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ORIGINAL ARTICLE

Hand eczema and occupational contact allergies in healthcare workers with a focus on rubber additives

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Background: Hand eczema (HE) in healthcare workers (HCWs) is common. Besides wet work, healthcare work also implies exposure to contact allergens.

Objectives: To assess HE and contact allergy related to occupational exposures in HCWs.

Methods: In a cross-sectional study, 311 HCWs with HE within the preceding 12 months and a control group of 114 HCWs without HE were investigated with the baseline series and a special patch test series based on substances found in the gloves, soaps, alcoholic hand disinfectants and hand creams provided at the hospitals.

Results: Contact allergy to rubber additives was significantly more common in HCWs with HE (6%) than in HCWs without HE (1%, P = .02). The corresponding percentages for fragrances were 11% and 3%, respectively (P = .004). Occupational HE was found in 193 of 311 (62%) HCWs. Of these, 22 of 193 (11%) had occupational allergic contact dermatitis, including 17 with glove-related rubber contact allergy. Contact allergy to diphenylguanidine was as common as contact allergy to thiurams. Occupational contact allergy to rubber additives was significantly associated with sick-leave related to HE.

Conclusion: Contact allergy to rubber additives in medical gloves is the most common cause of occupational allergic contact dermatitis in HCWs. Aimed patch testing with relevant rubber additives is mandatory when HE in HCWs is investigated.

KEYWORDS

contact allergy, diphenylguanidine, hand eczema, healthcare worker, patch test, rubber additive

1 | INTRODUCTION

Hand eczema (HE) is reported in 20% of healthcare workers (HCWs),[1–5] often in terms of irritant contact dermatitis (ICD).[6] Besides a high level of exposure to wet work[5,7–9] healthcare work involves exposure to potential contact allergens.[4,10,11] Occupational exposure has changed in recent years, owing to an increased emphasis on hand hygiene procedures,[12,13] including increased exposure to disposable non-sterile nitrile gloves.[5] Glove-related rubber allergens, preservatives and fragrances are the most commonly reported contact allergens causing occupational contact dermatitis (OCD) in HCWs.[6,14,15] Thiurams are rarely found in medical gloves, whereas dithiocarbamates are common.[16,17] However, thiurams remain among the most common rubber contact allergens found in HCWs.[11,15,18,19] Thiurams have been reported to be good markers for contact allergy to dithiocarbamates,[20,21] possibly because of chemical structural similarities. Moreover, in recent years, the frequency of contact allergy to diphenylguanidine (DPG) in surgical gloves has increased,[22,23] and has probably contributed to the increase in the frequency of positive test reactions to carba mix,[24–26] as DPG is part of carba mix. However, DPG has been reported to frequently cause false-positive or irritant reactions.[21,27]

We have previously reported HE prevalence and occupational exposure to soaps, alcoholic disinfectants, gloves and hand moisturizers in a questionnaire study on >9000 nurses, assistant nurses, and physicians.[5]

The primary aims of the present study in HCWs were to:

1. Identify possible contact allergens in the study group's current occupational hand skin exposures

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2. Investigate the occurrence and causes of occupational allergic contact dermatitis (ACD)

Secondary aims were to evaluate:

1. The relevance of positive patch test reactions to DPG
2. The impact of HE on the ability to perform mandatory hygiene procedures.

2 | METHODS

2.1 | Aimed patch test series

All disposable gloves, hand disinfectants, soaps and hand moisturizers procured by the hospital purchasing departments in the Southern Health Care Region of Sweden were surveyed for potential allergens. For soaps and moisturizers, this was based on ingredient labelling. For hand disinfectants, information was supplied by the manufacturers. All rubber gloves were analysed for rubber additives with high-performance liquid chromatography, as previously described.[16,23] Inclusion of rubber additives was based on previous and present analyses at the Department of Occupational and Environmental Dermatology (DOED), Malmö, as well as on literature data.[28] Known allergens in rubber gloves, soaps, disinfectants and hand creams, including those identified in the survey, were included in the patch test series. DPG was tested at both 1% and 2% pet. Prior to the study, an evaluation of the irritating potential of DPG concentrations higher than 1% was made. According to recommendations, concentrations were increased stepwise by 50%.[29] First, 22 controls (consecutive patients with suspected ACD) were tested with DPG 1.5% pet., and then another 22 controls were tested with DPG 2.25% pet. Of the controls tested with DPG 1.5%, 1 of 22 showed faint erythema (?+) on D3, and all were negative on D7. Similarly, of the controls tested with 2.25% pet., 1 of 22 showed faint erythema (?+) on D3, and all were negative on D7. Propylene glycol was tested at 5.0% pet., and 259 participants were also tested with propylene glycol 20% aq. Test preparations were obtained from Chemotechnique Diagnostics (Vellinge, Sweden) or prepared at the DOED (for details, see Table S1).

