

No immediate effect of regulatory reduction of chromium in leather among adult chromium allergic patients

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Conflict of interests

None declared.

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Abstract

Background

In March 2014, the European Commission issued a new regulation restricting the content of hexavalent chromium in leather to no more than 3 mg/kg. We previously performed a questionnaire study in January 2014 to characterize our patients with chromium contact allergy prior to regulatory intervention.

Objectives

To assess whether clinical characteristics, self-reported sources of chromium exposure and burden of disease changed in chromium allergic patients over time.

Methods

A questionnaire study was performed among 172 adult dermatitis patients with chromium allergy and 587 age- and sex-matched dermatitis patients without chromium allergy. A questionnaire was sent to all dermatitis patients patch tested from 2003 to 2018 on August 2019.

Results

The overall response rate was 61.2% (759/1241). Patients with chromium allergy were still more commonly affected by current foot dermatitis [odds ratio (OR)=3.82, 95% confidence interval (CI): 2.07-7.08] and hand dermatitis (OR=1.98, 95% CI: 1.13-3.49) compared to controls diagnosed during 2013-2018. The proportion of chromium allergic patients reporting dermatitis caused by leather exposure did not change during 2003-2012 versus 2013-2018 (71.0% vs. 66.2%, $p=0.5$). Furthermore, estimates on occupational performance and disease-severity, e.g. current dermatitis, number of anatomical locations with dermatitis, worst-case dermatitis and effect on work were similar in patients with chromium allergy for 2003-2012 versus 2013-2018.

Conclusion

No immediate sign of improvement was found in patients with chromium allergy concerning severity of disease and dermatitis from leather exposures five years after adoption of regulation against hexavalent chromium in leather. The regulation may have to be revised for better protection of those already sensitized.

Key words: Allergic contact dermatitis, chromium, disease-severity, leather, regulation

Introduction

Historically, the most common cause of chromium (Cr) sensitization has derived from skin contact with hexavalent Cr [Cr (VI)] in wet cement, primarily affecting construction workers.¹ Prompted by a highly effective regulatory intervention in 2005 by EU,² preceded by Sweden in 1989 and Denmark in 1983,³ the addition of ferrous sulphate to wet cement became compulsory to reduce the amount of water-soluble Cr (VI) to no more than 2 ppm. Subsequently, numerous studies have reported a substantial decline in cases of Cr allergic contact dermatitis (ACD) due to cement.^{4, 5} Currently, leather is considered the most common source of exposure in patients with Cr-induced ACD.⁶ In May 2015, a regulation was enforced by EU restricting the content of Cr (VI) to no more than 3 ppm in leather articles coming into contact with the skin.⁷ In a Danish questionnaire case-control study conducted prior to the regulation, including 121 cases with Cr-induced ACD and 443 age- and sex-matched dermatitis patients acting as controls during 2003-2012, respectively, 66.1% and 12.6% reported a history of dermatitis from leather exposure.⁸ Furthermore, Cr allergic patients had a lower quality of life and were more burdened by dermatitis compared to the control group.

In the preamble of the regulation, it was foreseen to be 80% effective in reducing the incidence of ACD due to Cr (VI) in leather.⁷ A recent study showed a significantly decreasing trend in the prevalence of Cr allergy for all exposures during 2002-2017,⁶ which might be an effect of the regulation on leather. In this questionnaire study we aimed at assessing whether an improvement occurred in self-reported measures of disease-severity and leather exposures leading to dermatitis in Cr allergic patients diagnosed during 2003-2018.

Materials and methods

Study population

From 1 January 2003 to 31 December 2018, a total of 12,792 adults aged 18 to 99 with suspected ACD were patch tested at the Department of Dermatology and Allergy, Herlev-Gentofte Hospital, Copenhagen, Denmark. All adult patients (≥ 18 years) with a positive patch test reaction to potassium dichromate (0.5% pet.) were age- and sex-matched in a 1:4 ratio to a control group of dermatitis patients with a negative patch test reaction to potassium dichromate (0.5% pet.), but possibly positive test reactions to other allergens. All data were retrieved from the National Database for Contact Allergy in Denmark. Their home addresses were obtained from the Danish central personal register which is a unique register of social information and health services.⁹ Patients were excluded if they did not wish to be

contacted for research purposes, had unknown addresses or were no longer alive. Permission was obtained from The Danish Data Protection Agency (VD-2018-132/I-Suite number: 6375).

