)	–
Diglycidyl ester of hexahydrophthalic acid (DGEHHPA; CAS no. 5493-45-8)	C: 0.5	681	9 (1.3)	0
Vinyl cyclohexene dioxide (CAS no. 106-87-6; ERL® 4206)	O: 0.5 ^{††}	720	4 (0.6)	0
Cycloaliphatic epoxy resin ERL® 4221 (CAS no. 2386-87-0) ^{§§}	O: 0.5 ^{††}	389	0	1–3 [†]

C, Chemotechnique, Vellinge, Sweden; O, in-house test substance; T, Trolab, Almirall Hermal GmbH, Reinbeck, Germany.

*Merck-Schuchardt, Hohenbrunn, Germany.

[†]In accordance with principles of the register, numbers smaller than 4 are not published.[‡]Procter & Gamble Ltd, Cincinnati, OH, USA.[§]Resolution Europe B.V., Hoogvliet, The Netherlands.[¶]EMS-Chemie AG, Domat/Ems, Switzerland.^{**}Bio-Rad, Watford, UK.^{††}Concentration of the resin.^{‡‡}Ladd Research Industries Inc., Williston, NJ, USA.^{§§}Union Carbide Benelux N.V., Antwerp, Belgium.**Aliphatic diglycidyl and triglycidyl ethers**

HDDGE was tested at the beginning of the study period in no more than 39 patients. We stopped testing it because of a large number of concomitant reactions to BDDGE seen prior to the present study. Two patients had allergic

reactions to HDDGE; both were allergic to BDDGE and had no identified specific exposure to HDDGE.

BDDGE was tested during the whole study period, and was positive in 35 patients. BDDGE was found in the products of 12 patients. Three tile setters had

Table 2. Patients without contact allergy to diglycidyl ether of bisphenol A resin (DGEBA-R), and their occupations, allergic reactions to epoxy compounds, exposure to reactive diluents and aliphatic epoxy resins, locations of dermatitis, and epoxy-related diagnoses

No.	Occupation/occupational field	Allergic reactions to epoxy compounds	Exposure to reactive diluents and related aliphatic epoxy resins	Location of dermatitis	Epoxy-related diagnosis
1	Cement worker/floor coating	DGEBA-R -, CGE +, PGE ++, Br-DGEBA +	Injectable resins for concrete repair Two-component floor coatings a few times a year	Hands	OACD from reactive diluents
2	Injection worker	DGEBA-R -, BDDGE ++, HDDGE ++, Quetol® 651 ++, Br-DGEBA +	Araldite® BY 158 0.5% + SDS: BDDGE 28–36%, DGEBA-R 64–72%	Hands	OACD from BDDGE
3	Tile setter (injection technique)	DGEBA-R -, BDDGE ++, TMPTGE +, DGEHHPA ++, DER 736 +, DGEBF-R +	Araldite® BY 158 resin 2% ++, 1% ++ SDS: BDDGE 28–36%, DGEBA-R 64–72% Analysis: BDDGE 28%, DGEBA 63%, tertiary butyl phenyl GE 0.2%, propylene glycol diglycidyl ether (= DER® 736) <0.01%; other aliphatic and cycloaliphatic compounds <0.1%	Hands, forearms	OACD from BDDGE
4	Tile setter	DGEBA-R -, BDDGE +	Seaming product SDS: BDDGE	Hands, forearms	OACD from BDDGE
5	Entrepreneur in floor coating	DGEBA-R?+, BDDGE+, PGE+, MDA +++, tris-DMP ++, MXDA +	Floor coating product A 2% + SDS: alkyl(C12–C14) GE 1–5%, DGEBA-R 30–100% Analysis: alkyl GE (C12–C14) 9.6%, BDDGE <0.02%, HDDGE <0.1%, aromatic and aliphatic mono GE <0.005% Floor coating product B SDS: (C12–C14) alkyl GE 1–5% Had used a brush with a fibreglass shaft	Face, neck	OACD from reactive diluents and epoxy hardeners
6	Cleaner	DGEBA-R – CGE + (in plastic and glue series) Epoxy compound series NT		Hands, forearms	OACD from rubber chemicals
7	Impregnation worker in the manufacture of electrical machines	DGEBA-R?+, BDDGE +, DGEBF-R +	Dome® XD 4159 1% +, 0.32% 7+ SDS: DGEBA/DGEBF 78–90%, BDDGE 4–10% Not found	Hands, forearms	OACD from DGEBF-R and BDDGE Patient 4 in ref. (7)
8	Silk printer in the manufacture of circuit boards	DGEBA-R –, BDDGE +, NPGDGE +, Quetol® 651 +, LX 112® +, DER® 736 +++, TGIC 10–3% +++, 1% ++, 0.3–0.1% +; MDA +++		Hands, forearms, face	OACD from MDA, 2-HEMA, and TGIC