2.2 | Study population

Respondents to a questionnaire study on HE distributed to 28 762 hospital employees in southern Sweden[5] were invited to participate. Study participants were selected by random sampling (by use of the Microsoft Excel random function) among those expressing an interest. Three groups of participants were selected: HCWs with HE, HCWs without HE, and other hospital employees with HE not using medical gloves at work. HCWs were defined as workers with patient-related work that requires adherence to hygiene procedures. The group included nurses, assistant nurses, physicians, and other professions such as physiotherapists. In all, 913 were invited to participate. The study was conducted from September 2014 until the end of January 2015 by a mobile team from the DOED visiting 11 hospitals. The employers permitted participation during working time. Patch testing was performed by biomedical scientists and assistant nurses, clinical examination and patch test readings were performed by occupational dermatologists, and logistics were the responsibility of a study coordinator.

Contact allergy was regarded as occupational if there was present or past occupational exposure. The clinical diagnoses of HE, irritant contact dermatitis (ICD) and endogenous dermatitis were made by the investigating physician on the basis of medical history and clinical findings. ACD was dependent on contact allergy to a substance to which the hands were exposed. OCD was dependent on occupational exposure and a temporal relationship between the HE and work.

2.3 | Patch testing

All participants were patch tested with the Swedish baseline series and the aimed patch test series (see above). Patch testing was performed according to ESCD guidelines, and reading was performed on day (D) 3 or D4, and on D7.[30] Patch test results were scored according to ICDRG recommendations.[31] IQ Ultra Chambers (Chemotechnique Diagnostics) with an area of 68 mm^2 were used to apply test preparations to the upper back. The dose applied was 25 mg (39 mg/cm^2) for petrolatum preparations and 20 μL (31 mL/cm^2) for liquid preparations; thus, the doses were comparable to doses recommended for Finn Chambers.[32,33] Micropipettes were used for the liquid test substances.[34] Fragrance mix I and II, as well as all liquid test preparations, were loaded into test chambers immediately before application; all other pet. test preparations were preloaded before testing and kept in a refrigerator.

2.4 | Clinical investigation

At the first visit, patch tests were applied (see below), and participants were asked to fill in a form on HE (syn.: hand dermatitis) history, present HE, and the influence of HE on hygiene procedures (soap, alcoholic disinfectant, and disposable gloves). At the second visit, this form served as the basis for the medical history documented at the consultation. On day (D) 3 or D4, the patch tests were read, clinical signs and the extent of hand skin disease were recorded in a form, and the participant's history was then discussed. On D7, information on the results of the patch tests was given, prescriptions were given when needed, and the participant received a structured summary of the investigations, including the cause(s) of the HE, and an information sheet on hand care and HE treatment. When necessary, participants were referred for supplementary investigation and/or further treatment. The study was approved by the Regional Ethical Review Board, Lund, Sweden (2013/151, 2014/339).

2.5 | Statistical analysis

As we assumed that interpretation of the relevance of the contact allergies identified would be more accurate for those with recent HE, HCWs with HE prior to, but not during, the past 12 months were not included in the analyses. Comparisons of contact allergy frequencies were made between HCWs with HE at some time within the past

TABLE 1 Background characteristics for 474 healthcare workers (HCWs)

Hand eczema at some time during the preceding 12 mo (*N* = 311)			Hand eczema previously but not during the preceding 12 mo (*N* = 49)			No history of hand eczema (*N* = 114)		
	n	%	*n*	(%)	*P*[a]	*n*	(%)	*P*[a]
Sex								
Female	270	87	44	90	.56[b]	94	82	.26[b]
Male	41	13	5	10		20	18	
Age (years)								
20-29	38	12	0	0	<.001[b]	10	9	.46[b]
30-39	88	28	5	10		28	25	
40-49	83	26	15	31		28	25	
50-59	77	25	20	41		35	31	
60-69	25	8	9	18		13	11	
Mean age (years) ± SD	43 ± 10.9		51 ± 8.4		<.001[c]	46 ± 10.4		.047[c]
AD								
No	163	52	30	61	.25[b]	89	78	<.001[b]
Yes	148	48	19	39		25	22	
Profession								
Assistant nurse	74	24	17	35	.44[b]	21	18	.70[b]
Nurse	178	57	24	49		69	61	
Physician	31	10	4	8		13	11	
Other[d]	28	9	4	8		11	10	

Abbreviations: AD, history of atopic dermatitis; SD, standard deviation.

[a] Comparison with HCWs with hand eczema in the preceding 12 months.

[b] χ^2 test, 2-sided.

[c] independent samples *t*-test.

[d] Other professions with patient-related work that requires adherence to hygiene procedures, for example, physiotherapists.

