

Patch testing with components of water-based metalworking fluids

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Water-based metalworking fluids (MWFs) may cause both irritant and allergic contact dermatitis. Several well-known MWF allergens are available for patch testing, but considering the wide variety of possible components used in MWF, our diagnostic arsenal covers only a small part of potential allergens. We therefore selected 13 frequently used MWF components that might be sensitizers and had not yet been tested routinely. In 5 centres, 233 dermatitis patients with present or past occupational exposure to MWF were patch tested with this and other panels. Only 7 patients showed positive reactions to the study panel. Allergic reactions to the emulsifier diglycolamine [syn. 2-(2-aminoethoxy) ethanol] were seen in 5 patients, and 1 patient each reacted positively to 2-amino-2-ethyl-1,3-propanediol (AEPD) and methyldiethanolamine (MDEA). Clinical relevance of the reactions to diglycolamine was unequivocally proven by its presence in the MWF from the patients' workplace in 3 cases. Diglycolamine seems to be an important MWF allergen, independently from monoethanolamine and diethanolamine. A test concentration of 1% petrolatum (pet.) appears to be appropriate. The importance of AEPD and MDEA as MWF allergens still remains to be established. The lack of positive test reactions to the other MWF components tested may be due to their low-sensitizing potential or too low a patch test concentration being used.

Key words: 2-(2-aminoethoxy) ethanol (diglycolamine); 2-amino-2-ethyl-1, 3-propanediol; contact allergy; iodopropynyl butylcarbamate; metalworking fluids; methyldiethanolamine; occupational; patch testing. © Blackwell Munksgaard, 2003.

Accepted for publication 12 September 2003

Introduction

Water-based metalworking fluids (MWFs) may cause irritant as well as allergic contact dermatitis (1–7). In this context, skin irritation is not only caused by wet work but by the alkaline pH of usually 8.5–9.6, emulsifiers and biocides in the MWF also contribute to irritation. As in any other comparable situation, irritant contact dermatitis due to MWF promotes and often precedes sensitization to MWF components (8). Well-known MWF allergens comprise the oxidation products of resin acids from distilled tall oil, which is used in about 80–90% of the MWF currently on the market (9–12), emulsifiers,

rust-preventive additives, biocides and extreme-pressure additives (13). In publications from the 1980s, fragrances or balsam of Peru are mentioned as potentially sensitizing MWF components (4, 14). However, according to information from the MWF-producing industry, these additives are no longer used in MWF. Nevertheless, in a recent study on contact allergies among metalworkers exposed to MWF, sensitization to fragrances was found not infrequently, which might indicate a possible exposure to fragrances (odour masks) added to MWF by the metalworking companies (12). The interdisciplinary task force on allergy diagnostics in the metalworking

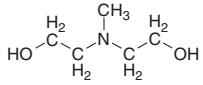
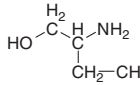
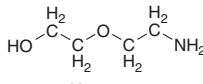
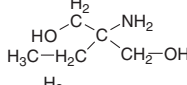
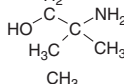
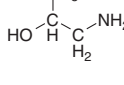
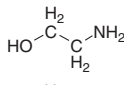
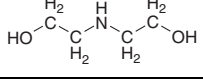
branch has recently published 2 lists of current and former allergens in MWF that are commercially available as patch test substances (15). This compilation, however, does not nearly cover all potential allergens in MWF. In the comments on the German occupational exposure threshold limit values ('MAK-Werte') published in 2000, more than 200 components used in MWF are listed, many of which not yet investigated regarding their allergenic potential in humans (16). Additionally, the composition of MWF is changing as the result of technological progress or in order to improve skin tolerability. Against this background, patch testing with frequently used MWF components, which might be sensitizers or which have not yet been investigated in humans in this respect, in addition to the commercially available MWF allergens, is one possible way to overcome the presumed diagnostic gap in MWF dermatitis. As a first step, we selected 13

such substances on the basis of information from the MWF-producing industry and patch tested them in dermatitis patients with present or past occupational exposure to MWF.

Materials and Methods

For this investigation, we selected 6 substances with structural similarity to the well-known sensitizers in MWF, monoethanolamine (MEA) or diethanolamine (DEA) (numbers 1–6 in Table 1), 3 lubricating agents (numbers 7–9 in Table 1), 2 corrosion inhibitors (numbers 10 and 11 in Table 1) and 2 biocides (numbers 12 and 13 in Table 1), which are frequently used in MWF but have not yet been tested in a large group of metalworkers. Patch test preparations of these substances were made at the pharmacy of the University Hospital of Göttingen from industrial chemicals used in MWF production obtained

Table 1. Metalworking fluid components used for patch testing and chemical structure of substances with structural similarity to monoethanolamine (MEA) or diethanolamine (DEA)

