

Contact allergy to allergens of the TRUE-test (panels 1 and 2) has decreased modestly in the general population

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Summary

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Conflicts of interest

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Background The prevalence of contact allergy in the general population is nearly 20%.

Objectives This study aimed to monitor the development of contact allergy to allergens from the TRUE-test (panels 1 and 2) between 1990 and 2006.

Methods Two random samples of adults from the general population in Copenhagen, Denmark, were invited to participate in a general health examination including patch testing. In 1990 and 2006, we patch tested and questioned 543 and 3460 adult Danes. Patch test readings were performed on day 2 only.

Results The overall prevalence decreased significantly from 15.5% in 1990 to 10.0% in 2006, mainly as a result of a decrease in thimerosal allergy from 3.4% to 0.8%. Furthermore, the prevalence of cobalt allergy and rubber-related allergens decreased from 1.1% to 0.2% and from 1.5% to 0.2%, respectively. Stratification by sex and age group revealed decreasing prevalences of contact allergy in all male age groups and in young and middle-aged female age groups (18–55 years) whereas increasing prevalences were observed among older women (56–69 years). The diverging trend observed in women was probably explained by a cohort effect due to a change in the prevalence of nickel allergy following the Danish regulation on nickel exposure.

Conclusions Although the overall prevalence of contact allergy decreased in the general population, frequent contact allergens such as fragrance mix II and methyl-dibromo glutaronitrile were not tested. Thus, contact allergy remains prevalent in the general population.

The prevalence of contact allergy in the general population has previously been estimated.^{1–5} Based on 17 studies, the prevalence ranged between 12.5% and 40.6%, with a weighted average of 19.5%.⁶ Traditionally, the three most common contact allergens are nickel, fragrances and thimerosal.⁶ In 1990,³ 1998⁴ and again in 2006, subjects from the general population in Copenhagen were invited to participate in a general health examination. Patch testing showed that the prevalence of contact allergy was 15.2% among 15–69-year-olds in 1990³ and 18.6% among 15–41-year-olds in 1998.⁴ Among 15–41-year-olds, the prevalence of contact allergy to cosmetic-related haptens increased significantly from 2.4% to 5.8% between 1990 and 1998 whereas the prevalence of thimerosal allergy decreased from 3.4% to 2.1%.⁴

The present study determined the prevalence of contact allergy to allergens from the TRUE-test (panels 1 and 2)

among 18–69-year-old Danes in 2006, and compared them with prevalences from the 1990 study. Changes in the prevalence of nickel, fragrance mix I and *Myroxylon pereirae* (Balsam of Peru) allergy have previously been addressed.^{7,8} The prevalence of nickel allergy decreased among women aged 18–35 years between 1990 and 2006 whereas the prevalence of fragrance mix I and *M. pereirae* sensitization followed an 'upside down V-shape' pattern among 18–41-year-old women (i.e. an increase from 1990 to 1998, followed by a decrease from 1998 to 2006). The continuous surveillance of contact allergy in the general population remains important in order to establish the burden of chemical exposure and its impact on human health. The current study offers patch test results from the only repeated cross-sectional study among adults in the general population.

Patients and methods

Study populations

In 1990 and 2006, two consecutive cross-sectional studies were organized by the same group of investigators. Danish adults (with Danish citizenship and born in Denmark) living in one of the same 11 municipalities of the Copenhagen County were invited to participate in a general health examination including patch testing. Study populations were random samples obtained from the Danish Central Personal Register, Ministry of Internal Affairs. Participants completed a postal questionnaire using the same questions: 'have you ever had your ears pierced?' and 'have you ever had eczema behind the knees or fronts of elbows?' An affirmative answer to the latter questions was used a marker of atopic dermatitis. The Ethical Committee of Copenhagen County approved all studies (KA-20060011).

Between February 1990 and January 1991, 567 (71.5%) of 793 invited 15–69-year-olds were patch tested (Table 1). In order to compare the results with those from the 2006 study, participants aged 15–17 years were excluded from further

analyses. Thus, 543 participants aged 18–69 years were patch tested. Between June 2006 and May 2008, 3471 (43.7%) of 7931 invited subjects aged 18–69 years showed up for health examination and 3460 participants were patch tested (Table 1). For practical reasons, persons below the age of 18 years were not invited in 2006, as an informed, written consent from the parents is now mandatory in Denmark.