12 months and HCWs without HE by use of the 2-sided Fisher's exact test. Comparisons were made for both single allergens and for groups of allergens. On the basis of occupational hand exposure to gloves, disinfectants, soaps, and emollients, 3 groups of allergens were considered—glove-related rubber additives, fragrance mixes I and II, and preservatives/biocides. A fourth group—metals—was included for comparison. Possible associations between contact allergies and HE diagnosis, and sick leave attributable to HE, were analysed with a two-sided Fisher's exact test. Multivariate analysis was performed with adjustments for sex, age, and history of atopic dermatitis. Data on doubtful patch test reactions and on the proportion of positive patch test reactions at D7 only are based on the test results for all study participants. For the background characteristics in different groups chi2 -test was used for comparison of categorical data, and the independent samples *t*-test for comparison of the mean ages. Statistical analyses were performed with SPSS Version 24 (IBM, Armonk, New York).

3 | RESULTS

Glove materials and additives, and ingredients in hand disinfectants, soaps, and moisturizers, are shown in Table S2A/B. In 2 gloves, no known allergens were detected: 1 sterile neoprene glove and 1 non-sterile vinyl glove. Most products did not contain fragrances, but 3 products (1 soap, 1 wash cream, and 1 moisturizer) contained "perfume", with no specific fragrance substance indicated. According to the labelling, imidazolidinyl urea was present in 1 hand cream.

Of 913 invited participants, 502 (55%) were patch tested. Lack of time due to shortage of staff at the workplace was reported in many cases. In all, 474 HCWs were fully investigated, 360 of 474 (76%) with history of HE, and 114 of 474 (24%) with no history of HE. In the HE group, 311 of 360 (86%) reported having had HE at some time during the preceding 12 months, and 49 of 360 (14%) reported having had HE prior to but not during the past 12 months (not included in the comparisons between HCWs with HE in the preceding 12 months and HCWs without HE). Twenty-eight hospital employees with HE and no history of occupational exposure to medical gloves were also investigated. Owing to the small number, no further analyses regarding contact allergy frequencies were made for this group. The characteristics of HCWs are shown in Table 1.

Contact allergy frequencies are shown in Table 2. OCD was found in 193 of 311 (62%) HCWs. Of these, 22 of 193 (11%) had occupational contact allergy, 17 had contact allergy to rubber additives (14 related to exposure to surgical gloves; 3 related to exposure to nitrile examination gloves), 1 had contact allergy to myristyl alcohol, and 4 had contact allergy to formaldehyde or formaldehyde releasers. Contact allergies to any glove-related rubber additives or to fragrance mix I and/or fragrance mix II were significantly more common in HCWs with HE in the preceding 12 months than in HCWs without HE (Table 3). Participants who were allergic to any glove-related rubber additives were more often concomitantly allergic to fragrance mix

TABLE 2 Positive patch test reactions stratified on hand eczema occurrence for 425 healthcare workers

	Hand eczema									
	Within the preceding 12 mo (*N* = 311)					Never (*N* = 114)				
	Total		+	++	+++[a]	Total		+	++	+++
	n	%	*n*	*n*	*n*	*n*	%	*n*	n	n
Nickel sulfate	61	19.6	14	30	17	26	22.8	4	19	3
Fragrance mix I	25	8.0	15	7	3	1	0.9	1		
Myroxylon pereirae	21	6.8	19	1	1	5	4.4	4	1	
Cobalt chloride	16	5.1	9	4	3	2	1.8		2	
Fragrance mix II	16	5.1	13	1	2	3	2.6	2	1	
Methyldibromo glutaronitrile	9	2.9	4	1	4	3	2.6	2	1	
Methylisothiazolinone (aq.)	9	2.9	4	5		2	1.8		2	
Diphenylguanidine 1%	8	2.6	4	1	3	0				
Colophonium	8	2.6	5	1	2	1	0.9		1	
Tixocortol-21-pivalate	8	2.6	5	2	1	1	0.9	1		
Diphenylguanidine 2%	7	2.3	2	2	3					
Thiuram mix	6	1.9	4	1	1	0				
Formaldehyde (aq.)	6	1.9	3	1	2	0				
Methylchloroisothiazolinone/methylisothiazolinone (aq.)	6	1.9	3	3		0				
p-Phenylenediamine	5	1.6	2	2	1	0				
Potassium dichromate	4	1.3	3	1		0				
Caine mix II	4	1.3	2	1	1	1	0.9	1		
Tetramethylthiuram monosulfide	4	1.3	3	1		0				
Tetraethylthiuram disulfide	3	1.0	1	2		0				
Cyclohexyl thiophthalimide	3	1.0	1	1	1	1	0.9	1		
Imidazolidinyl urea	3	1.0	3			0				
Myristyl alcohol	3	1.0	3			0				
Neomycin sulfate	2	0.6	2			0				
Quaternium-15	2	0.6		2		0				
Black rubber mix	2	0.6		2		1	0.9			1
Epoxy resin	2	0.6	1	1		0				
4-*tert*-Butylphenolformaldehyde resin	2	0.6		2		0				
Lichen acid mix	2	0.6)	1		1	0				
Tetramethylthiuram disulfide	2	0.6			2	0				
Quinoline mix	1	0.3			1	1	0.9		1	
Paraben mix	1	0.3			1	0				
Phenol formaldehyde resin	1	0.3		1		0				
Amerchol L 101	1	0.3			1	0				
Dipentamethylenethiuram disulfide	1	0.3			1	0				
Dibenzothiazyl disulfide	1	0.3			1	0				
Zinc dimethyldithiocarbamate	1	0.3			1	0				
Triphenylguanidine	1	0.3			1	0				
Sodium benzoate	1	0.3			1	0				
Dimethylaminopropylamine	1	0.3			1	0				

+++, extreme positive reaction; ++, strong positive reaction; +, weak positive reaction. All allergens in pet., except where indicated otherwise.

