

Patch test results with the metalworking fluid series of the German Contact Dermatitis Research Group (DKG)

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Based on the information of the interdisciplinary task force on allergy diagnostics in the metal branch, in 2001, the German Contact Dermatitis Research Group (DKG) compiled two metalworking fluid (MWF) test series with currently and previously used components, respectively. After 2 years of patch testing, we present results obtained with these series, based on data of the Information Network of Departments of Dermatology (IVDK). 251 metalworkers who were patch tested because of suspected MWF dermatitis in 2002 and 2003 were included in this retrospective data analysis. Of these, 206 were tested with the current MWF series and 155 with the historical MWF series. Among the current MWF allergens, monoethanolamine ranked 1st with 11.6% positive reactions. Diethanolamine (3.0%), triethanolamine (1.1%), and diglycolamine (1.9%) elicited positive reactions far less frequently. Allergic reactions to *p*-aminoazobenzene were frequently observed (6.0%), but the relevance of these reactions is still obscure. Positive reactions to biocides ranged from 4.5% for Bioban[®] CS 1135 to 0.5% for iodopropynyl butylcarbamate and 2-phenoxyethanol. Concomitant reactions to formaldehyde, which caused positive reactions in 3.3%, and formaldehyde releasers occurred to varying extents without conclusive pattern. No positive reactions were seen to dibutyl phthalate, di-2-ethylhexyl phthalate, tricresyl phosphate, isopropyl myristate or benzotriazole. With the historical MWF test series, positive reactions to methylidibromo glutaronitrile (MDBGN) were observed most frequently. However, sensitization via allergen sources other than MWF seems likely, as MDBGN, during the study period, has been one of the most frequent preservative allergens in cosmetics and body care products. Other historical MWF allergens comprised morpholinyl mercaptobenzothiazole (3.3%), benzisothiazolinone (BIT; 2.0%) and Bioban[®] P 1487 (1.3%). BIT is currently used in MWF again, so it was shifted to the current MWF test series. As decreasing reaction frequencies to former MWF allergens that are no longer used can be expected, the historical series should be re-evaluated after some years. The test series with current MWF allergens has to be kept up-to-date based on information from industry and to be kept concise by eliminating test substances which never cause positive reactions.

Key words: benzisothiazolinone; biocides (chloro)methylisothiazolinone (MCI/MI); colophonium; formaldehyde releaser; formaldehyde; metalworking fluid patch test series; methylidibromo glutaronitrile; monoethanolamine; occupational contact allergy. © Blackwell Munksgaard, 2004.

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Metalworking fluids (MWF) are one of the major causes of occupational skin disease in metalworkers (1–8). In several studies, the prevalence or 3-year incidence of hand eczema in metalworkers exposed to MWF was found to be 20–25%, with irritant contact dermatitis (ICD) being observed more frequently than allergic contact dermatitis

(ACD) (1, 2, 4). However, ICD often precedes and promotes sensitization (9). Moreover, other factors such as atopy have to be considered in the individual case, and mostly, occupational skin disease is a mixture of constitutional dermatitis and ICD and/or ACD (5, 7, 8, 10–13). When studying occupational MWF dermatitis, the

complexity of these products has to be taken into account. Usually, the bases of MWF are mineral oils or (semi)synthetic hydrocarbon compounds. Various admixtures such as emulsifiers, buffers, stabilizers, surfactants, antifog additives, foam inhibitors, tensides, lubricants, rust preventives, extreme-pressure additives and biocides (bactericides and fungicides) are commonly added (10, 11, 14–17). During the working process, further biocides may be added, and slideway oils or hydraulic oils may be introduced into the MWF by leakage (11, 16–18).

Some 15 years ago, contact allergies among metalworkers exposed to MWF were investigated in several studies. Predominantly, sensitizations to biocides, particularly formaldehyde releasers, were observed (3, 5, 19). Additionally, sensitizations to formaldehyde, benzisothiazolinone (BIT), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), colophonium, *p*-phenylenediamine (PPD), *p*-aminoazobenzene (PAAB), dichromate and cobalt have been described, but the clinical relevance of these findings could not always be established (3, 5, 19–22). During the last decade, sensitizations to the following MWF components have been described in case reports of metalworkers with occupational contact dermatitis (OCD): diglycolamine (23), ethylenediamine possibly as indicator for a sensitization to other amines (24), monoethanolamine (MEA) (25, 26), alkanolamineborates (27), a condensate of boric acid, MEA and fatty acids (28), fatty acid polydiethanolamide (29), oleyl alcohol (25), tertiary-butylhydroquinone (30), imazalil (31), iodopropynyl butylcarbamate (IPBC) (32), sodium pyrithione (33, 34), ethylhexylzinc dithiophosphate (29, 35) and oak moss resin (26). Recently, we reported the spectrum of contact allergens found in metalworkers exposed to water-based MWF (wb-MWF) with OCD, as the result of a multicentre study (FaSt study) from 1999 to 2001 (36). In that study, important MWF-related allergens were MEA, colophonium/abietic acid, cobalt, diethanolamine (DEA), formaldehyde, formaldehyde releasers, other biocides and fragrance mix (FM) (36).

