




ORIGINAL ARTICLE

Contact sensitization in metalworkers: Data from the information network of departments of dermatology (IVDK), 2010–2018

Steffen Schubert^{1,2} | Richard Brans^{3,4,5} | Anna Reich^{2,6} | Timo Buhl^{2,6}  |
 Christoph Skudlik^{3,4,5} | Claudia Schröder-Kraft⁷ | Michal Gina⁸ | Elke Weisshaar⁹ |
 Vera Mahler^{10,11}  | Heinrich Dickel¹² | Michael P. Schön^{2,6} | Swen M. John^{3,4,5} |
 Johannes Geier^{1,2}  | for the IVDK

¹Information Network of Departments of Dermatology (IVDK), Institute at the University Medical Center Göttingen, Göttingen, Germany

²Lower Saxony Institute of Occupational Dermatology, University Medical Center Göttingen, Göttingen, Germany

³Institute for Interdisciplinary Dermatologic Prevention and Rehabilitation (iDerm), University of Osnabrück, Osnabrück, Germany

⁴Department of Dermatology, Environmental Medicine and Health Theory, University of Osnabrück, Osnabrück, Germany

⁵Lower Saxony Institute of Occupational Dermatology, University of Osnabrück, Osnabrück, Germany

⁶Department of Dermatology, Venereology and Allergology, University Medical Center Göttingen, Göttingen, Germany

⁷Institute for Interdisciplinary Dermatological Prevention and Rehabilitation (iDerm), BG Hospital Hamburg, Hamburg, Germany

⁸Department of Occupational Dermatology, BG Hospital Falkenstein, Falkenstein, Germany

⁹Department of Occupational Dermatology, University of Heidelberg, Heidelberg, Germany

¹⁰Department of Dermatology, Allergy Unit, University Hospital Erlangen, Erlangen, Germany

¹¹Division of Allergology, Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines, Langen, Germany

¹²Department of Dermatology, Venereology and Allergology, Ruhr University Bochum, Bochum, Germany

Correspondence

Dr Steffen Schubert, IVDK - Information Network of Departments of Dermatology, Institute at the University Medical Center Göttingen, Geiststr. 3, 37073 Göttingen, Germany.

Email: sschube4@gwdg.de

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Abstract

Background: Metalworkers are exposed to a variety of contact allergens by handling tools, metals, metalworking fluids (MWFs), oils and greases, rubber materials, and so on. Most large-scale reports on contact allergy due to MWFs are more than 10-years-old, and there are only few studies on contact allergy in mechanics and other metal workers not exposed to MWFs.

Objectives: To describe a current spectrum of contact sensitization in metalworkers with occupational dermatitis (OD).

Patients and Methods: Retrospective analysis of patch test data collected by the Information Network of Departments of Dermatology (IVDK; 2010–2018), stratifying for 804 cutting metalworkers, 2197 mechanics, and 355 other metalworkers.

Results: Cutting metalworkers were most frequently sensitized to mono-ethanolamine (12.6%), colophonium/abietic acid (11.4%) and formaldehyde releasers (up to 8.5%) from the MWF series, and formaldehyde (4.6%) and iodopropynyl

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butylcarbamate (4.6%) from the baseline series. Sensitization among mechanics and other metalworkers indicates possible occupational exposure to MWFs, glues, and resins, although this may not be expected from their job titles.

Conclusions: The spectrum of MWF contact allergens remained largely unchanged during the last years. Taking a comprehensive occupational history is indispensable in order to not miss relevant allergen exposures.

KEYWORDS

colophonium, formaldehyde releaser, iodopropynyl butylcarbamate, mechanics, metalworkers, metalworking fluid, monoethanolamine, occupational dermatitis

1 | INTRODUCTION

Metalworking covers a wide range of occupations, including mechanics, machine operators, tool makers, lathe operators, assembly workers, and welders.¹⁻⁵ All these professions have some occupational exposures in common, whereas other exposures concern only specific occupational activities. Common exposures are metals, tools, oils or greases, cleaners and degreasing agents, plastic or rubber handles, or protective gloves. By contrast, not every metalworker is exposed to metalworking fluids (MWFs), which contain a special spectrum of contact sensitizers.¹ Contact allergy to ingredients of MWFs has been investigated extensively in the past,⁶⁻⁹ whereas large-scale reports on occupational contact sensitization in mechanics and other metalworkers (not exposed to MWFs) are less frequent.^{2,3,10} However, apart from case reports, publications on contact allergy due to MWFs, especially larger studies or retrospective data analyses, are more than 10-years-old. Main sensitizers in MWFs have been described to be formaldehyde (FA) and formaldehyde releasers, monoethanolamine (MEA), and resin acids from distilled tall oil (DTO), a widely used basic component of water-based MWFs.¹ Mechanics without occupational exposure to MWFs who have occupational dermatitis (OD) have been reported to be sensitized to metals, preservatives, rubber components, and/or adhesives.^{2,3,10} Our aim was to give an update on contact sensitization caused by MWFs and to describe the current pattern of occupational sensitization in metalworkers. Based on Information Network of Departments of Dermatology (IVDK) data of the years 2010 to 2018, we investigated the patterns of contact sensitization in three groups of metalworkers with OD representing different occupational exposures: cutting metalworkers (metalworkers exposed to MWFs on a daily basis), mechanics (usually without MWF exposure), and other metalworkers (not exposed to MWFs).

