

An attempt to improve diagnostics of contact allergy due to epoxy resin systems. First results of the multicentre study EPOX 2002

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Epoxy resin systems (ERSs) are a frequent cause of occupational allergic contact dermatitis. Sensitization occurs not only to the resins, but also to hardeners and reactive diluents. However, only a fraction of the ERS components currently in use are available for patch testing. With the multicentre study EPOX 2002, we attempted to improve diagnostics in this field by patch testing with components currently used in ERSs. During the first study period (October 2002 to July 2003), in addition to commercially available ERS patch test substances, 16 study substances (1 resin, 9 hardeners and 6 reactive diluents) were patch tested in 70 patients with suspected contact allergy due to ERSs and 22 patients with a prior positive patch test reaction to epoxy resin (ER) in the standard series. Most frequently, allergic reactions to ER based on diglycidyl ether of bisphenol A and F were observed (55.2% and 43.7%, respectively). Agreement between positive reactions to both resins, which can be explained by immunological cross-sensitization and/or coexposure, was substantial [Cohen's kappa 0.65 (95% CI: 0.49–0.80)]. Among the reactive diluents, 1,6-hexanediol diglycidyl ether (1,6-HDDGE) and 1,4-butanediol diglycidyl ether (1,4-BDDGE) were the most frequent allergens, with 19.5% and 18.4% positive reactions, respectively. Although agreement between positive reactions to 1,6-HDDGE and 1,4-BDDGE was even better than with the 2 resins, the sample size is considered too small to decide reliably whether 1,6-HDDGE alone could serve as a marker allergen for both. Allergic reactions to *p*-tert-butylphenyl glycidyl ether and to phenyl glycidyl ether (PGE) occurred in 11.5% of the patients tested, with only moderate agreement. All patients positive to cresyl glycidyl ether (6.8%) also reacted to PGE. Of the hardeners tested, *m*-xylylene diamine was the most frequent allergen (13.8%), followed by isophorone diamine (5.7%). No reactions were observed to several substances, the test concentration of which may have been too low and will be increased in the future.

Key words: 1,4-butanediol diglycidyl ether; 1,6-hexanediol diglycidyl ether; contact allergy; cresyl glycidyl ether; DGEBA-R; DGEBAF-R; epoxy resin; hardeners; isophorone diamine; *m*-xylylene diamine; occupational; phenyl glycidyl ether; *p*-tert-butylphenyl glycidyl ether; reactive diluents.

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Due to their unique properties, such as high mechanical, chemical and thermal resistance, epoxy resin systems (ERSs) are widely used in many trades and industrial fields. Some typical applications are: 2-component adhesives; floor coatings, particularly for factories, carparks, etc.; repairing of concrete; applications in the plastics industry, especially for structural composites and in the production of lightweight aeroplanes, boats or rotor blades for wind turbines; in painting and spray

painting, particularly for corrosion inhibition; in the metal branch for coating and lamination of metal parts and sheets and for fixing screws; in the electrical industry for insulation and in the production of electric motors, transformers, etc. (1–10).

The 2 basic components of an ERS are the resin and a curing agent (hardener). Additionally, ERSs contain diluents, plasticizers, fillers, pigments and other additives. Except for the electrical industry, cold-cured ERSs are used in the above mentioned

applications. In these ERSs, the resin component is mostly a mixture of resins based on diglycidyl ethers of bisphenol A (DGEBA) and bisphenol F (DGEBF), because the admixture of DGEBF resin (DGEBF-R) prevents DGEBA resin (DGEBA-R) from crystallization, thus making the ERSs easier to handle at low temperatures (8, 10). Curing is usually provided by amine hardeners (aliphatic, cycloaliphatic or aromatic amines), nowadays most frequently in the form of polyamine adducts, which, however, contain monomers in varying concentrations. The required viscosity is adjusted by reactive diluents, mostly various glycidyl ethers (2, 6, 8). Heat-cured ERSs are mainly used in the electrical industry, where DGEBA-R (without DGEBF-R) or resins based on glycidyl esters of tetrahydrophthalic acid are commonly used. Dicarboxylic anhydrides, such as tetrahydrophthalic anhydride, hexahydrophthalic anhydride and their derivatives, are used as curing agents. Heat curing is performed in special ovens at temperatures around 150° celsius or more (11).

