

Assessment of occupational exposure and spectrum of contact sensitization in metalworkers with occupational dermatitis: Results of a cohort study within the OCCUDERM project

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Conflict of Interest

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Abstract

Background

Metalworkers occupationally exposed to metals, tools, metalworking fluids (MWFs), technical oils, gloves, skin care products etc. frequently suffer from occupational dermatitis (OD).

Objectives

To investigate occupational exposure and to identify relevant occupational sensitizers in metalworkers with OD, and to evaluate suitability of current German patch test recommendations for this occupational group.

Patients and Methods

As part of the OCCUDERM project, occupational exposure of 230 metalworkers with suspected OD patch tested in the departments of dermatology in Göttingen and Osnabrück (both Lower Saxony, Germany) in 2012-2017 was recorded by questionnaire. This data, as well as results of patch testing with standardized allergens and with workplace material were analyzed.

Results

MWFs and skin care products were the most important exposures. Among MWF allergens, most frequently sensitizations to formaldehyde and formaldehyde releasers, colophony/abietic acid, and monoethanolamine were observed. Sensitization to methylisothiazolinone (MI) was frequent, probably as part of the general European epidemic of contact allergy to MI in leave-on cosmetics. Sensitization to glove ingredients only played a minor role.

Conclusions

The known occupational allergen spectrum could largely be confirmed. In order not to miss relevant sensitizations, patch testing with material from the patients' workplaces in parallel to baseline and MWF series is recommended. Sensitizations diagnosed could not always be linked to particular occupational exposures.

Introduction

Occupational exposure of metalworkers, i.e. metals, tools, metalworking fluids (MWFs), greases, technical oils and liquids, but also protective gloves, skin cleansing and skin care products comprise a variety of potential allergen sources¹⁻⁵. Some of the allergens may occur in more than one occupationally handled product, for instance preservatives and emulsifiers⁶. Most of the recent German studies or data analyses in the field of occupational contact allergy focus on allergens and frequencies of sensitization due to particular exposures, for instance MWFs or protective gloves, or in particular professional groups in general^{3, 7-9}. However, data correlating individual occupational exposures with individual sensitizations are scarce in these studies.

OCCUDERM, a research project covering experimental, clinical and educative aspects of occupational skin diseases, is run by the Lower-Saxonian Institute of Occupational Dermatology (Niedersächsisches Institut für Berufsdermatologie; NIB). NIB is a cooperative institute of the Institute for Interdisciplinary Dermatological Prevention and Rehabilitation (iDerm), the Department of Dermatology, Environmental Medicine and Health Theory of the University of Osnabrück (both Osnabrück, Germany), the Department of Dermatology, Venereology and Allergology of University Medical Center Göttingen (UMG), and the Information Network of Departments of Dermatology (IVDK) (both Göttingen, Germany). As part of the OCCUDERM project, a special questionnaire for metalworkers with suspected occupational dermatitis (OD) was created, focusing on materials handled at the workplaces, their ingredients, and personal protective equipment, in order to record occupational exposure and to identify potential allergen sources. By recording exposure and clinical data as well as patch test (PT) results, an attempt was made to establish a correlation between exposure and sensitization, and to check if current patch test recommendations for metalworkers with OD are still valid.

Patients and Methods

In all, data of 230 individuals with suspected occupational dermatitis (OD) and intense occupational exposure to metals, metalworking fluids, or metal tools, who were patch-tested either at the iDerm or the UMG between 2012 and 2017, were included in the study. A list of their occupations can be found in the online supplement (Table S1). For practical reasons, these patients are summed up as “metalworkers” in the following, although their professions are diverse, to some extent. Both Dermatology centres are located in Lower Saxony, Germany, and part of the IVDK which is a network of departments of dermatology in Germany, Switzerland, and Austria dedicated to the epidemiology of contact allergy. Its structure and routine operating procedures are described in detail elsewhere¹⁰.

After written informed consent, routine IVDK data was collected for these patients, including patients’ histories, clinical data, and patch test results. IVDK data are routinely recorded in local databases and, after pseudonymization, transmitted to the central office of the IVDK at the University of Göttingen twice a year. Data are subjected to standardized quality control, added to the central IVDK database, and analyzed according to international standards^{11, 12}.

In addition to the IVDK routine anamnesis, the above-mentioned questionnaire (Fig. S1, online supplement) was used by physicians to assess occupational exposures in metalworkers who were consecutively patch tested in Osnabrück (217 patients) or Göttingen (13 patients) in more detail. Patients patch tested in Osnabrück took part in a tertiary individual prevention programme (TIP) for patients with severe skin diseases suspected to be of occupational origin. It focused on occupational exposure to metals, MWFs, technical oils and lubricants, gloves, cleaning agents, solvents, degreasing agents as well as skin care, skin protection and skin cleansing products. Patch testing and evaluation of reactions was performed according to guidelines of the German Contact Dermatitis Research Group (DKG)¹³. For this data analysis PT reactions at day 3 (D3) were considered. Readings coded as +, ++ or +++, i.e. reactions with erythema, infiltration, papules and/or (coalescing) vesicles, were rated as positive. Generally, PT preparations were purchased from Almirall Hermal, Reinbek, Germany, (until 2013), and SmartPractice Europe, Reinbek, Germany (since 2014). Few PT preparations were purchased from Chemotechnique Diagnostics, Vellinge, Sweden. PT exposure time was 24 h in 94.3%, and 48 h in 5.7% of the cases. (The DKG

patch test guideline which was valid during the study period allowed both, 24 and 48 hours exposure time.) Hayes test chambers™ (HAL Allergie GmbH, Düsseldorf, Germany) were used in 77.4% of the patients, while in the remaining either Allergeaze™ clear PT chambers (17.0%) or Finn-Chambers-on-Scanpor™ (5.7%) were used (both SmartPractice Europe, Reinbek, Germany). Patch testing patients' material from workplaces was carried out according to international standards and DKG guidelines^{14, 15}. A brief overview of used test concentrations is given in table 3. When testing protective gloves, moistured 2 x 2 cm pieces of unused glove material (cuff, inside, and outside) was tested under occlusion (Fixomull® stretches for adhesion). When comparing proportions of anamnestic items in disjunct subgroups of patients, statistical significance ($p < 0.05$) was calculated using the Chi²-test. Data was managed and analyzed using the statistical analysis software SAS®, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Clinical data and occupational exposure

