

Patch test reactivity to metal allergens following regulatory interventions: a 33-year retrospective study

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Background: Contact allergy epidemics to chromate and nickel were addressed in Denmark in 1983 and 1990 by regulatory interventions.

Objectives: To evaluate whether regulatory interventions on nickel and chromate exposure have reduced the proportion of strong patch test reactions.

Methods: 22 506 patients with dermatitis aged 4–99 years were patch tested with nickel sulfate, potassium dichromate, or cobalt chloride between 1977 and 2009.

Results: The proportion of 3+ reactions to nickel sulfate was reduced and almost disappeared after the mid- and late 1980s (P -trend = 0.001). Today, 1+ and 2+ nickel reactions occur equally frequent. Cobalt chloride patch test reactivity reflected the nickel development to some degree. The proportion of 3+ reactions to potassium dichromate was reduced during the 1980s (P -trend = 0.13), whereas the proportion of 2+ reactions to potassium dichromate have increased in recent years.

Conclusions: The decrease in nickel sulfate and cobalt chloride 3+ patch test reactivity began long before the Danish nickel regulation came into effect. This could be because of research activity at the time as well as political attention in Northern Europe. The chromate content in cement regulation may have changed the epidemiology of patch test reactivity; however, in recent years, 2+ reactions to chromate have increased markedly, a development that should be carefully followed.

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Contact allergy is prevalent in the general population but especially in patients with dermatitis (1–4). In recent decades, different attempts have been made to limit contact allergy epidemics (5). The nickel problem was addressed in 1990 in Denmark and in 1994 in the EU by limiting nickel release (and initially the nickel content) from consumer items intended to come into direct and prolonged skin contact (5–7). The chromate problem in construction workers was addressed in 1983 in Denmark and in 2005 in the EU by compulsory addition of ferrous sulfate to cement, reducing the chromate content to not more than 2 p.p.m. (5). We have recently

shown that regulations on metal allergen exposure have changed the epidemiology of contact allergy to nickel and chromate in Denmark. Thus, the prevalence of nickel allergy has decreased in young female patients with dermatitis and young women from the general population following nickel regulation (8–10). However, the overall prevalence of nickel allergy remained stable as the prevalence of nickel allergy increased in middle-aged and older female patients with dermatitis over the same period, probably because of a cohort effect (9). The prevalence of chromate allergy caused by cement exposure decreased between 1985 and 1995 but

a significant increase has been observed in recent years, probably because of leather exposure (11). It has been debated whether the prevalence of cobalt allergy would increase following nickel regulation as it is probable that manufacturers may use cobalt instead of nickel in jewellery (6,12,13). A Danish study on female patients with dermatitis patch tested between 1985 and 2007 found no general increase in the prevalence of cobalt allergy (9). Furthermore, few inexpensive consumer items recently purchased in Denmark released cobalt in concentrations that would result in allergic cobalt dermatitis (manuscript in preparation).

There are several ways to monitor a contact allergy epidemic and the possible effect of regulatory intervention (5), for example, to determine the prevalence of positive patch test reactions to the allergen in question, exposure assessment by chemical analysis of allergens in products, and finally, to assess the relative strength and distribution of positive patch test reactions. We set out to use the latter method to evaluate the effect of nickel and chromate regulations in Denmark using patch test reactivity data to nickel, cobalt, and chromate in patients with dermatitis from a 33-year period. Our *a priori* hypothesis was that regulatory interventions on nickel and chromate exposures have resulted in a reduced strength of patch test reactivity in patients with dermatitis after regulation when compared with patch test reactivity before.

Materials and Methods

Study population

Patients with dermatitis who underwent routine patch testing with the European baseline series at Gentofte Hospital between 1 January 1977 and 31 December 2009 were included. The MOAHLFA (Male, Occupation, Atopic dermatitis, Hand eczema, Leg dermatitis, Facial dermatitis, Age above 40 years) index was not routinely registered throughout the study period. Thus, MOAHLFA registrations date back to 1994 (but only to 2001 for 'facial dermatitis').

Patch testing

Testing was performed throughout the study period with nickel sulfate 5% in petrolatum (pet.), cobalt chloride 1% in pet., and potassium dichromate 0.5% in pet. using Finn Chambers® (8 mm; Epitest Ltd Oy, Tuusula, Finland) on Scanpor® tape (Norgesplaster A/S, Alfarma, Vennesla, Norway). Patch test substances were from Hermal, Reinbek, Germany, throughout the study period. Other patch test substances that were investigated include neomycin sulfate 20% in pet. (1977–2009), benzocaine 5%

in pet. (1984–2009), formaldehyde 1% in aqua (1984–2009), epoxy resin 1% in pet. (1977–2009), and quaternium-15 1% in pet. (1985–2009).