Patch tests

Patch testing was performed by using panels 1 and 2 of the standardized ready-to-apply TRUE-test (ALK-Abelló A/S, Hørsholm, Denmark, in 1990; Mekos Laboratories, Hillerød, Denmark, in 2006). The haptens in the TRUE-test differed from the European baseline series by including thimerosal and excluding primine, sesquiterpene lactone mix, tixocortol pivalate, budesonide, hydroxyisohexyl-3-cyclohexene carboxaldehyde (HICC), methyldibromo glutaronitrile (MDBGN) and fragrance mix II. Furthermore, the TRUE-test contained black-rubber mix instead of N-isopropyl-N'-phenylparaphenylenediamine and caine mix (tetracaine, benzocaine and dibucaine) instead of benzocaine. Finally, formaldehyde was not

Table 1 The prevalence of contact allergy in 543 (1990) and 3460 (2006) adults aged 18–69 years from the general population in Copenhagen, Denmark

Allergens and mixtures of allergens	Positive reactions % (n)					
	Men		Women		Total	
	1990 (n = 269)	2006 (n = 1547)	1990 (n = 274)	2006 (n = 1913)	1990 (n = 543)	2006 (n = 3460)
Nickel sulphate	2.2 (6)	1.0 (15)	10.9 (30)	9.9 (189)	6.6 (36)	5.9 (204)
Wool alcohols ^a	0.4 (1)	0	0	0	0.2 (1)	0
Neomycin sulphate	0	0	0	0.1 (2)	0	0.1 (2)
Potassium dichromate	0.7 (2)	0	0.4 (1)	0.3 (5)	0.6 (3)	0.1 (5)
Caine mix	0	0	0	0.1 (2)	0	0.1 (2)
Fragrance mix I	1.1 (3)	1.4 (21)	1.1 (3)	1.8 (34)	1.1 (6)	1.6 (55)
Colophony	0.4 (1)	0.7 (11)	1.1 (3)	0.5 (10)	0.7 (4)	0.6 (21)
Epoxy resin	0.4 (1)	0.8 (12)	0.7 (2)	0.3 (6)	0.6 (3)	0.5 (18)
Quinoline mix ^a	0.4 (1)	0.1 (2)	0.4 (1)	0	0.4 (2)	0.1 (2)
Balsam of Peru ^a	0.7 (2)	0.1 (1)	1.5 (4)	0.1 (2)	1.1 (6)	0.1 (3)
Ethylenediamine dihydrochloride	0.4 (1)	0.1 (2)	0	0.3 (6)	0.2 (1)	0.2 (8)
Cobalt dichloride ^a	0.7 (2)	0.1 (1)	1.5 (4)	0.4 (7)	1.1 (6)	0.2 (8)
p-tert-Butylphenol formaldehyde resin ^a	1.1 (3)	0	1.1 (3)	0.1 (1)	1.1 (6)	0.1 (1)
Paraben mix ^a	0.4 (1)	0	0.4 (1)	0	0.4 (2)	0
Carba mix	0.7 (2)	0.1 (2)	0	0.1 (2)	0.2 (4)	0.1 (4)
Black rubber mix	0.4 (1)	0	0	0.2 (4)	0.2 (1)	0.1 (4)
Cl+ Me- Isothiazolinone ^a	0.4 (1)	0.3 (4)	1.1 (3)	0.1 (2)	0.7 (4)	0.2 (6)
Quaternium-15	0.4 (1)	0.2 (3)	0	0.2 (3)	0.2 (1)	0.2 (6)
Mercaptobenzothiazole ^a	0.4 (1)	0	0	0	0.2 (1)	0
p-Phenylenediamine	0	0	0	0.2 (4)	0	0.1 (4)
Formaldehyde	–	0.1 (2)	–	0.3 (5)	–	0.2 (7)
Mercapto mix ^a	0.7 (2)	0	0	0	0.4 (2)	0
Thimerosal ^a	3.7 (10)	0.4 (6)	3.3 (9)	0.6 (12)	3.5 (19)	0.5 (18)
Thiuram mix ^a	0.7 (2)	0	0.4 (1)	0.2 (3)	0.6 (3)	0.1 (3)
Totals	11.9 (32)	4.7 (73)	19.0 (52)	14.2 (272)	15.5 (84)	10.0 (345)