Table 2. continued

No.	Occupation/occupational field	Allergic reactions to epoxy compounds	Exposure to reactive diluents and related aliphatic epoxy resins	Location of dermatitis	Epoxy-related diagnosis
9	Assembler in the production of composite parts	DGEBA-R -, BDDGE +, TGAPAP +, DGEBA-R +	Araldite® LY 5052 2-1% ++ SDS: BDDGE 34-42%, DGEBA-R 60-72% Analysis: BDDGE 33%, DGEBA-R 18%, DGEBA-R 0.2%, PGE 0.2% No present exposure to cycloaliphatic epoxy resins (or reactive diluents) Possible past exposure in spray painting	Hands	OACD from DGEBA-R and BDDGE OCA to TGAPAP Patient 2 in ref. (7)
10	Assembler Ex-painter of tractor cabins	DGEBA-R -, DGEHHPA +, TGIC +		Hands, face, neck	OACD from TGIC

BDDGE, 1,4-butanediol diglycidyl ether; Br-DGEBA, brominated diglycidyl ether of bisphenol A resin; CGE, cresyl glycidyl ether; DGEBA/DGEBAF, mixture of DGEBA-R and diglycidyl ether of bisphenol F resin; DGEBAF-R, diglycidyl ether of bisphenol F resin; DGEHHPA, diglycidyl ester of hexahydrophthalic acid; DER 736, polypropyleneglycol diglycidyl ether; GE, glycidyl ether; HDDGE, 1,6-hexanediol diglycidyl ether; 2-HEMA, 2-hydroxyethyl methacrylate; LX112, propanetriol glycidyl ether; MDA, 4,4'-diaminodiphenylmethane; MXDA, *m*-xylylene diamine; NPGDGE, neopentylglycol diglycidyl ether; NT, not tested; OACD, occupational allergic contact dermatitis; OCA, occupational contact allergy; PGE, phenyl glycidyl ether; Quetol 651, ethyleneglycol diglycidyl ether; SDS, safety data sheet; TGIC, triglycidyl isocyanurate; TGAPAP, triglycidyl derivative of *p*-aminophenol; TMPTGE, trimethylolpropane triglycidyl ether; tris-DMP, 2,4,6-tris-(dimethylaminomethyl)phenol.

Table 3. Concomitant reactions to phenyl glycidyl ether and cresyl glycidyl ether, and to phenyl glycidyl ether and *p*-tertiary butyl phenol glycidyl ether

		Cresyl glycidyl ether		Total
		+ / + + / + + +	- / ? + / IR	
Phenyl glycidyl ether	+ / + + / + + +	14	16	30
	- / ? + / IR	2	615	617
	Total	16	631	647

		<i>p</i> -tert-Butyl phenol glycidyl ether		Total
		+ / + + / + + +	- / ? + / IR	
Phenyl glycidyl ether	+ / + + / + + +	8	0	8
	- / ? + / IR	11	196	207
	Total	19	196	215

IR, irritant reaction.