[a] Strongest patch test reaction recorded on either day 3/4 or day 7.

l and/or fragrance mix II and to preservatives than participants without contact allergy to any glove-related rubber additives (Table 4). In contrast, positive test reactions to metals were associated neither with HE nor with concomitant allergy to glove-related rubber additives (Tables 3 and 4). Of occupational contact allergies, 9 of 22 (41%) were detected with the baseline series, whereas 13 of 22 (59%) were found only by use of the aimed patch test series. Of HCWs with thiuram allergy, 3 of 9 did not react to thiuram mix, and reacted only to 1 of the thiurams tested separately (tetramethylthiuram monosulfide in 2 cases, and dipentamethylenethiuram disulfide in 1 case). All 9 DPG-allergic HCWs had been exposed to surgical gloves containing DPG. Positive test reactions to DPG 1.0% were found in 8 of 9. The

TABLE 3 Number of healthcare workers (HCWs) with contact allergy to different groups of allergens, stratified on hand eczema occurrence for 425 HCWs

	Hand eczema				
	Within the preceding 12 months (*N* = 311)		Never (*N* = 114)		
Number of HCWs with ≥1 positive patch test reactions to:	*n*	%	*n*	%	*P*[a]
Fragrances[b]	35	11	3	3	.004
Preservatives[c]	29	9	5	4	.11
Glove-related rubber additives[d]	20	6	1	1	.02
Metals[e]	70	23	26	23	.00

Number of HCWs with ≥1 positive patch test reactions in each allergen group.

[a] Fisher's exact test, 2-sided.

[b] Fragrance mix I and fragrance mix II.

[c] Methyldibromo glutaronitrile, methylisothiazolinone, formaldehyde, methylchloroisothiazolinone/methylisothiazolinone, imidazolidinyl urea, quaternium-15, paraben mix and sodium benzoate.

[d] Diphenylguanidine, thiuram mix, tetramethylthiuram monosulfide, tetraethylthiuram disulfide, cyclohexyl thiophthalimide, tetramethylthiuram disulfide, dipentamethylenethiuram disulfide, dibenzothiazyl disulfide, zinc dimethyldithiocarbamate and triphenylguanidine.

[e] Nickel sulfate, cobalt chloride, and potassium dichromate.

participant who reacted only to DPG 2.0% had a doubtful reaction to DPG 1.0%. Among all of the patch tested participants, doubtful reactions only were noted in 13 of 502 (2.6%) to DPG 1.0%, and in 10 of 502 (2.0%) to DPG 2% (Table S3); 3 of these were exposed to DPG-containing surgical gloves. No irritant reactions were found.

In all, 348 contact allergies were found. Of these, 79 (23%) were positive only at D7 (most commonly nickel sulfate). Doubtful reactions were most commonly seen to myristyl alcohol (16%; 81/502).

In 159 (51%) of the 311 participants with HE in the preceding 12 months, >1 diagnosis was made. In total, the diagnosis of ICD was made in 277 of 311 (89%), the diagnosis of endogenous dermatitis was made in 173 of 311 (56%), and the diagnosis of ACD was made in 26 of 311 (8%), including 22 with occupational ACD. A combined diagnosis of ICD and endogenous dermatitis was made in 132 of 311 (42%), a combined diagnosis of ICD and ACD was made in 14 of 311 (5%) and a combined diagnosis of ICD, endogenous dermatitis and ACD was made in 10 of 311 (3%). In 193 of 311 (62%), HE was occupational.

Among HCWs with HE in the preceding 12 months, 8% (24/311) had been on sick-leave because of HE, either during the past year or previously. There was an association between sick-leave and ACD (adjusted odds ratio [OR] 5.1 [95% confidence interval (CI): 1.7-15.3], *P* = .004), but not between sick-leave and ICD (*P* = .53) or endogenous dermatitis (*P* = .50). An association was found between sick-leave and contact allergy to glove-related allergens (adjusted OR 5.6 [95%CI: 1.9-17.0], *P* = .002).

When HE was most active, 71% found it difficult to use alcoholic hand disinfectant, whereas the majority had no difficulty in using disposable gloves (Figure 1).