2 | METHODS

The Information Network of Departments of Dermatology (or IVDK) is a network of 58 departments of dermatology in Germany, Switzerland, and Austria that is dedicated to clinical epidemiology of contact allergy. Its structure and routine operating procedures are described

in detail elsewhere.¹¹ Briefly, patients' histories, clinical data, and patch test (PT) results are recorded in local databases in the participating centers and, after pseudonymization, transmitted to the IVDK central office at the University Medical Center Göttingen twice a year. Data are subjected to standardized quality control, added to the central IVDK database, and analyzed according to international standards.^{12,13} Occupations (job titles) and suspected allergen sources are coded by experienced clinic dermatologists after patient interview.

All IVDK members are also members of the German Contact Dermatitis Research Group (DKG). Patch testing and evaluation of reactions are performed according to DKG guidelines.^{14,15} For the present data analysis, patch test reactions at day 3 (D3) were considered. In a few exceptional cases, when a PT reading was performed at D4 instead of D3, this reading was selected. Readings coded as +, ++, or +++, that is, positive reactions with erythema, infiltration, and possibly papules and/or (coalescing) vesicles were rated as positive. Patch test preparations were purchased from Almirall Hermal, Reinbek, Germany (until 2013), SmartPractice Europe, Greven, Germany (from 2014 on), and Chemotechnique Diagnostics, Vellinge, Sweden. Patch test exposure time was 1 day in 38.8% and 2 days in 61.2% of the patients. Finn-Chambers (8 mm inner diameter) on Scanpor tape or Hayes Test chambers were used.

Statistical significance ($P < .05$) of differences in proportions of anamnestic items or reaction frequencies in disjunct groups of patients was established on the basis of non-overlapping 95% confidence intervals (CIs). Data were managed and analyzed using the statistical analysis software SAS, version 9.4 (SAS Institute, Cary, North Carolina).

From January 2010 to December 2018, a total of 107 288 patients were patch tested in the departments of dermatology which are members of the IVDK. Of these, 17 952 (16.7%) had OD. Metalworkers ($n = 3356$) accounted for 18.7% of the OD patients and were subdivided into three subgroups, according to the criteria mentioned above: (a) 804 cutting metalworkers, that is, lathe operators, drillers, and toolmakers who are exposed to MWFs on a daily basis; (b) 2197 mechanics, car mechanics, machinists, locksmiths, and so on without routine MWF exposure (group "Mechanics"); (c) the group "other metalworkers" ($n = 355$), in which we subsumed all other professionals of the metal industry who are not exposed to MWFs, for example, welders, precision mechanics, electroplaters, locksmiths, or foundry operators.

Some of the occupational allergens in the metalworking industry are ubiquitous and therefore part of the DKG baseline series. To find out if contact sensitization from these allergens was significantly increased in metalworkers with OD, we selected a matching control group from IVDK patients not working in the metal industry as follows. Of the three subgroups of metalworkers, 89.6% were male and 91.4% were 20 to 60 years of age. To avoid a bias due to different age and sex distributions in the compared patient groups, we selected males at the age of 20 to 60 years from the IVDK data base, who had never worked in the metal branch and were patch tested from 2010 to 2018, as the control group, and compared their data to the corresponding subgroups (male, 20 to 60 years of age) in the study groups. The control group comprised 20 009 patients. Of these, 4788 (23.9%) were OD patients and 7965 (39.8%) had hand dermatitis.

3 | RESULTS

3.1 | Clinical data

A description of the three subgroups studied by using the MOAHLFA (Male, Occupational dermatitis, Atopic dermatitis, Hand dermatitis, Leg dermatitis, Face dermatitis, Age) index is shown in Table 1. In

addition, suspected allergen sources, age quartiles, and final diagnoses are listed. As far as MOAHLFA items are concerned, there were some statistically significant but not very large differences between the three groups. Cutting metalworkers had the highest proportions of men, hand dermatitis, and chronic irritant contact dermatitis. Moreover, the patients in this group were slightly older than in the other ones. As expected from the subgroup definitions, MWFs were most frequently suspected as an allergen source in cutting metalworkers, and less frequently in mechanics. Surprisingly, MWFs were mentioned as a suspected allergen source in about the half of the mechanics and one third of the "other metalworkers," who, according to their job titles, were not usually exposed to MWFs.

3.2 | DKG baseline series

The DKG baselines series was patch tested in about 92% of all study group patients. Patch test results with the DKG baseline series are presented in Table 2. Cutting metalworkers were significantly more often sensitized to colophonium than both of the other groups of metalworkers (10.9% vs 5.3% [mechanics] and 3.5% [others]); furthermore, they reacted positively to iodopropynyl butylcarbamate (IPBC) significantly more often than mechanics (4.6% vs 2.0). The

TABLE 1 MOAHLFA index, age quartiles, suspected allergen sources, and final diagnoses of the three study groups