Patch test series for diagnostics in metalworkers are commercially available. However, regarding the wide variety of substances and components used in MWF (15), it seems likely that relevant contact allergies may be overlooked because far from all potentially allergenic components are available as standardized patch test preparations. Additionally, the composition of MWF changes with time due to technological progress. Hence, for a valid allergy diagnostic in this field, it is important to adapt the MWF test

series to the current spectrum of occupational exposure. In the year 2000, the interdisciplinary task force on allergy diagnostics in the metal branch compiled 2 lists of MWF allergens commercially available as patch test substances (18). The 1st list contains substances currently used in MWF and the 2nd list substances which have only been used previously, mostly before 1994 (18). Based on this information, at the end of 2001, the German Contact Dermatitis Research Group (DKG) established 2 corresponding MWF series to be tested in addition to the standard series, the ointment base series and the preservative series (Tables 1 and 2) in patients with suspected ACD and exposure to MWF. This design was chosen, because it usually makes sense also to test the latter 2 series in metalworkers with suspected OCD. Additionally, to avoid duplicate patch tests, the DKG omitted from the MWF series those potential MWF allergens that are contained in the standard, ointment base or preservative series. After 2 years, we did a first analysis of these test series based on the data of the Information Network of Departments of Dermatology (IVDK) of the years 2002 and 2003.

Patients and Methods

As study group, we selected exclusively metalworkers tested because of suspected MWF dermatitis. In 2002 and 2003, altogether 16848 patients were patch tested in the departments of dermatology forming the IVDK. Of these patients, 251 (1.5%) fulfilled the criteria of the study and hence were included in the data analysis¹.

¹The following departments of dermatology (physicians) participated in the study (sorted by descending number of patients): Osnabrück (H. Dickel, S.M. John, N. Schürer, H.J. Schwanitz†), Dortmund (C. Pirker, R. Herbst, P.J. Frosch), Homburg/Saar (P. Koch), Mainz (D. Becker), Heidelberg (U. Jappe), Graz (B. Kränke, W. Aberer), Dresden (R. Aschoff), Würzburg (J. Arnold, A. Trautmann), Tübingen (G. Lischka, M. Röcken, T. Biedermann), Gera (J. Meyer), Freudenberg (Ch. Szliska), Göttingen (Th. Fuchs, J. Geier), Jena (A. Bauer, M. Kaatz, S. Schliemann-Willers), Essen (U. Hillen), Basel (A. Bircher), Berlin Charité (M. Worm, T. Zuberbier), Halle/Saale (G. Gaber, D. Lübke), München TU (J. Rakoski), Marburg (H. Löffler), Lübeck (J. Grabbe), Hamburg (R. Wessbecher), Erlangen (V. Mahler, M. Fartasch), Augsburg (A. Ludwig), Nürnberg (I. Müller), Mannheim (Ch. Bayerl), Heidelberg AKS (H. Dickel, E. Weisshaar, T.L. Diepgen), Münster (R. Brehler, B. Hellweg), München Schwabing (M. Agathos), Rostock (H. Heise), Ulm BWK (H. Pillekamp), München LMU (T. Oppel, B. Przybilla, F. Rueff).

Table 1. Test series 'MWF, current allergens' of the German Contact Dermatitis Research Group (DKG) and additional current MWF allergens in other DKG test series

Substance	Occurrence in MWF	Function in MWF
DKG MWF series (current allergens)		
Benzylhemiformal	wb-MWF	Biocide, formaldehyde releaser
4,4-Dimethyl-1,3-oxazolidine/3,4,4-trimethyl-1,3-oxazolidine (Bioban [®] CS 1135)	wb-MWF	Biocide, formaldehyde releaser
7-Ethylbicyclooxazolidine (Bioban [®] CS 1246)	wb-MWF	Biocide, formaldehyde releaser
Iodopropynyl butylcarbamate	wb-MWF	Biocide
N,N'-Methylene-bis-5-methyl-oxazolidine	wb-MWF	Biocide, formaldehyde releaser
Octylisothiazolinone	wb-MWF	Biocide
2-Phenoxyethanol	wb-MWF	Biocide
Sodium-2-pyridinethiol-1-oxide (sodium omadine)	wb-MWF	Biocide
1,3,5-Tris(2-hydroxyethyl)-hexahydrotriazine (Grotan BK [®])	wb-MWF	Biocide, formaldehyde releaser
Benzotriazole	wb-MWF and neat oils	Rust preventive
Diethanolamine ^a	wb-MWF	Rust preventive
Monoethanolamine	wb-MWF	Rust preventive
Dibutyl phthalate	Neat oils	Anti-wear additive
Di-2-ethylhexyl phthalate	Neat oils	Anti-wear additive
Isopropyl myristate	wb-MWF and neat oils	Anti-wear additive
<i>p</i> -tert-Butylphenol	Neat oils	Antioxidant
Tricresyl phosphate	?	Antioxidant
Abietic acid	wb-MWF	Emulsifier/surfactant
Diglycolamine [2-(2-aminoethoxy)ethanol]	wb-MWF	Emulsifier
<i>p</i> -Aminoazobenzene ^b	–	Dye
DKG standard series		
Formaldehyde ^c	wb-MWF	Top-up biocide
(Chloro-)methylisothiazolinone (MCI/MI)	wb-MWF	Top-up biocide
Lanolin alcohol	wb-MWF	Anti-wear additive
Zinc diethyldithiocarbamate ^d	neat oils	Anti-wear additive
Cetearyl alcohol	wb-MWF	Stabiliser/antiwear additive
Colophonium ^e	wb-MWF	Emulsifier/surfactant
Mercaptobenzothiazole	wb-MWF	Rust preventive
DKG ointment base series		
Propylene glycol	wb-MWF	Stabilizer
Polyethylene glycol (tested as polyethylene glycol ointment base)	–	Stabilizer/antiwear additive
Triethanolamine	wb-MWF	Rust preventive
Butylhydroxy toluol	Neat oils	Antioxidant
DKG preservative series		
Triclosan	neat oils	Biocide

wb-MWF, water-based metalworking fluid.