Occupational contact allergy due to ERS components occurs frequently in the exposed (6): components of ERS were the third most common cause of occupational allergic contact dermatitis in the Finnish Institute of Occupational Health in the 1970s and 1980s (5, 12). In the departments of dermatology forming the Information Network of Departments of Dermatology (IVDK) (13), the frequency of positive reactions to the epoxy resin (ER) (based on DGEBA) patch tested in the standard series ranged from 0.9% to 1.4% (women: 0.6–1.2%; men: 1.6–2.3%) in 1992–2000 (14). However, not only the resins, but also several curing agents and reactive diluents have been described as contact allergens. In their textbook chapter on ERs, Jolanki et al. mention not less than 27 hardeners and reactive diluents frequently used in ERS (6). Unfortunately, only a small fraction of these substances are yet commercially available as patch test substances. Hence, contact allergy to ERSs is presumably under-diagnosed.

To improve diagnostics in patients with presumed allergic contact dermatitis due to ERS, we performed the multicentre study EPOX 2002 (14, 15), consisting of 5 steps:

- (1) Identification of those ERS components which are most frequently used at present.
- (2) Compilation of 1 or several ER test series. Fortunately, during step 1, it turned out that in different applications (adhesives, coatings, painting and plastics production), the components of the ERS currently in use overlap broadly. Hence, it was sufficient to establish 1 universal set of allergens only.

- (3) Production of suitable patch test preparations of those ERS components not yet available as patch test preparations.
- (4) Patch testing in dermatitis patients exposed to ERS or patients with positive test reactions to ER in the standard series.
- (5) Evaluation of the results and redefinition of the ERS test series.

Results of the first study period are presented in this article.

Materials and Methods

For this study, 2 patch test series were compiled, the first consisting of ERS components commercially available as patch test substances, and the second containing frequently used components of cold-cured ERS with a presumed or reported allergenic potential. Information on the utilization of ERS components was received from the ERS producing and formulating industry. Test concentrations of the study substances were chosen according to information from the literature or analogously to chemically similar substances. The study substances, produced from industrial or laboratory chemicals, were prepared by Hermal, Reinbek, Germany. The test substance cycloaliphatic ER 0.5% petrolatum (pet.) was a donation from Chemotechnique, Malmö, Sweden. The other commercially available patch test substances were purchased from Hermal.

The first period of the study was performed from October 2002 to July 2003 in 18 departments of dermatology, all of them members of the German Contact Dermatitis Research Group (DKG) and the IVDK. Patients eligible for the study were (I) those with suspected ER dermatitis or (II) those with a positive reaction to ER in the standard series in the current or a recent patch test. In addition to the IVDK routine documentation, a special case record form concerning ERS exposure, including kind and duration of ERS-exposed work, products used, skin protection, affected skin sites and duration of the skin disease, was used in this study.

Patch tests were performed and read according to international guidelines (16) further refined by the DKG (17). Among the 92 patients tested, patch test application time was 1 day in 36 patients (39.1%) and 2 days in 56 patients (60.9%), in line with the routine patch test procedures in the respective centres. All tests were read at least until day 3.

Diagnostic quality of patch test preparations was assessed by calculating the reaction index

(RI) (18) and the positivity ratio (PR) (19). The RI describes the ratio of doubtful or irritant reactions to positive (allergic) reactions, having the value of +1 in case of all reactions observed being positive and -1 if only doubtful or irritant reactions occur. The PR is the percentage of weak positive reactions (+) among the total of positive reactions (+, ++, +++) observed. Well-investigated standard allergens normally have an RI of ≥ 0.5 and a PR of $< 75\%$. A PR of $> 80\%$, in particular when combined with a negative RI, indicates that the test preparation is not optimal and may have irritant properties (19).

For data analysis, reactions at day 3 were considered. Data were analysed at the IVDK data centre at the University of Göttingen (13), using the statistical program system SAS (version 8.2, SAS Institute, Cary, NC, USA). Differences in reaction frequencies in disjunct subgroups of patients were tested for statistical significance using Fisher's exact test. In view of the exploratory nature of statistical testing, no alpha adjustment was employed. We analysed concordance between selected, chemically similar allergens using Cohen's kappa with accompanying 95% confidence intervals (95% CIs), utilizing a method for deriving exact bootstrap CIs, which has recently been suggested for small samples, for which asymptotic estimates of precision may be inappropriate (20).