Patch testing

Patch testing had been performed with the European baseline and extended patch test series [Trolab allergens (Hermal, Reinbek, Germany) and Allergeaze allergens (SmartPractice, Canada) since April 2016)] with Finn Chambers[®] (8 mm; Epitest Ltd, Oy, Finland) on Scanpor[®] tape (Norgesplaster A/S, Alpharma, Vennesla, Norway). Dosing of the chamber had been performed with 20 mg of the test preparation. Potassium dichromate (0.5% pet.) had been used for testing and patch test readings performed according to the recommendations of the European Society of Contact Dermatitis (ESCD),¹⁰ with an exposure time of 2 days and readings being performed on day 2, 3 or 4, and 7. Patch test reactions designated as 1+, 2+ or 3+ were interpreted as positive reactions. Irritant responses and doubtful (+?) or negative readings were interpreted as negative responses.

Questionnaire

We used the same questionnaire as in the previous study⁸ (supplementary material) to identify differences between the study groups regarding clinical characteristics (age, sex, atopic dermatitis (AD), initial location of dermatitis, current location of dermatitis and the presence of other contact allergies), sources of exposure leading to dermatitis at present workplace, previous workplace or in spare-time (leather, jewellery, work tools, metalwork, cement, wood preservation and mobile phone) and burden of disease [impact on occupational

performance, medical needs over the last 12 months, personal perception of disease-severity ('current dermatitis', 'worst-case dermatitis', 'effect on work' and 'effect on spare-time') on a visual analogue scale (VAS) and an estimate of their quality of life using the Dermatology Life Quality Index (DLQI)]. The DLQI score was estimated according to published instructions resulting in a score between 0 and 30, with higher scores indicating a lower quality of life.¹¹ The validated official version in Danish was used. Permission to use the scale was obtained from <http://www.cardiff.ac.uk/dermatology>. Furthermore, a diagnosis of AD was defined according to the UK working party's diagnostic criteria.¹² Thus, the patient must have had an itchy skin condition during the past 12 months plus three or more of the following: (i) onset before the age of 2 years, (ii) a history of flexural involvement, (iii) a history of generally dry skin, and (iv) a personal history of other atopic diseases. A questionnaire was sent to all dermatitis patients patch tested during 2003-2018 on August 2019; 4 weeks later, a reminder was sent to the non-respondents and the study was closed for entry after another 4 weeks.

Data management

Data-analysis was done using the Statistical Products and Service Solution package (SPSS) for Windows (release 22.0). We stratified the respondents into two study cohorts; those patch tested between 2003-2012 and those tested between 2013-2018. This was done due to our previous study including patients during 2003-2012, but also as the regulation of Cr (VI) in leather was in a hearing in 2012, prior to

adoption (2014) and implementation (2015). The χ^2 -test of independence - or Fischer's exact test when the expected value in any of the cells of the contingency table was below 5 - was used to compare groups. All results are presented as odds ratios (OR) with 95% confidence intervals (CI). As DLQI data and VAS scores followed a non-parametric distribution, the Mann-Whitney *U*-test was performed to determine differences between groups and the results were presented as median values with an interquartile range (IQR). The Jonckheere-Terpstra test was used for trend analysis of non-parametric continuous variables whereas the linear-to-linear χ^2 -test was used for trend analysis of categorical variables. Two-sample t-tests were used for normal data. Testing of data for normality was done with the Shapiro-Wilk test.

The level of statistical significance was set at $\alpha=0.05$ for a single test. As a large number of independent tests ($m=108$) were performed, the Benjamini-Hochberg (BH) method was applied to control the type I error rate and to generate adjusted p-values.¹³ The BH-method uses the false discovery rate (FDR) - i.e. expected proportion of false-positives among all significant results - to deflate the type I error rate. In the BH-method, p-values from all tests performed are ranked in an ascending order and adjusted p-values are calculated using the formula $(I/m)*FDR$, where *I* denotes the rank of a p-value and *m* the total number of tests performed. The FDR was set to 5%.

Results

The overall response rate was 61.2% (759/1241), including 72.6% (172/237) in the case group and 58.5% (587/1004) in the control group. Female patients were the predominant gender comprising 68.6% of the respondents.

Characteristics of Cr allergic patients over time

The mean age of Cr allergic patients diagnosed during 2003-2012 versus 2013-2018 was 50.0 +/- 11.3 years and 56.0 +/- 14.7 years ($p=0.003$) (table 1). The presence of other contact allergies than Cr was comparable in Cr allergic patients diagnosed during 2003-2012 versus 2013-2018 (63.6% vs. 72.3%, $p=0.2$). No significant difference was found regarding the self-reported prevalence of hand dermatitis (72.9% vs. 70.8%, $p=0.9$) or foot dermatitis (54.2% vs. 50.8%, $p=0.8$) as the initial location of dermatitis comparing Cr allergic patients diagnosed in 2003-2012 versus 2013-2018. Similarly, no difference was recorded in the prevalence of current hand dermatitis (72.0% vs. 63.1%, $p=0.2$) or foot dermatitis (46.0% vs. 40.0%, $p=0.4$).