^aConcentration limited to maximum 0.2% in the wb-MWF concentrate (i.e. 0.01% in the wb-MWF when diluted to 5%) by the German TRGS 611 since 1993.

^bTested as marker for azo dyes from contamination with other technical oils, e.g. slideway oils or hydraulic oils.

^cReleased from formaldehyde releasers.

^dTested as a marker for sodium diethyldithiocarbamate.

^eAllergic reaction indicates contact allergy to oxidation products of resin acids.

The IVDK is a multicentre surveillance system on contact allergies, with more than 40 departments of dermatology in Germany, Austria and Switzerland participating. Patch test results and anamnestic data of all patients tested are recorded electronically in a standardized way and regularly transferred to the IVDK data centre at the University of Göttingen (37).

Patch tests were performed and read at least until day 3 (D3), according to the guidelines of the ICDRG and the DKG (38, 39). Patch test exposure time was 2 days in 208 patients (83%) and 1 day in 43 patients (17%) according to the routine test procedure in the respective centre. Patch test substances were obtained from

Hermal, Reinbek, Germany, except for sodium omadine, which was bought from Chemotechnique, Malmö, Sweden.

Data analysis was done at the IVDK data centre using the statistical program system SAS (version 8.2, SAS Institute, Cary, NC, USA) (37). Evaluation of patch test results was based on the reactions at D3. Reaction frequencies were supplemented with the exact 95% confidence interval (95% CI), allowing estimation of the precision of the observed proportion.

Data on clinical relevance of positive test reactions was not analysed in detail, because relevance assessment in the clinical routine process depends on too many uncontrollable variables

Table 2. Test series 'MWF, historical allergens' of the German Contact Dermatitis Research Group (DKG) and additional previous MWF allergens in other DKG test series

Substance	Occurrence in MWF	Function in MWF
DKG MWF series (current allergens)		
1,2-Benzisothiazolin-3-one, sodium salt ^a	wb-MWF	Biocide
Chlorocresol	neat oils	Biocide
Chloroxylenol	wb-MWF	Biocide
Dipentene (D,L-limonene)	wb-MWF	Biocide
Hexamethylene tetramine	wb-MWF	Biocide
2-Hydroxymethyl-2-nitro-1,3-propanediol (Tris Nitro [®]) ^b	wb-MWF	Biocide, formaldehyde releaser
Methyldibromo glutaronitrile (MDBGN)	wb-MWF	Biocide
4-(2-Nitrobutyl) morpholine/4,4'-(2-ethyl-2-nitro-trimethylene) dimorpholine (Bioban [®] P 1487) ^b	wb-MWF	Biocide, formaldehyde releaser
Phenyl-beta-naphthylamine	neat oils	Antioxidant
Morpholinyl mercaptobenzothiazole	wb-MWF	Rust preventive
Ethylenediamine dihydrochloride	wb-MWF	?
DKG standard series		
Paraben mix	wb-MWF	Biocide
MDGBN/2-phenoxyethanol (MDBGN/PE) ^c	wb-MWF	MDBGN: biocide
Myroxylon pereirae resin (MPR, balsam of Peru)	wb-MWF	Odour mask
Fragrance mix ^d	wb-MWF	?
DKG ointment base series		
Coconut diethanolamide ^b	wb-MWF	Emulsifier
DKG preservative series		
Bronopol [®] (2-bromo-2-nitropropane-1,3-diol) ^c	wb-MWF	Biocide, formaldehyde releaser
Chloroacetamide	wb-MWF	Biocide

wb-MWF, water-based metalworking fluid.

^aMay currently be used in MWF again, according to recent information from the lubricant industry.

^bProhibited in MWF by the German TRGS 611 since 1993.

^cIn contrast to PE, MDBGN is probably no longer used in MWF.

^dIt is unclear which fragrances are used in MWF, if at all.

^eNo longer used in MWF, but used in skin care products.

(experience of the physician treating the individual patient concerned, cooperation of the patient, information on the occupational materials handled, time available for extensive patient interview and information retrieval concerning the occupational exposure, etc.); so, this data has proven very heterogeneous and unreliable.