A description of the study population, i.e., 230 metalworkers with suspected OD, by the MOAHLFA index is given in Table 1. As expected, the population was dominated by men (96.5%) with hand dermatitis (90.9%). In 188 patients (81.7%) OD was confirmed after completion of the diagnostic procedure. Most common indications for patch testing were: exclusion of allergic contact dermatitis (ACD) (n = 91; 39.6%), suspected OD (n = 66; 28.7%), suspected ACD (n = 43; 18.7%) and expert opinions concerning OD (n = 28; 12.2%). Most frequent final diagnosis was chronic irritant contact dermatitis (ICD) in 91 patients (39.6%), followed by atopic dermatitis (AD) including atopic hand dermatitis (n = 54; 23.5%), ACD (n = 34; 14.8%) and hyperkeratotic hand eczema (n = 20; 8.7%).

About three quarters of the patients worked as mechanics, machinery workers and toolmakers (36.1%), metalworkers (cutting) (27.8%), or machine operators and fitters (11.3%) (Table S1). Main occupational activities were setting up machines, turning, blowing off workpieces with compressed air, milling, drilling, and grinding (Table 2). Major co-factors important for the pathogenesis of symptoms were documented in 196 patients. These were occlusion by gloves (n = 88; 44.9%), wet work (n = 41; 20.9%), and chemical (n = 30; 15.3%) as well as mechanical irritation (n = 19; 9.7%) (1 category could be chosen by physicians). Mean duration of wet work was 4.8 ± 2.3 hours per day.

127 of 230 patients specified their occupational exposure to metals. The vast majority was exposed to iron (n = 106), followed by aluminium (n = 81), nickel (n = 71), chromium (n = 67), cobalt (n = 59), copper (n = 55) and other metals (n = 46). Table 3 displays frequency of exposure to other occupationally used products.

Half of the patients (n = 115; 50%) reported use of protective gloves at work. Of all individual contact agents mentioned, 45% were always handled with gloves, and another 45% most of the time. In the remaining 10%, gloves were never used. Most types of gloves used were cotton or fabric gloves with nitrile coating (47 patients), nitrile rubber gloves (47 patients), leather gloves (25 patients) and polyamide fabric gloves with polyurethane coating (20 patients).

Patch test results

Concerning evaluation of PT results, our objective was to describe the current spectrum of contact sensitization in metalworkers with OD. Therefore, we did not consider the whole study group of 230 patients for analyzing reactions to standardized test series, but focused on patients with confirmed OD (n = 188). In addition, patients without hand dermatitis (n = 14) were excluded because the OCCUDERM questionnaire focused on manual exposures and occupational glove usage. For better comparison to published data, most of which are collected from men only, we further excluded women (n = 6) from this particular data analysis. Hence, 168 male metalworkers with (confirmed) occupational hand dermatitis (OHD) remained. Three DKG test series (baseline series, ointment bases, preservatives in topical preparations) were each tested in about 90% of these patients. Substances of these test series eliciting positive reactions are displayed in Table 4. In 103 patients, the DKG MWF series was tested. Complete test results with this series are presented in Table 5. Of 94 patients simultaneously tested with formaldehyde and five formaldehyde releasers currently in use, nine patients reacted to at least one of these formaldehyde releasers, and four of them also reacted to formaldehyde. One patient reacted to formaldehyde, but not to any of these formaldehyde releasers. Two out of four patients with a positive reaction to Bioban P 1487, which is no longer in use in wb MWF, reacted to formaldehyde, too. Concomitant reactions to colophony and abietic acid occurred in 6 of 89 patients tested with both substances. Hence the total number of patients reacting to colophony and/or abietic acid was 8 among 168 male metalworkers with confirmed OHD.

Beside occupational exposure data, Table 3 gives an overview of patch tested material from the patients' work places and PT results. Most frequently, protective gloves (in 101 of 115 patients) and wb MWF (in 75 of 138 patients) were patch tested. Positive reactions were documented in 11 male metalworkers with OHD tested with wb MWF and in four male OHD patients tested with gloves, respectively. Other technical lubricants, namely neat oil, other technical oils and greases and hydraulic oils, were tested in 14, 24 and two male OHD patients, respectively. Positive reactions were documented in two patients. One patient reacted to an engine oil (tested as is) as well as Methylchloroisothiazolinone (MCI)/MI (+) and MI (++). The other patient simultaneously reacted to a rolling oil (50% aq, ++), wb MWF (50% aq, ++), anticorrosive agents (50% aq, +), 2

types of gloves (palm and cuff tested as is, both ++), and a skin cleansing soap with abrasive bodies (0.5% aq, ++, see above). He had no positive reaction to a standard PT preparation although all relevant DKG test series were tested.