	Cutting metalworkers (N = 804)		Mechanics (N = 2197)		Other metalworkers (N = 355)	
	n	% [95%-CI]	n	% [95%-CI]	n	% [95%-CI]
Male	747	92.9 [90.9–94.6]	1966	89.5 [88.1–90.7]	294	82.8 [78.5–86.6]
Occupational dermatitis	804	100.0 ^a	2197	100.0 ^a	355	100.0 ^a
Atopic dermatitis (past or present)	221	27.5 [24.4–30.7]	621	28.3 [26.4–30.2]	93	26.2 [21.7–31.1]
Hand dermatitis	717	89.2 [86.8–91.2]	1819	82.8 [81.2–84.4]	280	78.9 [74.3–83.0]
Leg dermatitis	2	0.2 [0.0–0.9]	10	0.5 [0.2–0.8]	5	1.4 [0.5–3.3]
Face dermatitis	21	2.6 [1.6–4.0]	81	3.7 [2.9–4.6]	21	5.9 [3.7–8.9]
Age ≥40 years	542	67.4 [64.1–70.6]	1315	59.9 [57.8–61.9]	227	63.9 [58.7–68.9]
Age quartiles						
Q1 (25%)	36 years		30 years		33 years	
Q2 (median)	47 years		44 years		46 years	
Q3 (75%)	54 years		53 years		53 years	
Suspected allergen source (up to 3 could be indicated)						
Metalworking fluids	693	86.2 [83.6–88.5]	971	44.2 [42.1–46.3]	112	31.5 [26.7–36.7]
Metals	203	25.2 [22.3–28.4]	524	23.9 [22.1–25.7]	117	33.0 [28.1–38.1]
Protective gloves	197	24.5 [21.6–27.6]	579	26.4 [24.5–28.3]	99	27.9 [23.3–32.9]
Oils, greases	73	9.1 [7.2–11.3]	402	18.3 [16.7–20.0]	28	7.9 [5.3–11.2]
Final current diagnosis						
ACD	254	31.6 [28.4–34.9]	632	28.8 [26.9–30.7]	115	32.4 [27.6–37.5]
ICD	288	35.8 [32.5–39.2]	617	28.1 [26.2–30.0]	91	25.6 [21.2–30.5]
Other forms of skin disease	262	32.6 [29.4–35.9]	948	43.1 [41.1–45.3]	149	42.0 [36.8–47.3]

Note: Items with significant differences, at least between two of the patient groups, are highlighted in bold.

^aDue to group definition; CI, confidence interval; ACD, allergic contact dermatitis; ICD, chronic irritant contact dermatitis; "other forms of skin disease" subsumes atopic dermatitis, psoriasis, dyshidrotic eczema, hyperkeratotic eczema, airborne dermatitis, and so on.

TABLE 2 Patch test results with the DKG baseline series

Allergen	Conc.	Cutting metalworkers		Mechanics		Other metalworkers	
		n = 736		n = 2041		n = 325	
		n positive	% positive [95%CI]	n positive	% positive [95%CI]	n positive	% positive [95%CI]
<i>Metals</i>							
Nickel sulfate	5%	49	6.9 [5.1–9.0]	155	7.9 [6.8–9.2]	31	9.8 [6.8–13.7]
Cobalt chloride	1%	32	4.5 [3.1–6.3]	104	5.3 [4.3–6.4]	24	7.5 [4.9–11.0]
Potassium dichromate	0.5%	20	2.8 [1.7–4.3]	104	5.3 [4.3–6.3]	22	6.9 [4.4–10.3]
<i>Preservatives</i>							
MCI/MI (aq.)	0.01%	41	5.8 [4.2–7.8]	123	6.3 [5.2–7.4]	14	4.4 [2.4–7.3]
MI (aq.)	0.05%	54	7.7 [5.8–9.9]	139	7.3 [6.2–8.6]	16	5.3 [3.1–8.5]
MDBGN	0.3%	12	6.5 [3.4–11.1]	30	5.8 [4.0–8.2]	7	8.6 [3.5–17.0]
MDBGN	0.2%	18	3.4 [2.0–5.3]	56	3.8 [2.9–4.9]	6	2.5 [0.9–5.4]
Formaldehyde (aq.)	1%	33	4.6 [3.2–6.4]	50	2.5 [1.9–3.3]	6	1.9 [0.7–4.1]
Iodopropynyl butylcarbamate	0.2%	33	4.6 [3.2–6.4]	39	2.0 [1.4–2.7]	5	1.7 [0.5–3.8]
2-Bromo-2-nitro-1,3-propanediol	0.5%	9	1.4 [0.6–2.6]	13	0.7 [0.4–1.2]	0	0.0 [0.0–1.3]
Paraben mix	16%	7	1.0 [0.4–2.0]	15	0.8 [0.4–1.2]	2	0.6 [0.1–2.3]
<i>Fragrances</i>							
Fragrance mix I	8%	40	5.6 [4.0–7.6]	110	5.6 [4.6–6.7]	19	6.0 [3.7–9.3]
Fragrance mix II	14%	30	4.2 [2.8–5.9]	69	3.5 [2.7–4.4]	4	1.3 [0.3–3.2]
HICC	5%	12	1.7 [0.9–2.9]	29	1.5 [1.0–2.1]	3	0.9 [0.2–2.7]
<i>Myroxolon pereirae</i>	25%	35	4.9 [3.4–6.7]	109	5.5 [4.6–6.6]	11	3.5 [1.7–6.1]
Ylang ylang oil (<i>Cananga odorata</i>)	10%	12	1.7 [0.9–3.0]	29	1.5 [1.0–2.2]	3	1.0 [0.2–2.9]
Jasmine absolute (<i>Jasminum</i> spp.)	5%	7	1.0 [0.4–2.1]	12	0.6 [0.3–1.1]	3	1.0 [0.2–2.9]
Sandalwood oil (<i>Santalum album</i>)	10%	4	0.6 [0.2–1.5]	10	0.5 [0.3–1.0]	2	0.7 [0.1–2.4]
<i>Rubber</i>							
Thiuram mix	1%	28	3.9 [2.6–5.6]	74	3.8 [3.0–4.7]	9	2.8 [1.3–5.3]
IPPD	0.1%	8	1.1 [0.5–2.2]	42	2.1 [1.5–2.9]	2	0.6 [0.1–2.3]
MBT	2%	6	1.0 [0.4–2.1]	22	1.3 [0.8–2.0]	3	1.1 [0.2–3.2]
MBT	1%	1	0.8 [0.0–4.6]	2	0.6 [0.1–2.1]	0	0.0 [0.0–6.8]
Mercapto mix (CBS, MBTS, MOR)	1%	6	0.8 [0.3–1.8]	17	0.9 [0.5–1.4]	4	1.3 [0.3–3.2]
ZDEC	1%	3	0.4 [0.1–1.2]	15	0.8 [0.4–1.2]	0	0.0 [0.0–1.2]
<i>Plant materials</i>							
Colophonium	20%	78	10.9 [8.7–13.4]	104	5.3 [4.3–6.3]	11	3.5 [1.8–6.2]
Propolis	10%	18	2.5 [1.5–4.0]	42	2.1 [1.5–2.9]	10	3.1 [1.5–5.7]
Oil of turpentine	10%	14	2.0 [1.1–3.3]	25	1.3 [0.8–1.9]	6	1.9 [0.7–4.1]
Compositae mix	5%	0	0.0 [0.0–2.2]	7	1.5 [0.6–3.0]	3	4.3 [0.9–12.0]
Compositae mix II	5%	5	0.9 [0.3–2.1]	26	1.7 [1.1–2.5]	2	0.8 [0.1–2.9]
<i>Ointment bases</i>							
Lanolin alcohols	30%	12	1.7 [0.9–2.9]	28	1.4 [0.9–2.0]	4	1.3 [0.3–3.2]
Cetearyl alcohol	20%	2	0.3 [0.0–1.0]	5	0.3 [0.1–0.6]	1	0.3 [0.0–1.7]
<i>Resins/glues</i>							
Epoxy resin (DGEBA)	1%	9	1.3 [0.6–2.4]	70	3.6 [2.8–4.5]	14	4.4 [2.4–7.3]