Regarding the initial location of dermatitis, Cr allergic patients were more often affected by hand dermatitis (OR=2.54, 95% CI: 1.58-4.09, $p<0.001$) and foot dermatitis (OR=4.78, 95% CI: 3.02-7.58, $p<0.001$) compared to controls diagnosed in 2003-2012. A similar case-control pattern was found during 2013-2018 for initial hand dermatitis (OR=2.36, 95% CI: 1.30-4.27, $p<0.001$) and initial foot dermatitis (OR=5.18, 95% CI: 2.85-9.43, $p<0.001$). Furthermore, Cr allergic patients more often reported current hand dermatitis (OR=3.52, 95% CI: 2.20-5.64, $p<0.001$) and current foot dermatitis (OR=5.80, 95% CI: 3.56-9.46, $p<0.001$) compared to controls diagnosed during 2003-2012. The corresponding estimates during 2013-2018 were OR=1.98 (95% CI: 1.13-3.49, $p<0.001$) for hand dermatitis and OR=3.82 (95% CI: 2.07-7.08, $p<0.001$) for foot dermatitis.

Severity and QoL

DLQI scores and measures of disease severity presented as median (IQR) are summarized in Table 2. The median (IQR) DLQI score reported by Cr allergic patients diagnosed during 2003-2012 versus 2013-2018 was 2.0 (0-7.0) and 2.0 (1.0-6.5), respectively ($p=0.8$). As regards personal perception of disease severity using VAS, comparisons of Cr allergic patients diagnosed in 2003-2012 versus 2013-2018 did not show any significant difference concerning 'current dermatitis' [3.4 (1.0-5.6) vs. 2.4 (1.0-5.0), $p=0.5$], 'worst-case dermatitis' [9.0 (7.5-9.5) vs. 8.7 (7.4-9.5), $p=0.2$], 'effect on work' [5.0 (2.4-7.4) vs. 4.0 (1.8-7.1), $p=0.2$] and 'effect on spare-time' [5.1 (2.4-7.4) vs. 4.5 (1.7-6.1), $p=0.1$]. Additionally, we found no difference with respect to the initial [2.0 (1.0-3.0) vs. 3.0 (1.0-4.0), $p=0.13$] or current number [2.0 (1.0-3.0) vs. 2.0 (1.0-3.0), $p=0.92$] of anatomical locations with dermatitis in Cr allergic patients through 2003-2012 versus 2013-2018. Trend analysis of Cr allergic patients across 2013-2018 did not show any change regarding DLQI scores ($p_{\text{trend}}=0.8$), 'current dermatitis' ($p_{\text{trend}}=0.05$), 'worst-case dermatitis' ($p_{\text{trend}}=0.9$), 'effect on work' ($p_{\text{trend}}=0.2$) and 'effect on spare-time' ($p_{\text{trend}}=0.7$).

Compared to controls, Cr allergic patients diagnosed during 2003-2012 reported a significantly higher DLQI score [2.0 (0-7.0) vs. 1.0 (0-3.0), $p<0.001$], while no difference was found for the corresponding case-control comparison during 2013-2018 ($p=0.08$). Compared to controls, Cr allergic patients diagnosed during 2003-2012 reported more severe disease with respect to 'current dermatitis' [3.4 (1.0-5.6) vs. 1.8 (0.5-4.7), $p=0.002$], 'worst-case dermatitis' [9.0 (7.5-9.5) vs. 8.0 (6.5-9.4), $p<0.001$], 'effect on work' [5.0 (2.4-7.4) vs. 3.7 (0.8-6.6), $p=0.007$] and 'effect on spare-time' [5.1 (2.4-7.4) vs. 3.9 (1.1-6.1), $p=0.002$]. However, no difference was found for the latter-mentioned measures of severity comparing cases and controls diagnosed during 2013-2018.

Occupational status

No significant difference was found comparing Cr allergic patients diagnosed during 2003-2012 versus 2013-2018 regarding 'loss of job' (7.5% vs. 6.2%, $p=1.0$), 'change of job' (19.6% vs. 13.8%, $p=0.3$) or 'sick-leave from job' (28.0% vs. 16.9%, $p=0.1$) (Table 3). Compared to controls, Cr allergic patients diagnosed during 2003-2012 reported more 'sick-leave from job' (OR=2.35, 95% CI: 1.40-3.93, $p=0.001$) whereas no case-control difference was found during 2013-2018.