used BDDGE-containing seaming materials or injection resins. A BDDGE-containing resin was used by 2 model carpenters. Three workers in the manufacture of electrical machines had used a thixotropic resin that contained 6% BDDGE. Two composite fitters had used BDDGE-containing adhesives, and 2 laboratory nurses were sensitized to BDDGE in Leica® immersion oil. Six BDDGE-allergic patients (not tested with HDDGE) had been exposed to HDDGE: 2 sewage pipe relining workers, 1 worker from the aviation industry, 1 maintenance worker in a foundry, 1 worker in the manufacture of floor coatings, and 1 boat builder. In addition, we detected 0.1% and 0.2% HDDGE in the chemical analyses of the two above-mentioned adhesives from the electronic industry (see PGE and CGE). Four BDDGE-allergic patients were exposed to other aliphatic glycidyl ethers: 2 to alkyl (C12-C14) glycidyl ether (CAS no. 68609-97-2; Epoxide® 8), and 2 to 2-ethylhexyl glycidyl ether (CAS no. 2461-15-6).

Diethyleneglycol diglycidyl ether (DEGDGE; CAS no. 4206-61-5) was positive in 4 patients, all of whom were allergic to BDDGE and ethyleneglycol diglycidyl ether (Quetol® 651; CAS no. 2224-15-9; Fig. 4), a structurally related aliphatic epoxy resin. We did not find DEGDGE in their products.

We started to test trimethylolpropane triglycidyl ether (TMPTGE; CAS no. 30499-70-8) in June 2011, and so far have seen only 1 allergic reaction. The patient in question was a tile setter, but TMPTGE was not mentioned in the SDSs of the products that he used, or found in the chemical analysis of his resin. He had an allergic reaction to BDDGE, which was declared in the SDS of the resin.

Aliphatic monoglycidyl ethers and esters

BGE was tested in the plastic and glue series in 325 patients, yielding allergic reactions in 3 patients, but we did not find BGE in their products. Two of the patients had concomitant reactions to BDDGE, but the third patient was not tested with any other aliphatic glycidyl ether. Glycidyl ester of neodecanoic acid (Cardura® E 10; CAS no. 26761-45-5) was first tested at a concentration of 0.25% in 39 patients without any allergic reactions. Testing was then stopped. Later, a car painter tested positive to his car lacquers and later to Cardura® E 10 (1%), which was a component in the lacquers (8). We restarted testing Cardura® E 10, but have found no further cases. Neopentyl glycoldiglycidyl ether (NPGDGE; Grilonit® RV 1815; CAS no. 17557-23-2) was also tested at the beginning of the study period in 39 patients, and 1 allergic reaction was noted. The patient had concomitant allergic reactions to BDDGE and DEGDGE, but we did not find NPGDGE in his products.

Related aliphatic epoxy resins

In the group of related aliphatic epoxy resins, diglycidyl ester of hexahydrophthalic acid (DGEHHPA; CAS no. 5493-45-8) was the only test substance available commercially (Chemotechnique Diagnostics™ 'Cycloaliphatic epoxy resin'). We noted 9 allergic reactions to it, but identified exposure to DGEHHPA in only 1 of the patients, whose previous work had been in the manufacture of electrical machines. Polypropyleneglycol diglycidyl ether (DER® 736; CAS no. 9072-62-2) was positive in 10 patients, ethyleneglycol diglycidyl ether (Quetol® 651) in 8 patients, vinyl cyclohexene dioxide (ERL® 4206; CAS no. 106-87-6) in 4 patients, and propanetriol glycidyl ether (LX-112®; CAS no. 25038-04-4) in 2 patients, but none of these was specifically exposed. Four of the ethyleneglycol diglycidyl ether-positive patients had allergic reactions to DEGDGE, 2 had doubtful reactions, 1 was negative, and 2 were not tested with DEGDGE.

Aliphatic epoxy resins can be divided into cycloaliphatic compounds (DGEHHPA, vinyl cyclohexene dioxide, and ERL® 4221) and non-cyclic aliphatic compounds (DER® 736, Quetol® 651, and LX-112®). Twelve patients reacted to the cycloaliphatic epoxy resins and 13 to the non-cyclic aliphatic epoxy resins. The number of patients in the whole group was 19.