Note: During the study period, some allergen preparations were withdrawn from the baselines series and others added, resulting in varying numbers of patients tested. Vehicle is petrolatum, unless water (aq.) is specified. Allergens with significant differences, in comparison to at least one of the two other groups, are highlighted in bold.

Abbreviations: CI, confidence interval; DKG, German Contact Dermatitis Research Group; CBS, *N*-cyclohexyl-2-benzothiazyl sulfenamide; DGEBA, diglycidyl ether of bisphenol A; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde; IPPD, *N*-isopropyl-*N*-phenyl-*p*-phenylenediamine; MBT, 2-mercaptobenzothiazole; MBTS, Dibenzothiazyl disulfide; MCI, methylchloroisothiazolinone; MDBGN, methyl dibromo glutaronitrile; MI, methylisothiazolinone; MOR, morpholinylmercaptobenzothiazole; ZDEC, zinc diethylthiocarbamate.

(heterogeneous) group of other metalworkers was significantly more often sensitized to potassium dichromate (6.9% vs 2.8%) and epoxy resin (4.4% vs 1.3%) compared to cutting metalworkers.

When compared to the control group of 20 009 male patients aged 20 to 60 years who had never worked in the metal industry (Table S1), there were no significantly increased frequencies of sensitization to metals, fragrances, ointment bases, and most of the rubber materials contained in the DKG baseline series among all of the subgroups of male metalworkers of the same age. Male cutting metalworkers and mechanics 20 to 60 years old were significantly more often sensitized to colophonium, methylisothiazolinone (MI), methylchloroisothiazolinone (MCI)/MI, formaldehyde, and IPBC, when compared to the control group. Mechanics had a significantly higher proportion of sensitizations to methylidibromo glutaronitrile (MDBGN) when tested with 0.2% pet. and *N*-isopropyl-*N'*-phenyl-*p*-phenylenediamine (IPPD), in comparison to the control group. Cutting metalworkers had the lowest frequency of epoxy resin sensitization compared to all other subgroups of patients (statistically significant).

3.3 | DKG metalworking fluids series

Patch test results with the DKG metalworking fluid series are shown in Table 3. Generally, the highest proportions of positive reactions were observed among cutting metalworkers. Focusing on this occupational group, MEA was the leading allergen, with 12.6% positive reactions, followed by abietic acid (8.6%) and the formaldehyde releaser *N,N'*-methylene-bis-5-methyl-oxazolidine (8.5%). Other formaldehyde releasers elicited positive reactions in 2.3–7.2%, 1,2-benzisothiazolin-3-one in 3.7%, and octylisothiazolinone in 2.1% of the cutting metalworkers. With the exception of morpholinyl mercaptobenzothiazole (0.7%), *p*-*tert*-butylphenol (0.3%), and 2-phenoxyethanol (0.3%), all other MWF components of this series were tested positive in more than 1% of these patients. In the other two groups of metalworkers, sensitization frequencies were lower, but the ranking was roughly the same. Colophonium 20% pet. and/or abietic acid 10% pet. were patch tested in 770 cutting metalworkers. Of these, 88 (11.4%) reacted positively to at least one of these test preparations, and 51 patients reacted to both.

