Acta Derm Venereol 2016; 96: 237–240

CLINICAL REPORT

Contact Allergy in Danish Healthcare Workers: A Retrospective Matched Case-control Study

Jakob F. SCHWENSEN[1], Torkil MENNÉ[1], Mette SOMMERLUND[2], Klaus E. ANDERSEN[3], Charlotte G. MORTZ[3], Claus ZACHARIAE[4] and Jeanne D. JOHANSEN[1]

[1]Department of Dermato-Allergology, National Allergy Research Centre, Copenhagen University Hospital Gentofte, Hellerup, [2]Department of Dermatology, Aarhus University Hospital, Aarhus, [3]Department of Dermatology and Allergy Centre, Odense University Hospital, Odense, and [4]Department of Dermato-Allergology, Copenhagen University Hospital Gentofte, Hellerup, Denmark

Contact dermatitis in healthcare workers is a world wide problem. We conducted a retrospective observational study of the patch-test results of 1,402 healthcare workers and 1,402 matched controls with contact dermatitis who were treated at 3 hospitals departments in Denmark between 2007 and 2014. The primary objective was to determine whether healthcare work was associated with contact allergy to thiuram mix, used as a rubber accelerator ib rubber protective gloves. Unadjusted univariate analyses revealed that healthcare work was significantly associated with occupational contact dermatitis and hand dermatitis. Contact allergy to thiuram mix was more common in healthcare workers, and was significantly associated with having occupational contact dermatitis, hand dermatitis and older age. In conclusion, we report here a potential problem of contact allergy to thiurams in healthcare workers with contact dermatitis. Legislative authorities may in the future focus on the use of rubber accelerators in, for example, protective gloves, which are widely used by healthcare professionals. ***Key words: contact allergy; hand eczema; healthcare workers; occupational contact dermatitis; thiurmas.***

Accepted Aug 4, 2015; Epub ahead of print Aug 10, 2015

Acta Derm Venereol 2016; 96: 237–240.

Jakob F. Schwensen, National Allergy Research Centre, Department of Dermato-Allergology, Copenhagen University Hospital Gentofte, Kildegårdsvej 28, DK-2900 Hellerup, Denmark. E-mail: jakob.ferloev.schwensen.03@regionh.dk

A high prevalence of occupational contact dermatitis (CD) is seen with frequent "wet work" (1–3). In retrospective, epidemiological studies of occupational CD, healthcare is quantitatively one of the biggest groups (1, 2, 4). Healthcare workers are in daily skin contact with both irritants and allergens.

Both prospective and retrospective studies have investigated the frequency of hand dermatitis and contact allergy to various allergens in various groups of healthcare workers (3, 5–7). Contact allergy after repetitive skin contact with protective gloves (e.g. thiuram mix), drugs (e.g. tetrazepam) or disinfectants (e.g. formaldehyde and 2-bromo-2-nitro-1,3-propanediol) is frequent (5, 6). However, hitherto no matched case-control study has presented contact allergens associated with healthcare work. The aim of this study is to identify whether thiuram mix contact allergy and background variables are associated with healthcare work in patients with CD, based on patch-test results from 3 major dermatological departments in Denmark between 2007 and 2014. In addition, we investigate whether other allergens from the European baseline series are also associated with healthcare work.

MATERIALS AND METHODS

All cases from the 3 university hospital departments were registered in the (Danish) National Database for Contact Allergy following uniform guidelines (8).

Healthcare workers were retrieved from the database by means of occupational classification according the Danish version of the International Standard Classification of Occupation (DISCO-88), which has been explained elsewhere (9). Healthcare workers were coded with the following DISCO-codes: "2220, 2221, 2222, 2224, 2229, 2230, 3111, 3211, 3220, 3221, 3222, 3223, 3224, 3225, 3226, 3228, 3229, 3230, 3231, 5130, 5131, 5132, 5133 and 73101". The following occupational subgroups were included for analysis: auxiliary nurses (nurse assistants), chiropractors, doctors (including surgeons), dentists, dental nurses, dental technicians, laboratory workers at hospitals, medical secretaries, midwifes, nurses, occupational therapists, pharmacists, and physiotherapists.