Number	Substance	CAS number		Purity of the industrial chemical (as stated by the producer) (%)
1	Methyldiethanolamine (MDEA)	[105-59-9]		100
2	2-amino-1-butanol	[96-20-8]		95
3	2-(2-aminoethoxy)ethanol (diglycolamine)	[929-06-6]		100
4	2-amino-2-ethyl-1,3-propanediol (AEPD)	[115-70-8]		85*
5	2-amino-2-methyl-1-propanol (AMP)	[124-68-5]		75*
6	1-aminopropan-2-ol (monoisopropanolamine)	[78-96-6]		100
7	2-hexyldecanol-1 (isocetyl alcohol)	[2425-77-6]		100
8	Iso-tridecanol	[27458-92-0]		100
9	Oleic acid	[112-80-1]		100
10	1-hydroxyethyl-2-heptadecenyl-imidazoline	[95-38-5]		100
11	Methyl-1H-benzotriazole, sodium salt	[29385-43-1]		50*
12	1,6-dihydroxy-2,5-dioxahexane†	[3586-55-8]		100
13	Iodopropynyl butylcarbamate (IPBC)	[55406-53-6]		20*
	For comparison			
	MEA	[141-43-5]		
	DEA	[111-42-2]		

*Test preparation was made from an aqueous stock solution containing the stated concentration of the chemical.

†Formaldehyde releaser.

from Angus Chemie (Ibbenbüren, Germany), BASF (Ludwigshafen, Germany), Brenntag Eurochem (Mulheim, Germany), Deutsche Exxon Chemical (Köln, Germany), Henkel (Düsseldorf, Germany), Peter Greven Fett-Chemie (Bad Münstereifel, Germany), Rhein Chemie (Mannheim, Germany), Troy Chemie (Krefeld, Germany), Croda Oleochemicals (Goole, UK), Nipa Laboratories (Pontypridd, UK) and Huntsman (Zaventem, Belgium). Test concentrations were chosen according to published recommendation (17) or by analogy to test concentrations recommended for chemically related substances. In the case of iodopropynyl butylcarbamate (IPBC), the test preparation was made from a stock solution containing 20% IPBC. Hence, the test concentration [0.1% petrolatum (pet.)] of this 'industrial' IPBC was probably not determined very exactly. For additional routine patch testing (standard series and MWF series), commercially available test substances were purchased from Hermal (Reinbek, Germany).

The study period was from April 2000 to July 2002, including 5 departments of dermatology, i.e. Dortmund, Homburg/Saar, Dresden, Mainz and Göttingen, all of them being members of the German Contact Dermatitis Research Group (DKG) and the Information Network of Departments of Dermatology (IVDK). Patch testing with the study panel was not restricted to metalworkers with contact dermatitis who are currently exposed to MWF. In order not to miss previously acquired sensitizations to MWF components, we also tested dermatitis patients with previous MWF exposure. Patch tests were performed and read according to international guidelines (18) modified by the DKG (19). Among the 233 tested patients, patch test application time was 1 day in 2 centres (88 patients = 37.8%), and 2 days in 3 centres (145 patients = 62.2%), in line with the routine patch test procedures in the respective clinics. All tests were read at least until D3. For data analysis, only reactions at D3 were selected. Data were analysed at the IVDK data centre at the University of Göttingen (20), using the statistical program system SAS 8.2 (SAS Institute, Cary, NC, USA).

Results

A description of important demographic characteristics of the 233 patients according to the MOAHLFA index is given in Table 2. The age of this predominantly male population ranged from 19 to 75 years, with a mean age of 39.3 years (median 38 years). 108 patients (46.4%) were metalworkers currently exposed to MWF, and of these, 86 had occupational dermatitis. Altogether, 112 patients had at least 1 positive patch test reaction, and of these, 59 patients reacted positively to at least 1 allergen potentially present in MWF according to the above-mentioned allergen lists (15) (Table 3, allergens not causing positive reactions were omitted). Of the 86 metalworkers currently exposed to MWF who had occupational dermatitis, 3 reacted positively to MEA (3 of 53 patients tested, 5.8%), and 1 to DEA (1 of 68, 1.5%).