Concomitant reactions to formaldehyde and formaldehyde releasers used in MWFs are listed in Table 4. In 657 to 677 cutting metalworkers, both formaldehyde and a releaser were patch tested. Formaldehyde elicited positive reactions in 4.6% to 4.9%, and the releasers in 2.1% to 7.7%. The closest connections were observed with benzylhemiformal; 48.8% of the patients reacting to benzylhemiformal also reacted to formaldehyde, and vice versa this proportion was 64.5%. Altogether, 645 patients were patch tested with formaldehyde and all of the formaldehyde releasers listed in Table 4. Of these, 29 (4.5%) reacted to formaldehyde. Twenty-one (72.4%) of them also reacted to at least one formaldehyde releaser, and 16 (55.2%) to more than two releasers. Of the 619 patients without positive reaction to formaldehyde, only 49 (8.0%) reacted to at least one formaldehyde releaser, and only 17 (2.8%) reacted to more than two releasers.

3.4 | Other occupationally relevant DKG series

Details of reaction frequencies to the DKG preservative series, DKG ointment base series, DKG rubber series, DKG industrial biocides series, and DKG glues and resins series are presented in the online supplement (Tables S2 through S6). Some of the allergens listed in these tables have been moved to the DKG baseline series (or to other test series) during the study period. Hence, they are listed in more than one table. Reported reaction frequencies always correspond to patients tested with the respective test series. In Table 5, we summarized reaction frequencies to those allergens of these test series that elicited positive reactions in at least 2% or the patients tested in at least one of the three study subgroups. Sensitization to epoxy resin components and (meth)acrylate occurred most frequently in “other metalworkers,” followed by “mechanics,” whereas there was no relevant difference concerning rubber ingredients.

4 | DISCUSSION

With our large-scale retrospective data analysis, we were able to describe the current spectrum of contact sensitizations in cutting metalworkers with OD. The data show that there have been no significant changes within the last 10 years. We also demonstrated differences in exposure and sensitization patterns between these patients and mechanics as well as other metalworkers with OD.

4.1 | Ubiquitous preservatives

All three subgroups have one important aspect in common: The “epidemic” of contact allergy to MI, which was caused by its increased use in cosmetics from 2009 on and peaked in 2013/2014,^{16,17} introduces a certain bias into our data. The majority of patients sensitized to MI also react to MCI/MI in patch testing.^{16,18,19} MI and MCI/MI, however, are not only used as a preservative in cosmetics, but also in water-based MWFs.¹ Hence, both types of products represent plausible allergen sources of MI and/or MCI/MI in metalworkers, as already described before.²⁰ Sensitization to MI and MCI/MI was significantly increased in cutting metalworkers and mechanics when compared to the control group of patients who had never worked in the metal industry. However, it remained unclear whether increased MI and MCI/MI sensitization in cutting metalworkers and mechanics was due to the use of skin care products or due to exposure to MWFs. Unfortunately, from our data we cannot identify individual allergen sources.

In contrast to MI, nationwide exposure to MDBGN during the study period can largely be excluded, as MDBGN has been prohibited in cosmetics since 2008. Furthermore, MDBGN is prohibited in working or cutting fluid preservatives since 2009, and in film preservatives, fiber, leather, rubber, and polymerized material preservatives, construction material preservatives, and preservatives for liquid-cooling and processing systems since 2011. According to the EU biocidal products regulation, MDBGN is (only) approved for product

TABLE 3 Patch test results with the DKG metalworking fluid series

Allergen	Conc.	Cutting metalworkers % positive [95%CI] n (tested) = 681	Mechanics % positive [95%CI] n (tested) = 1181	Other metalworkers % positive [95%CI] n (tested) = 141
<i>Formaldehyde releasers</i>				
N,N'-methylene-bis-5-methyl-oxazolidine	1%	8.5 [6.5–10.9]	5.5 [4.3–7.0]	6.5 [3.0–11.9]
4,4-Dimethyl-1,3-oxazolidine/3,4,4-trimethyl-1,3-oxazolidine (Bioban CS 1135)	1%	7.2 [5.4–9.4]	4.1 [3.0–5.4]	1.4 [0.2–5.1]
Benzylhemiformal	1%	5.9 [4.2–7.9]	3.8 [2.8–5.1]	3.6 [1.2–8.2]
7-Ethylbicyclooxazolidine (Bioban CS 1246)	1%	2.9 [1.7–4.4]	1.6 [0.9–2.4]	0.7 [0.0–3.9]
1,3,5-Tris(2-hydroxyethyl)-hexahydrotriazine	1%	2.4 [1.4–3.9]	1.7 [1.0–2.6]	0.7 [0.0–4.0]
4-(2-Nitrobutyl) morpholine/4,4'-(2-ethyl-2-nitro-trimethylene)dimorpholine (Bioban P 1487)	1%	2.3 [1.3–3.7]	1.6 [1.0–2.6]	2.9 [0.8–7.2]
<i>Isothiazolinones</i>				
1,2-Benzisothiazolin-3-one, sodium salt	0.1%	3.7 [2.4–5.5]	2.4 [1.6–3.5]	2.2 [0.4–6.2]
Octylisothiazolinone	0.025%	2.1 [1.2–3.5]	0.9 [0.4–1.6]	0.0 [0.0–2.6]
<i>Alkanolamines</i>				
Monoethanolamine (MEA)	2%	12.6 [10.2–15.4]	5.4 [4.1–6.8]	5.0 [2.0–10.1]
Diethanolamine (DEA)	2%	3.6 [2.3–5.3]	1.6 [1.0–2.6]	1.4 [0.2–5.1]
Triethanolamine (TEA)	2.5%	2.1 [1.2–3.5]	0.9 [0.4–1.6]	0.0 [0.0–2.6]
Diglycolamine [2-(2-aminoethoxy)ethanol]	1%	2.6 [1.5–4.1]	1.0 [0.5–1.7]	0.0 [0.0–2.6]
<i>Other components</i>				
Abietic acid	10%	8.6 [6.6–11.0]	3.9 [2.9–5.2]	2.9 [0.8–7.2]
Glyoxal trimer dihydrate	1%	3.4 [2.1–5.0]	1.7 [1.1–2.7]	1.4 [0.2–5.0]
Sodium-2-pyridinethiol-1-oxide (sodium omadine) (aq.)	0.1%	1.1 [0.4–2.2]	1.0 [0.5–1.8]	0.0 [0.0–2.6]
Morpholinyl mercaptobenzothiazole	0.5%	0.7 [0.2–1.7]	1.1 [0.6–1.9]	2.8 [0.8–7.1]
<i>p</i> -tert-Butylphenol	1%	0.3 [0.0–1.1]	0.2 [0.0–0.6]	0.7 [0.0–3.9]
2-Phenoxyethanol	1%	0.3 [0.0–1.1]	0.3 [0.1–0.8]	0.0 [0.0–2.6]