^aAllergens that decreased significantly between 1990 and 2006. –, formaldehyde not tested in 1990.

included in the TRUE-test in 1990. Directions to apply the patch test panels to the upper back 2 days before examination were mailed together with the patch tests. They were read and photographed 1–1½ h after removal by N.H.N. in 1990 and by trained health care personnel in 2006 (supervised by J.P.T. and A.L.). Photographs were reviewed by N.H.N. and T.M. in 1990 and by T.M., N.H.N., A.L. and J.P.T. in 2006. This was done to assure that the International Contact Dermatitis Research Group (ICDRG) criteria were used consistently over time.⁹ Contact allergy was defined as a positive (at least grade 1+ according to ICDRG) patch test to at least one allergen or mix of haptens. Rubber allergy was defined as a positive patch test reaction to at least one of the following allergens: thiuram mix, mercapto mix, mercaptobenzothiazole, carba mix. When the patch had no skin contact upon patch test reading, or if the subject had removed it prior to testing as a result of known contact allergy, it was regarded as missing data.

Statistical analysis

Characteristics of subjects patch tested in 1990 and 2006 were compared using the χ^2 test. Due to a well-known marked sex difference in the prevalence of allergy to contact allergens, the analyses were stratified by sex. A logistic regression model was performed with 'contact allergy to at least one allergen' as the dependent variable and with sex ('women' vs. 'men'), age group ('18–35 years', '36–55 years', '56–69 years'), response to the question 'have you ever had your ears pierced?' ('yes' vs. 'no') and study year ('2006' vs. '1990') as the independent variables. Furthermore, a similar logistic regression analysis was performed with 'contact allergy to at least one allergen but not nickel' as the dependent variable and with the following independent variables: sex ('women' vs. 'men'), age group ('18–35 years', '36–55 years', '56–69 years') and study year ('2006' vs. '1990'). Finally, two identical analyses were performed with 'contact allergy to at least one allergen but not nickel, fragrance mix I and *M. pereirae*' and 'contact allergy to at least one allergen but not thimerosal' as the dependent variables, respectively. Adjustment for atopic dermatitis did not change the outcome of the above analyses and was therefore left out. Associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Data analyses were performed using the Statistical Products and Service Solutions package (SPSS Inc., Chicago, IL, U.S.A.) for Windows (release 15.0).

Results

The participation rate among men was 76.5% in 1990 but decreased to 39.1% in 2006 whereas the participation rate among women decreased from 75.6% in 1990 to 48.4% in 2006 as previously reported.⁷ The decreases were observed in all age groups.

Patch test results among 3460 subjects aged 18–69 years (1913 women and 1547 men) tested in 2006 are presented

in Table 1. In total 345 (10.0%) positive patch test reactions were identified and a higher proportion was observed among women (14.2%) than among men (4.7%). The most common contact allergens in 2006 were nickel (5.9%), fragrance mix I (1.6%), colophony (0.6%) and thimerosal (0.5%). Nickel allergy was more common in women (9.9%) than in men (1.0%). Finally, a positive patch test reaction to more than one allergen was observed among 21 (0.6%) subjects. All were nickel sensitized and the most common combination was allergy to fragrance mix I and nickel (42.9%) whereas concomitant nickel and cobalt allergy was less common (14%).

Patch test data from the 1990 study revealed that 84 (15.5%) positive reactions were identified among 543 18–69-year-olds (Table 1). Thus, the overall prevalence of contact allergy decreased from 15.5% in 1990 to 10.0% in 2006. This decrease was observed in men (1990 = 11.9% and 2006 = 4.7%) and women (1990 = 19.0% and 2006 = 14.2%). Furthermore, a decrease was observed in all male age groups and among young women ('18–35 years' and '36–55 years') whereas an increase was observed among older women ('56–69 years') (Table 2). The prevalence of thimerosal allergy demonstrated a large overall decrease from 3.5% in 1990 to 0.5% in 2006. The decrease of thimerosal allergy was observed in all age groups except among 56–69-year-old women where a slight increase was registered (Table 2). If thimerosal allergy was left out of the analyses, an overall decrease of contact allergy to at least one allergen was observed from 12.7% in 1990 to 9.6% in 2006 ($P < 0.03$). Other prevalent allergens also showed decreasing prevalences between 1990 and 2006 (Table 1): cobalt (from 1.1% to 0.2%), *p*-tert-butylphenol (PTBP) formaldehyde resin (from 1.1% to 0.1%), Cl+ Me- isothiazolinone (MCI/MI) (from 0.7% to 0.2%) and rubber-related allergens (from 1.5% to 0.2%). No significant increases were observed between 1990 and 2006.

