Fluctuations in the prevalence of chromate allergy in Denmark and exposure to chrome-tanned leather

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Summary

Background. A recent Danish study showed a significant increase in the prevalence of chromate contact allergy after the mid-1990s, probably as a result of exposure to leather products.

Objectives. To reproduce the results by analysing data from the period 1992–2009 at Odense University Hospital, Denmark. The temporal development in the occurrence of chromate contact allergy and assumed causative exposures were investigated.

Patients, Materials and Methods. A retrospective analysis of patch test data was performed ($n = 8483$), and medical charts from patients with chromate allergy (n = 231) were reviewed. Comparisons were made using the χ^2-test. A test of the reproducibility of the TRUE Test® was also performed. Logistic regression analyses were used to test for associations.

Results. No significant changes in the prevalence or exposure sources of chromate allergy during 1992–2009 were identified. Leather shoes (24.4%) were the most frequent exposure sources in chromate allergy, and were mainly registered in women, although the difference between men and women was not significant ($P = 0.07$). Cement and leather glove exposure occurred significantly more often in men than in women ($P = 0.002$). Foot dermatitis (40.3%) was the most frequent anatomical location, apart from hand eczema (60.6%). The reproducibility of the TRUE Test® was 93.3%.

Conclusions. Apart from hand eczema, the most frequent clinical picture of chromate allergy was foot dermatitis caused by leather shoe exposure. A tendency for an increasing prevalence of chromate contact allergy from 1997 was shown, but no significant change was detectable.

Key words: allergy; chromate; dermatitis; leather; patch test; reproducibility; statistics; TRUE Test®.

Leather products have been described as the most common cause of chromate contact allergy since the early 1990s in Denmark (1). Hansen et al. (2) observed that the most frequent clinical pattern of chromate dermatitis in 2002–2004 was foot dermatitis resulting from leather shoes and boots. Thyssen et al. (3) confirmed these trends in a newly published article. Previously, cement exposure was the most frequent cause of chromate allergy in Denmark, but the Danish legislation on adding ferrous sulfate to cement since 1983, in order to reduce the water-soluble chromium(VI) content to a maximum of 2 ppm, appears to have brought a reduction in the frequency of chromate allergy among workers in the construction industry (4, 5). Recently, Thyssen et al. (3)

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investigated the annual prevalence of chromate allergy among patients patch tested between 1985 and 2007 at Gentofte Hospital, Denmark. They found a significant decrease in the prevalence of chromate allergy from 1985 to 1994, owing to decreasing relevant cement exposure, and a significant increase in the prevalence of chromate allergy from 1995 to 2007, owing to increasing relevant leather exposure. The increasing prevalence was mainly a result of leather shoes causing foot dermatitis. This shift from occupational disease to consumer disease was in line with other contact allergy epidemics (6).

The present study investigated temporal fluctuations in the occurrence of chromate allergy as well as assumed causative exposures in the period 1992–2009 at Odense University Hospital, Denmark. The aim was to determine whether the results of Thyssen et al. (3) could be reproduced in patients patch tested at Odense University Hospital during part of the period. To make the results in this study comparable with those of Thyssen et al. (3), the methods used were as similar as possible, with the same statistical analyses and illustrations.

Patients and Methods

Design and study population

All patients with suspected allergic contact dermatitis patch tested between January 1992 and 2009 at the Department of Dermatology and Allergy Centre, Odense University Hospital, Denmark were included in the study. If patients had been patch tested on more than one occasion during the test period, the first result was used for the analysis.

Chromate patch test data were stratified by test year, sex, and age group. Information about the relevance of positive patch test reactions (current, past, or unknown), as well as the MOAHLFA (males, occupational dermatitis, atopic dermatitis, hand dermatitis, leg ulcers, facial dermatitis, age more than 40 years) (7) index, was collected, together with the patch test data from the allergen database.