Relevant exposure sources

Table 4 presents self-reported sources of exposure leading to dermatitis. As shown, leather exposure causing dermatitis was significantly more common in cases compared to controls within both study periods (OR₂₀₀₃₋₂₀₁₂=13.51, 95% CI: 8.14-22.42, $p<0.001$ and OR₂₀₁₃₋₂₀₁₈=17.51, 95% CI: 8.95-34.23, $p<0.001$). Leather exposure as a causative factor of dermatitis was reported by similar proportions of Cr allergic patients diagnosed during 2003-2012 versus 2013-2018 (71.0% vs. 66.2%, $p=0.5$). Additionally, an unchanged trend ($p_{\text{trend}}=0.7$) was found for self-reported leather exposure causing dermatitis in patients with Cr allergy diagnosed during 2013-2018. In contrary to 2003-2012, exposure to metalwork as a cause of dermatitis was more common in cases compared to controls throughout 2013-2018 (OR=3.23, 95% CI: 1.44-9.96, $p=0.008$).

Discussion

Main findings

In this post-regulatory questionnaire study, examination of Cr allergic patients over time did not show any significant change in perception of disease-severity nor in the proportion of self-reported leather exposures causing dermatitis.

Interpretation

In this study, we did not find a decline in the occurrence of foot dermatitis – nor hand dermatitis or other locations – in Cr allergic patients over time. Apart from reducing the occurrence of new cases of Cr-induced ACD, it is likewise pertinent to evaluate if the EU regulative has entailed an improvement in perception of disease-severity in patients with Cr allergy over time. It is conceivable that restricted levels of Cr (VI) in leather articles on the market might result in less disease-experience in already sensitized patients. However, we did not find any significant change in measures of disease-severity comparing Cr allergic patients diagnosed during 2003-2012 with those diagnosed during 2013-2018 (Table 2). In spite of this, we did notice similar levels in personal perception of disease-severity comparing cases and controls diagnosed during 2013-2018 as opposed to 2003-2012 (Table 2). The latter observation might suggest a diminished burden of disease in the most recently diagnosed Cr allergic patients. However, an increasing level of disease-burden in controls might explain the lack of case-control difference observed which might partly be due to the methylisothiazolinone epidemic outbreaking in 2010, peaking in 2013.¹⁴ The lack of improvement in disease-severity over time may also be attributed to the tertiary selection of our study population, hence mainly capturing the most severe cases of Cr allergy. Nevertheless, our Cr allergic patients reported very low levels of DLQI yielded by a median DLQI score of 2.0 for those diagnosed during 2003-2012 and 2013-2018, respectively (Table 2).

The self-reported prevalence of leather exposure as a causative factor of dermatitis was comparable for Cr allergic patients diagnosed in 2003-2012 versus 2013-2018 (71.0% vs. 66.2%, $p=0.5$); and is further supported by an unchanged trend in the self-reported proportion of leather exposures causing dermatitis in Cr allergic patients across 2013-2018 ($p_{\text{trend}}=0.7$). This is noteworthy as it might suggest that Cr-induced ACD due to leather exposure remains a substantial issue among those with Cr allergy despite legislative actions against Cr (VI) in leather. In a recent market survey (2018) on leather articles performed by The Environmental Protection Agency in Denmark, 10 out of 94 leather samples (10.6%) exceeded the limit value of 3 mg/kg. The highest measured values (11 mg/kg-28 mg/kg) were found in handbags.¹⁵ Despite a markedly lower proportion of leather articles on the Danish market exceeding 3 mg/kg Cr (VI) compared to a market survey from 2009 (44%),¹⁶ these levels might partially explain the insignificant differences found regarding dermatitis from leather exposure and severity of disease comparing cases during 2003-2012 and 2013-2018. Other factors include changing fashion trends, leather articles bought outside the EU and second-hand leather articles in end-use before 1 May 2015 which are not covered by the regulation. Furthermore, previous dose-response patch test studies have reported a 10% minimum elicitation threshold as low as 1 mg/kg for Cr (VI), hence elucidating the allergic potential of Cr (VI) levels lower than the regulatory limit value of 3 mg/kg.¹⁷ Ideally, no Cr (VI) should be present in leather. However, the reference method EN ISO 17075 used for quantification has a detection limit of 3 mg/kg. Additionally, it is important to note that the regulation on leather targets Cr (VI), thus not covering the presence of trivalent Cr despite several studies suggesting its capability of eliciting ACD in patients with Cr allergy.¹⁷⁻¹⁹ Furthermore, trivalent Cr present in the leather after tanning might undergo oxidation to Cr (VI) depending on various factors including pH, vegetable retanning, ammonia treatment, thermal and

photo-ageing, use of fatliquors and reducing agents.²⁰ Despite a seemingly decreasing trend in the occurrence of Cr (VI) on the Danish market, more market studies with a wide-range inclusion of leather products accompanied by epidemiological studies are warranted to address the efficiency of the EU regulation, both regarding leather-marketing and patient outcomes.