Results

In all, 92 patients in 18 centres* were tested with the 2 ERS series, 71 men and 21 women.

*The following 18 departments of dermatology (physicians) participated in the study (sorted by descending number of patients): Essen (U. Hillen), Heidelberg (U. Jappe), Osnabrück (H. Dickel, S. M. John, N. Schürer, H. J. Schwanitz[†]), Homburg/Saar (P. Koch), Dortmund (C. Pirker, R. Herbst, P. J. Frosch), Erfurt (H.-J. Schubert), München Schwabing (M. Agathos), München TU (J. Rakoski), Göttingen

(Th. Fuchs, J. Geier), Graz (B. Kränke, W. Aberer), Mainz (D. Becker), Rostock (H. Heise), Berlin (A. Rothe), Gera (J. Meyer), Buxtehude (B. M. Hausen), Dresden (R. Aschoff, G. Richter), Lübeck (J. Grabbe) and Marburg (H. Löffler). Their age ranged from 17 to 77 years (mean 44.2 ± 12.8 years; median 45 years). 6 of these patients had past or present atopic dermatitis, based on patient's history and/or current clinical findings. 70 patients were tested because of suspected ER contact dermatitis (subgroup A), and 22 because of a previously positive patch test reaction to ER from the standard series, without clear-cut history of ERS exposure (subgroup B). In subgroup A, 66 patients had an occupational, and 4 a non-occupational, exposure to ERS (Table 1). Comprising 25 patients, the building trade (bricklayers, concrete workers, floor layers and tile setters) represented the largest share of the occupationally exposed patients (38%). Unprotected skin areas and the anatomical site of the contact dermatitis in patients with occupational ERS exposure are summarized in Table 2. Altogether, face and/or neck were involved in 33 cases (all patients with neck dermatitis also had face dermatitis), while hands and/or arms were affected in 60 patients. In only 6 patients was the neck/face region affected while the hands or arms were not. 5 of these wore rubber gloves at work, but no face mask. 3 of these patients worked with 2-component adhesives, 1 was a spray painter, 1 a floor layer and 1 a bricklayer (no details of ERS exposure given). With the exception of the spray painter, it could not be determined from the data recorded whether involvement of the face in the 33 patients with face dermatitis was due to airborne dermatitis or secondary to accidental contamination by touching the face with the hands or gloves. Of the 51 patients who wore gloves when handling ERS, 24 used rubber gloves (including 5 patients who used nitrile gloves), 14 leather gloves, 6 cotton gloves, 4 vinyl gloves and 3

Table 1. Exposure to ERS in 70 patients tested for suspected epoxy resin dermatitis

	Patient count	Percent
Occupational exposure		
Floor laying	11	15.7
Metal industry, 2-component adhesives	10	14.3
Paint, varnish, lacquer	9	12.9
Construction work, repairing of concrete	8	11.4
Tile setting	6	8.6
Production of ERS in the chemical industry	4	5.7
Production, processing of plastic materials	4	5.7
Production of rotor blades for wind turbines	4	5.7
Other ERS exposure (single cases)	10	14.3
Non-occupational exposure		
2-component adhesives	4	5.7

ERS = epoxy resin system.

Table 2. Unprotected skin areas and localization of skin disease in 66 patients with occupational epoxy resin system exposure

	Unprotected area		Site of contact dermatitis	
	Count	Percent	Count	Percent
Hands	15	22.7	49	74.2
Arms	45	68.2	31	47.0
Neck	56	84.8	12	18.2
Face	60	90.9	33	50.0

gloves of unknown material. Among those 35 patients wearing no gloves at all (15 pat.) or gloves definitely not suitable for protection against ERS, i.e. leather or cotton gloves (20 pat.), the frequency of hand dermatitis was significantly higher [32 out of 35 patients (91.4%)] than among those patients wearing possibly appropriate gloves [17 out of 31 patients (54.8%); $P=0.0014$]. The time span from the beginning of the ERS exposure to the onset of skin problems could not be estimated reliably in most cases, because the beginning of ERS exposure was not known or exposure was irregular or intermittent. However, in other cases, this time span was definitely not more than 3 months (6 patients) and about 1 year in another 4 patients.

