

Sensitization to reactive diluents and hardeners in epoxy resin systems. IVDK data 2002–2011. Part II: concomitant reactions

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Summary

Background. Beside the basic resins, reactive diluents and hardeners are important sensitizers in epoxy resin systems (ERSs). Because of chemical similarities, immunological cross-reactivity may occur.

Objectives. To analyse concomitant reactivity among reactive diluents and hardeners in the patients concerned, as one integral part of a research project on the sensitizing capacity of ERSs (FP-0324).

Methods. A retrospective analysis of data from the Information Network of Departments of Dermatology (IVDK), 2002–2011, was performed.

Results. There was close concomitant reactivity to 1,6-hexanediol diglycidyl ether and 1,4-butanediol diglycidyl ether (1,4-BDDGE), and to phenyl glycidyl ether (PGE) and cresyl glycidyl ether (CGE), whereas reactions to *p*-tert-butylphenyl glycidyl ether occurred more independently from those to PGE and CGE. Concomitant reactions to butyl glycidyl ether and 1,4-BDDGE may point to a common allergenic compound derived from the metabolism of 1,4-BDDGE. Among the structurally more diverse group of hardeners, there was no evidence of immunological cross-reactions.

Conclusions. More detailed knowledge of cross-reactivity among ERS components facilitates the interpretation of patch test results and will allow safer ERSs to be composed in the future.

Key words: concomitant reactivity; cross-reactivity; epoxy resin systems; hardeners; occupational contact allergy; reactive diluents.

Beside the basic resins, hardeners and reactive diluents are important sensitizers in epoxy resin systems (ERSs) (1–7). This is the second part of a data analysis from the Information Network of Departments of Dermatology

(IVDK), 2002–2011, on sensitization to epoxy resin hardeners and reactive diluents, focusing on concomitant reactivity. In the first part, reaction frequencies in patients with and without sensitization to epoxy resin based on diglycidyl ether of bisphenol A (DGEBA) resin have been reported (8). Concomitant reactions to two or more reactive diluents, which are mainly aromatic and aliphatic glycidyl ethers, have recently been reported in a number of patients from the Finnish Institute of Occupational Health (FIOH) by Aalto-Korte et al. (7). Our data analysis, adding information on reaction patterns from German, Swiss and Austrian dermatitis patients, was part of a research project 'Ranking of epoxy resin components

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according to their sensitizing potency' (FP-0324), which was funded by the German statutory accident insurance [Deutsche Gesetzliche Unfallversicherung (DGUV)], and performed by the 'Forschungs- und Beratungsinstitut Gefahrstoffe' (FoBiG) (Freiburg, Germany; www.fobig.de) and the IVDK (www.ivdk.org) (9).

Patients and Methods

Routine operating and quality control procedures of the IVDK, which is a network of departments of dermatology in Germany, Switzerland and Austria dedicated to the epidemiological surveillance of contact allergy, are described in detail elsewhere (8, 10–12).

All IVDK members are also members of the German Contact Dermatitis Research Group [Deutsche Kontaktallergie-Gruppe (DKG)]. Patch tests are performed and read according to DKG guidelines (13). Patch test preparations (Table 1) were purchased from Almirall Hermal (Reinbek, Germany), except for *m*-xylylene diamine (MXDA) and trimethylolpropane triglycidyl ether, which were purchased from Chemotechnique™ (Vellinge, Sweden), and diethylene triamine (DETA), which was purchased from briar allergen™ (Greven, Germany) or SmartPractice® Germany (Barsbüttel, Germany). The patch test exposure time was 24 hr in 18.3% of the patients, and 48 hr in 81.7% of the patients. With a few (temporary) exceptions, Finn Chambers® on Scanpor® (inner diameter, 8 mm) were used as test chambers.

For this data analysis, patch test reactions at D3 were selected. In a few exceptional cases, when a reading was performed at D4 instead of D3, this reading was chosen. Readings coded as +, ++ or +++, that is, positive reactions with erythema, infiltration, papules and/or (coalescing) vesicles, according to scoring, were rated as positive in dichotomized analyses. Data management and analysis were performed with SAS™ 9.3 (SAS Institute, Cary, NC, USA).

Results

A total of 105 656 patients had been patch tested in the departments of dermatology joining the IVDK during the 10-year study period (2002–2011). A DGEBA resin was patch tested as part of the baseline series in 93 406 patients, representing 88.4% of all patients tested. Of these, 1453 patients (1.6%) showed a positive reaction, 529 (0.6%) a doubtful or irritant reaction, and 91 424 a negative reaction. [General remark: owing to the selection of the 10-year period 2002–2011, test results of EPOX 2002 (14) are also included in the present data analysis.] Frequencies of positive reactions to the hardeners and

reactive diluents listed in Table 1 are reported in the first part of our data analysis (8).