TABLE 4 Concomitant contact allergy to glove-related additives and either fragrances, preservatives or metals in 425 healthcare workers (HCWs)

HCWs with ≥1 positive patch test reactions to:		HCW with ≥1 positive patch test reactions to glove-related rubber additives[a]					Multivariate logistic regression[b]	
		No		Yes				
		n	%	*n*	%	*P*[c]	OR	95%CI
Fragrances[d]	No	373	92	14	67	.001		
	Yes	31	8	7	33		6.3	2.3-17.1
Preservatives[e]	No	377	93	14	67	.001		
	Yes	27	7	7	33		7.1	2.8-22.3
Metals[f]	No	304	92	18	91	1.0		
	Yes	25	8	9	9		0.9	0.4-2.9

Abbreviations: CI, confidence interval; OR, odds ratio. Number of HCWs with ≥1 positive patch test reactions in each allergen group.

[a] Diphenylguanidine, thiuram mix, tetramethylthiuram monosulfide, tetraethylthiuram disulfide, cyclohexyl thiophthalimide, tetramethylthiuram disulfide, dipentamethylenethiuram disulfide, dibenzothiazyl disulfide, zinc dimethyldithiocarbamate, and triphenylguanidine.

[b] Adjusted for sex, age, and history of atopic dermatitis.

[c] Fisher's exact test, 2-sided.

[d] Fragrance mix I and fragrance mix II.

[e] Methyldibromo glutaronitrile, methylisothiazolinone, formaldehyde, methylchloroisothiazolinone/methylisothiazolinone, imidazolidinyl urea, quaternium-15, paraben mix and sodium benzoate.

[f] Nickel sulfate, cobalt chloride, and potassium dichromate.

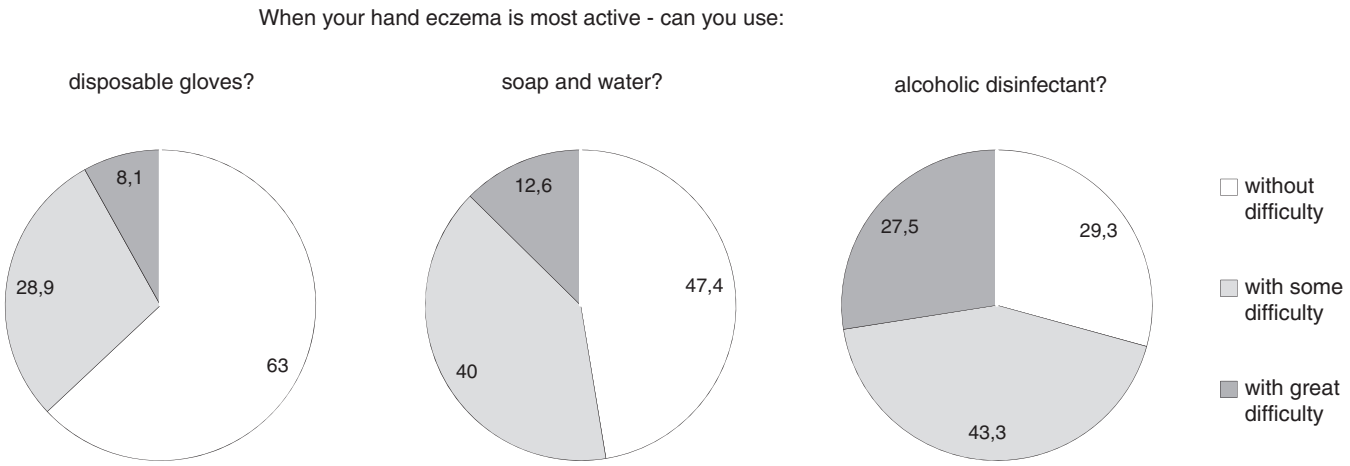

FIGURE 1 Influence of hand eczema on the ability to use disposable gloves, soap, and alcoholic skin disinfectant (percent)

4 | DISCUSSION

To the best of our knowledge, this is the first study on HCWs in which a survey of the contact allergens that are actually present in work materials has been performed. No thiurams were detected by chemical analysis, which is in line with previous reports.[16,17] However, participants sometimes also reported the occupational use of gloves, disinfectants or moisturizers other than those procured.

4.1 | Contact allergy and hand eczema

Rubber additive contact allergies were the most common occupational contact allergies found. Previous reports have indicated that the frequency of contact allergies to thiuram mix has decreased,[6,24,35] and that the frequency of contact allergy to carba mix (which includes DPG) has increased,[25,35] possibly because of the increase in the frequency of DPG contact allergy.[26] A recent Danish patch test study of HCWs participating in a randomized clinical HE trial[11] found thiuram mix contact allergy in 5%, which is higher than the prevalence of 1.9% found in our study. However, a prevalence of only 0.2% for thiuram mix was reported in the Swedish general adult population.[36] Higher frequencies (5%-12%) have been reported in retrospective studies on HCWs investigated for eczema,[11,14,15,18,19] which probably reflects different study designs, different selection of participants, and change over the years. In the present study, DPG allergy was the most common rubber contact allergy, indicating increased exposure to DPG-containing surgical gloves during the past decade. We have previously reported on 12 HCWs with occupational contact allergy to DPG in surgical gloves.[23] Two of these HCWs participated in the present study, due to continued eczema. Another 17 HCWs with contact allergy to DPG in their surgical gloves were investigated at our department in the time between the first report[23] and the present report. This indicates that glove-related contact allergies often cause substantial work problems prompting the HCWs to seek medical care. Patch testing with extracts of the suspected glove and with the glove "as is"[23] could have further increased the possibility of detecting relevant contact allergy to substances in gloves, but this was not possible to undertake in the setting of the present study.