Table 3 gives an overview of the frequency of positive test reactions to resins, hardeners and reactive diluents in the total study group ($n=92$) and the 2 subgroups mentioned above. In subgroup B, there were markedly more positive reactions to resins and less reactions to hardeners and diluents; however, these crude overall proportions did not differ significantly. The only significant difference was that, in subgroup B, there were more patients reacting to a resin without

any accompanying reaction to a hardener or reactive diluent ($P=0.006$). In subgroup B, only 16 of the 22 former positive patch test reactions to DGEBA-R could be reproduced (73%). Nevertheless, the resins were the main sensitizers in both subgroups: 36 of the 40 patients reacting to any substance of the 2 series in subgroup A had a positive reaction to a resin. In subgroup B, this share was 16 out of 17 patients.

Table 4 shows the reactions to the resins, hardeners and reactive diluents tested. Most frequently, positive test reactions were observed to ERs based on DGEBA and DGEBAF, followed by the reactive diluents 1,6-hexanediol diglycidyl ether (1,6-HDDGE) and 1,4-butanediol diglycidyl ether (1,4-BDDGE). 3 further reactive diluents elicited positive reactions frequently, i.e. phenyl glycidyl ether (PGE), *p*-tert-butylphenyl glycidyl ether (PTBPGE) and cresyl glycidyl ether (CGE). Among the hardeners, *m*-xylylene diamine (MXDA) was the most prominent allergen, with 13.8% positive reactions, followed by isophorone diamine (IPDA), and 4,4'-diaminodiphenyl methane (4,4'-DDM). All other ER components tested caused positive test reactions in single cases only, if at all.

The 2 rightmost columns of Table 4 summarize the RI and the PR as measures of the diagnostic quality of the test preparations. However, these data have to be interpreted very carefully, due to the generally small numbers of non-negative reactions. Nevertheless, the RI and PR values of the most frequent allergens mentioned above indicate fairly good diagnostic properties. Just 1,6-HDDGE and 1,4-BDDGE had a PR of 88% and 81%, respectively, which seems unsatisfactorily high at first sight;

Table 3. Overview over positive patch test reactions to allergens of the 2 epoxy resin series tested in the total study group and in the 2 subgroups, i.e., patients tested because of suspected epoxy resin dermatitis (subgroup A) and patients tested because of a prior positive patch test reaction to epoxy resin from the standard series without clear-cut history of epoxy resin system exposure (subgroup B)

Positive reaction to at least...	Subgroup A ($n=70$)		Subgroup B ($n=22$)		Total study group ($n=92$)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
1 substance from the 2 epoxy resin series tested	40	57	17	77	57	62
1 resin	36	51	16	73	52	57
1 resin without positive reaction to hardeners or reactive diluents	13	19	11	50	24	26
1 hardener	16	23	2	9	18	20
1 hardener without positive reaction to resins or reactive diluents	2	3	0	0	2	2
1 reactive diluent	21	30	4	18	25	27
1 reactive diluent without positive reaction to resins or hardeners	1	1	1	5	2	2
1 hardener or reactive diluent	27	39	6	27	33	36
1 hardener or reactive diluent without positive reaction to resins	4	6	1	5	5	5

Table 4. Patch test reactions at day 3 in the total study group (n = 92)