Patch tests were applied to the upper back and were occluded for 2 days. Readings were taken on D2, and on D3 or D4, and on D7 according to the recommendation from the International Contact Dermatitis Research Group (14). Thus, homogeneous redness and infiltration in the entire test area were scored as a 1+ reaction. Homogeneous redness, infiltration, and vesicles in the test area were scored as a 2+ reaction and homogeneous redness, infiltration, and coalescing vesicles in the test area as a 3+ reaction. A 1+, 2+, or 3+ reading was interpreted as a positive response. An irritant response, a doubtful (+?), or a negative reading was interpreted as a negative response.

Statistical analysis

The temporal development of patch test reactivity to metal allergens across test years was investigated with the χ^2 trend test (linear-by-linear association). Thus, we evaluated whether the relative proportion of, respectively, 1+ reactivity versus 2+ and 3+ reactivity in combination, 2+ reactivity versus 1+ and 3+ reactivity in combination, and 3+ versus 1+ and 2+ reactivity in combination differed significantly across test years. We also stratified these analyses by sex and age group to test whether different developments could be identified. To test whether a change in the distribution of 1+, 2+, and 3+ reactions to metal allergens over the study period took part in a general trend of changing patch test reactivity, the development of patch test reactivity to neomycin, benzocaine, formaldehyde, epoxy resin, and quaternium-15 was also investigated. The distribution of age was assessed by Kolmogorov–Smirnov test. Continuous data were summarized by median and interquartile (IQR) ranges. Data analyses were performed using the Statistical Products and Service Solutions package (SPSS Inc., Chicago, IL, USA) for windows (release 15.0).

Results

A total of 22 506 patients with dermatitis (64.0% women and 36.0% men) aged 4–99 years were patch tested with nickel sulfate, potassium dichromate, or cobalt chloride between 1977 and 2009. Their main characteristics have previously been described (9,15). The MOAHLFA index is shown in Table 1. The age of the study population was not normally distributed as assessed by Kolmogorov–Smirnov test ($P = 0.001$). The median age was 47 (IQR = 29) years.

Table 1. MOAHLFA index in patients with dermatitis who were metal patch tested at Gentofte Hospital during 1994–2009 (facial dermatitis was registered only since 2001)

Frequency of variables	All patients (<i>n</i> = 12 803), % (<i>n</i> / <i>n</i> _{total})	Nickel-allergic patients (<i>n</i> = 1281), % (<i>n</i> / <i>n</i> _{total})	Cobalt-allergic patients (<i>n</i> = 425), % (<i>n</i> / <i>n</i> _{total})	Chromate-allergic patients (<i>n</i> = 275), % (<i>n</i> / <i>n</i> _{total})
MOAHLFA index*				
Males	35.1 (4490)	10.5 (134)	22.1 (94)	32.4 (89)
Occupational dermatitis	13.7 (1757)	17.6 (225)	20.2 (86)	14.9 (41)
Atopic dermatitis	13.6 (1735)	12.3 (158)	15.5 (66)	13.1 (36)
Hand dermatitis	33.0 (4221)	39.0 (500)	52.7 (224)	54.5 (150)
Leg ulcers	8.5 (1092)	5.6 (72)	4.2 (18)	9.8 (27)
Facial dermatitis	20.5 (1419) [†]	20.4 (136) [‡]	19.4 (48) [§]	13.8 (24)
Age > 40 years	66.2 (8479)	56.0 (717)	60.2 (256)	78.5 (216)

*The MOAHLFA index stands for Male, Occupational dermatitis, Atopic dermatitis, Hand dermatitis, Leg ulcers, Facial dermatitis and Age above 40 years. It shows the characteristics of patients tested at a patch test clinic and may be used for comparison (23).

[†]6922 patients with dermatitis since 2001.

[‡]667 nickel-allergic patients since 2001.

[§]248 cobalt-allergic patients since 2001.

^{||}174 chromate-allergic patients since 2001.

The overall prevalence of contact allergy was 2.7% for chromate (men = 2.9% and women = 2.6%), 3.8% for cobalt (men = 2.8% and women = 4.4%), and 10.4% for nickel (men = 3.2% and women = 14.4%). In male patients, the prevalence of cobalt allergy decreased steadily and significantly from 8.3% in 1997 to 0.8% in 2009 (*P*-trend = 0.001), whereas the prevalence of nickel allergy remained relatively stable over the test period (the prevalence was 5.2% in 1977 and 4.6% in 2009). However, the temporal development of nickel allergy in male patients followed a weak U-shaped pattern with an initial slight decrease and a gradual increase in recent years.