Note: Vehicle is petrolatum, unless water (aq.) is specified.

Abbreviations: CI, confidence interval; DKG, German Contact Dermatitis Research Group.

TABLE 4 Concomitant reactions to formaldehyde (FA) and FA releasers in cutting metalworkers

FA releaser	n tested	FA positive (1% aq)		FA releaser positive (1% pet)		FA positive; FA releaser positive		% of FA releaser pos.
		n	%	n	%	n	% of FA pos.	
N,N'-methylene-bis-5-methyl-oxazolidine	677	33	4.9	52	7.7	22	66.7	42.3
4,4-Dimethyl-1,3-oxazolidine/3,4,4-trimethyl-1,3-oxazolidine (Bioban CS 1135)	675	32	4.7	48	7.1	19	59.4	39.6
Benzylhemiformal	675	31	4.6	41	6.1	20	64.5	48.8
7-Ethylbicyclooxazolidine (Bioban CS 1246)	674	31	4.6	20	3.0	10	32.3	50.0
1,3,5-Tris(2-hydroxyethyl)-hexahydrotriazine	657	32	4.9	14	2.1	9	28.1	64.3
4-(2-Nitrobutyl) morpholine / 4,4'-(2-ethyl-2-nitro-trimethylene)dimorpholine (bioban P 1487)	668	31	4.6	14	2.1	3	9.7	21.4

Abbreviations: aq, aqua; pet, petrolatum.

preservation during storage since July 2016.²¹ Therefore, also occupational exposure to MDBGN has been very limited over the last 10 years. Positive patch test reactions to MDBGN 0.2% pet. probably represent currently irrelevant sensitization, and false-positive reactions to MDBGN 0.3% pet. have to be considered.²²

IPBC, patch tested 0.2% pet., is used as a preservative (mainly fungicide) in industrial applications, for example, wood protective agents, pulp in paper production, water-based paints, or water-based MWFs,^{9,23,24} as well as in household products, cosmetics, and body care products. In earlier studies from 2000 to 2003, we found

TABLE 5 Patch test results with allergens not included in the baseline series

Allergen	Conc.	Cutting metalworkers % positive [95%CI]	Mechanics % positive [95%CI]	Other metalworkers % positive [95%CI]
Glues and resins series		n = 118	n = 704	n = 103
<i>Epoxy resin system components</i>				
1,6-Hexanediol diglycidylether	0.25%	0.9 [0.0–4.7]	4.0 [2.7–5.8]	6.9 [2.8–13.6]
1,4-Butanediol diglycidylether	0.25%	0.9 [0.0–4.7]	3.2 [2.0–4.8]	6.9 [2.8–13.6]
Phenyl glycidylether	0.25%	2.6 [0.5–7.3]	2.3 [1.3–3.7]	1.0 [0.0–5.3]
Cresyl glycidylether	0.25%	0.9 [0.0–4.7]	1.4 [0.7–2.6]	2.0 [0.2–6.9]
<i>p</i> -tert-Butylphenyl glycidylether	0.25%	0.0 [0.0–3.8]	2.0 [1.0–3.5]	0.0 [0.0–4.2]
<i>Acrylates/methacrylates</i>				
Methyl methacrylate	2%	1.7 [0.2–6.1]	2.0 [1.1–3.4]	4.0 [1.1–10.0]
2-Hydroxyethyl methacrylate	1%	1.7 [0.2–6.1]	3.8 [2.5–5.4]	6.1 [2.3–12.7]
2-Hydroxypropyl methacrylate	2%	1.7 [0.2–6.1]	4.5 [3.1–6.3]	7.1 [2.9–14.0]
Ethylenglycol dimethacrylate	2%	1.7 [0.2–6.1]	4.2 [2.8–6.0]	6.1 [2.3–12.7]
Triethyleneglycol dimethacrylate	2%	2.6 [0.5–7.4]	2.9 [1.8–4.4]	4.0 [1.1–10.0]
BIS-GMA	2%	0.0 [0.0–3.1]	1.4 [0.7–2.6]	2.0 [0.2–6.9]
Hydroxyethyl acrylate	0.1%	0.0 [0.0–3.1]	3.2 [2.0–4.8]	4.0 [1.1–10.0]
<i>Others</i>				
4,4'-Diaminodiphenylmethane	0.5%	4.3 [1.4–9.7]	2.9 [1.8–4.4]	3.9 [1.1–9.7]
Benzoylperoxide	1%	6.0 [2.5–12.0]	3.9 [2.6–5.6]	10.9 [5.6–18.7]
Phenol formaldehyde resin (Novolak)	5%	1.7 [0.2–6.0]	1.9 [1.0–3.2]	2.0 [0.2–6.9]
Ointment base series		n = 615	n = 1704	n = 257
Amerchol L 101	50%	2.0 [1.0–3.4]	1.7 [1.2–2.5]	1.6 [0.4–4.0]
Rubber series		n = 516	n = 1423	n = 213
Tetramethylthiuram monosulfide	0.25%	1.4 [0.6–2.8]	2.7 [1.9–3.7]	1.9 [0.5–4.8]
Tetraethylthiuram disulfide	0.25%	1.8 [0.8–3.3]	2.6 [1.8–3.5]	1.9 [0.5–4.8]
Morpholinyl mercaptobenzothiazol	0.5%	1.2 [0.4–2.5]	1.1 [0.6–1.7]	2.4 [0.8–5.4]
1,3-Diphenylguanidine	1%	1.9 [0.9–3.6]	2.2 [1.5–3.1]	4.7 [2.3–8.5]