Concomitant reactivity among reactive diluents

In contrast to the hardeners, most of which have considerably different chemical structures, there are some chemically closely related compounds among the reactive diluents. Both 1,6-hexanediol diglycidyl ether (1,6-HDDGE) and 1,4-butanediol diglycidyl ether (1,4-BDDGE) are aliphatic glycidyl ethers with a chain length differing by only two carbon atoms (Table 1). Phenyl glycidyl ether (PGE), cresyl glycidyl ether (CGE) and *p*-tert-butylphenyl glycidyl ether (PTBPGE) are aromatic glycidyl ethers without (PGE) or with (CGE and PTBPGE) side chains (Table 1). Therefore, immunological cross-reactivity is to be expected.

Concomitant reactions to reactive diluents in patients with sensitization to DGEBA resin are shown in Table 2. Of 452 patients tested with 1,6-HDDGE and 1,4-BDDGE, 191 (42.3%) reacted to 1,6-HDDGE, and 155 (34.3%) reacted to 1,4-BDDGE, respectively. The 144 patients reacting positively to both chemicals represent 75.4% of those reacting to 1,6-HDDGE, and 92.9% of those reacting to 1,4-BDDGE. Seventy-seven patients reacted to both PGE and CGE, representing 44% of the 175 patients reacting to PGE, and 95.1% of those reacting to CGE. Concomitant reactivity to PGE and PTBPGE was not as close. The 56 patients reacting to both of these compounds represent 60.2% of the 93 reacting to PGE, and 63.6% of the 88 reacting to PTBPGE. CGE and PTBPGE were tested in parallel in 336 patients, of whom 91 (27.1%) reacted to PTBPGE, and 44 (13.1%) to CGE. Twenty-eight patients reacted to both compounds, representing 63.6% of those reacting to CGE, and 30.8% of those reacting to PTBPGE.

Table 3 shows the reaction patterns in the 201 patients tested in parallel with PGE, CGE, and PTBPGE. Whereas isolated reactions to PGE or PTBPGE occurred comparably often (7.6% and 9.7%, respectively), isolated reactions to CGE were rare (0.9%). Most positive reactions to CGE were accompanied by reactions to PGE or to both PGE and PTBPGE.

Although butyl glycidyl ether (BGE) and 1,4-BDDGE are chemically not as closely related as 1,6-HDDGE and 1,4-BDDGE, we analysed concomitant reactions to BGE and 1,4-BDDGE because BGE is not very widely used, but frequently elicits positive patch test reactions. The results are shown in Table 4. This analysis was not restricted to DGEBA resin-positive patients, in order to have the results of all parallel patch tests with BGE and 1,4-BDDGE. Of the 6263 patients tested, 231 (3.7%) reacted to 1,4-BDDGE,

Table 1. Components of epoxy resin systems, with abbreviations, Chemical Abstract Service (CAS) numbers, and patch test concentrations, for which Information Network of Departments of Dermatology (IVDK) data 2002–2011 were analysed