Table 4 summarizes the patch test results obtained with the series of 13 industrial MWF components. Positive reactions occurred in only 7 patients, all of them being metalworkers currently exposed to MWF with work-related hand dermatitis. At the time of patch testing, these patients had been working in the metalworking industry for 2–20 years. 5 of these patients reacted to diglycolamine. The majority of these reactions were only + at D3, although a crescendo reaction pattern over time was observed in 3 cases, the remaining 2 patients showing a plateau reaction pattern. As far as reactions to diglycolamine were concerned, there was no difference between patients with 1 and 2 days patch test application time: among 144 patients with 2 days application time, 3 (2.1%) had a positive, and 2 (1.4%) had a doubtful reaction; among 84 patients in whom the patch tests were applied for 1 day only, there were 2 (2.4%) with a positive and 1 (1.2%) with a doubtful reaction. Only 1 of the diglycolamine-positive patients also reacted to MEA and DEA tested in the MWF series of the DKG. In 3 of the diglycolamine-positive patients, clinical relevance could be unequivocally confirmed by the presence of this emulsifier in the currently used MWF. The first of these patients has already been published as a case report (21). Further concomitant sensitization related to MWF in diglycolamine-positive patients was observed to benisothiazolinone and 4,4-dimethyl-1,3-oxazolidine/3,4,4-trimethyl-1,3-oxazolidine (Bioban CS 1135) in 1 patient each. Furthermore, 1 patient each reacted positively to 2-amino-2-ethyl-1,3-propanediol (AEPD) and methyldiethanolamine (MDEA), neither of them reacting to other MWF components, in particular not to MEA and DEA. No clinical relevance of the positive test reactions to AEPD

Table 2. Description of the 233 patients tested

		Count	Percentage
Male	M	207	88.8
Occupational dermatosis	O	154	66.1
Atopic dermatitis	A	41	17.6
Hand dermatitis	H	183	78.5
Leg dermatitis	L	4	1.7
Face dermatitis	F	3	1.6
Age 40 years or more	A	101	43.3

Table 3. Positive test reactions at D3 to potential current or former metalworking fluid allergens

Allergen	Patch test concentration	Patients tested	Patients with positive reaction	Percent positive
Fragrance mix	8% pet.	212	16	7.5
Colophonium	20% pet.	210	14	6.7
Methyldibromo glutaronitrile/phenoxyethanol	1% pet.	203	9	4.4
Balsam of Peru	25% pet.	212	9	4.2
Methyldibromo glutaronitrile	0.3% pet.	172	7	4.1
(Chlor)-methylisothiazolinone (MCI/MI)	0.01% aq.	212	7	3.3
Lanolin alcohol	30% pet.	217	6	2.8
Abietic acid	10% pet.	172	4	2.3
1,2-benzisothiazolinone, sodium salt	0.1% pet.	181	4	2.2
Monoethanolamine (MEA)	2% pet.	155	3	1.9
4,4-dimethyl-1,3-oxazolidine/3,4,4-trimethyl-1,3-oxazolidine (Bioban CS 1135)	1% pet.	185	2	1.1
Formaldehyde	1% aq.	212	2	0.9
Iodopropynyl butylcarbamate (IPBC)	0.1% pet.	228	2	0.9
Benzylhemiformal	1% pet.	167	1	0.6
Diethanolamine (DEA)	2% pet.	174	1	0.6
Propyleneglycol	20% aq.	174	1	0.6
4-(2-nitrobutyl)-morpholine/4,4'-(2-ethyl-2-nitromethylene)-dimorpholine (Bioban P 1487)	1% pet.	182	1	0.5
Octylisothiazolinone	0.025% pet.	188	1	0.5
Mercaptobenzothiazole	2% pet.	206	1	0.5
Chloroacetamide	0.2% pet.	212	1	0.5
Paraben mix	16% pet.	212	1	0.5
Bronopol (2-bromo-2-nitropropane-1,3-diol)	0.5% pet.	215	1	0.5
Coconut diethanolamide	0.5% pet.	215	1	0.5
Triethanolamine (TEA)	2.5% pet.	216	1	0.5

and MDEA could be found. However, not all the MWFs previously used by these 2 patients could be identified. Hence, previous occupational exposure and relevance could be regarded as possible at least. No positive reactions occurred to the 'industrial' IPBC in this test series, although in the MWF series of the DKG (Table 3), 2 patients reacted to the test preparation IPBC 0.1% pet. obtained from Hermal. Only a few doubtful reactions occurred with the new test series.

Discussion

In this investigation, we tested 13 MWF components not yet available as commercial patch test

preparations in 233 patients, some of these substances being tested for the first time in a large number of patients. According to our data, diglycolamine should be regarded as an important MWF allergen.