Patch testing with DPG is considered to cause a number of irritant reactions when it is tested 1% pet.[21,27] In the present study, testing with 2% pet. did not increase the frequency of doubtful reactions as compared with DPG tested at 1%, but neither did it increase the sensitivity of the DPG testing. Possibly, the different conditions used for preparing the 2 test preparations could have influenced the result. A lower test concentration of DPG, namely 0.33% pet., is less irritant than DPG 1.0%,[21] but might reduce the detection of contact allergy. In our experience, even weak allergic reactions can be of clinical significance, as we have seen several cases with weak contact allergy to DPG in which switching to gloves free from DPG was followed by disappearance of the HE. As a consequence of the present study, only DPG-free medical gloves are now procured in the Southern Health Care Region. It has been proposed to reintroduce carba mix into the European baseline series.[24] However, in the present study, as has been reported by others, isolated dithiocarbamate reactions seem to be rare.[21] Thiurams seem to be better markers for contact allergy to both thiurams and dithiocarbamates.[20] For screening purposes, it would possibly be better to add DPG 1.0% to the baseline series.

Disinfectants intended for use in operating theatres often have a complex composition, which can occasionally lead to contact allergy. Myristyl alcohol remains a difficult test substance, with frequent doubtful reactions.[37,38] However, we found 1 case with an occupationally relevant contact allergy, which shows that testing can be valuable in selected cases. For formaldehyde, the recommended test concentration has been increased,[39] making comparison with previous studies difficult. Contact allergy to formaldehyde was reported in 1.3% to 6.7% of HCWs in recent studies,[6,11,14,15,18,19] as compared with 1.9% in the present study. Occupational exposure, determined on the basis of ingredient labelling, was found for 4 of 11 participants sensitized to formaldehyde/formaldehyde releasers. However, ingredient labelling does not always reflect the true content of a skin care product, as has been shown for formaldehyde.[40] Furthermore, it has been shown that formaldehyde concentrations not indicated on the label can be clinically relevant in contact dermatitis.[41]

Contact allergy to fragrance mix (later termed fragrance mix I) has been reported in 8% to 12% of HCWs investigated for eczema,[6,11,14,15,19] which is comparable to the 8% found in our study. Contact allergy to fragrances, and especially fragrance mix I, was more common in HCWs with HE in the preceding 12 months than in HCWs

without HE, indicating that fragrance allergy can be of relevance for HE, as has been discussed by others.[42,43] Although nickel was the most common allergen, no association with HE was found. This in line with recent studies in the general population.[44,45]

In conclusion, the patch test results confirm that glove-related rubber additives are important occupational allergens, and that rubber additive contact allergy is most likely, at least with regard to DPG, to have been acquired at work. In contrast, fragrance contact allergy, although associated with HE, is much more likely to be acquired outside work. In fact, no case of occupational fragrance allergy was found in the present study.

Concomitant contact allergy to preservatives and fragrances has been reported,[46] as well as to different preservatives,[47] and to different rubber additives.[48] In this study, contact allery to fragrances was more common among those with contact allergy to glove-related rubber additives, which, to the best of our knowledge, has not been reported before. Previously, concomitant allergy to epoxy resins and fragrance, both in an occupational investigation and in patch tested dermatitis populations, has been found.[49,50] Concomitant allergies can be attributable to similar chemical structures, which is not obvious in this case, or to simultaneous or sequential exposure. The finding raises the question of whether previous allergy to fragrances can increase the risk of acquiring contact allergy to rubber additives or vice versa.

4.2 | Clinical diagnosis and impact on work

ACD was present in approximately 1 in 10 HCWs, in most cases concerning contact allergy to substances in medical gloves. In retrospective studies of HCWs investigated for suspected contact allergies, the proportion of ACD usually is higher,[6,19,51,52] which possibly reflects different selection of participants. In a Dutch study, HE seemed to have little impact on work in terms of absenteeism and presenteeism.[53] We found that ACD was associated with sick-leave attributable to HE, as was contact allergy to rubber allergens. This indicates that HE caused by rubber allergy could create difficulty in performing healthcare work. Furthermore, HE had the strongest impact on the ability to use alcoholic hand disinfectants, and can even lead to avoidance of alcoholic disinfectants,[54] which is of concern.

4.3 | Strengths, limitations, and conclusions

The strength of this cross-sectional study is that it clearly relates identified contact allergies with occupational exposure. The expected number of participants in the control groups (HCWs without HE and non-HCWs with HE) was not achieved, which could have led to an underestimation or overestimation of differences between the groups. As this risk was most obvious for the group of non-HCWs with HE, no comparisons were made with this group.