Medical records of patients with positive patch test reactions to chromate were reviewed regarding information about the anatomical location of dermatitis (hand, foot, leg, face/neck, arms, trunk, universal, only hand dermatitis) and relevant causative exposures (leather shoes, leather gloves, other leather exposure, cement, metal, cosmetics, graphic work and paint, and other chromium materials).

Finally, an analysis of the reproducibility of the TRUE Test® was performed on the basis of cases tested on more than one occasion during the test period.

Patch testing

TRUE Tests® (8), which include potassium dichromate 23 μg/cm^2, were used for patch testing. TRUE Tests® were applied on the upper back for 2 days, and read subsequently on day 2, day 3 or 4, and day 5 or 7. The reactions were scored as [−, irritant reaction (IR), ?, +, ++, +++], according to the recommendations of the International Contact Dermatitis Research Group. Negative reactions (−), IRs and doubtful reactions (?) were registered as a negative response. One + or more on any reading day was registered as a positive response.

Definitions

The consulting physician recorded the relevance of the positive patch test reactions to potassium dichromate. 'Current relevance' was noted in patients with a current dermatitis reaction in combination with a history of current exposure to chromate. 'Past relevance' was noted in patients with a positive patch test reaction to chromate in combination with a history of past dermatitis reaction and exposure to chrome. 'Unknown relevance' was noted in patients with dermatitis and chromate allergy without any knowledge of current or past chrome exposure. If the physician had performed no registrations concerning the relevance, it was also interpreted as 'unknown relevance'.

Statistics

Comparisons were made using the χ^2-test. A χ^2 trend test (linear-by-linear association) was performed to test for significant trends across test years. Two similar logistic regression models were used, with 'chromate allergy' as the dependent variable, and sex, age group ('0–30 years', '31–60 years', '>60 years') and test year ('1992–1997', '1998–2003', '2004–2009') as the independent variables. In the first model, a test for interaction between sex and test year was performed. In the second model, a test for interaction between age group and test year was performed. In both models, the log-likelihood ratio test determined whether the interactions were significant, and thus whether sex and age group should be taken into account when evaluating the prevalence of chromate allergy across test years. Results were expressed as odds ratios with 95% confidence intervals. The statistical significance level was set to 5% in all analyses. The statistical analyses were performed with IBM PASW® STATISTICS 18 (formerly SPSS STATISTICS).

Results

A total of 8483 patients with suspected allergic contact dermatitis (63.6% females and 36.4% males) aged

2–95 years were patch tested between 1992 and 2009. The overall prevalence of chromate allergy was 2.7% (3.0% of women and 2.3% of men).

The logistic regression models showed *P*-values of 0.43 and 0.13 for the interaction terms gender × test year and age group × test year, respectively. Thus, fluctuations in the prevalence of chromate allergy among patients patch tested during 1992–2009 were not significantly dependent on either sex or age group, and stratification by these factors was not performed. The temporal development of chromate allergy can therefore be presented for both genders and all age groups combined. Figure 1 illustrates the development of chromate allergy among patients patch tested between 1992 and 2009. The lowest prevalence was in 1997. However, when significant trends across test years were tested with the χ^2 trend test, there was no significant decrease or increase, which could support subdivision of the population into two groups. However, it is worth noting that there seemed to be a slightly increasing trend from 1997 to 2009 ($P = 0.11$ in a simple χ^2 trend test, and $P = 0.13$ in a logistic regression analysis including age and gender). There was also no significant difference on comparison of male and female patients, stratified by age group and patch test year (Table 1). However, the overall prevalence of chromate allergy was highest among patients aged 31–60 years (3.5%), and in this age group women had a higher prevalence than men (3.9% versus 2.9%).