Substance	CAS number	Type	Number of patients tested	Negative	?	+	++	+++	Irritant	% positive	RI	PR
Resins												
Epoxy resin based on DGEBA (DGEBA-R)	[1675-54-3]	C	87	38	1	20	23	5	0	55.2	1.0	42%
Epoxy resin based on DGEBF (DGEBF-R)	[9903-36-5]	S	87	48	1	16	17	5	0	43.7	0.9	42%
Cycloaliphatic epoxy resin		C	87	82	2	2	1	0	0	3.4	0.2	67%
Hardeners												
<i>m</i> -Xylylene diamine (MXDA)	[1477-55-0]	S	87	74	1	6	4	2	0	13.8	0.8	50%
Isophorone diamine (IPDA)	[2855-13-2]	C	87	82	0	2	1	2	0	5.7	1.0	40%
4,4'-Diaminodiphenyl methane (4,4'-DDM)	[101-77-9]	C	88	82	2	4	0	0	0	4.5	0.3	100%
Triethylene tetramine	[112-24-3]	C	83	80	2	1	0	0	0	1.2	-0.3	100%
Methanamine (hexamethylene tetramine)	[100-97-0]	C	78	76	1	1	0	0	0	1.3	0.0	100%
<i>N</i> -Aminoethyl piperazine	[140-31-8]	S	87	85	1	0	1	0	0	1.1	0.0	0%
Diethylene triamine	[111-40-0]	C	87	85	1	1	0	0	0	1.1	0.0	100%
Dipropylene triamine (DPTA)	[56-18-8]	S	87	86	0	1	0	0	0	1.1	1.0	100%
Trimethylhexane-1,6-diamine (mixture of isomers)	[25620-58-0]	S	87	83	3	0	1	0	0	1.1	-0.5	0%
2,4,6-Tris(dimethyl aminomethyl)phenol	[90-72-2]	S	87	85	2	0	0	0	0	0.0	-1.0	-
Aminoethylethanamine	[111-41-1]	S	87	86	1	0	0	0	0	0.0	-1.0	-
1,2-Diaminocyclohexane (mixture of isomers)	[694-83-7]	S	87	86	1	0	0	0	0	0.0	-1.0	-
Ethylenediamine-di-HCl	[107-15-3]	C	86	85	1	0	0	0	0	0.0	-1.0	-
4,4'-Methylene bis(cyclohexylamine)	[1761-71-3]	S	87	86	1	0	0	0	0	0.0	-1.0	-
Triethyleneglycol diamine	[929-59-9]	S	87	86	1	0	0	0	0	0.0	-1.0	-
Reactive diluents												
1,6-Hexanediol diglycidyl ether (1,6-HDDGE)	[16096-31-4]	S	87	68	2	15	1	1	0	19.5	0.8	88%
1,4-Butanediol diglycidyl ether (1,4-BDDGE)	[2425-79-8]	S	87	68	2	13	2	1	1	18.4	0.7	81%
<i>p</i> -tert-Butylphenyl glycidyl ether (PTBPGE)	[3101-60-8]	S	87	73	4	5	3	2	0	11.5	0.4	50%
Phenyl glycidyl ether (PGE)	[122-60-1]	C	87	74	3	7	3	0	0	11.5	0.5	70%
Cresyl glycidyl ether (CGE)	[26447-14-3]	C	88	79	3	5	1	0	0	6.8	0.3	83%
Butyl glycidyl ether	[2426-08-6]	C	87	84	0	2	1	0	0	3.4	1.0	67%
Trimethylolpropane triglycidyl ether	[3454-29-3]	S	87	82	3	2	0	0	0	2.3	-0.2	100%
C12/C14 Alkylglycidyl ether	[68609-97-2]	S	87	86	1	0	0	0	0	0.0	-1.0	-
Versatic acid glycidyl ester	[26761-45-5]	S	87	85	2	0	0	0	0	0.0	-1.0	-

RI = reaction index; PR = positivity ratio; C = commercially available patch test preparation; S = study substance.

however, the 95% CI was very broad, due to the limited number of positive reactions (64–99% and 54–96%, respectively).

Concomitant reactions to chemically related ERS components are listed in Table 5. Agreement between reactions to ERs based on DGEBA and DGEBF was substantial, as indicated by the kappa value. The 34 patients reacting to both resins represent a proportion of 94.4% of those reacting to DGEBF-R and 72.3% of those reacting to DGEBA-R. Regarding 1,6-HDDGE and 1,4-BDDGE, the agreement was even better. 13 patients reacted to both glycidyl ethers, representing 81.3% of those reacting to 1,4-BDDGE and 76.5% of those reacting to 1,6-HDDGE. Altogether, 20 patients reacted positively to 1 or both of these substances. By testing only with 1,6-HDDGE, only 17 of these sensitized patients, i.e. 85%, would have been detected. All of the 6 patients showing a positive reaction to CGE also reacted to PGE. In contrast, 5 patients each reacted solely to PGE, solely to PTBPGE or to both. Hence, the agreement of reactions was only moderate.

Of the 10 patients reacting positively to PGE, 4 started working with ERS in 2001–2003, while 6 patients already had occupational contact with ERS before 1999. However, as mentioned above, these data are not fully reliable in every case.