Reactive diluents and related aliphatic epoxy resins on the Finnish market

The numbers of the products containing each reactive diluent or aliphatic epoxy resin on the Finnish market

in 2014 are shown in Table 1. The figures are based on the chemical notifications filed in the Finnish Product Register of Chemicals.

Discussion

The frequencies of allergic reactions to individual reactive diluents varied between 0.9% and 8.8%. These figures are approximately the same as those in a US study comprising 167 individuals tested with three reactive diluents: CGE, PGE, and BGE (2.1%, 6.1%, and 1.0%, respectively) (9).

The reactive diluents that were most often positive – PTBPGE, PGE, BDDGE, and HDDGE – were the same as those in the EPOX 2002 study, although the order was different (10). The EPOX 2002 study comprised 70 patients with suspected contact allergy to epoxy compounds and 22 patients with prior positive patch test reactions to DGEBA-R. Our study population was much larger, but the EPOX 2002 study was prospective, and most patients were patch tested with the same series of allergens (10), whereas in the present retrospective study, it is difficult to compare the frequency of allergic reactions to different reactive diluents, because the number of patients tested with each reactive diluent has varied greatly. PGE and BDDGE were, however, tested throughout the study period. PGE gave the largest number of allergic reactions [41 (4.9%)], followed by BDDGE, with 34 (4.9%) allergic reactions. In the EPOX 2002 study, BDDGE was positive more often than PGE (19.5% versus 11.5%) (10).

Although the aromatic glycidyl ether PGE provoked the largest number of reactions, we did not find significant amounts of PGE in the products of the sensitized patients. At present, there are no products containing PGE in the Finnish Product Register of Chemicals. PGE is a known contaminant in commercial epoxy resins: in a Swedish study, concentrations in 20 products varied between 0.04% and 0.18% (11). The results of our chemical analyses were within the same range. The concentrations are so low that they do not explain sensitization to PGE (11). PGE was a relatively good indicator of CGE allergy: in accordance with the results of the EPOX 2002 study (10), the large majority of CGE reactions were associated with allergic reactions to PGE (Table 3), and some of the patients had used CGE-containing products in their work. Most PGE reactions, however, were not associated with exposure to aromatic monoglycidyl ethers, but all PGE-allergic patients except 1 had concomitant reactions to DGEBA-R. Pontén et al. have proposed that contact allergy to PGE may represent an immunological cross-reaction following primary sensitization to DGEBA-R (12). The chemical structures are indeed very

similar, and our exposure data support this explanation. Also in accordance with our results, Pontén et al. noted 4 reactions to PGE in a plant producing wind turbine rotor blades, although PGE was not used. All 4 patients had contact allergy to DGEBA-R (3). The value of testing PGE can be questioned if most of the reactions represent cross-allergy to DGEBA-R and specific exposure to PGE does not take place. CGE might be a better alternative, because exposure to CGE still exists, and we had 2 CGE-allergic patients who did not react to PGE. Similarly, in an Italian report of 10 patients exposed and sensitized to CGE, 3 patients did not react to PGE (or DGEBA-R) (13).

PTBPGE, which is also an aromatic glycidyl ether, was tested in the multicentre EPOX 2002 study in 73 patients. Five of these had allergic reactions (10). In the Finnish Product Register of Chemicals, PTBPGE is declared in a total of 26 products, whereas CGE is declared in seven products and PGE in none. This is in accordance with the information given by Geier et al. in the EPOX 2002 report, which claims that PGE and CGE are currently only rarely used in epoxy products, and that PTBPGE, in turn, is often found in epoxy systems (10). In the present study, the frequency of allergic reactions to PTBPGE (8.8%) was higher than the frequencies of PGE and BDDGE reactions (4.9% and 4.9%, respectively) during the same time period, but the clinical relevance of the reactions remained unclear, because significant exposure to PTBPGE was not identified. Wider chemical analyses might have detected exposure to PTBPGE in some patients. Although PTBPGE was an indicator of PGE allergy (Table 3), the majority of the PTBPGE-allergic patients did not react to PGE. Cross-allergy to other glycidyl ethers (such as DGEBA-R and DGEBF resin) might explain the large number of allergic reactions to PTBPGE.