The temporal development of patch test reactivity to nickel, cobalt, and chromate is displayed in Figs. 1–3. No differences were found regarding sex and age for any of the allergens. Apparently, the epidemiology of nickel patch test reactivity has changed over the test period because the proportion

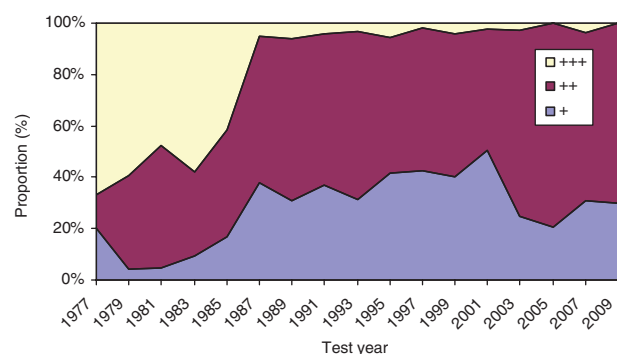


Fig. 1. Patch test reactivity to 5% nickel sulfate among 2335 nickel patch test positive patients seen at the Department of Dermatology, Gentofte Hospital, between 1977 and 2009. Patch test data are presented for every second year and represent an average of the two preceding years (e.g. 1977 and 1978 divided by 2 is presented as 1977); 2009 represents only 2009 data.

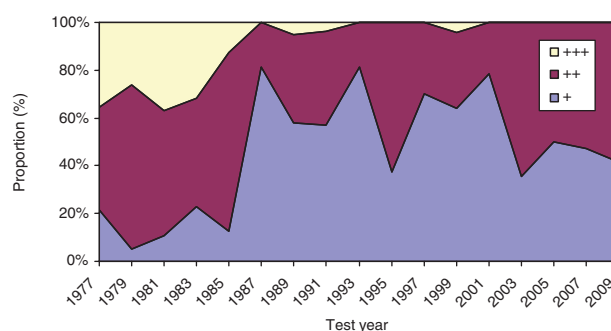


Fig. 2. Patch test reactivity to 1% cobalt chloride among 861 cobalt patch test positive patients seen at the Department of Dermatology, Gentofte Hospital, between 1977 and 2009. Patch test data are presented for every second year and represent an average of the two preceding years (e.g. 1977 and 1978 divided by 2 is presented as 1977); 2009 represents only 2009 data.

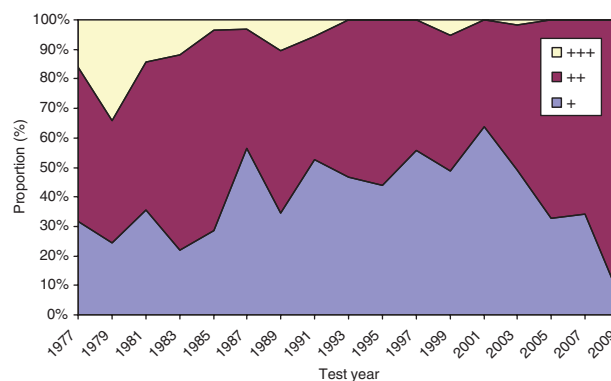


Fig. 3. Patch test reactivity to 0.5% potassium dichromate among 607 chromium patch test positive patients seen at the Department of Dermatology, Gentofte Hospital, between 1977 and 2009. Patch test data are presented for every second year and represent an average of the two preceding years (e.g. 1977 and 1978 divided by 2 is presented as 1977); 2009 represents only 2009 data.

of 3+ reactions has reduced and almost disappeared since the mid- and late 1980s (P -trend = 0.001) (Fig. 1). The prevalence of 1+ and 2+ reactions to nickel was relatively stable, although the proportion of 2+ reactions may have increased slightly in recent years. The distribution of cobalt patch test reactivity over the study period reflected the nickel development to some degree (Fig. 2). Thus, the proportion of 3+ reactions decreased during the 1980s (P -trend = 0.001) whereas the proportion of 1+ and 2+ reactions are predominant today and observed more or less equally frequent. Finally, the development of chromate patch test reactivity showed that the proportion of 3+ reactions was reduced during the 1980s (P -trend = 0.13) but the proportion of 2+ reactions to chromate has increased dramatically in recent years. When other patch test ingredients from the baseline series were investigated, we found only very little diversion in the temporal development of patch test reactivity and no general decreasing trend in strong patch test reactivity. Thus, for neomycin, a weak decrease in the frequency of 3+ reactivity was observed after 1986 but a stable development of 2+ reactivity; for formaldehyde, quarternium-15, benzocaine, and epoxy resin, a stable development of 1+, 2+, and 3+ reactivity was observed over the study period.