The study population comprised 1,402 healthcare workers consecutively registered between 1 January 2007 and 31 December 2013.

All healthcare workers were matched (1:1 case-control match) to a control group of patients with CD, who were not registered as healthcare workers in the database. Matching criteria were sex, age (± 1 year) and test year. The control group was occupied in the following occupations: office work ($n = 371$), teaching and nursery teaching ($n = 155$), cleaning ($n = 81$), hairdressing and cosmetology ($n = 75$), food industry work (e.g. cooks and bakers; $n = 61$), agricultural work ($n = 51$), blue-collar work ($n = 34$), transportation work ($n = 32$), metal processing sector work ($n = 20$), technician work ($n = 18$), painting ($n = 9$), and "others" ($n = 495$). The following information was available from the database: MOAHLFA-index (Male, Occupational CD, Atopic dermatitis, Hand dermatitis, Leg dermatitis, Face dermatitis and Age > 40 years), age, test year, and patch-test results of the European baseline series. In addition, information of patch-testing

 doi: 10.2340/00015555-2202
 ISSN 0001-5555

with methylisothiazolinone (MI) was also included. MI has first recently been included in the European baseline series in all 3 centres, and therefore not all patients were patch-tested with MI. Targeted testing with MI was excluded from the analyses.

Occupational CD was defined as eczema (CD) with a known or suspected temporal relation with an occupational exposure. If necessary, individual exposure assessment was conducted. In Denmark, doctors are obliged by law to notify all suspected or known occupational diseases, including skin diseases, to authorities, i.e. National Board of Industrial Injuries for worker's compensation.

Patch-tests were applied on the upper back in accordance with international guidelines (10). Occlusion time was 48 h and readings were performed at least once on D3 (or D4), and often also on D2 and D7, in accordance with the recommendations of the ICDRG (10). The patch-test readings of 9.7% patients were only performed once on D3 (or D4). Reactions of strength 1+, 2+ and 3+ were regarded as positive responses. Furthermore, a few NT:S (not tested:sensitized) were also regarded as positive responses (10). Irritant reactions, doubtful reactions and negative reactions were interpreted as negative responses.

Statistical analysis

All data analyses were performed with the statistical software SPSS™ version 19.0 SPPS™ Statistics Chicago, IL, USA; IBM PASW Statistics. The Pearson χ^2 test, Fischer's exact test and unadjusted odds ratios (OR) with 95% confidence intervals (95% CI) were applied for the univariate analyses of contact allergy to each allergen. Trend across test year was utilized with liner-by-linear χ^2 test for the MOALHFA-index. Binominal logistic regression analysis was conducted for contact allergy to allergens being significantly associated with healthcare as dependent variable and background variables of the MOALHFA-index as explanatory variables. All *p*-values are 2-sided, and 0.05 was chosen for statistical significance.

RESULTS

A total of 1,402 healthcare workers were patch-tested between 2007 and 2014, and these were matched with 1,402 patients with CD (controls).

The baseline characteristics for healthcare workers and controls according to MOAHLFA-index are listed in Table I. Of 1,402 healthcare workers, 421 patients (30%) had occupational CD and 754 patients (53.8%) had hand dermatitis. Healthcare work was furthermore in the unadjusted univariate analyses significantly associated with occupational CD and hand dermatitis, while an inverse and significantly association was observed for leg dermatitis compared with controls.

No significant changes in frequency regarding MOAHLFA-index were observed across test year for the group of healthcare workers.