BDDGE was the most commonly positive aliphatic reactive diluent in the present study population. Many sensitized patients were also exposed to BDDGE or to the chemically closely related HDDGE, and some to other aliphatic glycidyl ethers, such as alkyl (C12–C14) glycidyl ether. Among the DGEBA-R-negative patients, BDDGE was the most commonly positive reactive diluent, and in 3 cases was the sole cause of the epoxy-related occupational allergic contact dermatitis. Thus, BDDGE was the clinically most significant reactive diluent in the present series. Ann Pontén et al. found 2 BDDGE-allergic patients without concomitant allergic reactions to DGEBA-R in a study comprising 603 workers in the production of wind turbine rotor blades. BDDGE-containing products were also used at the plant (3). We stopped testing HDDGE too early to be able to make a comparison between BDDGE and HDDGE in the present study population. Both compounds are used on the Finnish market in an almost equal number

of products. In our study population, exposure to BDDGE was more common than exposure to HDDGE (13 versus 7 patients). In the EPOX 2002 study, HDDGE was slightly more commonly positive than BDDGE, and concomitant reactions were very common (10).

Björkner et al. reported allergic reactions to alkyl (C12–C14) glycidyl ether (Epoxide® 8) in 10 of 30 DGEBA-R-sensitive patients, and 3 of the sensitized patients had been in contact with products containing Epoxide® 8 (14). In the EPOX 2002 study, there were no allergic reactions (10). We stopped testing alkyl (C12–C14) glycidyl ether as early as 1992, and are not able to offer any new information on its clinical significance. It is the reactive diluent that is declared in the largest number of products in the Finnish Product Register of Chemicals, and was also quite commonly mentioned in the SDSs of the products used by our patients (8 patients, 5 of whom were sensitized to BDDGE). In the present situation, testing alkyl (C12–C14) glycidyl ether in parallel with other aliphatic glycidyl ethers such as BDDGE may still be worthwhile in order to confirm or rule out its sensitizing potential and possible cross-reactivity.

DEGDGE caused contact allergy in 3 Estonian ski factory workers, who had used Russian epoxy products containing this chemical. The patients also had allergic reactions to other reactive diluents, namely BDDGE and PGE. A concentration of 1% was used in the study, and this was irritant in some control patients at the FIOH (15). Subsequent patch testing in the routine epoxy chemical series with a 0.5% concentration yielded 2 additional cases, both with strong reactions to aliphatic (BDDGE) and aromatic (PGE) reactive diluents (15). We have found no other cases in the literature. In the present study population, allergic reactions were seen in 4 patients. They were all allergic to other aliphatic glycidyl ethers, but we did not find DEGDGE in their products. Cross-allergy to other glycidyl ethers is a possible explanation for the reactions.

Contact allergy to TMPDGE has been reported in 8 patients in the United States (16), in 2 patients in the multicentre EPOX 2002 study (10), in 2 Danish wind turbine rotor blade workers (3), and in 3 Taiwanese subway construction workers (17). The patients in the two latter studies had used TMPDGE-containing products. We recently introduced a commercial patch test preparation in our epoxy compound series, but our sole case did not use TMPDGE-containing products. The reaction possibly represented cross-allergy to other (aliphatic) glycidyl ethers. Not many products on the Finnish market are declared to contain TMPDGE, but it is too early to evaluate the clinical significance of this compound.