Table S2 summarizes test results with fresh or used wb MWF tested at different concentrations in 58 male metalworkers with OHD. Eleven patients showed positive reactions. A 100% concentration of fresh or used wb MWFs corresponds to 4-8% of the MWF concentrate diluted in water. Patch testing with unused (fresh) wb MWF from the patient's workplace at use concentration or with the MWF concentrate at 5% in water elicited more positive reactions than 25-50% aqueous dilutions of the wb MWF at workplace concentration. With the latter, proportions of doubtful and irritant reactions were higher, in relation to the positive reactions. With used wb MWF, patch testing at workplace concentration yielded the highest proportion of positive, but also of doubtful reactions.

Positive PT reactions to standardized preparations in patients reacting to material from their workplaces are listed in Table 6. Of those 11 patients reacting to wb MWF from their workplaces, 6 also reacted to standardized PT preparations, mostly to formaldehyde and formaldehyde releasers or other preservatives. However, 17 patients had not been patch tested with all relevant allergens, in most cases due to recent external patch testing (of which we have no outcome information). In 41 of the 58 patients who were patch tested with wb MWF from their workplaces, the DKG baseline series and MWF series were tested completely. Of these, 7 had a positive reaction to their MWFs, and in 5 of these 7 patients, sensitization to typical MWF allergens could be proven (see Table S3).

Only 4 of 79 patients who were tested with gloves as is from their workplaces, had a positive reaction. In order to correlate PT results with patients' gloves and results obtained with standard PT preparations, we contacted glove suppliers for information about the content of dithiocarbamates (DTC), thiurams, mercaptobenzothiazole (MBT) and its derivatives, thioureas and other sensitizing chemicals. We were able to obtain ingredient information of 82 of the 145 different types of tested gloves. In 22 patients, at least one glove surely containing either thiurams, DTC or MBT(-derivates) was tested, without any positive reaction. Four patients reacted positively to at least one glove (one patient to two gloves), none of them reacted to

rubber chemicals in the DKG series. Unfortunately, we could not get any reliable ingredient information in four of the five positively tested glove types, and the fifth one did not contain thiurams, DTC or MBT(-derivates). None of the four patients tested with 1,3-Diphenylguanidin (DPG)- containing gloves reacted positively. In three cases, positive reactions were only obtained by testing cuff material or material from the outside of the gloves. One of 125 patients reacted positively to tetramethylthiuram monosulfide (TMTM) without a positive reaction to the gloves used (two types containing DTC).

One patient reacted to both, skin care and skin protection preparations and had a concomitant PT reaction to MCI/MI and MI, which was contained in both types of preparations provided by the same company.

Discussion

Like in other studies on patients with OD^{16, 17}, ICD was more frequent than ACD in our study group. We cannot fully exclude that patch test application time of 24h only, which was used in most of the cases, may have slightly hampered diagnosis of contact sensitization. Additionally, AD played a role in about half of the patients (Table 1). In contrast to other studies on metalworkers with OD¹⁸ and in accordance with the recommendation to implement personal protective measures^{17, 19}, we found a remarkable high percentage of patients using skin care and skin protection products. This is likely due to the fact that our study group consisted mainly of severely affected patients whose usually long-standing disease had already been notified to the statutory accident insurance and which had already received support and teaching regarding use of personal protective equipment before inclusion in the study.

Most patients were exposed to a variety of occupationally used products, including topically applied dermatological preparations, skin cleansing products, w/ MWF, diverse technical lubricants and gloves.

During the study period (2012-2017) the epidemic of contact sensitization to MI due to its increased use in cosmetics reached its peak in 2013/2014^{20, 21}. As our patients frequently used skin protection and skin care products, they probably had a rather frequent and intense contact with MI, partly on pre-damaged skin. Hence, it is no surprise that MI was the leading allergen in the study group. Therefore, although it was the most frequent sensitizer in the study, MI cannot be identified as a new typical metalworker allergen, particularly as MI (without MCI) is not used for MWF preservation (personal communication with manufacturers). Now that MI sensitization in general is on the decline, future development has to be monitored in order to confirm or reject our assumption that metalworkers have no special risk of MI sensitization.

Frequency of sensitization to baseline series allergens in the study group did not differ significantly from those in the general patch test patient population²⁰ or, especially concerning colophony and formaldehyde, from sensitization rates in earlier studies on contact allergy in metalworkers^{3, 22}. However, considering the small overall sample size of our study group, only dramatic changes in sensitization frequencies would become significant, which means that minor

changes may have gone unidentified. Nevertheless, sensitization to ubiquitous allergens may be occupationally acquired. In our study group, occupational relevance of sensitization to metals was expounded by self-reported exposures to the respective metals in three patients reacting positive to nickel sulfate, in two patients reacting positive to potassium chromate, and in one patient reacting positive to cobalt chloride. In contrast, positive reactions to FM I in our study group (n = 7) lack occupational relevance because fragrances are not used in wb MWFs since 15 years^{3, 17, 23}. In addition, a considerable amount of positive reactions to FM I are false positive²⁴. Just about 50% of patients reacting positive to FM I (and negative to sorbitan sesquioleate), showed a positive PT reaction to breakdown testing of FM I components.