Note: Only those allergens are listed which elicited positive reactions in at least 2% or the patients tested in at least one of the 3 study groups. Additional results are presented in tables S2 to S6 in the online supplement. Vehicle is petrolatum.

Abbreviations: CI, confidence interval; DKG, German Contact Dermatitis Research Group; MDBGN, methylidibromo glutaronitrile; n, count.

sensitization to IPBC in less than 1% of the metalworkers with OD who were tested with the metalworking series.^{7,25,26} Corresponding IVDK data from 2005–2009 showed a sensitization frequency of 4%,⁸ which is close to what we found now (4.6%). Culprit sensitizers in cutting metalworkers could be MWFs or skin care products.

4.2 | Cutting metalworkers with OD—Focus on MWF components

Most frequent specific sensitizers among cutting metalworkers with OD were MEA (12.6% positive among cutting metalworkers tested with the DKG metalworking series), colophonium/abietic acid (11.4% positive, Table 3), formaldehyde releasers (up to 8.5%, Table 3), formaldehyde (4.6% among cutting metalworkers tested with the DKG baseline series), and IPBC (4.6%, Table 2). With the exception of IPBC, the same pattern, even with similar reaction frequencies, was found in

corresponding IVDK data analyses covering the years 1999–2001, 2002–2003, and 2005–2009, respectively.^{6,7,8}

In contrast to MEA, triethanolamine (TEA) is not only used in water-based MWFs, but also as an emulsifier in cosmetics, and in other industrial products.²⁷ Despite its widespread use, TEA rarely causes contact allergy.²⁷ Sensitization prevalences among MWFs exposed metalworkers with OD are even lower than sensitization to diethanolamine, which is strictly regulated in Germany since 1993, because of a potential formation of carcinogenic *N*-nitrosamines.¹

Tall oil is a by-product obtained during the production of sulfate pulp from pine wood for the paper industry. Distilled tall oil (or DTO) may contain up to 30% sensitizing resin acids.⁷ Sensitization to resin acids is diagnosed by patch testing with colophonium and/or abietic acid. Metalworkers with OD who were exposed to MWFs had a dramatically increased frequency of positive reactions to colophony and/or abietic acid, confirming their high risk of sensitization.^{6,8}

Formaldehyde releasers are used as preservatives in water-based MWFs and in system cleaners in metalworking factories. Metalworkers are exposed to the releasers as well as to formaldehyde itself and thus have an increased risk of sensitization to both. In our study, three of four cutting metalworkers who were sensitized to formaldehyde also reacted to at least one formaldehyde releaser (data not shown in detail). The closest concomitant reactivities with formaldehyde were observed with benzylhemiformal and *N,N'*-methylene-bis-5-methyl-oxazolidine (Table 4), both of them releasing high amounts of free formaldehyde compared to other formaldehyde releasers used in MWFs.^{9,28} However, these results have to be interpreted with caution, because patch test reactions to formaldehyde 1% aq. and to formaldehyde releasers are often weak and poorly reproducible.²⁹ In Germany, the use of Bioban P 1487 in MWF is prohibited since 1993 because of nitrosamine formation. Correspondingly, three of four patients sensitized to Bioban P 1487 were 50 years or older, and hence may have been sensitized before 1993. According to current information from the producer, Dow Chemical Company, the Biobans P 1487 and CS 1135 are no longer available in the European Union. Considering this, Bioban CS 1135, which has not been used in MWFs or in other industrial applications since 2015 (possibly even earlier), was deleted from the MWF PT series in 12/2019, and Bioban P 1487 should be omitted from the DKG metalworking fluid series as well as from the DKG industrial biocides series in the near future.

The use of morpholinyl mercaptobenzothiazole (MOR) as a rust preventive agent in MWFs has been stopped about 20 years ago. In the present study, the frequency of positive reactions to MOR when patch tested in the DKG MWF series was lowest among cutting metalworkers (0.7%). Mercaptobenzothiazole (MBT) derivatives are well-known rubber (glove) allergens. With MBT and the mercapto mix, the DKG baseline series reasonably contains well-established marker allergens for detecting contact allergy to MBT derivatives.