Strength and limitations

Strengths of this study include the high response rate, inclusion of a sex- and age-matched control group and controlling the type I error rate. This study was limited by a relatively short post-regulatory observation period, hence possibly not capturing the full effect of regulation. Furthermore, this study was limited by including the transition period (2013-2014) as part of the post-regulatory observation period which might be too soon to expect industrial adaptation despite reports of other regulated allergens showing decreasing trends in sensitization rates among dermatitis patients years before implementation of an upcoming EU ban.^{14,21} Nevertheless, no improvements were found in Cr allergic dermatitis patients as regards severity of disease nor dermatitis from leather exposures for other temporal stratifications (data not shown). Further limitations include selection bias as our dermatitis patients were included from a tertiary clinic, hence potentially having more severe dermatitis compared to patients seen at the general practitioner or at a dermatological practice. Recall bias was of importance as well possibly entailing an underestimation of dermatitis appearing years ago. Lastly, this study was limited by a potential increase in disease-burden in patients without Cr allergy, thus not acting as an ideal reference group.

Conclusion

No immediate sign of improvement was found in patients with Cr allergy concerning severity of disease and dermatitis from leather exposures five years following adoption of regulation against Cr (VI) in leather.

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Table 1 – Questionnaire study (2019): Baseline and clinical characteristics of dermatitis patients with and without chromium allergy.

Clinical characteristic	Cases 2003-2012 % (n=107)	Controls 2003-2012 % (n=358)	OR* (95% CI)	Cases 2013-2018 % (n=65)	Controls 2013-2018 % (n=229)	OR* (95% CI)	Cases 2003-2012 % (n=107)	Cases 2013-2018 % (n=65)	OR* (95% CI)
Age – mean (+/-SD)	50.0 (+/-11.3)	50.1 (+/-12.1)	-	56.0 (+/-14.7)	55.8 (+/- 13.0)	-	50.0 (+/-11.3)	56.0 (+/-14.7)	-
Sex – female	69.2 (74)	70.7 (253)	-	69.2 (45)	65.1 (149)	-	69.2 (74)	69.2 (45)	-
Atopic dermatitis	16.8 (18)	12.0 (43)	1.48 (0.81-2.70)	13.8 (9)	12.2 (28)	1.15 (0.52-2.59)	16.8 (18)	13.8 (9)	1.27 (0.53-3.03)
Other contact allergies – overall**	64.0 (68)	33.8 (121)	3.42 (2.18-5.36)	72.3 (47)	33.6 (77)	5.15 (2.81-9.47)	64.0 (68)	72.3 (47)	0.67 (0.34-1.30)
Nickel**	10.3 (11)	14.5 (52)	0.67 (0.34-1.34)	20.0 (13)	7.4 (17)	3.12 (1.43-6.82)	10.3 (11)	20.0 (13)	0.46 (0.19-1.10)
MCI/MI**	4.7 (5)	2.0 (7)	2.46 (0.76-7.91)	9.2 (6)	3.9 (9)	2.49 (0.85-7.26)	4.7 (5)	9.2 (6)	0.48 (0.14-1.64)
Initial location of dermatitis									
Face	17.8 (19)	29.9 (107)	0.51 (0.29-0.87)	21.5 (14)	35.4 (81)	0.50 (0.26-0.96)	17.8 (19)	21.5 (14)	0.79 (0.36-1.69)
Hands	72.9 (78)	51.4 (184)	2.54 (1.58-4.09)	70.8 (46)	50.7 (116)	2.36 (1.30-4.27)	72.9 (78)	70.8 (46)	1.11 (0.56-2.22)
Feet	54.2 (58)	19.8 (71)	4.78 (3.02-7.58)	50.8 (33)	16.6 (38)	5.18 (2.85-9.43)	54.2 (58)	50.8 (33)	1.15 (0.62-2.13)
Other	57.0 (61)	68.7 (246)	0.60 (0.39-0.94)	73.8 (48)	71.6 (164)	1.12 (0.60-2.09)	57.0 (61)	73.8 (48)	0.47 (0.23-0.92)
Current location of dermatitis									
Face	18.7 (20)	23.5 (84)	0.75 (0.44-1.29)	13.8 (9)	31.4 (72)	0.35 (0.16-0.75)	18.7 (20)	13.8 (9)	1.43 (0.61-3.33)
Hands	72.0 (77)	42.2 (151)	3.52 (2.20-5.64)	63.1 (41)	46.3 (106)	1.98 (1.13-3.49)	72.0 (77)	63.1 (41)	1.49 (0.78-2.86)
Feet	46.7 (50)	13.1 (47)	5.80 (3.56-9.46)	40.0 (26)	14.8 (34)	3.82 (2.07-7.08)	46.7 (50)	40.0 (26)	1.32 (0.70-2.44)
Other	54.2 (58)	58.1 (208)	0.85 (0.55-1.32)	64.6 (42)	57.6 (132)	1.34 (0.76-2.38)	54.2 (58)	64.6 (42)	0.65 (0.34-1.22)