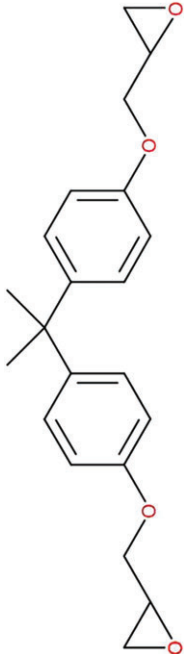
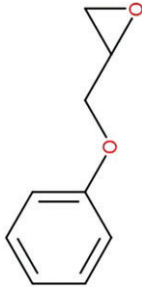
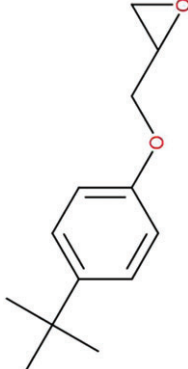
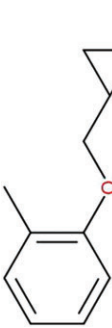
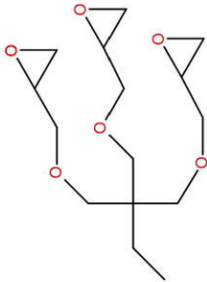
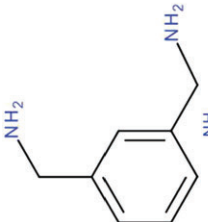
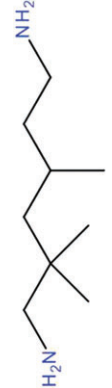
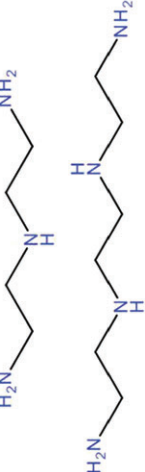
Substance	Abbreviation	Structural formula	CAS no.	Patch test concentration (pet.) (%)	Availability during study period
Resin					
Based on diglycidyl ether of bisphenol A	DGEBA resin		25068-38-6	1	All the time
Reactive diluents					
1,6-Hexanediol diglycidyl ether	1,6-HDDGE		16096-31-4	0.25	Since 2006
1,4-Butanediol diglycidyl ether	1,4-BDDGE		2425-79-8	0.25	Since 2006
Phenyl glycidyl ether	PGE		122-60-1	0.25	All the time
<i>p</i> -tert-Butylphenyl glycidyl ether	PTBPGE		3101-60-8	0.25	Since 2008
Cresyl glycidyl ether	CGE		26447-14-3	0.25	All the time
Butyl glycidyl ether	BGE		2426-08-6	0.25	All the time

Table 1. Continued

Substance	Abbreviation	Structural formula	CAS no.	Patch test concentration (pet.) (%)	Availability during study period
Trimethylolpropane triglycidyl ether Hardeners <i>m</i> -Xylylene diamine	TMPTGE		30499-70-8	0.25	Since 2008
	MXDA		1477-55-0	0.1	Since 2008
Isophorone diamine Trimethylhexane-1,6-diamine (mixture of isomers)	IPDA		2855-13-2	0.5	All the time
	TMHDA		25620-58-0	0.5	Since 2008
Diethylene triamine	DETA		111-40-0	1	All the time
Triethylene tetramine	TETA		112-24-3	0.5	Until 2010

The test vehicle was petrolatum.

Table 2. Results of parallel patch testing with chemically related reactive diluents in patients sensitized to diglycidyl ether of bisphenol A resin

		Positive	Negative, doubtful, irritant	Total
		1,4-BDDGE		
1,6-HDDGE	Positive	144	47	191
	Negative, doubtful, irritant	11	250	261
	Total	155	297	452
		CGE		
PGE	Positive	77	98	175
	Negative, doubtful, irritant	4	383	387
	Total	81	481	562
		PTBPGE		
PGE	Positive	56	37	93
	Negative, doubtful, irritant	32	206	238
	Total	88	243	331
		PTBPGE		
CGE	Positive	28	16	44
	Negative, doubtful, irritant	63	229	292
	Total	91	245	336

1,4-BDDGE, 1,4-butanediol diglycidyl ether; CGE, cresyl glycidyl ether; 1,6-HDDGE, 1,6-hexanediol diglycidyl ether; PGE, phenyl glycidyl ether; PTBPGE, *p*-tert-butylphenyl glycidyl ether.

Table 3. Results of parallel patch testing with phenyl glycidyl ether (PGE), cresyl glycidyl ether (CGE) and *p*-tert-butylphenyl glycidyl ether (PTBPGE) in 201 patients sensitized to diglycidyl ether of bisphenol A resin

PGE	CGE	PTBPGE	Patient count	%
+	–	–	25	7.6
+	+	–	12	3.7
+	–	+	28	8.5
+	+	+	28	8.5
–	+	–	3	0.9
–	+	+	0	0.0
–	–	+	32	9.7
–	–	–	201	61.1

+, positive reaction; –, doubtful, negative or irritant reaction.

Table 4. Concomitant reactions to butyl glycidyl ether (BGE) and 1,4-butanediol diglycidyl ether (1,4-BDDGE)

		1,4-BDDGE		
		Positive	Negative, doubtful, irritant	Total
BGE	Positive	60	13	73
	Negative, doubtful, irritant	171	6019	6190
	Total	231	6032	6263

and 73 (1.2%) reacted to BGE. Sixty patients reacted to both glycidyl ethers, representing 26.0% of those reacting to 1,4-BDDGE, but 83.3% of those reacting to BGE.