A logistic regression analysis with 'contact allergy to at least one allergen' as the dependent variable was performed (Table 3). It showed that 'contact allergy to at least one allergen' was associated with 'female sex' (OR = 2.11; CI = 1.58–2.82) and that a positive trend test was identified for age (OR = 1.18; CI = 1.01–1.37). Finally, it showed that study year '2006' was inversely associated with contact allergy (OR = 0.55; CI = 0.42–0.78). A similar logistic regression analysis with 'contact allergy to at least one allergen but not nickel' as the dependent variable and with sex, age and study year as the explanatory variables showed that 'contact allergy to at least one allergen but not nickel' was also associated with female sex (OR = 1.33; CI = 1.00–1.76) and inversely associated with study year '2006' (OR = 0.43; CI = 0.31–0.60). No association with age group was identified. The outcome of the analysis did not change if the dependent variable was replaced with 'contact allergy to at least one allergen but not nickel, fragrance mix I and *M. pereirae*' or with 'contact allergy to at least one allergen but not thimerosal'. Thus, a decrease in the prevalence of contact allergy was observed between

Table 2 The prevalence of contact allergy^a among adults from the general population in Copenhagen, Denmark (1990 and 2006)

Age group (years)	Study year					
	Men			Women		
	1990 (n = 269)	2006 (n = 1547)	Crude OR with 95% CI ^b	1990 (n = 274)	2006 (n = 1913)	Crude OR with 95% CI ^b
	% (n)	% (n)		% (n)	% (n)	
18–35 (n = 837)						
Contact allergy to at least one allergen ^a	13.1 (11)	4.9 (13)	0.34 (0.15–0.80)	24.5 (26)	15.2 (58)	0.55 (0.33–0.93)
Contact allergy to at least one allergen but not nickel ^a	8.5 (8)	4.2 (11)	0.47 (0.18–1.06)	9.9 (11)	5.2 (20)	0.50 (0.23–1.08)
Contact allergy to thimerosal	4.8 (4)	0.4 (1)	0.08 (0.01–0.72)	3.8 (4)	0	–
36–55 (n = 1917)						
Contact allergy to at least one allergen ^a	9.9 (12)	4.1 (30)	0.39 (0.19–0.78)	18.5 (23)	17.2 (161)	0.91 (0.56–1.48)
Contact allergy to at least one allergen but not nickel ^a	8.6 (11)	2.8 (21)	0.31 (0.15–0.66)	13.2 (17)	6.1 (57)	0.42 (0.24–0.76)
Contact allergy to thimerosal	3.3 (4)	0.3 (2)	0.08 (0.02–0.45)	4.0 (5)	1.2 (11)	0.29 (0.01–0.84)
56–69 (n = 1249)						
Contact allergy to at least one allergen ^a	14.1 (9)	5.5 (30)	0.35 (0.16–0.59)	6.8 (3)	8.9 (53)	1.33 (0.40–4.45)
Contact allergy to at least one allergen but not nickel ^a	12.3 (8)	5.1 (28)	0.38 (0.17–0.89)	4.3 (2)	4.3 (26)	1.00 (0.23–4.35)
Contact allergy to thimerosal	3.1 (2)	0.6 (3)	0.18 (0.03–1.07)	0	0.2 (1)	–

CI, confidence interval; OR, odds ratio. ^aIn 1990, formaldehyde was not included in the TRUE-test. ^bOR (95% CI) comparing the prevalence of contact allergy in 2006 with that in 1990.