Results

Among the study group, i.e. 251 metalworkers tested because of suspected MWF dermatitis, there were 63 turners (lathe operators) (25.1%), 26 milling cutters (10.4%), 25 tool makers (10.0%) and 6 grinders (2.4%). In the remainder, no specification was given beyond 'metalworker, chipping technology' or 'machine operator in the metalworking branch'. 124 patients (49.4%) had been working in their occupation since before 1994, while 82 patients (32.7%) started working with MWF in 1994 or later. In the remaining 45 patients (17.9%), the beginning of the MWF exposure was not mentioned. In the study population, there were 231 men (92.0%) and 115 patients (45.8%) at the age of 40 years or more. The age ranged from 17 to 62 years with a median of 38 years (mean 38.8 ± 11.4 years). 74 patients

(29.5%) were examined in the context of a medical assessment. 47 patients (18.7%) had past or present atopic dermatitis. 201 patients (80.1%) suffered from hand dermatitis. According to the course and anatomical site of the skin disease on the one hand and the occupational exposure (and, partly, occupational contact allergies) on the other hand, occupational dermatitis was finally diagnosed in 187 patients (74.5%). A final current diagnosis of ICD was made in 81 patients (32.3%), while ACD was diagnosed in 63 patients (25.1%). The remainder currently had various other forms of skin disease, e.g. dyshidrotic eczema, atopic dermatitis [22 patients (8.8%) each] or psoriasis [5 patients (2.2%)], etc.

The test series with current MWF allergens was tested in 206 patients (82.1% of the study population), and 88 positive reactions to allergens of this series occurred in 48 patients (23.3% of 206). Among those 155 patients (61.8%) tested with the series containing former, historical MWF allergens, 19 positive reactions were seen in 16 patients (10.3% of 155). The DKG standard series was patch tested in 221 patients (88.0% of the study population), and 128 positive patch test reactions occurred in 77 of these patients (34.8%).

Table 3. Patch test reactions at D3 to the German Contact Dermatitis Research Group (DKG) metalworking fluid (MWF) series (current allergens)

Substance	CAS-No.	Test concentration	Patients tested	Negative	?	+	++	+++	Irritant reaction	% positive (95% CI)
Monoethanolamine	[141-43-5]	2% pet.	199	159	16	19	4		1	11.6 (7.5–16.8)
<i>p</i> -Aminozobenzene	[60-09-3]	1% pet.	199	182	5	4	3	5		6.0 (3.2–10.3)
<i>N,N'</i> -methylene-bis-5-methyl-oxazolidine	[66204-44-2]	1% pet.	198	185	3	8	1		1	4.5 (2.1–8.5)
4,4-Dimethyl-1,3-oxazolidine/3,4,4-trimethyl-1,3-oxazolidine (Bioban [®] CS 1135)	[51200-87-4]/[5673-43-7]	1% pet.	198	183	6	9				4.5 (2.1–8.5)
Diethanolamine	[111-42-2]	2% pet.	200	188	6	5	1			3.0 (1.1–6.4)
7-Ethylbicyclooxazolidine (Bioban [®] CS 1246)	[7747-35-5]	1% pet.	197	190	2	3	2			2.5 (2.1–8.5)
Abietic acid	[514-10-3]	10% pet.	198	189	5	2	1	1		2.0 (0.8–5.8)
Diglycolamine (2-(2-aminoethoxy)ethanol) ^a	[929-06-6]	1% pet.	108	100	6	2				1.9 (0.2–6.5)
1,3,5-Tris(2-hydroxyethyl)-hexahydrotriazine (Groton BK [®])	[4719-04-4]	1% pet.	199	195	1	3				1.5 (0.3–4.3)
Benzylhemiformal	[14548-60-8]	1% pet.	199	192	3	3			1	1.5 (0.3–4.3)
Sodium-2-pyridinethiol-1-oxide (sodium omadine)	[3811-73-2]	0.1% aq.	185	183		2				1.1 (0.1–3.9)
Octylisothiazolinone	[26530-20-1]	0.025% pet.	199	196	1	2				1.0 (0.1–3.6)
Iodopropynyl butylcarbamate ^b	[55406-53-6]	0.1/0.2% pet.	186	181	4			1		0.5 (0.0–3.0)
<i>p</i> -tert-butylphenol	[98-54-4]	1% pet.	199	196	2			1		0.5 (0.0–2.8)
2-Phenoxyethanol	[122-99-6]	1% pet.	199	197	1		1			0.5 (0.0–2.8)
Dibutyl phthalate	[84-74-2]	5% pet.	199	197	2					0.0 (0.0–1.5)
Di-2-ethylhexyl phthalate	[117-81-7]	5% pet.	198	197	1					0.0 (0.0–1.5)
Tricresyl phosphate	[78-32-0]	5% pet.	199	198	1					0.0 (0.0–1.5)
Isopropyl myristate	[110-27-0]	10% pet.	196	196						0.0 (0.0–1.5)
Benzotriazole	[95-14-7]	1% pet.	199	199						0.0 (0.0–1.5)

^aLess patients tested because diglycolamine was not included in the current metalworking fluid (MWF) series until the beginning of 2003.^bTest concentration of iodopropynyl butylcarbamate was changed from 0.1 to 0.2% in December 2002.

Table 4. Pattern of patch test reactions at D3 to formaldehyde and formaldehyde releasers contained in the German Contact Dermatitis Research Group (DKG) test series with current MWF allergens in patients reacting positively to formaldehyde or at least one formaldehyde releaser.

Patient No.	Formaldehyde	N,N'-Methylene-bis-5-methyl-oxazolidine	Bioban [®] CS 1135	Bioban [®] CS 1246	Grotan BK [®]	Benzyl-hemiformal
1	++	-	-	-	-	-
2	+	+	+	+	-	+
3	+	+	+	-	+	+
4	+	-	?	+	-	-
5	+	-	-	-	-	-
6	+	-	-	-	-	-
7	+	NT	NT	NT	NT	NT
8	-	+	+	++	-	-
9	-	+	+	+	-	?
10	-	+	+	-	-	-
11	-	+	?	-	-	-
12	-	+	-	-	-	-
13	-	+	-	-	-	-
14	-	-	+	-	+	-
15	-	-	+	-	+	-
16	-	-	-	++	-	+
17	NT	++	+	-	?	-
18	NT	?	+	-	-	?