Table I. *Baseline characteristics according to MOAHLFA-index for healthcare workers and controls with contact dermatitis (CD)*

	Healthcare workers % (*n*)	Controls % (*n*)	Unadjusted OR (95% CI)
Male	8.6 (120)	8.6 (120)	1.00 (0.77–1.30)
Occupational CD	30.0 (421)	14.6 (205)	2.51 (2.08–3.02)
Atopic dermatitis	22.3 (312)	20.4 (286)	1.12 (0.93–1.34)
Hand dermatitis	53.8 (754)	46.0 (645)	1.37 (1.18–1.58)
Leg dermatitis	1.1 (15)	2.9 (41)	0.36 (0.20–0.65)
Face dermatitis	24.9 (349)	26.0 (365)	0.94 (0.79–1.12)
Age >40 years	60.3 (845)	60.3 (845)	1.00 (0.86–1.16)

OR: odds ratio; 95% CI: 95% confidence intervals; MOAHLFA-index: Male, Occupational contact dermatitis (CD), Atopic dermatitis, Hand dermatitis, Leg dermatitis, Face dermatitis and Age >40 years.

Table II shows positive patch-test reactions in healthcare workers and the matched controls. Unadjusted analysis revealed that contact allergy to thiuram mix was significantly associated with healthcare work. In contrast, the same analyses showed that potassium

Table II. *Positive patch-test reactions to allergens from the European baseline series for healthcare workers and controls with contact dermatitis*

	Healthcare workers % (*n*/total tested)	Controls % (*n*/total tested)	OR (95% CI)
Potassium dichromate	2.8 (39/1,401)	4.3 (60/1,398)	**0.64 (0.42–0.96)**
Neomycin sulphate	1.2 (17/1,400)	1.7 (24/1,399)	0.70 (0.38–1.32)
Thiuram mix	5.4 (75/1,401)	3.4 (48/1,398)	**1.60 (1.10–2.30)**
p-phenylenediamine	2.6 (36/1,396)	3.0 (42/1,397)	0.85 (0.54–1.34)
Cobalt chloride	5.3 (74/1,400)	5.9 (82/1,399)	0.90 (0.65–1.24)
Benzocaine	0.1 (1/698)	0.5 (2/432)	0.31 (0.03–3.41)
Formaldehyde	1.9 (27/1,397)	2.5 (35/1,395)	0.77 (0.46–1.27)
Colophonium	4.6 (64/1,399)	4.6 (64/1,400)	1.00 (0.70–1.43)
Myroxylon pereirae	3.1 (43/1,400)	3.0 (42/1,397)	1.02 (0.66–1.57)
N-isopropyl-*N*-phenyl-*p*-phenylenediamine	1.0 (7/699)	0.7 (3/432)	1.45 (0.37–5.62)
Lanolin alcohol	0.6 (8/1,401)	0.9 (12/1,399)	0.61 (0.25–1.48)
Epoxy resin	1.4 (19/1,401)	1.6 (23/1,399)	0.82 (0.45–1.52)
p-tert-butyl formaldehyde resin	1.1 (15/1,402)	1.8 (25/1,399)	0.59 (0.31–1.13)
Fragrance mix	7.7 (107/1,396)	8.4 (117/1,399)	0.91 (0.69–1.20)
Sesquiterpene lactone mix	0.9 (13/1,391)	2.5 (35/1,398)	0.37 (0.19–0.70)
Quaternium 15	1.2 (17/1,402)	1.9 (26/1,398)	0.65 (0.35–1.20)
Nickel sulfate	23.3 (325/1,392)	26.3 (366/1,394)	0.86 (0.72–1.02)
Methylchloroisothiazolinone/methylisothiazolinone	2.8 (39/1,399)	4.2 (58/1,395)	**0.66 (0.44–1.00)***
Mercaptobenzothiazole	0.6 (9/1,402)	0.6 (9/1,398)	1.00 (0.40–2.52)
Primin	0.2 (3/1,392)	0.4 (5/1,397)	0.60 (0.14–2.52)
Clioquinol	0.6 (4/698)	0.2 (1/432)	2.48 (0.28–22.30)
Paraben mix	0.3 (4/1,402)	0.3 (4/1,399)	1.00 (0.25–4.00)
Mercapto mix	0.9 (12/1,402)	1.0 (14/1,398)	0.85 (0.39–1.85)
Quinolin mix	0.7 (5/702)	0.5 (5/967)	1.38 (0.40–4.79)
2-bromo-2-nitro-1,3-propanediol	0.3 (4/1,389)	0.4 (6/1,394)	0.67 (0.19–2.37)
Iodopropynyl butylcarbamate	0.7 (10/1,390)	0.6 (8/1,395)	1.26 (0.94–3.19)
Hydroxyisohexyl 3-cyclohexene	4.0 (55/1,389)	3.7 (51/1,392)	1.08 (0.74–1.60)
Tixocortol 21-pivalate	0.7 (10/1,401)	1.3 (18/1,400)	0.55 (0.25–1.20)
Budesonide	0.9 (12/1,401)	1.3 (18/1,399)	0.66 (0.32–1.38)
Methyldibromo glutaronitrile	3.3 (46/1,392)	4.4 (61/1,398)	0.75 (0.51–1.12)
Imidazolidinyl urea	0.6 (8/1,398)	0.5 (7/1,395)	1.14 (0.41–3.16)
Diazolidinyl urea	1.1 (15/1,398)	1.1 (16/1,396)	0.94 (0.46–1.90)
Methylisothiazolinone	2.4 (25/1,060)	4.0 (37/919)	**0.58 (0.34–0.96)**