In 27 patients (38.6% of subgroup A), the epoxy products used were identified exactly, and infor-

mation about their composition could be obtained. While 7 of these patients had no reaction in the 2 epoxy series, all of the remaining 20 patients had at least 1 positive test reaction to an ingredient of the product used. The ERS components concerned were DGEBA-R in 15 patients, MXDA in 5 patients and 1,4-BDDGE in 2 patients.

Attempting to characterize an allergen pattern possibly related to airborne dermatitis due to ERS, we analysed positive reactions in the 33 patients with face and neck dermatitis. The reaction pattern of these 33 patients was very similar to that of the total study group. Of those 6 patients with face and neck dermatitis only, 4 had at least 1 positive reaction in the ER series, all reacting to DGEBA resin and 2 additionally to several glycidyl ethers. Hence, no particular pattern can be identified from these results.

Discussion

Our approach to improve diagnostics in patients with suspected ER dermatitis is based on patch testing with ERS components that are currently used in industrial applications. Hence, this study EPOX 2002 offers, for the first time, the opportunity to identify ERS components frequently responsible nowadays for contact allergy in this field.

Table 5. Concomitant reactions to chemically related epoxy resin components

		Epoxy resin based on DGEBF		Total
Epoxy resin based on DGEBA	+	34	13	47
	–	2	36	38
	Total	36	49	85
		Cohen's kappa 0.65 (95% CI: 0.49-0.80)		
		1,4-Butanediol diglycidylether		Total
1,6-Hexanediol diglycidylether	+	13	4	17
	–	3	67	70
	Total	16	71	87
		Cohen's kappa 0.73 (95% CI: 0.52-0.90)		
		Cresyl glycidyl ether		Total
Phenyl glycidylether	+	6	4	10
	–	0	76	76
	Total	6	80	86
		Cohen's kappa n.c.*		
		<i>p</i> -tert-Butylphenyl glycidyl ether		Total
Phenyl glycidylether	+	5	5	10
	–	5	71	76
	Total	10	76	86
		Cohen's kappa 0.42 (95% CI: 0.10-0.71)		

Reactions at day 3 are dichotomized as '+' (+, ++ or +++) and '–' (negative, doubtful or irritant).

*Cohen's kappa not calculated due to lack of isolated reactions to cresyl glycidyl ether.

Contact allergy to resins

Allergic reactions to DGEBA-R and DGEBF-R were observed most frequently, with a high degree of cross-reactivity, almost exactly to the same extent as recently described by Pontén et al. in their investigation of occupational contact allergies in a wind turbine rotor blade factory (9). The same authors have recently proven immunological cross-reactivity between DGEBA and 2 isomers of DGEBF, namely *p,p'*-DGEBF and *o,p'*-DGEBF (8, 21, 22). Our patch test preparation was made from Epicote 862[®], which, according to a chemical analysis performed at the Department of Dermatology in Malmö, contained 38% of *p,p'*-DGEBF, 36% of *o,p'*-DGEBF, 13% of *o,o'*-DGEBF and approximately 1% of DGEBA. Hence, the composition of the batch we used for patch testing differed slightly from that recently described by Pontén et al. (23). Although DGEBA was contained in our DGEBF-R-test preparation, it seems unlikely that reactions to the latter were due to DGEBA because its concentration was only about 25 p.p.m., and reported elicitation thresholds are only exceptionally that low (22). Concomitant reactions in our study may rather be explained by immunological cross-sensitization, as mentioned above. On the other hand, coexposure to both DGEBA-R and DGEBF-R is probably common in most occupational settings, rendering immunologically independent cosensitization a possible alternative explanation of coupled reactivity. Only 2 of the 36 patients allergic to DGEBF-R did not react to DGEBA-R. Hence, it is debatable if patch testing with DGEBF-R in addition to DGEBA-R is really necessary. Taking into consideration the risk of patch test sensitization (24), we would favour future routine patch testing with DGEBA-R alone in order to minimize this risk. A critical aspect might be that not all patients reacting to DGEBA-R are also sensitized to DGEBF-R, as in our study, with 13 of 47 patients. However, in view of the likelihood of cross-sensitivity between DGEBA-R and DGEBF-R, patients allergic to DGEBA-R would be advised to avoid contact to DGEBF-R anyway.