NT = not tested

Patch test results with the current MWF series are shown in Table 3. The leading allergen was MEA with 11.6% positive reactions. Of the 23 positive reactions, 19 did not exceed +, i.e. the positivity ratio was 83%. With 17 doubtful and irritant reactions, the reaction index was 0.15. The other 2 amines, i.e. DEA and diglycolamine, elicited positive reactions far less frequently, namely in 3.0% and 1.9%, respectively. After MEA, PAAB ranked 2nd with 6.0% positive reactions (12 of 199 patients tested). *p*-Phenylenediamine from the standard series was tested in 10 of the 12 PAAB-positive patients, and of these, 7 reacted positively to PPD. Positive test reactions to biocides ranged from 4.5% for N,N'-methylene-bis-5-methyl-oxazolidine and 4,4-dimethyl-1,3-oxazolidine/3,4,4-trimethyl-1,3-oxazolidine (Bioban[®] CS 1135) to 0.5% for IPBC and 2-phenoxyethanol (PE). In most of these substances, positive reactions were mainly or even exclusively weak positive, i.e. +. Abietic acid tested positively in 4 patients, 2 of them showing a strong allergic reaction. All patients positive to abietic acid also reacted to colophonium in the standard series. The only patient reacting positively to PE showed no reaction to methyldibromoglutaronitrile (MDBGN) or the combination of MDBGN and PE (MDBGN/PE) in the standard series. One patient had a +++ reaction to *p*-tert-butylphenol. Additionally, he reacted positively to tert-butylhydroquinone (+++) and to *p*-tert-butylphenol formaldehyde resin (+). No clinical relevance of these test reactions could be found. No positive reactions were seen to the

phthalates tested, to tricresyl phosphate, isopropyl myristate (IPM) or benzotriazole.

Concomitant reactions to formaldehyde in the standard series and/or formaldehyde releasers contained in this test series are shown in Table 4. Altogether, 18 patients reacted positively to formaldehyde or a formaldehyde releaser, but no conclusive pattern could be detected, although some concomitant reactions to 2 or more of these allergens occurred in individual patients.

A separate analysis of test reactions to the DKG series with former MWF allergens, observed in patients working with MWF since before 1994 and those who started later revealed no significant difference at all (data not shown), so we describe the summarized results for all patients. Test reactions to the historical MWF allergen series are shown in Table 5. Altogether, the yield was poor: positive reactions were seen to only 5 of the 11 allergens of this series. MDBGN, being a historical allergen in the context of MWF, evoked positive reactions in 8 patients. The standard series was tested in 6 of these patients, and only 3 of them reacted to the combination MDBGN/PE. Morpholinyl mercaptobenzothiazole (MOR) evoked positive reactions in 5 patients who were also tested with the standard series. 4 of these 5 patients reacted positively to mercapto mix, but none to mercaptobenzothiazole (MBT). All of the 3 positive reactions to BIT sodium salt occurred independently from octylisothiazolinone. 2 patients showed a positive reaction to 4-(2-nitrobutyl)morpholine/4,4'-(2-ethyl-2-nitro-trimethylene)dimorpholine

Table 5. Patch test reactions at D3 to the DKG metalworking fluid (MWF) series (former allergens)

Substance	CAS-No.	Test concentration	Patients tested	Negative	?	+	++	+++	Irritant reactions	% positive (95% CI)
Methyldibromo glutaronitrile	[35691-65-7]	0.3% pet.	153	144	1	7	1			5.2 (2.3–10.0)
Morpholinyl mercaptobenzothiazole	[102-77-2]	0.5% pet.	152	145	2	3	2			3.3 (1.1–7.5)
1,2-Benzisothiazolin-3-one, sodium salt	[2634-33-5]	0.1% pet.	152	145	3	2	1		1	2.0 (0.4–5.7)
4-(2-Nitrobutyl) morpholine/4,4'-(2-ethyl-2-nitro-trimethylene) dimorpholine (Bioban® P 1487)	[37304-88-4]	1% pet.	152	146	4	2				1.3 (0.2–4.7)
Chlorocresol	[59-50-7]	1% pet.	152	151		1				0.7 (0.0–3.6)
Chloroxylenol	[88-04-0]	1% pet.	152	149	3					0.0 (0.0–2.0)
Phenyl-beta-naphthylamine	[135-88-6]	1% pet.	153	151	2					0.0 (0.0–2.0)
Hexamethylene tetramine	[100-97-0]	1% pet.	151	151						0.0 (0.0–2.0)
2-Hydroxymethyl-2-nitro-1,3-propanediol (Tris Nitro®)	[126-11-4]	1% pet.	153	153						0.0 (0.0–2.0)
Dipentene (D,L-limonene)	[138-86-3]	2% pet.	154	154						0.0 (0.0–2.0)
Ethylenediamine dihydrochloride	[333-18-6]	1% pet.	154	154						0.0 (0.0–2.0)

(Bioban® P 1487), and none of these reacted to formaldehyde in the standard series.