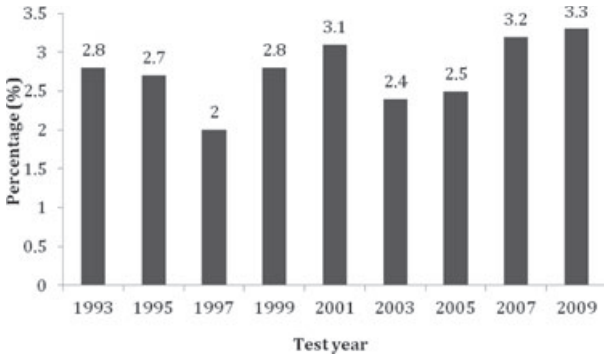

Fig. 1. The prevalence of chromate allergy among patients with dermatitis patch tested between 1992 and 2009 at Odense University Hospital, Denmark. The columns represent 2 years (the first column is 1992–1993, etc). A χ^2 trend test was performed to test for significant changes over time. There was no significant decrease or increase about 1997, which was the year with the lowest observed prevalence.

Table 2 shows the clinical characteristics of the 221 patients with chromate allergy. The total number of patients with positive patch test reactions during 1992–2009 was 231, but only 221 (95.7%) medical charts were retrieved. The MOAHLFA index showed that occupational dermatitis occurred significantly more often in men than in women, but apart from this there were no significant differences between men and women. The relevance of positive patch test reactions to chromate was current in 31.7%, past in 26.2%, and unknown in 43.4%, but there was no significant difference when men and women were compared. Current relevance was mainly noted for leather shoes (64.8%) and cement (14.3%). In contrast, past relevance was caused mainly by cement (71.4%). No patients were registered with combined exposure to both cement and leather. The most frequent relevant exposures involved leather products, which included leather shoes (24.4%), leather gloves (8.6%), and other leather products, such as furniture, watchbands, and coats (3.2%). In total, leather exposure was registered in 36.2% of the 221 patients with chromate allergy. Cement and leather glove exposure occurred significantly more often in men than in women ($P = 0.002$). Exposure to metal (10.0%) was mainly registered in men, and exposure to leather shoes was mainly registered in women, although the differences were not significant ($P = 0.07$). The anatomical locations of the dermatitis reaction were mostly the hands (60.6%) and feet (40.3%).

Table 1. The prevalence of chromate allergy among 8483 patients with dermatitis stratified by age group and patch test year

Frequency of variables	Chromate allergy, % (*n*/total)			*P*-value[a]
	All	Male patients	Female patients	
Age group (years)				
0–30	1.7 (39/2294)	1.1 (8/709)	2.0 (31/1585)	0.16
31–60	3.5 (157/4441)	2.9 (47/1649)	3.9 (110/2792)	0.06
>60	2.0 (35/1748)	2.1 (16/745)	1.9 (19/1003)	0.71
Patch test year				
1992–1997	2.6 (84/3284)	2.0 (23/1158)	2.9 (61/2126)	0.12
1998–2003	2.7 (73/2697)	2.0 (20/992)	3.1 (53/1705)	0.09
2004–2009	3.0 (74/2502)	2.9 (28/953)	3.0 (46/1549)	0.96

[a] *P*-value of χ^2-test comparing male and female patients.

Table 2. Clinical characteristics of the 221 patients with dermatitis and chromate allergy tested between 1992 and 2009