Concomitant reactivity among hardeners

Concomitant reactions to different hardeners may also occur. However, this coincidence is probably attributable to synchronous or metachronous concomitant exposure rather than immunological cross-reactivity induced by chemical structural similarities. Only DETA and triethylene tetramine (TETA) are closely related linear aliphatic amines with different lengths. Trimethylhexane-1,6-diamine is also an aliphatic amine, but with three small side chains, and therefore has a unique carbon chain skeleton and a different spatial configuration. MXDA is an aromatic amine, and isophorone diamine (IPDA) is a cycloaliphatic amine; hence, immunological cross-reactivity seems improbable. However, both are very widely used, so it is reasonably possible that patients have been exposed to both hardeners over the course of time. In addition, they are the most frequently observed sensitizers among the epoxy resin hardeners (8). Against this background, we restricted the analysis of concomitant reactions to hardeners to the pairings MXDA/IPDA and DETA/TETA.

Concomitant reactions to MXDA and IPDA, and to DETA and TETA, are shown in Table 5. Altogether, 3837 patients were patch tested with MXDA and IPDA. Eighty-one patients (2.1%) reacted positively to MXDA, and 50 patients (1.3%) to IPDA. Concomitant reactions to both were seen in 22 patients, representing 44% of the 50 patients reacting to IPDA, and 27% of the 81 patients reacting to MXDA. DETA and TETA were patch tested in 1074 patients. Of these, 12 (1.1%) reacted to DETA, and 7 (0.7%) to TETA. Three of these patients reacted to both DETA and TETA.

Table 5. Concomitant reactions to *m*-xylylene diamine (MXDA) and isophorone diamine (IPDA), and to diethylene triamine (DETA) and triethylene tetramine (TETA)

		Positive	Negative, doubtful, irritant	Total
		IPDA		
MXDA	Positive	22	59	81
	Negative, doubtful, irritant	28	3728	3756
	Total	50	3787	3837
		TETA		
DETA	Positive	3	9	12
	Negative, doubtful, irritant	4	1058	1062
	Total	7	1067	1074

Discussion

As mentioned in the first part of our data analysis (8), this is the largest number of patch test results with ERS components reported up to now, besides the FIOH data (6, 7). This offers the opportunity to study concomitant reactions to reactive diluents and epoxy resin hardeners in the dermatitis patients concerned. Pontén et al. showed immunological cross-reactivity of DGEBA resin and PGE; in guinea-pigs sensitized to DGEBA, they elicited allergic reactions to PGE (15). However, we are not aware of any experimental studies showing immunological cross-reactivity among reactive diluents. Therefore, it is worthwhile analysing clinical data in this respect.

Concomitant reactions to 1,6-HDDGE and 1,4-BDDGE, which are chemically very closely related, have been reported in 4 occupational dermatitis patients working in a Danish factory producing wind turbine rotor blades (16–18). However, in these cases, the ERS that the workers were exposed to contained both 1,4-BDDGE and 1,6-HDDGE. Therefore, it remained unclear whether concomitant sensitization was attributable to co-exposure or cross-reactivity. In our data, we found a high rate of concomitant reactions to 1,6-HDDGE and 1,4-BDDGE; hardly any reactions to 1,4-BDDGE occurred without reactions to 1,6-HDDGE, and, vice versa, 75% of the patients who reacted positively to 1,6-HDDGE also reacted to 1,4-BDDGE (Table 2). According to material safety data sheets (MSDSs) at the 'hazardous material information system' of the statutory accident insurance of the construction industry [Gefahrstoff-Informationssystem der BG BAU (GISBAU) www.bgbau.de/gisbau], 1,6-HDDGE is far more frequently used than 1,4-BDDGE (data not shown in detail). Therefore, we assume that, in most cases of concomitant reactivity, patients have primarily been sensitized to 1,6-HDDGE and subsequently reacted to 1,4-BDDGE on the basis of an immunological

cross-reaction. However, the possibility cannot be excluded that those sensitized to 1,4-BDDGE have also been exposed – and thereby sensitized – to 1,4-BDDGE. At the FIOH, 1,6-HDDGE had been tested in a limited number of patients only. Therefore, concomitant reactivity to 1,4-BDDGE could not be analysed on a large scale (7). However, Aalto-Korte et al. stated that exposure to 1,4-BDDGE was more common in their study population than exposure to 1,6-HDDGE, which may be the reason why 1,4-BDDGE was the clinically most significant reactive diluent in their test series (7).