*95% CI: 0.437–0.999. Significant values are in **bold** type.

dichromate (chromium), methylchloroisothiazolinone in combination with methylisothiazolinone (MCI/MI) and methylisothiazolinone (MI) was inversely associated with healthcare. Other rubber accelerators from the European baseline series (mercaptobenzothiazole and *N*-isopropyl-*N*-phenyl-4-phenylenediamine) were not significantly associated with healthcare.

Binary logistic regression model was performed to ascertain the effects of the background variables of the MOALHFA-index on the likelihood that healthcare workers had contact allergy to thiuram mix (dependent variable) (Table III). The logistic regression revealed that occupational CD, hand dermatitis and older age (age >40 years) were significantly associated with contact allergy to thiuram mix.

The sub-occupational classification is shown in Table IV. The biggest occupational sub-groups were "nurse" and "auxiliary nurses". Furthermore, the frequency of thiuram mix contact allergy within the occupational sub-groups is shown (Table IV).

Dentists and dental assistants, nurses and auxiliary nurses all had a sensitization frequency of thiuram mix of 6–7% in comparison with, for example, doctors 3.6% or pharmacists 0%. The occupational sub-groups were not included in a logistic regression model owing to a moderate sample size for several of the occupational sub-groups. Nonetheless, unadjusted univariate analyses of the frequency of thiuram mix contact allergy within the occupational sub-groups revealed no significant differences in the frequency of contact allergy to thiuram mix between the sub-groups (e.g. nurses vs. healthcare workers not being occupied as a nurse; doctors vs. healthcare workers not being occupied as a doctor).

Table III. *Distribution of the MOAHLFA-index for healthcare workers with contact allergy to thiuram mix (*n = *75)*

	Contact allergy % (*n*)	No contact allergy % (*n*)	OR (95% CI)	*p*-value
Male	6.7 (5)	8.7 (115)	0.64 (0.25–1.65)	0.64
Occupational rel.	62.7 (47)	28.2 (374)	2.61 (1.54–4.41)	<0.001
Atopic dermatitis	22.7 (17)	22.2 (295)	0.93 (0.51–1.70)	0.82
Hand dermatitis	86.7 (65)	52.0 (689)	4.75 (2.24–10.07)	<0.001
Leg dermatitis	0.0 (0)	1.1 (15)	0.00 (0.00)	1.00
Facial dermatitis	21.3 (16)	25.1 (333)	1.56 (0.84–2.93)	0.16
Age >40 years	68.0 (51)	59.9 (794)	1.70 (1.00–2.88)	<0.05

MOAHLFA-index: Male, Occupational contact dermatitis, Atopic dermatitis, Hand dermatitis, Leg dermatitis, Face dermatitis and Age >40 years.
OR (95% CI): odds ratio with 95% confidence interval performed by logistic regression modelling; rel.: relevance.