	Total ($n = 221$), % (n)	Males ($n = 71$), % (n)	Females ($n = 150$), % (n)	P-value[a]
MOAHLFA index				
Males	32.1 (71)	—	—	—
Occupational dermatitis	13.6 (30)	21.1 (15)	10.0 (15)	0.02
Atopic dermatitis	24.0 (53)	21.1 (15)	25.3 (38)	0.49
Hand dermatitis	60.6 (134)	66.2 (47)	58.0 (87)	0.24
Leg ulcers	5.2 (12)	4.2 (3)	6.0 (9)	0.59
Facial dermatitis	6.8 (15)	2.8 (2)	8.7 (13)	0.11
Age >40 years	67.9 (150)	73.2 (52)	65.3 (98)	0.24
Relevance of positive patch test reactions to chromate				
Current	31.7 (70)	33.8 (24)	30.7 (46)	0.64
Past	26.2 (58)	21.1 (15)	28.7 (43)	0.23
Unknown	43.4 (96)	45.1 (32)	42.7 (64)	0.74
Relevant exposures				
Leather shoes	24.4 (54)	16.9 (12)	28.0 (42)	0.07
Leather gloves	8.6 (19)	16.9 (12)	4.7 (7)	0.002
Other leather exposure[b]	3.2 (7)	2.8 (2)	3.3 (5)	0.84
Cement	3.2 (7)	8.5 (6)	0.7 (1)	0.002
Metal[c]	10.0 (22)	15.5 (11)	7.3 (11)	0.06
Cosmetics	0.9 (2)	1.4 (1)	0.7 (1)	0.59
Graphic work and paint	3.2 (7)	5.6 (4)	2.0 (3)	0.15
Other chromium materials[d]	1.4 (3)	1.4 (1)	1.3 (2)	0.96
Anatomical location of dermatitis				
Feet	40.3 (89)	29.6 (21)	45.3 (68)	0.03
Legs	10.9 (24)	7.0 (5)	12.7 (19)	0.21
Face/neck	12.7 (28)	5.6 (4)	16.0 (24)	0.03
Arms	15.8 (35)	16.9 (12)	15.3 (23)	0.77
Trunk	4.5 (10)	4.2 (3)	4.7 (7)	0.88
Universal	13.1 (29)	15.5 (11)	12.0 (18)	0.47
Hand dermatitis only[e]	22.2 (49)	35.2 (25)	16.0 (24)	0.001

[a] P-value of χ^2-test comparing males and females.
[b] Furniture, watchband, coat, bag, belt, accessories.
[c] Including welding.
[d] Engine oil, cleaning articles, other chromium-containing materials at work.
[e] Hand dermatitis only refers to patients with hand eczema as the only anatomical location, whereas hand dermatitis noted under the heading MOAHLFA is hand dermatitis in total (i.e. some patients had dermatitis in more locations than the hands).

However, some patients had dermatitis in more than one location; thus, a considerable proportion had dermatitis on the arms (15.8%) or face/neck (12.7%), as well as universal distribution (13.1%). The hand as the only anatomical location occurred significantly more often in men than in women ($P = 0.001$).

Information about sources of chromate exposure was examined in relation to each year. A χ^2 trend test was performed to determine whether the occurrence of chromate exposure (leather shoes, leather gloves, other leather sources, leather total, metal, and cement) showed a significant change across test years. In particular, this was done to detect fluctuations in the relevant exposure to cement and leather during 1992–2009. None of the exposures showed any significant trend across test years. Hence, no significant changes in the sources of the assumed causative chrome exposures during the 18-year period were identified.

The sub-analysis on the TRUE Test® reproducibility showed that 594 patients were tested on more than one occasion. The total number of patch test procedures performed on these patients was 1271. The number of patch tests applied to each patient varied from two to five, and time between the tests varied from 1 to 12 years. Of the 594 patients, 539 had negative results in all of their patch tests, whereas 15 had positive results in all of their patch tests. Taken together, 554 of the 594 patients had similar results in every patch test, so the reproducibility of the TRUE Test® was 93.3%. A negative followed by a positive result was reported in 3.2% of the patients, and a positive followed by a negative result was reported in 3.5% of the patients.

Discussion

This study showed that, during 1992–2009, leather products were registered as the most frequent sources of chrome exposure (36.2%) in chromate-allergic individuals, and that leather shoes (24.4%) were the most frequent leather items, particularly in women. Furthermore, leather shoes were registered as being of current relevance in 64.8%. Foot dermatitis (40.3%) was the most frequent clinical picture apart from hand eczema (60.6%). Taken together, the findings show an association between leather exposure and chromate allergy, which was especially reflected as foot dermatitis caused by leather shoes. With respect to cement, current relevance was low (14.3%) and past relevance was high (71.4%); this could be interpreted as a result of the addition of ferrous sulfate to cement introduced by Danish legislation since 1983 (4, 5). It would be interesting to obtain more information on the sensitization properties of chrome-tanned leather, regarding whether leather can sensitize in itself or just elicit an allergic reaction in previously sensitized patients. However, patients who had previously been sensitized by cement and had an allergic contact dermatitis elicited by leather were not identified in the medical charts. Annual fluctuations in the prevalence of chromate allergy and significant changes in exposure to chrome during the 18-year period did not present a v-shaped pattern with a significant decrease followed by a significant increase. Thus, there was a lack of consistency of association between the present study and that of Thyssen et al. (3), in spite of presumably comparable study populations and similar methods.