Reaction frequencies to allergens from the DKG metalworking fluid series (Table 5) were largely unchanged when compared to earlier study results^{3, 17}. However, as mentioned above, it has to be considered that the presented cohort of 103 metalworkers with OHD was very small and that significant changes can only be seen in larger study populations. In accordance with previous data, the most frequent MWF allergens were formaldehyde and formaldehyde releasers, monoethanolamine and abietic acid. Concomitant reactions to formaldehyde and formaldehyde releasers frequently occurred, probably indicating formaldehyde sensitization in most of the cases. However, sensitization to a formaldehyde releaser as a whole molecule is also possible²⁵. MEA is being used in wb MWF as an emulsifier with rust preventing properties and is well-known as one of the most frequent sensitizers in this occupational field. The cause of frequent sensitizations to abietic acid and/or colophony among metalworkers with OHD is the usage of distilled tall oil (DTO) as a basic material in wb MWF. DTO contains resin acids like abietic acid, and oxidation products of these acids, which are formed in the MWF during usage, are the main allergens in abietic acid and colophony^{9, 17}. Corresponding correlations were also found in those of our patients who were patch tested with MWF from their workplaces. In line with former IVDK data^{3, 17}, most of the reactions to colophony and abietic acid occurred in combination (in 6 of 8 patients). In a recent Finnish study on occupational colophony sensitization⁹, this correlation was not as close. This may be due to differing allergen sources. In the Finnish study, a large proportion of corresponding sensitizations were due to wood exposure, while in our study, exclusively DTO from MWF was the allergen source. Hence, it may be that in the Finnish study, at least partly, other colophony compounds than only abietic acid were the responsible sensitizers.

In those patients (n = 2) reacting positively to their wb MWF, but not to any standardized MWF allergens, other allergens have to be considered, because not all potential allergens in MWF are tested, e.g. 2-amino-2-methyl-1-propanol²⁶, coconut diethanolamide²⁷, and others²⁸. Hence, it is important to have valid information about the patients' MWF, at least a safety data sheet, and to do individual PTs with the suspected MWF and/or its components. Additionally, when patch testing used MWF from the patient's workplace, additives added to the MWF in the course of time during usage have to be considered. However, information on these additives are often difficult to obtain. Missing positive reactions to wb MWF in patients reacting to relevant standard PT preparations (which occurred in 7 of our patients) may be explained by too high dilution of the responsible allergens in the individual MWF test preparation. In addition, the inflamed and pre-damaged skin in OHD may lower the elicitation threshold for development of ACD at the workplace, while no positive PT reaction occurs when testing the MWF of the patient's workplace on the intact skin of the back¹⁷.

The majority of patients was patch tested with their protective gloves from the workplace (as is). Only five positive reactions in four patients were seen in our study. Three of the five gloves were tested positive only by testing cuff material or additionally material from the outside of the gloves. Leather gloves (including gloves with leather parts) were tested in 15 patients and did not evoke any positive reaction. In about half of the rubber gloves tested, the suppliers gave information on the containing potential allergenic vulcanizing agents. In the vast majority of the patients, negative reactions to rubber gloves correlated with negative test outcome of the rubber series. However, no correlation of PT reactions to rubber gloves with the corresponding rubber allergen in the standard PT preparations was seen. Vice versa, in three of five patients reacting positive to thiuram mix, their own gloves (of which 2 contained DTC) were tested, and all reacted negatively. However, as has been shown by Bergendorff et al., chemicals leaking from rubber gloves are not always the same as those which were used when manufacturing the glove, due to chemical reactions²⁹. Furthermore, changes in the rubber vulcanization process were introduced by some companies during the study period. Positive PT reactions to cuff material or the outside of gloves only, but not to other parts of the same gloves, are difficult to explain. Only new, unused gloves were tested, and hence the possibility that these reactions were directed to (non-visible) contaminants from the workplace can largely be excluded. Many metalworkers do not

wear protective gloves over their full work shift. When operating automated closed machines, wearing of gloves is not necessary during the whole process. Others are not allowed to use gloves due to handling of rotating machines (e.g. in turning, grinding etc.). Therefore, extent of glove occlusion and hence risk of sensitization is probably lower than in other wet work professions (e.g. cleaning personnel) or healthcare workers¹⁷. Furthermore, metalworkers mainly use partly coated protective gloves, which probably release lower amounts of sensitizers to the skin.

Ingredient information of skin care and protection products is easily available, due to the obligatory INCI declaration, facilitating correlation of patch test results with standardized preparations of cosmetic ingredients and patients' products. We only found six allergic reactions to such products in five OHD patients. Two of these patients also reacted to MCI/MI, and MI which were present in the products used. Six positive reactions to Amerchol L 101 and cocamidopropyl betaine (Table 4)^{30, 31}, could not be traced back to culprit products, which might be skin care or protection products as well as MWF.

Conclusions

- 1) Beside gloves and various technical oils, especially with MWFs as well as skin care and skin protection products represent potential allergen sources in metal workers with OHD.
- 2) Patch testing with material from the patient's workplace is important in metalworkers with OD, because not all potential allergens are commercially available as PT preparations.
- 3) In case of a positive reaction to workplace material, attempts should be made to identify the ingredients and eventually the culprit allergen. However, this is a time-consuming procedure requiring patience and special knowledge, and not every case can be solved in an acceptable time frame or due to missing information.
- 4) Rubber glove allergy obviously is not an important issue among metalworkers. A reason might be that metalworkers – in contrast to other employees, for instance nurses or cleaning personnel - usually do not wear fully coated occlusive gloves continuously for a long time which may limit exposure to glove allergens.

5) Contaminations of the workplace may be responsible for some PT reactions to gloves or other personal protective equipment.

6) Concerning our secondary aim, i.e. the re-evaluation of the MWF PT allergens, the sample size was too small to make significant statements. Therefore, we will do a second analysis of PT data of a larger sample of metalworkers exposed to MWF as part of the OCCUDERM project.