*: Chi-square or Fisher's exact test (if < 5). Significant results (FDR-adjusted) are illustrated in bold.

** : Derived from the Danish National Database for Contact Allergy.

Table 2 – Questionnaire study (2019): Dermatology life quality index (DLQI) and disease-severity in dermatitis patient with and without chromium allergy.

	Cases 2003-2012 (n=107)	Controls 2003-2012 (n=358)	P-value*	Cases 2013-2018 (n=65)	Controls 2013-2018 (n=229)	P-value*	Cases 2003-2012 (n=107)	Cases 2013-2018 (n=65)	P-value*
DLQI score Median (IQR) Range	2.0 (0-7.0) 0-30	1.0 (0-3.0) 0-27	<0.001	2.0 (1.0-6.5) 0-27	2.0 (0-5.0) 0-27	0.08	2.0 (0-7.0) 0-30	2.0 (1.0-6.5) 0-27	0.78
Current dermatitis (VAS) Median (IQR) Range	3.4 (1.0-5.6) 0-10	1.8 (0.5-4.7) 0-10	0.002	2.4 (1.0-5.0) 0-9.7	2.9 (0.7-5.0) 0-10	0.96	3.4 (1.0-5.6) 0-10	2.4 (1.0-5.0) 0-9.7	0.45
Worst-case dermatitis (VAS) Median (IQR) Range	9.0 (7.5-9.5) 0.5-10	8.0 (6.5-9.4) 0-10	<0.001	8.7 (7.4-9.5) 0.2-10	8.2 (7.0-9.5) 0-10	0.32	9.0 (7.5-9.5) 0.5-10	8.7 (7.4-9.5) 0.2-10	0.18
Effect on work (VAS) Median (IQR) Range	5.0 (2.4-7.4) 0-10	3.7 (0.8-6.6) 0-10	0.007	4.0 (1.8-7.1) 0-10	4.5 (1.0-7.3) 0-10	0.97	5.0 (2.4-7.4) 0-10	4.0 (1.8-7.1) 0-10	0.22
Effect on spare time (VAS) Median (IQR) Range	5.1 (2.4-7.4) 0-10	3.9 (1.1-6.1) 0-10	0.002	4.5 (1.7-6.1) 0-10	4.0 (1.5-6.5) 0-10	0.86	5.1 (2.4-7.4) 0-10	4.5 (1.7-6.1) 0-10	0.12
Initial number of anatomical locations with dermatitis Median (IQR) Range	2.0 (1.0-3.0) 0-11	2.0 (1.0-3.0) 0-10	0.21	3.0 (1.0-4.0) 0-10	2.0 (1.0-4.0) 0-10	0.03	2.0 (1.0-3.0) 0-11	3.0 (1.0-4.0) 0-10	0.13
Current number of anatomical locations with dermatitis Median (IQR) Range	2.0 (1.0-3.0) 0-10	1.0 (1.0-2.0) 0-10	<0.001	2.0 (1.0-3.0) 0-10	1.0 (1.0-3.0) 0-10	0.14	2.0 (1.0-3.0) 0-10	2.0 (1.0-3.0) 0-10	0.92

IQR, interquartile range; VAS, visual analogue scale.

*: Mann-Whitney *U*-test. Significant results (FDR-adjusted) are illustrated in bold.

Table 3 – Questionnaire study (2019): Occupational status and medical needs due to dermatitis during the last 12 months in patients with and without chromium allergy.