There was an important and significant difference concerning the coincidence of positive reactions to resins and hardeners and/or reactive diluents among the 2 subgroups of patients, i.e. those tested for suspected ER dermatitis (subgroup A) and those tested because of a positive test reaction to ER in the standard series without clear-cut history (subgroup B): while in subgroup A, 81% of those sensitized to a resin also reacted

positively to a hardener and/or diluent, this share was only 50% in subgroup B. In our opinion, this points towards a different route of exposure. Patients of subgroup A possibly became sensitized more often by exposure to a complete ERS, while some patients from subgroup B may have become sensitized by exposure to the resin only, as in patch testing. Because patch test sensitization to ER has been described earlier (24), possibly some of the positive test reactions to DGEBA-R without a history of ERS exposure are due to active sensitization from prior patch testing. Currently, the DKG is performing a study on patch test sensitization with respect to DGEBA-R. Moreover, some of the earlier weak positive test reactions to DGEBA-R in patients without a matching history may have been false positive, as suggested by the fact that only 73% of the positive patch tests could be reproduced upon re-testing.

The cycloaliphatic ER caused positive test reactions in only 3 patients. This resin is based on iglycidyl ester of hexahydrophthalic acid, i.e. represents resins used in heat-cured ERS used in the manufacture of electrical insulating components (25). Only 1 of our patients worked in this field, and he had no positive reaction to this resin. The clinical relevance of the positive reactions to cycloaliphatic ER remains unclear. All of these 3 patients also reacted to 1,4-BDDGE and other reactive diluents of the ERS test series. A similar coincidence of allergic reactions to cycloaliphatic ER and reactive diluents has been described by Jolanki in 1991 (26).

Contact allergy to hardeners

Among the hardeners, MXDA was the most frequent allergen. This was surprising because up to now, MXDA was reported to be an ERS allergen only in single cases (27–31). In contrast, MXDA has also been reported to be a relatively common allergen in other fields, e.g. in the production of polyurethane silk (32). According to our results, MXDA should be included in a future ER test series. In view of the pattern of test reactions (Table 4), 0.1% pet. can be considered suitable for patch testing. However, patch testing with MXDA is hampered by the low stability of the compound in pet. (33). Thus, further investigations to establish a patch test preparation suitable for routine testing are necessary.

IPDA, well known as a contact sensitizer in ERS (2, 5, 27–29, 31, 34–38) and present in many ERS formulations currently at the market, elicited allergic reactions in 5.7% of the patients tested, thus ranking second among the curing agents.

4,4'-DDM caused positive reactions in 4 out of 88 patients tested (4.5%). According to information from industry, 4,4'-DDM is only seldom used in ERSs nowadays. This information is supported by the observation that, in the products used by our patients which could be identified, 4,4'-DDM was not present. None of the 4,4'-DDM-positive patients reacted positively to *p*-phenylene diamine; hence, these reactions to 4,4'-DDM cannot be interpreted as a consequence of contact allergy to para amino compounds (39). The relevance of these weak positive test reactions remains unclear.

All other hardeners elicited only exceptional positive reactions or no reactions at all. However, the patch test concentrations of the study substances were conservatively chosen, fixing them at 0.25%. It cannot be excluded that this was too low, and relevant contact allergic reactions might have been overlooked in this way (this is supported by the fact that among the first 46 patients of the second study period, we already observed 4 positive reactions to dipropylene triamine 0.5% pet.). Hence, for the following study period, we have increased the test concentrations of 8 amine hardeners to 0.5%. With 4,4'-methylene bis(cyclohexylamine), this concentration has been tested by Pontén et al. (9), without any reaction in 5 occupationally exposed patients.

Contact allergy to reactive diluents

1,6-HDDGE and 1,4-BDDGE, both well-known ERS allergens (5, 9, 27, 40, 41), were the reactive diluents eliciting positive test reactions most frequently. As the molecules resemble each other very much – only the chain length differs by 2 CH₂-groups – allergic cross-reactions can be expected. Accordingly, the agreement between test reactions was substantial. However, by exclusively testing with 1,6-HDDGE, 3 of 20 patients reacting to at least one of both would have remained undetected. Because these data are based on results in 20 patients only, further investigations are needed before a decision can be made as to whether either 1,6-HDDGE or 1,4-BDDGE can serve as a marker allergen for both.