References

1. de Boer EM, van Ketel WG, Bruynzeel DP. Dermatoses in metal workers. (II). Allergic contact dermatitis. *Contact Dermatitis*. 1989;20(4):280-6.
2. Donovan JC, Kudla I, Holness DL. Hand dermatitis in auto mechanics and machinists. *Dermatitis*. 2007;18(3):143-9.
3. Geier J, Lessmann H, Skudlik C, Weisshaar E, Schnuch A. Kontaktallergie gegen Bestandteile von Kühlschmierstoffen. *Dermatologie in Beruf und Umwelt*. 2013;61(4):137-49.
4. Kanerva L, Jolanki R, Estlander T, Alanko K, Savela A. Incidence rates of occupational allergic contact dermatitis caused by metals. *Am J Contact Dermat*. 2000;11(3):155-60.
5. Gruvberger B, Isaksson M, Frick M, Ponten A, Bruze M. Occupational dermatoses in a metalworking plant. *Contact Dermatitis*. 2003;48(2):80-6.
6. Geier J, Lessmann H, Schumacher T, Eckert C, Bercker D, Boveleth W, et al. Vorschlag für die Epikutantestung bei Verdacht auf Kontaktallergie durch Kühlschmierstoffe. *Dermatologie in Beruf und Umwelt*. 2000;48(6):232-6.
7. Claßen A, Brans R, Geier J. Kontaktsensibilisierungen bei Kfz- Mechanikern mit Berufsdermatose. *Dermatologie in Beruf und Umwelt*. 2014;62(4):141-52.
8. Larese Filon F, Delneri A, Rui F, Bovenzi M, Mauro M. Contact Dermatitis in Northeast Italy Mechanics (1996-2016). *Dermatitis*. 2019;30(2):150-4.
9. Pesonen M, Suuronen K, Suomela S, Aalto-Korte K. Occupational allergic contact dermatitis caused by colophonium. *Contact Dermatitis*. 2019;80(1):9-17.
10. Schnuch A, Geier J, Lessmann H, Arnold R, Uter W. Surveillance of contact allergies: methods and results of the Information Network of Departments of Dermatology (IVDK). *Allergy*. 2012;67(7):847-57.
11. Uter W, Mackiewicz M, Schnuch A, Geier J. Interne Qualitätssicherung von Epikutantest-Daten des multizentrischen Projektes „Informationsverbund Dermatologischer Kliniken“ (IVDK). *Dermatologie in Beruf und Umwelt*. 2005;53:107-14.
12. Uter W, Schnuch A, Gefeller O, Allergies EwgESSoC. Guidelines for the descriptive presentation and statistical analysis of contact allergy data. *Contact Dermatitis*. 2004;51(2):47-56.
13. Schnuch A, Aberer W, Agathos M, Becker D, Brasch J, Elsner P, et al. Durchführung des Epikutantests mit Kontaktallergenen. Leitlinien der Deutschen Dermatologischen Gesellschaft (DDG) und der Deutschen Gesellschaft für Allergie und klinische Immunologie (DGAKI). *Journal der Deutschen Dermatologischen Gesellschaft*. 2008;6(9):770-5.

14. (DKG) DKG. Arbeitsanweisung_Epikutantestung_pateigenes_Material 2019 [2019-10-24]. Available from: http://dkg.ivdk.org/dok/Arbeitsanweisung_Epikutantestung_pateigenes_Material_2019-02-20.pdf.
15. Frosch PJ, Geier J, Uter W, Goossens A. Patch testing with the Patient's Own Products. In: Johansen JD, Frosch PJ, Lepoittevin J-P. Contact Dermatitis. 5. Berlin Heidelberg: Springer; 2011. p. 1107-19.
16. Sasseville D. Occupational contact dermatitis. *Allergy Asthma Clin Immunol*. 2008;4(2):59-65.
17. Geier J, Lessmann H, Schmidt A, Englitz H-G, Schnuch A. Kontaktekzeme durch Kühlschmierstoffe in der Metallindustrie. *Akt Dermatol*. 2003;29:185-94.
18. Kütting B, Weistenhofer W, Baumeister T, Uter W, Drexler H. Current acceptance and implementation of preventive strategies for occupational hand eczema in 1355 metalworkers in Germany. *The British journal of dermatology*. 2009;161(2):390-6.
19. Berndt U, Hinnen U, Iliev D, Elsner P. Hand eczema in metalworker trainees--an analysis of risk factors. *Contact Dermatitis*. 2000;43(6):327-32.
20. Geier J, Schubert S, Lessmann H, Schnuch A, Uter W, Dickel H, et al. Die häufigsten Kontaktallergene der Jahre 2015 – 2017: Daten des Informationsverbundes Dermatologischer Kliniken *Dermatologie in Beruf und Umwelt*. 2019;67:3-11.
21. Uter W, Geier J, Bauer A, Schnuch A. Risk factors associated with methylisothiazolinone contact sensitization. *Contact Dermatitis*. 2013;69(4):231-8.
22. Geier J, Lessmann H, Schnuch A, Uter W. Contact sensitizations in metalworkers with occupational dermatitis exposed to water-based metalworking fluids: results of the research project "FaSt". *Int Arch Occup Environ Health*. 2004;77(8):543-51.
23. Geier J, Lessmann H, Frosch PJ, Pirker C, Koch P, Aschoff R, et al. Patch testing with components of water-based metalworking fluids. *Contact Dermatitis*. 2003;49(2):85-90.
24. Geier J, Uter W, Lessmann H, Schnuch A. Fragrance mix I and II: results of breakdown tests. *Flavour and Fragrance Journal*. 2015;30:264-74.
25. Brinkmeier T, Geier J, Lepoittevin JP, Frosch PJ. Patch test reactions to Biobans in metalworkers are often weak and not reproducible. *Contact Dermatitis*. 2002;47(1):27-31.
26. Geier J, Forkel S, Heetfeld A, Lessmann H, Buhl T. Contact allergy to 2-amino-2-methyl-1-propanol in a metalworking fluid. *Contact Dermatitis*. 2018.
27. Aalto-Korte K, Pesonen M, Kuuliala O, Suuronen K. Occupational allergic contact dermatitis caused by coconut fatty acids diethanolamide. *Contact Dermatitis*. 2014;70(3):169-74.