Table 3 Logistic regression analysis with the outcome 'contact allergy' and with different explanatory variables performed in 4003 subjects patch tested in 1990 (n = 543) and 2006 (n = 3460)

Explanatory variables	Adjusted OR ^b with 95% CI
Study year	
1990	1 (reference)
2006	0.55 (0.42–0.78)
Sex	
Male	1 (reference)
Female	2.11 (1.58–2.82)
Age (years)	
18–35	1 (reference), ^a P < 0.04
36–55	0.97 (0.76–1.26)
56–69	1.42 (1.04–1.94)
Ear piercing	
No	1 (reference)
Yes	1.62 (1.22–2.16)

CI, confidence interval; OR, odds ratio. ^aP-value of trend test.
^bMutually adjusted for variables shown in table.

1990 and 2006 for the categories 'thimerosal' as well as 'contact allergens from the TRUE-test (panels 1 and 2) but not nickel, fragrance mix I and *M. pereirae*'.

Discussion

This study showed that the overall prevalence of contact allergy to the allergens of the TRUE-test (panels 1 and 2)

decreased in Denmark from 15.5% in 1990 to 10.0% in 2006 (Table 1). Stratification by sex and age group revealed decreasing prevalences in all male age groups and in the young and middle aged female age groups (18–55 years) whereas increasing prevalences were observed among middle-aged and older women (56–69 years) (Table 2). The diverging trend observed in young and middle-aged vs. older women was probably explained by a cohort effect due to a change in the prevalence of nickel allergy as it was decreasing in young women ear-pierced later than 1990 (i.e. after the Danish nickel regulation was passed) but increasing in women ear-pierced before 1990.⁸ However, when nickel allergy (and also fragrance mix I and *M. pereirae*) was omitted from the analysis, a significant decrease was still observed in most age groups between the two study years that was due to decreasing prevalences of other allergens (Tables 1 and 2). Of note, female sex remained associated with contact allergy even when nickel (and also fragrance mix I and *M. pereirae*) was omitted from the logistic regression analysis. This finding suggests that women may have a heavier exposure to chemicals than men and therefore a higher prevalence of contact allergy.¹⁰

A weakness of our study was the significantly decreasing rate of participation in all age groups from 1990 to 2006.⁷ To limit the influence of bias, our analyses were stratified by age group and sex, and therefore the observed trends were unlikely to be explained by differences in these variables between the studies. However, it cannot be ruled out that other characteristics differed between participants in the two studies (leading to an over- or under-representation of sensitized subjects). Although

we were unable to stratify for these unknown factors, we believe that data on the prevalence of contact allergy in repeated cross-sectional general population studies are likely to show more reliably the development of time trends of contact allergy than data obtained in series of patients admitted to specialized clinics. Of note is that the development, e.g. in the prevalence of nickel and fragrance contact allergy,^{7,8,11,12} observed in the present study was in line with clinical data supporting the validity of the observed trends. However, it should be acknowledged that increasing rates of nonparticipation in general population studies represents an important limitation.

The overall decrease of contact allergy to the allergens in the TRUE-test (panels 1 and 2) was mainly explained by a significant decrease in the prevalence of thimerosal allergy (Table 1). The decrease of thimerosal allergy between 1990 and 2006 was observed in all age groups among men whereas a slight increase was observed among older women (56–69 years), perhaps owing to a cohort effect. Thimerosal allergy is known to be prevalent in the general population due to its use as a preservative in vaccines and ophthalmic solutions.¹³ Furthermore, thimerosal has traditionally been widely used in biologics and vaccines in the U.S.A., which has resulted in a significant increasing prevalence of thimerosal allergy among North American dermatitis patients between 1984 and 1994.¹⁴ However, positive patch test reactions to thimerosal are generally very poor predictors of dermatitis reactions to thimerosal-containing vaccines.¹⁵ In Denmark, thimerosal allergy mainly derives from childhood vaccination as it has been an ingredient in vaccines since the 1950s and until March 1992. Because the Danish childhood vaccination programme is voluntary and free of charge, the vast majority of Danish children have been exposed to thimerosal through four decades. Furthermore, thimerosal may be an ingredient in vaccines against hepatitis and influenza virus, for example. However, steps have been taken in Denmark and in the rest of the world to strongly reduce or totally remove thimerosal from vaccines as thimerosal is a mercuric compound that may be nephrotoxic and neurotoxic at high doses. Furthermore, it has been suspected of causing neurodevelopmental disorders such as autism, although this association has been rejected.¹⁶ The observed decrease of thimerosal allergy in Denmark is interesting as it shows that when exposure to a contact allergen (whether nickel, thimerosal or other) is strongly reduced by an administrative initiative, a clear decrease of contact allergy can be registered in the general population.