In conclusion:

- Contact allergy to chemicals in medical gloves was the most common cause of ACD in HCWs.
- Disinfectants and soaps are rarely problematic with regard to contact allergy.
- ACD was found in approximately 1 of 10 HCWs with HE in the preceding 12 months.
- ICD was the most common cause of HE, and this fact stresses the importance of implementing educational programmes to maintain good skin health among HCWs.
- Almost 60% of occupational contact allergies were found only with the aimed test series, emphasizing the importance of individually aimed patch testing.

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Conflict of interest

The authors declare no potential conflict of interests.

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SUPPORTING INFORMATION

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

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Table S1. Patch test preparations

Preparation	Concentration (%)	Vehicle		Obtained from
Thiuram mix	1.0	Pet	G, B	i)
Tetramethylthiuram monosulfide	1.0	Pet	G	i)
Tetramethylthiuram disulfide	1.0	Pet	G	i)
Tetraethylthiuram disulfide	1.0	Pet	G	i)
Dipentamethylenethiuram disulfide	1.0	Pet	G	i)
Zinc dimethyldithiocarbamate	1.0	Pet	G	i)
Zinc diethyldithiocarbamate	1.0	Pet	G	i)
Zinc pentamethylenedithiocacbamate	1.0	Pet	G	ii)
Zinc dibutyldithiocarbamate	1.0	Pet	G	i)
Diphenylguanidine	1.0	Pet	G	i)
Diphenylguanidine	2.0	Pet	G	iii)
Triphenylguanidine	1.35	Pet	G	iv)
Mercapto mix	2.0	Pet	G, B	i)
2-Mercaptobenzothiazole	2.0	Pet	G	i)
N-cyclohexyl-2-benzothiazolesulfenamide	1.0	Pet	G	i)
Dibenzothiazyl disulfide	1.0	Pet	G	i)
Morpholinyl mercaptobenzothiazole	1.0	Pet	G	i)
Methylmercaptobenzimidazole	1.0	Pet	G	v)
Diphenylthiourea	1.0	Pet	G	i)
Cyclohexyl thiophthalimide	1.0	Pet	G	i)
Triphenyl phosphite	1.0	Pet	G	vi)
Cetylpyridinium chloride	0.1	Aq	G	vii)
Cetylpyridinium chloride	0.01	Aq	G	vii)
Benzisothiazolinone	0.05	Pet	G	i)
Black rubber mix	0.6	Pet	B	i)
Ethanol	70	Aq	D	viii)
Propyl alcohol	50	Aq	D	ix)
Isopropyl alcohol	100		D	iii)
2-Butanol	10	Aq	D	vii)
t-Butyl alcohol	70	Aq	D	vii)
Myristyl alcohol	5.0	Pet	D	x)
Didecyldimonium chloride 80 in H2O	0.01	Aq	D	xi)
Chlorhexidine digluconate	0.5	Aq	D	i)
Formaldehyde	2.0	Aq	B	i)
Quaternium-15	1.0	Pet	B	i)
Diazolidinyl urea	2.0	Aq	B	i)
Imidazolidinyl urea	2.0	Pet	M	i)
Methyldibromo glutaronitrile	0.5	Pet	B	i)
Methylchloroisothiazolinone/methylisothiazolinone	0.02	Aq	B	i)
Methylisothiazolinone	0.2	Aq	B	i)
Paraben mix	16.0	Pet	B	i)
Sodium benzoate	5.0	Pet	S, M	i)
Sorbic acid	2.0	Pet	S, M	i)
Propylene glycol	5.0	Pet	D, S	i)
Propylene glycol	20	Aq	D, S	ix)
Glycerol	10	Aq	D, M	xii)
Amerchol L 101	50.0	Pet	B	i)
Lauryl polyglucose	3.0	Pet	M	i)

Cetyl alcohol	5.0	Pet	M	i)
Polysorbate 80	5.0	Pet	M	i)
Sorbitan oleate	5.0	Pet	M	i)
Isopropyl myristate	20.0	Pet	M	i)
PEG-4 Rapeseedamide	0.3	Pet	S	xiii)
Cocamidopropyl betaine	1.0	Aq	S	i)
Dimethylaminopropylamine	1.0	Aq	S	i)
Lichen acid mix	0.3	Pet	B	i)
Fragrance mix I	8.0	Pet	B	i)
Fragrance mix II	14.0	Pet	B	i)
Myroxylon pereirae	25.0	Pet	B	i)
Colophonium	20.0	Pet	B	i)
Sesquiterpenlakton mix	0.1	Pet	B	i)
Nickel sulfate hexahydrate	5.0	Pet	B	i)
Cobalt chloride hexahydrate	0.5	Pet	B	i)
Potassium dichromate	0.5	Pet	B	i)
p-Phenylenediamine	1.0	Pet	B	i)
Epoxy resin	1.0	Pet	B	i)
4-tert-Butylphenolformaldehyde resin	1.0	Pet	B	i)
Phenol formaldehyde resin	1.0	Pet	B	i)
Toluenesulfonamide formaldehyde resin	10.0	Pet	B	i)
Neomycin sulfate	20.0	Pet	B	i)
Quinoline mix	6.0	Pet	B	i)
Caine mixII	10.0	Pet	B	i)
Tixocortol-21-pivalate	0.1	Pet	B	i)
Budesonide	0.01	Pet	B	i)