28. Geier J, Lessmann H. Metalworking fluids. In: Johansen JD, Mahler V, Lepoittevin JP, Frosch PJ. Contact Dermatitis. 6th Edition, in press: Springer Berlin Heidelberg; 2019.
29. Bergendorff O, Persson C, Ludtke A, Hansson C. Chemical changes in rubber allergens during vulcanization. *Contact Dermatitis*. 2007;57(3):152-7.
30. Uter W, Schnuch A, Geier J, IvdK. Contact sensitization to lanolin alcohols and Amerchol(R) L101 - analysis of IVDK data. *Contact Dermatitis*. 2018;78(5):367-9.
31. Schnuch A, Lessmann H, Geier J, Uter W. Is cocamidopropyl betaine a contact allergen? Analysis of network data and short review of the literature. *Contact Dermatitis*. 2011;64(4):203-11.

Table 1: MOAHLFA index of 230 metalworkers with suspected occupational dermatitis

		Count	Percent
Male	M	222	96.5
Occupational dermatitis	O	188	81.7
Atopic dermatitis (past or present)	A	111	48.3
Hand dermatitis	H	209	90.9
Leg dermatitis	L	0	0.0
Face dermatitis	F	3	1.3
Age >= 40 years	A	151	65.7

Table 2: Occupational activities of 230 metalworkers with suspected occupational dermatitis
(multiple items could be chosen by the patients)

Occupational activity	Count	Percent
Setting up machines	93	40.4
Turning	66	28.7
Blowing off work pieces with compressed air	64	27.8
Milling	55	23.9
Drilling	49	21.3
Grinding	46	20.0
Repair and Maintenance	19	8.3
(Dis-)Assembly of parts	12	5.2
Miscellaneous	11	4.8
Operating machines/robots	10	4.3
Fitting operations, welding	10	4.3
Cutting, punching, sawing	9	3.9
Sheet metal work, deflashing, pressing	7	3.0

Diverse miscellaneous activities	7	3.0
(Final) inspection, control	6	2.6
Electroplating	2	0.9
Cleaning work	2	0.9

Table 3: Usage of and patch testing with material from patients' workplaces.

	test conc. (vehicle)		Study group (n=230)		168 male metalworkers with OHD	
Product category		n	n PT	n pos PT	n PT	n pos PT
Skin protection creams	pure	188	15	5	12	4
Skin care creams	pure	186	6	2	6	2
Skin cleansing products without abrasive bodies	0.5 – 1 % (aq)	157	9	0	7	0
Wb MWF	4 – 8 % (aq)	138	75	14	58	11
Other technical lubricants	1 – 100% (oil/pet)	123	31	2	24	2
Gloves	pure	115	101	4	79	4
Skin cleansing products (scrubbing soaps)	0.5 – 1 % (aq)	95	2	1	2	1
Other occupational exposures	1 – 100% (aq/pet)	83	25	1	17	1
Cleaning products	0.1% (aq)	82	2	0	1	0
Hydraulic oil	1 % (oil)	58	2	0	2	0
Neat oil	5 – 100% (oil)	48	15	0	14	0
Degreasing agents		45	0	0	0	0
Solvents		45	0	0	0	0

Number of patients who stated occupational use of defined categories of products (n). Ranges of test concentrations and used vehicles for dilution are given (test conc./vehicle; aq = aqua, pet = petrolatum, oil = olive oil). Number of patients patch tested (n PT) with products of each category and number of patients reacting positively (n pos PT) to at least one of these patch tests in the total study group (n=230) and 168 male metalworkers with occupational hand dermatitis (OHD), respectively.

Table 4: Patch test preparations of the DKG baseline series, ointment base series and preservative series eliciting positive reactions in 168 male metalworkers with occupational hand dermatitis.