Discussion

The distribution of patch test reactivity to nickel, cobalt, and chromate changed over the 33-year observation period. Thus, the proportion of 3+ patch test reactions to nickel and cobalt decreased significantly during the 1980s and has almost remained absent since then (Figs. 1 and 2). It has previously been shown that concomitant nickel and cobalt allergy is frequent (16). This is mainly a result of simultaneous sensitization to nickel and cobalt, as the metals often occur together, and not a result of cross-sensitivity (17,18). As temporal trends of cobalt and nickel allergy were similar in Danish female patients with dermatitis tested between 1985 and 2007 (9), we also expected to see a similar development in patch test reactivity to the two metals in the current study. Apparently, the decrease in nickel and cobalt 3+ patch test reactivity began already in the early 1980s, long before the Danish nickel regulation came into effect in the years 1989–1991 (7). One would not have expected the decrease in nickel allergy to begin this early and our finding may have several explanations: (i) the nickel problem received much scientific attention during the 1970s and 1980s, and it is possible that some manufacturers changed the production of consumer items at an early point to prevent nickel release and allergy; (ii) there was a general European

political movement to prevent nickel allergy in the 1980s as governments in Sweden and Germany also tried to limit the nickel allergy problem by reducing the nickel content of piercing posts and labelling consumer items (6). This may also have influenced the use of nickel in consumer products; (iii) occupational nickel and cobalt exposure may have been reduced during the 1970s because of increased work hygiene and automation of work routines, which could have led to a reduction in the proportion of 3+ patch test reactions; (iv) although the criteria of positive patch test reactions remained unchanged over the test period, it is possible that changing staff in the patch test clinic at Gentofte Hospital have read and interpreted positive patch test reactions differently resulting in fewer 3+ reactions in recent years. However, to test this fallacy, we performed temporal analyses on other allergens from the baseline test series and found that no overall trend of decreasing patch test reactivity could be identified. This supports the validity of our data. Taken together, it was not possible to directly connect the decrease in 3+ patch test reactivity to the Danish nickel regulation as it occurred before its introduction; however, the scientific and political attention in Northern Europe may indirectly have influenced the beneficial development of patch test reactivity in Danish patients with dermatitis. It is generally acknowledged that systemic allergic nickel dermatitis and nickel dermatitis with secondary spread occur less frequently today than earlier (19). This is in accordance with our data which show that the frequency of strong patch test reactions to nickel has decreased over a 33-year period in Denmark. An effect of the EU Nickel Directive has also been shown outside Denmark, for example, in female patients with dermatitis in Sweden and Germany (20,21), and it is possible that similar developments in patch test reactivity can be observed in patients from these countries.

The distribution of patch test reactivity to chromate showed a non-significant decrease in the proportion of 3+ reactions during the test period (Fig. 3). We had available patch test data from only six test years before the introduction of the Danish chromate regulation in 1983, which makes it difficult to make a sufficient comparison of reactivity before and after regulation. However, it seems that the proportion of 3+ patch test reactions decreased following the regulation on the content of chromate in cement. Despite the limitations mentioned for the interpretation of nickel and cobalt, patch reactivity data are similar to the interpretation of chromate data; it is probable that the decreasing trend of 3+ reactivity may be attributed to the chromate regulation. Of particular interest, the proportion of 2+ patch test reactions to chromate has increased dramatically in recent years. This development

has occurred at the same time as the increase in the prevalence of chromate allergy in male and female patients with dermatitis, mainly because of leather exposure (11). The chromate allergy problem caused by leather should be carefully followed in the near future so that preventive measures can be taken to reduce morbidity. A weakness of our study was the absence of information on causative exposures for the different strengths of patch test reactions. However, we know from a recent Danish study that in 197 patients who had positive patch test reactions to chromium between 1995 and 2007, 54% of positive reactions were associated with current or past leather exposure (11). The overall decrease in strong patch test reactivity may to some degree be a consequence of reduced allergen concentrations during sensitization as shown by Friedmann (22).

In conclusion, this 33-year retrospective patch test study showed that the strength of patch test reactivity to nickel and cobalt decreased during the 1980s but that 1+ and 2+ reactions now seem to occur with equal frequency. The initial effect is probably an indirect effect of discussions on nickel regulation. The regulation on the content of chromate in cement may have decreased the proportion of 3+ patch test reactions to chromate. However, in recent years, 2+ reactions to chromate have increased markedly, a development that should be carefully followed.

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