Test reactions to those potential MWF allergens that are contained in the standard, ointment base or preservative series are shown in Table 6. Among the current MWF allergens, positive reactions to MCI/MI were most frequently observed (4.2%). Colophonium elicited positive reactions in 7 patients, and 4 of them also reacted to abietic acid, while the remaining 3 patients did not. Of the 7 patients reacting to formaldehyde, 6 were tested with formaldehyde releasers, and of these, 3 had a positive reaction to at least 1 of them. Relations between positive test reactions to formaldehyde and formaldehyde releasers are shown in detail in Table 4 (see above).

Concerning former MWF allergens in these test series, 10 patients reacted positively to Myroxylon pereirae resin (MPR, balsam of Peru), 9 to FM, and of these, 3 to both preparations. 3 patients showed a positive test reaction to coconut diethanolamide, and 2 of them also to cocamidopropyl betaine. All other current or former MWF allergens elicited positive reactions only in 1 or 2 patients, if at all.

Discussion

Our data analysis allows the distinction between important and less important MWF allergens, offering the chance to focus the MWF test series without loss of diagnostic value. In this context, the multicentre approach of the IVDK turns out to be a great advantage because results from a single centre could easily be biased by referral of patients from one or few regional metalworking companies, which might lead to overestimation and generalization of their specific problems.

Although our sample size was not that small, one has to be aware that even with about 200 patients tested, the proportions of positive reactions still have rather large 95% CIs. So, the calculated percentages have to be interpreted with caution, and no premature conclusions should be drawn.

At first sight, the fact that only 48 patients (23.3% of those tested) reacted to at least 1 allergen of the current MWF series, and only 16 (10.3%) to allergens of the former MWF series may seem disappointing. However, in our opinion, this does not point to a generally poor validity of the test series, but to a rather liberal indication for testing the MWF series in the study group. This is illustrated by the anamnestic data: exogenous (allergic or irritant) contact dermatitis were the main final diagnoses in merely 60% of the cases, while in the other 40%, clearly

Table 6. Patch test reactions at D3 to the potential current (c) or former (f) metalworking fluid (MWF) allergens in other test series

Substance	Test concentration	MWF allergen (c/f)	Patients tested	Negative	?	+	++	+++	Irritant reactions	% positive (95%-CI)
DKG standard series										
(Chloro-)methylisothiazolinone (MCI/MI)										
Colophonium	0.01% aq.	c	214	204	1	6	3			4.2 (1.9-7.8)
Formaldehyde	20% pet.	c	214	203	4	4	1	2		3.3 (1.3-6.6)
Lanolin alcohol	1% aq.	c	214	203	4	6	1			3.3 (1.3-6.6)
Zinc diethyldithiocarbamate (ZDEC)	30% pet.	c	214	211	1	1	1			0.9 (0.1-3.3)
Mercaptobenzothiazole	1% pet.	c	215	212	1	2				0.9 (0.1-3.3)
Cetearyl alcohol	2% pet.	c	214	213	1					0.5 (0.0-2.6)
Myroxylon pereirae resin (MPR, balsam of Peru)	20% pet.	c	214	213	1					0.0 (0.0-1.4)
Fragrance mix	25% pet.	f	214	198	6	7	2	1		4.7 (2.3-8.4)
Methyldibromo glutaronitrile/2-phenoxyethanol (MDBGN/PE)	8% pet.	f	214	203	2	6	1	2		4.2 (1.9-7.8)
Paraben mix	1% pet.	f	214	204	3	3	3	1		3.3 (1.3-6.6)
DKG ointment base series										
Propylene glycol	16% pet.	f	214	202	10	2				0.9 (0.1-3.3)
Triethanolamine	20% aq.	c	170	163	2	2		3		1.2 (0.1-4.2)
Butylhydroxy toluol	2.5% pet.	c	184	180	2	2				1.1 (0.1-3.9)
Polyethylene glycol ointment base	2% pet.	c	162	161	1					0.0 (0.0-1.8)
Coconut diethanolamide	100%	c	172	172						0.0 (0.0-1.7)
DKG preservative series	0.5% pet.	f	181	177	1	3				1.7 (0.3-4.8)
Triolosan	2% pet.	c	165	163	1	1				0.6 (0.0-3.3)
Bronopol® (2-bromo-2-nitropropane-1,3-diol)	0.5% pet.	f	176	170	3	1		1		1.1 (0.1-4.0)
Chloroacetamide	0.2% pet.	f	171	169	2					0.0 (0.0-1.7)

endogenous factors were considered more important in the pathogenesis. A final diagnosis of occupational skin disease was not stated in 100%, but only in 75% and 20% of the patients tested had not had hand eczema as main complaint. Only about 30% of the patients had a history of work-related skin disease that eventually led to an examination for a medicolegal assessment. Additionally, concerning the test series with former MWF allergens, it is to be expected that the frequency of sensitizations decreases with time, due to lack of allergen exposure. In the light of these circumstances, the overall yield of positive test reactions seems satisfactory.