For patch testing, industrially used chemicals were chosen, because they were more easily available than chemicals of analytical grade purity and had the advantage that they mimic workplace reality. As a disadvantage, some test concentrations were not entirely precise, because we were not able to monitor the purity of the chemicals stated by the producers. The test concentration of the 'industrial' IPBC was probably lower than 0.1%, which may be the reason

Table 4. Test reactions at D3 to the 13 metalworking fluid components listed in Table 1

Substance		Patients tested	–	?	+	++	% positive
2-(2-aminoethoxy)ethanol (diglycolamine)	1.0% pet.	228	220	3	4	1	2.2
2-amino-2-ethyl-1,3-propanediol (AEPD)	1.0% aq.	160	159		1		0.6
Methyldiethanolamine (MDEA)	1.0% pet.	229	228		1		0.4
2-amino-1-butanol	1.0% pet.	229	229				0.0
2-amino-2-methyl-1-propanol (AMP)	1.0% aq.	160	160				0.0
1-aminopropan-2-ol (monoisopropanolamine)	1.0% pet.	228	228				0.0
2-hexyldecanol-1 (isocetyl alcohol)	20.0% pet.	211	211				0.0
Iso-tridecanol	5.0% pet.	229	229				0.0
Oleic acid	5.0% pet.	229	228	1			0.0
1-hydroxyethyl-2-heptadecenyl-imidazoline	0.1% pet.	201	201				0.0
Methyl-1H-benzotriazole, sodium salt	1.0% aq.	125	125				0.0
1,6-dihydroxy-2,5-dioxahexane	1.0% pet.	201	200	1			0.0
Iodopropynyl butylcarbamate (IPBC)	0.1% pet.	228	227	1			0.0

why no reactions were seen, even though 2 patients reacted to basically the 'same' test preparation from Hermal, which was made from IPBC of high purity (>95%). This underlines the importance of using high-purity chemicals and sticking to exactly defined concentrations in the production of patch test preparations. However, according to a recent publication (22), in both preparations, the chosen patch test concentration was too low, and hence, probably false-negative test reactions might have occurred anyway.

Indication for patch testing with the 13 MWF components was not limited to patients currently exposed to MWF with suspected occupational dermatitis, but dermatitis patients with current or past exposure to MWF were generally eligible for being tested with the panel. This was performed, because we wanted to find out whether additional sensitizations to MWF components could also be detected among patients with previous 'historical' exposure. With this approach, it is no surprise that the percentage of positive reactions to any MWF component is not very high, as can be observed from Table 3. Only 59 patients, i.e. 25.3% of the test population, reacted to allergens that might occur or have occurred in MWF, and it is not even certain that the allergen source in each of these individuals was an MWF. On the contrary, particularly in many elderly patients tested, other sources of sensitization, e.g. to fragrances, balsam of Peru and (chlor)-methylisothiazolinone (MCI/MI), are more probable (23). In a recent study focusing exclusively on metalworkers exposed to water-based MWF with occupational dermatitis, higher reaction frequencies to MWF allergens have been noted, e.g. 10.9% positive reactions to MEA and 4.2% to DEA (12). The frequency of positive reactions to MEA and DEA amongst metalworkers with occupational dermatitis and current exposure to MWF presented here was only about half as high. This may be due to a shorter average duration of skin disease at the time of patch testing so that more patients were in an earlier state of occupational skin disease when contact dermatitis is predominantly due to irritation, and contact sensitization has not yet developed (8). We, however, have no data on the duration of skin disease in our patients.

All 7 patients reacting to 1 of the 13 MWF components of the investigated panel were metalworkers currently exposed to MWF with occupational dermatitis. Hence, in this subgroup ($n = 86$), the percentage of patients with sensitization to diglycolamine was 5.8%, which is comparable to the frequency of MEA sensitization among these patients. Diglycolamine is used in

MWF as an emulsifier, and it has become more common during the last 4–5 years. Currently, about 10% of the MWF formulae on the market contain diglycolamine. Its acute toxicity is low and undiluted, it has corrosive effects on the skin and eyes of rabbits. Diglycolamine showed no clear-cut sensitizing effect in a Buehler test in guinea pigs (24). Apart from the above-mentioned case report (21), we could not find any report of contact allergy to diglycolamine in humans in the literature. Despite the negative animal test, diglycolamine seems to be an important contact allergen in MWF according to our clinical data. This discrepancy may be explained by chronic irritation of metalworkers' skin due to prolonged MWF exposure, which facilitates sensitization. Sensitization to diglycolamine clearly occurs independently from MEA and DEA. According to our results, a test concentration of 1% pet. seems to be appropriate, regardless of whether the patch test is applied for 1 or 2 days. Currently, the DKG has added diglycolamine 1% pet. to the MWF test series as a study substance.

The importance of AEPD and MDEA as MWF allergens still remains to be established. Our data suggest that in spite of their chemical relationship to MEA or DEA, the 6 tested chemicals have to be evaluated individually from the allergological point of view.

The lack of positive test reactions to the other substances of our series may reflect their low-sensitizing potential. Alternatively, the chosen patch test concentration may have been too low in some cases, as with IPBC (see above). This view is supported by the fact that we did not observe irritant test reactions and only very few erythematous reactions. In conclusion, continuous adaptation of occupation-specific test series is needed to maintain and increase the diagnostic quality of patch testing in occupational dermatology. With regard to the metalworking industry, we are grateful to the MWF-producing industry for their close cooperation in this respect.

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