Table IV. *Occupational sub-classification of the healthcare workers with percentages of positive reactions to thiuram mix within each sub-occupation*

Sub-occupation	% (*n*)	Thiuram mix contact allergy, % (*n*/total tested)
Auxiliary nurses	14.6 (410)	6.1 (25/409)
Doctors	7.9 (111)	3.6 (4/111)
Dentists and dental assistants	5.0 (139)	7.2 (10/139)
Laboratory technicians	3.5 (99)	4.0 (4/99)
Medical secretaries	2.7 (77)	0 (0/77)
Midwifes	0.9 (25)	4.0 (1/25)
Nurses	14.1 (395)	6.8 (27/395)
Pharmacists	0.8 (22)	0.0 (0/22)
Physiotherapists and chiropractors	1.7 (47)	4.3 (2/47)
Others	2.5 (70)	2.9 (2/70)
Unspecified	0.2 (7)	0.0 (0/7)
Total	100 (1,402)	5.4 (75/1,402)

DISCUSSION

This retrospective matched case-control study shows that healthcare is associated with thiuram mix contact allergy in a cohort of patients with CD. In addition, contact allergy to thiuram mix was significantly associated with hand dermatitis, occupational CD, and age >40 years. Healthcare workers with CD significantly more often had hand dermatitis and occupational CD than controls. Hitherto, to our knowledge, no other study has conducted a retrospective matched case-control study of healthcare workers with CD.

Discouraged by the increasing trend of thiuram sensitivity in the 1990s and early 2000s, glove manufacturers have allegedly attempted to lower their use of rubber accelerators in the vulcanization process of rubber gloves (11). However, our data show that sensitization to thiuram mix in healthcare workers are common. This may indicate that thiurams (and carbamates) still are widely used in rubber protective gloves purchased on the Danish market, which is partly in accordance with a recent German stratified analysis of occupational cases among nurses made by Molin and co-workers (6).

No study has investigated the use of different rubber accelerators used in protective gloves comprehensively (11, 12). The chemical composition of rubber accelerators in rubber protective gloves is complex and may also vary during the vulcanization process (13). A recent study by Hansson and co-workers tried to evaluate the reactivity profile in patients with contact allergy to selected rubber accelerators (14). It is noteworthy that dithiocarbamates constitute a redox pair with thiurams. Thiuram mix in the European baseline series is therefore merely a patch-test marker for thiuram-carbamate sensitization. Nonetheless, it would therefore be advisable in the name of prevention to make ingredient labelling of protective gloves mandatory.

Hand dermatitis in nurse apprentices is common, with a 1-year prevalence of approximately 20–35% (3, 15–17). Other studies have estimated the point prevalence of hand dermatitis in nurses being twice as high as in the general population (1, 5, 16). This is in accordance with our findings, revealing that hand dermatitis was significantly associated with healthcare work. Approximately 30% of all healthcare workers with CD were notified as occupational CD (Table I), which is in line

with another, comparable and observational, study from the 1990s (5).

Our retrospective observational study is however limited. Our control group was not patch-tested with the more special patch-test series often used for testing healthcare workers with CD, e.g. components of surface or instruments disinfectants or different ointments. Another limitation is that although the majority of all patients (90.3%) had their patch-test readings done on days 2, 3 (or 4) and 7 (following the recommendations of International Contact Dermatitis Research Group [ICDRG]), 9.7% of the patch-test readings were only done once. This implies that immune reactions beyond day 3 (or 4) would have been missed.

The inverse association between healthcare work and contact allergy to chromium is noteworthy, especially in contrast to another study (6).

Interestingly, contact allergy to colophonium, which is often used in adhesive tapes, bandages and hydrocolloid dressings, was not associated with healthcare work. In general, the use of colophonium (and thus the rate of sensitization), has diminished (6, 18), and documented reports of occupational allergic CD to colophonium in healthcare workers are rare (19).

In conclusion, this retrospective observational case-control study reveals for the first time that, in a cohort of patients with CD, work in the healthcare sector is significantly associated with contact allergy to thiuram mix, hand dermatitis and occupational CD. In the future legislative authorities may focus on the use of thiurams and carbamates in, for example, protective gloves, as it seems that the improved production methods of protective gloves not yet have paid dividend to the skin health of the workers in the healthcare sector.