MEA, DEA, triethanolamine and diglycolamine

In accordance with the results of our multicentre study on comparable patients with OCD (FaSt study) of the years 1999–2001 (36), MEA proved to be one of the most important MWF allergens. Although in the latter study, more thoroughly investigated patients were involved (100% occupational dermatitis, 94.4% hand dermatitis and 73.1% medicolegal assessments), and hence indication for patch testing was probably more restrictive than in the present study group, the proportion of positive reactions to MEA was virtually the same in both studies [10.9% (95% CI; 5.9–18.0%) and 11.6% (95% CI; 7.5–16.8%), respectively]. In view of the different test populations, one might have expected the reaction frequency to MEA to be lower in this 2002/2003 data analysis. However, in our opinion, it is not justified to talk of an increasing problem, because the large 95%-CIs might hide a lower proportion of positive reactions in the present study group. Moreover, with a reaction index of 0.15 and a positivity ratio of 83%, the test preparation MEA 2% pet. cannot be regarded as optimal, but rather as a borderline irritant test substance. Hence, it is possible that some of the weak positive reactions are false positive. On the other hand, it cannot be excluded that some of the erythematous reactions are indicators of a weak sensitization, i.e. true allergic reactions. In the MWF, nowadays most of the MEA is present as reaction products of MEA with boric acid or other MWF components, and probably only a small fraction of MEA is present as such. Maybe, a parallel patch test with these reaction products might elucidate the questions of false positive or too weak allergic reactions, because a model like that would mimic the situation in the MWF, and hence workplace reality, better than the test with MEA alone. Cases of ACD due to such reaction products have already been reported (27, 28).

As shown in Table 1, not only MEA, but also DEA and triethanolamine (TEA) are used as rust preventives (corrosion inhibitors) in wb-MWF. The concentration of DEA is limited to 0.2% in the MWF concentrate in Germany by law (technical rule for hazardous substances TRGS 611) since 1993, because of the potential formation of carcinogenic *N*-nitrosamines (40). Due to this limitation, the use of DEA in wb-MWF has declined in recent years. This is probably reflected by the far lower frequency of sensitization to DEA (3.0%) compared to MEA (11.6%) in this study. TEA, which is also frequently used in creams and cosmetics, and hence is tested in the ointment base series, elicited even less positive reactions, namely 1.1%. We have no information on its prevalence in MWF currently on the market. Thus, the lower reaction frequency to TEA may not only be due to a lower sensitizing capacity, but also due to less frequent use in MWF. The gradation of the frequency of allergic reactions to MEA > DEA > TEA is the same as in the FaSt study (36).

Diglycolamine, which was recently described as a MWF allergen (23, 41), was included in the current MWF series in 2003; hence, the number of patients tested is rather low ($n = 108$), and the proportion of positive reactions is not that representative.

PAAB

PAAB is tested as a marker for contact allergy to azo dyes from contamination of the MWF with other technical oils, e.g. hydraulic oils or slideway oils, which are mostly coloured. However, we doubt that the positive reactions to PAAB can reliably be interpreted in this way. While concomitant reactions to PAAB and PPD are frequent and probably an indicator of a contact allergy to *p*-amino compounds (42), we know from the analysis of data concerning allergic reactions to textile dyes that PAAB is not a reliable marker for contact allergy to azo dyes (43). An increased risk of active sensitization has been described when PAAB and PPD are patch tested in parallel (44). In view of these circumstances, PAAB should be deleted from the MWF test series, although it was one of the more frequent allergens. In such cases, which may, however, not easily be suspected, the actual dyes in technical oils from the patients' workplace should probably be tested instead.

Formaldehyde, formaldehyde releasers and other industrial biocides

In the FaSt study, metalworkers with OCD exposed to wb-MWF had a significantly

increased risk of sensitization to formaldehyde, compared to men not working in the metalworking industry (odds ratio 4.1; 95% CI 1.5–9.2) (36). The proportions of positive reactions to formaldehyde in the FaSt study and in the present investigation were similar (4.8% and 3.3%, respectively) (36). Formerly, it was common to use formaldehyde solution for additional preservation of wb-MWF during usage. Nowadays, this seems to be a rare exception because mostly formaldehyde releasers are used for this purpose. The amount of formaldehyde released varies, depending on several factors such as pH, temperature, microbial contamination, etc. (45). Positive reactions to formaldehyde releasers occurred in a considerable proportion of patients, partly with and partly without a concomitant reaction to formaldehyde (Tables 3–5). In accordance with previous studies (46), patch test reactions to these substances were mostly weak. In view of the well-known poor reproducibility of these test reactions (46), their relevance has to be determined individually by exploring the workplace exposure in depth.

Benzisothiazolinone, which caused positive reactions in 2% of the patients tested, is being used more frequently in MWF again, according to recent information from the lubricant industry. For this reason, it was switched from the historical to the current MWF test series by the DKG in the beginning of 2004. Other biocides, such as sodium omadine, octylisothiazolinone, IPBC, PE, chlorocresol and chloroxylonol elicited positive reactions only in exceptional cases. However, in view of the limited number of patients tested, they should be kept in the MWF test series because they may be important individually.