Substance	Test preparation	Count tested	Pos	+	% positive reactions [95%-CI]
DKG baseline series					
Methylisothiazolinone	0.05 % aq	155	9	4	5.8 [2.7 - 10.7]
Fragrance mix I	8 % pet	138	7	7	5.1 [2.1 - 10.2]
Colophony	20 % pet	146	7	3	4.8 [1.9 - 9.6]
Formaldehyde	1 % aq	150	7	7	4.7 [1.9 - 9.4]
Nickel(II)sulfate, 6*H ₂ O	5 % pet	144	6	5	4.2 [1.5 - 8.8]
Methylchloroisothiazolinone / Methylisothiazolinone (MCI/MI)	100 ppm aq	151	6	4	4.0 [1.5 - 8.4]
Cobalt(II)chloride, 6*H ₂ O	1 % pet	145	5	5	3.4 [1.1 - 7.9]
Potassium dichromate	0.5 % pet	148	5	3	3.4 [1.1 - 7.7]
Thiuram mix	1 % pet	145	5	4	3.4 [1.1 - 7.9]
Fragrance mix II	14 % pet	144	4	2	2.8 [0.8 - 7.0]
Balsam of Peru (Myroxolon pereirae)	25 % pet	147	4	2	2.7 [0.7 - 6.8]
Epoxy resin	1 % pet	133	3	2	2.3 [0.5 - 6.5]
Propolis	10 % pet	147	3	2	2.0 [0.4 - 5.8]
Methyldibromo glutaronitrile *	0.2 % pet	107	2	2	1.9 [0.2 - 6.6]
N-Isopropyl-N'-phenyl-p-phenylenediamine (IPPD)	0.1 % pet	147	2	1	1.4 [0.2 - 4.8]
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC)	5 % pet	147	2	1	1.4 [0.2 - 4.8]
Iodopropynylbutyl carbamate (IPBC)	0.2 % pet	152	2	2	1.3 [0.2 - 4.7]
Oil of turpentine	10 % pet	147	1	1	0.7 [0.0 - 3.7]
Bronopol	0.5 % pet	153	1	1	0.7 [0.0 - 3.6]
Mercapto mix (CBS, MBTS, MOR)	1 % pet	147	1	1	0.7 [0.0 - 3.7]
Compositae Mix II	5 % pet	151	1	1	0.7 [0.0 - 3.6]
Jasmine absolute	5 % pet	154	1	0	0.6 [0.0 - 3.6]

DKG ointment bases					
Amerchol L-101	50 % pet	157	5	5	3.2 [1.0 - 7.3]
Coconut diethanolamide	0.5 % pet	157	1	1	0.6 [0.0 - 3.5]
DKG preservatives in topical preparations					
Quaternium 15 *	2 % pet	44	1	0	2.3 [0.1 - 12.0]
Chloroacetamide	0.2 % pet	157	1	0	0.6 [0.0 - 3.5]
Imidazolidinyl Urea (Germall 115)	2 % pet	157	1	1	0.6 [0.0 - 3.5]

* low number of patients due to change of test concentration in April 2016

Pos = number of patients reacting positive, CI = confidence interval, + = number of positive reactions rated as weak

Table 5: Patch test results with the DKG metal working fluid series in 103 male metalworkers with occupational hand dermatitis

Substance	Test preparation	Count tested	Pos	?/ir	+	% pos. [95%-CI]
Methylene-bis(methyloxazolidine)	1 % pet	101	8	6	8	7.9 [3.5 - 15.0]
4,4-Dimethyloxazolidine/3,4,4-Trimethyl-1,3-oxazolidine (Bioban CS 1135)	1 % pet	101	8	9	7	7.9 [3.5 - 15.0]
Abietic acid	10 % pet	95	7	4	5	7.4 [3.0 - 14.6]
7-Ethylbicyclooxazolidine (Bioban 1246)	1 % pet	99	5	0	5	5.1 [1.7 - 11.4]
Benzyl hemiformal	1 % pet	97	4	6	4	4.1 [1.1 - 10.2]
Monoethanolamine (MEA)	2 % pet	98	4	3	3	4.1 [1.1 - 10.1]
(Nitrobutyl)morpholine/(Ethylnitro-trimethylen)dimorpholine (Bioban P 1487)	1 % pet	100	4	13	4	4.0 [1.1 - 9.9]
2-(2-Aminoethoxy)ethanol (Diglycolamine)	1 % pet	95	2	2	2	2.1 [0.3 - 7.4]
2-Phenoxyethanol	1 % pet	96	1	0	1	1.0 [0.0 - 5.7]
p-tert-Butylphenol	1 % pet	95	1	0	1	1.1 [0.0 - 5.7]
Octylisothiazolinone	0.025 % pet	99	1	2	1	1.0 [0.0 - 5.5]
Glyoxal trimer dihydrate	1 % pet	98	1	3	1	1.0 [0.0 - 5.6]
1,3,5-Tris(2-hydroxyethyl)-hexahydrotriazine	1 % pet	98	0	1	0	0.0 [0.0 - 3.7]
Diethanolamine (DEA)	2 % pet	97	0	2	0	0.0 [0.0 - 3.7]
Morpholinylmercaptobenzothiazole	0.5 % pet	98	0	0	0	0.0 [0.0 - 3.7]
1,2-Benzisothiazolin-3-one, sodium salt	0.1 % pet	98	0	2	0	0.0 [0.0 - 3.7]
Sodium-2-Pyridinethiol-1-oxide	0.1 % aq	99	0	0	0	0.0 [0.0 - 3.7]
Triethanolamine (TEA)	2.5 % pet	103	0	1	0	0.0 [0.0 - 3.5]

Pos= number of patients reacting positive, ?/ir = count of patients with questionable or irritant reactions, + = number of patients with positive reactions rated as weak; %pos = percent positives, CI = confidence interval

Table 6. Positive patch test reactions to standardized patch test preparations in male metalworkers with occupational hand dermatitis reacting positive to material from their workplaces.