A similar constellation could be seen with PGE and CGE, which are aromatic glycidyl ethers that only differ in a methyl group at the benzene ring. Aalto-Korte et al. reported 647 patients who were patch tested with both PGE and CGE. Of these, 30 (4.6%) reacted to PGE, and 16 (2.5%) to CGE. Fourteen patients reacted to both glycidyl ethers, representing 87.5% of those reacting to CGE, and 47% of those reacting to PGE, respectively (7). In addition, 215 Finnish patients had been patch tested with PGE and PTBPGE, of whom 8 (3.7%) reacted to PGE, and 19 (8.8%) to PTBPGE. All of the 8 patients reacting to PGE also reacted to PTBPGE (7). In line with findings from the FIOH, we observed only very few reactions to CGE without a reaction to PGE (Tables 2 and 3), making immunological cross-reactions very probable in these cases, too. CGE is rarely used in ERSs for the construction industry on the German market, but is nevertheless used more frequently than PGE. According to the MSDSs at GISBAU, PTBPGE has a similar usage level as CGE. Cross-reactivity of PTBPGE with PGE and CGE, respectively, is present, but limited, as can be seen in Tables 2 and 3. Remarkably, the percentages of concomitant reactions to PGE and CGE, but not to PTBPGE and PGE, are quite similar to those observed by Aalto-Korte et al. (7). In all, the percentages of positive reactions to these reactive diluents were lower in the FIOH data, probably because of a more deliberate indication for patch testing. A different indication for patch testing would not affect the concordance of positive reactions if they were caused by immunological cross-reactivity only. However, if allergens are independent sensitizers from the immunological point of view, then concomitant reactivity will be affected by the indication for patch testing. Hence, in our opinion, it is likely that PTBPGE is an allergen on its own, and that not all positive reactions to it can simply be explained by cross-reactivity, although we could not determine from our data whether patients sensitized to PTBPGE were indeed exposed to this reactive diluent, owing to the lack of detailed product information.

The structural relationship between 1,4-BDDGE and BGE is limited. According to the MSDSs at GISBAU,

1,4-BDDGE is rarely used, and BGE is not used at all, in current ERSs utilized in the construction industry. Nevertheless, positive reactions to BGE have been noted. Of course, exposure to BGE might occur in other fields of ERS application, but we wondered whether reactions to BGE could – at least partly – be caused by cross-reactivity. Table 4 shows that 60 of 73 patients (82.2%) reacting to BGE also reacted to 1,4-BDDGE. We could not find any information about the metabolism of 1,4-BDDGE, but it might be hydrolysed, leaving a hydroxy-substituted molecule resembling BGE. Of course, this is purely hypothetical, but it provides a plausible explanation of why reactions to BGE occur in spite of its rare usage, and why reactions to BGE are so frequently accompanied by reactions to 1,4-BDDGE. Aalto-Korte et al. reported 3 patients reacting to BGE, but no corresponding exposure could be found. In 2 of them, 1,4-BDDGE was also tested, and both reacted positively (7). In addition, it is remarkable that BGE, which had a very high EC3 value in the local lymph node assay (19, 20), indicating low sensitizing potency, elicited positive patch test reactions in almost 11% of the patients tested (8). In our opinion, this constellation of findings supports the assumption that sensitization to BGE is mostly attributable to 'cross-reactivity' in patients primarily sensitized to 1,4-BDDGE, and not primary sensitization to BGE.

Our analysis of concomitant reactions to hardeners showed only very limited concordance of reactions to MXDA and IPDA, and to DETA and TETA, respectively. In the case of MXDA and IPDA, this was to be expected, as they are not chemically related. Hence, concomitant reactions can best be explained by exposure to both MXDA and IPDA in the ERS handled by the patients. Aalto-Korte et al. made similar observations in their patients, and they could prove corresponding exposures in most of the patients reacting to both amine hardeners (6). As at the FIOH (6), only a few of our patients reacted to DETA and/or TETA, and no far-reaching conclusions can be drawn from the analysis of concomitant reactions. At least, one can state that the data reported in Table 5 do not inevitably indicate immunological cross-reactivity.

Conclusions

Among the aromatic glycidyl ethers used as reactive diluents, there is a high degree of concomitant reactivity. In our opinion, PTBPG might be an allergen on its own, whereas PGE and CGE do cross-react on an immunological basis. Very probably, there is also immunological cross-reactivity between 1,6-HDDGE and 1,4-BDDGE, and, in addition, there is some evidence from our data that BGE might cross-react with 1,4-BDDGE. This knowledge

is helpful (i) for interpreting patch test results in occupational dermatitis patients, and (ii) for the composition of safer, less sensitizing ERSs in the future. Among the epoxy resin hardeners, we found no evidence for immunological cross-reactions.

Acknowledgements

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