According to the Finnish Product Register of Chemicals, epoxy products contain aliphatic reactive diluents much more often than aromatic reactive diluents. Although Cardura® E 10 is declared in the second largest number of epoxy products, allergic reactions to it seem to be rare and often isolated (18, 19). This is possibly attributable to Cardura® E 10's glycidyl ester structure, which might not easily cross-react with the glycidyl ethers that are typically present in most epoxy resin systems.

Aliphatic epoxy resins

Allergic contact dermatitis caused by DGEHHPA has only rarely been reported. The first report described 5 metal workers who had used DGEHHPA-containing cutting oil, 3 of whom did not react to DGEBA-R (20). The FIOH reported a series of 10 sensitized patients who worked in the manufacture of electrical insulators. Only 1 of the patients had contact allergy to DGEBA-R (4). Two metal workers had been sensitized to DGEHHPA in a neat oil, and neither of the patients had contact allergy to DGEBA-R (21). In the present series, only 1 of the 9 sensitized patients was identified as being exposed to DGEHHPA. One patient who formerly worked in spray painting did not react to DGEBA-R. Jensen & Andersen proposed cross-allergy between PGE and DGEHHPA (21). In the present study population, 6 of the 9 sensitized patients had contact allergy to PGE and 7 to aliphatic reactive diluents. Concomitant allergic reactions to non-cyclic aliphatic epoxy resins (Der® 736, Quetol® 651, and LX-112®) were seen in 5 patients, all of whom were also allergic to BDDGE. Thus, concomitant reactions to the aliphatic compounds were seen more often than reactions to PGE in patients with contact allergy to DGEHHPA.

We found only one report in the literature of allergic contact dermatitis caused by vinyl cyclohexene dioxide, another cycloaliphatic epoxy resin, in an electron microscopist (22). Our 4 patients who reacted to this substance did not have identified specific exposure to it. All had several concomitant allergic reactions to reactive diluents and/or other aliphatic epoxy resins.

Allergic reactions to non-cyclic aliphatic epoxy resins (DER® 736, Quetol® 651, and LX-112®) were noted in a total of 13 patients. All of these were allergic to BDDGE.

The few allergic reactions to other aliphatic reactive diluents (BGE, TMPTGE, DEGDGE, and NPGDGE) were also mostly seen in this group of patients. Three of the patients did not react to DGEBA-R or aromatic glycidyl ethers, but 5 of them reacted to DGEHHPA. Reactivity to aromatic epoxy compounds (aromatic reactive diluents and DGEBA-R) is possibly distinct from reactivity to aliphatic epoxy compounds (aliphatic reactive diluents, cycloaliphatic epoxy resins, and non-cyclic aliphatic epoxy resins).

In the present study, all of the patch tested compounds have epoxy groups, and concomitant reactions to several of them were very common. Reactions to PGE and CGE usually occurred together, and when PTBPGE was tested, all PGE-positive patients had allergic reactions to it. Apart from this, it was quite difficult to see clear patterns of concomitant reactions.

In conclusion, we describe the patch test reactions and exposure data of 67 patients who reacted to some reactive diluent or related aliphatic non-DGEBA/DGEBF epoxy resin. A total of 85% of the patients reacted to DGEBA-R in the baseline series. BDDGE was the clinically most significant compound among the 18 epoxy compounds tested. Most DGEBA-R-negative cases were related to BDDGE-containing products, and, in 3 cases, BDDGE was the sole cause of the epoxy-related occupational allergic contact dermatitis. PGE reactions were common, but clinically significant exposure was not found in sensitized patients. Some PGE-allergic patients had used products containing CGE, which is a structurally closely related substance. Some solitary DGEBA-R-negative patients also reacted to PGE or CGE. Although quite a lot of allergic reactions to PTBPGE were seen, their clinical relevance remained unclear, because we could not identify specific exposure. Allergic reactions to cycloaliphatic epoxy resins and non-cyclic aliphatic epoxy resins occurred to some extent, but patch testing with them provided limited independent value in the diagnostics. The patch testing of patients exposed to epoxy products requires BDDGE, and preferably also some aromatic reactive diluent such as CGE or PGE.

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