PGE, PTBPGE and CGE are chemically related aromatic glycidyl ethers used as reactive diluents in ERS which also caused positive patch test reactions in a considerable proportion of our patients. Contact allergy to PGE and CGE has been described in patients occupationally exposed to ERS allergens (5, 27, 40, 42). According to more recent information from industry (March 2004), PGE and CGE have only rarely been used in the last few years, while PTBPGE is

nowadays frequently found in industrially used ERS. In 6 of the 10 PGE-positive patients, sensitization may have been acquired several years ago, because they started working with ERS before 1999. In the remainder, the source of sensitization remained even more unclear. According to new data published by Pontén et al., contact allergy to PGE (which is a strong sensitizer by itself) may be the expression of an immunological cross-reaction following primary sensitization to DGEBA (43). In our study, 9 out of 10 patients allergic to PGE also reacted to DGEBA-R. In view of the sparse exposure data, cross-sensitization is a possible explanation for the majority of PGE reactions. Further analysis of concomitant test reactions disclosed that all patients reacting to CGE also had a positive test reaction to PGE. Hence, it can be assumed that contact allergy to CGE is possibly rather the expression of immunological cross-sensitization in patients allergic to PGE, than genuine primary contact allergy due to CGE itself. The same certainly does not apply to PGE/PTBPGE. Here, singular sensitizations occur as frequently as concomitant reactions, making immunological cross-reactivity rather improbable.

The other reactive diluents tested did not elicit any positive test reactions. As far as the study substances are concerned, as with the hardeners tested, false negative test reactions due to too low test concentrations cannot be excluded. In particular, for C12/C14 alkylglycidyl ether and versatic acid glycidyl ester, the chosen test concentration of 0.25%, although suitable for the other glycidyl ethers tested, may be too low because, due to their high molecular weight, the molar concentrations of the substances in the patch test preparation are lower. Hence, in the second study period, test concentrations of these diluents have been doubled to 0.5%.

Occupational exposure, skin protection, involvement of face and neck

At 38% of the total, patients working with ERS in the building trade were the largest occupational group among the patients concerned. Although this finding is in accordance with other published investigations (44), it may be surprising at first sight, because in other fields of application, above all in the production of rotor blades for wind turbines, the amount of ERS used during 1 working day is much higher. 2 factors may explain this finding: (i) skin protection is 'traditionally' inadequate in the construction trade – a problem still unsolved in Germany; (ii) according to our experience, many patients working in rotor

blade production develop skin problems after only a short time and quit their job (or are forced to do so) without extensive diagnostics being done.

The fact that hand dermatitis indeed was significantly lower (54.8% versus 91.4%) among those patients wearing (presumably) suitable gloves underlines that effective protection against ERS by gloves is generally possible. However, the selection of a suitable glove is difficult and depends on the particular ERS and other circumstances at the workplace (45).

Involvement of the face and/or neck was frequent among our patients, comprising 50% of those occupationally exposed. Face dermatitis may be due to contamination by touching the face with the hands or gloves, or due to airborne dermatitis from dust containing uncured ER or volatile ERS components (37, 40, 46–51). With few exceptions, our data did not provide reliable information as to the exact mode of exposure. No special allergen pattern pointing towards particularly hazardous volatile allergens in ERS could be identified.

Conclusions

The first period of the study EPOX 2002, comprising 92 patients, showed that the resins are the most important sensitizers. In view of the extent of cross-reactivity observed in our study, the immunological cross-reactions between 2 isomers of DGEBA and DGEBA-R and the fact that in most cold-cured ERS both resins are present, it seems justified to recommend patch testing with DGEBA-R only and to advise the patients concerned to avoid contact with DGEBA-R as well.

Altogether, 27 patients, i.e. 67.5% of the 40 patients with contact allergy to any ERS component, reacted to hardeners and/or reactive diluents, emphasizing the necessity to test with more than just a DGEBA-R in patients with suspected contact allergy due to ERS.

The most important sensitizers among the hardeners were MXDA and IPDA, and among the reactive diluents 1,6-HDDGE, 1,4-BDDGE, PGE and PTBPG. Based on our data, it cannot yet be decided if patch testing with 1,6-HDDGE is sufficient to detect contact allergies also to 1,4-BDDGE. As some test concentrations we have used in this study may have been too low, they have been increased in the second study period.

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