Pet = petrolatum ; G = in gloves; B = Swedish Baseline series ; M = in hand skin moisturisers ; D = in hand disinfectants ; S ; in soaps ; Aq = water ; i) = test preparations obtained from Chemotechnique Diagnostiques, Vellinge, Sweden; ii) - xiv) - test preparations prepared at the Department of Occupational and Environmental Dermatology, Malmö, Sweden - chemical substances obtained from: ii) = Robinson Brothers Ltd, West Bromwick, UK ; iii) = Fluka Analytical, Seelze, Germany ; iv) = Tokyo Chemical Industry Co., Tokyo, Japan ; v) = Bayer AG, Leverkusen, Germany ; vi) = Acros Organics, Geel, Belgium; vii) = Sigma-Aldrich (Steinheim, Germany) ; viii) = CCS Healthcare, Borlänge, Sweden ; ix) = WVR Chemicals, Radnor, Pennsylvania, USA ; x) = BODE Chemie GmbH, Hamburg, Germany ; xi) = Chemtronica, Stockholm, Sweden; xii) = pharmacy at the Skåne University Hospital; xiii) = Lahega Kemi AB, Helsingborg, Sweden

Table S2A. Possible allergens in medical gloves based on chemical analyses of the gloves

	Sterile surgical gloves			Non-sterile examination gloves		
	Latex[a] (n = 5)	Polyisoprene[b] (n = 5)	Neoprene (n = 1)	Latex (n = 1)	Nitrile (n = 7)	Vinyl n = (1)
Thiurams	0	0	0	0	0	0
Dithiocarbamate	3	4	0	0	7	0
Diphenylguanidine	0	3	0	0	1	0
Mercapto compounds	3	5	0	1	1	0
Thioureas	0	0	0	0	0	0
Benzisothiazolinone	0	0	0	0	2	0
Cetylpyridinium chloride	0	3	0	0	0	0

n = number of brands supplied by the employer ; a) Natural rubber latex ; b) Synthetic polyisoprene rubber
No glove-related rubber additives were found in one sterile latex glove and one neoprene glove. Dithiocarbamates only were found in one sterile latex glove and in 6 nitrile gloves. A combination of dithiocarbamates and mercapto compounds was found in one sterile latex and one sterile polyisoprene glove. A combination of diphenylguanidine and mecapto compounds was found in 3 polysisoprene gloves. A combination of dithiocarbamates, diphenylguanidine and mecapto compounds was found in one nitrile glove.

Table S2B. Possible allergens in hand disinfectants, liquid soaps and wash creams, and hand creams based on ingredients labelling and information supplied by the producer

	Hand disinfectant (n = 13)	Liquid soap and wash creams (n = 9)	Hand creams (emollients) (n = 7)
Chlorhexidine digluconate	1		
Myristyl alcohol	2		
Didecyldimethylammonium chloride	1		
Ethanol	9		
n-Propanol	5		
Isopropyl alcohol	13		
2-Butanol	3		
tert-Butanol	4		
Glycerol	12	6	4
Propylene glycol	5	3	0
Amerchol L 101		0	1
Cocamidopropyl betaine		7	0
Imidazolidinyl urea		0	1
Sodium benzoate		5	2
Potassium sorbate		2	3
’Perfume'		2	1

n = number of brands supplied by the employer

Table S3. Patch test reactions for diphenylguandine (DPG) in 502 hospital employees

Participant number	DPG 1%[a] D3/4	D7	DPG 2% number	D3/4
3[b]	+?	-	-	-
11[b]	+++	+++	+++	+++
41	-	-	+?	-
59[b]	+?	-	+?	+?
63	-	-	+?	-
92	+?	-	-	-
95	+?	-	-	-
135	-	-	+?	-
157[b]	+++	+++	-	+++
164[b]	+++	+	++	+
165	+?	-	-	-
170[b]	+?	++	+	-
179[b]	+	+	+	+
217	+?	-	-	-
220	+?	-	-	-
227[b]	+	-	-	-
245	+?	-	-	-
257[b]	-	+	-	+
277[b]	+?	+?	-	+?
288	+?	-	-	-
302[b]	-	+?	+	++
334	-	-	+?	-
348	-	-	+?	-
370	+?	-	-	-
378	-	-	+?	-
381	+?	-	+?	-
435	+?	-	+?	-
473[b]	+	+	-	+?
500	-	-	+?	-

D = Day ; a) % in petrolatum ; b) participant with a history of exposure to glove containing DPG.

All other participants showed no reactions on patch testing with DPG