There may be several explanations for the lack of consistency between the two studies. At first, the results by Thyssen et al. (3) might be expected to be reproduced, because the study populations were taken from the same country and time period, and therefore it might be assumed that there would be no present, significant difference. Reconsidering that assumption, there might be an actual, significant variation between the study populations. It is important to note that the study did not include the period around the introduction of the limitation of chromate in cement, as Thyssen et al. (3) did. To detect significant differences between the two study populations, a χ^2-test comparing the MOAHLFA index was performed. Occupational dermatitis occurred significantly more often in the study by Thyssen et al. (3), but otherwise there were no significant differences between the studies with regard to the MOAHLFA index. Thus, an overall significant difference between the study populations, which could explain the different results, was not detectable. Another explanation may be the size of the study population in the present study, which was half the size of the population in the study by Thyssen et al. (3). Thus, sampling error might be an issue, causing statistical uncertainty. However, a study population of 8483 patients is considerable. For information about clinical characteristics, almost all of the medical charts (95.7%) were retrieved, so there were no substantial shortcomings in this regard. However, a weakness in the present study was that unknown relevance was reported in 43.4% of the cases as compared with only 26.4% in the study by Thyssen et al. (3). As the reproducibility of the TRUE Test® results has been demonstrated to be high, it is unlikely that the large number of positive reactions with unknown relevance in the present study can be explained by false-positive reactions. Different judgements on clinical relevance between physicians at Odense and Gentofte Hospital may be a plausible explanation. A recent European multicentre study (9) showed a higher proportion of current and past relevance of positive patch test reactions to *p*-phenylenediamine (53.6% and 20.3%, respectively). Thus, a larger number of cases of current or past relevance of positive patch test reactions to chromate in the present study would have been desirable. In general, registrations of relevance are uncertain because of the individual assessment made by the physician. The same applies to variations in the precision of registrations about anatomical location, as well as relevant exposures in the medical charts, and therefore also to individual differences in the way that medical charts are read and understood. Therefore, there are still several uncertainties when comparing results from two apparently similar studies.

Although the results of Thyssen et al. (3) were not reproduced in the present study, they were certainly not disproved. Even though no significant changes in the prevalence of chromate allergy were detected, there still seemed to be a trend of a slightly increasing prevalence of chromate allergy from the nadir year 1997. This nadir year is close to the nadir year (1995) in the study by Thyssen et al. (3). Furthermore, this trend was also observed in Singapore (10), North America (11), and Sweden (12). Goon and Goh (10) showed nadir years in 1986–1990, with a prevalence of 2.7% followed by an increase to 5.6% in 2001–2003. Nguyen et al. (11) found nadir years with a prevalence of 2.0% in 1992–1996 followed by an increase to 6.0% in 2000. Finally, Lindberg et al. (12) found an increase from 2.8% in 1992 to 5.1% in 2000 among women. Hence, the trend did not seem to be a coincidence, but it would be desirable to reproduce the results within the same country. Finally, a recent study from Gentofte, Denmark supported a change in the epidemiology of chromate allergy, as the proportion of 3+ patch test reactions decreased, and they nearly

disappeared between 1977 and 1995, probably because of the chromate regulation (13). The proportion of 2+ reactions increased dramatically after 2001, perhaps because of leather exposure (13).