Product category	n PT	n patients pos to own material	n patient pos to std. allergens	Positive reactions to standardized allergen preparations	Allergen found / declared in own material?
Wb MWF	58	11	6	formaldehyde, colophony, abietic acid, formaldehyde releasers*, quaternium 15 (n = 1); MEA (n = 1); formaldehyde releasers* (n = 1); epoxy resin, thiuram mix, Bioban CS 1135 (n = 1); 2-Phenoxyethanol, iodpropynylbutyl carbamate (n = 1), p-tert-butylphenol, Bioban CS 1135 (n = 1)	insufficient information
Gloves	79	4	1	MCI/MI, MI (n=1)	no
Skin protection creams	12	4	2	MCI/MI, MI (n=1); epoxy resin, thiuram mix, Bioban CS1135 (n = 1)	MI: n = 1
Skin care creams	6	2	1	MCI/MI, MI (n=1)	MI: n = 1
Other technical lubricants	24	2	1	MCI/MI, MI (n=1)	no
Skin cleansing (scrubbing soaps)	2	1	0		no
Other occupational exposures	17	1	0		no

* = methylene-bis(methyloxazolidine), Bioban CS 1135, Bioban CS 1246, Bioban P 1487, and benzyl hemiformal

n PT = number of patch tested patients, n = number, wb MWF = water-based metal working fluid, MEA = monoethanolamin, MCI = methylisothiazolinone, MI = methylisothiazolinone, pos = positive, std = standard

OCCUDERM Documentation Sheet		
Occupational exposure of metalworkers		
Date: Clinic: Osnabrück / Göttingen Contact person: Tel.: e-mail: Case ID (WinAlldat/IVDK): Every patient has to be documented in WinAlldat/IVDK!		Pseudonymized patient identification
Occupation and professional activities		
Job title:		
Activities: ☐ Turning ☐ Milling ☐ Drilling ☐ Grinding ☐ Setting up machines ☐ Blowing off workpieces with compressed air ☐ Other activities, please specify:		
Occupational contact materials		
Contact material	Do you wear gloves when handling this contact material?	If yes, which gloves? Please specify.
☐ water-based metalworking fluid	☐ yes, always ☐ yes, partly ☐ no	
☐ non-water-miscible metalworking fluids (neat oils)	☐ yes, always ☐ yes, partly ☐ no	
☐ hydraulic oils	☐ yes, always ☐ yes, partly ☐ no	
☐ other technical oils / greases	☐ yes, always ☐ yes, partly ☐ no	
☐ degreasing agents	☐ yes, always ☐ yes, partly ☐ no	
☐ solvents	☐ yes, always ☐ yes, partly ☐ no	
☐ cleaning agents	☐ yes, always ☐ yes, partly ☐ no	
☐ other contact material:	☐ yes, always ☐ yes, partly ☐ no	

Figure S1: Questionnaire for recording occupational exposure (page 1/2).

Composition of metals handled at work		
☐ Iron	☐ Aluminium	
☐ Nickel	☐ Copper	
☐ Cobalt	☐ Others, please specify:	
☐ Chromium	☐ unknown	
Additional occupational skin strains		
Wet work: hours per work shift		
Occupational skin protection, skin cleansing, and skin care		
Please tick, id used	Product name (manufacturer)	Application frequency per work shift
☐ Skin protection product		
☐ Skin cleansing product with abrasive bodies		
☐ Skin cleansing product without abrasive bodies		
☐ Skin care products		
Skin care at home		
Product name (manufacturer)		Application frequency per day
Additional remarks and comments:		

Figure S1: Questionnaire for recording occupational exposure (page 2/2).

Table S1: Occupational groups of 230 metalworkers with suspected OD

Occupational group	Count	Percent
Mechanics, machinery workers, toolmakers	83	36.1
Metalworker (cutting)	64	27.8
Machinery mechanics and fitters	26	11.3
Unspecified occupations with metal exposure	13	5.7
Engineers, technicians and scientists	11	4.8
Electrical and electronic equipment mechanics and fitters	10	4.3
Metal finishing-, plating- and coating-machine operators	8	3.5
Welders and flame cutters	7	3.0
Precision workers in metal and related materials	4	1.7
Metalworker (non-cutting)	2	0.9
Storekeeper, transport labourers and freight handlers	2	0.9

Table S2: Reaction profile of water-based metalworking fluids (wb MWFs) from patients' workplaces, fresh and used, in 58 male metal workers with OHD

	test concentration	n PT	?	+	++	+++	ir	pos	%pos
fresh wb MWF	75-100% *	18	3	3	0	0	1	3	16.7
	25-50% *	32	4	3	0	0	3	3	9.4
	5% of the MWF concentrate	19	4	3	1	0	2	4	21.1
used wb MWF	100%	32	4	7	3	0	1	10	31.3
	25-50%	34	1	3	2	0	1	5	14.7
	5-10%	13	1	1	0	0	0	1	7.7

All dilutions made with water. PT = patch test, pos = positive, ? = questionable, ir = irritant

* of reported use concentration (usually 4-8%)

Table S3: Coupled positive reactions between groups of allergens in 41 male metal workers with occupational hand dermatitis

Workplace wb MWF	Formaldehyde(FA) and/or FA- releasers*	Colophony and/or abietic acid	Miscellaneous preservatives **	Miscellaneous wb MWF components ***	Additional standard preparations	Patient count
-	-	-	-	-	Not considered	27
+	-	-	-	-		2
-	+	-	-	-		2
-	-	+	-	-		3
-	-	-	-	+	Jasmin absolute	2
+	+	-	-	-	Epoxy resin, Thiuram mix	2
+	-	-	-	+		1
+	-	-	+	-		1
+	+	+	-	-	Quaternium 15	1

wb MWF = water-based metal working fluid

* = comprises Formaldehyd, Methylene-bis(methyloxazolidine), Bioban 1135, Bioban 1246, 1,3,5-tris(2-hydroxyethyl)-hexahydrotriazine, and Benzyl hemiformal

** = comprises Methylothiazolinone (MI), Methylchlorisothiazolinone (MCI)/MI, Iodopropylbutylcarbamate, 2-Phenoxyethanol

*** = comprises Monoethanolamin, p-tert.-Butylphenol, Glyoxal trimer dehydrate

Formattato: Tedesco (Germania)