	Cases 2003-2012 % (n=107)	Controls 2003-2012 % (n=358)	OR* (95% CI)	Cases 2013-2018 % (n=65)	Controls 2013-2018 % (n=229)	OR* (95% CI)	Cases 2003-2012 % (n=107)	Cases 2013-2018 % (n=65)	OR* (95% CI)
Occupational status									
Loss of job	7.5 (8)	5.6 (20)	1.37 (0.58-3.20)	6.2 (4)	5.7 (13)	1.09 (0.34-3.46)	7.5 (8)	6.2 (4)	1.23 (0.36-4.35)
Change of job	19.6 (21)	12.0 (43)	1.79 (1.01-3.18)	13.8 (9)	7.0 (16)	2.14 (0.90-5.10)	19.6 (21)	13.8 (9)	1.52 (0.65-3.57)
Sick-leave from job	28.0 (30)	14.2 (51)	2.35 (1.40-3.93)	16.9 (11)	16.6 (38)	1.02 (0.49-2.14)	28.0 (30)	16.9 (11)	1.92 (0.88-4.17)
Medical needs due to dermatitis during the last 12 months									
General practitioner consultation	29.9 (32)	24.0 (86)	1.35 (0.84-2.18)	40.0 (26)	26.6 (61)	1.84 (1.03-3.27)	29.9 (32)	40.0 (26)	0.64 (0.33-1.22)
Dermatologist consultation	23.4 (25)	18.7 (67)	1.32 (0.79-2.23)	43.1 (28)	26.6 (61)	2.08 (1.18-3.69)	23.4 (25)	43.1 (28)	0.40 (0.21-0.78)
No treatment	18.7 (20)	34.4 (123)	0.44 (0.26-0.75)	6.2 (4)	22.7 (52)	0.22 (0.08-0.64)	18.7 (20)	6.2 (4)	3.45 (1.14-11.11)
Emollients	61.7 (66)	40.5 (145)	2.37 (1.52-3.68)	55.4 (36)	46.7 (107)	1.42 (0.81-2.46)	61.7 (66)	55.4 (36)	1.30 (0.69-2.44)
Topical corticosteroid	60.7 (65)	36.6 (131)	2.68 (1.72-4.18)	69.2 (45)	45.0 (103)	2.75 (1.53-4.95)	60.7 (65)	69.2 (45)	0.69 (0.36-1.32)
Systemic corticosteroid	12.1 (13)	3.1 (11)	4.36 (1.89-10.05)	13.8 (9)	2.6 (6)	5.97 (2.04-17.48)	12.1 (13)	13.8 (9)	0.86 (0.35-2.13)
Immunosuppressive drugs	3.7 (4)	4.7 (17)	0.78 (0.26-2.37)	16.9 (11)	5.2 (12)	3.68 (1.54-8.80)	3.7 (4)	16.9 (11)	0.19 (0.06-0.63)

*: Chi-square or Fisher's exact test (if n < 5). Significant results (FDR-adjusted) are illustrated in bold.

Self-reported exposure sources*	Cases 2003-2012 % (n=107)	Controls 2003-2012 % (n=358)	OR** (95% CI)	Cases 2013-2018 % (n=65)	Controls 2013-2018 % (n=229)	OR** (95% CI)	Cases 2003-2012 % (n=107)	Cases 2013-2018 % (n=65)	OR** (95% CI)
Leather	71.0 (76)	15.4 (55)	13.51 (8.14-22.42)	66.2 (43)	10.0 (23)	17.51 (8.95-34.23)	71.0 (76)	66.2 (43)	1.25 (0.65-2.44)
Work tools	13.1 (14)	2.0 (7)	7.55 (2.96-19.24)	9.2 (6)	3.1 (7)	3.23 (1.04-9.96)	13.1 (14)	9.2 (6)	1.47 (0.54-4.00)
Metalwork	8.4 (9)	4.2 (15)	2.10 (0.89-4.95)	16.9 (11)	5.7 (13)	3.39 (1.44-7.97)	8.4 (9)	16.9 (11)	0.45 (0.18-1.15)
Wood preservation	14.0 (15)	1.7 (6)	9.57 (3.61-25.34)	7.7 (5)	4.4 (10)	1.83 (0.60-5.54)	14.0 (15)	7.7 (5)	1.92 (0.68-5.56)
Cement	15.9 (17)	1.7 (6)	11.08 (4.25-28.91)	9.2 (6)	3.1 (7)	3.23 (1.04-9.96)	15.9 (17)	9.2 (6)	1.85 (0.69-5.00)

Supplementary Table 1.

Questions included in the questionnaire sent to the cohort.