Colophonium

It is known that contact allergies to colophonium frequently occur among metalworkers with suspected cutting fluid dermatitis (5). In the FaSt study, it was shown that exposure to wb-MWF is particularly connected with colophonium sensitization; compared to metalworkers with OCD who were not exposed to wb-MWF, those with OCD and exposure to MWF had an eightfold increased risk of sensitization to colophonium (36). In contrast, in the present study, neither colophonium nor abietic acid seems to be a prominent allergen, because the reaction frequencies are no higher than in an average German clinical patch test population (47). This difference may be explained by patient selection; as mentioned above, in the FaSt study, far more patients were

examined for a medicolegal assessment, and patch test indication was more restrictive than in the present study. The mechanism of colophonium sensitization by exposure to MWF has been described in detail elsewhere (11, 36); a positive patch test reaction to colophonium indicates a sensitization to oxidation products of abietic acid and other resin acids (48). wb-MWFs may contain 0.2% to 0.4% distilled tall oil, which contains about 10% abietic acid and about 20% other resin acids. On exposure to air, which occurs during the normal working process, the resin acids would oxidize rather quickly (49–51). In most workplaces, the MWF dries up on the contaminated skin often compromised by cumulative irritation, and the concentration rises within minutes (52). Hence, occupational exposure to wb-MWF carries a high risk of sensitization. However, in each individual case, other allergen sources (e.g. plaster, etc.) have to be considered.

MCI/MI and MDBGN

These preservatives are not discussed together with the above-mentioned industrial biocides because they are well-known sensitizers in body care products and cosmetics, and may be contained in protective creams or emollients used at work. Hence, the particular exposure to MCI/MI or MDBGN has to be established in every metalworker sensitized, with special regard to the MWF used on the one hand and the domestic exposure on the other hand.

Due to its chemical properties, MCI/MI is not used as a preservative in the MWF concentrate, but as additional top-up biocide at the workplace (18). Hence, it is not sufficient to know the primary MWF preservation as declared in the material safety data sheet by the MWF producer. Additionally, the employer has to be asked which top-up biocide had been used.

MDBGN has been used some years ago for preservation of wb-MWF. According to information from the lubricant industry, it is currently not in use for this purpose (18). In the DKG standard series, MDBGN is tested in combination with PE at a total concentration of 1%, because this mixture has frequently been used as preservative. In this combination, MDBGN has a patch concentration of 0.2%. Patch testing with MDBGN 0.3% leads to more positive reactions, as in our present study. However, according to an earlier study of the DKG, many reactions obtained with this test concentration are probably irritant, i.e. false positive (53). Hence, particularly when testing

with MDBGN in high concentrations, the clinical relevance of every positive reaction has to be established, taking into account both domestic and occupational exposure, including skin care at work.

FM and MPR (balsam of Peru)

In the FaSt study, occupational exposure to wb-MWF was a significant risk factor for sensitization to fragrances in terms of positive patch test reaction to FM and (not significant) to MPR (36). In contrast, as with colophonium, the proportions of positive reactions to FM and MPR seem to be normal in the present study population, when compared to the reaction frequencies observed in men in the total test population of the IVDK (47). Until about 1990, fragrances or odour masks, even balsam of Peru, were mentioned as common components of wb-MWF (3, 8, 54). According to recent information from the lubricant industry, usually no fragrances are used in the MWF concentrate nowadays. However, it cannot be excluded that so-called odour masks are added to the MWF by metalworking companies during usage. Clearly, this does not mean that every fragrance allergy in exposed metalworkers is acquired from wb-MWF. In every individual case, a complete history has to be carefully taken, particularly with respect to other allergen sources (aftershave, deodorant, etc.). Sometimes, however, this investigation will detect occupational causation of fragrance allergy induced by wb-MWF (26).

Morpholinyl mercaptobenzothiazole (MOR)

MOR has been used previously as a rust preventive in MWF. However, it is uncertain whether the sensitizations to MOR that we found in our patients were acquired by a corresponding exposure. Usually, rubber gloves are a frequent allergen source for MOR (55).

Other allergens tested

All other allergens tested elicited positive patch test reactions only in exceptional cases. Hence, it is arguable that they should be omitted from the MWF test series and be tested only when such an exposure is definitely proven. Particularly, phenyl-beta-naphthylamine (PBN) and IPM are concerned. PBN is no longer used industrially due to potentially carcinogenic properties, and IPM is an extremely weak sensitizer or possibly not a sensitizer at all (56). Uter et al. (56), therefore, recommend that IPM should not be tested routinely, but tested only in case of suspected exposure as a possible source of ACD.

Conclusions

The DKG test series with current MWF allergens has acceptable diagnostic properties. In spite of their presumably low-sensitization potential, some substances, e.g. dibutyl phthalate, di-2-ethylhexyl phthalate and tricresyl phosphate, were included in the MWF series to uncover their possible roles as allergens in this context. It is arguable that they should be omitted from the series because no allergic reactions were observed. However, before making such a decision, more patients should be tested, and the extent of the current usage of these substances should be discussed with the lubricant industry. However, PAAB should definitely be omitted because the diagnostic information of a positive reaction is low, and the risk of active sensitization is apparently high. IPM seems not to be a sensitizer and can also be omitted from this test series.

The test series with former MWF allergens yields but few positive reactions. BIT is currently used again in MWF, and is therefore shifted to the current MWF series. In the course of time, it can be expected that reaction frequencies to substances which are no longer in use will decline further. Hence, in some years, it will be necessary to check the usefulness of this series again.

In general, the MWF test series have to be kept up-to-date based on exposure information from the lubricant industry and on continuous surveillance of sensitizations in the target group. For this purpose, the cooperation of dermatologists, occupational physicians, occupational safety specialists and representatives of the lubricant industry in the interdisciplinary task force on allergy diagnostics in the metal branch has proven very fruitful.

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