Besides the decrease of thimerosal allergy, the overall decrease of contact allergy between 1990 and 2006 was explained by a decrease in the prevalence of allergy to nickel, cobalt, MCI/MI, PTBP formaldehyde resin and rubber-related allergens. The observed decreases were all significant but it may of course be a result of random error. Furthermore, one should remember that the sample size was small when compared with clinical databases. It is possible that the Danish general population is less exposed to contact allergens today than almost 20 years ago as a result of personal precautions and protection in an increasingly educated population. Cobalt

is a hard metal that is common in combination with other metals such as nickel, chromium and tungsten to increase hardness and durability. Because it is often mixed with, or is an impurity in other metals, cobalt allergy may go along with nickel allergy in women or chromate allergy in men.¹⁷ It has been suggested that nickel sensitivity and irritant hand eczema precede cobalt allergy in metal workers whereas cross-sensitization is rare.^{18,19} Ear-piercing has been associated with cobalt allergy in the general population.²⁰ Some 11 (79%) of 14 positive cobalt reactions were observed in women in 1990 and 2006. However, seven women and two men were sensitized to cobalt only. The findings therefore suggest that combined cobalt and nickel allergy is not that prevalent in the general population. It has been speculated whether cobalt has replaced nickel in jewellery after the introduction of the nickel regulation.²¹ In comparison, the prevalence of concomitant patch test reactivity to cobalt and nickel is much higher among patients with dermatitis.^{22,23} This area needs further attention to clarify the significance of these findings.

The decrease of allergy to rubber-related allergens may possibly be a result of the focus on rubber gloves during the 1990s.²⁴ Rubber manufacturers reduced the content and use of accelerators as they are considered to be the most frequent contact sensitizer in rubber gloves. Hence, the use of thiurams was strongly reduced in single-use natural rubber latex gloves.²⁴ The decrease observed in the general population in Denmark parallels the decrease observed among dermatitis patients from the Gentofte University Hospital between 1995 and 2004.²⁴ Also, the prevalence of thiuram mix, mercapto mix, mercaptobenzothiazole and carba mix allergy has decreased recently among dermatitis patients in the U.S.A.^{14,25} The prevalence of chromate allergy in men decreased from 0.7% in 1990 to 0% in 2006 whereas it remained stable in women with 0.4% and 0.3% positive patch test reactions in 1990 and 2006, respectively. The decrease in the prevalence of chromate allergy in men could possibly be explained by an effect of the cement chromate regulation in Denmark²⁶ whereas the persistence of chromate allergy in women may be explained by continuous exposure to chromate in leather goods.²⁷ Finally, as patch test readings were performed only on day 2, the prevalence of allergy to late-reacting allergens such as p-phenylenediamine and neomycin may be underestimated. To study such allergens properly, later readings should be carried out.

This study showed that the prevalence of contact allergy to allergens of the TRUE-test (panels 1 and 2) decreased modestly to 10.0% in Denmark and that it was mainly explained by a lower prevalence of thimerosal allergy but also that cobalt, chromate (in men) and rubber allergy decreased. A recent study using the clinical epidemiology and drug utility research (CE-DUR) method estimated that 7.3–12.9% of the Danish population (> 18 years) was contact sensitized.²⁸ The CE-DUR estimate was based on allergens from the European baseline series and therefore thimerosal was not included.

Despite the prevalence of contact allergy showing a decrease in the general population in Denmark, one should be aware

that only day 2 readings were performed in this study. Thus, the true prevalence of contact allergy is expected to be higher as 27% of positive patch test reactions to nickel are missed when readings are not performed beyond day 2 in a general population.²⁹ Similarly, patch test studies performed among dermatitis patients have suggested that 24–34.5% of positive patch test reactions potentially are missed when readings are not performed beyond day 2.^{30–32} Furthermore, important high-prevalence contact allergens such as HICC, fragrance mix II and MDBGN are not included in the TRUE-test. The true prevalence of contact allergy in the general population is likely to be higher than 10%. Future studies are necessary to monitor the prevalence of contact allergy in the general population in Denmark.

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