Despite these observations, the question of statistical associations and causality arises. The second of Bradford Hills's (14) criteria for assessing causation from epidemiological studies is about consistency of association, which suggests that observations ought to be confirmed independently, by observing different persons in different places. When similar epidemiological studies show inconsistency, it must be considered that the statistical associations could have happened by chance, and that the correlation does not necessarily imply causation (15, 16). Thus, statistical associations are always subject to some uncertainty, and a single set of epidemiological data will not provide a sufficient basis on which to draw conclusions on cause-and-effect relationships. The problem exists particularly in retrospective studies, where data of interest regarding the suspected causal exposures are collected from cases investigated in the past. Unlike in prospective studies, there is no randomization, so bias arises (17). Nevertheless, once a connection between an exposure and a disease has been pointed out, it takes several studies to disprove it (15). This may cause bias in reporting in subsequent, similar studies, because the investigator taking the medical history then tends to ask the patient specifically about a certain exposure and associated symptoms. Thus, the expected association will be determined in advance, and recall bias and informational bias therefore arise. In addition, the potentially false cause-and-effect association will provide inappropriate and unnecessary measures for avoidance of exposure to prevent the symptoms (15).

Thus, is it difficult to say whether there was an actual, causal relationship between the increasing prevalence of chromate allergy and leather exposure, and the present study simply failed to identify it, or whether the demonstrated, statistical association was an expression of a coincidence rather than a causal relationship. The correlation between chrome allergy, to both chromium(III) and chromium(VI), and leather exposure was identified in several other studies in Denmark as well as in other countries (1, 2, 18, 19), but the question remains of whether leather exposure is the reason for the observed increase in the prevalence of chromate allergy in Denmark since the 1990s.

Patients with chromate allergic dermatitis following skin contact with leather products have been advised to seek out hypoallergenic alternatives, such as vegetable tanned leather with a low chromium content (20). However, Von Coevorden et al. (21) showed that hypoallergenic shoe leather might contain other allergens and cause allergic contact dermatitis as well. These allergens are not included in the European baseline series, because little is known about the tanning agents, and the shoe manufacturers have not made information available. Recommendations to prevent allergic contact dermatitis caused by leather, chrome-tanned as well as vegetable-tanned, could be plastic shoes or wearing an extra pairs of socks in the shoes (21). Suggestions to reduce the risk of developing allergic contact dermatitis caused by leather products could follow the recommendations in Germany on limiting the content of chromium(III) and chromium(VI) in leather products (http://www.bfr.bund.de/cd/9575, last accessed 2 March 2010).

Finally, chromated metal products may also be regarded as being hazardous to sensitized patients. In the present study, metal exposure was reported in 10.0%. Geier et al. (22) showed that release of chromium(VI) from chromated metal products may be high enough to elicit allergic reactions, concerning, for instance, work with screws and fittings. Thus, attention should be paid to possible hidden allergen exposure such as to chromated metal products.

The chromate patch tests used in the present study were TRUE Tests®, whereas the Gentofte study (3) used Trolab® allergen and Finn Chambers® on Scanpor® tape. However, this is not expected to affect the statistical analyses in the two studies.

The reproducibility of the TRUE Test® was 93.3%. A negative followed by a positive response was seen in 3.2% of the patients. As reproducibility was demonstrated in 93.3% of the patients, it is more likely that a great many of the 3.2% were sensitized between the first and the last test than that it was caused by low sensitivity or specificity. For comparison, Brasch et al. (23) showed a reproducibility of 90.8% with the TRUE Test® for chromate-positive patients. A positive followed by a negative result was seen in 3.5% of the patients, which may be regarded as a lack of reproducibility because of simple biological test variability, too low sensitivity or specificity, or variations in the interpretation of the patch tests by the physician, with both intra-individual and inter-individual differences. Furthermore, conditions that may interfere with the interpretations of patch test results must be considered, i.e. false-positive reactions caused by, for example, dermatitis at the patch test time, an effect of the tape, or artefacts, and false-negative reactions caused by, for example, treatment with corticosteroids, insufficient penetration of the allergen, or compound allergy (24). However, it must be concluded that the reproducibility of the TRUE Test® in 93.3% may be assessed as high.

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