Where on your body did you have rash/eczema when your skin condition started? (Please tick more than one box if appropriate)

Scalp; Face; Neck; Upper arms; Lower arms; Hands; Chest/stomach; Legs; Feet; other part of body, where?

Have you had rash/eczema during **the last 12 months?**

No; Yes, all the time; Yes, more than half the time; Yes, about half the time; Yes, less than half the time

Where was the rash/eczema last time? (Please tick more than one box if appropriate)

Scalp; Face; Neck; Upper arms; Lower arms; Hands; Chest/stomach; Legs; Feet; other part of body, where?

How would you assess the severity of the rash/eczema using a scale of 0 to 10, where 0 corresponds to no rash/eczema and 10 correspond to the worst imaginable rash/eczema? Mark on the line.

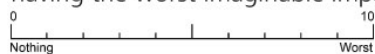
How severe are the rash/eczema today?



How severe were the rash/eczema when they were at their worst?



In your working life, how severely do you think rash/eczema affected you, on a scale of 0 to 10, where 0 corresponds to having no impact and 10 corresponds to having the worst imaginable impact? Mark on the line.



In your current job, do you have contact with things that cause you rash/eczema?

No; No, unemployed/retired; Don't know; Yes

If yes, are they any of the following products? (Please tick more than one box if appropriate)

Leather shoes; Leather gloves; Tools; Screws; Metalwork; Cement; Wood protection; Other.

How long had you been employed in this job when you first had a patch test? (e.g. 2 years and 3 months)

In your leisure time, how would you assess how severely the rash/eczema have affected you, using a scale of 0 to 10, where 0 corresponds to having no impact and 10 corresponds to having the worst imaginable impact? Mark on the line.



During your leisure time, have **you ever been** in contact with products that **caused** you rash/eczema?

No; Yes

If yes, were they any of the following products? (Please tick more than one box if appropriate)

Leather shoes; Leather gloves; Tools; Screws; Metalwork; Watch straps; Cement; Wood protection; Other.

How has **your** rash/eczema been treated in the last 12 months? (Please tick more than one box if appropriate)

No treatment; Moisturiser cream; Hormone cream /ointment (also called steroid cream);

Protopic or Elidel; Penicillin or other types of antibiotics; Corticosteroid tablets; Hay fever-/anti-itch tablets; Herbal medicine;

Immunosuppressant tablets (e.g. methotrexate (MTX), azathioprine (Imurel) etc.); Light treatment ; Other, please write:

Have you visited a general practitioner in the last year **because of** your rash/eczema?

Yes, once; Yes, 2-5 times; Yes, more than 5 times; No

Have you visited a dermatologist in the last year **because of** your rash/eczema?

No; Yes, once; Yes, 2-5 times; Yes, more than 5 times

Has a doctor ever told you that you have hay fever?

No; Yes; Don't know

Have you been in contact with products that caused you rash/eczema in previous jobs?

No; Don't know; Yes

If yes, were they any of the following products? (Please tick more than one box if appropriate)

Leather shoes; Leather gloves; Tools; Screws; Metalwork; Cement; Wood protection; Other.

Does the rash/eczema improve when you are away from your normal work, e.g. at weekends or when you are on holiday?

No; Yes, sometimes; Yes, usually; Yes, always; Don't know/no longer have eczema.

When you have had rash/eczema, how has it affected your daily life? Please tick ☐ whether you agree/disagree with the following statements.

I must often take special precautions:

Agree; Disagree

I am frequently bothered by eczema and itching:

Agree; Disagree

I have been on sick leave from my job:

Agree; Disagree

I have had to change occupation:

Agree; Disagree

I have become unemployed:

Agree; Disagree

I have retired: **Agree; Disagree**

It has not particularly affected my daily life:

Agree; Disagree

Other, please write:

Has a doctor ever told you that you have asthma?

No; Yes; Don't know

Have you ever had itchy skin, which you have scratched and rubbed a lot?

No; Yes

Have you had itchy skin, which you have scratched and rubbed a lot in the last 12 months?

No; Yes

How old were you when your skin condition started?

Less than 2 years old; Between 2 and 5 years old; Between 6 and 10 years old; More than 10 years old

Has your skin condition ever been present on your insides of elbows, back of the knees, ankles, neck or around the eyes?

No; Yes

If yes, has the skin condition been present on your insides of elbows, back of the knees, insteps, neck or around the eyes in the last 12 months?

No; Yes

Have you ever suffered from dry skin all over your body?

No; Yes

If yes, have you suffered from dry skin all over your body in the last 12 months?

No; Yes