More than 30 years ago, fragrances ("odour masks") were added to water-based MWFs to hide unpleasant smells.¹ Previously (1999–2001), we could show that metalworkers exposed to water-based MWFs with OD had an increased risk of fragrance sensitization.⁶ However, in all later studies or IVDK data analyses, including the one presented here, this was no longer found.^{7,8,25,26}

4.3 | Mechanics with OD—Focus on MWF components, rubber, and epoxy resin systems

MWFs were suspected as occupational allergen source in 44% of the mechanics (Table 1), which is about half as much as in cutting metalworkers. Remarkably, frequencies of sensitization to many of the typical MWF allergens described above were also more or less exactly half as high among mechanics than among cutting metalworkers.

Beyond MWF allergens, we found an increased frequency of sensitization to IPPD in this patient group (2%, and 2.4% when tested in the DKG rubber series). This is comparable to the proportion of

positive reactions to black rubber mix (containing IPPD), which was published by the North American Contact Dermatitis Research Group (NACDG) on occupationally related contact sensitization in mechanics and repairers (1.5%, ie, 4 of 272 patients tested).³ Corresponding occupational exposures are tires, handles, hoses, belts, and other black rubber products.

Generally, there is a high prevalence of contact sensitization to rubber ingredients among mechanics. In the above-mentioned NACDG study, as well as in an Italian study, carba mix, DPG, and thiurams were among the leading occupationally related allergens.^{2,3} We have also found sensitization to rubber allergens among mechanics with OD, but on a lower level than in the NACDG study. Although percentages of positive reactions are not directly comparable because of differences in patient selection, our results as well as the data from Italy and North America underscore the importance of sensitization to rubber ingredients among mechanics with OD.

In addition, mechanics may become occupationally sensitized to epoxy resins, as already demonstrated in the above studies.^{2,3} In our study, we found 3.6% of the mechanics with OD to be sensitized to epoxy resin and a remarkable proportion of sensitizations to reactive diluents and epoxy resin hardeners. Furthermore, Table 5 shows that sensitization to methacrylates is not uncommon in these patients. Mechanics handle corresponding epoxy or methacrylate adhesives, example, also in screw locks, and coatings to varying degrees.

4.4 | Other metalworkers with OD—Focus on glues, epoxy resin systems, and metals

This subgroup consisted of 355 patients with OD working in a variety of occupations with different occupational exposures, including welders, precision mechanics, and electroplaters. Surprisingly, MWFs were noted as a suspected allergen source in about one third of these patients, although MWF exposure was not self-evident from their job titles. However, sensitization to typical MWF allergens occurred markedly less frequently among "other metalworkers" than among mechanics with OD, which supports the assumption of a certain proportion of improper designation of other lubricants or cooling fluids as "MWF."

Remarkably, we found the highest frequencies of sensitization to epoxy resin and to additional epoxy resin system components in this subgroup of OD patients. In addition, methacrylates elicited positive reactions in these patients most frequently, which points toward a relevant occupational exposure to adhesives or coatings, similar to the group of mechanics. This was also not expected from the patients' job titles.

The presence of 80 welders, who had a high prevalence of sensitization to chromate (10%), but not to nickel or cobalt, may be an explanation for increased chromium sensitization in the group of 355 "other metalworkers with OD" (data not shown in detail). According to the literature, welders have a relevant chromium exposure by welding fumes which may cause airborne allergic contact dermatitis.⁵

5 | CONCLUSIONS

From our data, we conclude that during the last 10 years, there have been largely no significant changes in the spectrum of contact sensitizations in cutting metalworkers with OD. Leading MWF allergens are MEA, resin acids (colophonium/abiatic acid), formaldehyde releasers, and formaldehyde. Two formaldehyde releasers, that is, Bioban P1487 and Bioban CS 1135, are outdated, and should no longer be patch tested in a metalworking fluid series. Mechanics and other metalworkers may be occupationally exposed to MWFs, glues, and resins, although this may not be expected from their job titles. Hence in every case of suspected OD in these patients, taking a thorough and comprehensive occupational and medical history is indispensable. Beyond this, rubber ingredients are important occupational sensitizers in mechanics and other metalworkers.

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Steffen Schubert: Data curation; formal analysis; software; writing-original draft. **Richard Brans:** Conceptualization; funding acquisition; investigation; project administration; resources; writing-review and editing. **Anna Reich:** Conceptualization; investigation; resources; writing-review and editing. **Timo Buhl:** Investigation; resources; writing-review and editing. **Christoph Skudlik:** Conceptualization; funding acquisition; investigation; project administration; resources; writing-review and editing. **Claudia Schröder-Kraft:** Investigation; resources; writing-review and editing. **Michal Gina:** Investigation; resources; writing-review and editing. **Elke Weisshaar:** Investigation; resources; writing-review and editing. **Vera Mahler:** Investigation; resources; writing-review and editing. **Heinrich Dickel:** Investigation; resources; writing-review and editing. **Michael Schön:** Conceptualization; funding acquisition; project administration; resources; writing-review and editing. **Swen Malte John:** Conceptualization; funding acquisition; investigation; project administration; resources; writing-review and editing. **Johannes Geier:** Conceptualization; formal analysis; funding acquisition; project administration; software; writing-original draft.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

ORCID

Timo Buhl  <https://orcid.org/0000-0002-3139-129X>

Vera Mahler  <https://orcid.org/0000-0001-6471-1811>

Johannes Geier  <https://orcid.org/0000-0002-5047-8948>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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