REFERENCES

1. Schwensen JF, Friis UF, Menné T, Johansen JD. One thousand cases of severe occupational contact dermatitis. Contact Dermatitis 2013; 68: 259–268.
2. Skoet R, Olsen J, Mathiesen B, Iversen L, Johansen JD, Agner T. A survey of occupational hand eczema in Denmark. Contact Dermatitis 2004; 51: 159–166.
3. Visser MJ, Verberk MM, van Dijk FJ, Bakker JG, Bos JD, Kezic S. Wet work and hand eczema in apprentice nurses; part I of a prospective cohort study. Contact Dermatitis 2014; 70: 44–55.
4. Dickel H, Kuss O, Blesius CR, Schmidt A, Diepgen TL. Occupational skin diseases in Northern Bavaria between 1990 and 1999: a population-based study. Br J Dermatol 2001; 145: 453–462.
5. Schnuch A, Uter W, Geier J, Frosch PJ, Rustemeyer T. Contact allergies in healthcare workers. Results from the IVDK. Acta Derm Venereol 1998; 78: 358–363.
6. Molin S, Bauer A, Schnuch A, Geier J. Occupational contact allergy in nurses: results from the Information Network of Departments of Dermatology 2003–2012. Contact Dermatitis 2015; 72: 164–171.
7. Strauss RM, Gawkrodger DJ. Occupational contact dermatitis in nurses with hand eczema. Contact Dermatitis 2001; 44: 293–296.
8. Menné T, Johansen JD, Sommerlund M, Veien NK, Danish Contact Dermatitis G. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. Contact Dermatitis 2011; 65: 3–12.
9. Schwensen JF, Menné T, Thyssen JP, Veien N, Funding A, Nielsen N, et al. Occupational contact dermatitis in blue collar workers: results from a multicentre study from the Danish Contact Dermatitis Group (2003–2012). Contact Dermatitis 2014; 71: 348–355.
10. Wilkinson DS, Fregert S, Magnusson B, Bandmann HJ, Calnan CD, Cronin E, et al. Terminology of contact dermatitis. Acta Derm Venereol 1970; 50: 287–292.
11. Geier J, Lessmann H, Uter W, Schnuch A, Information Network of Departments of D. Occupational rubber glove allergy: results of the Information Network of Departments of Dermatology (IVDK), 1995–2001. Contact Dermatitis 2003; 48: 39–44.
12. Knudsen BB, Hametner C, Seycek O, Heese A, Koch HU, Peters KP. Allergologically relevant rubber accelerators in single-use medical gloves. Contact Dermatitis 2000; 43: 9–15.
13. Bergendorff O, Persson C, Ludtke A, Hansson C. Chemical changes in rubber allergens during vulcanization. Contact Dermatitis 2007; 57: 152–157.
14. Hansson C, Ponten A, Svedman C, Bergendorff O. Reaction profile in patch testing with allergens formed during vulcanization of rubber. Contact Dermatitis 2014; 70: 300–308.
15. Schmid K, Broding HC, Uter W, Drexler H. Transepidermal water loss and incidence of hand dermatitis in a prospectively followed cohort of apprentice nurses. Contact Dermatitis 2005; 52: 247–253.
16. Ibler KS, Jemec GB, Flyvholm MA, Diepgen TL, Jensen A, Agner T. Hand eczema: prevalence and risk factors of hand eczema in a population of 2274 healthcare workers. Contact Dermatitis 2012; 67: 200–207.
17. Flyvholm MA, Bach B, Rose M, Jepsen KF. Self-reported hand eczema in a hospital population. Contact Dermatitis 2007; 57: 110–105.
18. Fall S, Bruze M, Isaksson M, Liden C, Matura M, Stenberg B, et al. Contact allergy trends in Sweden – a retrospective comparison of patch test data from 1992, 2000, and 2009. Contact Dermatitis 2015; 72: 297–304.
19. Kanerva L, Estlander T. Occupational allergic contact dermatitis from colophony in 2 dental nurses. Contact Dermatitis 1999; 41: 342–343.